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ORIGINAL ARTICLE

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The effect of treatment delay on quality of life and overall survival in head and neck cancer patients

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Abstract

Objective: Head and neck squamous cell carcinomas (HNSCC) are rapidly developing tumours, and substantial delay in treatment initiation is associated with decreased overall survival. The effect of delay on health-related quality of life (HRQOL) is unknown. The aim of this study was to assess the impact of delay on QOL and overall survival.

Methods: Patients with mucosal HNSCC were prospectively included. HRQOL and 2-year overall survival were analysed using linear mixed-model analyses and cox regression, respectively. Delay was defined as care pathway interval (CPI) of ≥30 days between first consultation and treatment initiation.

Results: Median CPI was 39 days for the 173 patients included. A trend towards higher HRQOL-scores (indicating better HRQOL) during 2-year follow-up for patients with delay in treatment initiation was visible in the adjusted models (HRQOL summary score—β: 2.62, 95% CI: 0.57–4.67, $p = 0.012$). Factors associated with decreased overall survival were moderate comorbidities (HR: 5.10, 95% CI: 1.65–15.76, $p = 0.005$) and stage-IV tumours (HR: 12.37, 95% CI: 2.81–54.39, $p = 0.001$). Delay was not associated with worse overall survival.

Conclusion: Timely treatment initiation is challenging, especially for patients with advanced tumours and initial radiotherapy treatment. Encountering delay in treatment initiation did not result in clinically relevant differences in HRQOL-scores or decreased overall survival during 2-year follow-up.

KEYWORDS
head and neck neoplasms, overall survival, quality of life, time-to-treatment, treatment delay

1 | INTRODUCTION

Head and neck squamous cell carcinomas (HNSCC) are relatively rare. HNSCC are potentially fast-growing tumours, in an anatomically and functional complex area (Dejaco et al., 2019; Jensen & Overgaard, 2007). Disease stage at diagnosis is a strong indicator for prognosis (Du et al., 2019). As a result, timely diagnosis and treatment initiation is crucial, and numerous initiatives to reduce delay are described (Schutte et al., 2018; van Huizen et al., 2018). The complexity of the HNSCC population, with a high prevalence of frailty (Bras et al., 2020; de Vries et al., 2020) and comorbidities (Stordeur et al., 2020), might contribute to prolonged time to treatment initiation.

The quality-indicator norm for timely treatment initiation in the Netherlands is set at 30 days, stating that treatment should be initiated within 30 days after first consultation in a head and neck oncology centre (HNOC) (Dutch Head and Neck Society, 2017). Internationally, a 30-day cut-off is frequently studied and used as well (Murphy et al., 2016; Sharma et al., 2016; Tsai et al., 2017).

The effect of prolonged time to treatment has recently been described in a recent systematic review (Schoonbeek, Zwertbroek, et al., 2021), reporting a strong association between delay and decreased overall survival. Although survival rates of HNSCC in general are increasing (Pulte & Brenner, 2010), the treatment of these complex tumours in vital areas can result in severe disabilities and permanent loss of function. Survival as primary outcome measure does not adequately reflect patient perspective. Therefore, long-term patient-reported health-related quality of life (HRQOL) scores are increasingly considered a valuable additional endpoint. Although highly relevant, the effect of delay on HRQOL has not been previously described. The direct effects of prolonged time to treatment initiation (i.e., tumour progression and more extensive treatment) might be indirectly reflected in patient HRQOL perception.

The aim of this prospective study was therefore to investigate the effect of delay on the course of HRQOL and on overall survival, using the quality-indicator cut-off of 30 days. Assessment of these effects might result in further understanding of the impact of delay and subsequent improvement of care pathways.

2 | METHODS

2.1 | Study design and patient selection

Patients were included from the data-biobank registered in the Dutch Trial Register (registration number NL7839). Detailed information on inclusion of patients and data collection were described in a covering paper (Sidorenkov et al., 2019). This prospectively collected databiobank registered all consecutive patients after obtaining written informed consent, treated in either the departments of head and neck surgery, oral and maxillofacial surgery or radiation oncology in this tertiary HNOC. All patients were reviewed in the multidisciplinary tumour board and treated according to (inter)national guidelines. The current study protocol was approved by the scientific board of the databiobank.

