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Published in:
Radiotherapy and Oncology

DOI:
10.1016/j.radonc.2024.110107

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2024

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Frank, M. H., van Dijk, B. A. C., Schoonbeek, R. C., Zindler, J., Devriese, L. A., van Es, R. J. J., Merkx, M. A. W., & de Bree, R. (2024). Differences in the association of time to treatment initiation and survival according to various head and neck cancer sites in a nationwide cohort. *Radiotherapy and Oncology*, *192*, Article 110107. https://doi.org/10.1016/j.radonc.2024.110107

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Radiotherapy and Oncology 192 (2024) 110107

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Differences in the association of time to treatment initiation and survival according to various head and neck cancer sites in a nationwide cohort

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ARTICLE INFO

Keywords:
Head and neck cancer
Delayed treatment
Cubic spline
Overall survival
Time to treatment

ABSTRACT

Objectives: To assess whether there are differences in the effects of time to treatment interval (TTI) on patient survival for head and neck cancer (HNC) sites in order to provide evidence that can support decision-making regarding prioritizing treatment.
Materials and methods: Patients in the Netherlands with a first primary HNC without distant metastasis between 2010 and 2014 were included for analysis (N = 10,486). TTI was defined as the time from pathologic diagnosis to the start of initial treatment. Overall survival (OS), cox regression analyses and cubic spline hazard models were calculated and visualized.
Results: Overall, the hazard of dying was higher (HR = 1.003; 95 % CI 1.001–1.005) with each additional day until treatment initiation. The pattern, as visualized in cubic spline graphs, differed by site the hazard increased more steeply with increasing TTI for oral cavity cancer. For oropharyngeal and laryngeal cancer, a slight increase commenced after a longer TTI than for oral cavity cancer, while there was hardly an increase in hazard with increasing TTI for hypopharyngeal cancer.
Conclusion: The relationship between longer TTI and decreased survival was confirmed, but slight variations in the pattern of the hazard of dying by TTI by tumour site were observed. These findings could support decisions on prioritizing treatment. However, other aspects such as extent of treatment and quality of life should be investigated further so this can also be included.

Introduction

The incidence of cancer and related mortality are increasing rapidly worldwide. The incidence was estimated at 14.1 million cases in 2012 and increased to over 19.3 million new cases in 2020, while cancer-related deaths increased from 8.2 million in 2012 to almost 10 million in 2018 [1]. Approximately 900,000 new head and neck cancers (HNC) are reported annually [1,2]. HNC is an umbrella term that encompasses mainly epithelial malignancies that arise in the oral cavity, pharynx and larynx. Almost all of these epithelial malignancies are squamous cell carcinomas (SCCs), for which the most important risk factors are tobacco and alcohol consumption [3], although HPV has now become the most relevant risk factor for oropharyngeal cancer [4,5]. In the Netherlands, just over 3,000 HNCs are diagnosed annually [6].

HNCs are most common in the oral cavity, larynx, oropharynx and hypopharynx. Of these, oropharyngeal malignancies have shown the greatest increase in recent years [7]. This has mainly been attributed to an increased incidence of Human Papilloma Virus (HPV) related malignancies [4,8,9]. Head and neck squamous cell carcinomas (HNSCC) are potentially fast-growing tumours in an anatomically and

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https://doi.org/10.1016/j.radonc.2024.110107
Received 18 September 2023; Received in revised form 16 January 2024; Accepted 17 January 2024
Available online 21 January 2024
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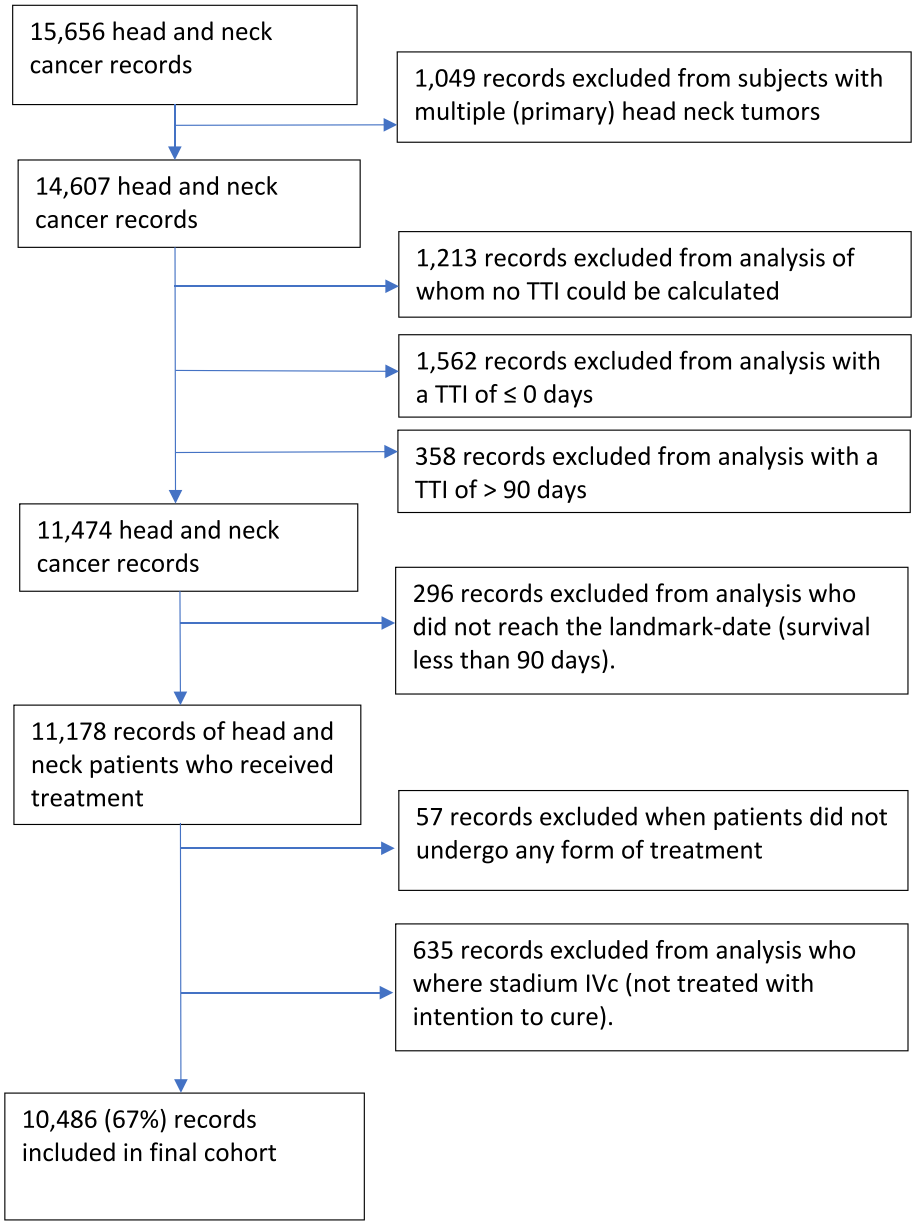

