Advanced stage head and neck cancer

Factors related to delay in seeking a diagnosis

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HEAD AND NECK CANCER

Incidence

In head and neck malignancies, the most common type of malignant tumour is one that arises from the surface squamous epithelium of the upper aerodigestive tract.[1] Tumours of the brain, eye, thyroid, skin and (non) Hodgkin's disease are not included in this category. Approximately 32% of the newly diagnosed carcinomas of the head and neck in the Netherlands occur in the oral cavity, 28% in the larynx, 18% in the oropharynx and hypopharynx, 8% in the lip, 5% in the major salivary glands and 9% in the remaining sites (nasopharynx, nasal cavity, paranasal sinus and middle ear).[2]

In the Netherlands, each year approximately 2500 patients are diagnosed with a tumour in the head and neck. This is approximately 4% of all newly diagnosed malignancies and in the Netherlands head and neck tumours are the seventh and eleventh most common cancers in men and women, respectively.[2] In middle aged (45-59 years) men head and neck cancer reached even the fourth place after lung, colon and prostate cancer.[3] The male to female ratio for larynx cancer changed from 8.4 to 6.1 and for oral and pharynx cancer from 2.1 to approximately 1.5 in the period 1989-1998.[2] This change in male to female ratio is particularly due to an increased consumption of tobacco and alcohol in women.

The last 10 years the incidence of oral cancer has been rising every year with approximately 3.5%. This is mainly due to an increase of the number of women diagnosed with oral cancer.[2] The increase for oropharynx cancer was 5% every year and due to an increase in men and women. The incidence of larynx cancer remained stable over the last 10 years, although there is a slight increase for women and a corresponding decrease in men.[4] In some countries there is a rise in incidence of cancer of the larynx during the last decades.[5] Recent reports have shown an increased incidence of squamous cell carcinoma in women and in patients younger than 40 years.[6]

Increasing incidence of advanced stage tumours

Advanced stage (IV) oral tumours has been rising by 1% every year since 1990 at the cost of less advanced stages.[2] For oropharyngeal cancer there was no such trend, but most patients were diagnosed as stage IV tumours, respectively 61% in men and 53% in women. Presentation of patients with larynx cancer was more likely to be in advanced stage in 1998

compared to the early 1990s. Also in the United States an increase in patients presenting with an advanced (IV) stage was seen for larynx cancer.[7]

Risk factors

It has been demonstrated that drinking alcohol and smoking tobacco are the major risk factors for developing squamous cell carcinomas of the head and neck.[8-18] The risk of head and neck cancer among heavy drinkers is highest for sites in direct contact with alcohol.[19-21] The combined effect of heavy drinking and smoking increases the risk of developing head and neck cancer even more.[22-27] It has also been demonstrated that patients who smoke and drink have an increased risk of metachronous and synchronous tumours.[28] Other, but more rare risk factors mentioned are asbestosis, smoking marihuana, chewing betel quid (in Asian countries), sunlight (cancer of the lip) and human papilloma virus.[29-33]

Survival

Survival of head and neck cancer depends on prognostic factors related to the primary tumour, cervical lymph nodes (number of positive cervical lymph nodes, extracapsular extension, level and size of lymph nodes), distant metastases and patient related factors (age, race, alcohol and tobacco exposure and comorbidity).[34]

Outcome of cancer treatment in literature is often measured as the percentage of patients who is still alive after a follow up period of 5 years after treatment. Five-year survival depends on the site of the primary tumour and the clinical stage at diagnosis (Table 1). The wide range of 5-year survival percentages are due to different sites of the primary tumour. Notwithstanding optimized treatment protocols for the management of head and neck cancer, survival has not much improved.[35-37]

Head and neck cancer and its treatment have a huge impact on quality of life. The localization of the tumour and the often disfiguring treatment interfere with some of the most fundamental aspects of daily functioning, such as talking, breathing and eating. Patients have to cope with a range of disease-related symptoms and side-effects of treatment. For example, patients may experience swallowing problems, impairment of speech, pain, or a dry mouth after treatment. Moreover, unlike other forms of cancer, the disfigurement after head and neck surgery cannot be hidden. In particular, patients who are diagnosed with an advanced tumour need extensive and costly treatment, in most cases both surgery and radiotherapy. Patients

who have undergone this treatment reported a lower quality of life than those who have undergone either surgery or radiotherapy alone.[41-43] Therefore, to reduce morbidity and mortality as well as treatment costs, early detection of head and neck cancer is extremely important.

Table 1. 5-year survival rate according to the AJCC classification[38]

				5-year survival[a]			
Clinical stage	T	N	M	Larynx	Oropharynx	Hypopharynx	Oral cavity
I	T1	N0	M0	86-100%	49-100%	50-74%	88-91%
II	T2	N0	M0	69-88%	29-86%	36-63%	63-80%
III	T3	N0	M0	36-80%	23-76%	26-41%	60-75%
	T1-T3	N1	M0				
IV	T4	N0-N3	M0-M1	32-63%	11-59%	5-41%	32-59%
	T1-T4	N2-N3	M0-M1				

[a] 5-year survival rate depends on site of the tumour[39;40]

Delay in diagnosis

Early detection of head and neck cancer is believed to be the most effective way to improve survival.[44;45] Diagnostic delay can be defined as the period from awareness of first tumour related symptoms to eventual diagnosis. Cancer diagnosis can be delayed by patients, by doctors or both. Therefore, a distinction is often made between patient and professional delay. Patient delay can be described as the period of time between first noticing a symptom and their first consultation with a health care professional. Professional delay can be described as the time from the patient's first medical consultation to the definitive diagnosis or treatment. Total diagnostic delay is the sum of patient and professional delay. It is reasonable to assume that delay is related to the stage of the disease at the time of diagnosis. Thus, the detection of cancer in an early stage of the disease could improve survival. Although our assumption seems reasonable, literature is far from conclusive, which will be addressed in the following paragraph.

Delay in head and neck cancer diagnosis

Literature shows that among head and neck cancer patients the average total diagnostic delay ranged from 3 to more than 7 months, while the median total diagnostic delay ranged from 1.5 to 6.7 months (Table 2). Total diagnostic delay of less than 3 months was seen in 42-66% of the patients, while more than 6 months delay occurred in 21-41% of the patients.

The average patient delay varies from 7.3 weeks to 6 months, while the median patient delay varied from 18.5 days to 12.2 months (Table 3). The percentage of patients who postponed seeking medical care for more than 3 months ranged from 20-34% and around 45% for patients with larynx cancer.

Studies about professional delay are not always easy to compare, while different definitions are used. Professional delay has been defined as the time between first medical consultation and histopathological diagnosis or to treatment. Other studies divided professional delay into delay between the first medical visit to a health care professional and the first visit to the hospital (referral delay) and delay between the first hospital visit and diagnosis or treatment (Table 4). The average professional delay varied from 22 days to 11.3 weeks, while the median professional delay varied from 4 days to 3.52 months. The average referral delay varied from 8.4 days to 5.8 weeks. The median referral delay varied from 6 days to 4 weeks.

Several studies investigated the relationship between delay and disease outcome parameters. Most studies used tumour stage as an outcome measure[46-61], but some studies used tumour size[62-66], survival rate[67-71], local recurrence rate[72] or tumour volume.[73]

Some studies showed a correlation between advanced-stage cancer and increased professional delay.[74-78] Other studies, however, did not show any relationship.[79-87] One study found that small tumours showed more professional delay in a cohort of oral cancer patients.[88] Whereas some studies show a relation between advanced-stage cancer and increased patient delay for oral cancer[89], hypopharyngeal cancer[90] or larynx cancer[59;91], others do not.[92-104]

Several studies indicated that survival was worse for patients who had shown patient delay[105] or experienced professional delay[106;107], although the results were not confirmed in other studies.[108;109] A study among oropharyngeal cancer patients showed a significant tumour volume increase during waiting time for radiotherapy with, as a consequence, an average loss of probability in tumour control of 16-19%.[110]

Table 2. Total delay (period from first tumour-related symptoms until diagnosis)

Author	Year	Localization	Mean	Median	Range		Definition
Silverman	1988	oral	3-5 months				symptom-diagnosis
Jovanovic	1992	oral	125 days	46 days	14 days-2 years		symptom-diagnosis
Wildt	1995	oral	162 days	122 days	19-783 days		symptom-admission hospital for treatment
Dhooge	1996	H&N				53% ≤3 months	symptom-diagnosis
Dost	1996	H&N		21 weeks			symptom-diagnosis
Rubright	1996	oral	5.38 months				symptom-staging by ENT
Mlacak	1997	glottis	3 months				symptom-diagnosis
		supra/subglottis	>7 months				symptom-diagnosis
Allison	1998	UADT		4 months	1 week-20 months		symptom-treating specialist
Dolan	1998						
Koscielny	1999	H&N	14-17 weeks	6-7 weeks			symptom-H&N clinic
Raitola	2000	larynx					
Habermann	2001	larynx		130 days			
Kerdpon	2001	oral	141.8 days		0-1085 days		symptom-treating specialist
Koivunen	2001	oropharynx/hypopharynx		3.6 months	0-21 months		
Pitiphat	2002	oral				48% <21 days	symptom-diagnosis
Onizawa	2003	oral		2.7 months	0.4-63 months		symptom-diagnosis
Teppo	2003	glottis		6.7 months	1-79 months		symptom-diagnosis
		supraglottis		5.2 months	2-21 months		symptom-diagnosis

Table 3. Patient delay

Author	Year	Localization	Mean	Median	Range		Definition
Pera	1986	larynx/hypopharynx		12.2 months	1-180 months		
Scully	1986	oral		74.5 days	67-82 days		symptom-general practitioner
				18.5 days	0-172 days		symptom-dentist
Guggenheimer	1989	oral/oropharynx	17 weeks		1 day->1 year		
Dimitroulis	1992	oral	134 days		6 days-8 years		
Jovanovic	1992	oral	103 days	35 days	7 days-2 years		
Schnetler	1992	oral		2.5 months			
Vernham	1994	H&N	4.6-6.1 months				
Wildt	1995	oral	106 days	71 days	0-600 days		
Dost	1996	H&N		13 weeks	7-19 weeks		
Mlacak	1997	glottis	2 months				
		supra/subglottis	6 months				
Allison	1998	oral/pharynx/larynx		2 months	0-18 months		
Dolan	1998	H&N	3.5 months				
Amir	1999	lip/oral	7.4 weeks	4 weeks			
		larynx/pharynx	12.3 weeks	3 weeks			
Koscielny	1999	H&N		2-5 weeks	9-11 weeks		
		oropharynx		4 weeks			
		hypopharynx		4.5 weeks			
		oral		3.5 weeks			
		supraglottis		4 weeks			
		glottis		8 weeks			
Hollows	2000	oral	22.5 weeks				
Raitola	2000	larynx		4.2 months			
Habermann	2001	larynx		75 days	44-135 days	43.3% >3 months	
Kantola	2001	tongue		1 month	0-46 months		
Kerdpon	2001	oral	91 days		0-720 days		
Koivunen	2001	oro/hypopharynx		1 month	0-12 months	39% >2 months	
Carvalho	2002	H&N		3 months	1 week-96 months		
Onizawa	2003	oral		1.6 months	0-60 months		
Teppo	2003	larynx		2 months		46% ≥3 months	
McLeod	2005	oral	19 weeks	13 weeks	1-104 weeks		

Table 4. Professional delay, including referral delay

Author	Year	Localization	Mean	Median	Range		Definition
Scully	1986	oral		4 days	0-232 days		ENT-diagnosis
				31 days	7-100 days		GP-ENT
				40 days	0-177 days		Dentist-ENT
Guggenheimer	1989	oral/oropharynx	20 weeks		2 weeks-1 year		HCP-diagnosis
Merletti	1990	larynx/hypopharynx	-	-	-		
Dimitroulis	1992	oral	58 days		2 days -3.2 years	57% <2 weeks	ENT-diagnosis
Jovanovic	1992	oral	22 days	11 days	1 day -6 months		ENT-diagnosis
Schnetler	1992	oral		10 days	3 days -1 year		ENT-specialist
				4 weeks	1 week-8 months		Dentist-specialist
Kowalski	1994	oral					Physician-H&N department
Vernham	1994	H&N	11.3 weeks				ENT-diagnosis
			5.8 weeks				HCP-ENT
Wildt	1995	oral	45 days	18 days	1-384 days	20% >2 months	GP/dentist-biopsy
Dost	1996	H&N		4 weeks	3-6 weeks		GP-ENT referral delay
				4 weeks			ENT-diagnosis
Pinholt	1997	oral				13% no delay	Referral delay by GP/dentist
						12% 1-3 weeks	
						33% 1-3 months	
						22% 4-9 months	
						13% 1-3 years	
Allison	1998	H&N		1 month	0-12 months		HCP-treating specialist
Allison	1998	UADT		1month	days -12 months	71% <1 month	HCP-treating specialist
Koscielny	1999	H&N	5.6 weeks	1.8 weeks			GP-H&N clinic
Hollows	2000	oral	14.5 days	-	0-176 days	69% <7 days	GP-ENT
			8.4 days		0-90 days		Dentist-ENT
Habermann	2001	larynx		25 days	6-83 days	55% <1 month	Physician-H&N department
				12 days	7-24 days	61.1% <2 weeks	ENT-treatment
Kantola	2001	tongue		0.7 months	0.1-18.2 months		HCP-ENT
Kerdpon	2001	oral	51.2 days		0-730 days		HCP-treating specialist
Koivunen	2001	oropharynx		0.9 months	0-7 months		ENT-diagnosis
		hypopharynx		1.6 months	0-9 months		
Carvalho	2002	H&N		1 month	1 day-3 months		ENT-diagnosis
Jones	2002	H&N	5.1 weeks		2-12 weeks		HCP-ENT
Sharp	2002	H&N		67-89 days			HCP-treatment
Onizawa	2003	oral		6 days	0-240 days		HCP-ENT
Teppo	2003	larynx		3.0 months			ENT-diagnosis
Ho	2004	oropharynx		3.52 months	0-30 months	40% >3 months	ENT-diagnosis
McLeod	2005	oral		1 week	0-38 weeks	39% <2 weeks	Referral delay
Tandon	2005	H&N	2.3 weeks		0.1-18.3 weeks		H&N clinic-diagnosis

Although some reports show some evidence that delay affects survival, literature is not consistent. The discrepancies found between the various studies might be attributed to the different definitions of delay. There is also large variation in the methods used to collect data on diagnostic delay. Most studies used medical records[59;111-119], some patients' questionnaires[120-124] or patients' interview data[125-128] or a combination of both interviews and medical records.[129;130] An aspect that is inherent in studies of patient delay is that the nature of the data are retrospective, and therefore subject to recall bias.