Patients seen between 2014 (October) and 2016 (May) were enrolled (Figure 1). Inclusion criteria yielded a first primary HNSCC located in either the oral cavity, oropharynx, hypopharynx or larynx. When baseline HRQOL scores were not available, patients were excluded. Patients treated with palliative treatment intention or synchronous second primary tumour were excluded as well.

2.2 | Definitions and data collection

The number of days between first consultation in this HNOC and treatment initiation (either date of surgery, or first day of radiotherapy or chemoradiation) was defined as Care Pathway Interval (CPI) (Schoonbeek, de Vries, et al., 2021). This interval was dichotomized into two groups: patients starting treatment within 30 days, and patients with start of treatment ≥30 days (the 'delayed' group), based on the quality-indicator norm set by the Dutch Head and Neck Society (Dutch Head and Neck Society, 2017).

Patient, tumour and treatment characteristics were provided by the databiobank and were supplemented with time to treatment and follow-up data. The Union for International Cancer Control (UICC) TNM classification was used to report tumour stage (Sobin et al., 2009), and the Adult Comorbidity Evaluation (ACE-27) was used to grade presence of comorbidities, dividing patients into four categories (none, mild, moderate or severe) (Piccirillo, 2000).

The primary outcome was HRQOL, measured by the validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) at baseline (before treatment initiation), and at 3, 6, 12 and 24 months after treatment initiation (Aaronson et al., 1993). The EORTC-QLQ-C30 scoring manuals were used to calculate summary scores, global health status, functional scales and symptom scales (EORTC Study Group, 2013; Fayers et al., 2001). For these scales, scores range from 0 to 100, with a higher score indicating a better level of functioning/global health status or a high level of symptomatology (symptom scores). Within our analyses, a positive β indicates a higher score.

2.3 | Statistical analysis

SPSS® Statistics version 25.0 (Armonk, NY: IBM Corp.) was used to analyse data. Descriptive statistics are presented as means and standard deviations, medians and quartiles, or absolute numbers and percentages, depending on their distribution. Student's t tests, the Mann–Whitney U test or the χ^2 test were used for comparison, depending on the type of variable studied.

To analyse repeated continuous measures such as HRQOL scores, linear mixed-effect models (LMM) were used. These models are validated for accurate analysis, allowing for missing data points without discarding entire cases (Shek & Ma, 2011). As described earlier (Bjordal et al., 2000; de Vries et al., 2020; Roick et al., 2020), HRQOL

