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Original Article

The effect of delayed primary treatment initiation on adverse events and recurrence in older head and neck cancer patients

Rosanne C. Schoonbeek [a,*], Suzanne Festen [b], Bernard F.A.M. van der Laan [c], Boudewijn E.C. Plaat [a], Johannes A. Langendijk [d], Boukje A.C. van Dijk [e,f], György B. Halmos [a]

[a] University of Groningen, Department of Otorhinolaryngology, Head and Neck Surgery, University Medical Center Groningen; [b] University of Groningen, University Center for Geriatric Medicine, University Medical Center Groningen; [c] Haaglanden Medical Center, Department of Otorhinolaryngology, Head and Neck Surgery, The Hague, the Netherlands; [d] University of Groningen, Department of Radiation Oncology, University Medical Center Groningen; [e] University of Groningen, Department of Epidemiology, University Medical Center Groningen; and [f] Netherlands Comprehensive Cancer Organization (IKNL), Department of Research, Utrecht, the Netherlands

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ABSTRACT

Background and purpose: As a result of rapid tumor growth in head and neck squamous cell carcinoma (HNSCC), delay in treatment initiation can result in tumor progression and inferior outcome. Especially older and frail patients are prone to develop adverse events. The aim of this study was to assess the effect of delay on development of adverse events and recurrence in older HNSCC patients.

Materials and methods: This cohort study with prospectively collected data included all newly diagnosed, curatively treated HNSCC patients (≥60 years) between 2015 and 2017. Time-to-treatment interval and geriatric domains were assessed. Adverse events were defined as postoperative complications (Clavien-Dindo classification) and acute radiation-induced toxicity (Common Terminology Criteria of Adverse Events). Multivariable regression models were performed, using adverse events and recurrence as outcome variables.

Results: A total of 245 patients were included. Median time-to-treatment was 26 days for surgery patients and 40 days for radiotherapy patients ($p < 0.001$). Delayed treatment initiation was not associated with postoperative complications or acute radiation-induced toxicity.

Delay was significantly associated with recurrence risk within two years after treatment initiation in a model adjusted for stage and tumor location in patients treated with initial surgery (HR:4.1, 95%CI:1.2–14.0, $p = 0.024$). For patients treated with radiotherapy, delay was not significantly associated with recurrence risk.

Conclusion: Delayed treatment initiation was independently associated with increased recurrence risk in patients treated with initial surgery. Delay was not associated with short-term adverse events. These findings highlight the importance of establishing fast-track care pathways to minimize delays and improve especially long-term outcome.

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Head and neck squamous cell carcinomas (HNSCC) are tumors with a rapid growth pattern, with an estimated mean volume increase of around 2% per day [1,2]. Prognosis mainly depends on the stage of disease at diagnosis. More advanced tumors, comprising almost two-thirds of all patients, require extensive multimodality treatment in a functionally and esthetically vital area, which may result in permanent disabilities afterwards [3].

As a result of the aging society, the proportion of older patients with HNSCC increases subsequently [4,5]. HNSCC patients include an already complex population, prone to frailty [6–8]. Besides a focus on survival and recurrence risk as primary outcome, a shift towards patients' preferences is increasingly advocated [9–11]. Maintaining independence for example could be a prioritized outcome for patients [12], and minimizing adverse events such as postoperative complications and acute radiation-induced toxicity could contribute to this aim. Especially frail patients with large, locally advanced tumors are at risk for developing adverse events [13,14].

During diagnostic work-up for new HNSCC patients, disease stage as well as assessment of frailty and patients' preferences should be established and considered in deciding on treatment options.

However, due to the rapid growth of HNSCC, timely start of treatment is essential, as delay in treatment initiation is associated with tumor progression and inferior survival [15–17]. It is there-

* Corresponding author at: Hanzeplein 1, 9700 RB, Groningen, the Netherlands.
E-mail address: r.c.schoonbeek@umcg.nl (R.C. Schoonbeek).

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fore a logistic challenge to on the one hand take time to fully assess the patient and on the other hand ensure timely treatment initiation.

Although highly interesting, the effect of prolonged time-to-treatment on adverse events has never been investigated. This might be a prominent consideration, as adverse events may result in loss of independence, and maintaining independence has shown to be a prioritized health outcome in older patients [18].

The aim of this study was to determine the effect of delay on adverse events in older patients treated with initial surgery or initial radiotherapy. Furthermore, associations between geriatric parameters and time-to-treatment interval were investigated. Lastly, the impact of delayed treatment initiation on recurrence risk was studied.

Materials and methods

Study design and patient selection

All newly diagnosed patients with head and neck squamous cell carcinoma (HNSCC) seen in 2015–2017 in the University Medical Center Groningen (UMCG), a tertiary head and neck cancer referral center, were eligible for inclusion. Patients were prospectively enrolled in the institutional OncoLifeS data biobank (Dutch Trial Register registration number: NL7839) [19].

