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CHAPTER 4

The association of treatment delay and prognosis in head and neck squamous cell carcinoma (HNSCC) patients in a Dutch comprehensive cancer center.

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ABSTRACT

OBJECTIVE

The increasing volume of head and neck squamous cell carcinoma (HNSCC) patients can lead to longer intervals between histopathological diagnosis and primary treatment. This could cause psychological distress to the patient, but more importantly could possibly lead to tumor progression and decreased survival. Accordingly, this study investigates these relationships.

METHODS

The correlation of professional delay and clinical characteristics of 2493 patients, treated between 1990 and 2011 with oral, oropharyngeal, hypopharyngeal and laryngeal SCC, was investigated. Patients were divided in two groups based on treatment delay, defined as the interval between histopathological diagnosis and initial treatment. Univariate and multivariate proportional hazards models were used to assess disease specific survival (DSS) and disease free survival (DFS).

RESULTS

Year of diagnosis, tumor site and therapy were significantly related to treatment delay. Tumor stage was not related to treatment delay. Multivariate regression models revealed that the group with a delay of more than 30 days had a better DSS (HR .838, CI .697–.922, $p = .041$) and DFS (HR .816, CI .702–.947), $p = .007$) than the group treated within 30 days.

CONCLUSION

In our study, treatment delay up to 90 days is not related to impaired survival. This argument can be used extremely cautiously to comfort patients who have to wait several weeks for treatment. Although, possible tumor progression during treatment delay could have led to increased morbidity subsequent to more extensive treatment. Also, possible negative psychological impact of delay in treatment should not be underestimated.

KEY WORDS

Head and neck, squamous cell carcinoma, professional delay, treatment delay, waiting time, prognosis, survival

INTRODUCTION

Along with the ageing of the population and despite reduced smoking, the total volume of cancer patients is continuously increasing in Western Europe, resulting in a growing demand for treatment capacity¹. Furthermore, as high volume centers have proven to provide better care, there is a worldwide tendency to centralize cancer care²⁻⁴. When providers face difficulties in matching this increasing demand with sufficient capacity, waiting lists for treatment can emerge^{5,6}. The resulting diagnostic or treatment delay might cause the patient and relatives psychological distress⁷, but more importantly, may give the tumor the opportunity to grow and metastasize, which could ultimately lead to impaired survival. Multiple studies did analyze this relation between treatment delay and prognosis and found no influence of a delay longer than one month on the survival for breast⁸, lung⁹, colorectal¹⁰ and pancreatic cancer¹¹. However, a study from South Korea reported a significantly improved prognosis for patients with stomach, colon, rectal, pancreatic, lung and breast cancer who were surgically treated within one month¹² and a Canadian study reported similar results in bladder cancer¹³. In head and neck cancer, the world's sixth most common malignancy, screening and early detection is complex and often not routine practice. The main reasons are the lack of a reliable diagnostic modality for screening and the limited awareness and knowledge of early signs and symptoms¹⁴⁻¹⁶. Especially tumors in the naso- and hypopharynx are associated with extended patient delays, while glottic larynx tumors are detected relatively early due to the earlier onset of symptoms such as hoarseness¹⁷. As described in several studies, HNSCCs are relatively rapidly proliferating malignancies, the tumor volume doubling time being reported 30 days or less in individual cases¹⁸⁻²⁰. This rapid growth, together with factors such as the patient's insufficient knowledge about the disease and inability to recognize alarm symptoms^{17,21} is resulting in more than 60% of the patients being diagnosed with advanced stage at diagnosis.

Consequently, the prognosis is rather poor with a mortality rate over 50%. Since tumor stage is the most important prognostic factor and decisive in the choice of treatment, it is supposed that reducing the total delay (i.e. patient delay and professional delay) for treatment is desirable²²⁻²⁴. In the guidelines of the Dutch Head and Neck Society it is stated that 80% of the patients should be treated within 30 days after their first appointment²⁵. In practice this goal is sometimes hard to achieve^{26,27}. Although intuitively plausible, the prognostic impact of treatment delay has not been studied thoroughly. In this population based retrospective cohort study, we aimed to investigate the association of treatment delay and long-term survival of HNSCC patients in a Dutch comprehensive cancer center.