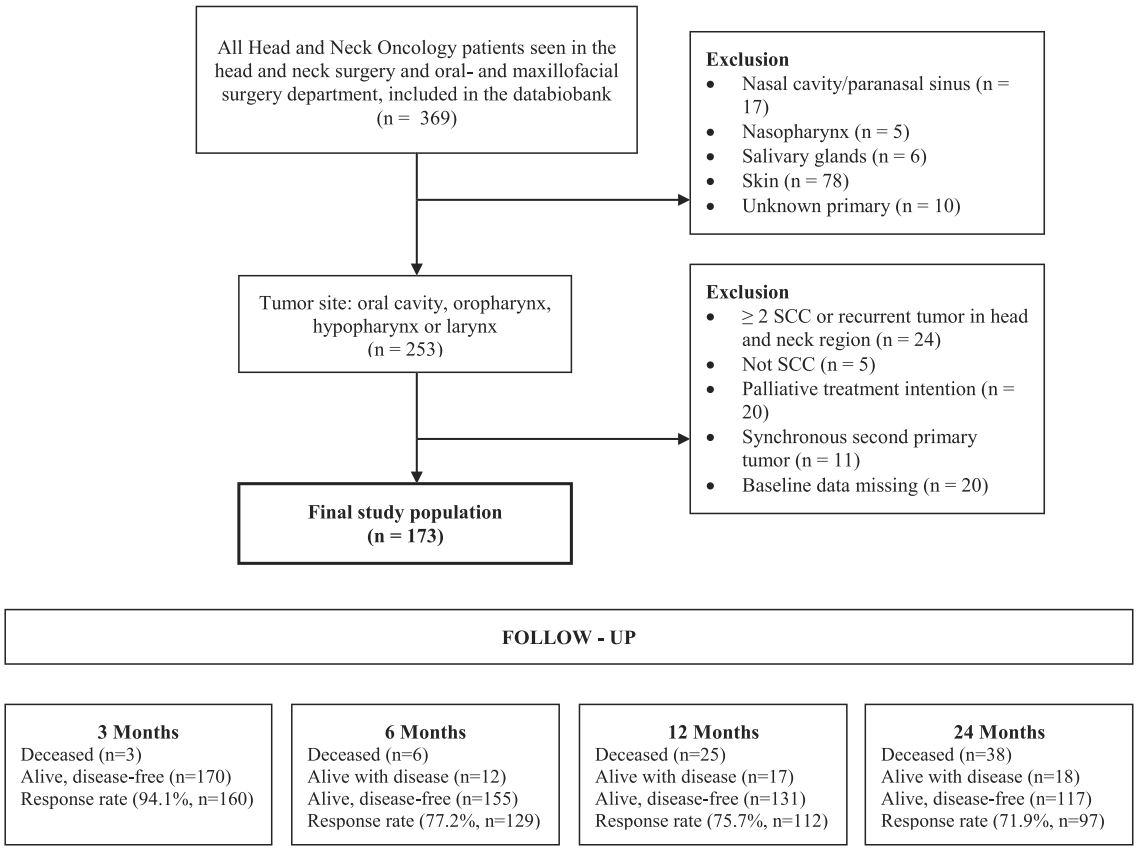

FIGURE 1 Flowchart of study population, including inclusion and exclusion criteria and follow-up characteristics. SCC: squamous cell carcinoma. Response rate based on alive, disease-free patients

decreases during the weeks after treatment, to recover over time subsequently. In this study, the 3- to 24-month interval was therefore treated as being linear. Death or tumour recurrence led to exclusion from further HRQOL analyses from that time point onwards.

For the LMM analyses, the compound symmetry covariance type was set after model fit comparing using likelihood ratio testing. Fixed effects included the *intercept* and the parameters *time*, *delay* (CPI, dichotomous), and *delay* * *time*. The predicted coefficients (β) represent the difference in HRQOL score of the corresponding domain for patients with (≥30 days) and without (<30 days) delay in treatment initiation at 3 months after treatment (*delay*) and over time per year (*delay* * *time*), also reporting 95% confidence intervals (CI) and p-values. All models were adjusted for baseline scores, age, sex, comorbidities, tumour site and stage and initial treatment modality. An intercept was included for random effects for between subject differences. Predicted values and standard errors were used for graphical representation (using GraphPad Prism version 8, GraphPad Software, San Diego, CA), and estimation method was set to Maximum Likelihood.

Cox regression analysis was performed to assess the effect of delay (and other parameters) on 2-year overall survival, establishing hazard ratio's (HR, >1 indicating a higher risk of deceasing). To validate the models, cox proportional hazard assumptions were verified.

A two-sided $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

A total of 173 patients had complete HRQOL baseline scores and were enrolled in this study (Figure 1). Mean age was 65.9 years (±10.3), and the majority was male (71.1%). Laryngeal carcinomas were present in 36.4%, and the second most common tumour site was the oral cavity (30.6%). Response rates of the HRQOL questionnaires ranged between 83% and 94% during follow-up. During the 2 years of follow-up, 38 patients (21.9%) died.

3.2 | Care pathway interval

Baseline characteristics were compared for patients starting treatment within 30 days, versus patients starting ≥30 days (the 'delayed' group), displayed in Table 1. The proportion of current smokers was greater in the delayed group (56.4% vs. 31.1%, $p = 0.006$, respectively). Patients with oropharyngeal and hypopharyngeal tumours were more frequently represented in the delayed group ($p < 0.001$), just like patients treated with initial radiotherapy or chemoradiation ($p < 0.001$). Stage II and IV tumours were mostly represented in the delayed group ($p < 0.001$).