Patients presenting with a first primary HNSCC located in the oral cavity, oropharynx, hypopharynx or larynx, aged 60 years or older, treated with curative treatment intention were included. Patients with distant metastasis, synchronous second primary tumors and patients who deceased before start of treatment or received treatment elsewhere were excluded.

All patients were discussed in the multidisciplinary tumor board and treated according to (inter)national guidelines[20]. This study protocol was approved by the OncoLifes Scientific Board.

Definitions and outcome measures

Time-to-treatment was defined as the Care Pathway Interval (CPI): days between first consultation in our center and start of treatment (day of surgery; for initial surgery patients, or first day of radiotherapy or chemoradiation; combined as initial radiotherapy patients) [21]. Based on initial treatment, the median CPI was determined and all patients starting treatment after the median were regarded as "delayed". CPI was also analyzed as a continuous variable.

Patient, tumor, and treatment characteristics were collected through the OncoLifes data biobank and Electronical Patient Files. Since a mismatch between biological and calendar age might be present in patients with HNSCC [6], a lower cut-off of 60 years was used instead of 70 years in this study to prevent missing younger frail patients. Patients with oropharyngeal carcinomas were divided into HPV positive oropharyngeal carcinomas and other (HPV negative and unknown). The unknown HPV status group (n = 11) mainly consisted of patients treated in the beginning of the inclusion period, in which HPV diagnostics were not routinely carried out. The Union for International Cancer Control (UICC) TNM classification (7th edition) was used to report tumor stage [22]. Presence of comorbidities were scored using the Adult Comorbidity Evaluation (ACE-27) [23]. The definition of polypharmacy was use of $\geq$5 different medications. The screening tool Geriatric 8 (G8) was used to assess frailty (scores $\leq$14 were considered frail) [24].

Postoperative complications were scored within 30 days after surgery using the Clavien-Dindo classification (Appendix IA) [25]. Physician-rated acute radiation-induced toxicity was classified using the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0), at 12 weeks after treatment initiation [26]. The included items and grading system are summarized in Appendix IB.

For both postoperative complications and acute radiation-induced toxicity grade $\geq$ 2 scores were considered clinically relevant adverse events.

Recurrences, including locoregional and distant recurrences, were determined during two-year follow-up.

Statistical analysis

SPSS® Statistics (version 25.0, Armonk, NY: IBM Corp.) was used for statistical analyses. Descriptive statistics were presented as mean values and standard deviations for normally distributed continuous variables, absolute numbers and percentages for dichotomous or ordinal variables and medians and quartiles for non-normally distributed continuous variables. Depending on their distribution, continuous variables were compared using unpaired Student's t-tests or the Mann-Whitney U test. The χ^2 or Fisher's exact test was used to compare ordinal variables.

To assess the effect of time-to-treatment interval (CPI) on adverse events (postoperative complications for surgery patients; acute radiation-induced toxicity for radiotherapy patients) two separate logistic regression analyses were carried out. Delay was incorporated as continuous variable as well as dichotomously (cut-off determined by initial treatment median CPI). All independent factors with $p < 0.10$ in univariable analyses were included in multivariable analyses.

The association between CPI and recurrence risk was analyzed using Cox regression analysis. Patients who died before complete follow-up were censored. After checking whether the cox proportional hazard assumption was met, hazard ratios were established (>1 indicating a higher risk of recurrence within two years after start of treatment). A two-sided $p < 0.05$ was considered statistically significant.

For visualization of the association between recurrence and delay, Kaplan-Meier curves were established, including Log-Rank testing and a table including the number of events.

Results

In total, 245 patients were enrolled (Fig. 1) with a mean age of 71.1 years (±7.4). Initial surgery was performed in 111 patients, whereas 134 patients received initial radiotherapy or chemoradiation (Table 1). The radiotherapy group consisted of a higher proportion of current smokers (51.8% vs. 24.7% in the surgery group, $p < 0.001$) and heavy drinkers (34.9% vs. 16.3%, $p = 0.002$).

Most patients with oropharyngeal and hypopharyngeal carcinomas were treated with radiotherapy (with or without concomitant chemotherapy) whereas patients with oral cavity carcinomas were mostly treated surgically. Patients with a laryngeal carcinoma were treated with initial radiotherapy (n = 49, 45%) or initial surgery (n = 60, 55%).

More than half of the patients presented with locally advanced disease (III-IV, 57.1%). Surgically managed patients were for the largest part either stage I or stage IV tumors. Forty-eight percent of patients, treated with initial radiotherapy, had stage IV disease.

