Impact of Delay on Hospitalization in Older Patients With Head and Neck Cancer: A Multicenter Study

Rosanne C. Schoonbeek, MD¹, Suzanne Festen, MD, PhD², Roza Rashid³, Boukje A.C. van Dijk, PhD⁴,⁵, György B. Halmos, MD, PhD¹, and Lilly-Ann van der Velden, MD, PhD³

Abstract

Objective. To assess the impact of delay in treatment initiation on hospitalization, overall survival, and recurrence in older patients with head and neck cancer (HNC).

Study Design. Retrospective multicenter study.

Setting. Two tertiary referral centers.

Methods. All patients with newly diagnosed HNC (≥60 years) treated between 2015 and 2017 were retrospectively included. Time-to-treatment intervals were assessed (ie, calendar days between first visit and start of treatment). Multiple multivariable models were performed with hospital admission days (>14 days), survival, and recurrence as dependent outcome variables.

Results. In total, 525 patients were enrolled. The mean age was 70.7 years and 70.7% were male. Median time to treatment was 34.0 days, and 36.3% started treatment within 30 days (P = .576 between centers). Patients with radiotherapy had longer time to treatment than surgical patients (39.0 vs 29.0 days, P < .001). Current smoking status, stage IV tumors, and definitive radiotherapy were significantly associated with delay in the multivariable analysis. Time-to-treatment interval ≥30 days was a significant predictor of longer hospital admission (>14 days) in the first year after treatment in an adjusted model (odds ratio, 4.66 [95% CI, 2.59-8.37]; P < .001). Delay in treatment initiation was not associated with overall survival or tumor recurrence.

Conclusion. This study highlights the importance and challenges of ensuring timely treatment initiation in older patients with HNC, as treatment delay was an independent predictor of hospitalization. During oncologic workup, taking time to consider patient-centered outcomes (including minimizing time spent in hospital) while ensuring timely start of treatment requires well-structured, fast-track care pathways.

Keywords

head and neck neoplasms, treatment delay, hospitalization, time to treatment, overall survival

Received October 27, 2021; accepted December 17, 2021.

As a result of today’s aging society, the proportion of older patients within the head and neck cancer (HNC) population is subsequently increasing.¹,² Treatment for patients with HNC often yields intensive multimodality treatment in an anatomically and functionally complex area, sometimes resulting in severe disabilities and permanent loss of function.³,⁴ Patients with HNC are often more frail than patients with other forms of solid malignancies.⁵ Frailty can be defined as being prone to adverse outcomes and declines in quality of life after a stressful event (eg, oncologic treatment) due to decreased physiologic reserves and homeostatic mechanisms.⁶,⁷ Locoregional tumor control and survival as primary outcomes are of high importance. However, especially in the older patients, a shift toward patient-centered outcomes is increasingly advocated, with an emphasis on quality of life and maintaining independence as guiding determinants in treatment decisions.⁸

A valuable patient-centered outcome is the amount of time spent at home, since most patients prefer that over time spent in hospital.⁹,¹⁰ With so many patients with HNC being frail, the risk of postoperative complications and acute radiation-induced toxicity is high,⁵,¹¹,¹² resulting in the need to spend more time in hospital. Although not a direct reflection of time spent at home, the number of hospital admission days can be used as alternative.⁹,¹⁰

¹Department of Otorhinolaryngology and Head and Neck Surgery, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
²University Center for Geriatric Medicine, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
³Department of Head and Neck Oncology and Surgery, Netherlands Cancer Institute/Antoni van Leeuwenhoek, Amsterdam, the Netherlands
⁴Department of Research, Netherlands Comprehensive Cancer Organisation, Utrecht, the Netherlands
⁵Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Corresponding Author:
Rosanne C. Schoonbeek, MD, Department of Otorhinolaryngology and Head and Neck Surgery, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, the Netherlands.
Email: r.c.schoonbeek@umcg.nl
In the Netherlands, HNC care is centralized into 8 head and neck oncology centers (HNOCs). Most HNOCs have implemented fast-track diagnostic workup trajectories. Consideration of patient-centered outcomes and shared decision making take time and can delay oncological workup. The effects of these delays can be serious due to tumor progression during the waiting time. This can result in more extensive treatment and lower survival rates.\(^{13-15}\)

To ensure timely treatment initiation, quality indicator norms are set in some countries, such as Denmark and the Netherlands.\(^{16,17}\) In the latter, this norm is set at 30 days, starting from first consultation at the HNOC to start of treatment.\(^{16}\) However, this is achieved in only 34% of the patients diagnosed within the HNOC,\(^ {18}\) underlining the need to identify predictors of delay and adjust care pathways accordingly. Internationally, a 30-day cutoff is frequently studied and pursued.\(^{13,15,19}\)

The effect of delay in hospitalization in the year following treatment in patients with HNC is unclear. Furthermore, the effect of delay on overall survival and locoregional tumor control in the subgroup of older patients with HNC is not yet established. This multicenter study aims to investigate these associations in 2 high-volume tertiary referral centers to provide guidance in shared decision making in the current real-life population.