Fig. 1. Flowchart of study population.

functionally complex area [10]. Traditionally oral cavity and laryngeal cancers are diagnosed at an early stage in 58 % and 66 % respectively, whereas oro- and hypopharyngeal cancers were mainly diagnosed at an advanced stage in 74 % and 80 % respectively [11], which is a strong prognostic indicator [12]. However, because since 2017 staging includes HPV-status, oropharyngeal SCC is more often classified as early stage, which reflects the observed improved overall and disease-free survival for HPV-associated oropharyngeal cancers [4,13]. In the Netherlands, approximately 50 % [5,9] of oropharyngeal cancers are nowadays HPV related.

In the Netherlands all citizens are obliged to be insured for medical aid by law, and care for HNC patients is centralized in eight specialized centres and six preferred partner hospitals (head and neck oncology centres; HNOCs) that collaborate in the framework of the Dutch Head and Neck Society (NWHHT). In these HNOCs all new patients are consulted at their first visit by both a head and neck surgeon and radiation oncologist. Various medical federations have joined forces to optimize care for oncological patients. This has resulted in indicators recorded in a document edited by the Institution for Oncological Cooperation (SONCOS) [14]. According to these guidelines, the start of the therapy for new patients should ideally begin within 30 days after first consultation at an HNOC [14]. Although many studies have shown that waiting time is related to patient outcomes [15–24], differences between tumour sites and stages, are not always taken into consideration [25]. During the COVID-19 pandemic, while healthcare systems were struggling to use their resources as efficiently as possible, new dilemmas in hospital care arose around optimizing the usage of (scarce) resources. Which patients needed treatment and when, who could wait and – more importantly – who could not [26], and whether triaging would be necessary [27]. For HNCs, various protocols have been proposed on consensus-based algorithms for dealing with patients during the pandemic [26,28,29]. Mehanna et al gave recommendations for head and neck surgical oncology practice in a setting of severe resource constraints with a consensus-based advice [26]. Between the different sites of HNC, there may be differences in the effect of time to treatment initiation (TTI) on treatment outcomes, such as survival [26]. The aim of this study was to examine the association of TTI and survival (OS) by site.

Patients and methods

Patients in the Netherlands with a primary HNC (ICD-O-3 C00–C14 or C30–C32 [30]) diagnosed between 2010 and 2014 were included (N = 15,656) from the Netherlands Cancer Registry (NCR), managed by the Netherlands Comprehensive Cancer Organisation (IKNL). Patient demographics (sex, age and survival status), clinical factors (tumour site and stage), treatment details and relevant dates (date of diagnosis, date of first treatment and date of death) were extracted.

Patients were divided into groups according to tumour site: lip (C00.0–C00.2, C00.6, C00.9), oral cavity (ICD-O-3 C00.3–C00.5, C02.0–C05.0, C05.8–C05.9, C06.0–C06.9), oropharynx (C01.9, C05.1–C05.2, C09.0–C10.9), nasopharynx (C11.0–C11.9), nasal cavity, sinuses and middle ear (C30.0–C31.9), hypopharynx (C12.0–C13.9), larynx (C32.0–C32.9) and major salivary glands (C07.0–C08.9).

Tumour stage was defined according to the Union for International Cancer Control TNM, 7th edition [31]. The clinical stage was used. Stages I–II were defined as early-stage disease, and stages III–IVB were defined as advanced-stage disease. The date of diagnosis was considered the date of pathological confirmation of cancer. The start of treatment was defined as the date of surgery or the first day of (chemo) radiotherapy.

TTI was defined as the interval between histopathological diagnosis and treatment initiation. It was analysed as a continuous variable and as a dichotomous variable cut-off of at the median TTI. Survival time was defined as the number of days between the landmark date (date of histopathological diagnosis + 90 days) and the date of death or the date of censoring (date of emigration or date of record linkage if still alive). Vital status was obtained from the yearly linkage to the municipal registries.

