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Determinants of delay and association with outcome in head and neck cancer: A systematic review

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ABSTRACT

Introduction: Head and neck cancers (HNC) are relatively fast-growing tumours, and delay in treatment initiation is associated with tumour progression and adverse outcome. An overview of factors contributing to delay can provide critical insights on necessary adjustments to optimize care pathways. This systematic review aims to identify factors associated with delay and summarize the effect of delay on oncological outcome measures.

Methods: A search strategy was conducted according to PRISMA guidelines to search electronic databases for studies assessing the carepathway interval (days between first visit in head and neck oncology center and treatment initiation) and/or time-to-treatment-initiation interval (days between histological diagnosis and treatment initiation) and 1) determinants of delay and/or 2) effect of delay on outcome within these timeframes. Due to heterogeneity between included studies, a meta-analysis was not possible.

Results: Fifty-two studies were eligible for quantitative analysis. Non-Caucasian race, academic setting, Medicaid/no insurance and radiotherapy as primary treatment were associated with delay. Advanced tumour stage was related to increased time-to-treatment initiation in the four common sites combined (oral cavity, oropharynx, hypopharynx, larynx). Separate determinants for delay in different tumour locations were identified. In laryngeal, oral cavity cancer and the four common HNC sites combined, delay in start of treatment is associated with decreased overall survival, although no cut-off time point could be determined.

Conclusion: Race, facility type, type of insurance and radiotherapy as primary treatment were associated with delay and subsequent inferior survival in the four common sites combined.

Introduction

Head and neck cancer (HNC) represents the seventh most common type of cancer worldwide, with an incidence of approximately 600.000 patients per year and 250.000 deaths each year [1,2]. The oral cavity, oropharynx, hypopharynx and larynx are the four sites mostly affected [3]. Histologically, HNC are mostly squamous cell carcinomas developing in the upper airway epithelium (HNSCC).

HNSCC are relatively fast-growing compared to other tumours and more than two-thirds of patients present with locally advanced disease [4,5]. Prognosis at time of diagnosis mainly depends on

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tumour stage, with a higher tumour stage resulting in worse outcome. Prolongation in time-to-treatment initiation is associated with tumour progression and decreased survival [6]. Therefore, timely start of treatment is essential [7–9].

The various time intervals between referral to a hospital, confirmation of malignant disease and start of initial treatment are influenced by patient, tumour and healthcare characteristics. The diagnostic process in HNC is complex and time-consuming, often requiring biopsy under general anaesthesia and multiple imaging modalities for accurate staging. Moreover, HNC patients are a varied population with a high incidence of comorbidities and frailty [10]. An additional challenge in HNC patients is treatment planning: locally advanced disease requires multimodality therapy consisting of surgery and adjuvant (chemo)radiation or primary chemoradiation therapy.

These logistic challenges in the diagnostic and treatment-planning phase expose HNC patients to delay. Increased time-to-treatment initiation is an important quality indicator assessing value-based healthcare [11]. Creating a sustainable healthcare system, providing value-based healthcare (balancing high quality of care at reasonable costs), is a current global topic [11–13]. Facilitating timely start of treatment might be a factor that can be relatively rapidly and easily adjusted in care pathways; however, its effect must be established. When factors predicting delay can be identified, care trajectories may be adjusted and optimized accordingly.

Earlier reviews on this topic addressed mostly the effect of delay on oncological outcome rather than describing determinants associated with increased time to initiate treatment [14,15]. These reviews also did not take into consideration other important outcomes, such as functional outcome and quality of life. Providing an overview of the reported factors that contribute to delay can provide critical insights on how to adjust and optimize care pathways.

Therefore, the aim of this systematic review was to provide an overview of all available studies 1) describing which factors contribute to delay and 2) reporting the effect of delay on different outcome measures in a systematic manner.

Material and methods

Study identification and selection

According to the PRISMA statement for transparent reporting of systematic reviews and meta-analysis [16], a study and search protocol was conducted and prospectively registered in the PROSPERO database (ID: CRD42020191772). An information specialist was consulted to assist in developing the search strategy for multiple electronic databases: MEDLINE (PubMed), Embase and Web of Science (Appendix A). The final search was performed on March 5, 2020.

Publications describing 1) factors contributing to delay after the first presentation in a hospital or at the time of definitive diagnosis and before the start of initial treatment and/or studies describing 2) the association between longer time-to-treatment initiation and outcome (survival [overall survival, disease-specific survival]), recurrence rate, functional outcome, quality of life, complications and toxicity) were included. Studies were eligible for inclusion when the following criteria were met: sample size $\geq$10 patients, tumour site involving oral cavity, oropharynx, hypopharynx and/or larynx and histological tumour type is squamous cell carcinoma. No limitations on time period were applied. Papers not containing original research, abstracts only, conference proceedings and reviews, case studies and studies not written in English were excluded (Fig. 1). Eligible studies had to provide a clear definition of delay, specifically identifying the time points of the interval involved.

Titles and abstracts of the search results were screened by two independent researchers, applying the described in- and exclusion criteria. Cohen's κ was used to express interobserver agreement. In case of discrepancies, a third independent researcher was consulted to reach consensus. After title and abstract selection, the remaining studies were examined by full-text analysis in a similar manner, and non-eligible studies were excluded with defined reasons. References of the included papers were screened as well for possible incorporation, using the same procedures as described above. When inclusion criteria were only met for a part of the study group, the data involving the relevant group were included for further analysis.

Data extraction

Relevant data derived from the included papers were extracted using a standardized form, consisting of the country and study period, data source, sample size, study population specifics (including in- and exclusion criteria), patient and tumour characteristics, exact definition of delay (TTI: time-to-treatment initiation interval: interval between (confirmation of histopathological) diagnosis and start of treatment, and CPI: carepathway interval, time between first visit in head and neck oncology center and start of treatment), mean and median delay, cut-off value of delay, reported predictors of delay, reported outcomes and reported follow-up. The extracted data were double-checked by two independent researchers. In order to present a clinically relevant overview, reported results will be presented by tumour site with clear interpretation explanations provided for each table. For the combined group (oral cavity, oropharynx, hypopharynx and larynx: termed 'four common sites'), only study populations that consisted of $\geq$90% of these four sites are included.

Study quality assessment

To determine the quality of the included studies, the 'Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies' was used [17]. The NOS assesses the selection and comparability of the study groups and the ascertainment of outcomes of interest.

Results

Study selection

After deduplication, 2227 potentially eligible studies were retrieved (Fig. 1). Interobserver agreement (Cohen's κ) was 0.72 (absolute agreement: 93.6%) and 0.65 (absolute agreement: 87.1%) for title and abstract selection and full-text assessment, respectively. A total of 239 full-text articles were screened, eventually yielding 52 eligible studies included in quantitative synthesis. Main reasons for exclusion were studies focussing on delay in the prehospital setting or studies presenting insufficient data or that did not define delay. A meta-analysis could not be performed due to heterogeneity in study populations and described outcomes.

Characteristics of included studies

The majority of included studies comprised cohort studies using retrospective or national databases (Table 1). Sample size ranged considerably between 47 and 274.630 patients and included studies were published between 1997 and 2020. Of these, only 8 reports were published before 2010 (15.4%). Exact definitions of delay varied between studies (Fig. 2), with 41 studies describing TTI, seven studies focussing on CPI and three studies focussing on both.

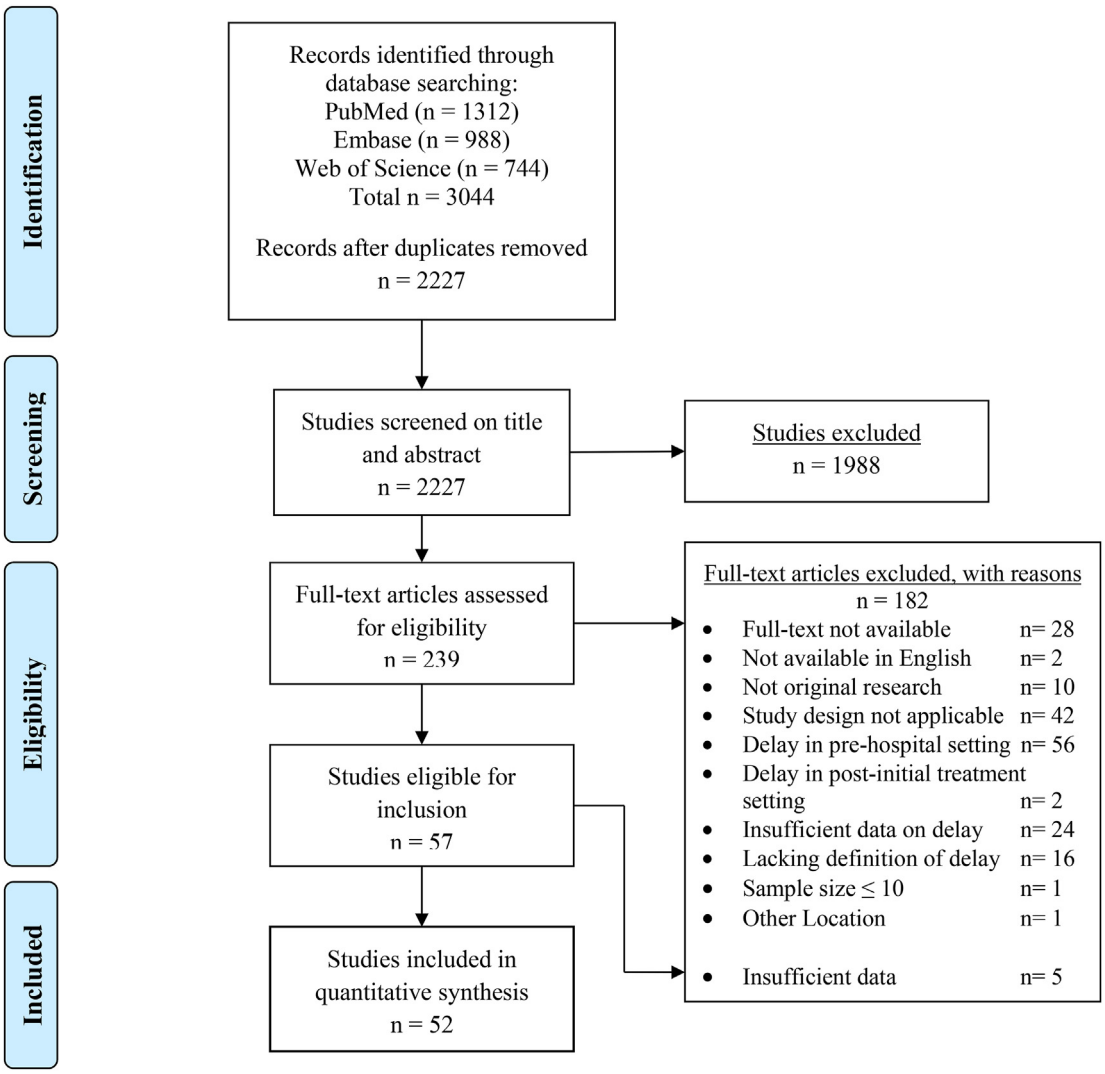


Fig. 1. PRISMA Flowchart of the selection process.[1]
‡Online in color only.