**Methods**

**Study Design and Patient Selection**

All consecutive patients with newly diagnosed head and neck squamous cell carcinoma (HNSCC) seen between 2015 and 2017 in the outpatient clinics of the University Medical Center Groningen (UMCG) and the Netherlands Cancer Institute (Antoni van Leeuwenhoek hospital, Amsterdam [AvL]) were included. Both hospitals are 1 of the 8 HNOCs within the centralized care setting for patients with HNSCC in the Netherlands, implemented by the Dutch Head and Neck Society.

For the UMCG, patients were prospectively enrolled in the OncoLifeS data biobank (Dutch Trial Register NL7839).\(^ {20}\) For the AvL, patients were retrospectively included through a database management system.

To be eligible for inclusion, patients had to be \(\geq 60\) years old, presenting with first primary HNSCC in the oral cavity, oropharynx, hypopharynx, or larynx. Patients with distant metastasis or synchronous second primary tumors, patients who died before the start of treatment, and patients treated elsewhere were excluded.

The current study protocol was approved by the OncoLifeS scientific board (UMCG) and the Institutional Review Board (AvL). All cases were discussed in the local multidisciplinary tumor board and treated according to international guidelines.

**Definitions and Data Collection**

The care pathway interval (CPI) was defined as the number of calendar days between the first visit in the HNOC and the start of treatment (ie, the first day of radiotherapy or chemotherapy or the day of surgery).\(^ {21}\) CPI and all analysis involving CPI as a dependent or independent parameter were calculated for cases managed with curative intention. Based on internationally used cutoffs and the quality indicator norm set by the Dutch Head and Neck Society, CPI was dichotomized into patients starting treatment <30 days and \(\geq 30\) days (delayed group).\(^ {16}\)

Patient, tumor, and treatment characteristics were collected and supplemented with CPI and follow-up data. Tumor stage was reported with the UICC TNM classification (seventh edition; Union for International Cancer Control).\(^ {22}\) The presence of comorbidities was graded with the ACE-27 (Adult Comorbidity Evaluation–27).\(^ {23}\) Polypharmacy was defined as use of \(\geq 5\) medications.

The number of days spent in hospital (any department, excluding outpatient clinic visits) was measured in the first year after treatment initiation. For analyses, hospital admission days were dichotomized into \(\leq 14\) vs >14 days, as defined by Chesney et al.\(^ {9}\)

**Statistical Analysis**

SPSS Statistics version 25.0 (IBM Corp) was used for analyses. Descriptive statistics were presented depending on their distribution, and comparisons were made via the Student \(t\) test, Mann-Whitney \(U\) test, or \(\chi^2\) test.

The association between covariables and CPI (dichotomized <30 and \(\geq 30\) days) was analyzed with logistic regression analysis. Logistic regression was also used to assess predictors for >14 hospital admission days (hospitalization). Age was analyzed as a continuous and dichotomized value (<70 vs \(\geq 70\) years). All independent factors with \(P < .1\) in univariable analysis were included in the multivariable analysis.

Cox regression analyses were performed to assess the effect of delay on 2-year overall survival and recurrence risk, establishing hazard ratios (HRs; >1 indicating a higher risk of dying or recurrence) after checking whether the Cox proportional hazard assumption was met. A 2-sided \(P < .05\) was considered statistically significant.

**Results**

**Patient Characteristics and Differences Between Centers**

In total, 525 patients were enrolled in this study (UMCG, \(n = 254\); AvL, \(n = 271\); Figure 1). The mean \(\pm SD\) age was 70.7 \(\pm 7.6\) years and the majority were male (70.7%; Table 1). This did not statistically differ between centers, nor did smoking and drinking status, body mass index, and comorbidities.

The proportion of patients with polypharmacy was larger in the UMCG (68.8% vs 52.6%, \(P = .001\)). Patients with oropharyngeal cancer and stage IV tumors were more frequently represented in the AvL group than the UMCG group (34.3% vs 22.0% \([P < .001]\) and 49.4% vs 40.9% \([P < .001]\), respectively). In the UMCG, the proportion of patients with laryngeal cancer was higher (44.1% vs 25.8%).

Most patients were treated with curative intention (91.8%). Surgery was the treatment modality most frequently reported.
CPI and Determinants of Delay

The median interval between first consultation and start of treatment (CPI) was 39.0 days for the UMCG as compared with 33.0 for the AvL ($P = .060$; Figure 2). In total, 175 patients (36.3%) started treatment within 30 days (UMCG, 35.1%; AvL, 37.6%; $P = .576$). Patients treated with initial surgery had a median CPI of 29.0, as opposed to 39.0 days for patients with initial radiotherapy ($P < .001$).

In the univariable model, current smoking status, advanced-stage tumor at diagnosis, and initial treatment with radiotherapy or chemoradiation were associated with delay (CPI $\geq$30 days) in treatment initiation (Table 2). In the multivariable model, current smoking status (odds ratio [OR], 2.2 [95% CI, 1.1-4.6]; $P = .026$), stage IV tumors (OR, 3.1 [95% CI, 1.7-5.8]; $P < .001$), and initial radiotherapy (OR, 4.2 [95% CI, 2.4-7.2]; $P > .001$) remained significantly associated with delay. 