TABLE 1 Baseline characteristics of study population

Characteristic	All $n = 173$	CPI < 30 days $n = 61$	CPI ≥ 30 days $n = 112$	p value
Age	65.9 ± 10.3	65.3 ± 11.0	66.2 ± 9.9	0.581
Sex				0.237
Male	123 (71.1%)	40 (32.5%)	83 (67.5%)	
Female	50 (28.9%)	21 (42.0%)	29 (64.7%)	
Smoking status				**0.006**
Never	18 (10.5%)	9 (50.0%)	9 (50.0%)	
Former	72 (42.1%)	33 (45.8%)	39 (54.2%)	
Current	81 (47.4%)	19 (23.5%)	62 (76.5%)	
Drinking status				0.301
Never	38 (22.6%)	17 (44.7%)	21 (55.3%)	
Former	30 (17.9%)	12 (40.0%)	18 (60.0%)	
Mild/moderate	57 (33.9%)	19 (33.3%)	38 (66.7%)	
Heavy	43 (25.6%)	11 (25.6%)	32 (74.4%)	
ACE-27				0.679
None	41 (23.7%)	13 (31.7%)	28 (68.3%)	
Mild	66 (38.2%)	22 (33.3%)	44 (66.7%)	
Moderate	42 (24.3%)	15 (35.7%)	27 (64.3%)	
Severe	24 (13.9%)	11 (45.8%)	13 (54.2%)	
Polypharmacy				0.148
None or <5 medications	117 (67.6%)	37 (31.6%)	80 (68.4%)	
≥5 medications	56 (32.4%)	24 (42.9%)	32 (57.1%)	
BMI				0.253
Low	7 (4.1%)	2 (28.6%)	5 (71.4%)	
Middle	79 (46.2%)	23 (29.1%)	56 (70.9%)	
High	85 (49.7%)	35 (41.2%)	50 (58.8%)	
Tumour site				**<0 .001**
Oral cavity	53 (30.6%)	31 (58.5%)	22 (41.5%)	
Oropharynx	50 (28.9%)	4 (8.0%)	46 (92.0%)	
Hypopharynx	7 (4.0%)	1 (14.3%)	6 (85.7%)	
Larynx	63 (36.4%)	25 (39.7%)	38 (60.3%)	
Histopathological grade				0.230
Well differentiated	26 (19.0%)	13 (50.0%)	13 (50.0%)	
Moderately differentiated	88 (64.2%)	34 (38.6%)	54 (61.4%)	
Poorly differentiated	23 (16.8%)	6 (26.1%)	17 (73.9%)	
Stage of disease				**<0.001**
Stage I	47 (27.2%)	32 (68.1%)	15 (31.9%)	
Stage II	24 (13.9%)	5 (20.8%)	19 (79.2%)	
Stage III	23 (13.3%)	10 (43.5%)	13 (56.5%)	
Stage IV	79 (45.7%)	14 (17.7%)	65 (82.3%)	
Treatment modality				**<0.001**
Surgery	77 (44.5%)	51 (66.2%)	26 (33.8%)	
Radiotherapy	59 (34.1%)	7 (11.9%)	52 (88.1%)	
Chemoradiation	37 (21.4%)	3 (8.1%)	34 (91.9%)	

Note: All data are presented as number of cases (percentage) or mean ± standard deviation (SD). Left column: column percentages; middle and right column: row percentages.
Abbreviations: ACE-27, Adult Comorbidity Evaluation; CPI, care pathway interval.

In total, 61 patients (35.3%) started treatment within 30 days. Median CPI was 39.0 days and differed for patients with initial surgery treatment (27.0 days) and patients with initial radiotherapy (39.0 days, $p < 0.001$, Figure 2, left panel). For patients with stage I–II tumours, median CPI was 29.0 days, compared with 39.0 for patients with stage III–IV tumours ($p < 0.001$, Figure 2, right panel).

3.3 | Health-related quality of life

The effect of delay in treatment initiation on HRQOL, using a linear mixed model analysis for different domains of the EORTC-QLQ-C30, is presented in Table 2 and plotted over time in Figure 3 for patients with treatment initiation within 30 days (blue line) versus patients starting treatment ≥30 days (red line). Delay in treatment initiation was associated with a significantly stronger increase in summary score (resembling a better HRQOL) for the 24-month follow-up (β: 2.62, 95%CI: 0.57 to 4.67, $p = 0.012$). Three months after treatment initiation, the summary score was lower for patients starting treatment ≥30 days, in models adjusted for baseline HRQOL and relevant parameters (β: −1.14, 95% CI: −5.15 to 2.86, $p = 0.574$).

Although a similar trend is visible (i.e., worse scores at 3 months [*delay*], but recovery over time, *delay * time*), the differences in the trend of global health status (β: 2.54, 95% CI: −0.87 to 5.94, $p = 0.143$), and the course of functional scales were not statistically significant (i.e., for physical functioning—β: 2.39, 95% CI: −0.12 to 4.90, $p = 0.062$).