One study described the interval between referral and treatment initiation [18]. Tumour stage was the most described determinant (28 studies, Fig. 3), followed by treatment modality, age and gender (24 studies). Risk factors for HNSCC (smoking and drinking) were relatively less described.

Determinants of delay

To provide a clinically relevant overview of the reported determinants of delay, Table 2 displays factors associated with TTI for laryngeal, oral cavity and oropharynx SCC and the four most common sites combined (the previously mentioned, including hypopharynx SCC).

All four common sites

The majority of the studies reported no significant association between gender; smoking and drinking status; histopathological grade; and use of alternative medicine and delay [18–26].

Notable findings included an increased risk of delay for African-American or Hispanics compared to Caucasian patients [7,18,22,27,28]. Academic facility was reported as a risk factor for prolonged TTI, as were transition of care [7,22,23,27], and insurance by Medicaid (in USA studies) [7,18,22,27]. Increasing comorbidity index (Charlson) was associated with increased risk of delay [19,29], although three other studies found no significant association between comorbidity and delay [22,24,27].

Within the determinant tumour site, oropharyngeal carcinoma (OPC) was associated with the longest delay by five studies [19,21–23,26]. Increasing tumour stage tends to be associated with increased TTI [22–24,27].

Radiotherapy as initial treatment was strongly associated with longer TTI, found by all studies assessing the effect of treatment modality [19,22,23,26,27]. Within the radiotherapy department, patients receiving proton therapy experienced increased TTI compared to photon therapy (OR 1.69, CI: 1.26–2.30 [30]).

Oral cavity

Gender, race, living in a remote area, and incidental findings

[1] Derived from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. https://doi.org/10.1371/journal.pmed1000097. Available through: www.prisma-statement.org.

Table 1
Study characteristics for TTI and CPI.

Time-to-Treatment Initiation Interval

Study Characteristics									Baseline Characteristics		
No.	Author (year)	Country	Study Design	Study Period	Data Source	Sample Size (n)	Study Population Specifics	NOS	TTI^	TTI cut-off^^	Follow-up (median)
1	Amsbaugh 2018 [42]	USA	RCS	2009–2014	PCD	144	Inclusion: oropharyngeal SCC, AJCC stage I-II, treated with (chemo) radiation. Exclusion: metastatic disease, synchronous primary cancer, previous HNSCC.	8	HPV-: 45 (±19); HPV+: 47 (±16)[$]	<32: 62 (43.1%) ≥32: 82 (56.9%)	27.8 m
2	Caudell 2011 [18]	USA	RCS	1995–2007	RCD	427	Inclusion: stage III-IV HNC patients (all sites) treated with initial radiotherapy. Exclusion: prior treatment HNC, palliative intention.	7	34 (7–441)[§]	≤34: 215 (50.4%), >34: 212 (49.6%)	51.5 m (surviving patients)
3	Chevalier 2016 [67]	France	RCS	2007–2013	RCD	63	Inclusion: T1-4N0 SCC (hypopharynx, larynx, oropharynx) treated with (chemo)radiation. Exclusion: distant metastasis.	7	Hypopharynx: 62.5 (37–102). Larynx: 63 (19–128). Oropharynx: 58.5 (29–99)[§]	<30: 2 (3.7%) ≥50: 52 (96.3%)	Hypopharynx: 41 m, Larynx: 47 m, Oropharynx: 42 m.
4	Chiou 2016 [31]	Taiwan	RCS	2007	NCD	2703	Inclusion: oral cavity HNC. Exclusion: missing diagnostic data, initial treatment date >365 days after diagnosis.	9	22.45 (±18.91)[$]	<21: 1583 (58.6%) >21: 1120 (41.4%)	1573d (=52.4 m)
5	Fujiwara 2017 [32]	USA	RCS	1998–2011	NCD	4868	Inclusion: oral cavity SCC treated with primary surgical resection. Exclusion: multiple cancer diagnoses, incomplete pathologic staging, treatment date information or unknown vital status.	8	30 (±29.3)[$]	Q4 ≥45	5y (NFS)
6	Goel 2019 [37]	USA	RCS	2010–2014	NCD	3550	Inclusion: stage III-IV oropharyngeal SCC treated with curative intent surgical resection and adjuvant (chemo)radiation. Exclusion: local destructive therapy (cryotherapy, laser excision), unknown time intervals (or TTI>180 days) or missing follow-up.	8	26 (IQR 14–39)[§]	NR (continuous)	32 m (IQR: 21–73, for surviving patients)
7	Grønhøj 2018 [38]	Denmark	RCS	2000–2014	NCD	1177	Inclusion: oropharyngeal SCC receiving curative-intended treatment. Exclusion: incomplete TTI data and TTI>365 days. (HPV status: + if P16+ AND HPV+, other combinations are defined as HPV-)	7	36 (IQR: 28–53)[§]	≤30: 378 (32.1%) 31-60: 578 (49.1%) >60: 221 (18.8%).	3.6y (IQR: 1.86–6.07)
8	Hemmi 2019 [33]	Japan	RCS	2011–2015	RCD	47	Inclusion: stage I-II oral cavity SCC treated with primary surgery. Exclusion: distant metastasis or synchronous tumours and patients with positive (or <4 mm) surgical margins.	6	NR	≤21: 17 (36.2%) >21: 30 (63.8%)	5y (NFS)
9	Kompelli 2019 [44]	USA	RCS	2006–2014	NCD	53426	Inclusion: laryngeal SCC. Exclusion: non-SCC, stage IVC, palliative intent, unknown TTI/survival time.	8	NR	<46: 20082 (75.2%, not delayed) 46-73: 4654 (17.4%, at risk of delay), >73: 2004 (7.5%, delayed)	34.2 m (IQR: 14.8–64.8)
10	León 2003 [21]	Spain	RCS	1985–1998	RCD	797	Inclusion: HNSCC (4 main sites + nasofaryngeal SCC, n = 41) treated with curative-intent radiotherapy. Exclusion: ≥2 primaries, lost-to-follow-up <3 years. Study population mostly consisted of glottis SCC (n = 500, 62.7%).	8	44 (1–273)[§]	Q1: <33 (199), Q2: 33–44 (199), Q3: 45–60 (199), Q4: >60 (200)	3-5y (NFS)
11	Liao 2017 [35]	Taiwan	RCS	2004–2010	NCD	18677	Inclusion: oral cavity SCC. Exclusion: in situ carcinoma, history of cancer, unknown staging, stage IVC disease, TTI>365 days.	8	19 (IQR: 13–28)[§]	<30: 15128 (81%) 31-60: 2615 (14%) 61-90: 374 (2%) >91: 560 (3%)	5y (NFS)
12	Liao 2019 [7]	USA	RCS	2005–2017	RCD	956	Inclusion: HNSCC (4 main sites, nasopharynx and nose/sinus). Exclusion: stage IVC disease, palliative treatment, TTI = 0.	9	40 (IQR: 28–56)[§]	≤60: 757 (79.2%), >60: 199 (20.8%)	32 m (IQR: 14–17)
13	Light 2017 [54]	USA	RCS	2003–2011	RCD	106 (group 1 = 52, group 2 = 54)	Inclusion: veterans with oropharyngeal SCC treated with curative-intent (chemo)radiation. Exclusion: stage IVC disease, follow-up <5 years. *Intervention*: implementation of multidisciplinary clinic, including nutritionist, cancer care navigator and speech language pathologist (before: *group 1*, after: *group 2*).	7	*Group 1*: 58 (±42) *Group 2*: 48 (±18)[$]	NR	*Group 1*: 64 m, *Group 2*: 63 m
15	Morse 2019 [48]	USA	RCS	2004–2013	NCD	4722	Inclusion: hypopharyngeal SCC treated with primary (chemo) radiation. Exclusion: previous primary cancer, metastases, carcinoma in situ or missing T-stage, missing follow-up.	8	37[§]	Q1 & Q2: ≤37 (not delayed). Q3: excluded. Q4: ≥54 (delayed, exact n = NFS).	5y (NFS)
16	Morse 2018 (1) [45]	USA	RCS	2004–2013	NCD	33819	Inclusion: laryngeal SCC treated with (combination of) surgery or (chemo)radiation. Exclusion: distant metastases, other primary cancer, carcinoma in situ or missing T/N-stage, incomplete surgical margins or vital status.	8	All: 32. Surgical: 28. Non-surgical: 33[§]	Q1 & Q2: not delayed (surgical: ≤28, non-surgical: ≤33). Q3: excluded. Q4: delayed (surgical: ≥44, non-surgical: ≥47). Exact n = NFS	5y (NFS)
17	Morse 2018 (2) [39]	USA	RCS	2010–2013	NCD	4089	Inclusion: oropharyngeal SCC treated with (chemo)radiation. Exclusion: other primary cancer, neoadjuvant chemotherapy, incomplete radiotherapy course, staging, HPV or vital status.	8	35[§]	Q1 & Q2: ≤35 (n = 2012, not delayed). Q3: excluded. Q4: ≥50 (n = 1032, delayed).	5y (NFS)
18	Morse 2018 (3) [40]	USA	RCS	2010–2013	NCD	3708	Inclusion: oropharyngeal SCC treated with primary surgery. Exclusion: other primary cancer, neoadjuvant chemotherapy, incomplete adjuvant radiotherapy course, staging, surgical margins, nodal status or vital status.	8	All: 27. HPV-: 27. HPV+:26[§]	Q1 & Q2: ≤27 (delayed). Q3: excluded. Q4: ≥38 (delayed).	5y (NFS)
19	Murphy 2016 [22]	USA	RCS	1998–2011	NCD	51655	Inclusion: oral tongue, oropharynx, larynx and hypopharynx SCC, curative treatment intent. Exclusion: stage IVC or unknown stage, TTI>365 days.	8	26 (IQR: 12–41)[§]	≤30: 30744 (60%), 31–60: 15636 (30%), 61–90 days: 3648 (7%), >90: 1627 (3%)	84 m (range 0–120.5)
20	Naghavi 2016 [28]	USA	RCS	1998–2013	RCD	1802	Inclusion: HNSCC (4 main sites + nasopharynx) treated with radiotherapy (definitive or adjuvant). Exclusion: distant metastasis, unknown race status.	6	NR	≤45: 904 (50%), >45: 898 (50%)	34 m
21	Polesel 2017 [23]	Italy	RCS	2003–2009	RCD	1616	Inclusion: invasive HNSCC (4 main sites) treated with curative intent. Exclusion: incomplete follow-up.	9	28 (IQR: 13–45)§	<30: 855 (52.9%), 30–44: 356 (22%), 45–89:301 (18.6%), >90: 104 (6.4%)	5y (NFS)
22	Sharma 2016 [41]	USA	RCS	2003–2006	NCD	6606	Inclusion: stage III-IV oropharyngeal SCC treated with definitive chemoradiation. Exclusion: distant metastasis, surgery before (chemo)radiation, induction chemotherapy, start of treatment >120 days after diagnosis.	8	32	≤30: 3020 (45.7%), >30 days: 3586 (54.3%).	5y (NFS)
23	Stordeur 2020 [29]	Belgium	RCS	2009–2014	NCD	8812	Inclusion: first primary SCC (4 main sites) treated with curative intent. Exclusion: unknown CCI score, multiple invasive tumours, lost-to-follow-up.	9	32 (IQR: 19–46)[§]	NR	5.3y (survival)
24	Tan 2016 [68]	Australia	RCS	2009–2011	PCD + SAQ	158	Inclusion: HNSCC (4 main sites + nasal cavity/paranasal sinus and salivary glands) treated with curative or palliative intent.	6	42 (0–429)[§]	NR	3-5y. Lost-to-follow-up: n = 10 (6.3%)
25	Tham 2019 [24]	USA	RCS	2009–2016	RCD	294	Inclusion: HNSCC (4 main sites) treated with initial curative-intent surgery. Exclusion: incomplete medical records or missing follow-up, recurrent SCC.	9	32[§] ± 79	Q1: ≤14 days, n = 68, Q2: 15–29, n = 71, Q3: 30–49, n = 76, Q4 ≥50, n = 79.	651d (703d for surviving patients)