Median time-to-treatment was 26 days for initial surgery patients and 40 days for initial radiotherapy patients ($p < 0.001$, Supplementary Table 1A). As shown in Table 2, factors associated with delay in treatment initiation in the multivariable model were high risk of malnutrition (OR: 3.4, 95%CI: 1.1–11.0, $p = 0.041$), oral cavity carcinoma (OR: 3.6, 95%CI: 1.3–9.9, $p = 0.014$) and advanced stage tumors (OR: 5.4, 95%CI: 2.2–13.3, $p < 0.001$). Age, frailty, and

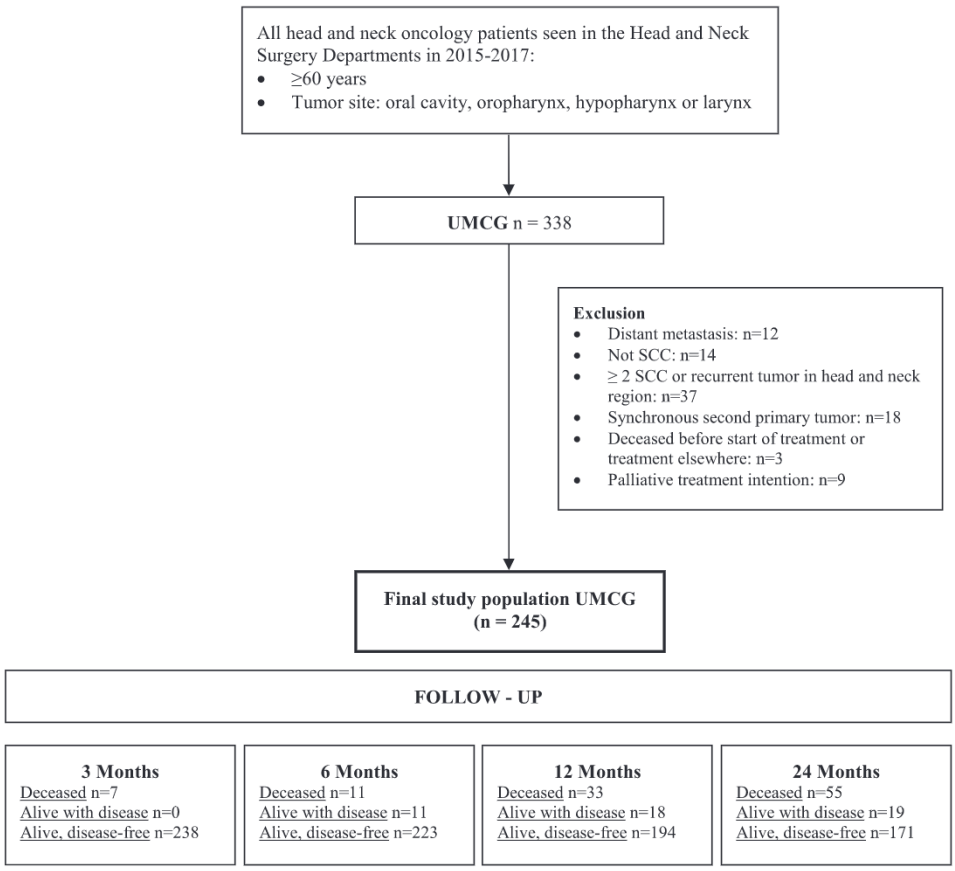


Fig. 1. Flowchart of study population, including in- and exclusion criteria and follow-up characteristics. SCC: squamous cell carcinoma.

other geriatric domains (functional, socio-economic, cognitive and psychological status) were not associated with time-to-treatment.

In 37% of the patients, grade ≥ 2 postoperative complications were present (Supplementary Table 1B). In univariable analysis of patients treated with surgery, delay (dichotomous using the cut-off and as continuous variable), frailty, oral cavity tumors and advanced stage were associated with complication risk (Supplementary Table 2). In multivariable analyses, locally advanced stage remained the only significant factor associated with postoperative complications (OR: 6.5, 95%CI: 1.7–24.7, p = 0.006, Fig. 2). Delay (dichotomized) was not significantly associated with postoperative complications in the adjusted model (HR: 2.2, 95%CI: 0.6–8.7, p = 0.246).

Half of the patients experienced grade ≥ 2 acute radiation-induced toxicity. Delay (as continuous variable), oropharyngeal and hypopharyngeal carcinomas, locally advanced tumors and concomitant chemoradiation were associated with higher rates of acute radiation-induced toxicity in univariable analysis (Fig. 2, Supplementary Table 3). In multivariable analysis, non-HPV positive (HPV negative or unknown HPV status) oropharyngeal carcinomas (OR: 3.4, 95%CI: 1.2–9.4, p = 0.018) and concomitant chemotherapy (OR: 2.7, 95%CI: 1.1–6.7, p = 0.033) were independent factors associated with acute radiation-induced toxicity.