PATIENTS AND METHODS

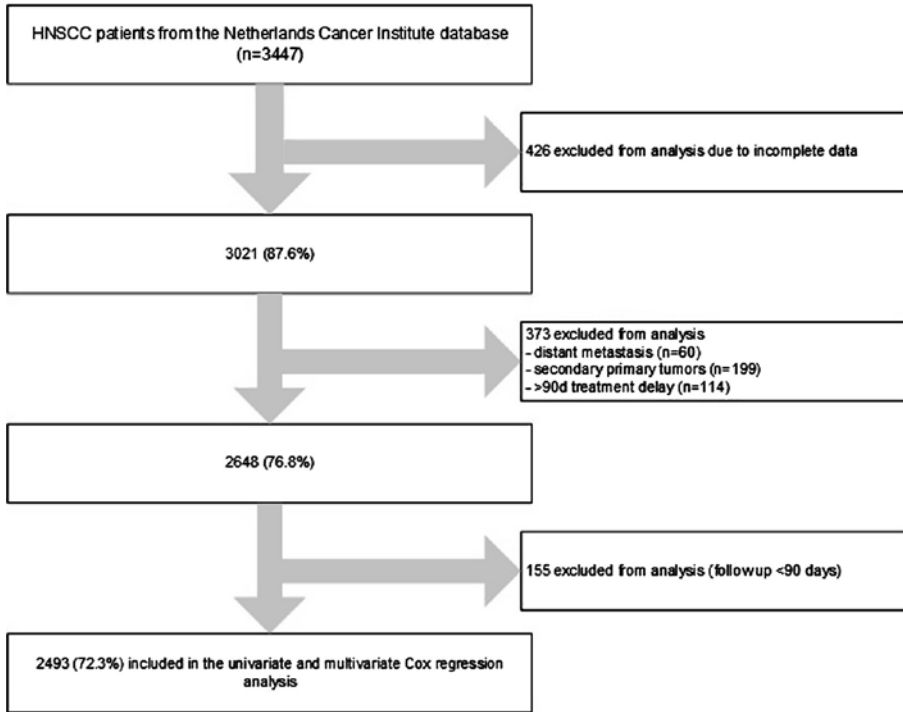
STUDY POPULATION

We identified patients that were registered in The Netherlands Cancer Institute (NCI) database between 1990 and 2011 with newly diagnosed, previously untreated, squamous cell carcinomas in oral cavity (ICD-10, C02–C05, C06–08), oropharynx (ICD-9, C01, C051–52, C09–10), larynx (ICD-10, C32) and hypopharynx (ICD-10, C12–13) (n = 3447).

Patient and tumor characteristics such as sex, age, date of registration, date of pathological diagnosis, anatomical site of tumor, TNM classification, treatment modality and date, date of recurrence, survival and cause of death were extracted from the tumor register and were complete in 3021 patients. Patients with distant metastasis at diagnosis (n = 60) were excluded, as well as patients with secondary primary tumors (n = 199) and patients who had an excessive treatment delay (>90 days), e.g. due to comorbidity (n = 114). In order to prevent time-dependent bias, we created a landmark at 90 days and excluded all patients lost to follow up within 90 days in our univariate and multivariate stepwise Cox proportional hazards regression analysis (n = 155). Eventually 2493 patients were eligible for the study and were included for analysis (Fig. 1).

DEFINITION OF PROFESSIONAL DELAY

In our study we categorized professional delay into different categories: referral delay, diagnostic delay, total treatment delay and treatment delay at the Netherlands Cancer Institute. Referral delay was defined as the interval between the date of a tumor positive histopathological diagnosis elsewhere and the date of registration at the Netherlands Cancer Institute. We defined NCI diagnostic delay as the period elapsed between the date of registration and the date of histopathological diagnosis at our institute. For dependency analyses, both types of delay were divided into two groups: 0–14 days and >14 days.



Total treatment delay was defined as the interval between the date of a tumor positive histopathological diagnosis and the date of initial therapy whereas NCI treatment delay was the delay from the first visit to the NCI. To measure the association of treatment delay and survival, the patients were divided into two groups, based on delay: 0–30 days and >30 days. This categorization was chosen as the first group (0–30 days) is a group treated with acceptable delay; the second group (>30 days) represents the population that is treated after the 30 days waiting time that is recommended by the Dutch Head and Neck Society²⁵. The different types of professional delay mentioned above are summarized in Fig. 2.



STATISTICAL ANALYSIS

Differences in categorical data were analyzed by using the chisquare test and means were compared using the non-parametric Kruskal Wallis test. A p value ≤ 0.05 was considered statistically significant. In our multivariate regression model, we included variables that are known to be prognostic factors for survival (i.e. tumor stage, age, sex, tumor site, year of diagnosis). The assumption of the proportional hazards model was tested by using log-log plots. Primary outcome measure was disease specific survival (DSS), which was defined as the time elapsed after the landmark of 90 days from histopathological diagnosis to disease specific death (underlying cause of death was an HNSCC). Patients dying due to not-disease related causes or who were still alive at the time of follow-up were censored. Disease free survival (DFS) was defined as the interval between 90 days from histopathological diagnosis and locoregionally or systemic recurrence of disease. Patients without recurrence were censored. SPSS 20 (SPSS Inc., Chicago, IL) was used for analysis.