Patients with multiple primary HNCs were included for their first HNC and excluded (N = 1,049; 6.7 %) for additional HNC's. Cases were included only if a TTI could be calculated (1,213 cases excluded; 8 %). In the TTI calculation, patients with a TTI of ≤0 days (N = 1,562; 10 %) or over 90 days (N = 358; 2 %) were additionally excluded. Patients with a TTI of 0 days were excluded because they likely had very small tumours that were completely surgically removed as part of the excisional biopsy. Patients with a TTI of over 90 days were excluded because this extreme delay in treatment was likely due to factors such as severe comorbidities or intercurrent disease.

To prevent guarantee-time bias, only patients who survived the first 90 days (landmark date) were included (all cases should have a comparable starting point for survival to offset differences in treatment duration and/or direct treatment side effects), leading to the exclusion of 296 (1.9 %) patients. Patients who did not undergo treatment for any reason were also excluded (N = 57; 0.4 %). Finally, 635 (4.1 %) stage IVC cases were excluded, as their treatment had no curative intention. Thus, 10,486 (67 %) patients were included in the analysis (Fig. 1).

Statistical analysis and outcome measures

Descriptive and survival data were analysed using Stata/SE 16.1. The analysis included Student's *t*-test, the two-samples Wilcoxon test and the chi-squared test of independence. Survival was calculated using survival analyses and displayed per tumour site by stage for the dichotomous TTI cut-off at the median TTI. After checking the proportional hazard assumption, Cox regression analysis was performed to assess the hazard of dying for TTI. Age, sex, stage and therapy were evaluated as potential confounders but turned out not to confound this association and thus a multivariable model was not constructed. Additionally, TTI was used as a continuous variable using a restricted cubic spline function with five knots [32]. The cubic spline was constructed with the reference point at the median TTI. Therefore, cubic spline graphs show the risk of dying relative to the risk at the median TTI. Two-sided p-values of < 0.05 were considered statistically significant.

Table 1
Patient characteristics and association of patient and tumour characterics with time to treatment (TTI) for patients with a first primary head and neck tumour in the Netherlands, 2010–2014 (N = 10,486).

Characteristics	Total number (%) by characteristic				TTI (days)	
	All	TTI 1–38 days	TTI > 38 days	p-value[a]	Median	p5-p95
All	10,486 (100)	5338 (51)	5148 (49)		38	16–70
Sex				0.394		
Male	7006 (67)	3567 (51)	3439 (49)		38	16–70
Female	3480 (33)	1772 (50)	1708 (50)		38	17–69
Age				0.013		
<40	220 (2)	134 (61)	86 (39)		35	14–67
40–49	760 (7)	401 (53)	359 (47)		37	16–69
50–59	2460 (23)	1231 (50)	1229 (50)		38	17–72
60–69	3731 (36)	1921 (51)	1810 (49)		38	16–70
≥70	3315 (32)	1651 (50)	1664 (50)		39	16–71
Tumor Site				<0.001		
Oral Cavity	3145 (30)	1656 (53)	1489 (47)		37	18–68
Oropharynx	2215 (21)	965 (44)	1250 (56)		41	18–72
Larynx	2721 (26)	1490 (55)	1231 (45)		36	15–70
Hypopharynx	718 (7)	376 (52)	342 (48)		37	16–69
Lip	548 (5)	317 (58)	231 (42)		35	13–69
Nasopharynx/ paranasal sinus/nasal cavity	723 (7)	319 (44)	404 (56)		40	19–72
Salivary glands	416 (4)	215 (52)	201 (48)		38	17–74
Stage				<0.001		
I	2925 (28)	1650 (56)	1275 (44)		36	15–68
II	2081 (20)	997 (48)	1084 (52)		40	17–70
III	1626 (16)	814 (50)	812 (50)		39	16–71
IVa	3352 (31)	1622 (48)	1730 (52)		39	18–72
IVb	453 (4)	232 (51)	221 (49)		38	15–70
IVc (*excluded*)	0	0	0			
NA	49 (0.5)	23 (47)	26 (53)			
Initial Therapy				<0.001		
Surgery	5261 (50)	2975 (57)	2286 (43)		36	15–68
Radiotherapy	4022 (38)	1728 (43)	2294 (57)		41	19–74
Systemic/ radiotherapy	1122 (11)	595 (53)	527 (47)		37	16–69

Abbreviations: HNSCC, Head and Neck Squamous Cell Carcinoma.
NA, not applicable (TNM staging not possible at the time).
a Chi-square test of independence.

Table 2
Univariable Cox regression analyses for HNSCC patients treated in The Netherlands (n = 10,486).

