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Determinants of treatment waiting times for head and neck cancer in the Netherlands and their relation to survival

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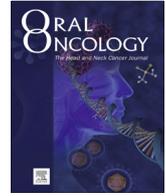
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SUMMARY

Introduction: Waiting to start treatment has been shown to be associated with tumor progression and upstaging in head and neck squamous cell carcinomas (HNSCCs). This diminishes the chance of cure and might lead to unnecessary mortality. We investigated the association between waiting times and survival in the Netherlands and assessed which factors were associated to longer waiting times.
Methods: Patient (age, sex, socioeconomic status (SES), tumor (site, stage) and treatment (type, of institute of diagnosis/treatment) characteristics for patients with HNSCC who underwent treatment were extracted from the Netherlands Cancer Registry (NCR) for 2005–2011. Waiting time was defined as the number of days between histopathological diagnosis and start of treatment. Univariable and multivariable Cox regression was used to evaluate survival.
Results: In total, 13,140 patients were included, who had a median waiting time of 37 days. Patients who were more likely to wait longer were men, patients with a low SES, oropharynx tumors, stage IV tumors, patients to be treated with radiotherapy or chemoradiation, and patients referred for treatment to a Head and Neck Oncology Center (HNOC) from another hospital. The 5-year overall survival was 58% for all patients. Our multivariable Cox regression model showed that longer waiting time, was significantly related to a higher hazard of dying (p < 0.0001).
Conclusion: This is the first large population-based study showing that longer waiting time for surgery, radiotherapy or chemoradiation is a significant negative prognostic factor for HNSCC patients.

Introduction

Waiting times for cancer treatment are a serious challenge for doctors and health care policy makers [1,2]. The ongoing shift of cancer care towards centralized comprehensive cancer centers that are treating higher patient volumes shows evident improvement of quality of care [3,4]. However, the increasing volume is imposing a burden on available diagnostic and treatment resources [1,5]. Encouraged by governments and patient lobbies, fast-track programs are introduced throughout Europe to optimize care pathways and minimize the time for diagnosis, staging and treatment. There is evidence that these programs are reducing total waiting time, though these initiatives are not leading to waiting times that meet current standards set by professional societies and authorities [6–11].

Longer intervals between the confirmation of a malignant tumor and initial treatment could potentially induce anxiety and lower patient satisfaction [12,13]. The major concern arises when waiting for treatment causes progression of disease, decreased tumor control, more extensive treatment, increased costs and impaired survival. Several studies explored this relationship in different cancer sites and found a correlation with prognosis in patients with uterine [14], and breast [15] cancer. On the other

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hand, in colorectal [16] and bladder [17] cancer, there was no or little evidence for this association.

In head and neck cancer, there are no consistent results regarding the relationship of waiting time and survival. A systematic review assessing 4238 patients showed a slight significant decrease in survival associated with longer waiting times for radiotherapy in HNSCC patients [18]. However, a recent study including all types of treatment (N = 2493) in the Netherlands Cancer Institute revealed that there was no relation between waiting time for treatment up to 90 days and impaired survival. In one of the sub-analyses, a poorer survival was found for patients with shortest waiting time (<2 weeks) for treatment, and better survival for patients with moderate or longer waiting time [11]. This can be explained by the 'waiting time paradox', as a result of confounding by indication; patients with more advanced, rapidly progressive tumors and more severe symptoms are treated earlier, but have a higher mortality, leading to a U-shaped association between waiting time and survival [19,20].

In the Netherlands, the total volume of head and neck cancer patients increased with more than 50% from 1,942 in 1989 to 2,970 in 2011 [21]. Care is mainly provided by eight geographically allocated Head and Neck Oncology Centers (HNOCs), certified since 1984 by the Dutch Head and Neck Society (DHNS). In 2001, the DHNS anticipated to the growing number of patients per Center and to assure a high standard of care set the maximum duration between diagnosis and treatment at 30 days [22]. In a recent study, this target was only satisfied for 34% of the head and neck squamous cell carcinoma (HNSCC) patients between 1990 and 2011 [10,11].