RESULTS

STUDY POPULATION

Patient characteristics ($n = 2493$) are summarized in Table 1, categorized by total treatment delay. More than two-thirds of the patients were men (median 61 years, range 19–94 years) and nearly one-third female (median 61 years, range 30–94 years). More than 30% of the HNSCCs were found in the oropharynx, almost 60% of the malignancies were diagnosed at an advanced tumor stage (Stage III–IV) and the distribution of the initial treatment modality, surgery or radiotherapy/chemoradiation, was about even. 1730 (69%) patients (Table 2) were referred for treatment to the Netherlands Cancer Institute with a pathologically confirmed diagnosis, whereas in 763 (31%) patients the pathological diagnosis was made in our institute (Table 3).

PROFESSIONAL DELAY

The median time between the histopathological diagnosis and initial treatment was 39 days (25–75% IQR 26.5–51). Table 1 reveals that year of diagnosis, tumor site and therapy were all significantly related to treatment delay ($p < 0.05$). The median treatment delay in the period between 1990 and 1994 (31 days (25–75% IQR 22–42)) was significantly shorter than in the following periods (median ranging from 38 to 41.5 days). Tumors that were found in the hypopharynx (35 days (25–75% IQR 23–47)) and larynx (35 days (25–75% IQR 25–48)) were significantly treated with less delay as tumors in the oral cavity (38 days (25–75% IQR 27–50.5)) or oropharynx (41 days (25–75% IQR 30–54)).

Table 1. Characteristics and total treatment delay of all HNSCC patients treated in the Netherlands Cancer Institute (n=2493)

Characteristics	Total number (%) by characteristic, divided in subgroups based on total treatment delay				Total treatment delay (days) in relation to characteristic		
	All	0-30 days	>30 days	p-Value ^a	Median (25-75% IQR)	Mean ± SEM	p-Value ^b
All	2493	810 (32)	1683 (68)		39 (26.5–51)	39.12 ± .38	
Sex				0.926			0.295
Male	1779	579 (32)	1200 (68)		38 (27–50)	38.88 ± .44	
Female	714	231 (32)	483 (68)		40 (26–52)	39.71 ± .71	
Age				0.821			0.312
<40	55	17 (31)	38 (69)		38 (23–47)	36.84 ± 2.43	
40–49	311	98 (31)	213 (69)		39 (27–49)	39.35 ± .99	
50–59	765	258 (34)	507 (66)		39 (26–52)	39.10 ± .69	
60–69	775	240 (31)	535 (69)		40 (28–52)	40.22 ± .66	
>70	587	197 (34)	390 (66)		37 (26–50)	37.77 ± .80	
Year of diagnosis				<0.001			<0.001
1990–1994	360	175 (49)	185 (51)		31 (22–42)	32.66 ± .85	
1995–1999	504	156 (31)	348 (69)		40 (28–52)	40.31 ± .85	
2000–2004	717	177 (25)	540 (75)		42 (31–56)	43.03 ± .72	
2005–2010	912	302 (33)	610 (67)		38 (26–49)	37.93 ± .61	
Tumor site				<0.001			<0.001
Oral cavity	668	217 (32)	451 (68)		38 (27–50.5)	39.14 ± .72	
Oropharynx	836	212 (25)	624 (75)		41 (30–54)	42.25 ± .61	
Hypopharynx	272	107 (39)	165 (61)		35 (23–47)	35.93 ± 1.10	
Larynx	717	274 (38)	443 (62)		35 (25–48)	36.67 ± .74	
Stage				0.530			0.787
Stage I-II	1004	319 (32)	685 (68)		38.5 (27–50)	38.75 ± .60	
Stage III-IV	1489	491 (33)	998 (67)		39 (26–51)	39.37 ± .48	
Treatment				<0.001			<0.001
Surgery ± RT	1185	484 (41)	326 (25)		34 (22–47.5)	35.09 ± .55	
(C)RT	1308	701 (59)	982 (75)		41 (31–54)	42.77 ± .49	

Abbreviations: HNSCC, Head and Neck Squamous Cell Carcinoma; IQR, InterQuartile Range; RT, radiotherapy; CRT, chemoradiotherapy

^a Chi-square test of independence (chi-square test for trend when applicable).^b Kruskal Wallis test.