			HR (continuous per additional day of TTI)		HR (≤median vs > median)	Median
		N (%)	univariable	N > median (%)	univariable	
All		10,486	**1.003 (1.001–1.005)**	5,148	1.053 (0.992–1.118)	38
	Early stage	5,055 (48)	**1.004 (1.001–1.008)**	2,385 (47)	**1.115 (1.005–1.238)**	
	Advanced stage	5,431 (52)	1.001 (0.999–1.003)	2,763 (51)	0.952 (0.881–1.028)	
Oral Cavity		3,145	**1.010 (1.006–1.013)**	1548	**1.212 (1.086–1.352)**	37
	Early stage	1,855 (59)	**1.007 (1.001–1.012)**	843 (45)	**1.185 (1.003–1.400)**	
	Advanced stage	1,290 (41)	**1.007 (1.002–1.012)**	705 (55)	1.104 (0.950–1.281)	
Larynx		2,721	1.002 (0.999–1.006)	1327	1.026 (0.907–1.161)	36
	Early stage	1,609 (59)	1.004 (0.998–1.010)	815 (51)	1.102 (0.907–1.339)	
	Advanced stage	1,112 (41)	1.002 (0.998–1.007)	512 (46)	1.030 (0.874–1.213)	
Oropharynx		2,215	1.004 (1.000–1.008)	1,062	0.995 (0.873–1.133)	41
	Early stage	469 (21)	1.004 (0.994–1.014)	213 (45)	0.999 (0.734–1.359)	
	Advanced stage	1,746 (79)	1.002 (0.997–1.006)	849 (49)	0.967 (0.833–1.124)	
Hypopharynx		718	0.997 (0.991–1.003)	357	0.883 (0.730–1.067)	37
	Early stage	98 (14)	0.999 (0.982–1.018)	59 (60)	0.820 (0.458–1.470)	
	Advanced stage	620 (86)	0.997 (0.990–1.004)	298 (48)	0.943 (0.761–1.168)	

Results

Table 1 shows the characteristics of the study population and the median TTI per characteristic. The patients' median age was 64 (p5–p95: 46–83) years. Most tumours were found in the oral cavity (29 %) and larynx (25 %) and diagnosed at stage IV (31 %) or I (28 %). The median TTI was 38 days. Patients starting treatment with surgery had a median TTI of 36 days, while patients starting with radiotherapy had a median TTI of 41 days.

The five-year survival rate was 56 %. This rate equalled 57 % for the oral cavity, 62 % for the larynx, 52 % for the oropharynx and 42 % for the hypopharynx.

For the entire cohort a longer TTI was significantly associated with a higher risk of dying (HR: 1.003, 95 % CI: 1.001–1.005) on a continuous scale (Table 2), but not using the median 38-day cut-off (HR: 1.053, 95 % CI: 0.992–1.118) (Table 2). A TTI of 57 days or longer was associated with a significantly higher risk of dying than the median TTI of 38 days (HR: 1.10, 95 % CI: 1.01–1.20; Fig. 2a).

Stratified for stage the overall survival curves showed statistically significant worse survival for a TTI greater than the median TTI for early stage tumours ($p < 0.01$; Table 2). In Fig. 2, the bar graphs show the relative numbers of cases per stage for every 10-day TTI interval. The share of early-stage (I–II) tumours declined with a longer TTI (Fig. 2b and supplemental figure S1).

In the univariable Cox regression analysis in the oral cavity cancer group, the HR was 1.010 (95 % CI: 1.007–1.014) for each additional day of TTI. The risk of dying was 1.212 (95 % CI: 1.087–1.352) times higher when the median of TTI of 37 days was overdue (Table 2). The cubic spline (Fig. 3a) shows no significant association between TTI and risk of death up to 57 days but does show a significantly higher risk after 57 days (HR: 1.20, CI: 1.01–1.44) compared to the median of 37 days. Stratified for stage the survival analysis showed a significant association for TTI categorized according to the 37-day cut-off for early-stage disease only ($p < 0.01$). Again, the share of early-stage tumours declined over TTI (Fig. 3b and supplemental figure S2).

For laryngeal tumours, TTI had no significant effect on the hazard of dying (HR per additional day of TTI: 1.002; 95 % CI:0.999–1.006) (Table 2). The risk of dying was only non-significantly increased after a very long TTI when compared to the median TTI of 36 days (Fig. 4a). Likewise, no effect was observed when TTI was stratified by stage (Table 2). Most laryngeal malignancies included were advanced stage tumours (Fig. 4b and supplemental figure S3). The decline in share of early-stage tumours over time was less pronounced.

The hazard of dying for oropharyngeal cancer increased non-significantly with 1.004 (95 % CI 1.000–1.008) per additional day of TTI (Table 2). The cubic spline graph in Fig. 5a shows a noticeable dip in the midrange of 35 to 45 days (median 41 days). No difference in survival between a TTI up to the median TTI for either early-stage or advanced-stage tumours was observed. Almost all tumours were advanced-stage at diagnosis (Fig. 5b and supplemental figure S4).

For hypopharyngeal cancer the hazard of dying decreased non-significantly with each additional day of TTI (HR: 0.997; 95 % CI: 0.991–1.003) (Table 2). For hypopharyngeal tumours, the cubic spline graph in Fig. 6a shows a higher but decreasing trend in the risk of dying up to the median TTI of 37 days compared to the median of 37 days, after which it remained stable. TTI was not significantly associated with survival in either early- or advanced-stage tumours (Table 2). Only 21 % of these tumours were diagnosed at an early-stage (Fig. 6b). Interestingly, the proportion of early-stage tumours increased with increasing TTI (Fig. 6b and supplemental figure S5).

Discussion

As expected, in the overall HNC cohort, a longer TTI was associated with a higher risk of dying. This association was statistically significant for the overall group and the subgroup of oral cavity tumours. Stratified for stage, this was also statistically significant for early staged tumours overall and for oral cavity cancer and advanced-staged tumours in oral cavity group. For all other sites/stage groups per site no statistically significant association was found. The pattern of the hazard of dying over TTI (cubic spline) differed slightly by tumour site and stage.

