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ORIGINAL ARTICLE

Determinants of delay in the head and neck oncology care pathway: The next step in value-based health care

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Abstract

Objective: Head and neck squamous cell carcinomas (HNSCC) are relatively fast-growing tumours, and delay of treatment is associated with tumour progression and adverse outcomes. The aim of this study is to identify determinants of delay in a head and neck oncology centre.

Methods: This cohort study with prospectively collected data investigated associations between patient (including geriatric assessment at first consultation), tumour and treatment characteristics and treatment delay. Two quality indicator intervals assessing value-based healthcare were studied: care pathway interval (CPI, interval between first visit in an HNOC and treatment initiation) and time-to-treatment initiation (TTI, interval between histopathological confirmation of HNSCC and treatment initiation), using regression analyses.

Results: Stage-IV tumours and initial radiotherapy were independent predictors of delay in CPI. Initial radiotherapy was associated with delay in TTI. Overall, 37% of the patients started treatment within 30 days after first consultation (67% in case of initial surgical treatment and 11.5% if treated with (chemo)radiation, $p < 0.001$). Geriatric assessment outcomes were not associated with delay. Indicators for delay in initial surgery patients were stage-IV tumours (CPI).

Conclusion: The majority of HNSCC patients encounter delay in treatment initiation, specifically in patients with advanced-stage tumours or when radiotherapy is indicated.

KEYWORDS
delay, geriatric assessment, head and neck squamous cell carcinoma, time-to-treatment initiation, value-based health care

1 | INTRODUCTION

Head and neck squamous cell carcinomas (HNSCC) are fast-growing tumours, developing in anatomically challenging and functionally sensitive sites (Dejaco et al., 2019; Jensen et al., 2007). Prognosis strongly depends on the extend of disease at diagnosis (Du et al., 2019). Consequently, timely start of treatment is essential.

The time interval between entering a head and neck oncology centre (HNOC) and start of treatment is increasing and is influenced by tumour, healthcare and patient characteristics (Carlsen et al.,

2019; Harten et al., 2015; Murphy et al., 2015). Within this timeframe, time-consuming diagnostic investigations (including biopsies for histopathological confirmation under general anaesthesia), multidisciplinary board meetings and often multiple consultations to establish a treatment plan and subsequent treatment planning take place.

The current global focus on value-based health care (VBHC) strives to provide high quality of care (oncologic outcome in terms of survival as well as quality of life) at the most reasonable costs to create a sustainable healthcare system. Whereas quality of life involves patients' perspective, all healthcare providers carry a responsibility to define quality of care and advise patients regarding survival and quality of life outcomes. This time interval ('waiting time') is a prominent quality indicator involving the care process to establish VBHC (Takes et al., 2020).

An additional factor possibly contributing to delay is the complexity of the HNSCC population. The burden of functional, cognitive and social deficits is demonstrated to be significant (van Deudekom et al., 2017) and the population is known by a high incidence of frailty and comorbidities (Bras et al., 2020).

In the Netherlands, the Dutch Head and Neck Society (DHNS) requires that the interval between first visit in a HNOC and start of treatment (Care Pathway Interval, CPI) should comprise less than 30 days for at least 80% of the patients (Dutch Head & Neck Society, 2017). This norm was achieved in only 34% in a large Dutch study for patients diagnosed within the HNOC (Harten et al., 2014).

The effect of delay in treatment initiation on oncological outcomes has been studied previously, focusing mainly on the effect on (disease-free) survival. In HNSCC, delay was associated with decreased survival (Harten et al., 2014; Liao et al., 2019; Murphy et al., 2016). However, factors causing delay are less extensively analysed, and specifically, the association between delay and more detailed (geriatric) parameters, relevant in today's ageing society, are not yet described.

Therefore, the aim of this study was to describe factors associated with delay, including the above-mentioned geriatric characteristics, to identify determinants of delay. As a result, care pathways can be adjusted and improved accordingly to contribute to VBHC.

2 | METHODS

2.1 | Study design and patient selection

In this cohort study, patients eligible for inclusion were identified through the OncoLifeS databiobank, a prospectively collected database including all consecutive patients seen in either the department of head and neck surgery or oral and maxillofacial surgery in the University Medical Centre Groningen (UMCG), a tertiary HNOC. OncoLifeS has been approved by the Medical Ethical Board of the UMCG, and the current study protocol was approved by the OncoLifeS scientific board.

Patients were included if their first consultation took place between 2014 (October) and 2016 (May), if the tumour was located in the oral cavity, oropharynx, hypopharynx or larynx and if the tumour was a first primary HNSCC. Patients were excluded if treatment intention was not curative, the date of diagnosis was unknown or if a synchronous malignancy was present. All patients were discussed in a multidisciplinary board and treated according to national guidelines.

Subgroup analyses were performed for the study population excluding patients treated with transoral laser surgery (TOLS), since these patients require less treatment planning. Furthermore, stratified analyses were performed for patients treated with primary surgery and patients treated with primary (chemo)radiation, because radiotherapy patients require different treatment planning.

2.2 | Definition of time points

Care pathway interval was defined as the interval between first consultation in this HNOC and start of treatment (either date of surgery or first day of (chemo)radiation). Time-to-treatment initiation interval (TTI) is the interval between the date of histological confirmation of HNSCC and start of treatment. The timing of the biopsy leading to definitive diagnosis is diverse in the design of Dutch healthcare system and the various steps of the most common care pathways are illustrated in Figure 1.

Care pathway interval and TTI were dichotomised into two groups according to a duration of less than 30 days or ≥30 days (delayed). This norm is used as a quality indicator to evaluate the quality of care and was used for CPI (Dutch Head & Neck Society, 2017). In this study, in accordance with previous literature, this cut-off was used for TTI as well. Patients with a TTI of 0 (n = 8) were excluded from TTI analyses, because these patients received diagnosis and treatment initiation on the same day.

2.3 | Data collection

The databiobank and electronic medical files provided patient, tumour and treatment characteristics (Sidorenkov et al., 2019). The database was supplemented with exact diagnosis data, confirmed by a manual check in the National Pathology Database for patients with biopsies prior to referral to secure accurate measurements of the above-mentioned time intervals. Tumour stage was reported following the Union for International Cancer Control TNM Classification 7th edition (Sobin et al., 2009).

Patients were evaluated using a geriatric assessment at the first day of consultation at the outpatient clinic. Data on the following domains were collected: comorbidities, use of medication, use of tobacco and alcohol, social support, nutritional, functional, cognitive and psychological status. Comorbidity was assessed using the Adult Comorbidity Evaluation (ACE-27) (Piccirillo, 2000), classifying patients into four categories (none, mild, moderate or severe).