Characteristic	Total number (%) by characteristic, divided in subgroups based on referral delay to the NCI			Referral delay (days) in relation to characteristic			Total number (%) by characteristic, divided in subgroups based on NCI treatment delay			NCI Treatment delay (days) in relation to characteristic			p Value ^a
	All	0-14 days	>14 days	p Value ^a	Median (25-75% IQR)	Mean ± SEM	p Value ^b	0-30 days	>30 days	p value ^c	Median (25-75% IQR)	Mean ± SEM	
All	1730	1265 (73)	465 (27)		11 (7-15)	12.67 ± 2.34		810 (47)	920 (53)		31 (23-41)	32.78 ± 3.39	
Sex													
Male	1226	898 (73)	328 (27)	.855	11 (7-15)	12.82 ± 2.81	.359	584 (48)	642 (52)	.290	31 (23-41)	32.69 ± 3.00	.640
Female	504				10 (7-15)	12.29 ± 4.21		226 (45)	278 (55)		22 (22-41)	33.01 ± 6.41	
Age													
< 40	44	28 (64)	16 (36)	.134	11 (8-15)	12.73 ± 1.375	.751	25 (57)	19 (43)	.000	28.5 (17.5-34)	28.05 ± 2.015	.063
40-49	236	165 (70)	71 (30)		11 (7-16)	13.06 ± 6.40		113 (48)	123 (52)		31 (21.5-38)	31.43 ± 3.95	
50-59	516	379 (73)	137 (27)		11 (7-15)	13.03 ± 4.48		243 (47)	273 (53)		31 (23.5-41)	32.65 ± 6.18	
60-69	546	406 (74)	140 (26)		10 (7-15)	12.71 ± 4.38		250 (46)	296 (54)		31 (23-41)	33.40 ± 6.05	
>70	388	287 (74)	101 (26)		10 (7-15)	11.89 ± 4.22		179 (46)	209 (53)		31 (23-41)	33.44 ± 7.00	
Year of diagnosis													
1990-1994	259	211 (82)	48 (18)	.196	8 (4-13)	9.59 ± 4.89	.000	169 (65)	90 (35)	.000	26 (17-34)	27.16 ± 8.55	.000
1995-1999	381	269 (71)	112 (29)		10 (7-16)	12.99 ± 5.14		175 (46)	206 (54)		31 (22-42)	33.21 ± 7.23	
2000-2004	501	346 (69)	155 (31)		11 (7-16)	13.67 ± 4.74		179 (36)	322 (64)		34 (27-45)	36.15 ± 6.55	
2005-2010	589	439 (75)	150 (25)		11 (8-15)	12.96 ± 3.80		287 (49)	302 (51)		31 (23-38.5)	32.11 ± 5.33	
Tumor site													
Oral cavity	488	325 (67)	163 (33)	.000	11.5 (8-17)	13.99 ± 4.66	.000	273 (56)	215 (44)	.085	28.5 (20-39)	30.00 ± 6.09	.000
Oropharynx	620	454 (73)	166 (27)		10 (7-15)	12.83 ± 4.19		250 (40)	390 (60)		32 (24-41)	33.94 ± 5.48	
Hypopharynx	151	111 (74)	40 (26)		11 (7-15)	12.56 ± 8.09		70 (46)	81 (54)		31 (23-41)	32.93 ± 1.169	
Larynx	471	375 (80)	96 (20)		9 (7-14)	11.11 ± 3.56		217 (47)	254 (53)		32 (24-41.5)	34.08 ± 6.88	
Stage													
Stage I-II	701	541 (77)	160 (23)	.002	10 (7-14)	12.08 ± 3.35	.375	343 (49)	358 (51)	.147	31 (22-41)	33.05 ± 5.42	.880
Stage III-IV	1029	724 (70)	305 (30)		11 (7-16)	13.07 ± 3.20		467 (45)	562 (55)		31 (23-41)	32.59 ± 4.35	
Treatment													
Surgery ± adjuvant radiotherapy	797	568 (71)	229 (29)	.108	11 (7-15)	12.95 ± 3.58	.254	477 (60)	320 (40)	.000	27 (19-38)	28.95 ± 4.87	.000
Radiotherapy/chemomodulation	933	697 (75)	236 (25)		10 (7-15)	12.43 ± 3.08		333 (36)	600 (64)		34 (27-43)	36.05 ± 4.45	

Abbreviations: HNSCC, Head and Neck Squamous Cell Carcinoma; NCI, Netherlands Cancer Institute; IQR, Inter-Quartile Range. ^a Chi-square test of independence (chi-square test for trend when applicable). ^b Kruskal-Wallis test.