Within the symptom scales, patients with delay had worse fatigue and constipation scores at 3 months after treatment initiation; however, significant recovery over time to better (lower) scores were visible (fatigue: β: −5.31, 95% CI: −9.54 to −1.08, $p = 0.014$, constipation: β: −5.96, 95% CI: −9.72 to −2.19, $p = 0.002$).

Unadjusted HRQOL scores are reported and plotted over time in Table S1 and Figure S1.

3.4 | Overall survival

The presence of comorbidities, tumour site and tumour stage were significantly associated with a higher hazard of dying in the univariable cox regression model (Table S2). Delay—both as a continuous and dichotomous parameter—was not associated with risk of dying 2 years after treatment initiation.

In the multivariable model, the hazard of dying was five times higher for patients with moderate comorbidities compared with patients without comorbidities (HR: 5.10, 95% CI: 1.65 to 15.76, $p = 0.005$). Compared with patients with oral cavity carcinoma, patients with laryngeal carcinomas had a lower hazard of dying (HR: 0.22, 95% CI: 0.07 to 0.70, $p = 0.011$), and stage IV tumours were strong independent predictors for a higher hazard of dying (HR: 12.37, 95% CI: 2.81 to 54.39, $p = 0.001$).

4 | DISCUSSION

This cohort study with prospectively collected data is the first to describe relation between treatment delay and trends in HRQOL. Only 35.3% of the patients started treatment within the Dutch quality-indicator norm of 30 days. Remarkably, no inferior HRQOL was found in relation to treatment delay, but a trend towards stronger increase in HRQOL scores during 2-year follow-up for patients with delay in treatment initiation was visible in models adjusted for relevant confounders. For the summary score, this stronger increase in the slope for patients with delay was statistically significant.

Factors associated with decreased overall survival were presence of moderate comorbidities and stage IV tumours. Prolonged time-to-treatment initiation was not associated with worse overall survival.

4.1 | Delay in the care pathway and effect on overall survival

The results in this study confirm the structural problem in aiming for timely treatment on the one hand, and the time needed for additional investigation, multidisciplinary board meetings and decision-making on the other hand. Other reports found a similar percentage of patients starting treatment within 30 days (van Harten et al., 2014), although faster time intervals as a result of interventions

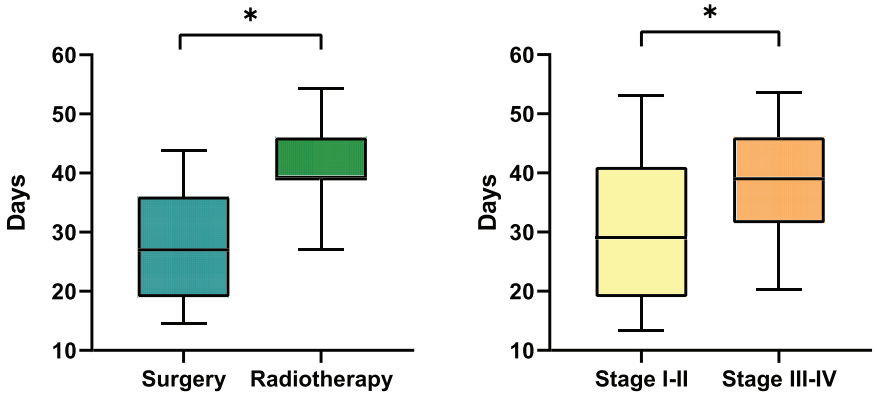

FIGURE 2 Care pathway interval (CPI) distribution, stratified by initial therapy (left) and disease stage (right). Asterisk (*) indicates a significant difference (left: $p < 0.001$, right: $p < 0.001$)

TABLE 2 Health-related quality of life: Results of the linear mixed model analysis for different domains of the EORTC-QLQ-C30