Waiting time for treatment of HNSCC patients in the Netherlands seems to be a major problem; however, at the same time the relevance is unclear since waiting time for treatment has not been established as a prognostic factor. This study was performed to investigate which factors are correlated with longer waiting time for treatment of HNSCCs. Additionally, we examined the impact of waiting on survival in patients with a HNSCC in a nationwide population-based study.

Patients and methods

Population

Patients were selected from the Netherlands Cancer Registry (NCR), managed by the Comprehensive Cancer Centre the Netherlands (IKNL). All patients in the Netherlands with newly diagnosed head and neck cancer (ICD-O-3 C00-C14 or C30-C32) [23] diagnosed from 2005 through 2011 (21108 records for 20621 patients) were identified. We excluded non-epithelial tumors (melanoma, sarcoma and hematological malignancies; N = 1800, 9% of all records). Patients who did not undergo treatment, for any reason, were excluded, considering this group was not subject to waiting time (N = 1232, 6%).

Each individual tumor was described by patient demographics (sex, age, socioeconomic status (SES)), clinical factors (e.g. tumor site and stage) and treatment details as well as logistical measures to allow for waiting time calculations and referrals (date of histopathological diagnosis, date of start of treatment, institute of diagnosis and institute of treatment (both anonymous)). Patients with missing data on any of the variables above were excluded (N = 2324, 11%). Also, patients with lip tumors (N = 1356, 6%) were excluded, since the prognosis is relatively good and commonly treated outside a Head and Neck Oncology Centre (HNOC). Additionally, we excluded patients with distant metastases at diagnosis (N = 275, 1%) and second primary tumors (N = 328, 2%), since these patients have a relatively poor prognosis and mostly not treated

with a curative intent. Furthermore, patients who experienced a waiting time between diagnosis and treatment that was longer than 90 days (N = 392, 2%) were excluded since the majority of patients with a waiting time of more than 90 days had specific reasons such as severe comorbidity or intercurrent disease causing this extreme delay in treatment.

There is inequality in this type of analysis [24], since for example a patient with a waiting time of 70 days has to survive at least 70 days to be included in this study, while a patient treated at day 5 after diagnosis and dying at day 10 would be included in this study without having to survive a specified time period. To tackle this inequality, we created a landmark at 90 days and excluded patients with a follow up shorter than 90 days after diagnosis (N = 253, 1%).

Eventually, 13,140 (64%) patients were included for analysis (Fig. 1).

Definitions and classifications

Date of diagnosis was defined as the date of the pathology report with histopathological (or cytological) confirmation of the clinical diagnosis. Start of treatment was defined as the date of surgery or first day of chemoradiation or radiotherapy. Subsequently, waiting time was defined as the interval between the date of diagnosis and start of treatment. Prior to assessing the association between waiting time and patient characteristics, we chose cut off points to create patient groups where the interval between diagnosis and initial treatment was 0–30 days and >30 days. We chose this categorization as the first group (0–30 days) is a group treated with acceptable waiting time as recommended by the Dutch Head and Neck Society (DHNS) [22]; the second group (>30 days) represents the population that is treated with longer than 30 days waiting time. Waiting time was also used as a continuous variable in our analysis.

Patients were categorized in different groups based on tumor site; oral cavity (ICD-O-3 C02.0-C05.0, C06.0-C06.9), oropharynx (C01.9, C05.1-C05.9, C09.0-C10.9), nasopharynx/nasal sinuses (C11.0-C11.9, C30.0-C31.9), hypopharynx (C12.0-C13.9), larynx (C32.0-C32.9) and (malignant) salivary glands (C07.0-C08.9). Pathological staging (IV) was performed using the pathological TNM stage (when not available, completed with the clinical stage), 6th edition (2002) for tumors diagnosed from 2005 through 2009 and TNM, 7th edition (2010) for tumors diagnosed in 2010 or 2011. If pathological stage was unavailable, clinical stage was used. Patients were placed in 3 groups based on treatment modality; surgery, surgery + adjuvant radiotherapy and primary radiotherapy/chemoradiation.