(*continued on next page*)

Table 1 (*continued*)

Time-to-Treatment Initiation Interval											
Study Characteristics									Baseline Characteristics		
No.	Author (year)	Country	Study Design	Study Period	Data Source	Sample Size (n)	Study Population Specifics	NOS	TTI^	TTI cut-off^^	Follow-up (median)
26	Tsai 2017 [36]	Taiwan	RCS	2004–2010	NCD	21263	Inclusion: oral cavity SCC. Exclusion: distant metastases at diagnosis, multiple primary cancers, incomplete data, death within 1 months of confirmed diagnosis.	8	24.3 ± 76.4[$]	≤30: 18193 (85.6%), 31–120: 2498 (11.8%), >120: 572 (2.7%)	44.0 m (±29.2)[$]
27	Tumati 2019 [25]	USA	RCS	2006–2014	RCD	277	Inclusion: HNSCC (4 main sites) treated with curative surgery and adjuvant radiotherapy. Exclusion: history of prior radiotherapy, not completing full radiotherapy course, <3 months follow-up.	8	33 (IQR: 18–50)[§]	≤50: 211 (76.2%), >50: 66 (23.8%).	33 m (IQR 12–59, for surviving patients). Lost-to-follow-up: 39 (14.1%).
28	Van Harten 2014 [26]	Nether-lands	RCS	1990–2011	NCD	2493	Inclusion: first primary HNSCC (4 main sites). Exclusion: distant metastasis, TTI>90 days, follow-up <90 days.	8	39 (IQR: 26.5–51)[§]	≤30: 810 (32%) >30, 1683 (68%)	44.14 m[$] (starting point: 90d after diagnosis)
29	Van Harten 2015 [69]	Nether-lands	RCS	2005–2011	NCD	13140	Inclusion: first primary HNSCC (4 main sites + nasal cavity/paranasal sinus and salivary glands). Exclusion: distant metastasis at diagnosis, TTI >90 days, follow-up <90 days.	7	37 (IQR: 24–49)[§]	≤30: 4755 (36%), >30: 8383 (64%)	5y (NFS)
32	Davis 2006 [70]	USA	RCS	1996–1999	PCD + SAQ	79	Inclusion: veterans with first primary HNSCC (4 main sites + salivary gland, middle ear and sino-nasal carcinomas) with completed questionnaires. Only 79 patients underwent treatment (47.3%).	4	AM user: 48 (95% CI, 30–67). AM nonuser: 30 (18–40)[$]	NR	N/A
33	Groome 2006 [47]	Canada	RCS	1982–1995	NCD	1156	Inclusion: laryngeal SCC (only glottis and supraglottis).	8	NR	Supraglottic SCC <3w: 92 (19.6%), 3-6w: 229 (48.7%), >6w: 149 (31.7%). Glottic SCC <3w:133 (20.7%), 3-6w: 295 (45.8%), >6w: 216 (33.5%).	N/A
34	Guizard 2016 [19]	France	RCS	2008–2010	RCD	1519	Inclusion: first primary invasive carcinomas (4 main sites + unknown primaries). Exclusion: history of cancer (for TTI analysis also: no treatment or treatment with brachytherapy, unknown stage).	8	35 (IQR: 21–54)[§]	NR	N/A
37	Jin 2019 [30]	USA	RCS	2004–2015	NCD	132198	Inclusion: HNSCC (4 main sites + salivary gland and sino-nasal carcinomas) receiving radiotherapy (only definitive used in this review). Exclusion: metastatic disease at diagnosis, incomplete surgery/biopsy data, treatment >365 days after diagnosis.	7	Proton: 55 (IQR: 37–75). Photon: 42 (29–64)[§]	Proton: >6w: 65.2%. Photon: >6w: 49.5%.	N/A
38	Kato 2008 [20]	USA	RCS	2003–2005	RCD + SAQ	149	Inclusion: HNC (4 main sites, not only SSQ: 10% unspecified, 4% lymphomas). Exclusion: prior history HNC, diagnosed at the same time as initial treatment.	4	27 (95%CI, 22–31)[§]	NR	N/A
39	Murphy 2015 [27]	USA	RCS	1998–2011	NCD	274630	Inclusion: HNSCC (oral tongue, oropharynx, larynx, and hypopharynx) treated with curative intent. Exclusion: distant metastasis at presentation, treatment >365 days after diagnosis or with chemotherapy alone, incomplete TTI, TTI >365 days.	8	26[§]	NR	N/A
41	Patel 2012 [71]	USA	RCS	2005–2007	RCD	100	Inclusion: HNSCC (4 main sites + nasopharynx, paranasal sinus and unknown primary). Exclusion: history of HNSCC, inadequate follow-up.	5	48[§]	NR	N/A
42	Patil 2016 [56]	USA	RCCS	2005–2006 [group 1] vs. 2008–2009 [group 2]	RCD	117 (group 1 = 51, group 2 = 66)	Inclusion: veterans with HNSCC (4 main sites + nasopharynx/nasal cavity). *Intervention*: implementation of multidisciplinary team approach, including visits to multiple specialist in one day ("one-stop") and appointing a case manager (before and after implementation, *group 1* and *group 2*).	6	*Group 1*: 35 (0–153). *Group 2*: 27 (0–95)[§]	NR	N/A
43	Perlow 2018 [72]	USA	RCS	2014–2016	RCD	239	Inclusion: non-metastatic oropharyngeal or laryngeal cancer. Exclusion: <18 years old.	8	Safety Net Hospital: 58 (95% CI 47.4–68.6). Private Academic Hospital: 44 (95% CI 40.3–47.9)[$]	Safety Net Hospital >45: 58.9%. Private Academic Hospital >45: 37.7%. (Regression analysis: continuous)	N/A
44	Raman 2019 [43]	USA	RCS	2008–2018	RCD	101	Inclusion: HPV positive oropharyngeal SCC. Exclusion: negative or unknown HPV status.	5	*p16 neg on FNA*: 32, *p16 pos on FNA*: 40.5[$]	NR	N/A
45	Richard-son 2018 [73]	USA	RCS	2000–2012	RCD	338	Inclusion: veterans with oropharyngeal or laryngeal SCC treated with curative intent. Exclusion: recurrent disease, previous HNSCC treatment.	5	Initial surgery: 24. Initial radiotherapy: 48[§]	NR	2.5y
46	Rogers 2007 [74]	UK	RCS	1992–2002	RCD	559	Inclusion: oral (n = 62, 11%) and oropharyngeal SCC (n = 489, 87%) treated with primary surgery.	6	21 (IQR: 12–30)	NR	N/A
48	Barton 1997 [52]	Australia	RCS	1993–1995	RCD	581	Inclusion: laryngeal SCC, stage T1-2, treated with curative intent radiotherapy.	7	24 (2–91)[§]	NR (continuous)	6.8y. (5% lost-to-follow-up <2 years, 31% no follow-up <1 year).
49	Brouha 2000 [53]	Nether-lands	RCS	1980–1996	RCD	362	Inclusion: T1N0M0 glottic laryngeal SCC treated with radiotherapy.	8	43 (9–180)	<31: 79 (21.9%), 31–60: 222 (61.7%), >60: 59 (16.4%).	4.4y. (lost-to-follow-up: n = 1).
50	DeGraaff 2019 [49]	USA	RCS	2004–2017	RCD	633	Inclusion: HNSCC (4 main sites, nasopharynx, nose and paranasal sinus, salivary glands) treated with curative intent (definitive or adjuvant) radiation therapy. Exclusion: distant metastasis at time of diagnosis, prior therapy for previous HNC or not treated definitively.	8	NR	≤27: 164 (25.9%), 28–41: 158 (25.0%), 42–60: 163 (25.7%), >60: 148 (23.4%)	36.2 m (±29.5)[$]
51	Ho 2018 [50]	USA	RCS	2004–2013	NCD	15064	Inclusion: HNSCC (4 main sites) treated with curative-intent primary surgery and adjuvant radiotherapy. Exclusion: unknown staging or time intervals, treatment >365 days after diagnosis, lost to follow-up, distant metastasis during diagnosis.	9	34.5 (±24.2)[§]	<53: 12653 (84.0%), ≥53: 2411 (16.0%)	54.3 m (95%CI: 53.6–55.2)[$]
52	Xiao 2018 [6]	USA	RCS	2005–2014	NCD	60194	Inclusion: HNSCC (4 main sites) treated with primary definitive surgery. Exclusion: distant metastasis at time of diagnosis, unknown TTI and TTI of 0 or >365 days, unknown or incomplete staging data or follow-up data.	9	NR	≤27: 24994 (41.5%), 28–41: 15883 (26.4%), ≥42: 19317 (32.9%).	10y (NFS)