A conceptual model of delay

For this study a model of delay is used that was proposed by Andersen and Cacioppo[131] and based on earlier work of Shafer *et al.*[132] In this model, the patient component of total delay is divided into appraisal, illness, behavioural and scheduling delay (Figure 1). Appraisal delay is defined as the period which elapses from the moment an individual detects unexplained signs or symptoms until the moment he or she concludes to be ill. Illness delay is defined as the number of days elapsed from the moment an individual concludes to be ill until the moment he/she decides to seek medical help. The next two stages are behavioural delay, which represents the time elapsed between the decision to seek medical help and making an appointment with a general practitioner, and scheduling delay which represents the time elapsed between making an appointment and first receiving medical attention. In the model of Andersen and Cacioppo the period from first medical attention until treatment is called treatment delay. To get a better insight in the different forms of professional delay we medical specialist delay and treatment delay. We think that exploring these different stages of patient and professional delay could serve as a base for interventions that might have a positive influence on the stage of the disease at presentation and survival.

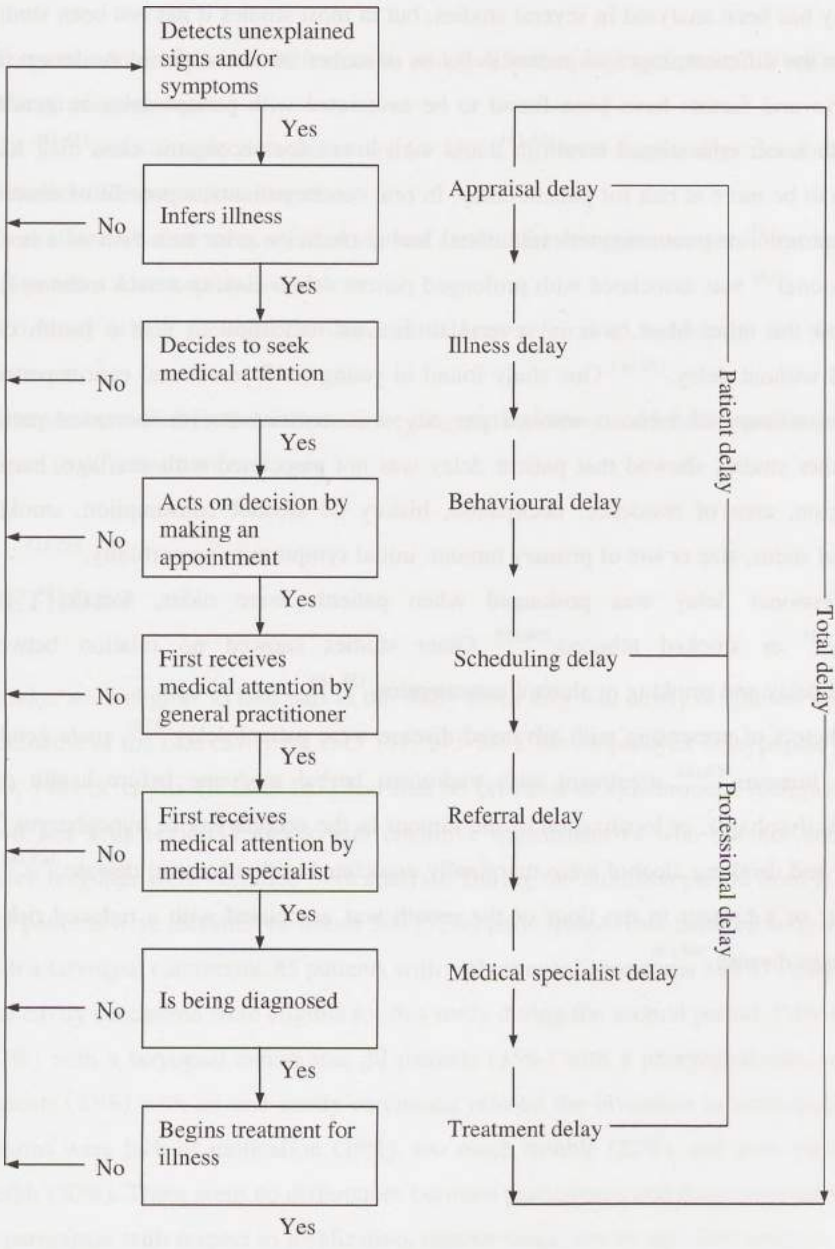

Figure 1. Andersen's model of total patient delay in which the stages of professional delay are modified for the present study.

Factors related to patient and professional delay

Patient delay has been analysed in several studies, but in most studies it has not been studied according to the different stages of patient delay as described in the model of Andersen and Cacioppo. Several factors have been found to be associated with patient delay in general. Patients with lower educational level[133;134], and with lower socioeconomic class[135;136] have been shown to be more at risk for patient delay. In oral cancer patients, a poor fit of dentures as first symptom[137] or treatment with traditional herbal medicine prior to a visit of a health care professional[138] was associated with prolonged patient delay. Having a neck mass as first symptom, on the other hand, was in several studies an indication to visit a health care professional without delay.[139-143] One study found in young (<45 years) oral cancer patients that a lower amount of tobacco smoked per day was associated with increased patient delay.[144] Other studies showed that patient delay was not associated with sex, age, marital status, religion, area of residence, occupation, history of alcohol consumption, smoking habits, dental status, size or site of primary tumour, initial symptom or comorbidity.[145-153]

Professional delay was prolonged when patients were older, female[154], had comorbidity[155] or smoked tobacco.[156;157] Other studies showed no relation between professional delay and smoking or alcohol consumption.[158-160]

Predictors of presenting with advanced disease were patient delay[59;161], male gender, less visible tumours[162;163], treatment with traditional herbal medicine before health care consultation, dysphagia, or localization of the tumour in the oropharynx or hypopharynx.[164-166] Old age and drinking alcohol were marginally associated with advanced disease.[167;168] A painful ulcer or a tumour in the flour of the mouth was associated with a reduced risk of advanced stage disease.[169;170]

AIMS OF THIS THESIS

- To gain more insight into the extent to which different stages of patient delay are related to different tumour stages.
- To gain more insight into the extent to which different stages of professional delay are related to different tumour stages.
-To evaluate whether tobacco smoking and alcohol consumption are predictive for prolonged delay and/or advanced disease.
- To study which factors contribute to delayed referral to a hospital for diagnosis and treatment.
- To examine which factors influence the diagnostic process and whether professional delay is related to different tumour stages

METHODS

Patients were eligible to take part in the study when they had newly diagnosed squamous cell carcinoma of the oral cavity (ICD-O 141, 143-145), the oropharynx or hypopharynx (ICD-O 146, 148) or larynx (ICD-O 161) and had no previous or synchronous malignancies in the head and neck region. Patients with cognitive impairment or who did not understand the Dutch language were excluded from analysis. During the inclusion period from 2000 to 2002, 427 patients were recruited of whom 306 (72%) participated. One hundred sixty-nine patients with a laryngeal carcinoma, 85 patients with a pharyngeal carcinoma and 173 patients with an oral cavity carcinoma were eligible for this study during the accrual period. Fifty-two patients (37%) with a laryngeal carcinoma, 30 patients (35%) with a pharyngeal carcinoma and 39 patients (23%) with an oral cavity carcinoma refused the invitation to participate. The main reasons were lack of motivation (29%), too much trouble (22%), and poor physical/mental health (30%). There were no differences between participants and those patients who refused to participate with respect to localization, tumour stage, sex or age. Our analyses were based on data for 117 patients with a laryngeal carcinoma, 55 patients with a pharyngeal carcinoma and 134 patients with an oral cavity carcinoma. Two hundred ten patients were male and 96 were female. The patients' age ranged from 34 to 89 years with a mean age of 62 years. Two-

hundred seven patients were diagnosed with a small (T1-T2) tumour and 99 with a large (T3-T4) tumour. Regarding the clinical stage, 172 patients were diagnosed with early stage (I-II) disease and 134 patients with advanced stage (III-IV).

To minimize recall bias, patients were interviewed after diagnosis but before treatment; for those who would undergo surgery, the interview was held 1 or 2 days before treatment; in the case of radiotherapy and/or chemotherapy, they were interviewed just before or during the first treatment sessions. Each interview took approximately 60-75 minutes.

To enhance reliability we used different data sources to verify the course of events with regard to seeking medical care and treatment. To the best of our knowledge, there are no studies that used information from the partner or a close relative to verify the data on diagnostic delay. The partner was asked about the care seeking process, the visits to the healthcare professional, until the start of treatment. The response rate for the partners of the patients was 76%. Also information of the general practitioner and/or referring dentist was collected. They were sent a questionnaire asking about the policy from first visit of the patient for tumour-related symptoms until the referral to a medical specialist. The response rate for the general practitioners and/or dentists was 94%.

Data on tumour characteristics, such as T stage and localization were obtained from the medical records. The tumours were registered according to the International Classification of Diseases for Oncology (ICD-O) and the TNM classification.[171]

OUTLINE OF THE THESIS

Chapter 2 describes the analysis of the change in incidence of large (T4) tumours in head and neck cancer patients diagnosed in the period 1980-2000 at the University Medical Centre Utrecht. The figures are compared with data from the Netherlands Regional Cancer Registry (IKMN) and the National Cancer Registration (NCR).

Chapter 3 analyses the different stages of patient delay and whether these stages are related to different tumour stages in larynx cancer patients.

Chapter 4 analyses the different stages of patient delay and whether these stages are related to different tumour stages in oral and pharynx cancer patients.

Chapter 5 analyses the role of alcohol and smoking in diagnostic delay of head and neck cancer patients.

Chapter 6 analyses which factors contribute to delayed referral to a hospital for diagnosis and treatment.

Chapter 7 analyses which patient- and tumour-related factors influence the diagnostic process and whether professional delay is related to different tumour stages.

Chapter 8 contains the general discussion.

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Chapter 2

Increasing incidence of advanced stage head and neck tumours

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Abstract

The aim of this study was to determine whether the incidence of advanced stage (T4) head and neck tumours has increased. We analysed retrospective 3178 patients diagnosed with oral, pharyngeal, or laryngeal cancer in the period 1980 to 2000 at the University Medical Centre Utrecht (UMCU), the Netherlands. There was a statistically significant increase in the proportion of T4 head and neck tumours compared with non-T4 tumours over the period 1980 to 2000. Linear regression analysis estimated an increase of 0.9% every year. The observed increase in T4 tumours at UMCU shows up in figures from the Netherlands Regional Cancer Registry (IKMN) and the National Cancer Registration (NCR). Although these bodies report for fewer years, this finding refutes the possibility of selected referral to the University Medical Centre Utrecht. In conclusion, the number of head and neck cancer patients presenting with an advanced stage carcinoma (T4) has increased over a period of 21 years.

INTRODUCTION

At the University Medical Centre Utrecht (UMCU), all new patients presenting with tumours of the head and neck since 1980 have been entered prospectively in a database. This database was designed to provide information about patient characteristics, risk factors such as smoking and alcohol consumption, tumour classification and treatment, and outcome variables of patients diagnosed at our hospital.

Since 1989, the Netherlands Cancer Registry has published the annual incidence rates of cancer in the Netherlands. Data on all newly diagnosed tumours are submitted to the Netherlands Cancer Registry by regional cancer registries. In 1997, there were 65,000 newly diagnosed cases of cancer: 34,000 among males and 31,000 among females. This represents an increase of 9,000 cases in eight years, mainly caused by the growth of the elderly population.[1] Of these newly diagnosed tumours, 2350 occurred in the head and neck region (4%).

Despite the possibility of early diagnosis of head and neck tumours, there is a strong clinical suggestion that the number of patients with an advanced stage of disease is growing compared to the number with tumours showing limited disease. To evaluate whether this trend is real, we retrospectively analysed data of 3178 patients with head and neck malignancies localized in the oral cavity (including 35 lip carcinomas), pharynx, and larynx. The majority of these cancers are related to excessive alcohol consumption and smoking habits. There is even evidence that alcohol and tobacco act synergistically.[2-10] These risk factors, together with the factors of sex, age, and localization of the tumour, were compared for the different tumour stages.

An increase in incidence of advanced head and neck tumours could be related to a late presentation of patients with cancer symptoms to a general practitioner or dentist. Factors that might be related to or influence patient delay, e.g. health behaviour, anxiety and depression, coping, optimism and denial, warrant further research.

PATIENTS AND METHODS

We analysed the records of all patients who had been diagnosed at UMCU in the period 1980 to 2000 with a squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. The tumours were registered according to the International Classification of Diseases for Oncology (ICD-O) and the TNM classification (UICC 1987). Patients were excluded from the analysis if their ICD-O code and/or clinical TNM classification were missing from the records. Patients with *in situ* carcinomas or a history of head and neck carcinoma were also excluded. Carcinomas of the nasopharynx (ICD-O 147) were excluded because other aetiological factors besides smoking and alcohol play an important role in the development of these tumours.