Hospital Admission Days

The mean number of days spent in hospital in the first year after the start of curative treatment was $9.5 \pm 3.6$ for UMCG patients and $10.3 \pm 5.7$ for AvL patients ($P = .096$). Age, comorbidities, tumor site, stage, treatment modality, reconstructive surgery, and delay in treatment initiation were associated with $>14$ hospital admission days in the univariable model. Delay in treatment initiation was a strong significant predictor of $>14$ days spent in hospital in the first year after treatment in an adjusted model (OR, 4.3 [95% CI, 2.4-7.8]; $P < .001$; Figure 3 and Supplementary Table S1, available online).

Initial treatment with radiotherapy was associated with decreased chance of $>14$ hospital admission days (OR, 0.2 [95% CI, 0.1-0.4]; $P < .001$), whereas advanced tumor stage increased the risk of $>14$ days spent in hospital (for stage IV tumors; OR, 9.9 [95% CI, 3.5-28.2]; $P < .001$). Reconstructive surgery was a significant predictor for longer hospital stay ($>14$ days) in the adjusted model as well (OR, 3.1 [95% CI, 1.3-7.7]; $P = .015$). Similar results were observed when time to treatment was analyzed as a continuous variable.
Table 1. Baseline Characteristics of Study Population.\textsuperscript{a}

| Characteristic                  | All (N = 525) | UMCG (n = 254) | AvL (n = 271) | P value |
|---------------------------------|---------------|----------------|---------------|---------|
| Age, y                          |               |                |               |         |
| Mean ± SD                       | 70.7 ± 7.6    | 71.3 ± 7.4     | 70.3 ± 7.9    | .132    |
| Interquartile range             | 64.2-75.9     | 66.0-75.8      | 64.0-76.0     |         |
| Sex                             |               |                |               | .631    |
| Male                            | 371 (70.7)    | 182 (71.7)     | 189 (69.7)    |         |
| Female                          | 154 (29.3)    | 72 (28.3)      | 82 (30.3)     |         |
| Smoking status                  |               |                |               | .302    |
| Never                           | 58 (12.2)     | 20 (9.9)       | 38 (14.0)     |         |
| Former                          | 240 (50.6)    | 102 (50.2)     | 138 (50.9)    |         |
| Current                         | 176 (37.1)    | 81 (39.9)      | 95 (35.1)     |         |
| Drinking status                 |               |                |               | .629    |
| Never                           | 103 (22.1)    | 47 (24.0)      | 56 (20.7)     |         |
| Former                          | 73 (15.6)     | 33 (16.8)      | 40 (14.8)     |         |
| Mild/moderate                   | 164 (35.1)    | 63 (32.1)      | 101 (37.3)    |         |
| Heavy                           | 127 (27.2)    | 53 (27.0)      | 74 (27.3)     |         |
| ACE-27                          |               |                |               | .866    |
| None                            | 89 (17.6)     | 38 (16.2)      | 51 (18.8)     |         |
| Mild                            | 185 (36.6)    | 89 (38.0)      | 96 (35.4)     |         |
| Moderate                        | 148 (29.3)    | 68 (29.1)      | 80 (29.5)     |         |
| Severe                          | 83 (16.4)     | 39 (16.7)      | 44 (16.2)     |         |
| Polypharmacy                    |               |                |               | .001    |
| 0 or <5 medications             | 272 (59.3)    | 130 (68.8)     | 142 (52.6)    |         |
| ≥5 medications                 | 187 (40.7)    | 59 (31.2)      | 128 (47.4)    |         |
| Body mass index                 |               |                |               | .180    |
| Low                             | 21 (4.6)      | 5 (2.6)        | 16 (6.1)      |         |
| Middle                          | 211 (46.4)    | 87 (45.5)      | 124 (47.0)    |         |
| High                            | 223 (49.0)    | 99 (51.8)      | 124 (47.0)    |         |
| Tumor site                      |               |                |               | <.001   |
| Oral cavity                     | 155 (29.5)    | 70 (27.6)      | 85 (31.4)     |         |
| Oropharynx                      | 149 (28.4)    | 56 (22.0)      | 93 (34.3)     |         |
| Hypopharynx                     | 39 (7.4)      | 16 (6.3)       | 23 (8.5)      |         |
| Larynx                          | 182 (34.7)    | 112 (44.1)     | 70 (25.8)     |         |
| Stage of disease                |               |                |               | <.001   |
| I                               | 120 (22.9)    | 77 (30.3)      | 43 (15.9)     |         |
| II                              | 81 (15.4)     | 29 (11.4)      | 52 (19.2)     |         |
| III                             | 86 (16.4)     | 44 (17.3)      | 42 (15.5)     |         |
| IV                              | 238 (45.3)    | 104 (40.9)     | 134 (49.4)    |         |
| Treatment intention             |               |                |               | <.001   |
| Curative                        | 482 (91.8)    | 245 (96.5)     | 237 (87.5)    |         |
| Palliative                      | 43 (8.2)      | 9 (3.5)        | 34 (12.5)     |         |
| Curative treatment modality     |               |                |               | <.001   |
| Surgery                         | 193 (40.0)    | 112 (45.7)     | 81 (34.2)     |         |
| Reconstructive                  | 69 (35.8)     | 41 (36.6)      | 28 (34.6)     | .123    |
| Radiotherapy                    | 173 (35.9)    | 92 (37.6)      | 81 (34.2)     |         |
| Chemoradiation                  | 116 (24.1)    | 41 (16.7)      | 75 (31.6)     |         |

Abbreviations: ACE-27, Adult Comorbidity Evaluation–27; AvL, Antoni van Leeuwenhoek hospital (Amsterdam); UMCG, University Medical Center Groningen.