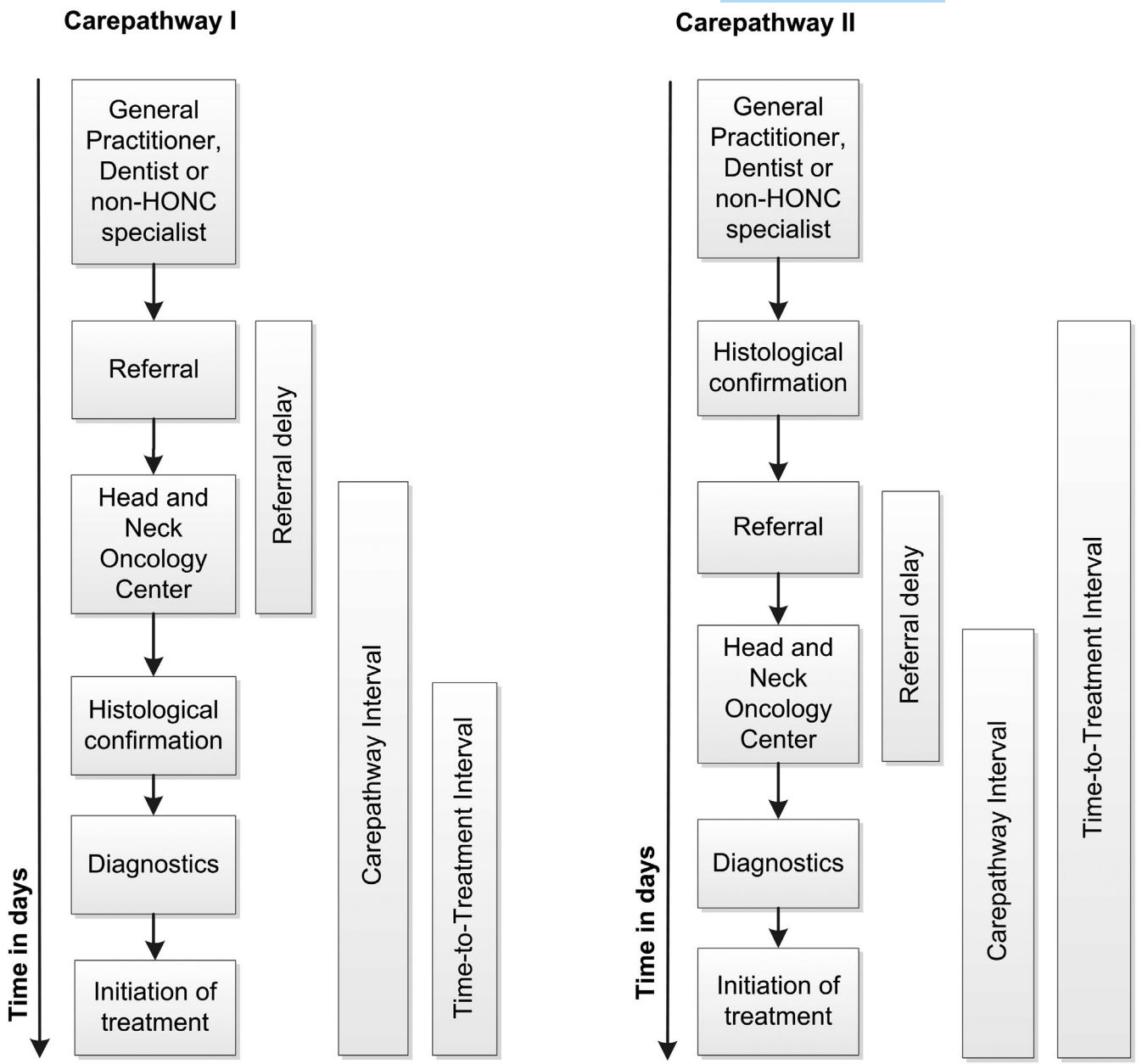

FIGURE 1 Visualisation of the various care pathways for head and neck oncology patients. Care pathway I: patients entering the HNOC without confirmed diagnosis. Care pathway II: patients entering the HNOC with histopathological confirmation of diagnosis. Additional diagnostic imaging was not performed in patients with confirmed or suspected T1a glottic carcinoma. HNOC: head and neck oncology centre

The Malnutrition Universal Screening Tool (MUST) was used to asses nutritional status (Elia, 2003). Functional status was based on Activities of Daily Living (Katz-ADL), Instrumental Activities of Daily Living (IADL), Timed Up & Go (TUG) and history of falls (Katz et al., 1963; Lawton & Brody, 1969; Podsiadlo & Richardson, 1991). Social support consisted of patient-reported questionnaires regarding personal relationships. Cognitive functioning was determined using the Mini Mental State Examination (MMSE) and assessment of risk factors for delirium (Folstein et al., 1975; Oud et al., 2015), while psychological status was measured using the Geriatric Depression Scale (GDS-15) (Sheikh & Yesavage, 1986). Geriatric assessment was completed with two frailty screening instruments: the Groningen Frailty Indicator (GFI) and the Geriatric 8 (G8) (Bellera et al., 2012; Schuurmans et al., 2004).

2.4 | Statistical analysis

Data were analysed using SPSS® Statistics version 25.0 (Armonk, NY: IBM Corp.). Descriptive statistics were presented as mean values and standard deviations for normally distributed continuous variables, medians and quartiles for non-normally distributed

continuous variables and absolute numbers and percentages for dichotomous or ordinal variables. Continuous variables were, depending on their distribution, compared using unpaired Student's *t* tests or the Mann–Whitney *U* test. Ordinal variables were compared using the χ^2 or Fisher's exact test.

Univariable and multivariable regression analyses were performed using a dichotomised dependent variable (logistic regression) and a continuous dependent variable (linear regression using a General Linear Model, presented only in Supplementary Tables) for both CPI and TTI. The association between patient, tumour and treatment characteristics and either CPI or TTI was studied. All independent covariables with $p < 0.10$ in univariable analysis were included in multivariable analysis. A two-sided $p < 0.05$ was considered statistically significant.

3 | RESULTS

A total of 369 patients were potentially eligible for inclusion. In- and exclusion criteria were applied, as depicted in Figure 2, resulting in a final study cohort of 192 patients. Baseline characteristics are displayed in Table 1. Mean age was 65.6 years and the majority was male (69.8%). Median CPI was 39.0 days (Q1: 22.3, Q3: 46.0) and median TTI was 40.0 days (Q1: 28.0, Q3: 54.8).

3.1 | Care pathway interval—determinants of delay

37.0% of the patients started treatment within 30 days after first consultation in our institution. For 62% of the patients, the histopathological diagnosis was confirmed prior to referral to the HNOC. Of these patients, 40.3% started treatment <30 days after first presentation in the HNOC compared to 31.5% of the patients with biopsies within the HNOC ($p = 0.219$). The delayed group (≥30 days) consisted of a larger proportion of current smokers compared to patients treated within 30 days (77.0% vs. 23.0%, $p = 0.001$, respectively). Patients with a oropharyngeal or hypopharyngeal tumour more frequently belonged to the delayed group than patients with oral cavity of laryngeal cancer (Table 1). Other risk factors for delay were advanced tumour stage and (chemo)radiation as treatment modality.