Furthermore, patients were assigned to four different groups based on whether they were diagnosed and/or received their first treatment in a Head and Neck Oncology Center (HNOC).

- diagnosed and first treatment in a non-HNOC
- diagnosed in a non-HNOC and first treatment in a HNOC
- diagnosed and first treatment in a HNOC
- diagnosed in a HNOC and first treatment in a non-HNOC

Socioeconomic status (SES) for each patient was determined using validated relative scores provided by The Netherlands Institute for Social Research (SCP), based on postal code [25]. The mean from the relative scores of 2006 and 2010 was used to place patients into tertiles, labeled low SES, medium SES and high SES.

Vital status information was obtained by linkage to the municipal records. Survival time was defined as the number of days between the ninetieth day after the date of diagnosis (landmark) and the date of death or the date of censoring (date of emigration or date of record linkage).
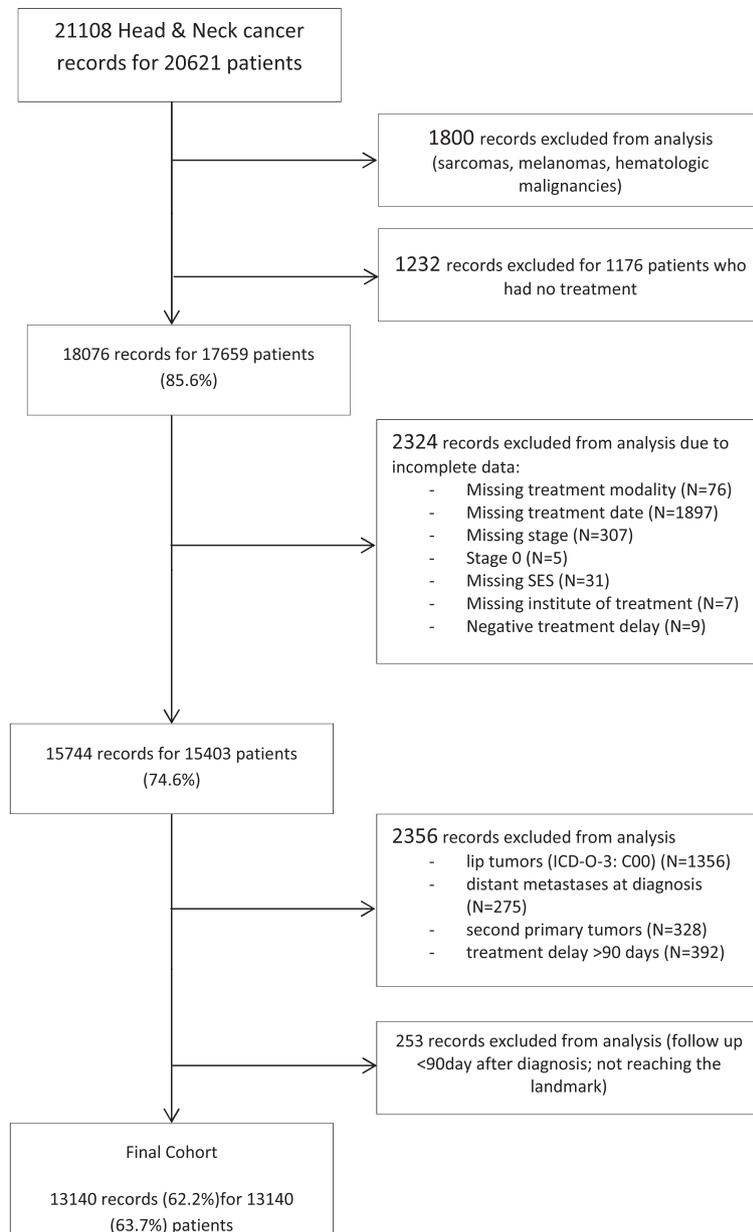
Figure 1. Flow chart study population.