Table 1 (*continued*)

Time-to-Treatment Initiation Interval											
Study Characteristics									Baseline Characteristics		
No.	Author (year)	Country	Study Design	Study Period	Data Source	Sample Size (n)	Study Population Specifics	NOS	TTI^	TTI cut-off^^	Follow-up (median)
Care Pathway Interval											
Study Characteristics									**Baseline Characteristics**		
No.	**Author (year)**	**Country**	**Study Design**	**Study Period**	**Data Source**	**Sample Size (n)**	**Study Population Specifics**	**NOS**	**CPI^**	**CPI cut-off^^**	**Follow-up (median)**
14	Lopez 2019 [75]	Spain	RCS	1998–2008	RCD	231	Inclusion: oral and oropharyngeal SCC. Exclusion: ≥2 primaries, recurrences and patients with histological SCC diagnosis prior to HNOC arrival.	8	20 (IQR: 15–29)$	Terciles groups I: <19, II: 19–25 (ref), III: >25 (exact n = NFS).	1953d (IQR: 487–3535)
24	Tan 2016 [68]	Australia	RCS	2009–2011	PCD + SAQ	158	Inclusion: HNSCC (4 main sites + nasal cavity/paranasal sinus and salivary glands) treated with curative or palliative intent.	6	45 (0–244)§	NR	3-5y. Lost-to-follow-up: n = 10 (6.3%)
28	Van Harten 2014 [26]	Nether-lands	RCS	1990–2011	NCD	2493	Inclusion: first primary HNSCC (4 main sites). Exclusion: distant metastasis, TTI>90 days, follow-up <90 days.	8	*Biopsy elsewhere*: 31 (23–41). *Biopsy at HNOC*: 36 (26–48)§	*Biopsy elsewhere*: ≤30: 810 (47%), >30: 920 (53%). *Biopsy in HNOC*: ≤30: 259 (34%), >30: 504 (66%).	44.14 m$ (starting point: 90d after diagnosis)
30	Amar 2010 [46]	Brazil	RCS	1996–2004	RCD	217	Inclusion: laryngeal SCC. Exclusion: not starting treatment (analyses are performed on 217 patients).	6	49 (1–347)$	NR	N/A
31	Carlsen 2019 [76]	Denmark	RCS	2014–2016	NCD	650	Inclusion: all HNSCC (4 main sites + unknown primaries, salivary gland and sino-nasal carcinomas). Exclusion: no treatment or palliative chemotherapy. *CPI: from referral to start of treatment.*	8	Surgery: 14, Radiotherapy: 27§	Surgery: <28: 234 (92.9%), ≥28: 18 (7.1%). Radiotherapy: <32: 314 (78.9%), ≥32: 84 (21.1%).	N/A
35	Itamura 2019 [77]	USA	RCS	2014–2017	RCD	104	Inclusion: first primary HNSCC (4 main sites), treated with initial surgery and adjuvant (chemo)radiation, with biopsy prior to referral to HNOC. Exclusion: missing information (NFS).	6	Medicare: 23 (±18), HMO: 29 (±15), PPO: 25 (±14)§	NR	N/A
36	Jaspers 2011 [34]	Nether-lands	RCS	2004–2006	RCD	142	Inclusion: oral cavity SCC. Exclusion: palliative treatment intention.	6	35 (±16.5)$	NR	N/A
40	Ouwens 2009 [55]	Nether-lands	PCCS	2003 (group 1) vs. 2005–2006 (group 2)	PCD + RCD	311 (group 1 = 189, group 2 = 172)	Inclusion: all HNSCC. *Intervention:* implementation of an integrated care program (involving 1) patient information record from a specialist nurse, 2) start of multidisciplinary intake day and fixed timeslots for additional investigations and 3) standard dietician consultation). *Group 1*: before implementation, *group 2*: after implementation.	8	*Group 1*: 36. *Group 2*: 29§	<30: *group 1:* n = 35 (29%); *group 2: n*=77 (54%).	N/A
44	Raman 2019 [43]	USA	RCS	2008–2018	RCD	101	Inclusion: HPV positive oropharyngeal SCC. Exclusion: negative or unknown HPV status.	5	*p16 neg on FNA*: 48, *p16 pos on FNA*: 55.5$	NR	N/A
47	Van Huizen 2018 [57]	Nether-lands	RCCS	2007 (group 1) vs. 2008, 2010, 2013 (group 2)	RCD + SSI	89 (group 1 = 21, group 2 = 68)	Inclusion: HNC (4 main sites + nasopharynx) treated curatively. Exclusion: unknown primaries, recurrent of ≥2 primary. *Intervention*: implementation of a multidisciplinary first-day consultation (MFDC, providing a preliminary diagnostic plan), before (*group 1*) and after (*group 2*).	7	*Group 1*: 32.6 (±13.8). *Group 2*: 22.2 (±9.2, = 2008), 23.7 (±8.4 = 2010), 29.3 (±11.3 = 2013)§	*Group 1* < 30: 52%. *Group 2* < 30: 83% (2008), 71% (2010), 54% (2013).	N/A

Symbols: ^ in days, §: median (range), $: mean (±SD), ^^ in days, n (%). Abbreviations: AM: alternative medicine, d: days, HMO: health maintenance organization, HNC: head and neck cancer, HNOC: head and neck oncology center, HNSCC: head and neck squamous cell carcinoma, HPV: human papilloma virus, IQR: interquartile range (Q1-Q3), m: month(s), NCD: national cancer registry/database, NR: not reported, NFS: not further specified, PCCS: prospective case-control study, PCD: prospectively collected database, RCD: retrospectively collected database, RCCS: retrospective case-control study, RCS: retrospective cohort study, SAD: self-administered questionnaires, SSI: semi-structured interviews, y: year(s). Colours: determinants + effect of delay, determinants of delay, effect of delay.‡Online in colour only.

during diagnostic work-up were not associated with delay [31–36]. Three studies described increasing risk of delay with increasing age (OR 1.22–2.07 [31,32,35]). Fuijwara et al. reported prolonged TTI in academic facilities and transitions of care between facilities (OR 2.17, CI: 1.49–3.15 and OR 2.52, CI: 2.15–2.95, respectively), as well as for patients without insurance or when insured with Medicaid (OR 2.24–2.52) [32]. Increasing stage and non-surgical treatment was significantly associated with increased likelihood of delay [35,36].

Results on the effect of comorbidities on delay are contradictory: two studies described an increased risk of delay when comorbidity scores increase [32,35], whereas another study described a lower risk of delay in the highest comorbidity index score (OR 0.76, CI: 0.59–0.98) [31].

Oropharynx

Gender and comorbidities were not related to delay [37–41]. Hispanic and other non-white patients had increased TTI [39,41], as did patients treated in academic facilities (OR 1.26–1.52) [37,39,41] and patients with no or Medicaid insurance [37,39–41]. The association of stage on delay was conflicting: three studies report increasing chances of delay with higher stages, whereas another found lower stages at higher risk of delay compared to stage III/IV patients [39]. The same authors reported increased risk of delay for patients treated with surgery alone (without adjuvant (chemo)radiation) [40], whereas Grønhøj et al. described an increased chance of delay for patients treated with (chemo)radiation [38].

HPV negative patients had increased TTI in two studies [38,40]. However, four other studies revealed no association between HPV status and delay [37,39,42,43].

Larynx

In laryngeal SCC, significant findings correlating with delay were race, with increased risk for African-American patients (HR: 1.44, CI: 1.32–1.56 [44]), Hispanic patients (HR 1.83, CI 1.43–2.33 [44]) and decreased risk for white patients compared to non-white patients (HR: 0.61, CI: 0.55–0.66, in a non-surgical cohort only [45]) and facility type (increased risk of delay in academic centres, OR 1.47 [44,45]). Insurance type (Medicaid/not insured) was associated with increased risk of delay [44,45]. Tumour stage showed conflicting effects on delay: in surgical patients, increasing T-stage resulted in decreased risk of delay, while the opposite was true for patients treated with initial radiotherapy [45]. Gender and socio-economic status were not associated with delay [45–47].

Hypopharynx

Only one report exists concerning determinants of delay for patients with hypopharyngeal carcinomas (n = 3850) [48].