Geriatric assessment showed a significantly higher number of patients with risk of malnutrition in the delayed group. Other domains, including frailty scores, did not significantly differ (Table 2).

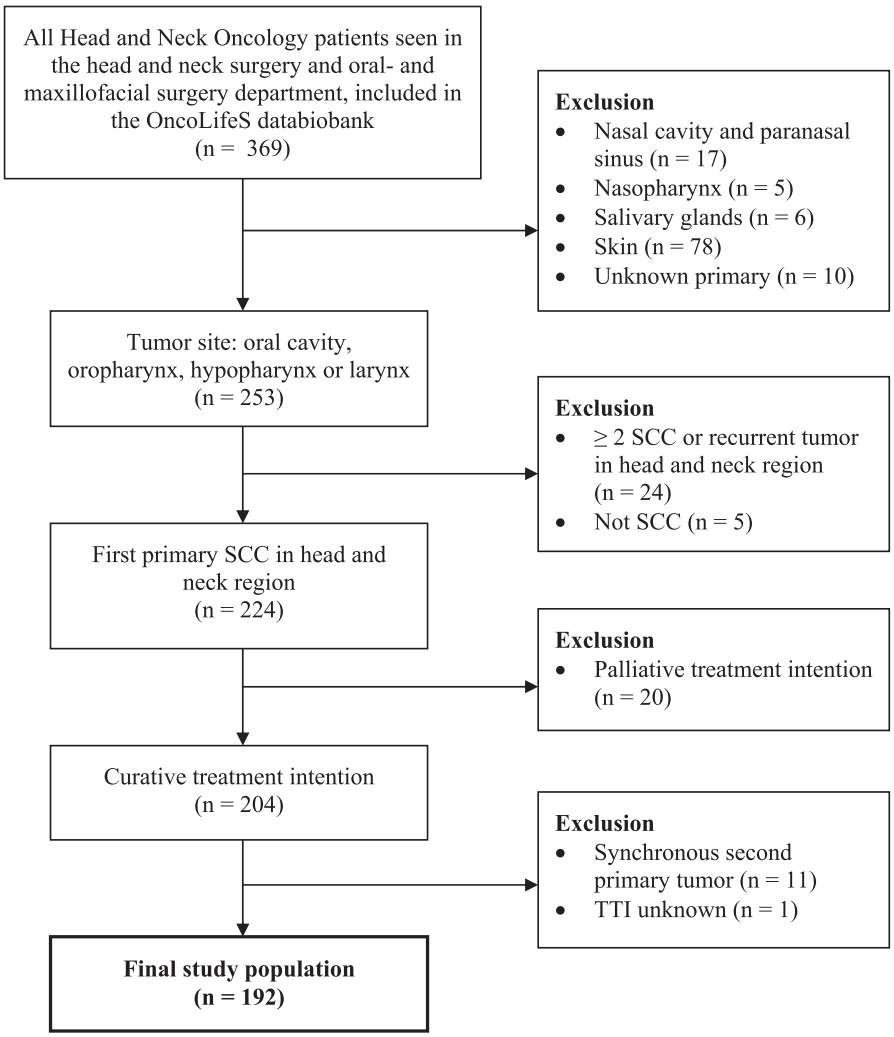

FIGURE 2 Flowchart of study population, including in- and exclusion criteria. SCC, squamous cell carcinoma; TTI, time-to-treatment interval

TABLE 1 Patient, tumour and treatment characteristics of the entire study cohort and divided into patients with CPI <30 days (no delay) versus CPI ≥30 days (delay)

	Value (*n* = 192, %)	Value (*n* = 71, 37.0%)	Value (*n* = 121, 63.0%)	
Characteristic	**All**	**CPI <30 days**	**CPI ≥30 days**	***p*-value**
Age				
Mean ± SD	65.6 (±10.5)	65.5 (±11.6)	65.7 (±9.8)	0.838
Sex				
Male	134 (69.8%)	47 (66.2%)	87 (71.9%)	0.406
Female	58 (30.2%)	24 (33.8%)	34 (28.1%)	
Smoking status				
Never	18 (9.4%)	9 (13.2%)	9 (7.7%)	0.001
Former	80 (41.7%)	39 (57.4%)	41 (35.0%)	
Current	87 (45.3%)	20 (29.4%)	67 (57.3%)	
Drinking status				
Never	46 (24.0%)	22 (32.8%)	24 (20.5%)	0.175
Former	35 (18.2%)	14 (20.9%)	21 (17.9%)	
Mild/moderate	58 (30.2%)	19 (28.4%)	39 (33.3%)	
Heavy (>2/day)	45 (23.4%)	12 (17.9%)	33 (28.2%)	
ACE-27				
None	47 (24.5%)	17 (23.9%)	30 (24.8%)	0.869
Mild	73 (38.0%)	27 (38.0%)	46 (38.0%)	
Moderate	47 (24.5%)	16 (22.5%)	31 (25.6%)	
Severe	25 (13.0%)	11 (15.5%)	14 (11.6%)	
Polypharmacy				
None or <5 medications	127 (66.1%)	44 (62.9%)	83 (69.7%)	0.330
≥5 medications	62 (32.3%)	26 (37.1%)	36 (30.3%)	
BMI				
Low	9 (4.7%)	2 (2.9%)	7 (5.8%)	0.177
Middle	82 (42.7%)	25 (36.8%)	57 (47.5%)	
High	97 (50.5%)	41 (60.3%)	56 (46.7%)	
Tumour site				
Oral cavity	58 (30.2%)	35 (49.3%)	23 (19.0%)	< 0.001
Oropharynx	53 (27.6%)	4 (5.6%)	49 (40.5%)	
Hypopharynx	7 (3.6%)	1 (1.4%)	6 (5.0%)	
Larynx	74 (38.5%)	31 (43.7%)	43 (35.5%)	
Timing of biopsy				
During work-up in HONC	73 (38.0%)	23 (32.4%)	50 (41.3%)	0.219
Before referral to HONC	119 (62.0%)	48 (67.6%)	71 (58.7%)	
Histopathological grade				
Well differentiated	31 (16.1%)	17 (27.4%)	14 (15.2%)	0.065
Moderately differentiated	95 (49.5%)	38 (61.3%)	57 (62.0%)	
Poorly differentiated	28 (14.6%)	7 (11.3%)	21 (22.8%)	
Stage of disease				
Stage I	53 (27.6%)	37 (52.1%)	16 (13.2%)	<0.001
Stage II	30 (15.6%)	8 (11.3%)	22 (18.2%)	
Stage III	26 (13.5%)	11 (15.5%)	15 (12.4%)	
Stage IV	83 (43.2%)	15 (21.1%)	68 (56.2%)	

(Continues)

TABLE 1 (Continued)

Characteristic	Value (*n* = 192, %) All	Value (*n* = 71, 37.0%) CPI <30 days	Value (*n* = 121, 63.0%) CPI ≥30 days	*p*-value
Initial treatment modality				
Surgery	88 (45.8%)	59 (83.1%)	29 (24.0%)	**< 0.001**
Radiotherapy	65 (33.9%)	9 (12.7%)	56 (46.3%)	
Chemoradiation	39 (20.3%)	3 (4.2%)	36 (29.8%)	
Reconstructive surgery				
Without reconstruction	50 (56.8%)	41 (69.5%)	9 (31.0%)	0.001
With reconstruction	38 (43.2%)	18 (30.5%)	20 (69.0%)	

Abbreviations: ACE-27, Adult Comorbidity Evaluation; BMI, body mass index; CPI, Care pathway Interval; HNOC, head and neck oncology centre; Reconstructive surgery, (free) skin transplant or flap reconstruction.