\textsuperscript{a}Values are presented as No. (%) unless noted otherwise. Bold indicates P < .05.
Delay (CPI/C21 > 30 days) was not associated with hazard of dying in univariable analysis (HR, 1.2 [95% CI, 0.8-1.9]; P = .285). Time to treatment as a continuous variable was also not associated with decreased survival in univariable analysis (HR, 1.0 [95% CI, 1.0-1.0]; P = .436). In the multivariable model, the following indicated an increased hazard of dying within 2 years after start of treatment: low BMI (HR, 3.4 [95% CI, 1.5-7.7]; P = .003), middle BMI (HR, 1.6 [95% CI, 1.0-2.6]; P = .034), oral cavity carcinomas (HR, 3.0 [95% CI, 1.6-5.7]; P = .001), and stage IV tumors (HR, 4.6 [95% CI, 2.0-10.7]; P < .001) (Table 3).

In univariable analysis, delay as a continuous variable (per day) was associated with hazard of recurrence; however, this association did not remain significant in the adjusted model. Age ≥70 years (HR, 1.8 [95% CI, 1.2-2.8]; P = .005), former drinking status (HR, 2.2 [95% CI, 1.1-4.4]; P = .020), heavy drinking status (HR, 2.4 [95% CI, 1.3-4.5]; P = .004), and stage IV tumors (HR, 3.4 [95% CI, 1.7-6.7]; P = .001) resulted in a significantly increased hazard of recurrent disease within 2 years after treatment initiation in a multivariable model (Supplemental Table S3, available online).

**Discussion**

In this multicenter cohort study, the effect of delay on hospitalization, overall survival, and recurrence risk in older patients with HNC was investigated. Treatment was initiated within 30 days after first consultation in only about one-third of the cases (36.3%). Patients treated with definitive radiotherapy had a significant, 5-times higher risk to delayed treatment initiation as compared with patients treated with initial surgery.

Delay was an independent predictor for hospitalization (adjusted for age, comorbidities, tumor site and stage, and treatment modality), highlighting the importance of timely treatment. Advanced tumor stage was associated with hospitalization as well, whereas patients treated with radiotherapy were likely to experience fewer days in hospital in the year posttreatment as compared with patients treated with surgery.

Delay in treatment initiation was not associated with overall survival or tumor recurrence.

**CPI and Determinants of Delay**

The proportion of patients starting treatment within 30 days was similar in both centers. Because of the centralized setting of HNC care in the Netherlands and the similar treatment protocols according to national guidelines, the 2 high-volume HNOCs were highly comparable. This study confirms the difficulties encountered in aiming for early start of treatment while focusing on patient-centered outcomes and pursuing shared decision making at the same time.

In this study, we did not find an association between delay and age. The proportion of patients treated within 30 days is comparable to other studies describing younger patients or investigating delay in elderly patients (<70 vs ≥70 years). This can be explained by the fact that due to the lifestyle of patients with HNC, a mismatch between chronological and biological age can often be experienced. Although no consensus exists regarding the use of an age cutoff, this study used a lower cutoff (60 years vs 70) to not miss possibly younger frail patients.

The association between current smoking status and delay is somewhat surprising. This association has not been extensively described, although the 3 reports that did study this association did not find a significant contribution to delay. An older report examined predictors for delay in first presentation with HNC and did find heavy drinkers and smokers to be...
associated with delay. The authors suggested that dismissive behavior and underestimating the severity of illness might be the underlying explanation, presuming patient delay rather than professional delay.  

Stage IV tumors and radiotherapy are predictors for delay, corresponding to existing literature. Stage IV tumors and radiotherapy are predictors for delay, corresponding to existing literature. Radiotherapy treatment requires extensive pretreatment planning (dental assessment and extractions, molds, and mask preparations). Furthermore, advanced-stage tumors might be eligible for radiotherapy treatment, whereas lower-stage tumors can be surgically managed.