The frequencies of the different grades of adverse events are displayed in Supplementary Tables 4 and 5.

Among the 245 patients, 20% (n = 49) developed recurrent disease during the two years follow-up (n = 38 locoregional recurrence, n = 9 distant recurrence and n = 2 both locoregional and distant recurrence). Initial treatment modality was not associated with recurrence risk.

For patients treated with initial surgery, delay (cut-off at 26 days as well as continuous, Supplementary Table 6), tumor location (oral cavity carcinomas) and locally advanced tumors were risk factors for recurrence in the univariable model. After adjusting for tumor stage and tumor location, delay remained a significant prognosticator for recurrence risk within two years after treatment initiation (Table 3). Patients with delay in treatment initiation had 4.1 times increased hazard of recurrence (95%CI: 1.2–14.0, p = 0.024, Kaplan-Meier Log-Rank p = 0.001, Fig. 3A). When time-to-treatment was used as continuous variable per 5 days duration of the time-to-treatment interval in the multivariable model, the hazard of recurrence increased by 1.13 (95%CI: 1.0–1.3, p = 0.032) (Supplementary Table 6).

Tumor site (HPV-negative or unknown HPV status oropharyngeal tumors) and locally advanced tumors were associated with increased recurrence risk in the univariable model for radiotherapy patients (Supplementary Table 7).

In the adjusted model, locally advanced tumors were associated with tumor recurrence (HR: 4.2, 95%CI: 1.3–13.8, p = 0.018), whereas treatment with chemoradiation was associated with a significant lower recurrence rates (HR: 0.3, 95%CI: 0.1–0.7, p = 0.011, Table 3). Delay was not associated with tumor recurrence in patients treated with initial radiotherapy.

Discussion

In this prospective cohort study, delay in treatment initiation was not associated with increased risk of postoperative complications or acute radiation-induced toxicity.

However, delay was a significant prognosticator of tumor recurrence, even after adjustment for stage and tumor location in patients treated with initial surgery. Compared to patients without delay, patients who encountered delay before start of treatment had four times higher recurrence risk. For patients treated with ini-

Table 1
Baseline characteristics of study population.

Characteristic	All (n = 245)	Surgery (n = 111)	Radiotherapy (n = 134)	p-value
Age (y)				0.185
mean ± SD	71.1 ± 7.4	71.8 ± 7.6	70.6 ± 7.3	
IQR (p25-p75)	65.6–75.3	66.1–77.7	64.8–74.6	
Sex				0.102
Male	176 (71.8%)	74 (66.7%)	102 (76.1%)	
Female	69 (28.2%)	37 (33.3%)	32 (23.9%)	
Smoking status				**<0.001**
never	20 (10.1%)	12 (13.5%)	8 (7.3%)	
former	100 (50.3%)	55 (61.8%)	45 (40.9%)	
Current	79 (39.7%)	22 (24.7%)	57 (51.8%)	
Drinking status				**0.002**
never	47 (24.5%)	31 (36.0%)	16 (15.1%)	
former	31 (16.1%)	13 (15.1%)	18 (17.0%)	
mild/moderate	63 (32.8%)	28 (32.6%)	35 (33.0%)	
Heavy	51 (26.6%)	14 (16.3%)	37 (34.9%)	
ACE-27				0.167
none	37 (16.2%)	11 (10.4%)	26 (21.1%)	
mild	89 (38.9%)	43 (40.6%)	46 (37.4%)	
moderate	65 (28.4%)	32 (30.2%)	33 (26.8%)	
Severe	38 (16.6%)	20 (18.9%)	18 (14.6%)	
Polypharmacy				0.615
none or <5 medications	128 (69.2%)	59 (71.1%)	69 (67.6%)	
≥5 medications	57 (30.8%)	24 (28.9%)	33 (32.4%)	
Frailty screeners				
Frail (G8)	95 (52.8%)	40 (50.0%)	45 (45.0%)	0.504
Non-frail (G8)	85 (47.2%)	40 (50.0%)	55 (55.0%)	
BMI (kg/m^2)				0.337
Low (<18.5)	5 (2.7%)	2 (2.5%)	3 (2.8%)	
Middle (≥18.5 and <25)	85 (45.5%)	32 (39.5%)	53 (50.0%)	
High (≥25)	97 (51.9%)	47 (58.0%)	50 (47.2%)	
Tumor site				**<0.001**
Oral cavity	68 (27.8%)	59 (53.2%)	9 (6.7%)	
Oropharynx	54 (22.0%)	2 (1.8%)	52 (38.8%)	
Hypopharynx	14 (5.7%)	1 (0.9%)	13 (9.7%)	
Larynx	109 (44.5%)	49 (44.1%)	60 (44.8%)	
Stage of disease (TNM7)				**<0.001**
Stage I	77 (31.4%)	55 (49.5%)	22 (16.4%)	
Stage II	28 (11.4%)	8 (7.2%)	20 (14.9%)	
Stage III	41 (16.7%)	13 (11.7%)	28 (20.9%)	
Stage IV	99 (40.4%)	35 (31.5%)	64 (47.8%)	
Initial treatment modality				
Surgery	111 (45.3%)			
Radiotherapy	93 (38.0%)			
Chemoradiation	41 (16.7%)			