All significant values are bold.

Current smoking, heavy drinking, oropharyngeal, hypopharyngeal or laryngeal tumours, poorly differentiated tumours, tumour stage II-IV, initial treatment with (chemo)radiation and high risk of malnutrition were associated with CPI of ≥30 days in a univariable logistic regression analysis. In the multivariable regression analysis, stage IV (OR 7.97 (95% CI: 1.99–31.97), $p = 0.003$) and initial treatment with radiotherapy (OR 9.93 (95%CI: 2.75–35.92), $p < 0.001$) remained statistically significantly associated to CPI≥30 days (Table 3).

3.2 | Time-to-Treatment Interval—determinants of delay

A total of 57 patients (29.7%) started treatment within 30 days of histopathological confirmation of malignant disease (Table S1). Only 17.6% of the patients with confirmed diagnosis prior to presentation in a HNOC had TTI <30 days versus 55.4% of the patients with biopsy within the HNOC ($p < 0.001$).

Univariable logistic regression analyses demonstrated increasing age, polypharmacy (use of ≥5 medications), oropharyngeal carcinomas, poorly differentiated tumours, stage II or IV tumours, initial treatment with (chemo)radiation and limitations in IADL as independent predictors of delay. Only initial treatment with radiotherapy lasted as independent predictor in a multivariable model (OR: 3.60, 95% CI: 1.03–12.6, $p = 0.044$) (Table 3).

3.3 | Initial therapy: surgery vs. (chemo)radiation

Subgroup analyses were performed to identify predictors within the group of patients treated with initial surgery ($n = 88$) or (chemo)radiation ($n = 104$). Median CPI was 24.5 days for surgical patients versus 40.0 days for (chemo)radiation patients ($p < 0.001$). Within the surgery group, 67.0% was treated within 30 days, compared to 11.5% of the (chemo)radiation group (CPI, $p < 0.001$). TTI was also significantly longer in the radiotherapy group (median 47.0 vs. 33.0 days in the surgery group, $p < 0.001$). Patients receiving reconstructive surgery were more likely to start treatment ≥30 days and were all patients with advanced-stage tumours (stages III–IV).

In a multivariable model, using logistic regression analysis for surgery patients, stage-IV tumours were seven times (OR: 7.470 [95% CI: 1.43–39.08], $p = 0.017$, Table 4) more likely to have CPI ≥30 days compared to stage I tumours. For the surgery group, performing reconstructive surgery was not independently associated with delay (in CPI or TTI) in the multivariable models.

For radiotherapy patients, no predictors for CPI ≥30 days remained significant in the multivariable model (Table 4).

3.4 | Transoral laser surgery (TOLS) versus non-TOLS treatment

Transoral laser surgery was performed in 28 patients, of which 85.7% started treatment <30 days, compared to 28.7% of the other surgically treated patients ($p < 0.001$, CPI). The TOLS group experienced a significantly faster CPI: median 15.0 vs. 39.0 days for non-TOLS patients (including all other patients, $p < 0.001$). 78.6% of the TOLS patients had confirmed diagnosis prior to referral, and TTI did not significantly differ between TOLS vs. non-TOLS. Subgroup analyses were performed only on the non-TOLS patients.

Oropharyngeal tumour location was significantly associated with a CPI ≥30 days in multivariable logistic regression analysis (OR: 6.21 [1.04–37.12], $p = 0.045$). Factors associated with TTI ≥30 days for non-TOLS patients in univariable analyses are displayed in a forest plot (Figure 3). In a multivariable model, age (OR per increase of one year of age: 1.06 (1.02–1.11), $p = 0.006$), sex (OR for females vs. males: 0.41 (0.19–0.92), $p = 0.029$) and initial treatment (OR for radiotherapy: 2.63 [1.33–19.90], $p = 0.018$) were independent determinants of TTI ≥30 days.

4 | DISCUSSION

Time intervals within care pathways are routinely used as quality indicators to assess quality of care: the norm set by the Dutch Head

TABLE 2 Geriatric Assessment characteristics at first presentation in the HNOC for the entire study cohort and divided into patients with CPI <30 days (no delay) vs. CPI ≥30 days (delay)

	Value (*n* = 192)	Value (*n* = 71, 37%)	Value (*n* = 121, 63%)	
Characteristic	**All**	**CPI <30 days**	**CPI ≥30 days**	***p*-value**
Nutritional status				
MUST				
Low risk	130 (72.2%)	56 (84.8%)	74 (64.9%)	0.013
Medium to high risk	50 (27.8%)	10 (15.2%)	40 (13.2%)	
Functional status				
ADL				
No restrictions (<1)	157 (90.8%)	55 (90.2%)	102 (91.1%)	0.737
Restrictions (≥1)	16 (9.2%)	6 (9.8%)	10 (8.9%)	
IADL				
No restrictions (<1)	156 (81.3%)	55 (77.5%)	101 (83.5%)	0.303
Restrictions (≥1)	36 (18.8%)	16 (22.5%)	20 (16.5%)	
TUG				
No restrictions (<10)	125 (68.7%)	45 (68.2%)	80 (69.0%)	0.883
Mild restrictions (10–20)	50 (27.5%)	19 (28.8%)	31 (26.7%)	
Restrictions (>20)	7 (3.8%)	2 (3.0%)	5 (4.3%)	
History of falls				
No	157 (92.9%)	55 (93.2%)	102 (92.7%)	0.905
Yes	12 (7.1%)	4 (6.8%)	8 (7.3%)	
Socio-economic status				
Education				
Low level	74 (45.1%)	27 (45.0%)	47 (45.2%)	0.989
Middle level	50 (30.5%)	18 (30.0%)	32 (30.8%)	
High level	40 (24.4%)	15 (25.0%)	25 (24.0%)	
Marital status				
In a relationship	123 (71.1%)	47 (78.3%)	76 (67.3%)	0.126
Widow or single	50 (28.9%)	13 (21.7%)	37 (32.7%)	
Cognitive status				
MMSE				0.685
Normal cognition (>24)	174 (91.1%)	63 (90.0%)	111 (91.7%)	
Declined cognition (≤24)	17 (8.9%)	7 (10.0%)	10 (8.3%)	
Risk of delirium				
No	103 (53.6%)	43 (60.6%)	60 (50.0%)	0.157
Yes	88 (45.8%)	28 (39.4%)	60 (50.0%)	
Psychological status				
GDS-15				0.483
No signs of depression (<6)	155 (89.6%)	56 (91.8%)	99 (88.4%)	
Signs of depression (≥6)	18 (10.4%)	5 (8.2%)	13 (11.6%)	
Frailty screeners				
G8				0.230
Non-frail (>14)	85 (45.7%)	35 (51.5%)	50 (42.4%)	
Frail (≤14)	101 (54.3%)	33 (48.5%)	68 (57.6%)	
GFI				0.353
Non-frail (<4)	120 (69.4%)	45 (73.8%)	75 (67.0%)	
Frail (≥4)	53 (30.6%)	16 (26.2%)	37 (33.0%)	