**Table 2. Univariable and Multivariable Logistic Regression Analyses for CPI $\geq$30 Calendar Days.**

| Variable | Univariable | Multivariable |
|----------|-------------|---------------|
|          | Odds ratio (95% CI) | P value | Odds ratio (95% CI) | P value |
| **Patient characteristics** | | | | |
| Age: $\geq$70 y | 0.89 (0.61-1.29) | .541 | | |
| Sex: female | 0.93 (0.61-1.40) | .717 | | |
| **Smoking status** | | | | |
| Never | Reference | | Reference | |
| Former | 1.01 (0.55-1.86) | .963 | 1.09 (0.56-2.13) | .799 |
| Current | 2.30 (1.20-4.41) | .012 | 2.24 (1.10-4.55) | .026 |
| **Drinking status** | | | | |
| Never | Reference | | | |
| Former | 1.11 (0.58-2.11) | .761 | | |
| Mild/moderate | 0.94 (0.56-1.60) | .829 | | |
| Heavy | 1.62 (0.90-2.89) | .105 | | |
| **Body mass index** | | | | |
| Low | Reference | | | |
| Middle | 1.35 (0.50-3.64) | .559 | | |
| High | 1.00 (0.37-2.67) | .995 | | |
| **ACE-27** | | | | |
| None | Reference | | Reference | |
| Mild | 1.05 (0.62-1.79) | .862 | | |
| Moderate | 0.97 (0.56-1.70) | .921 | | |
| Severe | 1.09 (0.56-2.11) | .806 | | |
| **Polypharmacy** | 1.20 (0.80-1.81) | .381 | | |
| **Tumor and treatment characteristics** | | | | |
| **Tumor site** | | | | |
| Oral cavity | Reference | | Reference | |
| Oropharynx | 1.34 (0.81-2.21) | .250 | | |
| Hypopharynx | 1.03 (0.48-2.22) | .945 | | |
| Larynx | 0.95 (0.60-1.50) | .815 | | |
| **Stage of disease** | | | | |
| I | Reference | | Reference | |
| II | 2.52 (1.38-4.61) | .003 | 1.55 (0.78-3.09) | .211 |
| III | 1.86 (1.04-3.33) | .036 | 1.27 (0.62-2.61) | .510 |
| IV | 3.10 (1.94-4.97) | <.001 | 3.14 (1.70-5.80) | <.001 |
| **Treatment modality** | | | | |
| Surgery | Reference | | Reference | |
| Radiotherapy | 5.45 (3.34-8.89) | <.001 | 4.18 (2.43-7.18) | <.001 |
| Chemoradiation | 1.73 (1.08-2.77) | .021 | 0.77 (0.42-1.41) | .388 |
| Center: AvL | 0.90 (0.62-1.30) | .576 | | |

Abbreviations: ACE-27, Adult Comorbidity Evaluation–27; AvL, Antoni van Leeuwenhoek hospital (Amsterdam); CPI, care pathway interval.

* Patients with curative treatment intention: n = 482. Bold indicates $P < .1$ for univariable and $P < .05$ for multivariable.
of delay on hospital admission days has not been previously investigated.

This study found that patients with a delay (≥30 days) do have a 4-times higher risk of hospitalization (>14 hospital admission days) in the year after treatment initiation. This analysis is adjusted for confounders (ie, age, comorbidities, tumor site and stage, and treatment modality including major surgery), given that surgically treated patients generally start their treatment earlier. For postoperative patients, loss of time at home is associated with poor functional outcomes (depression, difficulty with self-care, limited social activity, and mobility).34

Although the consequences of decreased time at home are alarming, the explanation for this finding in the elderly population is less obvious. Prolonged time-to-treatment initiation might result in tumor progression25 and more extensive (surgical) treatment and subsequent longer in-hospital recovery, although this association cannot be objectively determined retrospectively. Tests to rule out collinearity of covariables were performed, confirming an insignificant collinearity among the variables. Even though the health insurance policies and supportive care at home facilities are equal for all inhabitants in the Netherlands, these findings should be interpreted with caution, since it is difficult to adjust for possible socioeconomic drivers of prolonged hospital stay.

These findings should be taken into consideration during pretreatment counseling and can be used to manage patients’ expectations toward hospitalization time. Also, posttreatment decline in functioning needs to be addressed during counseling at the outpatient clinic. Implementation of early geriatric assessment in the early diagnostic phase may assist in personalized pretreatment counseling.16,36 Our results should be interpreted in the absence of preoperative geriatric assessment, since frailty is a known predictor of hospitalization.37

Advanced tumor stages were associated with hospitalization, which might be explained by the more sophisticated and multidisciplinary surgical treatments for these selected patients (ie, collaboration with the plastic surgeon, higher risk of postoperative infection after extensive surgery18).

**Overall Survival and Recurrence Rate**

A CPI ≥30 days was not associated with overall survival or recurrence rate. Other studies, in contrast, did find an association between delay and lower overall survival rates, although this effect was significant only for delays of 45 to 90 days.13,31,39 In this cohort, the number of patients with such extensive delays was too small for analysis.

This illustrates the complicated interpretation of previous studies. First, the definition used for “delay” is not often well defined and widely varies among reports. Second, no consensus exists on the number of days regarded as an acceptable waiting time. A recent systematic review on this topic showed a wide range in median CPI of 20 to 55.5 days.14

Rygalski et al reported a median time to surgery of 33 days for a large cohort of patients with HNC (n = 37,730), starting from date of diagnosis (either clinical description or histologically confirmed). Longer time to surgery was associated with decreased overall survival; however, this effect was apparent only after time to surgery >67 days, far above the study’s median40 and the median in our study.

The effect of delay on locoregional tumor control is less extensively analyzed, and the reported findings show conflicting results. In line with our findings, 2 studies did not find a significant association between longer waiting time and recurrence.26,57 Liao et al, however, described an increased risk of recurrence of patients with a waiting time >60 days.41

In conclusion, the effect of delay in time-to-treatment initiation on overall survival and recurrence risk seems most prominent in delays >60 days—a situation that rarely occurs in the setting of centralized HNC treatment in the Netherlands.