Nonwhite race, insurance type (Medicaid, HR: 1.43, 95%CI: 1.07–1.9, p = 0.015), low T stage, N2 stage (HR: 1.31, 95%CI: 1.04–1.64, p = 0.021) and transition in care (HR: 2.14, 95%CI: 1.77–2.57, p < 0.001) were independently associated with prolonged time-to-treatment initiation. Sex, age, facility type and comorbidities were not associated with delay.

Effect of delay – overall survival

Four common sites

In six out of nine studies, delay resulted in decreased overall survival [6–8,23,28,49]. Notably, this association was mostly seen in the group with the longest TTI, the shortest significant delay being 45 days and the longest 90 days (Table 3). On the other hand, three studies showed no association between waiting time and survival [18,24,50].

Oral cavity

Three studies concerning the oral cavity reported that delay was a predictor of decreased survival [31,35,51]. Specifically, Liao et al. used TTI <30 days as reference and groups 31–60 days (HR 1.10, CI: 1.03–1.18), 61–91 days (HR 1.26, CI: 1.08–1.46) and more than 91 days (HR 1.26, CI:1.12–1.41) were all significantly associated with increased risk of death [35]. Only Fujiwara et al. found no association between delay and survival [32].

Oropharynx

The majority of studies in the OPC showed no association between delay and overall survival [37–40,42]. Sharma et al. on the other hand, found an association between delay and decrease in survival (OR 1.12, CI: 1.03–1.20) [41]. Grønhøj et al. specifically investigated HPV status, reporting no association between delay and survival in the HPV-positive patients, whereas a delay of >60 days led to a decreased survival rate in the HPV-negative patients (HR 1.60, CI: 1.04–2.45) [38].

Larynx

TTI of 46–73 days and more than 73 days TTI were associated with decreased survival according to Kompelli et al. (HR 1.26, CI: 1.18–1.35 and HR 1.09, CI: 1.04–1.15 respectively) [44]. Morse et al. also reported decreased survival in the non-surgical group (HR 1.08, CI: 1.02–1.14); however in the surgical group, no association between delay and survival was found [45].

Hypopharynx

Prolonged time-to-treatment interval (≥54 days) was not associated with decreased overall survival (HR: 0.92, 95%CI: 0.82–1.03, p = 0.150), compared to patients treated ≤37 days [48].

Other effects

Recurrence risk

No significant relation was found between delay and recurrence risk in laryngeal carcinoma [52,53]. There was a significant difference in delay between the oral cavity groups with and without recurrence, demonstrating a mean TTI of 33.6 and 21.9 days, respectively [33]. In OPC patients, a TTI >31 days resulted in a significantly higher risk of distant progression (HR 4.16, CI: 0.60–2.44) [42].

Studies reporting recurrence in the four most common sites of HNC showed conflicting results. Liao et al. found that delay was related to increased risk of recurrence (OR 1.77, CI: 1.07–2.9) and according to Tumati et al. delay led to increased risk of distant metastasis (HR 2.51, CI: 1.09–5.78) [7,25]. However, two other studies reported no relation between delay and recurrence [18,21].

Contradictory results were found in disease-free and disease-specific survival. Delay was associated with both increased disease-free and disease-specific survival, according to Van Harten et al. (HR 0.82, CI: 0.70–0.95 and HR 0.84, CI 0.70–0.92, respectively) [26]. In contrast, three other studies found no association between delay and disease-free survival [18,38,42] and Tumati et al. reported no relation between cause-specific mortality and delay [25].

Interventional approaches

Four of the included studies described interventions to decrease delay in TTI/CPI [54–57]. All involved implementation of a multidisciplinary clinic; the exact composition varied from including a care navigator or a dietician in the team to plan all visits in one day and use fixed timeslots for additional investigations. In all reports, the interventions were effective in decreasing waiting time. Only Light et al. assessed differences in survival, finding no significant differences in overall survival and increased disease-specific survival rates for the intervention group [54].

Discussion

The aim of this systematic review was to provide tools to increase timely treatment initiation for HNC patients by describing which determinants are associated with delay and to assess the effect of delay on outcome measures.

Factors associated with increased time-to-treatment are treatment with radiotherapy, non-Caucasian race, Medicaid or no insurance and treatment at academic facilities. Furthermore, an association between prolonged time intervals and decreased survival was demonstrated. Unfortunately, due to the diversity of the definitions, variables, and outcome measures in the published studies, it was not possible to perform a pooled analysis.

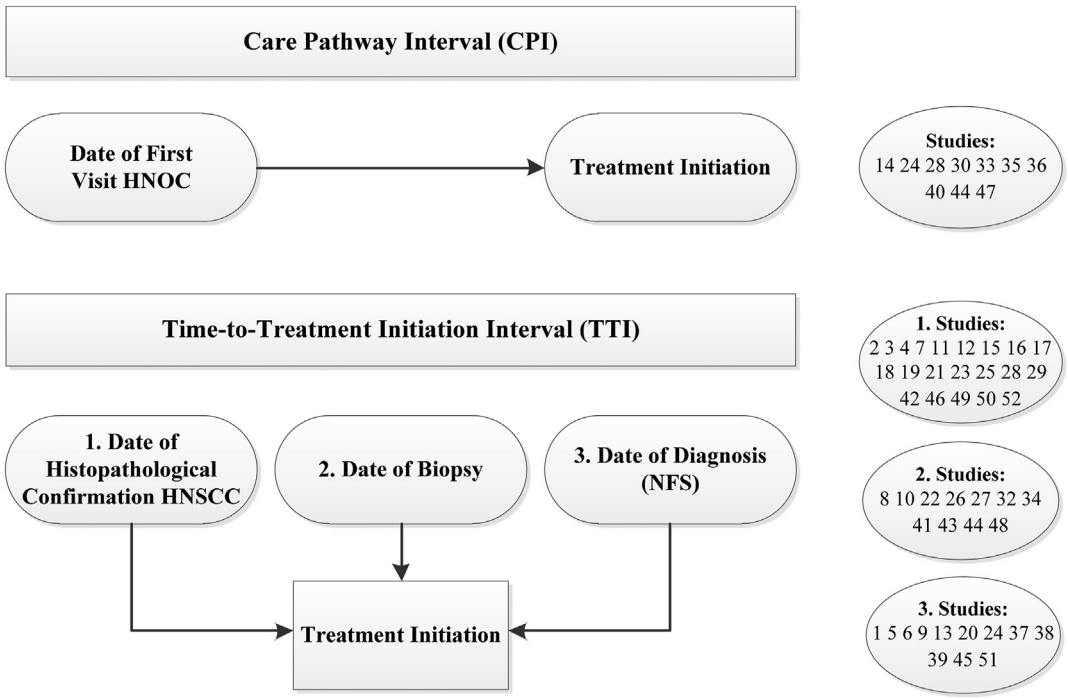
Reporting time-to-treatment initiation

Although 57 studies reporting on one or both of the study aims were examined, the variety in cut-off values and definitions of delay were considerable and descriptions of the organization of care pathways are lacking. Consequently, a meta-analysis on the 52 studies remaining for quantitative analysis did not prove possible.

It is important to establish a clear, uniform way of describing the time intervals before treatment initiation, especially since this time frame can be used as a quality indicator in assessing value-based healthcare. Examples of reports demonstrating quality analysis and reporting are Chiou et al. [31] and Van Harten et al. [26]: both reports use a clear definition of the time interval studied (the latter including an overview of the care pathway) and use rigorous statistics to identify independent factors associated with delay. Time intervals could then be compared (inter)nationally and over time. An earlier suggested uniform way of reporting time interval is the Aarhus model of Weller et al. [58]. This statement provides recommendations for uniform definitions and recognizes the importance of early diagnosis in improving outcomes of cancer patients. This is a general guideline, however, more detailed descriptions of the in-hospital care pathway (such as distinguishing between CPI and TTI) are needed.

Both CPI and TTI are interesting and highly relevant time intervals to study, and both provide insight in the organization of oncological care. Both intervals inherit limitations in interpretation as well; for TTI a delay following inconclusive biopsies might be overlooked, whereas CPI may not adequately reflect the (sometimes time-consuming) diagnostic procedures performed before patients were referred to a HNOC. To properly compare waiting time internationally, reporting both CPI and TTI seems beneficial.

The term “delay” is ambiguous: a reasonable amount of time is necessary to perform diagnostic procedures and discuss a



HNOC: head and neck oncology center. HNSCC: head and neck squamous cell carcinoma. NFS: not further specified.

Fig. 2. Definitions of delay reported in included studies.
HNOC: head and neck oncology center. HNSCC: head and neck squamous cell carcinoma. NFS: not further specified.