Statistical analysis

All analyses were carried out with SPSS statistical software. Linear regression analyses were performed to test whether the percentage of T4 tumours relative to tumours in other stages had increased and to predict the increase in the incidence of advanced head and neck tumours. This was also done to analyse changes in incidence relative to sex, age, alcohol consumption, and smoking habits. The results were compared with the national (NCR) and regional (IKMN) cancer data obtained from the Comprehensive Cancer Centre Utrecht.

RESULTS

In total, 4693 patients were diagnosed at our clinic with head and neck cancer from 1980 to 2000. Of that number, 1406 patients were excluded according to the above-mentioned criteria. The exact TNM stage of 109 patients (3.4%) was unknown or could not be classified. This percentage varied from 0 to 6% over the years. Analyses were done on the data for the remaining 3178 patients. Of these tumours, 1175 (37%) were situated in the oral cavity (ICD-O 141, 143, 144, 145), 35 (1%) on the lips (ICD-O 140), 628 (20%) in the pharynx (ICD-O 146, 148, 149), and 1340 (42%) in the larynx (ICD-O 161). Over 60% of all laryngeal

carcinomas were glottic larynx carcinomas. Seventy-five percent of the patients diagnosed were male, and the median age was 63 years (range 20-96 years).

In absolute numbers, there was an increase at every site (Table 1). The relative number of patients with oral cavity and pharyngeal carcinomas increased, whereas the relative number of carcinomas of the larynx decreased (Table 2). Patients with lip carcinomas were not included in our analyses because there were too few of them.

Table 1.Total number and percentage of T4 tumours for laryngeal, pharyngeal, oral cavity and lip carcinomas

	Larynx		Pharynx		Oral cavity		Lip		Total	
Cohort	No.	% T4	No.	% T4	No.	% T4	No.	% T4	No.	% T4
1980-1982	82	9.8	13	38.5	46	10.9	0	0	141	10.6
1983-1985	154	10.4	35	25.7	65	20.0	2	0	256	14.8
1986-1988	161	13.7	57	47.4	120	23.3	3	0	341	22.6
1989-1991	257	12.5	105	50.5	173	20.8	7	16.7	542	22.5
1992-1994	223	17.9	112	31.3	221	25.8	5	20.0	561	23.7
1995-1997	248	16.1	140	40.7	253	30.8	10	10.0	651	27.0
1998-2000	215	14.0	166	38.0	297	26.6	8	12.5	686	25.2
Total	1340	14.0	628	39.2	1175	25.2	35	11.4	3178	23.1

Overall, the relative number of patients with a T4 stage carcinoma increased significantly. In the period 1980 to 1982, one out of nine patients had a T4 carcinoma; in the period 1998 to 2000, this rose to one out of four patients. This increase in the proportion of T4 carcinomas with respect to carcinomas in the remaining stages was statistically significant (Table 2).

Table 2. Regression analyses run *separately* for different dependent variables

Dependent variable	R^2	*p*-value	B	95% CI
% T1	.62	.000	-0.8	-1.1 – (-0.5)
% T2	.15	.087	0.2	0.0 – 0.5
% T3	.24	.023	-0.3	-0.6 – (-0.1)
% T4	.63	.000	0.9	0.6 – 1.2
% larynx	.72	.000	-0.5	-0.6 – (-0.3)
% pharynx	.64	.000	0.8	0.5 – 1.1
% oral cavity	.37	.004	0.5	0.2 – 0.8

The regression analysis showed a linear model. The non-standardised coefficient was 0.9, which means that every year the proportion of T4 carcinomas increased on by 0.9% average. This increase mainly resulted from oral cavity carcinomas (Table 3). For the T4 laryngeal

tumours, there was an increasing trend. The result of the regression for T4 pharyngeal tumours was not significant.

Table 3. Regression analyses run *separately* for different dependent variables

Dependent variable	R^2	*p*-value	B	95% CI
% T4 larynx	.56	.054	0.7	0.0 – 3.3
% T4 pharynx	.26	.243	0.3	-0.3 – 0.8
% T4 oral cavity	.75	.012	0.9	0.3 – 1.5

Figure 1 shows the linear regression for the proportion of T4 larynx, pharynx and oral cavity carcinomas based on 3-year periods. The relative number of T1 carcinomas decreased significantly by 0.8% every year. In the period 1980 to 1982, 39% were diagnosed as a T1 tumour; in the period 1998 to 2000, this was 27%. The relative number of T2 and T3 tumours did not change over time (Table 2).

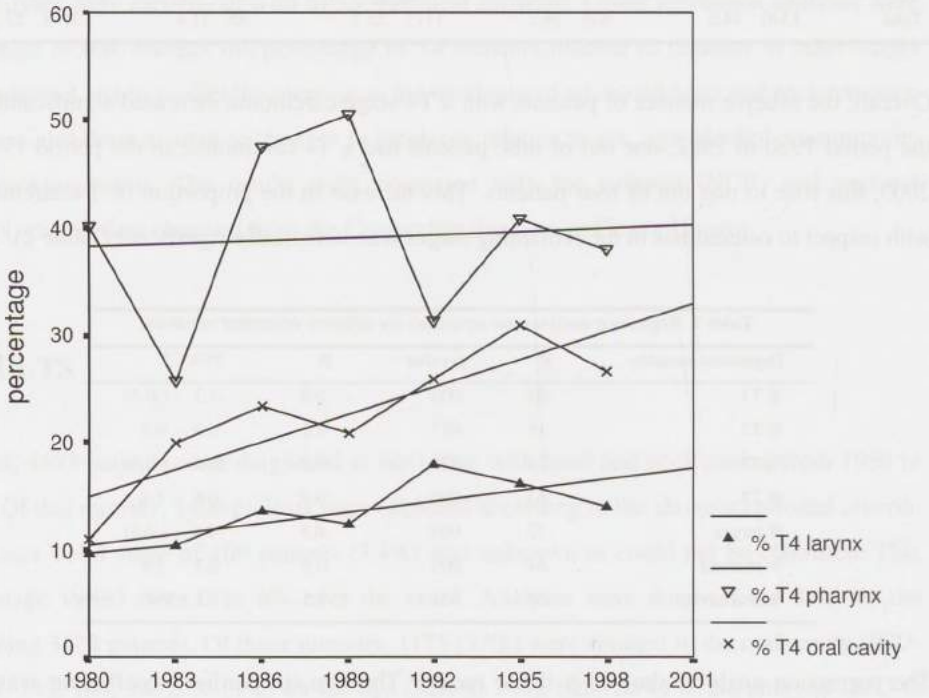

Figure 1. Linear regression for percentage of T4 larynx, pharynx, and oral cavity carcinomas in our clinic for the period 1980 to 2000.

The percentage of women diagnosed at UMCU with head and neck cancer rose from 20% in 1980 to 1984 to 28% in 1996 to 2000 (R^2=.90, p=.004). More than 26% of those women had a stage T4 tumour, compared to 22% of the men.

The percentage of head and neck cancer patients who claimed they had stopped smoking at the first consultation in our clinic increased significantly from 10% to 25% (R^2=.97, p=.000) over the years. The percentage of patients who did not smoke, smoked 0-20, or >20 cigarettes per day fluctuated around 10%, 37% and 30% respectively; these shares did not increase or decrease over time.

There was no obvious trend in alcohol consumption. The number of patients who did not drink on a daily basis, who consumed 1-4 units/day, or who had >4 units/day was stable over the years at 47%, 34%, and 19% respectively.

National figures show a relative increase in the number of patients with pharyngeal and oral cavity tumours, whereas the number of laryngeal tumours decreased.[1] The national percentage of T4 tumours rose from 18% in 1989 to 23% in 1997 (Figure 2). The 0.9% increase among our population did not differ from that found nation wide (p=.68). The number of patients treated at our clinic compared with the total number of patients treated in the Netherlands remained proportionally the same (national figures from 1989). Referrals from the region did not change with respect to the stage (regional figures from 1986).

DISCUSSION

The increase in T4 head and neck carcinomas observed at our clinic over a period of 21 years was statistically significant. Changes in the tumour stage and localization of the lesion at diagnosis have also been reported in the international literature.[11;12] Furthermore, the incidence of oral and pharyngeal cancer has risen in former east Germany as well as in England and Scotland.[13]

To exclude selective referral as an explanation of the increase observed at our institution, we compared our findings with regional and national figures. Although the regional and national registries cover fewer years, the increase in the percentage of T4 tumours remained proportionally the same across the data sources. Thus, this similarity probably excludes selective referral to our clinic as a possible explanation.

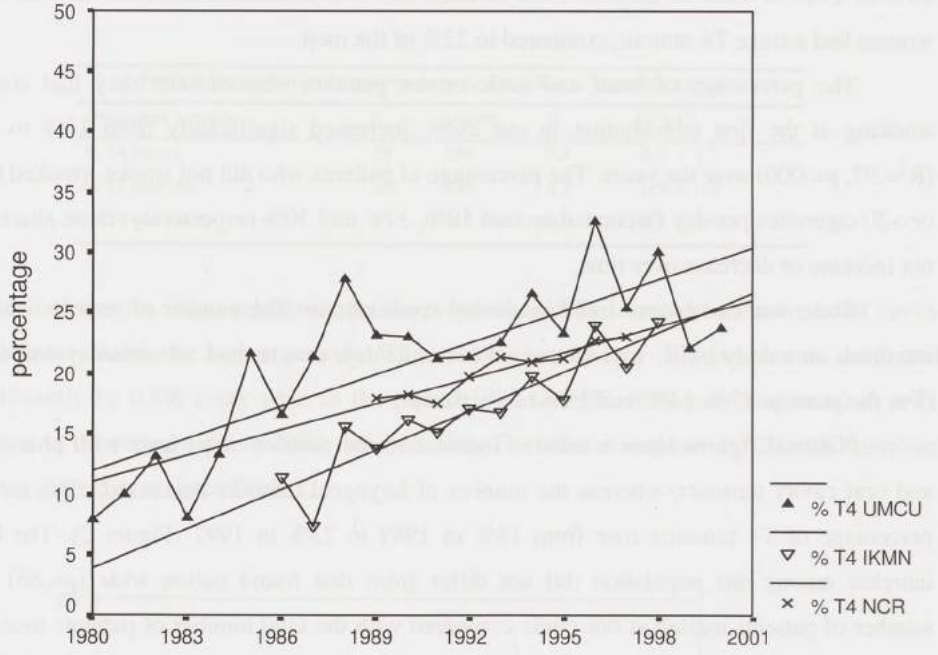

Figure 2. Linear regression for percentage of T4 stage head and neck carcinomas in our clinic (UMCU), regional (IKMN), and national (NCR).

Another explanation might be an improvement in the imaging techniques made possible by computerized tomographic (CT) scans and the introduction of magnetic resonance imaging (MRI). Better detection of the invasion of tumours in the surrounding tissue, e.g. into cartilage or bone, would supposedly explain the increase in the diagnosis of T4 tumours. However, most T4 carcinomas are of such a size that invasion could not be missed on the CT scans of the early 1980s. Besides, the clinical T stage of those patients who had undergone surgery in our clinic did not differ from the T stage assessed by our pathologist.

In our analysis, we found a significant increase in the percentage of women diagnosed with head and neck cancer. However, this did not correspond to a higher percentage of T4 tumours in our clinic, because the number of women was too small.

It is well known that patients with advanced stage head and neck carcinomas tend to be heavy smokers and drinkers.[14] Our analysis confirmed that patients with advanced head and neck cancer smoked and drank more than the general population.

In the Netherlands, alcohol consumption was at its highest during the mid-seventies and the eighties.[15;16] This peak was followed by a slight decline, and the numbers stabilised during the nineties. Since 1989, there has been an increase in the percentage of people who consume three or more alcoholic drinks a day. Although the percentage of people who drink alcohol remained stable, the level of consumption has increased. From the late sixties until the early nineties, the percentage of smokers declined, although the consumption of tobacco was the highest in the seventies. The rise in alcohol consumption and smoking could be related to the higher incidence of oral and pharyngeal carcinomas. The combination of heavy drinking and smoking could be an important factor in the increase of T4 carcinomas in particular.

Lastly, the increase in the number of elderly patients caused by an aging population could be an explanation for the higher incidence of T4 tumours. Better treatment options could lead to more referrals of elderly persons with advanced stage head and neck carcinomas to a cancer centre than in the past. Coebergh *et al.*[17] have shown that advanced age is a factor in late presentation. But, in our T4 patient population, the increase in the number of patients aged 40 to 50 was greater than the increase among patients aged over 80 years.

Our data showed an increase in the number of patients with a head and neck carcinoma. The number of patients with a T4 tumour increased even more rapidly, resulting in a higher percentage of T4 tumours over the years 1980 to 2000. This increase appears to represent a national trend. Because late presentation of head and neck carcinomas results in a worse prognosis, high morbidity, and high treatment costs, it is important to determine which factors are responsible for a delayed presentation. Efforts to improve the early diagnosis of this patient population should focus on factors influencing patient delay such as health behaviour, coping and denial, and/or professional delay.[18-20] Also, lack of awareness seems to be an important factor in late presentation of disease.[21] The worse prognosis, the high morbidity, and the high treatment costs of this patient population would clearly justify further research.

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Chapter 3

Laryngeal cancer patients: Analysis of patient delay at different tumour stages

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Abstract

Background. The aim of this study was to determine the length of stages (appraisal, illness, behavioural and scheduling) of patient delay in head and neck cancer patients and to find out if these delays were related to the stage of the disease at diagnosis.

Methods. Before treatment, 117 newly diagnosed laryngeal cancer patients were interviewed about their prediagnostic period. To determine the length of the different stages of patient delay, patients were asked about their symptoms, attributions of symptoms and reasons to postpone medical consultation. A questionnaire was sent to the general practitioner and to a close relative in order to verify their answers.