Scale	Parameters	Estimate (β)	95% CI	*p* value
Summary score	Delay	−1.14	−5.15 to 2.86	0.574
	Delay * Time	2.62	0.57 to 4.67	**0.012**
Global health status/HRQoL	Delay	−2.97	−9.21 to 3.27	0.349
	Delay * Time	2.54	−0.87 to 5.94	0.143
Functional scales				
Physical functioning	Delay	1.58	−3.24 to 6.39	0.520
	Delay * Time	2.39	−0.12 to 4.90	0.062
Role functioning	Delay	2.36	−5.51 to 10.23	0.555
	Delay * Time	2.37	−2.34 to 7.08	0.323
Emotional functioning	Delay	−0.65	−7.57 to 6.26	0.852
	Delay * Time	1.67	−2.02 to 5.36	0.373
Cognitive functioning	Delay	2.97	−2.79 to 8.72	0.310
	Delay * Time	0.95	−2.02 to 3.92	0.529
Social functioning	Delay	3.55	−3.33 to 10.43	0.310
	Delay * Time	−0.92	−4.75 to 2.92	0.639
Symptom scales				
Fatigue	Delay	3.79	−3.56 to 11.14	0.310
	Delay * Time	−5.31	−9.54 to −1.08	**0.014**
Nausea and vomiting	Delay	1.70	−2.86 to 6.25	0.463
	Delay * Time	−2.71	−6.04 to 0.62	0.110
Pain	Delay	3.77	−2.65 to 10.19	0.248
	Delay * Time	−3.71	−8.21 to 0.79	0.106
Dyspnoea	Delay	−0.24	−7.38 to 6.90	0.947
	Delay * Time	−2.52	−7.29 to 2.26	0.300
Insomnia	Delay	−2.77	−11.88 to 6.34	0.550
	Delay * Time	1.40	−3.49 to 6.28	0.575
Appetite loss	Delay	−0.38	−7.72 to 6.96	0.919
	Delay * Time	−4.25	−9.67 to 1.17	0.124
Constipation	Delay	5.97	0.77 to 11.17	**0.025**
	Delay * Time	−5.96	−9.72 to −2.19	**0.002**
Diarrhoea	Delay	2.96	−2.08 to 7.99	0.248
	Delay * Time	−3.61	−7.58 to 0.36	0.075
Financial difficulties	Delay	−1.78	−8.51 to 4.95	0.602
	Delay * Time	−1.59	−5.49 to 2.31	0.423

Note: The model is adjusted for sex, age, comorbidities, tumour location and stage, initial treatment modality and corresponding baseline scores.
Abbreviations: CI, confidence interval; HRQoL, quality of life.

(i.e., fast-track diagnostics, including imaging and flexible video-endoscopic biopsies under topical anaesthesia) in the care pathway are described as well (Schutte et al., 2018; Schutte et al., 2020).

In line with previously reported results (Guizard et al., 2016; Murphy et al., 2015; Murphy et al., 2016; Polesel et al., 2017; Schoonbeek, de Vries, et al., 2021; van Harten et al., 2014), factors associated with delay were advanced tumour stage and primary radiotherapy treatment. Radiotherapy patients may require more extensive pre-treatment planning, such as dental assessment and extractions, and subsequent delayed preparation of a mask.

We found no association between CPI of 30 days or more and inferior overall survival, in contrast to other studies (DeGraaff et al., 2019; Ho et al., 2018; Liao et al., 2019; Murphy et al., 2016; Naghavi et al., 2016; Polesel et al., 2017; Xiao et al., 2018). However, in these studies, this association was only significant starting from a delay of more than 45 days (up to the longest delay of 90 days) (Murphy et al., 2016; Naghavi et al., 2016; Polesel et al., 2017). The underlying pathophysiological mechanism is thought to be tumour progression and subsequent stage migration in patients with prolonged time-to-treatment interval (Amsbaugh et al., 2018; Xiao