tial radiotherapy or chemoradiation, this association was not present.

In this cohort, age was not related to delay in treatment initiation. This finding is in accordance with a comparable recent study by Carlsen and colleagues [27]. Presence of frailty and deficits in various geriatric domains (i.e. functional, socioeconomic, cognitive domains) did not result in increased risk of delay, which is not yet reported in literature. Even though it requires time to perform diagnostic investigations, assess patients' general health status and treatment preferences and establish a multidisciplinary discussed treatment plan, restrictions in different geriatric domains and presence of frailty did not seem to have significant contribution to the time-to-treatment interval in this cohort. Although we hypothesized that patients with restrictions in geriatric domains would more frequently encounter delay, it is possible that efficient collaboration with the geriatric department did prevent delay in these patients. Another explanation might be that frail patients were not subject to additional investigations compared to non-frail patients, such as referral to other specialists outside the HNSCC multidisciplinary team.

The only geriatric domain associated with delay was nutritional status: patients with high risk of malnutrition had a three times higher risk of delay in an adjusted model. This might be explained by the general aim and guidelines to optimize nutritional support before start of treatment. Patients who are malnourished at presentation are referred for dietetic consultation and early (and often intensive) intervention to improve treatment outcome [28], and consequently encounter delay in start of treatment. Indeed, a previous report found a significant higher risk of postoperative complications for patients with intermediate risk of malnutrition compared to patients with low or high risk [14].

Tumor characteristics were found to be the main drivers of prolonged time-to-treatment in this study. Specifically, advanced stage tumors (stage III-IV) and oral cavity carcinomas posed increased odds of delay. The finding of increased risk of delay in advanced stage tumors is confirmed in multiple other papers [15,29–31]. Advanced stage tumors require more extensive treatment planning, such as extensive reconstructions for patients treated with surgery, larger irradiation field including pretreatment dental assessment and possible extractions and possible prophy-

Table 2
Factors associated with delay in an univariable and multivariable logistic regression model (dependent variable: delay*).

	Univariable		Multivariable	
Variable	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value
Patient Characteristics				
Age (continuous)	0.99 (0.95–1.02)	0.380		
Age (≥70y)	0.77 (0.47–1.28)	0.320		
Sex (female)	1.51 (0.86–2.65)	0.150		
Smoking status				
never	ref	ref		
former	1.23 (0.46–3.26)	0.681		
current	1.62 (0.60–4.39)	0.344		
Drinking status				
never	ref	ref	ref	ref
former	0.69 (0.28–1.73)	0.433	0.74 (0.22–2.55)	0.639
mild/moderate	0.46 (0.21–0.99)	**0.046**	0.58 (0.21–1.58)	0.283
heavy	0.83 (0.38–1.85)	0.654	0.46 (0.16–1.33)	0.150
BMI				
low	3.92 (0.42–36.34)	0.229		
middle	0.69 (0.38–1.23)	0.208		
high	ref	ref		
ACE-27				
none/mild	ref	ref		
moderate/severe	0.98 (0.58–1.65)	0.942		
Polypharmacy	1.44 (0.77–2.69)	0.255		
Nutritional status				
MUST				
Low risk	ref	ref	ref	ref
Medium risk	2.30 (0.85–6.21)	0.101	1.46 (0.44–4.85)	0.699
High risk	3.13 (1.13–8.64)	**0.028**	3.40 (1.05–11.04)	**0.041**
Functional status				
IADL (limitations)	1.26 (0.64–2.49)	0.503		
TUG				
No restrictions	ref	ref		
Mild restrictions	1.19 (0.63–2.25)	0.583		
Restrictions	0.54 (0.19–1.57)	0.261		
Socio-economic status				
Education				
Low level	ref	ref		
Middle level	0.93 (0.45–1.91)	0.835		
High level	0.60 (0.27–1.33)	0.209		
Marital status (no relationship)	1.03 (0.54–1.95)	0.941		
Cognitive status				
MMSE (limited cognitive abilities)	1.69 (0.74–3.87)	0.214		
Psychological status				
GDS-15 (possible depression)	1.53 (0.47–5.01)	0.485		
Frailty screeners				
G8	1.45 (0.80–2.61)	0.216		
Tumor and treatment characteristics				
Tumor site				
Larynx	ref	ref	ref	ref
Oral cavity	3.75 (1.98–7.13)	**<0.001**	3.58 (1.30–9.85)	**0.014**
Oropharynx - other	2.69 (1.23–5.88)	**0.013**	0.78 (0.25–2.44)	0.672
Oropharynx - HPV positive	3.01 (1.12–8.46)	**0.029**	1.41 (0.35–5.66)	0.625
Hypopharynx	1.35 (0.44–4.16)	0.606	0.46 (0.10–2.10)	0.319
Stage of disease				
Stage I/II	ref	ref	ref	ref
Stage III/IV	4.05 (2.36–6.95)	**<0.001**	5.42 (2.21–13.27)	**<0.001**
Treatment modality				
Surgery	ref	ref		
Radiotherapy	0.85 (0.49–1.47)	0.546		
Chemoradiation	1.54 (0.74–3.18)	0.250		