Results. There was no significant difference in the length of patient delay between early- (T1-T2) and advanced- (T3-T4) stage disease (9 vs. 5 weeks; p=.07). Only tumour site was significantly associated with patient delay. The median total patient delay for glottic and supraglottic tumours were 10 and 4 weeks, respectively (p=.00). Hoarseness/voice change was the most common mentioned symptom. Patients attributed their symptom most frequent to a common cold/infection or had no idea about the cause. Medical attention was postponed because symptoms were interpreted as innocuous/benign or the symptom was thought not to be serious enough. The main reason to visit the general practitioner was the persistent hoarseness. Behavioural and scheduling delays were of minor importance.

Conclusions. Patient delay was significantly longer in cases of glottic cancer, but diagnosis at an early stage of the disease was more frequent among these patients than among patients with supraglottic cancer. Advanced supraglottic cancer probably has a late onset of symptoms. Thus, earlier intervention will probably not result in a significantly higher proportion of small supraglottic cancers being diagnosed.

INTRODUCTION

In the Netherlands, the most common cancer in the head and neck is cancer of the larynx. For the period 1989 to 1998, the Dutch Cancer Registry shows a declining incidence of glottic cancer for males but not for females. Laryngeal cancer is diagnosed in men approximately seven times more often than in women. In contrast to the declining incidence, the death rate caused by laryngeal cancer rose by approximately 7% over the same period.[1] This is because more patients are initially seen with tumours in advanced stages.[2-9]

The objective of this prospective study was to analyse patient delay in cases of laryngeal cancer. It is reasonable to assume that the duration of symptoms is related to the stage of the disease at the time of diagnosis. However, the literature is inconclusive on this matter; whereas some studies show a relation between longer duration of symptoms and advanced disease,[6,10] others do not.[11-14] Also the site of the tumour (glottic versus supraglottic) seems to be related to the stage of the disease at diagnosis.[2,13,15,16]

According to a stage model developed by Andersen and Cacioppo,[17] the patient component of the total delay may be divided into appraisal, illness, behavioural and scheduling delay (Table 1). Most studies of delay in head and neck cancer are based on a retrospective analysis of medical records or on interviews after treatment. The latter method probably generates less accurate data, because it is not always easy for a patient to remember when the symptoms started. Although our study design is retrospective, we minimized the recall bias by interviewing the patients just before treatment.

Table 1. Definition of the different stages of patient delay according to the model of Andersen *et al.*

Type of delay	Definition
Appraisal delay	Period from unexplained symptoms until the moment he/she considers to be ill
Illness delay	Number of days from the time an individual concludes to be ill to the day he/she decides to seek medical help
Behavioural delay	Time elapsed between the decision to seek medical help and making an appointment with a general practitioner
Scheduling delay	Time elapsed between making an appointment and first receiving medical attention

This article examines patient delay in a consecutive cohort of patients with laryngeal cancer to find out whether the stages of patient delay are related to tumour stages.

PATIENTS AND METHODS

Patients were eligible to take part in the study if they had newly diagnosed squamous cell carcinoma of the larynx and had no previous or synchronous malignancies in the head and neck region. Those who had a cognitive impairment or who did not understand the Dutch language were excluded from the analysis. During the period 2000 to 2002, letters were sent to patients diagnosed at the Department of Otorhinolaryngology at University Medical Centre Utrecht, inviting them to participate.

In total, 169 patients were diagnosed during the accrual period. Fifty-two patients (31%) refused to participate. The main reasons were lack of motivation (37%), too much bother (29%) or poor physical/mental health (25%). No differences were found between the participants and the patients who refused to participate with respect to tumour stage, sex or age. The analysis is based on data on 117 patients.

To determine the duration of the stages of delay, we interviewed the patients before treatment: for those who were to undergo surgery, the interview was held one or two days before treatment; in the case of radiotherapy and/or chemotherapy, they were interviewed just before or during the first treatment session. Each interview took approximately 60 to 75 minutes. Patients were asked about their first tumour-related symptoms. Regarding the stage of appraisal delay, the patients were asked what they thought had caused their first symptoms and to recall when they had first inferred illness. Regarding the stage of illness delay, the patients were asked why they had consulted a general practitioner (GP) and whether they had been encouraged by others to do so. The stage of behavioural delay was explored by asking why they had postponed medical consultation. The length of the stage of scheduling delay was calculated from the date of the first medical consultation. A questionnaire was then sent to the GP and to a close relative to verify their answers. To determine the length of the different stages of delay, we compared the data obtained from the patients with that from the GP and the relative. When the duration of the total patient delay reported by the relative exceeded that mentioned by the patient by one month and the relative indicated that the patient had postponed seeking medical attention, we used the data obtained from the relative. The date of first medical contact was derived from the information given by the GP. Only tumour-related symptoms were used to determine the length of the different stages of delay.

Tumour characteristics such as T classification and localization were obtained from the medical records. The tumours were registered according to the International Classification of Diseases for Oncology (ICD-O) and the TNM classification[18]. Because the pattern of first symptom(s) of glottic carcinomas differs from that found in subglottic and supraglottic carcinomas, patients with these types of lesions were analysed as separate groups.

Statistical analysis

In line with the literature, the delay periods were divided into three categories: <1 month, 1 to 3 months, and >3 months. Patient delays in the first category correspond to the recommendation of the Dutch Cancer Society. All analyses were carried out with SPSS statistical software. The chi-square test was applied to categorical data and the Kruskal-Wallis test to continuous data.

RESULTS

Patient characteristics

Most persons in the study were elderly men. Two-thirds of the patients had a tumour in the vocal cords, and 92% of the patients were diagnosed at an early stage (T1-2) of disease (Table 2). The nonglottic carcinoma group consisted of 35 persons with supraglottic, two with subglottic, and two with transglottic carcinomas. Significantly more of the patients in this group were diagnosed at an advanced stage (T3-4) of disease, especially when neck node metastases were taken into account (stage III-IV). Sixty-eight patients (58%) were smokers and 46 (39%) were ex-smokers; three patients had never smoked. Ninety-six patients (82%) drank alcohol; 21 (18%) either did not or had stopped.

In terms of personal attributes, patients with small (T1-T2) tumours did not differ from those with advanced (T3-T4) tumours, and patients with glottic tumours did not differ from patients with nonglottic tumours. Specifically, they did not differ in marital status, living situation, education, work, income, smoking, alcohol intake or age (Table 2).

Table 2. Patient and tumour characteristics

Characteristics	No. patients (%) Glottic (n=78)	Nonglottic (n=39)	*p*-value
TNM			0.00
T1-T2	72 (92)	23 (59)	
T3-T4	6 (8)	16 (41)	
Stage			0.00
I-II	71 (91)	17 (44)	
III-IV	7 (9)	22 (56)	
Gender			0.27
male	63 (81)	28 (72)	
female	15 (19)	11 (28)	
Age			0.90
<65 year	39 (50)	20 (51)	
≥65 year	39 (50)	19 (49)	
Marital status			0.13
married/living together	61 (78)	35 (90)	
alone/divorced/widowed	17 (22)	4 (10)	
Living situation*			0.62
alone	13 (17)	5 (13)	
with family	65 (83)	33 (87)	
Education*			0.36
low	44 (56)	24 (63)	
middle	20 (26)	11 (29)	
high	14 (18)	3 (8)	
Work*			0.90
employed	24 (36)	14 (40)	
unemployed	7 (10)	3 (9)	
retired	36 (54)	18 (51)	
Income*			0.15
less than modal	48 (72)	28 (85)	
more than modal	19 (28)	5 (15)	
Smoking			0.23
0-20 cigarettes/day	19 (24)	11 (28)	
20-40 cigarettes/day	19 (24)	13 (33)	
≥40 cigarettes/day	2 (3)	4 (10)	
Stopped smoking			
<10 years	19 (24)	6 (15)	
≥10 years	17 (22)	4 (10)	
never smoked	2 (3)	1 (3)	
Alcohol			0.73
not daily	13 (17)	6 (15)	
1-4 drinks/day	35 (45)	19 (49)	
>4 drinks/day	14 (18)	9 (23)	
none	16 (21)	5 (13)	

** The addition sum does not equal 78 for glottic and 39 for nonglottic tumours*

Patient delay

The median length of time of total patient delay for laryngeal tumours was 8 weeks. Seventy-five percent of the patients had symptoms for more than one month. There was no significant difference in median total delay for T1-T2 tumours compared to T3-T4 tumours (Table 3). Taking into account the involvement of neck node metastases, the median total delay was also not significant for small (stage I-II) tumours compared to advanced (stage III-IV) disease (9 weeks versus 5 weeks). The median total patient delay for glottic and nonglottic tumours was respectively 10 and 4 weeks. This difference was statistically significant (Kruskal-Wallis: χ^2=15.01, p=.000). Forty percent of the patients with a glottic carcinoma waited for more than three months, compared with 18% of the patients with nonglottic carcinomas.

Table 3. Median patient delay (weeks, 25% to 75% interval) compared for early- (T1-T2) and advanced-stage (T3-T4) disease

	T1-T2		T3-T4			
	No. patients	Median delay, wk (25%-75%)	No. patients	Median delay, wk (25%-75%)	p-value	χ^2
Larynx*	95	9 (4-18)	22	5 (2-14)	.07	3.29
Glottic†	72	9 (5-21)	6	13 (7-78)	.30	1.08
Nonglottic†	23	4 (2-13)	16	3 (1-6)	.25	1.34

** Total patient delay*

† Appraisal delay

According to the model of Andersen and Cacioppo, appraisal delay is the period from the detection of unexplained symptoms until a patient considers himself or herself to be ill. Most of the patients said they did not infer illness until they visited the GP or even the ear, nose, and throat specialist. Therefore, we could not distinguish a separate stage for illness delay among the patients in our study. Only 27% of the patients inferred illness before they decided to seek medical help. Thus, we calculated appraisal delay as starting when the patient first experienced symptoms until the day he or she decided to seek medical help. The median appraisal delay for glottic cancer was significantly longer than for nonglottic cancer (9 weeks versus 4 weeks, Kruskal-Wallis: χ^2=13.93, p=.000). Comparison of small (T1-2) and advanced-stage (T3-4) disease for both glottic and nonglottic tumours showed no significant difference in appraisal delay (Table 3). Ninety-one percent of the patients made an appointment with their GP within one week after deciding to seek medical attention for their symptoms. Only four (3%) of the patients had a behavioural delay of more than 3 weeks.

Scheduling delay did not occur. All of the patients were seen within 8 days; 97% were seen within 2 days.

In 96% of the cases of glottic carcinoma, the first symptom was hoarseness or voice change (Table 4). For three patients, dyspnoea was the first symptom. Two patients with hoarseness became aphonic, and one developed (referred) otalgia later. In 44% of the patients with a supraglottic carcinoma, hoarseness or voice change was the first symptom. For 13%, the only problem was difficulty swallowing; 10% had a sore throat, and 24% had more than one symptom. One patient with difficulty swallowing reported that he had later developed a sore throat and otalgia. Another patient with hoarseness reported that he had later developed a sore throat. Only 17% of the patients with a glottic carcinoma had symptoms that started less than 4 weeks before the first medical visit compared to 49% for patients with nonglottic carcinoma. Among patients with glottic carcinoma, the median duration of appraisal delay was 2.2 months for the symptom of hoarseness/voice change.

Table 4. First symptoms reported by the patients for glottic and nonglottic cancer subdivided for different patient delay periods (percentages in parentheses)

	Glottic			Nonglottic		
Symptom	<4 wk	5-12 wk	>12 wk	<4 wk	5-12 wk	>12 wk
Hoarseness/voice change	12 (16)	33 (44)	30 (40)	6 (35)	5 (30)	6 (35)
Dyspnoea	1 (33)		2 (67)	1 (50)		1 (50)
Problems swallowing					4 (80)	1 (20)
Sore throat				3 (75)	1 (25)	
Neck mass				1 (100)		
General symptoms				1 (100)		
Hoarseness and sore throat				2 (67)	1 (33)	
Hoarseness, sore throat and otalgia				2 (100)		
Sore throat and otalgia				2 (100)		
Sore throat and swallowing problems				1 (100)		
Hoarseness, swallowing problems and a neck mass						1 (100)
Total	13 (17)	33 (42)	32 (41)	19 (49)	11 (28)	9 (23)

For symptoms reported by more than three patients with a supraglottic carcinoma, the median duration of appraisal delay was 1.0 month for hoarseness/voice change, 1.3 months for dysphagia, and 0.6 month for a sore throat.

Almost one third of the patients attributed their first symptoms to a common cold (Table 5). Nine patients with a glottic carcinoma and three with a supraglottic carcinoma

thought their symptoms were caused by cigarette smoking. Only four patients attributed their initial symptoms to cancer, whereas approximately one third of the patients had no idea what had caused their first symptoms. The patients mentioned a variety of other causes: infection, voice strain, stress, intubation, or irritation caused by a fish bone. Five patients with a glottic carcinoma had previously had a benign tumour removed and thought their symptoms were caused by a recurrence.

Table 5. Median total patient delay (weeks, 25%-75% interval) for different attribution of first tumour symptoms subdivided by localization

Attribution	Glottic		Nonglottic	
	No. patients (%)	Median total patient delay (25%-75%)	No. patients (%)	Median total patient delay (25%-75%)
Common cold	21 (27)	9 (4-15)	12 (31)	4 (2-21)
Infection	4 (5)	6 (3-13)	3 (8)	3 (2-5)
No idea	19 (24)	11 (7-21)	14 (28)	4 (1-12)
Voice misuse/abuse	6 (8)	9 (6-21)	1 (3)	5 -
Stress	3 (4)	5 (3-8)	1 (3)	3 -
Smoking	9 (12)	28 (17-40)	3 (8)	4 (4-9)
Benign tumour	5 (6)	15 (6-28)		-
Malignant tumour	2 (3)	28 -	2 (5)	8 (2-13)
As a result of other illness	4 (5)	4 (3-5)	1 (3)	28 -
Personal characteristic	4 (5)	17 (3-64)		
Fish bone			2 (5)	3 (2-3)
Intubation	1 (1)	2 -		

Among patients with a glottic carcinoma, 52% had postponed seeking medical attention because they interpreted the symptoms as innocuous/benign or thought the symptoms were not serious enough to warrant going to the doctor. This was the case for 35% of the patients with nonglottic carcinomas. Eleven patients (16%) with a glottic and two (6%) with a nonglottic carcinoma said they never go to the doctor as soon as a problem arises. Eight patients (12%) with a glottic and six patients (19%) with a nonglottic carcinoma waited to see whether the symptoms would go away spontaneously; of these 14 patients, 64% eventually went to see a GP within a month. Eight patients (12%) with a glottic and 12 (39%) with a supraglottic carcinoma reported that they did not wait very long; their median delays were respectively, 3 and 2 weeks. Five patients (7%) with a glottic tumour either tried to resolve the problem themselves or ignored the symptom. Twenty patients were not included in our analysis of reasons to postpone seeing a doctor; they were excluded because they had visited the GP for reasons other than a tumour-related symptom.