Characteristic	Total number (%) by characteristic, divided in subgroups based on referral delay to the NCI			Referral delay (days) in relation to characteristic			Total number (%) by characteristic, divided in subgroups based on NCI treatment delay			NCI Treatment delay (days) in relation to characteristic			
	All	0-14 days	>14 days	p Value ^a	Median (25-75% IQR)	Mean ± SEM	p Value ^b	0-30 days	>30 days	p value ^c	Median (25-75% IQR)	Mean ± SEM	p Value ^d
All	763	472 (62)	291 (38)		10 (1-22)	13.55 ± 3.44		259 (34)	504 (66)		36 (2.6-48)	38.32 ± 687	
Sex													
Male	553	341 (62)	212 (38)	.856	10 (1-22)	13.49 ± 6.41	.949	188 (34)	365 (66)	.961	35 (2.6-48)	37.68 ± 782	.285
Female	210	131 (62)	79 (38)		10 (1-22)	13.72 ± 10.32		71 (34)	139 (66)		38 (2.7-48)	40.02 ± 1.406	
Age													
< 40	11	9 (82)	2 (18)	.213	10 (0-14)	12.73 ± 5.328	.858	4 (36)	7 (64)	.757	31 (17-52)	35.82 ± 6.060	.424
40-49	75	46 (61)	29 (39)		12 (3-19)	14.33 ± 2.249		27 (36)	48 (64)		36 (2.5-45)	37.52 ± 2.470	
50-59	249	162 (65)	87 (35)		8 (1-21)	12.56 ± 8.72		86 (34)	163 (76)		36 (2.6-48)	38.04 ± 1.168	
60-69	229	135 (59)	94 (41)		10 (1-21)	14.05 ± 1.001		65 (28)	164 (72)		36 (2.8-48)	40.26 ± 1.223	
>70	199	120 (60)	79 (40)		11 (1-24)	13.97 ± 10.21		77 (39)	122 (61)		35 (2.3-48)	36.99 ± 1.359	
Year of diagnosis													
1990-1994	101	73 (73)	28 (28)	.875	9 (3-16)	12.08 ± 1.361	.000	50 (49)	51 (51)	.023	31 (21-45)	34.24 ± 1.975	.000
1995-1999	123	70 (57)	53 (43)		13 (7-20)	15.01 ± 1.229		47 (38)	76 (62)		36 (2.2-47)	37.09 ± 1.900	
2000-2004	216	112 (52)	104 (48)		13 (1-26.5)	15.68 ± 9.94		47 (22)	169 (78)		41 (31-55)	42.98 ± 1.205	
2005-2010	323	217 (67)	106 (33)		6 (0-20)	12.03 ± 8.91		115 (36)	208 (64)		34 (2.6-46)	36.96 ± 1.011	
Tumor site													
Oral cavity	180	142 (79)	38 (21)	.000	1 (0-13)	8.97 ± 1.119	.000	83 (46)	97 (54)	.063	31 (2.2-45)	34.95 ± 1.371	.004
Oropharynx	216	152 (70)	64 (30)		8 (0-19)	11.61 ± 10.38		57 (26)	159 (77)		38 (28.5-51)	40.85 ± 1.294	
Hypopharynx	121	76 (63)	45 (37)		11 (4-21)	14.42 ± 1.293		41 (34)	80 (66)		38 (2.6-48)	38.43 ± 1.720	
Larynx	246	102 (41)	144 (59)		17 (6-27)	18.18 ± 8.87		78 (32)	168 (68)		36.5 (27-48)	38.52 ± 1.220	
Stage													
Stage I-II	303	145 (48)	158 (52)	.000	15 (1-29)	17.56 ± 9.22	.000	93 (31)	210 (69)	.124	39 (2.7-53)	41.53 ± 1.138	.000
Stage III-IV	460	327 (71)	133 (29)		7 (1-17)	10.91 ± 6.39		166 (36)	294 (64)		34 (2.6-45)	36.21 ± 8.45	
Treatment													
Surgery ± adjuvant radiotherapy	388	269 (69)	119 (31)	.000	6 (0-19)	12.49 ± 8.78	.000	195 (50)	193 (50)	.000	30 (2.0-44)	33.57 ± 1.039	.000
Radiotherapy/chemoradiation	375	203 (54)	172 (46)		13 (4-23)	14.65 ± 6.28		64 (17)	311 (83)		40 (3.2-52)	45.25 ± 8.21	

Abbreviations: HNSCC, Head and Neck Squamous Cell Carcinoma; NCI, Netherlands Cancer Institute; IQR, Inter-Quartile Range. ^a Chi-square test of independence (chi-square test for trend when applicable). ^b Kruskal Wallis test.