Statistical analysis and outcome measures

Differences in categorical data were analyzed using the chi-square test, while not-normally distributed continuous data were compared using the non-parametric Kruskal Wallis test. Overall survival (OS) was calculated using SPSS 20® (SPSS Inc., Chicago, IL) and multivariable Cox regression using R (package rms version 3.6-3). The assumption of the proportional hazards model was evaluated by using log–log plots.

OS was assessed by Kaplan Meier curves and hazard ratio of dying were calculated using Cox regression. In our multivariable regression model, waiting time was used as a continuous variable with a restricted cubic spline with four knots [26]. Furthermore, we included variables that are known to be prognostic factors for survival and were significant in our univariable analyses (i.e. tumor stage, age, sex, tumor site). Also, we included socioeconomic status and type of diagnosis/treatment center as variables in our survival analysis. A *p* value <0.05 was considered statistically significant.

Results

Population characteristics

Table 1 shows the characteristics of the total study population (N = 13,140). Summarizing, the median age for men was 63 (range 10–97) and 63 (range 0–98) for women. Most tumors were found in the oral cavity (33%) and larynx (28%) and diagnosed at Stage I (31%) or Stage IV (36%).

Seventy-nine percent of the patients were treated in one of the eight HNOCs. The average number of patients treated in a HNOC from 2005 through 2011 was 186 per year. This number increased every year from 153 in 2005 to 228 in 2011.

Waiting time for treatment

As shown in Table 1, the median interval between diagnosis and treatment was 37 days (25–75% IQR 24–49) Patients who were

Table 1
Patient characteristics and association of selected risk factors with waiting times for treatment of HNSCC patients in the Netherlands, 2005–2012 (N = 13,140).

Characteristic	Total number (%) by characteristic, divided in subgroups based on waiting time				Total waiting time (days) in relation to characteristic	
	All	0–30 days	>30 days	*p*-value[a]	Median (25–75% IQR)	*p*-value[b]
All	13140	4755 (36)	8383 (64)		37 (24–49)	
Sex				0.021		0.008
Male	8869	3150 (35)	5719 (65)		37 (25–49)	
Female	4271	1605 (38)	2666 (62)		37 (23–49)	
Age				<0.001		<0.001
<40	394	218 (55)	176 (45)		28 (0–42)	
40–49	1094	405 (37)	689 (63)		36.5 (24–48)	
50–59	3491	1199 (34)	2292 (66)		38 (26–50)	
60–69	4355	1528 (35)	2827 (65)		37 (26–49)	
>70	3806	1405 (37)	2401 (63)		37 (23–50)	
Tumor site				<0.001		<0.001
Oral cavity	4309	1657 (38)	2652 (62)		36 (23–48)	
Oropharynx	2525	679 (37)	1846 (73)		41 (29–54)	
Nasopharynx/paranasal sinus/nasal cavity	952	290 (30)	662 (70)		40 (27–52)	
Hypopharynx	896	280 (31)	616 (69)		38 (28–51)	
Larynx	3721	1464 (39)	2257 (61)		35 (23–49)	
Salivary glands	737	385 (52)	352 (48)		29 (0–48)	
Social Economic Status				.001		<0.001
Low	4380	1539 (35)	2841 (65)		38 (25–50)	
Medium	4390	1538 (35)	2852 (65)		37.5 (26–50)	
High	4370	1678 (38)	2692 (62)		36 (23–48)	
Stage				<0.001		<0.001
Stage I	4102	1997 (49)	2105 (51)		31 (6–45)	
Stage II	2374	754 (32)	1620 (68)		39 (27–50)	
Stage III	1960	615 (31)	1345 (69)		40 (27–52)	
Stage IV	4704	1389 (30)	3315 (70)		40 (28–53)	
Initial therapy				<0.001		<0.001
Surgery	3833	1938 (51)	1895 (49)		30 (10–43)	
Surgery + adjuvant therapy	3571	1479 (41)	2092 (59)		35 (21–48)	
Radiotherapy/chemoradiation	5736	1338 (23)	4398 (77)		42 (31–55)	
Institute of diagnosis & treatment				<0.001		<0.001
Diagnosed and treated in non-HNOC	2353	1175 (50)	1178 (50)		31 (0–47)	
Diagnosed in non-HNOC & treated in HNOC	5723	943 (16)	4780 (84)		44 (35–55)	
Diagnosed and treated in HNOC	4677	2467 (53)	2210 (47)		29 (19–41)	
Diagnosed in HNOC & treated in non-HNOC	387	170 (44)	217 (56)		33 (24–44)	