The main reason why patients with glottic tumours consulted a GP was a persistent or increased hoarseness (Table 6). The main reasons given by patients with a supraglottic tumour were a persistent hoarseness, dysphagia, sore throat, or worsening of these symptoms. Sixteen patients (21%) with a glottic tumour and four (10%) with a supraglottic tumour visited the GP for a symptom unrelated to the tumour. Thirteen patients with a glottic carcinoma were encouraged by others to consult their GP. Only these 13 patients showed a significantly longer delay (χ^2=7.69, p=.006); their median delay was 3.5 months.

Table 6. Median total patient delay (weeks, 25%-75% interval) for different reasons given by the patients to visit their general practitioners, subdivided by localization

Reason	Glottic		Nonglottic	
	No. patients (%)	Median total patient delay (25%-75%)	No. patients (%)	Median total patient delay (25%-75%)
Persistent hoarseness	32 (41)	8 (4-13)	10 (26)	3 (2-3)
Dysphagia			4 (10)	5 (4-10)
Sore throat			5 (13)	3 (2-14)
Neck mass			1 (3)	1
Increased hoarseness	16 (21)	9 (3-29)	4 (10)	9 (4-22)
Increased dysphagia			1 (3)	2
Worsening sore throat			2 (5)	1
Increased dyspnoea			2 (5)	16
Otalgia new complaint	1 (1)	25	3 (8)	13 (1-22)
Not tumour-related complaint	16 (21)	12 (4-25)	4 (10)	4 (3-37)
Encouraged by others	13 (17)	15 (10-28)	3 (8)	11 (2-42)

DISCUSSION

It is reasonable to assume that symptoms caused by large tumours will be of a considerably longer duration than those caused by small tumours. Nonetheless, we did not find a difference in the length of total patient delay between small and advanced laryngeal carcinomas. Although perhaps surprising, this finding is in accordance with that of several previous studies, which did not show a correlation between symptom duration and tumour stage at the time of diagnosis.[4,11-14] Raitiola and Pukander[6] showed a significant difference in symptom duration between stage I-II and stage III-IV disease, but they did not find a difference according to tumour site. In our study, however, the localization of the tumour (i.e., glottic vs. supraglottic) corresponded to a significant difference in total patient delay. Patients with a

glottic tumour waited more than twice as long as patients with a nonglottic carcinoma before deciding to consult their GP. It could be because of the nature of the symptoms characteristic of the two types of lesion. Or the more frequent combination of symptoms seen in supraglottic carcinomas may have induced the patient to take action sooner. We also agree with Merletti *et al.*[15] who hypothesized that patients with symptoms connected to less aggressive and slower growing (glottic) tumours are less alarmed by them than those with symptoms arising from rapidly growing, aggressive (supraglottic) tumours.

There seems to be a shorter duration of symptoms in advanced-stage laryngeal cancer. But this is mainly due to the fact that most supraglottic tumours were diagnosed at an advanced stage of disease, and their symptoms had been of short duration.

The most common symptom reported by patients with glottic carcinomas was hoarseness. This was also the main symptom of supraglottic cancer. Although the median duration of hoarseness was significantly shorter in patients with supraglottic than in those with glottic carcinomas, most of the patients with supraglottic cancer were diagnosed at a late stage of disease. The other reported symptoms (e.g., dysphagia, sore throat, dyspnoea) had a shorter median duration. This supports the prevailing impression that symptoms appear late in supraglottic cancer.[6,13]

The majority of the patients attributed their symptoms to something innocuous such as a common cold or infection. Only four patients (3%) suspected a malignancy. As many as one fourth of the patients had no idea what caused their symptom. This concurs with the finding of Amir *et al.*[19] that 72% of head and neck cancer symptoms were interpreted as a minor disorder and only 4% of the patients suspected cancer. Because of the seemingly harmless nature of the symptoms, illness was mostly inferred after the visit to a GP or specialist.

In this study, we found that most of the patients postponed consultation to a GP because they interpreted their symptoms as harmless or not bothersome. This may be due to the nature of the symptom or to the patient's expectations of what the GP would say.[20] Some patients were probably not convinced that their GP could help them or did not want to bother the doctor with their complaint. This is probably also true for the patients who preferred to wait and see if the symptom would go away by itself.

Ultimately, the reason to consult their GP was the persistent hoarseness or the duration of the dysphagia or sore throat. The patients also consulted the GP if the symptom got worse. Some patients visited their GP for a complaint unrelated to the tumour and would otherwise have consulted the doctor at a later stage. Patients who were encouraged by others to consult

their GP show more appraisal delay and would have shown more delay if they had not been encouraged to take action.

In our study, the majority of patients with a laryngeal carcinoma did not show behavioural or scheduling delay. This is probably an effect of our healthcare system. There is no financial obstacle to consulting a GP because of the obligatory healthcare insurance.

In conclusion, our results did not show a difference in the length of delay between early- and advanced-stage disease. Although patients with a glottic tumour showed significantly longer delay than those with a supraglottic tumour, most of them were diagnosed with a lesion at an early stage of disease. This is probably due to the early onset of symptoms in glottic carcinomas and the long symptom-free period characteristic of supraglottic tumours. Because the prognosis of head and neck cancer is related to the stage of the disease, the only way to improve survival rates is to detect a tumour at an earlier stage. Because of the relatively late onset of symptoms in advanced supraglottic disease, only screening and detection in an asymptomatic stage of the disease could improve the survival rates. Because of the low incidence of laryngeal cancer, screening is not an option. Nevertheless, the general public must be made aware of the symptoms and risk factors of laryngeal cancer. Moreover, the GP must be urged to give special attention to those patients who are at risk of developing laryngeal cancer.

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Chapter 4

Oral and pharyngeal cancer: Analysis of patient delay at different tumour stages

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Abstract

Background. The aim of the present study is to examine which factors are related to patient delay in a cohort of consecutive patients with pharyngeal cancer and oral cancer and to determine whether the different stages of patient delay (ie, appraisal, illness, behavioural and scheduling) were related to different tumour stages.

Methods. Before treatment, 55 patients with pharyngeal cancer and 134 patients with oral cancer were interviewed about their prediagnostic period. To verify the data, a questionnaire was sent to the general practitioner and/or dentist and a close relative.

Results. Patients with a delay of more than 30 days were significantly more often diagnosed in late-stage (T3-T4) disease (pharynx, p=.01, OR=4.5; oral, p=.01, OR=3.2). No sociodemographic characteristics were associated with patient delay.

Conclusions. Prolonged patient delay was associated with late-stage disease for both patients with pharyngeal cancer and patients with oral cancer. Although for most patients the symptoms are vague or might look like a common cold or infection, the general public should be better informed about tumour symptoms. This may enhance earlier visits to a health care professional.

INTRODUCTION

Early detection of head and neck cancer is believed to be the most effective way to improve survival.[1;2] From 1989 to 1998, the incidence of oral and pharyngeal cancer increased in the Netherlands. During the same period, the mortality rate for these cancers rose for both men and women, mainly due to an increase of advanced stage (IV) disease.[3] This trend was seen in other European countries as well.[4]

It is reasonable to assume that the duration of symptoms is related to the stage of the disease at diagnosis. Therefore, we analysed patient delay in oropharyngeal, hypopharyngeal and oral cancer and its relation to the stage of tumour growth at the time of diagnosis. Although our assumption is reasonable, the literature on this matter is far from conclusive. A correlation between advanced-stage cancer and increased patient delay was shown for oral cancer by Kerdpon and Sriplung[5] and for hypopharyngeal cancer by Carvalho et al.[5;6] Other studies, however, did not show any relation.[2;7-11]

Most of the studies on delay in head and neck cancer are based either on retrospective analysis of medical records or on interviews after treatment. Data acquired in this way are probably less accurate, because it is not always easy for patients to remember when symptoms started. Although our study design is retrospective, we tried to minimize the recall bias by interviewing the patients just before treatment and verifying the data with a questionnaire sent to a close relative and their general practitioner (GP) and/or dentist. We also divided the patient delay into several stages according to the model of Andersen and Cacioppo[12] (eg, appraisal, illness, behavioural and scheduling delay). To gain more insight into patient delay, we asked patients about their first symptom and what they attributed them to. If they had postponed medical consultation, we asked why they had done so and also what had made them decide to see a GP or dentist after all.

The present study examines the factors related to patient delay in a consecutive cohort of patients with pharyngeal and oral cancer. Although we are aware that part of total delay is caused by misdiagnosis, inappropriate referral, or treatment,[2;9;10;13-17] the aim of this study is to determine whether the different stages of patient delay, as proposed by Andersen, are related to different tumour stages.

PATIENTS AND METHODS

Patients were eligible to take part in the study if they had newly diagnosed squamous cell carcinoma of the oropharynx or hypopharynx (International Classification of Diseases for Oncology [ICD-O] 146, 148) or oral cavity (ICD-O 141, 143-145) and had no previous or synchronous malignancies in the head and neck region. Patients with cognitive impairment or who did not understand the Dutch language were excluded. From 2000 to 2002, patients who had been diagnosed at the Department of Otorhinolaryngology and Maxillofacial Surgery at University Medical Centre Utrecht were sent a letter inviting them to participate.

Eighty-five patients with a pharyngeal carcinoma and 173 patients with an oral cavity carcinoma were eligible for this study during the accrual period. Thirty patients (35%) with a pharyngeal carcinoma and 39 patients (23%) with an oral cavity tumour refused the invitation to participate. The main reasons were lack of motivation (23%), too much trouble (17%), and poor physical/mental health (28%). There were no differences between the participants and those patients who refused to participate with respect to tumour stage, sex, or age. Our analyses were based on data for 55 patients with a pharyngeal carcinoma and 134 patients with an oral cavity carcinoma.

Interview

To determine the length of the various stages of delay, patients were interviewed just before surgery; if receiving radiotherapy and/or chemotherapy, they were interviewed just before or during the first treatment sessions. For a complete description of the method used to explore the different stages of patient delay we refer to the publication by Brouha *et al.*[18]. When a patient was seen by not only a general practitioner but also a dentist, the data were also verified with a questionnaire sent to the dentist.

Data on drinking and smoking habits were obtained from the interviews. Tumour characteristics, such as T stage and localization, were obtained from the medical records. The tumours were registered according to the International Classification of Diseases for Oncology (ICD-O) and the TNM classification.[19]

Statistical analysis

All analyses were carried out with SPSS statistical software (version 10.0). Odds ratios and 95% confidence intervals were estimated by logistic regression analysis. The chi-square test was used to analyse categorical data, and the Kruskal-Wallis test (KW test) was used for continuous data.

RESULTS

Patient characteristics

Most of the pharyngeal cancer patients were men (78%). They ranged in age from 41 to 85 years, with a mean of 59 years. Forty patients (73%) smoked, eight (15%) had quit, and seven (13%) had never smoked cigarettes. Thirty-seven patients (67%) drank alcohol, whereas 18 (33%) did not, at least not daily. In the oral cancer group, 58% were men. Their age ranged from 35 to 88 years with a mean of 61 years. Seventy-three patients (54%) smoked, 35 (26%) had quit, and 26 (19%) had never smoked. Seventy-four patients (55%) drank alcohol and 60 patients (45%) did not drink, at least not on a daily basis.

Patient delay

Patients with a pharyngeal carcinoma are often diagnosed in late (T3-T4) stage disease and showed significantly more delay than those diagnosed with early (T1-T2) stage disease (Table 1). The difference was not significant when neck node metastases were taken into account. Patients with oral cavity carcinomas were more frequently diagnosed in early-stage disease than in advanced-stage, but oral cancer patients with advanced-stage disease showed significantly more delay than those with early-stage disease. This was also true when neck node metastases were taken into account. However, having a neck node metastases was not related with delay.

Marital status (married or divorced/widowed), living situation (alone or with family), education (low, intermediate, or high), and income (less or more than modal) were not associated with patient delay for either pharyngeal or oral cavity carcinomas. Smoking and drinking were not related to patient delay in pharyngeal or oral cancer patients (Table 1).