*Median for patients treated with initial surgery: 26 days, median for patients treated with initial radiotherapy: 40 days.

lactic percutaneous endoscopic gastrostomy in patients treated with chemoradiation.

The association between oral cavity carcinomas and delay might be the result of the comparison with the reference category (laryngeal carcinomas), since these two tumor sites are mainly surgically managed. For laryngeal carcinomas, the range in tumor volume is widespread – transoral laser surgery of T1a laryngeal carcinomas might be relatively easily planned, whereas a higher proportion of oral cavity carcinomas might involve multidisciplinary surgery including reconstructive surgery, requiring logistic challenges.

Adverse events are frequently reported, especially in older and frail populations, such as patients with HNSCC [13,14,32]. Also in this prospective cohort, adverse events occurred in comparable frequency, although we did not find associations between delay and treatment related adverse events, i.e. either postoperative compli-

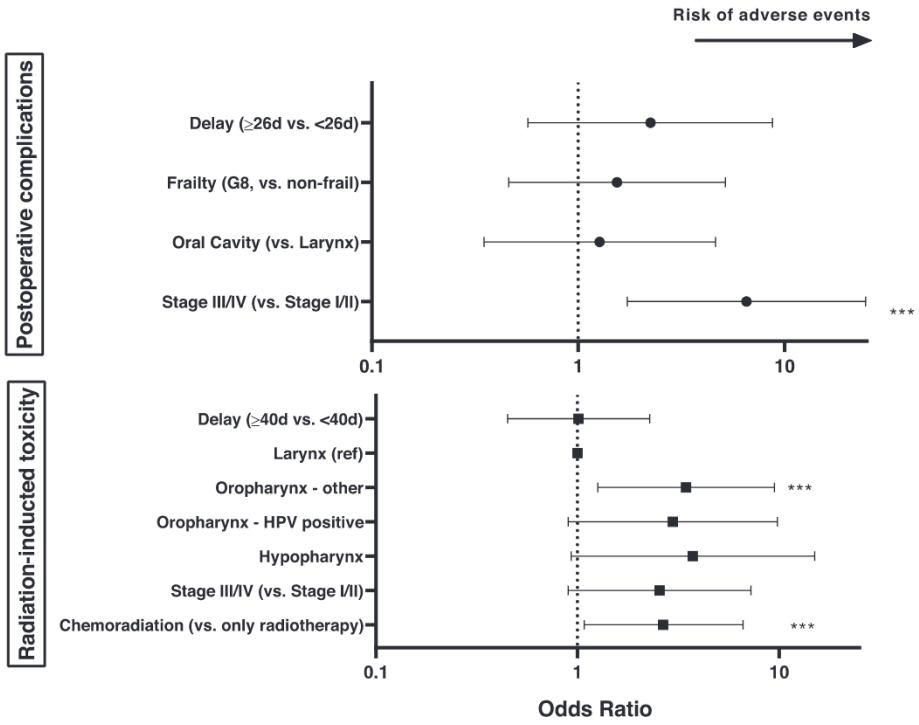


Fig. 2. Odds ratio of adverse events for postoperative complications (initial surgery patients, n = 111, upper) and acute radiation-induced toxicity (initial radiotherapy patients, n = 134, lower).

Table 3
Multivariable Cox regression model displaying recurrence risk within two years after start of treatment, for patients treated with initial surgery and initial radiotherapy or chemoradiation.