Abbreviations: ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; G8, Geriatric 8; GDS-15, Geriatric Depression Scale 15; GFI, Groningen Frailty Indicator; HNOC, head and neck oncology centre; MMSE, Mini Mental State Examination; MUST, Malnutrition Universal Screening Tool; TUG, Timed Up and Go.

All significant values are bold.

TABLE 3 Multivariable logistic regression analyses for CPI and TTI

	OR (95% CI) for ≥30 days CPI		OR (95% CI) for ≥30 days TTI	
Variable	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Age			1.037 (0.99–1.09)	0.115
Smoking status				
Never	ref	ref		
Former	0.765 (0.15–4.00)	0.751		
Current	0.998 (0.18–5.61)	0.998		
Drinking status				
Never	ref	ref		
Former	0.582 (0.12–2.84)	0.504		
Mild/moderate	2.149 (0.58–8.01)	0.255		
Heavy (>2/day)	1.806 (0.45–7.25)	0.404		
Polypharmacy			1.544 (0.61–3.92)	0.361
Tumour site				
Oral cavity	ref	ref	ref	ref
Oropharynx	1.581 (0.20–12.71)	0.667	2.878 (0.55–15.01)	0.210
Hypopharynx	1.526 (0.12–19.75)	0.746	0.445 (0.05–3.86)	0.463
Larynx	1.798 (0.54–5.99)	0.339	1.220 (0.44–3.41)	0.705
Histopathological grade				
Well differentiated	ref	ref	ref	ref
Moderately differentiated	1.957 (0.55–6.97)	0.300	0.72 (0.26–2.00)	0.525
Poorly differentiated	2.107 (0.41–10.89)	0.374	1.902 (0.41–8.76)	0.409
Stage of disease				
Stage I	Ref	ref	ref	ref
Stage II	2.540 (0.49–13.23)	0.268	1.62 (0.37–7.05)	0.520
Stage III	3.262 (0.69–15.37)	0.135	1.207 (0.34–4.34)	0.773
Stage IV	7.967 (1.99–31.97)	0.003	1.631 (0.52–5.15)	0.405
Treatment modality				
Surgery	ref	ref	ref	ref
Radiotherapy	9.931 (2.75–35.92)	<0.001	3.602 (1.03–12.57)	0.044
Chemoradiation	6.026 (0.64–56.67)	0.116	1.482 (0.28–7.86)	0.644
Nutritional status				
MUST				
Low risk	ref	ref		
Medium risk	1.530 (0.32–7.33)	0.594		
High risk	2.844 (0.55–14.78)	0.214		
Functional status				
IADL (restrictions)			2.678 (0.82–8.76)	0.103

Abbreviations: CI, confidence interval; CPI, Care pathway Interval; IADL, Instrumental Activities of Daily Living; MUST, Malnutrition Universal Screening Tool; TTI, time-to-treatment interval; Only significant variables ($p < 0.10$) in univariable analyses were entered into the multivariable model; Polypharmacy, use of ≥5 medications.

All significant values are bold.

and Neck Society is to initiate treatment within 30 days after first consultation in a HNOC for 80% of the patients. In this cohort study, using prospectively collected data, 37% of the HNSCC patients started treatment within 30 days after first consultation in a HNOC. This is similar to other reports (34–47%), indicating that delay in treatment initiation is a structural problem (Harten et al., 2014). With the knowledge that longer waiting times can lead to tumour progression, resulting in more extensive treatment and even worse outcomes (Liao et al., 2019; Murphy et al., 2016), timely treatment initiation should be priority in assessing value-based health care.

TABLE 4 Multivariable logistic regression analysis assessing the Odds Ratio of ≤30 days CPI in patients treated with surgery vs. (chemo)radiation

	Surgery		(Chemo)radiotherapy	
Variable	**Odds ratio (95% CI)**	***p*-value**	**Odds ratio (95% CI)**	***p*-value**
Drinking status				
Never			Ref	ref
Former			1.546 (0.25–9.74)	0.643
Mild/moderate			1.215 (0.16–9.01)	0.849
Heavy (>2/day)			8.160 (0.65–102.29)	0.104
Tumour site				
Oral cavity			ref	ref
Oropharynx			9.195 (0.87–96.71)	0.065
Hypopharynx			[a]	[a]
Larynx			5.870 (0.68–50.75)	0.108
Histopathological grade				
Well differentiated	ref	ref		
Moderately differentiated	3.902 (0.64–23.65)	0.139		
Poorly differentiated	3.889 (0.43–34.99)	0.226		
Stage of disease				
Stage I	ref	ref		
Stage II	2.153 (0.29–16.18)	0.456		
Stage III	1.321 (0.19–9.20)	0.779		
Stage IV	7.470 (1.43–39.08)	**0.017**		
Reconstructive surgery	3.439 (0.87–13.63)	0.079		
Treatment without Laser surgery	0.881 (0.11–7.09)	0.881		
IADL (restrictions)			0.308 (0.06–1.71)	0.178
MMSE (Declined cognition (≤24))			0.805 (0.11–6.03)	0.833

Abbreviations: CI, confidence interval; CPI, care pathway interval; IADL, Instrumental Activities in Daily Living; MMSE, mini mental state examination. Only significant variables ($p < 0.10$) in univariable analyses were entered into the multivariable model.

[a]Number of patients is too small to perform analyses.