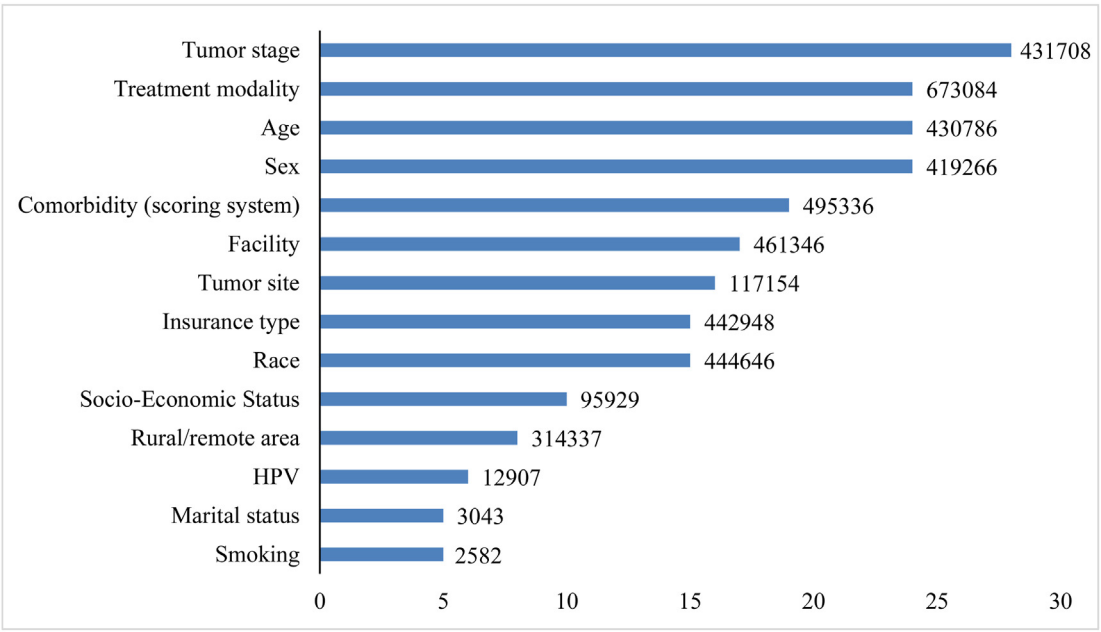


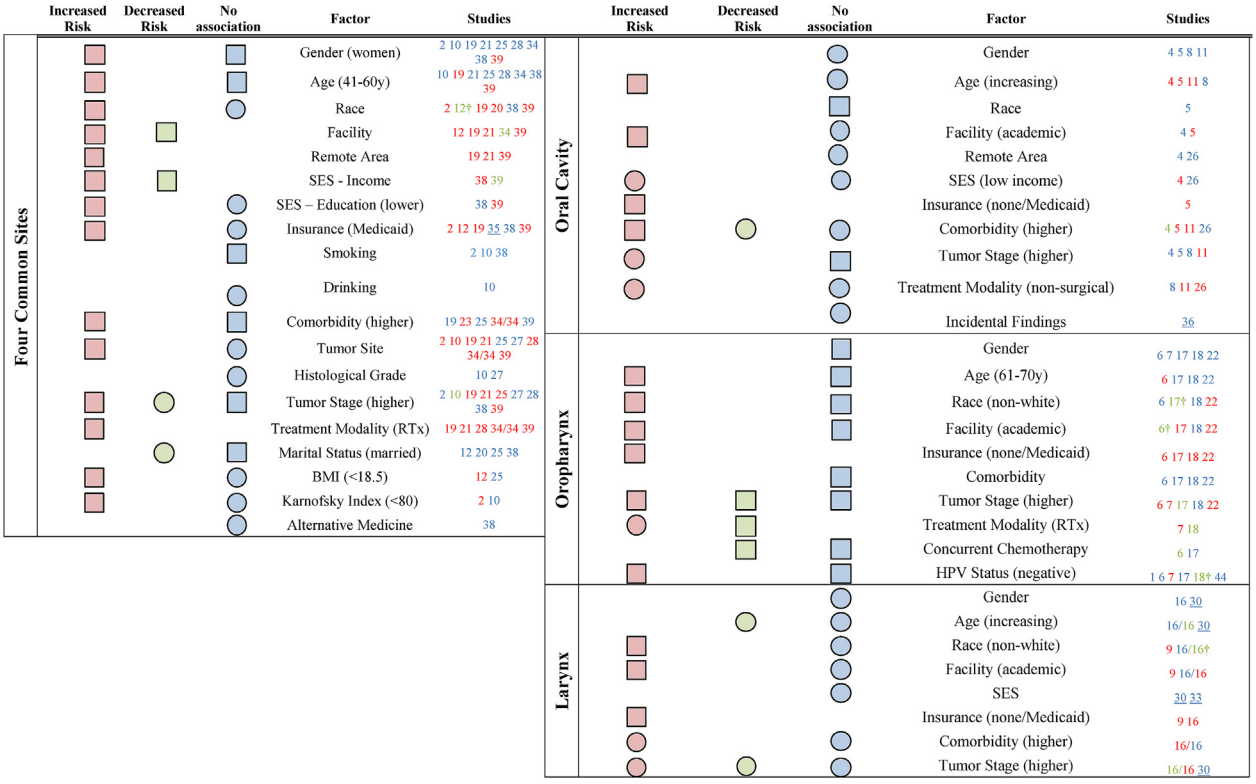
Fig. 3. Number of studies and total combined sample size assessing determinants of delay.

(multidisciplinary) final treatment plan. Rushing into treatment might result in increased morbidity. The term "prolonged time-to-treatment", with a clear definition, can be more appropriate.

Based on NOS-scale, the overall quality of the included cohort studies was average to good. RCTs would be the study type delivering the highest level of evidence. However, it is impossible ethically to allocate patients to "delay" and "non-delay groups". Therefore, determinants and the effect of delay and subsequent advice on ultimate cut-off(s) still must be ascertained from observational studies.

Two other reviews recently addressed delay in HNC [14,15]. Both focus on the effect of delay on outcome rather than describing

Table 2
Determinants of delay for each site and the four main sites combined (oral cavity, oropharynx, hypopharynx, larynx).



determinants of delay. Moreover, the challenge lies in presenting the results in a clinically relevant fashion.

Effect of delay

Across other tumour types, a systematic review assessing surgically treated colon carcinoma patients reported no association between delay and survival [59], whereas another systematic review regarding the impact of time-to-treatment across all cancer types described an association between shorter time-to-treatment and favourable outcomes in melanomas, breast, colorectal, head and neck and testicular carcinomas [60]. In HNC, treatment delay predicted tumour, nodal and stage group upstaging [6,42]. Tumour progression during waiting time may be the underlying mechanism for increased mortality rates in patients with increased TTI.

An association between delay and decreased overall survival was demonstrated in laryngeal cancer, oral cavity cancer and in the combination of the four common sites, although there are also studies that did not find this relationship [18,24,32,50]. Particularly in OPC, the majority of the studies did not support this association. A possible explanation could be the heterogeneity of the aetiology in OPC and consequently different prognosis of HPV-positive versus HPV-negative OPC [61]. This may also be due to the fact that in the case of OPC, a higher proportion of patients are treated with primary (chemo)radiotherapy and not with upfront surgery. It seems that in the case of primary irradiation of macroscopic tumours, the outcome depends not only on the duration of waiting for treatment, but also on tumour cell kinetics, their intrinsic radiosensitivity and other radiobiological characteristics, which can vary significantly between individual tumours. On the other hand, these do not affect tumours primarily treated with surgery [62].

The association of delay with OS is most readily appreciated with longer delays (45 days or more); the longer the delay, the higher the hazard ratio for decreased survival (Table 3). Or to put it another way: prolonging the delay increases the likelihood of its impact on patient survival.

Based on the reported results of this review, consensus on an optimal cut-off is not supported by evidence. However, the effect of delay on decreased survival seems to become of importance after approximately 42 days (four common sites combined), 30 days (oral cavity) and 46 days (larynx). Evidence of a clear cut-off is of substantial clinical interest; furthermore, it would be helpful to provide tumour-site specific guidelines and contribute to a norm on value-based health care.

Apart from the impact of delay on overall survival, more extensive treatment as a result of tumour progression during waiting time might also lead to increased treatment-related morbidity and costs. Studies investigating this hypothesis are lacking.

Determinants of delay

In this review, essentially two types of studies emerge. Studies based on national cancer registries, provide a large sample size but relatively few, more standardized variables. However, one must be aware of limitations inherent in the large cancer registry data, such as unmeasured confounding. Furthermore, data provided by this type of registries usually allow for multiple variables to be associated with the outcome of interest, with possible multicollinearity among covariates [63]. Their findings should be interpreted as such. There are also small cohort studies based on hospital registries, reporting on a limited population with possible selection bias, but with more detailed information.

Rarely investigated determinants of delay are risk factors (such

Table 3
Effect of delay on overall survival for each site and the four main sites combined (oral cavity, oropharynx, hypopharynx, larynx).

	Increased survival	Decreased survival	No association	Study	Groups	Significant effects
Four Common Sites			■	Caudell (2011)[18]	≤34, >34	
		■		Liao (2019)[7]	≤60, >60	HR 1.69, CI: 1.32-2.18
		■	■	Murphy (2016)[22]	<30, 31-60, 61-90, >91	HR 1.13, CI: 1.08-1.19; HR 1.29, CI: 1.21-1.38
		●		Naghavi (2016)[28]	≤45, >45	OS 66% vs. 69%
		■	■	Polesel (2017)[23]	<30, 31-44, 45-89, >90	HR 1.47, CI: 1.05-2.05
			●	Tham (2019)[24]	Quartiles	
		■	■	De Graaff (2019)[49]	0-27, 28-41, 42-60, >60	HR 0.548, CI: 0.367-0.819
			■	Ho (2018)[50]		
		■	■	Xiao (2018)[6]	0-6 (7-day groups continued), >70	HR 1.11, CI: 1.01-1.21
Oral Cavity		●		Chiou (2016)[31]	<21, >21	Log rank 0.037
			■	Fujiwara (2017)[32]	Quartiles	
		■		Liao (2017)[35]	<30, 31-60, 61-90, >90	HR 1.10, CI: 1.03-1.18 ; HR 1.26, CI: 1.08-1.46 ; HR 1.26, CI:1.12-1.41
		■		Tsai (2017)[36]	<30, 30-120, >120	HR 1.18, CI: 1.11-1.25, HR 1.32, CI:1.19-1.47
Oropharynx			■	Amsbaugh (2018)[42]		
			■	Goel (2019)[37]	HPV+ HPV-	
		■	▪	Grønhøj (2018)[38]	HPV+ <30, 31-60, >60 HPV- <30, 31-60, >60	HR 1.60, CI:1.04-2.45
			■	Morse (2018) (2)[39]	HPV+ Quartiles HPV- Quartiles	
			■	Morse (2018) (3)[40]	HPV+ Quartiles HPV- Quartiles	
		■		Sharma (2016)[41]	<30, >30	OR 1.12, CI: 1.03-1.20
Laryn		■		Kompelli (2019)[44]	<46, 46-73, >73	HR 1.09, CI: 1.04-1.15; HR 1.26, CI: 1.18-1.35
		■	▪	Morse (2018) (1)[45]	Surgical <28, >44 Non-surgical <33, >47	HR 1.08, CI: 1.02-1.14

as smoking, use of alcohol), functional status (social status, cognitive qualities) and number of diagnostic investigations. Unfortunately, many national cancer registries do not regularly include these variables.