Table 4. Univariate and weighted multivariate Cox regression analyses for HNSCC patients treated in the Netherlands Cancer Institute (n = 2493).					
		Univariate	Multivariate	Univariate	Multivariate
	No.	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Sex					
Male	1779	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Female	714	.917 (.780–1.078)	.884 (.751–1.042)	.980 (.851–1.129)	.935 (.810–1.079)
Age					
<40	55	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
40–49	311	.970 (.590–1.596)	1.038 (.629–1.713)	1.008 (.648–1.566)	1.084 (.695–1.689)
50–59	765	.945 (.586–1.524)	1.101 (.681–1.782)	.973 (.637–1.486)	1.115 (.728–1.706)
60–69	775	.868 (.537–1.403)	1.115 (.687–1.810)	.911 (.596–1.393)	1.133 (.739–1.739)
>70	587	.833 (.511–1.359)	1.191 (.726–1.952)	.802 (.520–1.238)	1.049 (.676–1.626)
Year of diagnosis					
1990–1994	360	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1995–1999	504	1.057 (.847–1.319)	.913 (.728–1.147)	1.014 (.832–1.236)	.941 (.768–1.152)
2000–2004	717	1.130 (.913–1.400)	.972 (.777–1.217)	1.008 (.834–1.219)	.929 (.761–1.133)
2005–2010	912	.910 (.723–1.146)	.798 (.629–1.011)	.823 (.674–1.006)	.762 (.621–.936)
Tumor site					
Oral cavity	668	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Oropharynx	836	1.189 (.993–1.424)	.814 (.668–.993)	.985 (.840–1.154)	.776 (.651–.925)
Hypopharynx	272	1.278 (1.008–1.621)	.849 (.661–1.090)	1.023 (.825–1.270)	.778 (.620–.977)
Larynx	717	.601 (.489–.738)	.577 (.459–.725)	.592 (.496–.707)	.584 (.479–.713)
Stage					
Stage I-II	1004	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Stage III-IV	1489	3.007 (2.540–3.560)	2.774 (2.313–3.326)	2.003 (1.745–2.300)	1.884 (1.622–2.189)
Treatment					
Surgery ± adjuvant radiotherapy	1185	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Radiotherapy/chemoradiation	1308	1.131 (.980–1.306)	1.365 (1.155–1.612)	.975 (.859–1.107)	1.184 (1.021–1.374)
Total treatment delay					
0–30 days	810	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
>30 days	1683	.870 (.749–1.009)	.838 (.708–.992)	.835 (.732–.953)	.816 (.702–.947)
NCI treatment delay					
0–30 days	1069	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
>30 days	1424	.889 (.770–1.026)	.905 (.767–1.069)	.878 (.773–.998)	.955 (.824–1.106)

Abbreviations: HNSCC, Head and Neck Squamous Cell Carcinoma; ref, reference; HR, Hazard ratio; CI, Confidence Interval; NCI, Netherlands Cancer Institute.

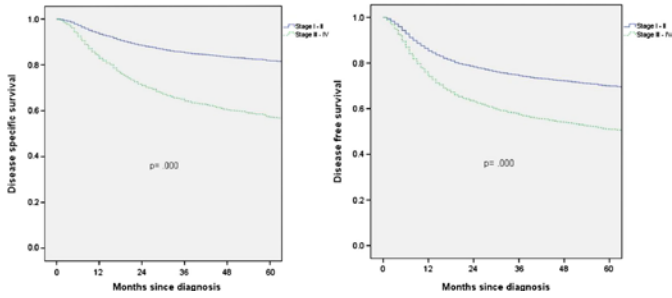


Figure 3. Adjusted Kaplan-Meier curves for stage. Disease Specific Survival (DSS) left, Disease Free Survival (DFS) right.

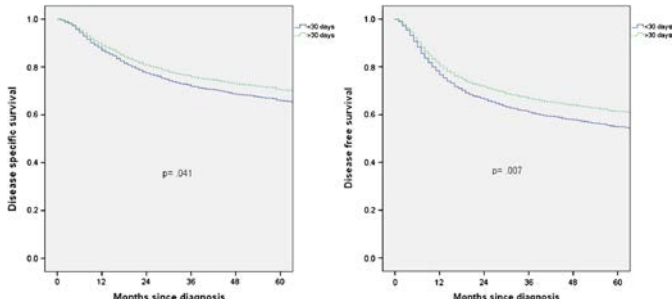


Figure 4. Adjusted Kaplan-Meier curves for total treatment delay. Disease Specific Survival (DSS) left, Disease Free Survival (DFS) right.