	Surgery		Radiotherapy	
Variable	Hazard Ratio (95% CI)	p-value	Hazard Ratio(95% CI)	p-value
CPI (cut-off median*)	4.11 (1.21–13.95)	**0.024**	1.77 (0.81–3.86)$^{\int}$	**0.154**$^{\int}$
Tumor and treatment characteristics				
Tumor site				
Larynx	ref	ref	ref	ref
Oral cavity	1.78 (0.60–5.30)	0.299	-	-
Oropharynx - other	-	-	1.64 (0.64–4.22)	0.302
Oropharynx - HPV positive	-	-	0.19 (0.02–1.54)	0.121
Hypopharynx	-	-	1.33 (0.40–4.48)	0.644
Stage of disease				
Stage I/II	ref	ref	ref	ref
Stage III/IV	1.04 (0.42–2.60)	0.929	4.19 (1.28–13.78)	**0.018**
Chemoradiation	-	-	0.27 (0.10–0.74)	**0.011**

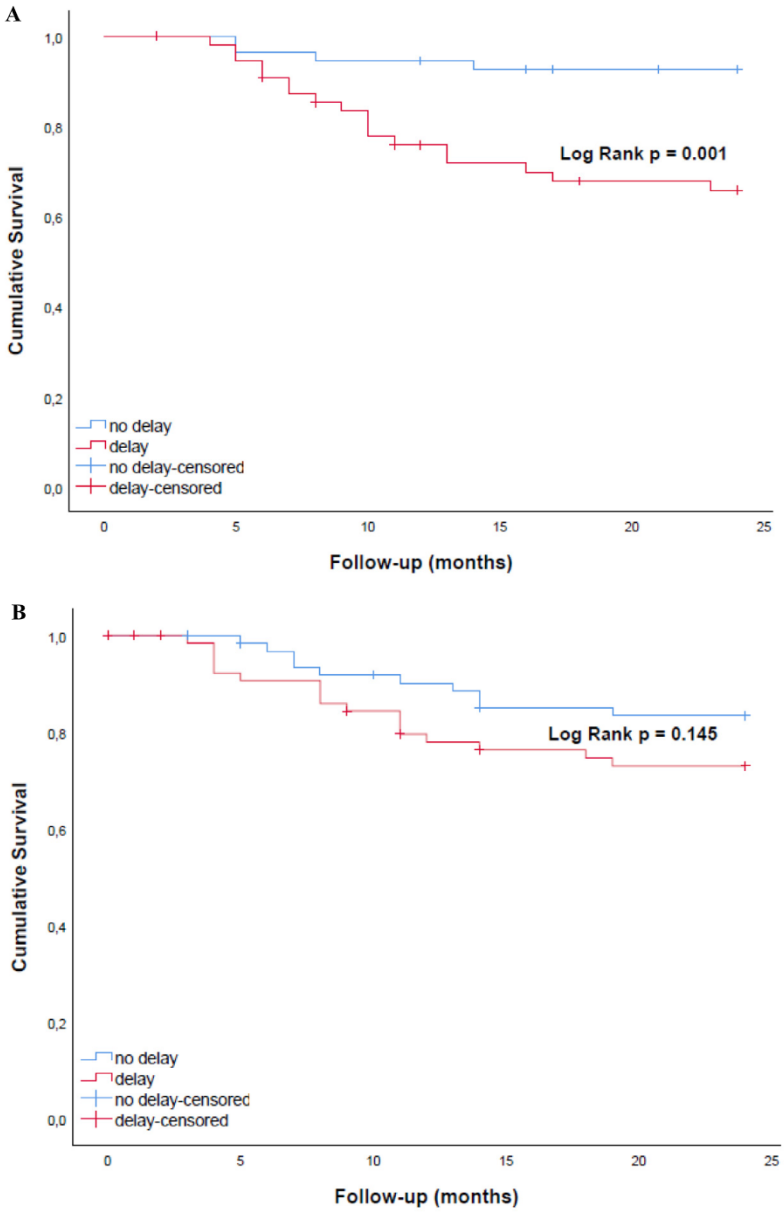
*Median for patients treated with initial surgery: 26 days, median for patients treated with initial radiotherapy: 40 days.
$\int$ CPI for radiotherapy: univariable regression is displayed (NS).

cations or acute radiation-induced toxicity. Reasons for this finding could be the lack in outliers of longer delays (of months) in our population. Based on the findings in this study, prolonged time-to-treatment of limited length (days rather than weeks), does not seem to result in an increase in adverse events. These results must be interpreted in the absence of comparisons to existing reports, since the effect of delay on adverse events has not been described previously.

Furthermore, we did not observe a significant association between frailty and postoperative complications, whereas other recent reports did find frailty to be associated with risk of especially postoperative complications [14,33]. A possible explanation might be adjustment for tumor stage in our multivariable model, which was such a strong prognosticator of postoperative complications, that other, less strong associations, might be overlooked. This might be the case for delay as well. Moreover, all patients enrolled in our study were treated with curative intention, introducing a possible selection bias by excluding the patients that did not receive curative treatment due to frailty reasons.