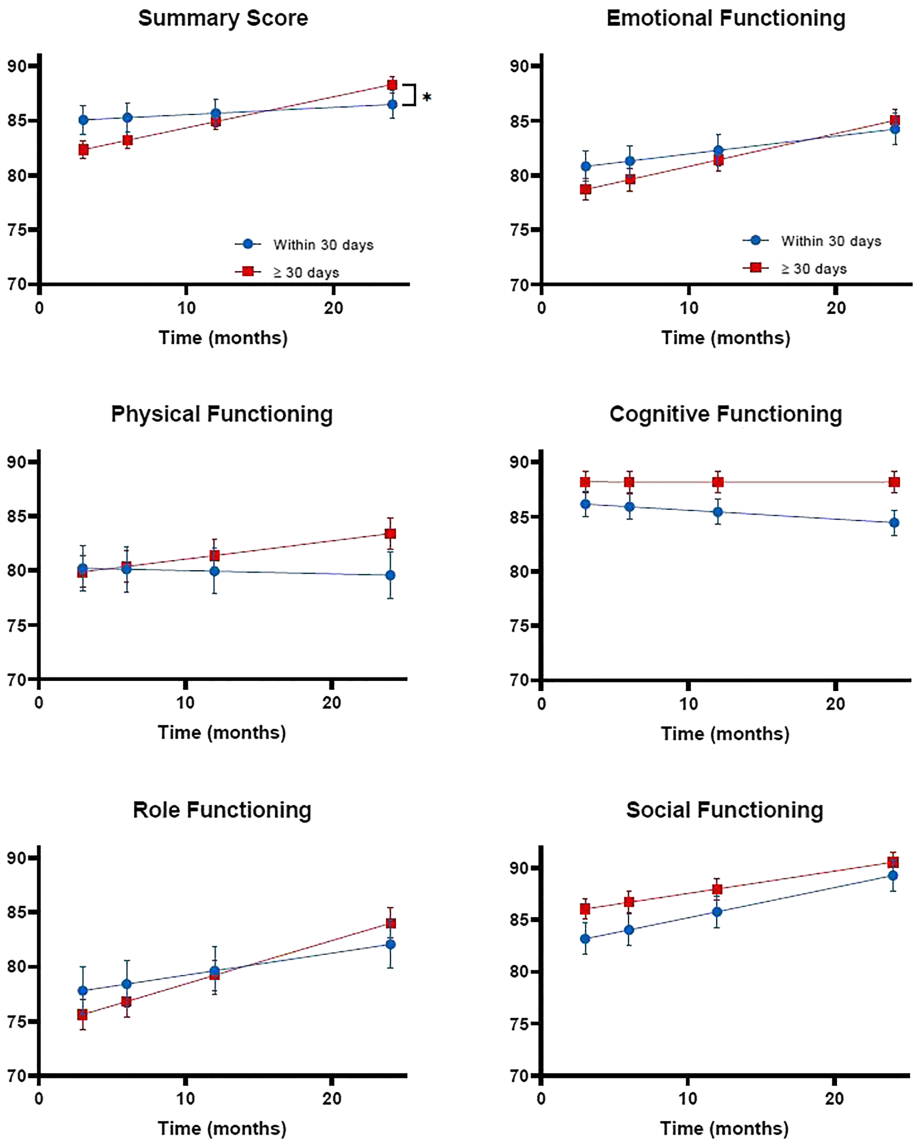

FIGURE 3 Quality of life—predicted values and standard error by linear mixed models for functional scales (EORTC-QLQ-C30) for patients with delay in treatment initiation (red) versus no delay (blue). Asterisk (*) indicates a significantly different trend over time between CPI < 30 and CPI ≥ 30 groups. The model is adjusted for sex, age, comorbidities, tumour location and stage, initial treatment modality and corresponding baseline scores

et al., 2018). Based on the described literature, it seems that the longer the delay, the higher the risk of impact on survival. In the present cohort, the cut-off of 30 days was examined firstly because of the nationally implemented quality-indicator norm and secondly because it is often used in recent studies; however, future studies on larger cohorts may investigate different cut-offs, that is, 45 days or 60 days. However, due to the sample size of this cohort, and because delays of more than 60 days were rare in this study population, assessment of these cut-offs was not viable. Furthermore, analysing time as a continuous variable might be helpful, although in this study this showed similar results (as reported in the Supporting Information).

Notably, a few studies did not find decreased survival rates in patients who encountered delay, similar to this study (Caudell et al., 2011; Ho et al., 2018; Tham et al., 2019). Consensus and scientific evidence on an optimal cut-off is not yet existing, and might be preferred to be site-specific recommendations, instead of choosing one cut-off for all head and neck tumour sites, as these tumours are quite diverse. For such a study, a larger and more homogeneous study population is needed. Furthermore, tumour progression due to delay might not only result in decreased survival, but also in more extensive treatment, higher costs and treatment-related mortality.