For oral cavity tumours, the 5-year survival rate in this study (57 %) was comparable to the survival in similar cohorts (55–63 %) [33–36]. The increasing hazard of dying with a longer TTI might be explained by the reported fast tumour growth rate (3.1 ± 1.5 %) per day and a higher likelihood of distant metastasis with an increasing TTI [10,37]. In this study a negative impact of TTI on OS was found for oral cavity tumours, which is in line with Tomioka et al. [37]. In that study, only advanced-stage (bony invasion, distal positive lymph nodes and extra nodal extension) factors were associated with a decreased OS [37,38]. Dejaco

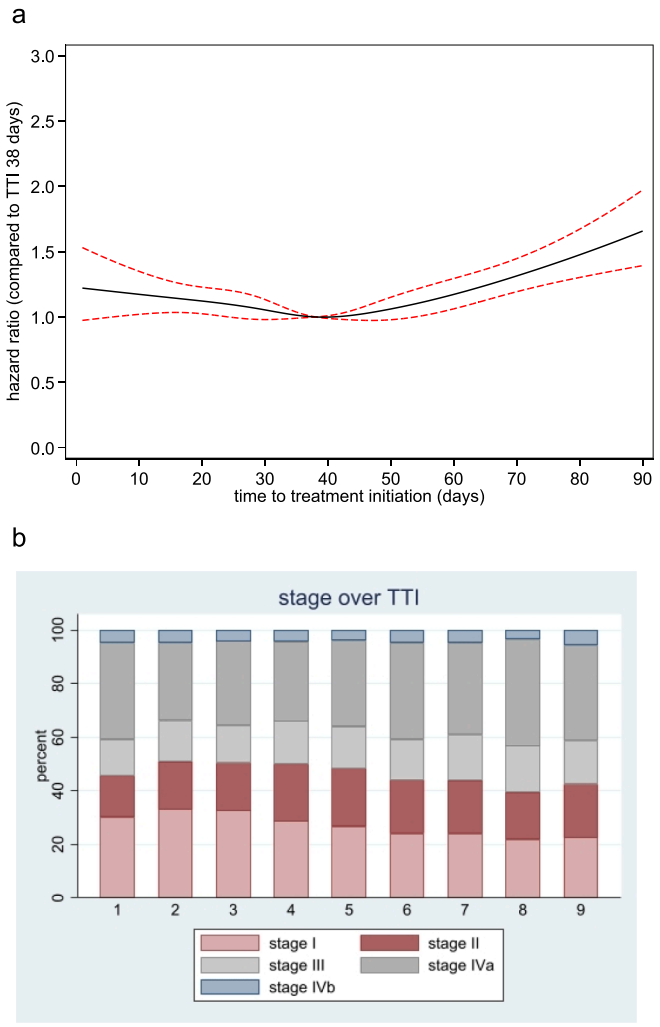

Fig. 2. Combined graphs for the entire cohort; a) the cubic spline demonstrating the course of the HR for dying over TTI (black) and corresponding 95 % CI and b) relative distribution of stages over TTI categories (1 = 1–10 days, 2 = 11–20 days, 3 = 21–30 days etc.).

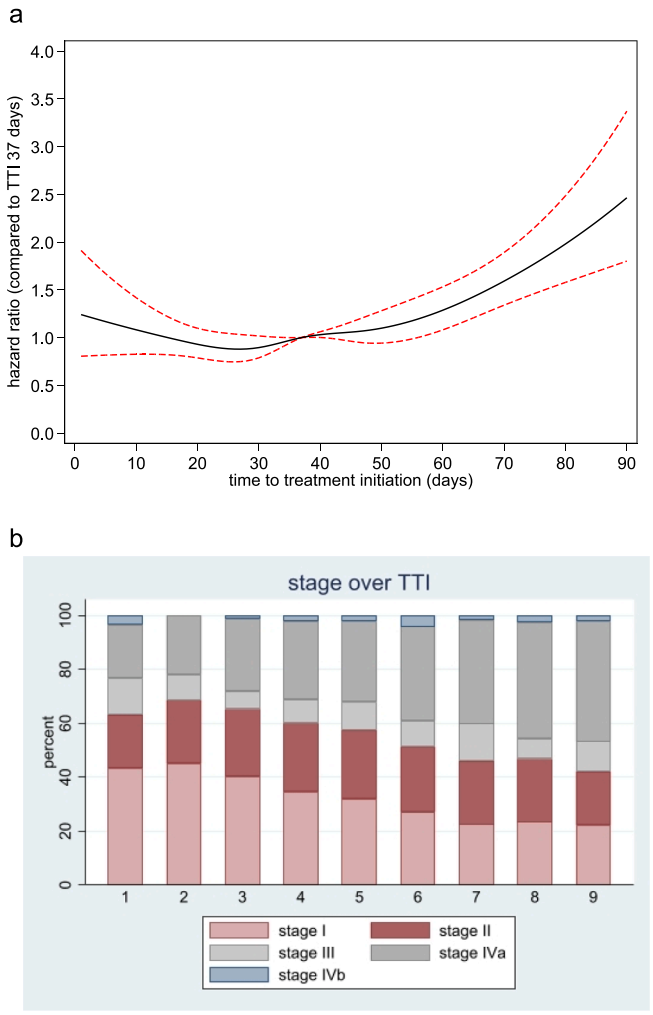

Fig. 3. Combined graphs for oral cavity cancer; a) the cubic spline demonstrating the course of the HR for dying over TTI (black) and corresponding 95 % CI and b) relative distribution of stages over TTI categories (1 = 1–10 days, 2 = 11–20 days, 3 = 21–30 days etc.).

et al. [10] described new cartilage or bone infiltrations in 10 out of 123 patients and new central lymph node necrosis in eight patients during waiting time (median 24 days). However, the authors observed no significant impact on survival, probably due to the low number of events and adapted treatment plan[10]. Other studies comparing diagnostic and radiotherapy planning imaging have demonstrated a significant higher tumor volume in the radiotherapy planning scan after a median of 28 days, which indicates a significant tumor progression during the median 28 days diagnosis-to-treatment interval [39,40]. Such developments may have a considerable impact on functional and cosmetic outcomes, thus greatly affecting quality of life [38].