The main parameters associated with acute radiation-induced toxicity were oropharyngeal carcinomas and concomitant chemotherapy, consisted with earlier reports [14,34]. Concomitant chemotherapy, which is often applied in patients with oropharyngeal carcinomas, might result in poor treatment tolerance. This may have been reflected in occurrence of acute radiation-induced toxicity.

Although it could be assumed that longer time-to-treatment might result in tumor progression and maybe even stage migration and shift from unimodality to multimodality treatment, this association is impossible to establish retrospectively. The only studies



	Total N	N of events
Surgery – overall	111	22
Surgery – delayed	56	18
Surgery – not delayed	55	4
Radiotherapy – overall	134	27
Radiotherapy – delayed	68	17
Radiotherapy – not delayed	66	10

Fig. 3. Kaplan Meier curves for associations between delay and risk of recurrence for patient treated with initial surgery (A) and radiotherapy or chemoradiation (B).

approaching this interaction are radiotherapy reports comparing the diagnostic and planning scans in a relatively small sample size. These studies report an estimated mean volume increase of around 2% per day [1,2]. In the absence of these objective measurements, the effect of prolonged time-to-treatment is focused on derivatives of possible tumor progression, such as overall survival, quality of life, hospitalization and recurrence risk.

We found a strong association between delay and recurrence risk in patients treated with initial surgery, which might be an indirect result of tumor progression during waiting time before start of treatment. Liao et al. and Tumati et al. both described a higher risk of recurrence for patients who had time-to-treatment >60 or >50 days, respectively [35,36]. These are different, less strict thresholds compared to the thresholds used in our population (median of 26 days for initial surgery patients, and 40 days for initial radiotherapy patients).

However, for patients treated with initial radiotherapy no association between delay and recurrence was found. This is consistent with other reports describing radiotherapy patients only [37–40]. A rapid start of radiotherapy treatment seems to be of less importance regarding recurrence risk, compared to patients treated with surgery, whereas the risk of recurrence for the entire cohort is

independent of treatment modality. Possibly, the gradual, long course of radiotherapy treatment should be regarded as a continuous interruption of tumor growth. Given the narrow range in time-to-treatment interval in patients with initial radiotherapy, we can only conclude that these small differences were not related to recurrence risk in those treated with radiotherapy.

Although the sample size of this cohort might be too small for firm statements, it seems as though especially patients with early stage may benefit from early start of treatment.

While this study has focused on the (objectively measured) delay in hospital, the delay prior to entering the secondary or tertiary care system can be quite substantial [41,42]. We believe that beside awareness programs (such as the Make Sense Campaign of the European Head and Neck Society [43,44]), the organization of care in a (regional) network[45], with efficient communication and collaboration between general practitioners, secondary and tertiary referral centers might reduce waiting times.

Setting a cut-off to define treatment delay might be useful in establishing a benchmark for quality of care and carrying out an acceptable duration of the care pathway for new HNSCC patients. As earlier suggested [35], this benchmark might be treatment modality dependent. In this study, we tried to give an example of the use of a different benchmark for initial surgery and initial radiotherapy patients, based on the median time-to-treatment in this cohort. To further understand the impact on the results and conclusions, analyses on the same variables were also performed using time-to-treatment as a continuous variable (Supplementary Information). These should be interpreted in the knowledge that time-to-treatment is a variable with a skewed nature and highly differs for the radiotherapy and surgery group. Knowing that delay as a continuous variable is still associated with increased recurrence risk strengthens our conclusions.

To improve extrapolation of our results, the main analyses were repeated for a subgroup of patients aged 65 and older (Supplementary Table 8), showing similar results.

Patient with recurrent HNSCC or patients with multiple primary tumors were excluded, because these patients enter a different care pathway compared to patients with a first primary HNSCC.

Future prospective studies, including a larger sample size might investigate the effect of delayed treatment initiation on the type of recurrence (i.e. locoregional recurrence and distant metastasis separately) and progression-free survival.

Conclusion

This study demonstrates that delayed treatment initiation is independently associated with increased recurrence risk for patients treated with initial surgery. This association was not apparent in patients treated with initial radiotherapy. Delay was not associated with short-term adverse events (postoperative complications or acute radiation-induced toxicity). Older or frail patients did not experience longer time-to-treatment intervals: the opposite is true for malnourished patients, patients with advanced staged tumors and patients treated with radiotherapy.

These findings highlight the importance of establishing fast-track care pathways to minimize delays and improve especially long-term outcome for patients treated with initial surgery.

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Data availability statement

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

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None.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.06.001.

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