4.2 | The effect of delay on health related QOL

Assessment of HRQOL has been increasingly recognised as important treatment outcome and is used for clinical decision-making (Rogers et al., 2016). Summary HRQOL score was higher for patients with delay in treatment initiation, the predicted cumulative difference in score after twenty-four months is 4.6 points (*Delay* * *Time* * 1.75 for the 2-year score). Although statistically significant, this is not considered clinically relevant. The study of Binenbaum determined the minimal clinically important difference in EORTC QLQ-C30 score for oral cavity and oropharyngeal SCC patients to be perceived as beneficial, which might mandate change in management (Binenbaum et al., 2014). For global scores, this was determined as a difference of

9.43 points, for the functional domains scores ranged between 9.6 and 12.8 points and for fatigue and constipation the clinically relevant difference was found to be 11.62 and 11.09, respectively. The improving trend in symptom scores found in this study was comparable to another study describing the trend of HRQOL symptom scores in patients with HNSCC (Van den Bosch et al., 2021) and might be the driver of the higher summary score in patients with delayed treatment initiation. Albeit, the difference in HRQOL trends seems not clinically relevant.

The overall QOL trajectory described by Binenbaum et al. is similar to the trends of this cohort, although the follow-up of this cohort is 1 year longer prolonging the increasing trend. A study by Rogers and Lowe in patients with oral carcinomas found that at a group level, HRQOL at 10 years was similar to that at 2 years follow-up (Rogers & Lowe, 2020).

Delay had no influence on HRQOL shortly after treatment regardless of baseline scores and other relevant parameters. However in long term (during 2 years of follow-up) for patients without delay, the HRQOL trajectories showed an increasing trend in most domains, whereas HRQOL trends in patients with delay were increasing in all domains.

The effect of delay on HRQOL summary scores can be interpreted as a stabilisation of summary HRQOL for patients without delay, together with rapid recovery for patients with delay in treatment initiation. Possibly, better pre-treatment optimisation of general health status in the delayed group (i.e., nutritional and mental support) partially explains these surprising findings.

Literature describing the association between delay and HRQOL is very scarce, and even non-existing for HNSCC. For patients with ovarian and endometrial cancer, increased total delay (from the start of symptoms to start of treatment) was associated with worse HRQOL (Global Health Status, EORTC-QLQ-C30), although the timing and actual scores of the HRQOL measurements are unclear (Robinson et al., 2012).

To exclude the effect of patients treated with trans-oral laser surgery (TOLS), who are represented for the majority in the group treated within 30 days, a subanalysis was performed (data not shown). The adjusted models were similar to the models presented in this study, displaying a similar trend for higher scores in delayed patients, although the difference is not expected to result in a clinically significant difference. Variations in confounders, used in the linear mixed-models were tested (such as addition of adjuvant treatment and smoking status as variables); however, this did not alter findings and the strongest statistical model was chosen to report.

4.3 | Strengths and limitations

The prospective inclusion of patients, reporting the widely used and established EORTC-QLQ-C30 questionnaires, the relatively homogenous population consisting of only squamous cell carcinomas of the four most common sites in the head and neck region, and the follow-up of 2 years are valuable strengths of this study. The high response rate of follow-up HRQOL data on all detailed domains is scarce in HNSCC research and extrapolation of the results using the mixed-models provides reliable results. Furthermore, complete follow-up HRQOL data in an already rare malignancy such as HNSCC are scarce.

A limitation encountered is the relatively small sample size compared to large (national) database studies and a follow-up of 2 years might be too short to firmly establish the association between delay and survival. Nevertheless, the conclusions of this study should be interpreted with regard to the relatively small sample size. The results in this study focused solely on the EORTC QLQ-C30 and not on other PROMs. Future studies can additionally consider studying trends in other PROMs, such as the EORTC QLQ-HN35; however, a recent study by Van den Bosch reported similar trends for C30 and HN35 (Van den Bosch et al., 2021). Furthermore, HPV status was not known in all oropharyngeal patients, who were mainly represented in the group with delayed treatment initiation. This may affect the course of HRQOL and should be considered in future studies.

5 | CONCLUSION

Timely treatment initiation is challenging, and this study adds to the understanding of the impact of delay on HRQOL and survival in HNC patients. Encountering delay before the start of treatment did result in a statistically better course of HRQOL for HNC patients with delay in treatment initiation during two-year follow-up, although this difference was not clinically relevant. A clear benefit in terms of higher HRQOL scores for patient starting treatment within 30 days was absent. Moreover, a CPI ≥ 30 days did not lead to increased risk of dying in this study.

These findings cautiously raise the question whether the advised 30-day cut-off would eventually result in better HRQOL and increased survival and further studies with larger cohorts are needed.

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CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available upon reasonable request directed to the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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