Patients treated with radiotherapy or chemoradiation had to wait significantly longer than patients who underwent primary surgery (41 days (25–75% IQR 31–54) vs. 34 days (25–75% IQR 22–47.5)), caused by the high number of oropharyngeal cancer patients in this group. The median treatment delay was not related to tumor stage.

In Table 2, the characteristics of the patients who had their biopsy elsewhere and were then referred to the NCI are depicted. On average, almost 13 days passed between the pathological diagnosis and the date of first visit at the NCI. This was shorter in the period between 1990 and 1994 (10 days) and also shorter for laryngeal cancer (11 days). Mean NCI treatment delay after the first visit for patients who arrived at the Netherlands Cancer Institute with a histopathological diagnosis confirmed elsewhere, was almost 33 days. These patients had a mean total treatment delay of 45 days. Only in very young patients (<40 years old), those surgically treated, in the first period (1990–1994) and those with oral cancer, over 50% were treated within 30 days. In all other groups, more than half of the patients had a NCI treatment delay over 30 days. In Table 3 the patients are listed who had their biopsy at the NCI. The mean NCI treatment delay of this group was almost 39 days. In this group, the diagnostic delay was shorter in oral and oropharyngeal cancer patients because these often had biopsies in the outpatient clinic. For the NCI treatment delay, only oral cancers had a shorter interval. Patients treated in the first time period, more advanced stages and surgically treated cases had a shorter NCI treatment delay.

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Mean follow up time after starting point (90 days after diagnosis) was 44.14 months (range 0–238). Disease specific 5-year survival (DSS) for 2493 patients diagnosed with HNSCC between 1990 and 2011 was 68.0%, disease free 5-year survival (DFS) 58.7%. The relative hazard ratios for DSS from univariate and multivariate Cox regression analyses are shown in Table 4. Advanced stage disease (Stage III–IV) was the worst prognostic factor in univariate and multivariate analyses for DSS (HR 2.774, CI 2.313–3.326, $p = .000$) and DFS (HR 1.884, CI 1.622–2.189, $p = .000$) (Fig. 3).

The multivariate Cox proportional hazards regression analyses we performed revealed that patients with a treatment delay of 30 days or less were associated with diminished disease specific survival (HR .838, CI .697–922, $p = .041$). Fig. 4 shows the Kaplan Meier curves for the different treatment delay intervals related to disease specific survival, adjusted for sex, age, year of diagnosis, stage and therapy. Multivariate analysis for disease free survival resulted in a similar relationship (HR .816, CI .702–947), $p = .007$). Our multivariate proportional hazards model also reveals that patients who were treated between 2005 and 2011 had a significantly better DFS than in all prior periods, in spite of the fact that treatment delay was not shorter in this period. NCI treatment delay showed that there was a non-significant trend towards a better outcome with longer delays.

DISCUSSION

In our institute, the order of treatment is made on a first come, first serve basis. Although exceptions are made for patients whom we think have rapidly progressive tumors, in general we do not take age, stage of disease or social aspects into account. In this article the association of professional delay and disease specific and disease free survival in HNSCC patients is studied. Multiple studies described that these malignancies are subject to a typical rapid growth and reported a doubling time of 30 days or less^{18–20}. Hypothetically, longer delays lead to locoregionally more advanced disease and metastasis. The presently recommended time between first appointment at a head and neck cancer center and treatment should not exceed 30 days according to the Dutch guidelines²⁵. As in patients who come to our hospital without a histologically proven HNSCC there is also an interval between the first visit to the clinic and the pathological diagnosis (as biopsies are often taken during the examination under general anesthesia), the actual diagnostic delay should be added to the treatment delay and that is why in these patients we use the NCI treatment delay.