In general, gender is consistently not associated with delay. Variables consistently associated with delay are insurance type (Medicaid/not insured), race (non-Caucasian), care at academic facilities and primary radiotherapy. Insurance type, care at academic facilities (compared to mostly (comprehensive) community centres) and race can partly be explained by the fact that these studies were performed in the USA. In European health care systems (where most/all patients are insured and most reports are originating from academic facilities), the association between insurance or race and delay is not reported. Due to this majority of studies performed in the USA (31/52), careful interpretation of these findings is needed. Future studies representing European and Asian patients and care systems should be performed to provide a more global view of determinants of delay.

Radiotherapy patients may require longer treatment planning due to pre-treatment interventions (e.g.: preparing a patient-specific mask and radiation planning, pre-treatment dental assessment and extractions). The limited capacity for treatment with radiotherapy in some countries can also significantly contribute to delay in starting radiotherapy [64,65].

The presence and severity of comorbidities and the effect of tumour stage are conflicting. Some facilities may treat patient with severe comorbidities or high tumour stage with priority, while other facilities report longer time-to-treatment in these patients, possibly as a result of more extensive additional investigations and multidisciplinary board discussions on which treatment is suited. A bias in reporting the results for patients with substantial comorbidity is likely; such patients may not receive standard treatment, and are therefore not included in reports (many studies only include patients with curative treatment intention).

Strengths and limitations

Using the validated PRISMA methodology for systematic reviews, a comprehensive overview of clinically relevant themes was provided. This resulted in a novel, site-specific approach.

However, the existing literature is heterogeneous, using varying definitions of time intervals and encompassing a wide variety in study populations, with very different sets of registered characteristics and, thus, available data. As a result, a meta-analysis could not be performed, limiting robustness of the data. For the same reasons, separate analyses of primary irradiated and surgically treated patients as well as different cancer-specific outcomes were not possible. Reports describing the effect of prolonged time-to-treatment initiation on recurrence and tumour upstaging were scarce and the effect on quality of life or toxicity were not reported at all.

Clinical implications and suggestions for further research

Intervention studies are needed, describing clear changes in the care pathway and the effect on time intervals. These should investigate tools and protocols to minimize waiting times. A recent intervention study demonstrated the effect of implementation of a well-described fast-track integrated care program: it produced improvement in both survival rates and patient satisfaction, at similar costs [66].

Reports on the effect of diagnostic investigations and incidental findings during diagnostic evaluation on delay are scarce, as are reports of subgroup analyses (such as low tumour stage vs. higher tumour stage and surgical vs. non-surgical cohorts). This information could contribute to better assess the risk of delay based on specific patient-, tumour- and hospital characteristics for an individual patient faced with the diagnosis head and neck cancer.

Race (non-Caucasian), facility type (academic), type of insurance

(Medicaid/none) and radiotherapy as primary treatment were associated with delay in the four common sites combined. The care trajectory in patients receiving radiotherapy should be critically reviewed and improved protocols may be needed to reduce the time of preparing patients for radiation therapy. Where relevant, the gap between available and required radiotherapy capacities needs to be filled. Studies to define an optimal cut-off are needed, using time as continuous variable, to provide evidence-based and possibly tumour-site specific standards.

The organization of care in a (regional) network, with efficient communication and collaboration between general practitioners, secondary, and tertiary referral centres can reduce waiting times [11]. Both CPI and TTI are interesting time intervals to study. They can function as readily measured quality indicators for good clinical practice: striving to minimize delays should improve outcomes.

The effect of prolonged waiting time for HNC patients is prominently associated with decreased survival. The effects on other, also important, outcomes (e.g. quality of life, costs) are underreported. Based on existing literature, initial radiotherapy treatment, treatment in academic facilities, and non-Caucasian patients are independent factors associated with increased waiting time. In reporting delay, a uniform definition of the time interval studies is crucial. Based on this review, both CPI and TTI are interesting time intervals to study. The first step to improve outcome in HNC patients, is to improve care pathways according to these findings.

CRediT authorship contribution statement

Rosanne C. Schoonbeek: Conceptualization, Methodology, Data curation, Writing – original draft. **Julia Zwertbroek:** Data curation, Visualization. **Boudewijn E.C. Plaat:** Conceptualization, Writing – review & editing. **Robert P. Takes:** Writing – review & editing. **John A. Ridge:** Writing – review & editing. **Primož Strojan:** Writing – review & editing. **Alfio Ferlito:** Writing – review & editing. **Boukje A.C. van Dijk:** Methodology, Writing – review & editing. **György B. Halmos:** Conceptualization, Writing – review & editing, Supervision.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.02.029.

Declaration of interests

None.

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References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.
2 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359–86.
3 Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. Nat Rev Cancer 2011;11(1):9–22.
4 Dejaco D, Steinbichler T, Schartinger VH, Fischer N, Anegg M, Dudas J, et al. Specific growth rates calculated from CTs in patients with head and neck squamous cell carcinoma: a retrospective study performed in Austria. BMJ Open 2019;9(2):e025359.
5 Jensen AR, Nellemann HM, Overgaard J. Tumor progression in waiting time for radiotherapy in head and neck cancer. Radiother Oncol 2007;84(1):5–10.
6 Xiao R, Ward MC, Yang K, Adelstein DJ, Koyfman SA, Prendes BL, 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):1400–14.
7 Liao DZ, Schlecht NF, Rosenblatt G, Kinkhabwala CM, Leonard JA, Ference RS, 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):1001–9.
8 Murphy CT, Galloway TJ, Handorf EA, Egleston BL, Wang LS, Mehra R, 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):169–78.
9 Du E, Mazul AL, Farquhar D, Brennan P, Anantharaman D, Abedi-Ardekani B, et al. Long-term Survival in Head and Neck Cancer: Impact of Site, Stage, Smoking, and Human Papillomavirus Status. Laryngoscope 2019;129(11):2506–13.
10 Bras L, Driessen D, de Vries J, Festen S, van der Laan B, van Leeuwen BL, et al. Patients with head and neck cancer: Are they frailer than patients with other solid malignancies? Eur J Cancer Care (Engl) 2020;29(1):e13170.
11 Takes RP, Halmos GB, Ridge JA, Bossi P, Merkx MAW, Rinaldo A, et al. Value and Quality of Care in Head and Neck Oncology. Curr Oncol Rep 2020;22(9):92. https://doi.org/10.1007/s11912-020-00952-5.
12 Roman BR, Awad MI, Patel SG. Defining value-driven care in head and neck oncology. Curr Oncol Rep 2015;17(1):424.
13 Tsevat J, Moriates C. Value-Based Health Care Meets Cost-Effectiveness Analysis. Ann Intern Med 2018;169(5):329–32.
14 Graboyes EM, Kompelli AR, Neskey DM, Brennan E, Nguyen S, Sterba KR, et al. Association of Treatment Delays With Survival for Patients With Head and Neck Cancer: A Systematic Review. JAMA Otolaryngol Head Neck Surg 2019;145(2):166–77.
15 Schutte HW, Heutink F, Wellenstein DJ, van den Broek GB, van den Hoogen FJA, Marres HAM, et al. Impact of Time to Diagnosis and Treatment in Head and Neck Cancer: A Systematic Review. Otolaryngol Head Neck Surg 2020;162(4):446–57.
16 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj 2009;339:b2535.
17 Wells G, S.B., O'Connell D, et al. The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in metaanalyses. Ottawa, Canada: Department of Epidemiology and Community Medicine, University of Ottawa. Available trough: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, assessed at March 17, 2020.
18 Caudell JJ, Locher JL, Bonner JA. Diagnosis-to-Treatment Interval and Control of Locoregionally Advanced Head and Neck Cancer. Archives of Otolaryngology-Head & Neck Surgery 2011;137(3):282–5.
19 Guizard AV, Dejardin O, Launay L, Bara S, Lapotre-Ledoux B, Babin E, 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):3951–8.
20 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 and Neck-Journal for the Sciences and Specialties of the Head and Neck 2008;30(4):446–54.
21 Leon X, de Vega M, Orus C, Moran J, Verges 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):277–81.
22 Murphy CT, Galloway TJ, orf EA, Egleston BL, Wang LS, Mehra R, 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):169–78.
23 Polesel J, Furlan C, Birri S, Giacomarra V, Vaccher E, Gr, et al. The impact of time to treatment initiation on survival from head and neck cancer in north-eastern Italy. Oral Oncol 2017;67:175–82.
24 Tham T, Leung E, Khaymovich J, Mitha S, Olson C, Wotman M, et al. Evaluation of Time to Surgery and Its Effect on Prognosis in Head and Neck Cancer. Oncol Res Treat 2019;42(7):387–95.
25 Tumati V, Hoang L, Sumer BD, Truelson JM, Myers LL, Khan S, et al. Association between treatment delays and oncologic outcome in patients treated with surgery and radiotherapy for head and neck cancer. Head Neck 2019;41(2):315–21.