Abbreviations: HNSCC, Head and Neck Squamous Cell Carcinoma; IQR, Interquartile Range; HNOC, Head and Neck Oncology Center.
  [a] Chi-square test of independence (chi-square test for trend when applicable).
  [b] Non-parametric Mann–Whitney test (Kruskal Wallis test when applicable).

likely to wait significantly (*p* < 0.05) longer for treatment were diagnosed with a tumor in the oropharynx (41 days, 25–75% IQR 29–54), had advanced stage (IV) disease (40 days, 25–75% IQR 28–53), had a low SES (38 days, 25–75% IQR 25–50), were treated with radiotherapy or chemoradiation (42 days, 25–75% IQR 31–55) and were diagnosed in a non-HNOC and treated in a HNOC (44 days, 25–75% IQR 35–55).

There were 1432 (10%) patients treated on the same day the diagnosis was histopathologically confirmed (waiting time = 0). Eighteen percent of these patients had a tumor in the salivary glands (vs. 4% in the group with a waiting time > 0 days), 71% had a Stage I tumor (vs. 26%), 100% were surgically treated (vs. 51%) and 55% were diagnosed and treated in a non-HNOC (vs. 13%).

Survival

The five-year overall survival (OS) in our total study population was 58% (95% CI 58% – 60%). After adjusting for all variables that were significantly prognostic in our univariable regression models, our multivariable Cox regression model showed that longer waiting time, using the median of 37 days as a reference point, was significantly related to a higher hazard of dying (*p* < 0.0001) (Table 2 and Fig. 2). As shown in Fig. 2, the curve ascends sharply to 25 days, then the curve plateaus, until approximately 2 months, after which the hazard of dying increases rapidly again. Survival curves for different waiting times show a similar association in Fig. 3.

Patients with a high socioeconomic status score had a lower hazard of dying than patients with a low SES (HR 0.89, 95% CI 0.81 – 0.94). Furthermore, patients who were referred to a HNOC for diagnosis and treatment had a significantly lower hazard of dying (HR 0.89, 95% CI 0.82 – 0.98), while those diagnosed in a HNOC and treated in a non-HNOC had a higher hazard of dying (HR 1.33, 95%CI 1.12 – 1.58) (Table 2)).

Using waiting time as a categorical variable, divided in groups defined by the DHNS; there was no significant difference in survival measured between the group that was treated after the deadline of 30 days after diagnosis, and the patients that were treated before 30 days in a multivariable analysis (HR 1.00, 95% CI, 0.94 – 1.07).

Discussion

In the Netherlands, waiting times in healthcare is a heavily debated subject since these waiting times rose to an unacceptable level in the 1990s, due to the disincentive for medical specialists and hospitals to increase production as a result of the introduction of fixed budgets and limitation of capacity [27]. In 2001, the Dutch Head and Neck Society wrote a guideline on quality and organization of care that stated that 80% of the head and neck cancer patients should be treated within 30 days after diagnosis [22]. In our current study, only 36% of the patients with an HNSCC, diagnosed between 2005 and 2011, were treated within the given

Table 2

Univariable and multivariable[a] Cox regression analyses for HNSCC patients treated in the Netherlands, 2005–2012 (N = 13,140).