The average total treatment delay in our study was more than 38 days, whereas the NCI treatment delay was almost 33 and 40 days for patients who either had their biopsy elsewhere or in the NCI. Patients who had a pathological diagnosis elsewhere and referred to our institute for treatment (65%) even had an average total treatment delay of 45 days. As reported by Chen et al²⁸ in patients with radiotherapy as their single treatment modality, we expected a negative impact of lengthy waiting times on patient outcome. On the contrary, we found that patients treated within 30 days had significantly the worst outcome, a relationship that was found earlier by Leon et al²⁹. A possible explanation could be that patients with advanced stage disease are being treated quicker, due to the greater risk of becoming inoperable or because they have more complaints. However, in this series, stage III–IV disease was not associated with shorter waiting times. In the pre-analyses we performed, we divided the treatment delay in 4 patient groups (0–14 d, 15–28 d, 29–42, >42 d) and concluded that the DSS and DFS of the first group (0–14 days) was significantly worse compared with all other groups. The other groups showed no significant difference in-between. Consequently, the poor survival of the patients with a treatment delay less than 30 days is due to the outcome of the patients with 0–14 days delay. From the databases, in this group we could not find differences in tumor or patient characteristics that were different from the other groups and could explain this prognostic finding. A possible explanation for the poorer prognosis of patients treated within 30 days could therefore be that we selected patients with a history of rapidly tumor progression or pain and thus biologically aggressive tumors to be treated with minimal delay. There are several studies that investigated the relationship between professional delay and prognosis in HNSCCs patients. Seoane et al. summarized the effect of diagnostic delay on survival in a systematic review and found diagnostic delay as a significant moderate risk factor for mortality in HNSCCs³⁰. A systematic review that investigated the relationship between waiting time before radiotherapy and survival found that treatment delay is a prognostic factor for local recurrence and overall survival as well²⁸. The majority of studies performed in other areas of cancer care found no significant relationship between treatment delay and prognosis^{8–11}. In contrast to these findings, a very large study conducted in South Korea did report an influence of surgical

treatment delay on long-term patient survival in different types of cancer. Unfortunately they did not control for tumor stage, that could have possibly altered the main outcomes and thus they may have overestimated the effect of delay¹². Despite our large patient population (n = 2493) and long follow up (0–238 months), there are limitations to this analysis, mostly because of the nonrandomized retrospective nature of this study. A prospective study would obviously be unethical and impossible to conduct. In our institute, delays are mainly caused by limitations of diagnostic and treatment capacity. However, individual circumstances and logistics of treatment planning are not systematically recorded. It is possible that other important parameters, such as fast tumor progression or patient complaints and preferences have influenced treatment delay. Furthermore, comorbidities requiring preoperative analysis might have influenced treatment delays. As pretreatment imaging possibilities have dramatically increased, these are certainly used more widely now as compared to the early 1990s. The treatment modality has also shifted more toward chemoradiation in these two decades, and this might explain a better outcome for patients treated more recently. We were not able to control for smoking status, alcohol abuse and socioeconomic characteristics. Factors like these can have an important negative impact on survival^{31–33} and might have had an effect on treatment delay as well^{34–37}. Although most of these factors are known to prolong the interval between diagnosis and treatment, in our study this longer interval does not lead to a worse prognosis. Further, in the database of the NCI there are no data available on date of first symptoms or referral date from a general practitioner or medical specialist. Therefore we could not analyze the hazard ratios of total patient and total professional delay (referral delay, diagnostic delay and treatment delay) and compare the prognostic values of the different types of delay with each other. While we found in this study that the shortest treatment delay was associated with the worst prognosis, we certainly do not want to propagate longer waiting times. Although there was no influence on prognosis, the possible tumor growth might have led to more extensive treatment and thus increased morbidity and costs. Individual cases were seen that became inoperable in the waiting time, or had to undergo more extensive treatment. The negative psychological impact of a delay in treatment should also not be underestimated. Several studies demonstrated that the waiting phase between diagnosis and therapy is a frustrating and stressful period for patients and close relatives^{7,38–40}. This stress is hard to bear and can even possibly lead to disturbed relationships with the treating physicians and impaired compliance in postoperative care and follow up⁴¹.

CONCLUSION

Our study indicates that the delay in referral, diagnosis and treatment is quite long in the Netherlands Cancer Institute, and in the majority of patients the national guidelines are not met. Currently a fast-track program is set up to diminish these delays. In this population, the interval between diagnosis and treatment is not a prognostic factor for survival. This argument can cautiously be used to comfort patients who indeed have to wait for several weeks for treatment. For the mentioned psychological reasons as well as the possible increased morbidity as a result of more extensive surgery and/or expanded radiation fields, it is still of great importance for policymakers to consider treatment delay as an indicator for quality of care and patient well-being. We believe that, next to providing sufficient diagnostic and treatment capacity in order to anticipate adequately to the increasing cancer incidence, further research should be conducted with the objective of improving the logistics of head and neck cancer care and to make a better selection of patients needing urgent care.

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