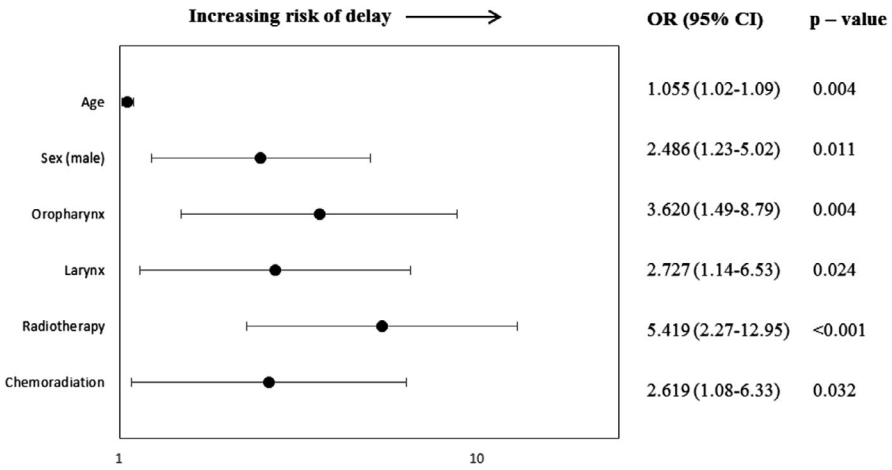

FIGURE 3 Odds ratios for TTI ≥30 days with exclusion of patients treated by transoral laser surgery: logistic regression analyses (univariable). Reference categories are according to tables. Age is the only continuous variable. OR, odds ratio; CI, confidence interval

4.1 | Determinants of delay

In this study cohort, independent determinants for CPI delay (≥30 days) were stage-IV tumours and initial treatment with radiotherapy. However, Harten et al. (2014) demonstrate the opposite effect for stage: a significantly decreased CPI for stage III–IV tumours, compared to stage I–II tumours (34 vs. 39 days, respectively). A possible explanation could be that advanced tumour stages are treated with priority in other facilities.

A strong independent predictor of delay in TTI (≥30 days) was initial treatment with radiotherapy, similar to other studies describing the effect of treatment modality on delay (Guizard et al., 2016; Harten et al., 2014; Murphy et al., 2015, 2016; Polesel et al., 2017). Significant predictors within the group of patients receiving radiotherapy could not be identified in our logistic corrected models; however, in multivariable linear analysis moderate comorbidities were independently associated with longer CPI in radiotherapy patients. Predictors for delay in patients treated with primary radiotherapy in literature are tumour site (oral cavity shorter TTI), T- and N-stage (shorter TTI with increasing T- and N-stage [León et al., 2003]) and treatment with proton therapy instead of regular photon therapy (Jin et al., 2019).

In the absence of evident patient or tumour characteristics explanatory for the prolonged CPI in patients treated with radiotherapy in this cohort, this might rather be as a result of planning and logistic factors. Examples are extensive treatment planning and possible extra interventions (such as extraction of teeth) before the start of radiotherapy. Unfortunately, these factors were not collected as part of this study.

Although not collected and analysed in this study, possible adjustments in the care pathway could be to implement multidisciplinary first-day consultation to minimise the delay for patients with expected radiotherapy treatment and to use fixed time slots for additional investigations. The radio-oncologist can arrange for additional scans to be performed already in the radiotherapy mask and the dentist can already asses dental status and organise the following pre-treatment steps.

In our study, geriatric domains were not associated with delay in treatment initiation, although we hypothesised that frailer patients may be at risk for delay. Adequate collaboration with the geriatric department within our institution could be an explanation. An inclusion bias for frail patients might be present: this study population comprised only patients with curative-intended treatment.

Indicators for delay within patients treated with initial surgery were stage-IV tumours (CPI). Performing reconstructive surgery was not independently associated with delay for CPI or TTI. For delay in CPI, reconstructive surgery showed a borderline non-significant independent association with delay. As larger tumours require more extensive surgery with the involvement of multiple teams (e.g. plastic surgeons) and postoperative care in the ICU, it is to be expected that treatment planning for advanced-stage tumours takes longer; however, this effect was non-significant in the multivariable models in this study.

4.2 | Transoral laser surgery

Patients treated with TOLS (mostly stage I laryngeal carcinomas) experience significantly shorter CPI and may blur the results for the other surgically treated patients. These patients are commonly reported together with the other HNSCC patients as a whole, while they adhere to an obvious different care trajectory. Patients treated by TOLS benefit from fast surgery planning (minor surgery) and less diagnostic interventions due to low-stage tumours. To prevent bias, a subgroup analysis was performed on the study population, excluding laser surgery patients, demonstrating sex (male), age and initial radiotherapy as predictors of delay in the non-TOLS group. Future studies should perform subgroup analyses on both TOLS and non-TOLS patients to further clarify determinants of delay.

4.3 | Strengths and limitations

It should be noted that the 30-day cut-off set by the DHNS is not supported by evidence. An even more strict target is pursued in Denmark since 2017: CPI must not exceed 7 days for primary surgery or 11 days for radiotherapy (Grønhøj et al., 2018). As a result, authors assessing delay often use different cut-offs and do not always report regression analysis based on continuous values as well. To minimise the impact of using this cut-off on distorting the results, we also performed a linear regression analysis using the time intervals as continuous values. The differences between logistic and linear results were negligible; however, they are transparently presented in the Supplementary Section (Tables 3 and 4).

In this study, CPI and TTI were used as outcome variables. Both time measures yield limitations. A limitation encountered in interpreting TTI is that a possible delay following earlier inconclusive biopsies can be overlooked. With CPI, although this interval can be more easily influenced, as it takes place in one centre, the amount of diagnostics performed before first consultation in a HNOC might influence the duration.

This study comprises a limited number of patients compared to other studies describing delay using national databases. However, the data were prospectively collected and missing data regarding time intervals were hand-checked and added. Most databases based on national registries exclude patients with missing data, because it is not possible to retrieve the data, possibly leading to bias.

Furthermore, despite the relatively small number of patients, this study adds to the scarce literature describing geriatric domains in HNSCC patients, using validated measurements. The association between delay and geriatric domains has, to our knowledge, not been described previously.

The main focus of this study was to examine the hospital interval, not taking into account the referral delay and more importantly, the delay prior to entering the secondary care system, which can be quite substantial (Amir et al., 1999; Helsper et al., 2017).

The time period studied is a limitation of this study, and the effect of delay on outcome measures was not analysed. However, the determinants of delay are less well defined and studied, which was the main reason for this report, and we do not have reasons to believe that more contemporary data would alter findings.

4.4 | Biopsy before or after referral to HNOC

In the Netherlands, HNSCC care is centralised and 96% of the patients are treated in one of the eight HNOC (Halmos et al., 2018).

In many HNOC, timing of biopsy differs: either patients enter the HNOC with confirmed histologic reports or they enter with a suspicious lesion and biopsy has to be performed within the HNOC. As a result, both CPI and TTI are interesting time intervals to study. In this cohort, 62% of the patients had confirmed diagnosis prior to referral to the HNOC. However, the amount of patients starting treatment within 30 days after first consultation in a HNOC was not significantly different between patients without or with histopathological confirmed diagnosis (31.5% vs. 40.3%, respectively), contrary to expectation. A possible explanation could be that additional diagnostics (i.e. imaging) upon referral are not yet performed or performed using a different protocol. Furthermore, the logistical challenges of the revision of the histology may also be a bottleneck. This study did not assess the effect of additional diagnostics and delay.