Our decision to exclude tumours with a TTI of 0 days affected the larynx more than other sites, as small T1a tumours (with a generally good prognosis) are often excised during combined diagnostic and therapeutic (micro)laryngoscopy. This is the reason why most tumours in the laryngeal carcinoma subgroup had an advanced stage. Therefore, our findings are not directly generalizable to all laryngeal cancers. In line with previous studies [19,35,41], we found no difference in OS between laryngeal patients treated within 36 days (median) and those treated after 36 days.

Oropharyngeal tumours are usually diagnosed at an advanced stage [42], which is reflected in our data. Higher stage tumours usually need a more complex workup for multimodality treatments, which probably explains the relatively high median TTI of 41 days. However, hypopharyngeal tumours are also diagnosed at an advanced stage and in this group the median TTI equals 37 days which is similar to the median TTI observed for oral cavity cancer and laryngeal cancer which are more often diagnosed at early stage. Although several studies have shown that waiting time is associated with tumour progression, individual patients may be only slightly affected by treatment delays [39,43,44]. HPV could play a role [45] since HPV-associated SCC is currently considered as a distinct clinical entity and may partially explain the favourable clinical outcomes since these tumours are treatment sensitive, even though they present at a more advanced stage [8,25,42]. However, since our data is from the period 2010–2014, when HPV status was not commonly used in clinical practice and hence unavailable in the NCR, we were unable to distinguish HPV-related from unrelated oropharyngeal tumours.

For hypopharyngeal tumours, our findings suggest no increased risk of dying in relation to the TTI, with most cases having advanced stage disease at presentation. This might be because patients with advanced-stage disease ideally qualify for multimodality treatments, which may offer the best chances of survival, even though the planning and preparation period for multimodal therapy takes time, leading to a longer TTI e.g., exceeding the median of 37 days [16,21]. Patients who do not qualify for chemotherapy because of comorbidity or age, may have a shorter TTI due to less complex preparations for monomodality treatment (radiotherapy) but also an expected shorter survival due to their

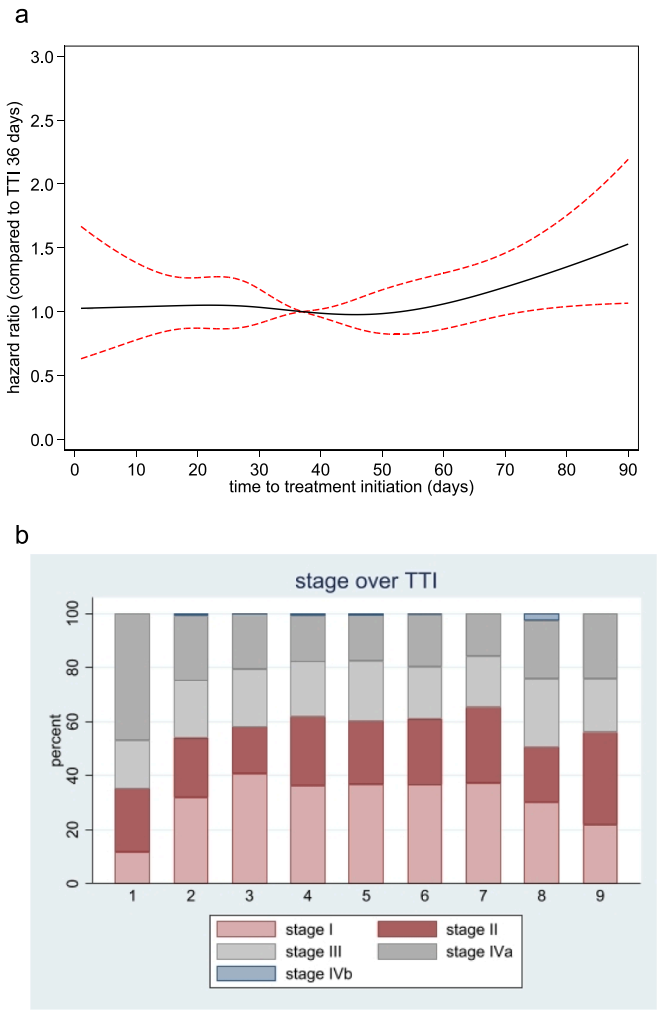

Fig. 4. Combined graphs for laryngeal cancer; a) the cubic spline demonstrating the course of the HR for dying over TTI (black) and corresponding 95 % CI and b) relative distribution of stages over TTI categories (1 = 1–10 days, 2 = 11–20 days, 3 = 21–30 days etc.).