Table 1. Odds Ratios (OR) with 95% Confidence Interval (CI) for patients with pharyngeal or oral cavity cancer

	Pharyngeal cancer				Oral cavity cancer			
	delay				delay			
Characteristics	<30	≥30	*p*- value	OR (95% CI)	<30	≥30	*p*-value	OR (95% CI)
Gender								
male	16	26		1.0 (referent)	33	41		1.0 (referent)
female	7	5	0.21	0.4 (0.1-1.6)	27	27	0.54	0.8 (0.4-1.6)
Age								
<65	21	21		1.0 (referent)	39	38		1.0 (referent)
≥65	2	10	0.05	5.0 (1.0-25.6)	21	30	0.29	1.5 (0.7-3.0)
Localization								
oropharynx	16	21		1.0 (referent)				
hypopharynx	7	10	0.89	1.1 (0.3-3.5)				
visible					51	57		1.0 (referent)
less visible					9	11	0.86	1.1 (0.4-2.8)
Smoking								
smoker	17	22		1.0 (referent)	33	34		1.0 (referent)
ex-smoker	3	5	0.75	1.3 (0.3-6.8)	12	23	0.15	1.9 (0.8-4.4)
non-smoker	3	4	0.97	1.0 (0.2-4.8)	15	11	0.47	0.7 (0.3-1.8)
Alcohol intake								
drinker	15	22		1.0 (referent)	31	37		1.0 (referent)
none/not daily	8	9	0.65	0.8 (0.2-2.4)	29	31	0.76	0.9 (0.4-1.8)
TNM								
T1-T2	13	7		1.0 (referent)	48	38		1.0 (referent)
T3-T4	10	24	0.01	4.5 (1.4-14.5)	12	30	0.01	3.2 (1.4-6.9)
Stage								
I-II	4	5		1.0 (referent)	38	31		1.0 (referent)
III-IV	19	26	0.90	1.1 (0.3-4.6)	22	37	0.04	2.1 (1.0-4.2)
N category								
0	7	13		1.0 (referent)	45	46		1.0 (referent)
≥1	16	18	0.39	0.6 (0.2-1.9)	15	22	0.36	1.4 (0.7-3.1)

Furthermore, the combination of smoking more than 20 cigarettes and consuming more than four alcoholic drinks a day had no relation to patient delay. Neither did the localisation of the tumour (in the oropharynx or hypopharynx). Although the localisation of oral cancer in terms of visible/less visible did not show a relation with delay, less visible tumours were diagnosed significantly more often in advanced stage disease (anterior site: 79 (73%) T1-T2, 29 (27%) T3-T4, posterior site: 7 (35%) T1-T2, 13 (65%) T3-T4, χ^2=11.4, p=0.01).

According to Andersen's model, appraisal delay is the period from unexplained symptoms until the patient considers himself or herself to be ill. Because only 35% of the patients with pharyngeal cancer and 21% of the patients with oral cancer inferred illness before they decided to seek medical help, we could not distinguish a separate stage for illness delay for most of the patients. For this reason, in our study we calculated appraisal delay from the day the patient experienced a symptom until the day the patient decided to seek medical help. Appraisal delay for pharyngeal and oral cavity carcinomas had respectively a mean of 45 (range, 20-84) and 28 (range, 14-78) days. Most patients did not show behavioural delay. Ninety-six percent of the patients with pharyngeal cancer and 90% of the patients with oral cavity cancer patients made an appointment within one week after deciding to seek medical help for their symptoms. Scheduling delay for patients with pharyngeal and oral cancer did not occur.

Symptom presentation

For pharyngeal carcinomas, the median appraisal delay was significantly different for the tumour-related symptoms mentioned by the patients (Table 2; KW test, p=0.02, χ^2=11.8). The delay was longer among patients with pharyngeal cancer whose first symptom was a sore throat than among patients with dysphagia or a neck mass. When a neck mass was mentioned as a first symptom, all of the patients with pharyngeal cancer were diagnosed in T1-T2 stage.

Table 2. Median appraisal delay (days, 25% to 75% interval) by first symptoms reported

	Pharyngeal cancer		Oral cavity cancer	
Symptom	No. patients (%)	Median appraisal delay (25%-75%)	No. patients (%)	Median appraisal delay (25%-75%)
Dysphagia	4 (7)	26 (15-42)	2 (2)	23 (15-30)
Sore throat	17 (31)	57 (26-69)	4 (3)	12 (5-19)
Neck mass	8 (15)	11 (2-28)	3 (2)	7 (7-20)
Lesion			21 (16)	46 (15-73)
Mass			9 (7)	29 (18-10)4
Irritation			10 (8)	20 (14-32)
Painful lesion			19 (15)	19 (12-31)
Pain (no lesion)			16 (13)	28 (16-121)
>1 symptom	11 (20)	68 (25-164)	15 (12)	46 (13-144)
Later extra symptom	14 (26)	68 (28-146)	29 (23)	65 (23-183)

Note: pharyngeal cancer patients with more than one symptom reported as second symptom dysphagia, otalgia, coughing up blood, voice change, weight loss, or a neck mass; patients with oral cancer reported otalgia, weight loss, or haemorrhage.

For oral carcinomas, the median appraisal delay varied by the type of symptom experienced by the patients (KW test, p=0.02, χ^2=20.0). Patients with oral cancer with dysphagia, a sore throat, a neck mass, irritation, or a painful lesion showed a shorter appraisal delay than patients with a lesion, a mass, or pain without a visible lesion.

Attribution of symptoms

Most patients with pharyngeal cancer attributed their symptoms to a common cold or infection (Table 3). Ten patients had no idea what had caused their symptoms; only two patients thought that a malignancy was the cause. These different attributions of symptoms mentioned by the patients did not show a significant difference in median appraisal delay (KW test, p=0.41, χ^2=8.2).

Most patients with a tumour in the oral cavity attributed their symptoms to an infection or blamed dental problems or problems with their prosthesis. About 20% of the patients with oral cancer had no idea what the cause of their symptoms was. Only four thought a malignancy was involved. These variables showed a significant difference in median appraisal delay (KW test, p=0.01, χ^2=20.3). More patient delay was found among patients who attributed their symptoms to their prosthesis or dental problems and among patients who had no idea of the cause.

Table 3. Median appraisal delay (days, 25% to 75% interval) by attribution of first tumour symptoms

	Pharyngeal cancer		Oral cavity cancer	
Symptom	No. patients (%)	Median appraisal delay (25%-75%)	No. patients (%)	Median appraisal delay (25%-75%)
No complaints	1 (2)	- -	3 (2)	- -
Prosthesis/dental	2 (4)	71 (20-121)	31 (24)	46 (21-155)
Common cold	9 (18)	45 (30-60)	4 (3)	20 (3-56)
Infection	18 (36)	36 (16-184)	39 (30)	20 (13-53)
No idea	10 (20)	54 (24-155)	28 (22)	34 (19-139)
Smoking/alcohol	2 (4)	-	2 (2)	- -
External factor	3 (6)	30 (1-60)	15 (12)	24 (12-60)
Benign tumour	3 (6)	7 (1-30)	2 (2)	- -
Malignant tumour	2 (4)	74 (35-112)	4 (3)	12 (3-24)

Reasons to postpone

Patients with oral or pharyngeal cancer said they had postponed seeking medical attention because they thought the symptom was harmless or because it did not bother them. Others reported that they do not go to the doctor quickly/often, ignored their symptom or were anxious to visit a doctor.

Reasons to consult a GP/dentist

For most patients with pharyngeal cancer, the reason to see a GP was the persistence of the symptom (Table 4). In these patients, the median patient delay was 45 days. Two other reasons they gave were worsening of a symptom and developing a new complaint. A number of patients were encouraged by some other person to visit their GP. These various reasons to visit a GP were associated with a median patient delay ranging from 20 to 112 days, but the differences were not significant (KW test, p=0.08, χ^2=9.94).

Table 4. Median appraisal delay (days, 25% to 75% interval) by patient's main reasons to see GP/dentist

	Pharyngeal cancer		Oral cavity cancer	
Symptom	No. patients (%)	Median appraisal delay (25%-75%)	No. patients (%)	Median appraisal delay (25%-75%)
Persistent complaint	23 (44)	45 (16-62)	59 (46)	18 (13-36)
Worsening of complaint	6 (12)	60 (40-244)	28 (22)	76 (23-152)
Extra complaint		-	5 (4)	36 (16-372)
Otalgia new complaint	2 (4)	-	5 (4)	76 (25-179)
Neck mass new complaint	7 (13)	20 (1-30)	4 (3)	22 (6-46)
Not tumour-related complaint	7 (13)	112 (14-180)	20 (16)	14 (0-35)
Encouraged by others	7 (13)	77 (27-164)	7 (5)	119 (48-149)

For patients with oral cancer, the main reason to go to a GP or dentist was the persistence of the symptom. The median patient delay was 18 days. The mentioned variables in Table 4 showed a significant difference in median patient delay (KW test, p=0.00, χ^2=25.4). Patients who visited the GP or dentist primarily for a reason other than a tumour-related complaint showed less appraisal delay. Patients whose complaint worsened showed a longer appraisal delay.

DISCUSSION

The length of patient delay that we found for oral cancer is in accordance with reports in the literature; patient delay varies from three weeks to 1.6 months.[9;10;20;21] We found a positive relation between patient delay and the T classification at diagnosis. Some studies have demonstrated a relation between patient delay and the TNM stage at tumour diagnosis,[5;6;22] whereas others have not.[2;7-11;15;17] When neck node metastases were taken into account, there was a significant relation between patient delay and late-stage (III-IV) disease for patients with oral cancer but not for patients with pharyngeal cancer. This is probably because pharyngeal carcinomas metastasize at an early stage.

Patients with oral and pharyngeal cancer who had more than one symptom or developed another tumour-related symptom during the appraisal period showed a longer delay and were more often diagnosed with T3-T4 disease. For most patients, however, the development of a neck mass was a reason to consult a GP without delay. Eighty percent of the pharyngeal and all of the patients with oral cancer who had a neck mass as the first symptom were diagnosed with T1-T2 disease. A neck mass is probably alarming to most patients and, therefore a reason to consult a GP without delay. Although pain, with or without a visible lesion, may be an important sign of a tumour, pain itself does not seem to induce people to visit the GP or dentist. Other studies also show that pain does not induce a person to visit a doctor.[10] In such cases, pain probably does not interfere with the patients' functioning; these patients may treat themselves with over-the-counter painkillers.

The majority of the patients attributed their symptoms to something innocuous such as a common cold or infection. Patients with an oral carcinoma often attributed their symptom to problems with their prosthesis or to complaints of dental origin. A malignant tumour was rarely suspected.

In this study, we found that most of the patients postponed consulting a GP because they interpreted their symptoms as harmless or not bothersome. This interpretation may be due to the nature of the symptom or the expected reaction of the GP or dentist.[23] Some patients were probably not convinced that their GP or dentist could help them or did not want to bother them with their complaint. This is probably also true for the patients who preferred to wait and see if the symptom would go away by itself.

Ultimately, the reason to consult a doctor was the duration or worsening of a complaint. Some patients visited their doctor for a complaint unrelated to the tumour and would otherwise have gone to the doctor at a later stage. Patients who were encouraged by others to consult their doctor showed more appraisal delay; they would probably have shown even more delay if they had not been encouraged to take action.

Quite a few of the patients with pharyngeal cancer visited the GP/dentist without delay, but they already had T3-T4 disease. These tumours probably developed late symptoms or were growing aggressively. Patients with pharyngeal carcinomas who were diagnosed with T1-T2 disease and waited more than 30 days probably had symptoms at an early stage of their disease. Of the patients who waited more than 30 days, quite a few already had T3-T4 disease. This is the group of patients we must focus on; it could be rewarding to encourage earlier visits to a GP or dentist.

The clinical stage at diagnosis is the most important factor of survival for patients with head and neck cancer. Our goal is to diagnose patients at an early stage in order to improve both the survival rate and the quality of life. Screening is not an option, because the incidence of head and neck tumours is low. We believe that the most feasible way to diagnose patients at an earlier stage is to inform the public more about the causes of head and neck cancer. For most patients, the symptoms are vague or might seem like a common cold or infection. Thus, the general public must be made aware that if a symptom lasts more than three weeks, there is sufficient reason to consult a GP or dentist. At the same time, doctors should be aware that the symptoms presented by the patients might be caused by a tumour. Therefore, any patient with suspicious symptoms or physical findings should be proper evaluated.

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Chapter 5

The role of alcohol and smoking habits in patient delay among head and neck cancer patients

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Abstract

Objective: It is reasonable to assume that prolonged delay is associated with an advanced stage of the cancer at diagnosis. In this study we analysed the effects of drinking and smoking habits on diagnostic delay and the T stage of the tumour at diagnosis.

Patients and Methods: A total of 427 patients with newly diagnosed head and neck carcinomas were eligible for this study. Of these, 306 (72%) actually participated: 134 (77%) with an oral tumour, 117 (69%) with a larynx tumour and 55 (65%) with a pharynx tumour. Patient delay was defined as the length of time between the appearance of the first tumour-related symptoms and the first visit to a physician. When this period exceeded 30 days, it was called delay. T3-4 tumours were defined as advanced tumours. Drinking behaviour was classified in three types: light (0-2 drinks/day); moderate (3-4 drinks/day); and heavy (>4 drinks/day). Smoking habits were classified into four types: never; stopped; light (0-20 cigarettes/day); and heavy (>20 cigarettes/day).

Results: Logistic regression showed that there were significantly more heavy drinkers than light drinkers (p=0.04; OR 1.8; 95%CI 1.0-3.1) in the delay group than in the non-delay group. Light smokers showed a tendency towards prolonged delay (p=0.06; OR 2.2; 95%CI 1.0-5.0). Both heavy drinking (p=0.01; OR 2.0; 95%CI 1.2-3.6) and heavy smoking (p=0.03; OR 3.1; 95%CI 1.1-8.4) were risk factors for a patient to be diagnosed with a large tumour.

Conclusions: This study shows that heavy drinking is a risk factor for prolonged delay in presenting with head and neck cancer and for presenting with a large tumour in the head and neck region. Excessive smoking is only a risk factor for being diagnosed with a large tumour, although there is a weak association between smoking and prolonged delay.

INTRODUCTION

Cancer of the upper aerodigestive tract is the fourth most common type in the European Union.[1] For oral and pharyngeal cancer, both the incidence and mortality rates have been rising in most European countries, especially among the younger age group.[2;3] Macfarlane *et al.*[4] estimated that in the period 2003 to 2007, mortality from upper aerodigestive tract cancer will increase in northern and central Europe as a result of changes in alcohol consumption over the past 20 years.