	No.	Hazard of dying	
		Univariable	Multivariable[a]
		HR (95% CI)	HR (95% CI)
Waiting time for treatment (per 7 days)	13140	1.07 (1.06–1.08)	see Fig. 2 (p < 0.0001)
Sex			
Male	8869	1.00 (ref)	1.00 (ref)
Female	4271	.84 (.79–.90)	.83 (.78–.89)
Age (per year)	13140	1.03 (1.03–1.03)	1.04 (1.03–1.04)
Tumor site			
Oral cavity	4309	1.00 (ref)	1.00 (ref)
Oropharynx	2525	1.21 (1.11–1.31)	.78 (.71–.86)
Nasopharynx/paranasal sinus/nasal cavity	952	.94 (.83–1.06)	.75 (.66–.85)
Hypopharynx	896	2.01 (1.82–2.23)	1.00 (.89–1.12)
Larynx	3721	.84 (.77–.90)	.69 (.63–.76)
Salivary glands	737	.65 (.57–.76)	.68 (.59–.10)
Social Economic Status			
Low	4380	1.00 (ref)	1.00 (ref)
Medium	4390	.94 (.88–1.01)	.97 (.90–1.04)
High	4370	.84 (.78–.90)	.87 (.81–.94)
Stage			
Stage I	4102	1.00 (ref)	1.00 (ref)
Stage II	2374	1.61 (1.45–1.78)	1.44 (1.29–1.61)
Stage III	1960	2.33 (2.10–2.57)	2.20 (1.96–2.46)
Stage IV	4704	3.95 (3.64–4.28)	3.72 (3.36–4.12)
Treatment			
Surgery	3833	1.00 (ref)	1.00 (ref)
Surgery + adjuvant therapy	3571	1.70 (1.57–1.85)	.93 (.84–1.03)
Radiotherapy/chemoradiation	5736	2.10 (1.95–2.27)	1.38 (1.24–1.53)
Institute of diagnosis/treatment			
Diagnosed and treated in non-HNOC	2353	1.00 (ref)	1.00 (ref)
Diagnosed in non-HNOC & treated in HNOC	5723	1.21 (1.11–1.31)	.89 (.82–.98)
Diagnosed and treated in HNOC	4677	1.41 (1.29–1.53)	1.05 (.96–1.15)
Diagnosed in HNOC & treated in non-HNOC	387	1.90(1.61–2.24)	1.33 (1.12–1.58)