26 van Harten MC, de Ridder M, Hamming-Vrieze 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):282–90.
27 Murphy CT, Galloway TJ, orf EA, Wang L, Mehra R, Flieder DB, et al. Increasing time to treatment initiation for head and neck cancer: an analysis of the National Cancer Database. Cancer 2015;121(8):1204–13.
28 Naghavi AO, Echevarria MI, Strom TJ, Abuodeh YA, Ahmed KA, Venkat PS, et al. Treatment delays, race, and outcomes in head and neck cancer. Cancer Epidemiol 2016;45:18–25.
29 Stordeur S, Schillemans V, Savoye I, Vanschoenbeek K, Leroy R, Macq G, et al. Comorbidity in head and neck cancer: Is it associated with therapeutic delay, post-treatment mortality and survival in a population-based study? Oral Oncol 2020;102:104561.
30 Jin MC, Harris JP, Sabolch AN, Gensheimer M, Le QT, Beadle BM, et al. Proton radiotherapy and treatment delay in head and neck squamous cell carcinoma. Laryngoscope 2019. https://doi.org/10.1002/lary.28458.
31 Chiou SJ, Lin W, Hsieh CJ. Assessment of duration until initial treatment and its determining factors among newly diagnosed oral cancer patients: A population-based retrospective cohort study. Medicine (Baltimore) 2016;95(50):e5632.
32 Fujiwara RJ, Judson BL, Yarbrough WG, Husain Z, Mehra S. Treatment delays in oral cavity squamous cell carcinoma and association with survival. Head Neck 2017;39(4):639–46.
33 Hemmi T, Yusa K, Kasuya S, Yamanouchi H, Ishikawa S, Kobayashi T, et al. Influence of interval between biopsy and surgery on prognosis of patients with early-stage oral squamous cell carcinoma: A preliminary study. Journal of Oral and Maxillofacial Surgery Medicine and Pathology 2019;31(3):159–62.
34 Jaspers GW, Witjes MJ, Groen HJ, Groen H, Rodiger LA, Roodenburg JL. Strategies for patients with newly diagnosed oral squamous cell carcinoma and a positive chest CT. A cohort study on the effects on treatment planning and incidence. Eur J Surg Oncol 2011;37(3):272–7.
35 Liao CT, Chen HN, Wen YW, Lee SR, Ng SH, Liu TW, et al. Association between the diagnosis-to-treatment interval and overall survival in Taiwanese patients with oral cavity squamous cell carcinoma. Eur J Cancer 2017;72:226–34.
36 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.
37 Goel AN, Frangos M, Raghavan G, Sangar S, Lazaro S, Wang MB, et al. Survival impact of treatment delays in surgically managed oropharyngeal cancer and the role of human papillomavirus status. Head Neck 2019;41(6):1756–69.
38 Gronhoj C, Jensen D, Dehlendorff C, Norregaard C, Andersen E, Specht L, 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):375–81.
39 Morse E, Judson B, Husain Z, Burtness B, Yarbrough W, Sasaki C, et al. National treatment times in oropharyngeal cancer treated with primary radiation or chemoradiation. Oral Oncol 2018;82:122–30.
40 Morse E, Judson B, Husain Z, Burtness B, Yarbrough WG, Sasaki C, et al. Treatment Delays in Primarily Resected Oropharyngeal Squamous Cell Carcinoma: National Benchmarks and Survival Associations. Otolaryngol Head Neck Surg 2018;159(6):987–97.
41 Sharma S, Bekelman J, Lin A, Lukens JN, Roman BR, Mitra N, et al. Clinical impact of prolonged diagnosis to treatment interval (DTI) among patients with oropharyngeal squamous cell carcinoma. Oral Oncol 2016;56:17–24.
42 Amsbaugh MJ, Yusuf M, Cash E, Silverman C, Potts K, Dunlap N. Effect of time to simulation and treatment for patients with oropharyngeal cancer receiving definitive radiotherapy in the era of risk stratification using smoking and human papillomavirus status. Head Neck 2018;40(4):687–95.
43 Raman A, Sen N, Ritz E, Fidler MJ, Revenaugh P, Stenson K, et al. Heterogeneity in the clinical presentation, diagnosis, and treatment initiation of p16-positive oropharyngeal cancer. Am J Otolaryngol 2019;40(5):626–30.
44 Kompelli AR, Li H, Neskey DM. Impact of Delay in Treatment Initiation on Overall Survival in Laryngeal Cancers. Otolaryngol Head Neck Surg 2019;160(4):651–7.
45 Morse E, Fujiwara RJT, Judson B, Mehra S. Treatment delays in laryngeal squamous cell carcinoma: A national cancer database analysis. Laryngoscope 2018;128(12):2751–8.
46 Amar A, Chedid HM, Franzi SA, Rapoport A. Diagnostic and therapeutic delay in patients with larynx cancer at a reference public hospital. Braz J Otorhinolaryngol 2010;76(6):700–3.
47 Groome PA, Schulze KM, Keller S, Mackillop WJ, O'Sullivan B, Irish JC, et al. Explaining socioeconomic status effects in laryngeal cancer. Clin Oncol (R Coll Radiol) 2006;18(4):283–92.
48 Morse E, Berson E, Fujiwara R, Judson B, Mehra S. Hypopharyngeal Cancer Treatment Delays: Benchmarks and Survival Association. Otolaryngol Head Neck Surg 2019;160(2):267–76.
49 DeGraaff LH, Platek AJ, Iovoli AJ, Wooten KE, Arshad H, Gupta V, et al. The effect of time between diagnosis and initiation of treatment on outcomes in patients with head and neck squamous cell carcinoma. Oral Oncol 2019;96:148–52.
50 Ho AS, Kim S, Tighiouart M, Mita A, Scher KS, Epstein JB, et al. Quantitative survival impact of composite treatment delays in head and neck cancer. Cancer 2018;124(15):3154–62.
51 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).
52 Barton MB, Morgan G, Smee R, Tiver KW, Hamilton C, Gebski V. Does waiting time affect the outcome of larynx cancer treated by radiotherapy? Radiother Oncol 1997;44(2):137–41.
53 Brouha XD, Op De Coul B, Terhaard CH, Hordijk GJ. Does waiting time for radiotherapy affect local control of T1N0M0 glottic laryngeal carcinoma? Clin Otolaryngol Allied Sci 2000;25(3):215–8.
54 Light T, Rassi EE, Maggiore RJ, Holl J, Reed J, et al. Improving outcomes in veterans with oropharyngeal squamous cell carcinoma through implementation of a multidisciplinary clinic. Head Neck 2017;39(6):1106–12.
55 Ouwens MM, Hermens RR, Hulscher MM, Merkx MA, van den Hoogen FJ, Grol RP, et al. Impact of an integrated care program for patients with head and neck cancer on the quality of care. Head Neck 2009;31(7):902–10.
56 Patil RD, Meinzen-Derr JK, Hendricks BL, Patil YJ. Improving access and timeliness of care for veterans with head and neck squamous cell carcinoma: A multidisciplinary team's approach. Laryngoscope 2016;126(3):627–31.
57 van Huizen LS, Dijkstra PU, van der Laan B, Reintsema H, Ahaus KTB, Bijl HP, et al. 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 Serv Res 2018;18(1):820.
58 Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, et al. The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. Br J Cancer 2012;106(7):1262–7.
59 Hangaard Hansen C, Gögenur M, Tvilling Madsen M, Gögenur I. The effect of time from diagnosis to surgery on oncological outcomes in patients undergoing surgery for colon cancer: A systematic review. Eur J Surg Oncol 2018;44(10):1479–85.
60 Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. Br J Cancer 2015;112:S92–107. Suppl 1(Suppl 1).
61 Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363(1):24–35.
62 Žumer B, Pohar Perme M, Jereb S, Strojan P. Impact of delays in radiotherapy of head and neck cancer on outcome. Radiat Oncol 2020;15(1):202.
63 Blanchard P, Garden AS. Looking Beyond the Numbers: Highlighting the Challenges of Population-Based Studies in Cancer Research. J Clin Oncol 2016;34(19):2317–8.
64 Grau C, Defourny N, Malicki J, Dunscombe P, Borras JM, Coffey M, et al. Radiotherapy equipment and departments in the European countries: final results from the ESTRO-HERO survey. Radiother Oncol 2014;112(2):155–64.
65 Rosenblatt E, Izewska J, Anacak Y, Pynda Y, Scalliet P, Boniol M, et al. Radiotherapy capacity in European countries: an analysis of the Directory of Radiotherapy Centres (DIRAC) database. Lancet Oncol 2013;14(2):e79–86.
66 Schutte HW, van den Broek GB, Steens SCA, Hermens R, Honings J, Marres HAM, et al. Impact of optimizing diagnostic workup and reducing the time to treatment in head and neck cancer. Cancer 2020;126(17):3982–90.
67 Chevalier C, Bertaut A, Quivrin M, Vulquin N, Des C es, et al. Impact of waiting time on nodal staging in head and neck squamous-cell carcinoma treated with radical intensity modulated radiotherapy. Clin Transl Radiat Oncol 2016;1:27–32.
68 Tan JY, Otty ZA, Vangaveti VN, Buttner P, Varma SC, Joshi AJ, et al. A prospective comparison of times to presentation and treatment of regional and remote head and neck patients in North Queensland, Australia. Intern Med J 2016;46(8):917–24.
69 van Harten MC, Hoebers FJ, Kross KW, van Werkhoven ED, van den Brekel MW, van Dijk BA. Determinants of treatment waiting times for head and neck cancer in the Netherlands and their relation to survival. Oral Oncol 2015;51(3):272–8.
70 Davis GE, Bryson CL, Yueh B, McDonell MB, Micek MA, Fihn SD. Treatment delay associated with alternative medicine use among veterans with head and neck cancer. Head Neck 2006;28(10):926–31.
71 Patel UA, Brennan TE. Disparities in head and neck cancer: assessing delay in treatment initiation. Laryngoscope 2012;122(8):1756–60.
72 Perlow HK, Ramey SJ, Silver B, Kwon D, Chinea FM, Samuels SE, et al. Assessment of Oropharyngeal and Laryngeal Cancer Treatment Delay in a Private and Safety Net Hospital System. Otolaryngol Head Neck Surg 2018;159(3):484–93.
73 Richardson PA, Kansara S, Chen GG, Sabichi A, Sikora AG, Parke RB, et al. Treatment Patterns in Veterans with Laryngeal and Oropharyngeal Cancer and Impact on Survival. Laryngoscope Investig Otolaryngol 2018;3(4):275–82.
74 Rogers SN, Pabla R, McSorley A, Lowe D, Brown JS, Vaughan ED. An assessment of deprivation as a factor in the delays in presentation, diagnosis and treatment in patients with oral and oropharyngeal squamous cell carcinoma. Oral Oncol 2007;43(7):648–55.
75 Lopez-Cedrun JL, Otero-Rico A, Vazquez-Mahia I, Seoane J, Garcia-Caballero L, Seoane-Romero JM, et al. Association between hospital interval and survival in patients with oral cancer: A waiting time paradox. PLoS One 2019;14(10):e0224067.
76 Carlsen AH, Eriksen JG, Godballe C, Johansen J, Sorensen JA, Bjorndal 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):259–64.
77 Itamura K, Kokot N, Sinha U, Swanson M. Association of insurance type with time course of care in head and neck cancer management. Laryngoscope 2019;130(11):E587–92.