**Strengths and Limitations**

The data used in this study and the criteria for inclusion and exclusion represent real-world data, with minimal risk of selection bias. Patients with recurrent disease or synchronous secondary HNSCC were excluded because they have increased chances of worse outcome regarding the primary endpoints analyzed in this study (hospital admission days and overall survival) as a result of a difference in treatment options (ie, previous irradiation in case of recurrent disease or more extensive treatment in case of multiple primary tumors). Moreover, these patients will enter a different care pathway as compared with patients with first primary HNSCC, having a known general health status (recurrence) or a need for additional investigations (second primary tumors).

A longer follow-up on days at home could add to the literature. In line with previous studies, when time at home is mentioned, the reverse is actually measured: the time spent in hospital.9,10 It cannot be stated with certainty that patients were actually at home; therefore, time spent out of hospital might be a more accurate terminology.
Using cutoffs for delay and hospitalization—variables with a skewed nature—can be arbitrary. As such, dichotomization might be the most sensible approach. A disadvantage of this method can be that a shift in the number of patients per group results in different outcome. To minimize the impact on the results and subsequent conclusions, analyses on the same variables based on linear procedures with continuous dependent variables were performed and did not lead to significant alterations (Supplementary Information, available online).

Table 3. Cox Regression Model Displaying the Hazard of Dying Within 2 Years After Start of Treatment With Curative Intention (n = 482).a

| Variable | Univariable | Multivariable |
|----------|-------------|---------------|
| Hazard ratio (95% CI) | P value | Hazard ratio (95% CI) | P value |

Delay

Cutoff: ≥30 d | 1.24 (0.84-1.85) | .285 |
Continuous | 1.00 (0.99-1.01) | .436 |

Patient characteristics

Age: ≥70 y | 1.75 (1.19-2.56) | .004 |
Sex: female | 1.43 (0.97-2.12) | .073 |

Smoking status

Never | Reference |
Former | 1.11 (0.56-2.20) | .760 |
Current | 1.40 (0.70-2.79) | .338 |

Drinking status

Never | Reference |
Former | 0.98 (0.52-1.83) | .973 |
Mild/moderate | 0.57 (0.32-1.01) | .053 |
Heavy | 1.17 (0.69-1.98) | .572 |

Body mass index

Low | 3.36 (1.62-6.97) | .001 |
Middle | 1.58 (1.03-2.41) | .035 |
High | Reference |

ACE-27

None | Reference |
Mild | 2.00 (1.00-4.01) | .050 |
Moderate | 2.74 (1.36-5.51) | .005 |
Severe | 3.18 (1.51-6.72) | .002 |

Polypharmacy | 1.73 (1.16-2.58) | .008 |

Tumor site

Oral cavity | 3.16 (1.96-5.10) | <.001 |
Oropharynx | 1.92 (1.14-3.21) | .014 |
Hypopharynx | 2.27 (1.11-4.64) | .024 |
Larynx | Reference |

Stage of disease

I | Reference |
II | 2.12 (0.99-4.52) | .053 |
III | 1.45 (0.64-3.29) | .371 |
IV | 4.10 (2.22-7.54) | <.001 |

Treatment modality

Surgery | Reference |
Radiotherapy | 1.08 (0.70-1.64) | .738 |
Chemoradiation | 0.95 (0.58-1.54) | .830 |
Reconstructive surgery | 1.47 (0.84-2.57) | .174 |
Center: AvL | 1.07 (0.74-1.55) | .727 |

Abbreviations: ACE-27, Adult Comorbidity Evaluation–27; AvL, Antoni van Leeuwenhoek hospital (Amsterdam).

*Bold indicates P < .1 for univariable and P < .05 for multivariable.
The association of specific surgical procedures or radiotherapy treatment on hospitalization time was not analyzed in this study; however, the intention was to establish a pragmatic impression of the time spent at home after HNC treatment.

**Conclusion**

This study highlights the importance and challenges to ensure timely treatment initiation of HNC. A prolonged CPI (≥30 days) was an independent predictor of hospitalization in older patients with HNC during the year following treatment. In the present study, delay in treatment initiation was not associated with decreased overall survival or recurrence risk.

During oncologic workup, taking time to consider patient-centered outcomes (including minimizing time spent in hospital) while ensuring timely start of treatment requires well-structured, fast-track care pathways.

**Author Contributions**

Rosanne C. Schoonbeek, conception and design, drafting, data acquisition, data interpretation, critical revision, approval, accountable; Suzanne Festen, conception and design, data interpretation, critical revision, approval, accountable; Roza Rashid, design, data acquisition, critical revision, approval, accountable; Boukje A.C. van Dijk, design, data interpretation, critical revision, approval, accountable; György B. Halmos, conception and design, data interpretation, critical revision, approval, accountable; Lilly-Ann van der Velden, conception and design, data interpretation, critical revision, approval, accountable.

**Disclosures**

Competing interests: None.

Sponsorships: None.

Funding source: None.

**ORCID ID**

Rosanne C. Schoonbeek (https://orcid.org/0000-0002-3103-943X)

**Supplemental Material**

Additional supporting information is available in the online version of the article.