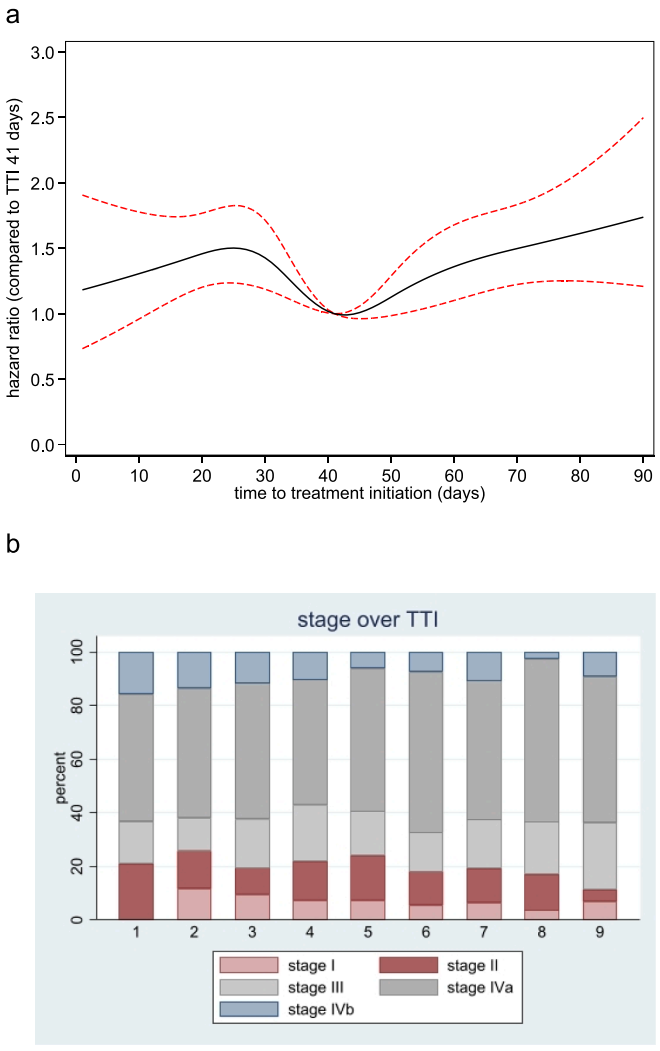

Fig. 5. Combined graphs for oropharyngeal cancer; a) the cubic spline demonstrating the course of the HR for dying over TTI (black) and corresponding 95 % CI and b) relative distribution of stages over TTI categories (1 = 1–10 days, 2 = 11–20 days, 3 = 21–30 days etc.).

comorbidity and age. The absence of a higher risk of dying with a longer TTI may further be explained by the relatively lower growth rate (2 % per day) of these tumours [10]. The five-year OS rate was low (42 %). This is consistent with previously reported rates of less than 50 % three to five years after treatment [46–51].

With the general advancements in multimodality HNC care [25] several weeks may elapse as a patient moves through the initial care path from diagnosis to treatment [15,52,53]. With the complexity of the different entities and stages of malignancies and increasing treatment options [25], more patient-specific treatment pathways are being developed at HNOCs. Adaptations need to consider each patient's specific situation, such as comorbidities [16,54–56]. In case of an excessive TTI, this may be the result of extensive pre-treatment preparations due to comorbidities (which may also affect OS) or medical or dental preparations before (chemo)radiotherapy [16,57]. Extensive pre-treatment preparations will ideally lead to a higher chance of survival, but an extended interval between diagnosis and treatment additionally adds to patient anxiety and potentially affects disease progression [16,21,38,58,59]. The absence of a difference in OS between patients waiting longer than the median or less may give the impression that a longer TTI does not affect survival chances, even though Schutte et al. found that TTI was reduced and OS significantly increased after improvements in the (diagnostic) care pathways at their HNOC [60]. An explanation for this discrepancy could be that other factors could be at play in the comparison of the different time periods or that with a longer TTI treatment changes and e.g. larger resections were performed or more extensive radiation was administered, affecting survival chances. Furthermore, the waiting time paradox [61], according to which the aggressiveness of the disease itself may result in a delay, may play a role: it is possible that patients with fast-growing or advanced-stage tumours bypass the waiting list and receive a more prompt treatment, which may have been the case for laryngeal and hypopharyngeal cancer. An additional aspect that should be considered is that if larger resections or more extensive radiation plans were required, this could affect surgery- or chemoradiation-associated morbidity [38] and consequently quality of life. Unfortunately, this information was not available for this study and this should be investigated in future studies.

When confronted with capacity burdens, such as during the COVID-19 pandemic, choices have to be made as to which types of care should be provided under all circumstances and which types can be postponed [26,27]. For advanced-stage head and neck malignancies the availability of post-operative critical care facilities, either ICUs or medium care units, is essential for high-risk surgery; therefore shortages may prolong the TTI [27,28,62–64]. However, Schoonbeek et al. showed a drop in incidence during the first COVID-19 wave of 25 % and also a drop in the median care pathway interval (interval between date of first consultation HNOC and start treatment) and TTI despite the overloaded