It has been demonstrated that drinking alcohol and smoking tobacco are the major risk factors for developing squamous cell carcinomas of the head and neck.[5-8] The combined effect of heavy drinking and smoking increases the risk of developing oral or pharyngeal cancer even more.[2;6]

Although we have the impression that the patients who are heavy drinkers and smokers show more delay than other patients at our clinic, this is not confirmed by other studies. For instance, Elwood *et al.*[9] did not find evidence that patient delay is related to alcohol and smoking habits among laryngeal cancer patients. Three other groups did found no relationship between patient delay and alcohol consumption among oral cancer patients.[10-12] In one study, that of Pitiphat *et al.*[12], former smokers had an increased risk of delay, although there was no relationship with the quantity of cigarettes smoked.

A study by de Boer *et al.*[13] showed that female patients with cancer of the oral cavity and oropharynx and who were heavy drinkers (>5 units/day) and smokers tended to present with late-stage disease. A study of about 3000 head and neck cancer patients showed the same relationship.[14] Significantly more head and neck cancer patients diagnosed with a T4 tumour were heavy drinkers (>4 units/day) or heavy smokers (>20 cigarettes/day) than those patients diagnosed with a T1 tumour. Trigg *et al.*[15] showed that a relatively high proportion of patients with advanced-stage laryngeal cancer were heavy drinkers and smokers.

The aim of the present study was to investigate whether heavy drinking and smoking are related to delayed presentation of head and neck cancer.

PATIENTS AND METHODS

Patients were eligible for this study if they had newly diagnosed squamous cell carcinoma of the oral cavity (International Classification of Diseases for Oncology [ICD-O] 141, 143-145), pharynx (ICD-O 146, 148) or larynx (ICD-O 161). Between 2000 and 2002, patients who had been diagnosed at the Department of Otorhinolaryngology and Maxillofacial Surgery at the University Medical Centre Utrecht were sent a letter inviting them to participate. Those patients who did not understand the Dutch language or who had cognitive impairment were excluded.

In total, 427 patients were eligible for this study during the accrual period. Of the 169 patients with a laryngeal carcinoma, 117 (69%) took part; of the 85 patients with a pharyngeal carcinoma, 55 (65%) were enrolled; and of the 173 patients with an oral cavity carcinoma, 134 (77%) participated. The main reasons for refusal were lack of motivation (29%), too much bother (22%), and poor physical/mental health (30%). There were no differences between participants and those patients who refused to participate with respect to tumour localization, tumour stage, sex or age.

Patient delay in this study was defined as the period between the first appearance of tumour-related symptoms and the first visit to a general practitioner (GP) or dentist. To obtain data about the onset of the symptoms, patients were interviewed just before treatment. To verify these data, a questionnaire was sent to the GP and/or dentist as well as to a close relative. Data on the first medical contact were derived from the information given by the GP or dentist. If patients had tumour-related symptoms for more than 30 days, they were included in the delay group.

Data on drinking and smoking habits were obtained from the interviews. Drinking behaviour was classified in three types: 0-2 drinks/day (light); 3-4 drinks/day (moderate); and >4 drinks/day (heavy). Average daily tobacco consumption was calculated in terms of the number of cigarettes smoked; one cigar is equivalent to four cigarettes and one pipe to two cigarettes, based on the weight of the tobacco. Smoking habits were classified in four types: never; stopped; 0-20 cigarettes/day (light); and >20 cigarettes/day (heavy). Patients who stopped smoking six months previously or after cancer diagnosis were included with the current smokers, and were classified by their previous intake.

Tumour characteristics, such as T stage and localization, were obtained from the medical records. The tumours were registered according to the International Classification of Diseases for Oncology (ICD-O) and the TNM classification.

Statistical analysis

The data were analysed using the statistical package SPSS 10.0 for Windows. Odds ratios and 95% confidence intervals were estimated by logistic regression analysis. The chi-square test was applied to categorical data.

RESULTS

Table 1 shows the patient characteristics of the study population. Most of the patients were men. They ranged in age from 35 to 91, with a mean of 62 years. The mean ages at time of diagnosis for men and women were comparable (62 and 63 years, respectively). The mean age for larynx, pharynx and oral cancer patients were 64, 60 and 62 years, respectively.

Figure 1 shows the combined consumption of alcohol and tobacco. All of the heavy drinkers were also smokers or had been smoking before being diagnosed with a tumour. Most of the heavy drinkers smoked more than 20 cigarettes a day.

Younger patients (<65 years) drank and smoked significantly more than elderly patients (≥65 years). Of the younger group, 33% had more than four drinks a day, and 37% smoked more than 20 cigarettes a day, compared to 11% and 10%, respectively for the older group. Half of the elderly patients had quit smoking, compared to 16% of the younger patients. Heavy drinking and smoking behaviour was significantly more common among males than females (data not shown). Thirty per cent of the men had more than four drinks a day, compared to 10% of the women.

Fifty-nine percent of the patients showed a delay of 30 days or more, and 28% showed a delay of over three months. The median patient delay for the total study population was 45 days. Oral cancer patients showed significantly less patient delay (median 34 days) than pharynx cancer patients (median 48 days), and pharynx cancer patients showed less delay

than larynx cancer patients (median 54 days). Neither age nor sex was significantly associated with patient delay.

Table 1. Patient characteristics of the study population

Characteristics	No. patients (%)
Sex	
male	212 (69)
female	94 (31)
Age (years)	
<65	184 (60)
≥65	122 (40)
Smoking	
never	30 (10)
stopped*	90 (29)
0-20 cigarettes/day	105 (34)
>20 cigarettes/day	81 (27)
Drinking	
0-2 drinks/day	180 (59)
3-4 drinks/day	52 (17)
>4 drinks/day	74 (24)
Tumour localisation	
larynx	117 (38)
pharynx	55 (18)
oral cavity	134 (44)
Tumour size	
T1	107 (35)
T2	100 (33)
T3	36 (12)
T4	63 (21)

* *stopped smoking more than six months before diagnosis*

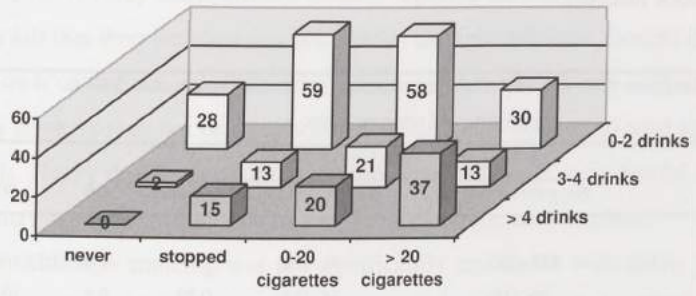

Figure 1. Combined smoking and alcohol consumption for the study population. Values are absolute numbers.

Table 2. Odds Ratios (OR) with 95% Confidence Interval (CI) for patient delay (≥30 days) by drinking and smoking habits

	No delay	Delay			
	No. patients (%)	No. patients (%)	*p*-value	OR	(95% CI)
Alcohol consumption					
0-2 drinks/day	85 (63)	91 (55)		1.0	(referent)
3-4 drinks/day	24 (18)	26 (16)	0.97	1.0	(0.5-1.9)
>4 drinks/day	25 (19)	48 (29)	0.04	1.8	(1.0-3.1)
Smoking					
never	18 (13)	12 (7)		1.0	(referent)
stopped	42 (31)	48 (29)	0.21	1.7	(0.7-4.0)
0-20 cigarettes/day	41 (31)	60 (36)	0.06	2.2	(1.0-5.0)
>20 cigarettes/day	33 (25)	45 (27)	0.10	2.0	(0.9-4.8)
Alcohol and smoking					
≤4 drinks/day	109 (81)	117 (71)		1.0	(referent)
>4 drinks/day and stopped	6 (5)	9 (5)	0.5	1.4	(0.5-4.1)
>4 drinks/day and smokes	19 (14)	39 (24)	0.04	1.9	(1.0-3.5)

DISCUSSION

The length of patient delay found in our study is in accordance with that reported in the literature. For larynx cancer, Teppo *et al.*[16] reported a median patient delay of two months. The median patient delay for oral and pharynx cancer varied from three weeks to two

months.[17-21] Only one study, that by Carvalho *et al.*[22], showed a median patient delay of three months for head and neck tumours.

Table 3. Odds Ratios (OR) with 95% Confidence Interval (CI) for late-stage disease (T3-T4) by drinking and smoking habits

	T1-T2	T3-T4			
	No. patients (%)	No. patients (%)	*p*-value	OR	(95% CI)
Alcohol consumption					
0-2 drinks/day	125 (62)	51 (52)		1.0	(referent)
3-4 drinks/day	36 (18)	14 (14)	0.89	0.9	(0.5-1.9)
>4 drinks/day	40 (20)	33 (34)	0.01	2.0	(1.2-3.6)
Smoking					
never	24 (12)	6 (6)		1.0	(referent)
stopped	64 (32)	26 (27)	0.34	1.6	(0.6-4.4)
0-20 cigarettes/day	69 (34)	32 (33)	0.22	1.9	(0.7-5.0)
>20 cigarettes/day	44 (22)	34 (35)	0.03	3.1	(1.1-8.4)
Alcohol and smoking					
≤4 drinks/day	161 (80)	65 (66)		1.0	(referent)
>4 drinks/day and stopped	9 (5)	6 (6)	0.4	1.7	0.6-4.8
>4 drinks/day and smokes	31 (15)	27 (28)	0.01	2.2	1.2-3.9

To the best of our knowledge, our study is the first to show that heavy drinking is related to prolonged patient delay. As in most other studies of patient delay, we chose 30 days as the cut-off point. Prolonged delay was also seen for the combination of heavy drinking and smoking. Although there was a weak association between smoking and delay, it only approached significance for light smokers (0-20 cigarettes a day). A study by Pitiphat *et al.*[12] showed that former smokers had the highest risk of delaying. In that study it was suggested that this was due to a false sense of security shared by the patient and the GP. One reason why other authors did not find a relation between alcohol consumption and patient delay could be the different ways in which alcohol and smoking behaviour were classified. Furthermore, different composition of the study population may influence the outcome of the analysis. Another reason could be that the period of delay is not a reliable measure; it is not always easy for a patient to remember when the symptoms started, especially when they developed gradually. Our data probably show less bias than those of other studies because of our method of data collection. Our interviews were held just before treatment, and the data were verified with using information from the GP/dentist and a close relative.

Patients go to the GP for an explanation of their symptom or for treatment of their complaint. A study about alcohol abusers reported several reasons for not seeking treatment. Some felt that their problem was not serious enough and some thought they could handle it on their own or did not want to admit they needed help.[23] It was suggested in that study that heavy drinkers may not be so concerned about health issues and tend to ignore early warning signals. Heavy drinkers may delay more because they are more fearful of consulting a GP or they may suppress their symptom with extra alcoholic consumption.

Although smoking was not significantly associated with delay, it was clearly closely related to advanced tumours. Also, heavy drinking and the combination of heavy drinking and smoking were associated with advanced tumours. This finding is in accordance with earlier reports.[13-15] The combination of heavy drinking and smoking was significantly related to delay, probably due to the fact that most of the heavy drinkers were also smokers.

Our analyses suggest that heavy drinkers and smokers underestimate the importance of issues associated with illness, causing delay and consequently more advanced tumours at diagnosis. Therefore, healthcare professionals must pay extra attention to this particular patient population and not yield to the dismissive behaviour of the patient.

Cancer incidence could be reduced and survival improved by a health education campaign, which should include information about the risk factors for developing head and neck cancer. It has been shown that over 85% of patients diagnosed with head and neck cancer were unaware of the causative factors of their tumour.[24] This information gap leads to late presentation, which in turn contributes to poor survival.[25] Furthermore, people do not recognise the symptoms related to head and neck cancer. Therefore, the campaign should also provide information about cancer symptoms and the importance of going to the doctor early. The Dutch guidelines for head and neck cancer advise patients not to postpone seeing a GP when symptoms persist for three weeks in the case of hoarseness or six weeks for dysphagia and sore throat. Thus, increased public awareness may lead to a reduced exposure to risk factors and to an earlier visit to a GP or dentist when cancer symptoms are suspected.

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Chapter 6

Delay in hospital referral of head and neck cancer patients

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Submitted

Abstract

Background. The aim of this study was to identify which patient- and tumour-related factors are associated with the referral process of the general practitioner or dentist.

Methods. Three hundred six patients with a carcinoma of the larynx, pharynx, or oral cavity were included in the study. Logistic regression analyses were used to identify risk factors for delayed referral.

Results. The median referral delay was 28 days. Thirty-eight percent of the patients were referred at the first visit, 36% were treated with medication, and 25% got a wait-and-see policy. Patients with a sore throat or dysphagia were referred least frequently at the first visit. Patients with a T4 tumour were referred to a medical specialist significantly less frequently at the first visit (OR=0.5; p=.03). Oral cancer patients (OR=1.7; p=.04) and persons with symptoms lasting longer than 30 days (OR=2.1; p=.004) were referred significantly more often at the first visit.

Conclusions. These results suggest that in primary care it is often difficult to decide when to refer a patient to a specialist. Referral guidelines for suspected head and neck cancer are presented here to prevent delayed referral.

INTRODUCTION

Incidence of head and neck tumours has been rising in the past few decades. Especially the incidence of advanced stage tumours has increased.[1-3] An important contributing factor is patient delay.[4] Yet in 30% of the cases, professional factors contribute to a prolonged diagnostic interval.[5-7] Minimizing this diagnostic delay may result in diagnosis at an earlier stage of the disease, which usually leads to better prognosis.[8;9] A better understanding of the referral process would facilitate earlier diagnosis. Some studies show conflicting results on the clinical impact of the amount of time lapsed from presentation to diagnosis.[10-15] However, exploring these factors might have a positive influence on the stage of the disease at presentation and thereby also on survival.

We therefore examined the treatment regimes and referral process of the general practitioner (GP) and dentist in a consecutive cohort of head and neck cancer patients. In addition, we evaluated which patient- or tumour-related factors influence the referral process. This involved asking the GPs/dentists if they suspected the presence of a tumour at a patient's first visit. To our knowledge, this is the first comprehensive study analysing the referral process and the existence of tumour suspicion in primary care in patients who were eventually diagnosed with head and neck cancer.