Patients with confirmed histological diagnosis experienced a significantly longer TTI, raising the question whether it would be quicker to perform all biopsies within the HNOC. A disadvantage of that option would be an increased workload in the HNOC and theoretically also load of non-malignant pathology, possibly causing prolonged waiting times as well.

4.5 | Clinical perspectives

The organisation of care in a (regional) network, providing efficient communication and collaboration between general practitioners, secondary and tertiary referral centres can decrease TTI and CPI (Takes et al., 2020). A major aspect influencing the duration of TTI/CPI is performing diagnostic procedures (i.e. biopsies, imaging). Clear protocols and guidelines for both secondary and tertiary referral centres could avoid unnecessary or repeated procedures, contributing to cost-effectiveness and timely start of treatment. Also, improving IT solutions, such as shared electronic patient record systems, could fasten the diagnostic process and reduce the rate of repeated diagnostic tests.

4.6 | Interventions to decrease delay

Several studies report the effect of interventions to decrease delay. Ouwens et al. describe a successful reduction in CPI after implementation of an integrated care program, involving fixed time slots for additional investigations and standard dietician consultation, resulting in an increase from 29% of patients treated <30 days before to 54% after implementation. However, in this study the norm of 80% is still not reached (Ouwens et al., 2009). A similar intervention (including multidisciplinary first-day consultation providing a preliminary diagnostic plan) is implemented and analysed by Van Huizen et al., describing similar results (before intervention 52%, after intervention 54%–83% compliance to the DHNA norm) (Huizen et al., 2018).

In conclusion, this study highlights several determinants predicting delay before the start of treatment in HNSCC. Identified risk factors of delay were patients with advanced-stage tumours and treatment with radiotherapy. Geriatric assessment outcomes were not related to delay.

Timely treatment initiation is challenging in HNSCC patients with fast-growing tumours in anatomically complex areas. Interventions expediting waiting times, especially to adjust care pathways for patients treated with radiotherapy, are desired. Diagnosis and treatment of HNSCC patients should be performed within regional head and neck oncological care networks, streamlining diagnostic procedures and aiming for optimal collaboration throughout care facilities.

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CONFLICTS OF INTERESTS

All authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

All listed authors have made substantial contributions to this manuscript and have given approval of this version to be published, in accordance to the journal's authorship policy.

RCS, BECP, BACvD and GBH involved in conception and design. JdV, LB and RCS involved in acquisition of data. RCS, BAC and GBH involved in analysis and interpretation of data. RCS involved in drafting the manuscript. RCS, BECP, LB, JdV, BACvD and GBH involved in revising the manuscript.

DATA AVAILABILITY STATEMENT

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

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REFERENCES

Amir, Z., Kwan, S. Y., Landes, D., Feber, T., & Williams, S. A. (1999). Diagnostic delays in head and neck cancers. *European Journal of Cancer Care*, *8*(4), 198–203. https://doi.org/10.1046/j.1365-2354.1999.00165.x

Bellera, C. A., Rainfray, M., Mathoulin-Pélissier, S., Mertens, C., Delva, F., Fonck, M., & Soubeyran, P. L. (2012). Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Annals of Oncology*, *23*(8), 2166–2172. https://doi.org/10.1093/annonc/mdr587

Bras, L., Driessen, D. A. J. J., Vries, J., Festen, S., Laan, B. F. A. M., Leeuwen, B. L., Bock, G. H., & Halmos, G. B. (2020). Patients with head and neck cancer: Are they frailer than patients with other solid malignancies? *European Journal of Cancer Care*, *29*(1), e13170. https://doi.org/10.1111/ecc.13170

Carlsen, A. H., Eriksen, J. G., Godballe, C., Johansen, J., Sørensen, J. A., & Bjørndal, K. (2019). Impact of age, comorbidity, and WHO performance status on delay of treatment in patients undergoing fast-track work-up for head and neck cancer. *Journal of Geriatric Oncology*, *10*(2), 259–264. https://doi.org/10.1016/j.jgo.2018.06.003

Dejaco, D., Steinbichler, T., Schartinger, V. H., Fischer, N., Anegg, M., Dudas, J., Posch, A., Widmann, G., & Riechelmann, H. (2019). Specific growth rates calculated from CTs in patients with head and neck squamous cell carcinoma: A retrospective study performed in Austria. *British Medical Journal Open*, *9*(2), e025359. https://doi.org/10.1136/bmjopen-2018-025359

Du, E., Mazul, A. L., Farquhar, D., Brennan, P., Anantharaman, D., Abedi-Ardekani, B., Weissler, M. C., Hayes, D. N., Olshan, A. F., & Zevallos, J. P. (2019). Long-term survival in head and neck cancer: impact of site, stage, smoking, and human papillomavirus status. *The Laryngoscope*, *129*(11), 2506–2513. https://doi.org/10.1002/lary.27807

Dutch Head and Neck Society. (2017). Multidisciplinaire Normering Oncologische Zorg in Nederland. SONCOS Normeringrapport 5 - 2017. Retrieved from https://richtlijnendatabase.nl/gerelateerde_documenten/f/11825/43SONCOS-normeringsrapport-versie-5.pdf

Elia, M. (2003). *The "MUST" report. Nutritional screening for adults: A multidisciplinary responsibility. Development and use of the "malnutrition universal screening tool" (MUST) for adults*. British Association for Parenteral and Enteral Nutrition (BAPEN).

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Grønhøj, C., Jensen, D., Dehlendorff, C., Nørregaard, C., Andersen, E., Specht, L., Charabi, B., & von Buchwald, C. (2018). Impact of time to treatment initiation in patients with human papillomavirus-positive and -negative oropharyngeal squamous cell carcinoma. *Clinical Oncology*, *30*(6), 375–381. https://doi.org/10.1016/j.clon.2018.02.025

Guizard, A.-V., Dejardin, O., Launay, L., Bara, S., Lapôtre-Ledoux, B., Babin, E., Launoy, G., & Ligier, K. (2016). 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. *European Archives of Oto-Rhino-Laryngology*, *273*(11), 3951–3958. https://doi.org/10.1007/s00405-016-4056-8

Halmos, G. B., Bras, L., Siesling, S., van der Laan, B., Langendijk, J. A., & van Dijk, B. A. C. (2018). Age-specific incidence and treatment patterns of head and neck cancer in the Netherlands-A cohort study. *Clinical Otolaryngology*, *43*(1), 317–324. https://doi.org/10.1111/coa.12991

Helsper, C. C. W., van Erp, N. N. F., Peeters, P., & de Wit, N. N. J. (2017). Time to diagnosis and treatment for cancer patients in the Netherlands: Room for improvement? *European Journal of Cancer*, *87*, 113–121. https://doi.org/10.1016/j.ejca.2017.10.003

Jensen, A. R., Nellemann, H. M., & Overgaard, J. (2007). Tumor progression in waiting time for radiotherapy in head and neck cancer. *Radiotherapy and Oncology*, *84*(1), 5–10. https://doi.org/10.1016/j.radonc.2007.04.001

Jin, M. C., Harris, J. P., Sabolch, A. N., Gensheimer, M., Le, Q.-T., Beadle, B. M., & Pollom, E. L. (2019). Proton radiotherapy and treatment delay in head and neck squamous cell carcinoma. *Laryngoscope*, https://doi.org/10.1002/lary.28458.

Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., & Jaffe, M. W. (1963). Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. *JAMA*, *185*, 914–919. https://doi.org/10.1001/jama.1963.03060120024016

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist*, *9*(3), 179–186.

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

Liao, D. Z., Schlecht, N. F., Rosenblatt, G., Kinkhabwala, C. M., Leonard, J. A., Ference, R. S., Prystowsky, M. B., Ow, T. J., Schiff, B. A., Smith, R. V., & Mehta, V. (2019). 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 Otolaryngology–head & Neck Surgery*, *145*(11), 1001–1009. https://doi.org/10.1001/jamaoto.2019.2414

Murphy, C. T., Galloway, T. J., Handorf, E. A., Egleston, B. L., Wang, L. S., Mehra, R., Flieder, D. B., & Ridge, J. A. (2016). Survival impact of increasing time to treatment initiation for patients with head and neck cancer in the United States. *Journal of Clinical Oncology*, *34*(2), 169–178. https://doi.org/10.1200/jco.2015.61.5906

Murphy, C. T., Galloway, T. J., Handorf, E. A., Wang, L., Mehra, R., Flieder, D. B., & Ridge, J. A. (2015). Increasing time to treatment initiation for head and neck cancer: An analysis of the National Cancer Database. *Cancer*, *121*(8), 1204–1213. https://doi.org/10.1002/cncr.29191

Oud, F. M., de Rooij, S. E., Schuurman, T., Duijvelaar, K. M., & van Munster, B. C. (2015). Predictive value of the VMS theme 'Frail elderly': delirium, falling and mortality in elderly hospital patients. *Nederlands Tijdschrift Voor Geneeskunde*, *159*, A8491.

Ouwens, M. M. M. T. J., Hermens, R. R. P. M. G., Hulscher, M. M. E. J. L., Merkx, M. A. W., van den Hoogen, F. J. A., Grol, R. P., Wollersheim, H. C. H., & Marres, H. A. M. (2009). Impact of an integrated care program for patients with head and neck cancer on the quality of care. *Head and Neck*, *31*(7), 902–910. https://doi.org/10.1002/hed.21041

Piccirillo, J. F. (2000). Importance of comorbidity in head and neck cancer. *Laryngoscope*, *110*(4), 593–602. https://doi.org/10.1097/00005537-200004000-00011

Podsiadlo, D., & Richardson, S. (1991). The timed "Up & Go": A test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society*, *39*(2), 142–148. https://doi.org/10.1111/j.1532-5415.1991.tb01616.x

Polesel, J., Furlan, C., Birri, S., Giacomarra, V., Vaccher, E., Grando, G., Gobitti, C., Navarria, F., Schioppa, O., Minatel, E., Bidoli, E., Barzan, L., & Franchin, G. (2017). The impact of time to treatment initiation on survival from head and neck cancer in north-eastern Italy. *Oral Oncology*, *67*, 175–182. https://doi.org/10.1016/j.oraloncology.2017.02.009

Schuurmans, H., Steverink, N., Lindenberg, S., Frieswijk, N., & Slaets, J. P. (2004). Old or frail: What tells us more? *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *59*(9), M962–M965. https://doi.org/10.1093/gerona/59.9.m962

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist: the Journal of Aging and Mental Health*, *5*(1–2), 165–173. https://doi.org/10.1300/J018v05n01_09

Sidorenkov, G., Nagel, J., Meijer, C., Duker, J. J., Groen, H. J. M., Halmos, G. B., Oonk, M. H. M., Oostergo, R. J., van der Vegt, B., Witjes, M. J. H., Nijland, M., Havenga, K., Maduro, J. H., Gietema, J. A., & de Bock, G. H. (2019). The OncoLifeS data-biobank for oncology: A comprehensive repository of clinical data, biological samples, and the patient's perspective. *Journal of Translational Medicine*, *17*(1), 374. https://doi.org/10.1186/s12967-019-2122-x

Sobin, L. H., Gospodarowicz, M. K., & Wittekind, C. (2009). *TNM classification of malignant tumours*, 7th: ed. Wiley-Blackwell.

Takes, R. P., Halmos, G. B., Ridge, J. A., Bossi, P., Merkx, M. A. W., Rinaldo, A., Sanabria, A., Smeele, L. E., Mäkitie, A. A., & Ferlito, A. (2020). Value and quality of care in head and neck oncology. *Current Oncology Reports*, *22*(9), 92. https://doi.org/10.1007/s11912-020-00952-5

van Deudekom, F. J., Schimberg, A. S., Kallenberg, M. H., Slingerland, M., van der Velden, L. A., & Mooijaart, S. P. (2017). Functional and cognitive impairment, social environment, frailty and adverse health outcomes in older patients with head and neck cancer, a systematic review. *Oral Oncology*, *64*, 27–36. https://doi.org/10.1016/j.oraloncology.2016.11.013

van Harten, M. C., de Ridder, M., Hamming-Vrieze, O., Smeele, L. E., Balm, A. J., & van den Brekel, M. W. (2014). The association of treatment delay and prognosis in head and neck squamous cell carcinoma (HNSCC) patients in a Dutch comprehensive cancer center. *Oral Oncology*, *50*(4), 282–290. https://doi.org/10.1016/j.oraloncology.2013.12.018

van Harten, M. C., Hoebers, F. J., Kross, K. W., van Werkhoven, E. D., van den Brekel, M. W., & van Dijk, B. A. (2015). Determinants of treatment waiting times for head and neck cancer in the Netherlands and their relation to survival. *Oral Oncology*, *51*(3), 272–278. https://doi.org/10.1016/j.oraloncology.2014.12.003

van Huizen, L. S., Dijkstra, P. U., van der Laan, B. F. A. M., Reintsema, H., Ahaus, K. T. B., Bijl, H. P., & Roodenburg, J. L. N. (2018). Multidisciplinary first-day consultation accelerates diagnostic procedures and throughput times of patients in a head-and-neck cancer care pathway, a mixed method study. *BMC Health Services Research*, *18*(1), 820. https://doi.org/10.1186/s12913-018-3637-1

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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