Abbreviations: HNSCC, Head and Neck Squamous Cell Carcinoma; ref, reference; HR, Hazard ratio; CI, Confidence Interval; HNOC, Head and Neck Oncology Center.
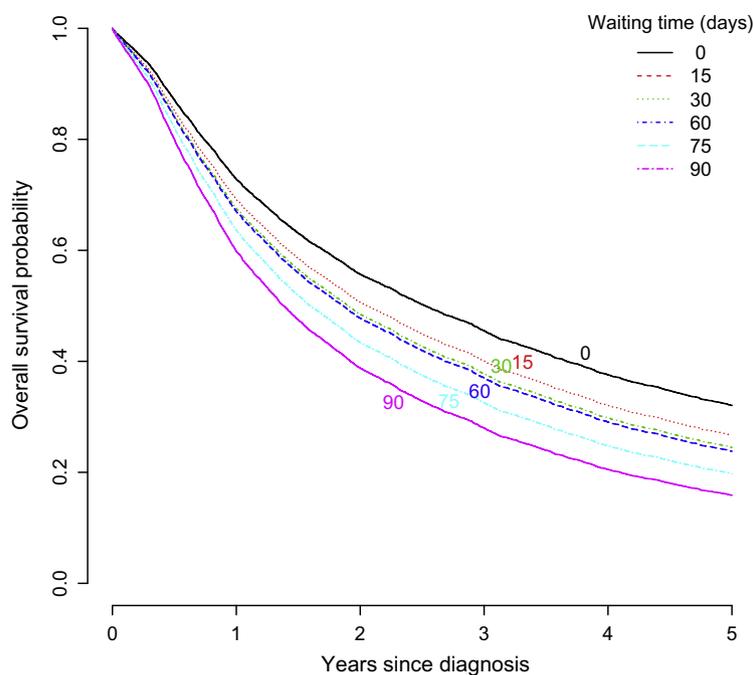
[a] Adjusted for sex, age, tumor site, SES, stage, treatment and institute of diagnosis/treatment.
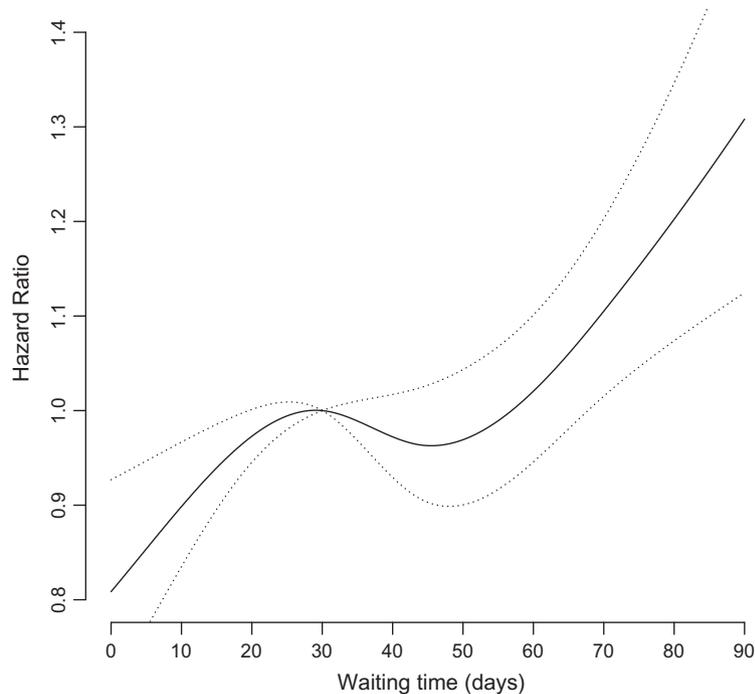
Figure 2. Spline curve for the estimated association between waiting time and survival. The hazard ratio has been set to 1 at the reference of 30 days.

timeframe. Median time between diagnosis and treatment was 37 days, comparable with a recent study in a HNOC in the Netherlands that showed a median interval of 39 days [11]. In 2008, another Dutch HNOC introduced an integrated care program in order to improve quality of care, resulting in almost a 20% decrease of waiting time for treatment to a median interval of 29 days [10].

Figure 3. Predicted survival curves based on the multivariable model by waiting time. Predictions are adjusted to sex, age, tumor site, SES, stage, treatment and institute of diagnosis/treatment.

Though, prior to continuation of the program and further implementation, more research was warranted to investigate cost-effectiveness. In Denmark, a country with a similar healthcare system, median waiting time for treatment in HNSCC patients in 2010 was 25 days, versus 47 days in 2002. This improvement was the result of a fast track program that started in 2007 and focused on multidisciplinary team boards and joint clinics enabling immediate counseling and treatment planning after histopathological diagnosis [6].

We found that patients with a relatively low socioeconomic score (SES) had a median waiting time almost 10% longer than patients with a high SES score. This finding is concordant with earlier reports showing longer waiting times for patients with a lower SES, e.g. in breast cancer [28]. However, low SES was also associated with a higher stage (35% stage IV in low SES versus 32% stage IV in high SES) and were therefore treated with chemoradiation more frequently. An additional possible explanation could be that patients with a higher SES exhibit a more assertive behavior towards doctors and demand treatment with minimal delay [29]. Also, as patients with lower SES scores have higher levels of comorbidity [30], it could be that these patients needed more pretreatment analyses that postponed definitive treatment. This level of comorbidity could, together with the higher incidence of smokers and alcohol abusers in this group, possibly explain the poorer survival of patients with a lower SES.