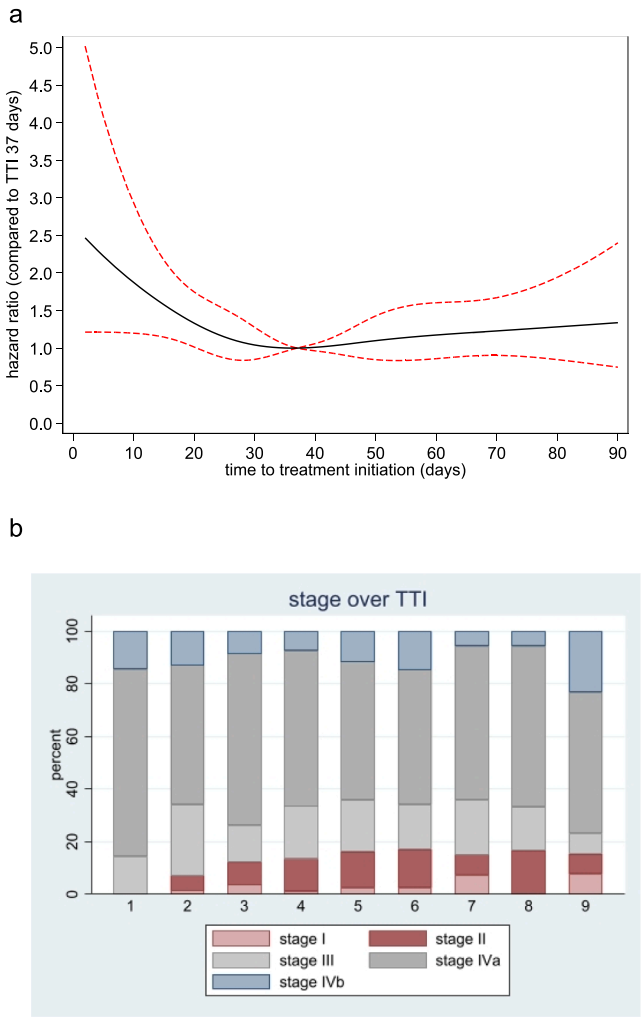

Fig. 6. Combined graphs for hypopharyngeal cancer; a) the cubic spline demonstrating the course of the HR for dying over TTI (black) and corresponding 95 % CI and b) relative distribution of stages over TTI categories (1 = 1–10 days, 2 = 11–20 days, 3 = 21–30 days etc.).

healthcare system in the Netherlands [65], implicating that HNC care was well maintained during COVID-19 here.

Mehanna et al. described, in their recommendations for head and neck surgical oncology practice in a setting of acute severe resource constraint during the COVID-19 pandemic, that for small oral cavity tumours (T1-T2 N0) it was not acceptable to delay surgery more than 8 weeks though 55 % percent of these head and neck specialists would accept a waiting time up till 8 weeks. Our data support that accepting a waiting time up till 8 weeks is on the edge of accepting an increasing HR for dying for oral cavity tumours. 47.5 % of recipients accepted a delay for small laryngeal tumours up to 8 weeks which seems in accordance with the data from this study. For advanced cases (all sites) there was strong agreement that surgery could not be delayed beyond four weeks [26]. Although this seems very plausible from a clinical point of view this is not supported by our data.

This study is based on population-based data from The Netherlands where a national collaboration to centralize HNC's exists, which may lead to slightly different findings compared to health care systems in other nations. A limitation of this study is that it analysed real-life population-based data, thus confounding by indication must be considered. Specific individual circumstances or (lack of) compliance leading to unconventional treatments with deviant TTIs may have affected our results. Moreover, the incidence date (mainly the date of confirming biopsy) was considered the starting point of TTI; [66] using the TTI poses challenges, as biopsies may be performed at different points in the pre-treatment workflow: some patients have a longer or shorter TTI (time of histopathological confirmation to start of treatment), while in reality the waiting time in the HNOC may be similar. Furthermore, comorbidity [16] and frailty [67] have been associated with an increased TTI and may so be associated with the hazard of dying. Preparations for the treatment of frail patients and patients with more comorbidities may take longer. On the other hand, these patients may not be suitable for concurrent systemic treatment, which may reduce the (logistic) preparations for treatment. Since frailty and comorbidity were not available, we could not establish the role of these factors. Finally, although this study contained data from a large cohort, only the biggest subgroups established significant results. The number of cases in most subgroups was lower; in these subgroups the power was most likely insufficient to statistically significantly show the small increases in hazards of dying as reported in the current study. This study focuses on the effect of TTI on survival given a specific HNC subsite. However, this is not the only important outcome parameter of HNC treatment. Prolonged waiting time may result in more extensive treatment because of tumour growth during TTI [38] which likely results in decreased functional and aesthetic outcome [68] and decreased quality of life [69]. Unfortunately, these data were not available. A short interval between diagnosis and treatment is beneficial for oncological, functional and psychological reasons[70]. If time is needed for a proper workup or to accommodate the patient, a longer TTI may be justified. However, if equally proper workup and treatment planning can be shortened, it is most likely that a shorter TTI can improve survival [60].

Conclusion

In this study the relationship between TTI and survival was confirmed, most clear for OSCC, but slight variations in the pattern of the hazard of dying by TTI for different tumour sites were observed. These findings could help to aid decisions on prioritizing treatment, but the relationship of TTI and other aspects such as quality of life should be investigated further so this can also be included in this decision making.

CRediT authorship contribution statement

Michaël H. Frank: Conceptualization, Formal analysis, Methodology, Methodology, Visualization, Writing – original draft. **Boukje A.C. van Dijk:** Conceptualization, Formal analysis, Methodology, Resources, Software, Supervision, Validation, Writing – review & editing. **Rosanne C. Schoonbeek:** Writing – review & editing. **Jaap Zindler:** Writing – review & editing. **Lot A. Devriese:** Writing – review & editing. **Robert J.J. van Es:** Writing – review & editing. **Matthias A.W. Merkx:** Resources, Writing – review & editing. **Remco de Bree:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

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.

Acknowledgements

The authors thank the registration teams of the Comprehensive Cancer Centre Netherlands for the collection of data for the Netherlands Cancer Registry.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110107.

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