**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.

**References**

1. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol.* 2009;27(17):2758-2765. doi:10.1200/jco.2008.20.8983
2. Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. *Br J Cancer.* 2016;115(9):1147-1155. doi:10.1038/bjc.2016.304
3. Coca-Pelaz A, Halmos GB, Strojan P, et al. The role of age in treatment-related adverse events in patients with head and neck cancer: a systematic review. *Head Neck.* 2019;41(7):2410-2429. doi:10.1002/hed.25696
4. Takes RP, Halmos GB, Ridge JA, et al. Value and quality of care in head and neck oncology. *Curr Oncol Rep.* 2020;22(9):92. doi:10.1007/s11912-020-00952-5
5. Bras L, Driessen D, de Vries J, et al. Patients with head and neck cancer: are they frailter than patients with other solid malignancies? *Eur J Cancer Care (Engl).* 2020;29(1):e13170. doi:10.1111/ecc.13170
6. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet.* 2013;381(9868):752-762. doi:10.1016/s0140-6736(12)62167-9
7. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet.* 2019;394(10206):1365-1375. doi:10.1016/s0140-6736(19)31786-6
8. Stegmann ME, Festen S, Brandenburg D, et al. Using the Outcome Prioritization Tool (OPT) to assess the preferences of older patients in clinical decision-making: a review. *Maturitas.* 2019;128:49-52. doi:10.1016/j.maturitas.2019.07.022
9. Chesney TR, Haas B, Coburn NG, et al. Patient-centered time-at-home outcomes in older adults after surgical cancer treatment. *JAMA Surg.* 2020;155(11):e203754. doi:10.1001/jamasurg.2020.3754
10. Festen S, van der Wal-Huisman H, van der Leest AHD, et al. The effect of treatment modifications by an onco-geriatric MDT on one-year mortality, days spent at home and postoperative complications. *J Geriatr Oncol.* 2021;12(5):779-785. doi:10.1016/j.jgo.2020.12.003
11. Bras L, de Vries J, Festen S, et al. Frailty and restrictions in geriatric domains are associated with surgical complications but not with radiation-induced acute toxicity in head and neck cancer patients: a prospective study. *Open Oncol.* 2021;118:105329. doi:10.1016/j.oralloncology.2021.105329
12. Moroney LB, Helios J, Ward EC, et al. Patterns of dysphagia and acute toxicities in patients with head and neck cancer undergoing helical IMRT concurrent chemotherapy. *Open Oncol.* 2017;64:1-8. doi:10.1016/j.oralloncology.2016.11.009
13. Murphy CT, Galloway TJ, Handorf EA, et al. Survival impact of increasing time to treatment initiation for patients with head and neck cancer in the United States. *J Clin Oncol.* 2016;34(2):169-178. doi:10.1200/jco.2015.61.5906
14. Schoonbeek RC, Zwertbroek J, Plaat BEC, et al. Determinants of delay and association with outcome in head and neck cancer: a systematic review. *Eur J Surg Oncol.* Published online March 6, 2021. doi:10.1016/j.ejso.2021.02.029
15. Sharma S, Bekelman J, Lin A, et al. Clinical impact of prolonged diagnosis to treatment interval (DTI) among patients with oropharyngeal squamous cell carcinoma. *Open Oncol.* 2016;56:17-24. doi:10.1016/j.oralloncology.2016.02.010
16. Dutch Head and Neck Society. *Multidisciplinaire Normering Oncologische Zorg in Nederland.* Dutch Head and Neck Society; 2017. SONCOS Normeringgrapport 5-2017
17. Gronhoj C, Jensen D, Dehlerodff C, et al. Impact of time to treatment initiation in patients with human papillomavirus–positive and –negative oropharyngeal squamous cell carcinoma. *Clin Oncol (R Coll Radiol).* 2018;30(6):375-381. doi:10.1016/j.clon.2018.02.025
18. van Harten MC, de Ridder M, Hamming-Vriese O, Smeele LE, Balm AJ, van den Brekel MW. The association of treatment delay and prognosis in head and neck squamous cell carcinoma (HNSCC) patients in a Dutch comprehensive cancer center. *Oral Oncol*. 2014;50(4):282-290. doi:10.1016/j.joraloncology.2013.12.018

19. Tsai WC, Kung PT, Wang YH, Huang KH, Liu SA. Influence of time interval from diagnosis to treatment on survival for oral cavity cancer: A nationwide cohort study. *PLoS One*. 2017;12(4):e0175148. doi:10.1371/journal.pone.0175148

20. Sidorenkov G, Nagel J, Meijer C, et al. The OncoLifeS database: a comprehensive repository of clinical data, biological samples, and the patient’s perspective. *J Transl Med*. 2019;17(1):374. doi:10.1186/s12967-019-2122-x

21. Schoonbeek RC, de Vries J, Bras L, Plaat BEC, van Dijk BAC, Halmos GB. Determinants of delay in the head and neck oncology care pathway: the next step in value-based health care. *Eur J Cancer Care (Engl)*. Published online February 8, 2021. doi:10.1111.ecc.13419

22. Sobin LH GM, Wittekind C. *TNM Classification of Malignant Tumours*. 7th ed. Wiley-Blackwell; 2009.

23. Piccirillo JF. Importance of comorbidity in head and neck cancer. *Laryngoscope*. 2000;110(4):593-602. doi:10.1097/00005537-200004000-00011