Forty-four percent of our population was diagnosed in a non-HNOC and referred and treated in a HNOC. These patients had a median waiting time for treatment of 44 days, probably due to a delay in referral. Despite this longer waiting time, this group had the lowest hazard of dying in our multivariable Cox regression analysis. Treating patients in specialized, centralized centers thus seems to have a greater impact on survival than waiting time. On the other hand, this waiting time can easily be shortened by early referral to a HNOC once suspicion for a malignancy is present. We additionally found a higher hazard of dying in patients with shorter waiting times for the group that was diagnosed in a HNOC and treated in a non-HNOC. These were mainly patients referred for radiotherapy in a hospital near their hometown.

In 1432 (10%) of our patients, the waiting time equaled zero days. These were mainly patients with favorable prognosis, evidenced by low-stage tumors and the histopathological diagnosis confirmed by the resection. Exclusion of this group from the analysis was not necessary since the multivariable analysis included stage, localization and type of treatment. However, an additional analysis excluding patients with a treatment time of zero days, did not alter our conclusions.

As opposed to the single center Dutch study that reported no relationship between longer waiting times and disease-specific and disease free survival in HNSCC patients [11], we hypothesized an impaired overall survival as a consequence of longer waiting times. Accordingly, our multivariable Cox regression model showed that longer waiting time, was significantly related to a higher hazard of dying. A similar relationship was found in a review by Chen [18] in patients with an HNSCC treated with radiotherapy. Intuitively, this probably is due to progression of the tumor to a more advanced stage, considering the rapid growth of HNSCCs [31,32]. Also, we did not find a U-shaped association between waiting time and survival, as described in earlier studies investigating the prognostic value of waiting time [11,19,20]. Possibly, confounding by indication may have occurred in these studies, as a result of specific hospital policies, prioritizing patients with rapidly progressing tumors. Another explanation could be that since the previous studies were smaller, estimates were more prone to be affected by outliers, which levels out in this large population.

We found that the 30 day cut-off for evaluating the waiting time as stated by the DHNS had no prognostic value; there was no statistical difference found in survival between patients that were treated before 30 days and the group that was treated after 30 days. This has probably to do with the fact that there is no biological reason to assume that exactly 30 days of waiting time would be prognostic, tumors are progressing continuously over time. Nonetheless, the curve that represents the hazard of dying rapidly ascends up to 25 days and after 2 months. As tumors will progress more evenly, it is difficult to explain this curve biologically. Possibly biases in treatment planning play a role. Since almost 10% of our population are treated with more than 2 months waiting time, this

finding should be an extra incentive to put more emphasis on reducing waiting time for those patients. However, also in the first 3 weeks there seems to be a significant impact of waiting times on prognosis, and the plateau could be an artifact based on planning policies in hospitals. Therefore, we think it is of great importance for policymakers and professional societies to set goals on quality of care, in which waiting times should play an important role. Regular audit procedures should make hospitals and doctors to adhere to these quality parameters.

In our retrospective study, we focused on the relationship between waiting time and overall survival. Information on tumor growth, morbidity of more extensive treatment, quality of life and levels of psychological distress during waiting times would have been a very relevant addition. Unfortunately, in the Netherlands Cancer Registry, there was no specific data available on individual preferences or tumor growth rates that could have influenced the way in what order patients were treated. Also, we did not have any details on smoking/alcohol (ab-) use and comorbidity levels, which possibly could have led to longer waiting times, as well as a poorer prognosis.

Conclusion

In conclusion, this is the first large population-based study showing that a longer waiting time for surgery, radiotherapy or chemoradiation is a significant negative prognostic factor for HNSCC patients. Besides the negative prognostic impact of longer waiting times, we found a better survival for patients who are treated in a HNOC. We therefore recommend referring cancer patients and patients with suspicious lesions to a specialized Head and Neck Oncology Center as early as possible, preferably using instant (online) referral systems to minimize delays. Furthermore, waiting times for treatment for patients with a HNSCC in the Netherlands are relatively long, compared with the waiting times reported in a specific Dutch Hospital and in Denmark after intervention. Thus, initiatives to optimize treatment pathways in comprehensive cancer centers should be implemented further to improve quality of care.

Conflict of interest

Acknowledgements

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