24. Carlsen AH, Eriksen JG, Godballe C, Johansen J, Sørensen JA, Bjørndal K. Impact of age, comorbidity, and WHO performance status on delay of treatment in patients undergoing fast-track work-up for head and neck cancer. *J Geriatr Oncol*. 2019;10(2):259-264. doi:10.1016/j.jgo.2018.06.003

25. Kato I, Neale AV. Does use of alternative medicine delay treatment of head and neck cancer? A Surveillance, Epidemiology, and End Results (SEER) cancer registry study. *Head Neck*. 2008;30(4):446-454. doi:10.1002/hed.20721

26. Festen S, Eriksen JG, Godballe C, Johansen J, Sørensen JA, Bjørndal K. Impact of age, comorbidity, and WHO performance status on delay of treatment in patients undergoing fast-track work-up for head and neck cancer. *J Transl Med*. 2011;137(3):282-285. doi:10.1001/archoto.2011.20

27. León X, de Vega M, Orús C, Morán J, Vergés J, Quer M. The effect of waiting time on local control and survival in head and neck carcinoma patients treated with radiotherapy. *Radiother Oncol*. 2003;66(3):277-281. doi:10.1016/s0167-8140(03)00022-7

28. Brouha X, Tromp D, Hordijk GJ, Winnubst J, De Leeuw R. Role of alcohol and smoking in diagnostic delay of head and neck cancer patients. *Acta Otolaryngol*. 2005;125(5):552-556. doi:10.1080/00016480510028456

29. Guizard AV, Dejardin O, Launay L, et al. What are the real waiting times for therapeutic management of head and neck cancer: a study in the general population in the north-west of France. *Eur Arch Otorhinolaryngol*. 2016;273(11):3951-3958. doi:10.1007/s00405-016-4056-8

30. Murphy CT, Galloway TJ, Handorf EA, et al. Increasing time to treatment initiation for head and neck cancer: an analysis of the National Cancer Database. *Cancer*. 2015;121(8):1204-1213. doi:10.1002/cncr.29191

31. Polese J, Furlan C, Birri S, et al. The impact of time to treatment initiation on survival from head and neck cancer in north-eastern Italy. *Oral Oncol*. 2017;67:175-182. doi:10.1016/j.joraloncology.2017.02.009

32. Jerath A, Austin PC, Wijeyesundera DN. Days alive and out of hospital: validation of a patient-centered outcome for perioperative medicine. *Anesthesiology*. 2019;131(1):84-93. doi:10.1097/ALN.0000000000002701

33. Groff AC, Colla CH, Lee TH. Days spent at home—a patient-centered goal and outcome. *N Engl J Med*. 2016;375(17):1610-1612. doi:10.1056/NEJMp1607206

34. Lee H, Shi SM, Kim DH. Home time as a patient-centered outcome in administrative claims data. *J Am Geriatr Soc*. 2019;67(2):347-351. doi:10.1111/jags.15705

35. Xiao R, Ward MC, Yang K, et al. Increased pathologic upstaging with rising time to treatment initiation for head and neck cancer: a mechanism for increased mortality. *Cancer*. 2018;124(7):1400-1414. doi:10.1002/cncr.31213

36. Festen S, Kok M, Hopstaken JS, et al. How to incorporate geriatric assessment in clinical decision-making for older patients with cancer: an implementation study. *J Geriatr Oncol*. 2019;10(6):951-959. doi:10.1016/j.jgo.2019.04.006

37. Goldstein DP, Sklar MC, de Almeida JR, et al. Frailty as a predictor of outcomes in patients undergoing head and neck cancer surgery. *Laryngoscope*. 2020;130(5):E340-E345. doi:10.1002/lary.28222

38. Peters TT, van Dijk BA, Roordenburg JL, van der Laan BF, Halmos GB. Relation between age, comorbidity, and complications in patients undergoing major surgery for head and neck cancer. *Ann Surg Oncol*. 2014;21(3):963-970. doi:10.1245/s10434-013-3375-x

39. Naghavi AO, Echevarria MI, Strom TJ, et al. Treatment delays, race, and outcomes in head and neck cancer. *Cancer Epidemiol Biomarkers Prev*. 2016;25(1):25-33. doi:10.1158/1055-9965.EPI-15-0531

40. Rygalski CJ, Zhao S, Eskander A, et al. Time to surgery and survival in head and neck cancer: A Surveillance, Epidemiology, and End Results (SEER) cancer registry study. *Head Neck*. 2020;42(7):1400-1414. doi:10.1002/hed.29312

41. Naghavi AO, Echevarria MI, Strom TJ, et al. Treatment delays, race, and outcomes in head and neck cancer. *Cancer Epidemiol Biomarkers Prev*. 2016;25(1):25-33. doi:10.1158/1055-9965.EPI-15-0531

42. Liao DZ, Schlecht NF, Rosenblatt G, et al. Association of delayed time to treatment initiation with overall survival and recurrence among patients with head and neck squamous cell carcinoma in an underserved urban population. *JAMA Otolaryngol Head Neck Surg*. 2019;145(11):1001-1009. doi:10.1001/jamaoto.2019.2414