MATERIAL AND METHODS

Patients were eligible to take part in this study if they had newly diagnosed squamous cell carcinoma of the oral cavity (ICD-O 141, 143-145), the oropharynx or hypopharynx (ICD-O 146,148), or larynx (ICD-O 161) and had no previous or synchronous malignancies in the head and neck region. Patients with cognitive impairment or who did not understand the Dutch language were excluded from analysis. From 2000 to 2002, patients who had been diagnosed at the Department of Otorhinolaryngology and Maxillofacial Surgery at UMC Utrecht were sent a letter inviting them to participate. Their GPs and/or dentists were sent a questionnaire about the date of the first visit, their treatment, and date of referral to a hospital.

One hundred sixty-nine patients with a laryngeal carcinoma, 85 patients with a pharyngeal carcinoma, and 173 patients with an oral cavity carcinoma were eligible for this

study during the accrual period. Fifty-two patients (37%) with a laryngeal carcinoma, 30 patients (35%) with a pharyngeal carcinoma, and 39 patients (23%) with an oral cavity carcinoma refused the invitation to participate. The main reasons were lack of motivation (29%), too much trouble (22%), and poor physical/mental health (30%). There were no differences between the participants and those patients who refused to participate with respect to localization, tumour stage, sex, or age. Our analyses were based on data for 117 patients with a laryngeal carcinoma, 55 with a pharyngeal carcinoma, and 134 with an oral cavity carcinoma.

To determine the length of delay, patients were interviewed just before surgery; if receiving radiotherapy and/or chemotherapy, they were interviewed just before or during the first treatment sessions. The patients were asked about their first tumour-related symptoms, the first date of medical consultation, the treatment, and the date of referral to a hospital. To verify these data, a questionnaire was sent to a close relative. The date of the first medical contact was derived from the information given by the GP or dentist. The GPs/dentists were asked if they had suspected a tumour at the first visit and also asked when they referred the patient. Tumour characteristics, such as T stage and localization, were obtained from the medical records. The tumours were registered according to the International Classification of Diseases for Oncology (ICD-O) and the TNM classification.[16]

Statistical analysis

All analyses were carried out with SPSS statistical software for Windows version 12.0. Odds ratios and 95% confidence intervals were estimated by logistic regression analysis. The chi-square test was used to analyse categorical data.

RESULTS

There were 210 men and 96 women aged 34 to 89 years (mean, 62 years). Of the 306 head and neck cancer patients, 18 went directly to a specialist. A GP/dentist referred the other 288 patients, 108 (38%) of whom were referred at the first visit (Figure 1). One hundred three (36%) patients were initially treated with medication, and 71 (25%) got a wait-and-see policy.

Data on 6 patients (2%) were not available. The median referral delay was 28 days (range 0-755 days), respectively 35 days for patients with laryngeal cancer, 29 days for patients with pharyngeal cancer, and 15 days for patients with oral cavity carcinomas. Thirty-four (11%) patients were referred by their dentist and 254 (88%) by their GP. The median delay was respectively 29 and 14 days. Patients who were initially treated with medication had a median delay of 51 days (range 9-223 days). Their delay was not significantly different from the 44 days (range 0-755 days) of the patients who got a wait-and-see policy. Patients who were referred at the first visit had a median waiting time of 6 days between referral and specialist consultation. The remaining 63% of the patients who were referred after 2 to 7 consultations had a median waiting time of respectively 33, 70, 78, 82, 134, or 170 days. The mean number of visits to the GP/dentist was 2.2.

The GPs and dentists were asked if they had suspected the presence of a tumour at the patient's first visit. Data on 206 patients were available. There was suspicion of a tumour in 95 cases (37%) but none in the remaining 165 (63%). Only 73% of the patients in whom a tumour was suspected were referred at the first visit. There was significantly more suspicion at the first visit when the tumours occurred in either the pharynx (OR=2.5; 95%CI (1.2-5.5); p=.02) or the oral cavity (OR=4.6; 95%CI (2.4-8.6); p=.00) compared with tumours situated in the larynx. This was also the case when the tumour symptoms persisted for more than 30 days (OR=1.7; 95%CI (1.0-3.0); p=.046). A marginal significance was found for patients who drank >4 units per day in combination with smoking >20 cigarettes per day (OR=2.0; 95%CI (1.0-4.2); p=.052). Other variables such as tumour size and tumour stage were not associated with tumour suspicion. The GP or dentist did not associate certain symptoms with a tumour (Table 1). In less than 33% of the cases, hoarseness, dyspnoea, sore throat, irritation, or mass in the throat made the physician suspicious of a tumour. When patients presented with a lesion, a mass, a neck mass, pain or a painful lesion, suspicion of a tumour arose in more than half the cases.

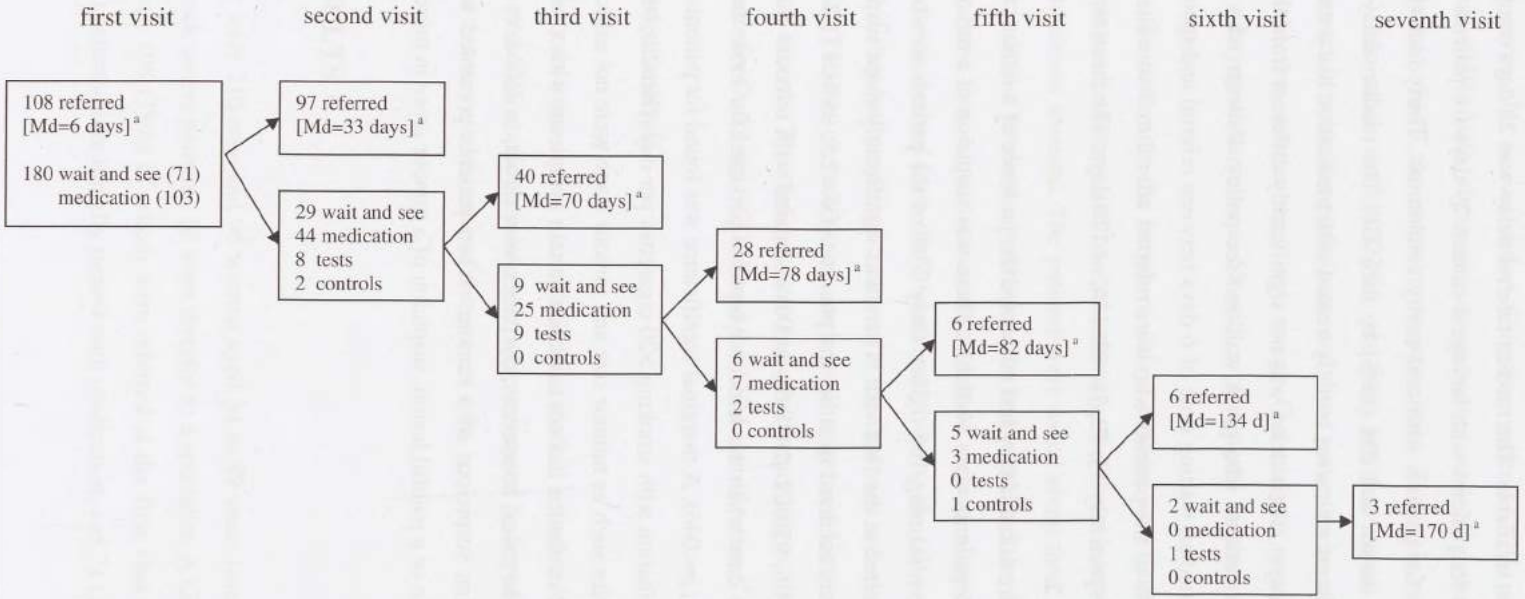

Figure 1. Flow chart of management strategies in primary care. Medical therapy includes antibiotics, antimycotics, and mouthwashes. Tests include blood tests and X-rays of thorax or sinuses.

[a] Represents the median number of days from first visit to GP/dentist until the day of referral.

Note: 18 patients went directly to a specialist.

Table 1. Number of patients in whom the GP/dentist suspected a tumour at first visit. The last two columns give median number of days between first GP consultation and first visit to a medical specialist for patients referred after the first visit and patients not referred after the first visit, according to their initial symptom.

	Positive tumour suspicion	Direct referral		No direct referral	
Symptoms	No. patients (%)	No. patients (%)	Median referral delay	No. patients (%)	Median referral delay
Pain	17 (57)	14 (52)	1	13 (48)	27
Neck mass	6 (50)	5 (45)	5	6 (55)	30
Mass	7 (76)	9 (69)	7	4 (31)	34
No symptom	2 (67)	4 (67)	3	2 (33)	38
Painful lesion	9 (50)	7 (41)	1	10 (59)	39
Lesion	14 (61)	14 (56)	3	11 (44)	40
Otalgia	2 (50)	2 (67)	4	1 (33)	44
Hoarseness	19 (24)	33 (39)	15	51 (61)	53
Dysphagia	6 (35)	3 (18)	3	14 (82)	53
Dyspnoea	0 (0)	0 -	-	3 (100)	71
General symptoms	3 (60)	3 (60)	16	2 (40)	72
Sore throat	7 (16)	7 (16)	7	38 (84)	77
Mass in throat	0 (0)	1 (33)	-	2 (67)	80
Irritation	4 (33)	4 (29)	4	10 (71)	91

Note: 18 patients visited a specialist without consulting their GP or dentist. Not all of the patients were referred at the first visit when there was tumour suspicion and visa versa.

Over half the patients who reported pain, a mass, or a lesion or had either no symptoms or general ones (e.g., fatigue, tightness of the chest, or weight loss) were referred at the first visit. In contrast, patients with a sore throat or dysphagia were least frequently referred at the first visit. Instead, they were initially treated with medication or got a wait-and-see policy. Medication was given to 61% of the patients with a sore throat and to 39% of the patients with dysphagia. Patients who were not referred at the first visit had a longer median waiting time, ranging from 27 days for those who reported pain to 91 days for those with symptoms of irritation. Patients with hoarseness or a painful lesion were referred at an earlier stage if their complaints had lasted for more than 30 days (data not shown).

Analysis showed that patients diagnosed with a T4 tumour were referred to a medical specialist significantly less frequently than patients with a T1 tumour (Table 2). Patients with oral cancer or who had complaints for more than 30 days were referred to the specialist significantly more often at the first visit. Heavy smokers seem to be less frequently referred at the first visit than patients who have never smoked (p=.065). Except for educational level,

sociodemographic variables such as age, sex, marital status (married or divorced/widowed), living situation (alone or with family), and income (less or more than modal) were not associated with the referral process at first visit. Patients with an intermediate level of education were referred significantly more frequently.

Table 2. Odds Ratios (OR) with 95% Confidence Interval (CI) for patients not directly referred according to tumour and social variables

	No	Yes			
	No. patients (%)	No. patients (%)	*p*-value	OR	(95% CI)
T stage					
T1	52 (29)	44 (41)		1.0	(referent)
T2	61 (34)	34 (31)	0.16	0.7	(0.4-1.2)
T3	23 (13)	13 (12)	0.32	0.7	(0.3-1.5)
T4	44 (24)	17 (16)	0.03	0.5	(0.2-0.9)
Localization					
larynx	74 (41)	34 (31)		1.0	(referent)
pharynx	35 (19)	17 (16)	0.88	1.1	(0.5-2.1)
oral cavity	71 (39)	57 (53)	0.04	1.7	(1.0-3.0)
Duration complaint					
<30 days	84 (47)	31 (30)		1.0	(referent)
>30 days	94 (53)	73 (70)	0.004	2.1	(1.3-3.5)
Age					
≤65 years	111 (62)	67 (62)		1.0	(referent)
>65 years	69 (38)	41 (38)	0.95	1.0	(0.6-1.6)
Sex					
male	126 (70)	76 (70)		1.0	(referent)
female	54 (30)	32 (30)	0.95	1.0	(0.6-1.7)
Smoking					
never	14 (8)	15 (14)		1.0	(referent)
stopped	48 (27)	31 (29)	0.25	0.6	(0.3-1.4)
0-20 cigarettes/day	65 (36)	37 (34)	0.14	0.5	(0.2-1.2)
>20 cigarettes/day	53 (29)	25 (23)	0.07	0.4	(0.2-1.1)
Alcohol intake					
drinker	108 (60)	60 (56)		1.0	(referent)
none/not daily	72 (40)	48 (44)	0.46	1.2	(0.7-1.9)
Alcohol and smoking					
≤4 drinks/day	135 (75)	82 (76)		1.0	(referent)
>4 drinks/day and stopped	8 (4)	6 (6)	0.7	1.2	(0.4-3.7)
>4 drinks/day and smokes	37 (21)	20 (19)	0.7	0.9	(0.5-1.6)

Note: 'duration of complaints' data on 6 patients was missing.

DISCUSSION

The length of referral delay found in this study was in accordance with other reports in the literature.[17-19] Only the studies on oral carcinomas conducted by Hollows *et al.*[20], Onizawa *et al.*[21], and McLeod *et al.*[22] showed less referral delay. In the study by Hollows *et al.*, 69% had been referred within one week. The mean period was 8.4 days when patients were referred by a dentist and 14.5 days when they were referred by a GP. In the studies by Onizawa *et al.* and McLeod *et al.*, the median delay was 1 week.

The flow chart depicted in figure 1 show that 29% of the patients were referred after three or more visits, increasing the median delay to 70-170 days. It was striking that patients who were eventually diagnosed with a T4 tumour had been less frequently referred at the first visit than patients with a T1 tumour. One explanation could be that quite a few of the T4 tumours were located in the oropharynx and hypopharynx. They were thus less accessible for examination compared with the more visible oral cavity carcinomas. Patients with the latter type were referred significantly more often at the first visit. This study showed that lesions in the oral cavity were considered significantly more likely to be malignant. Another explanation could be that tumour progression occurred during this referral period. A study by Waaijer *et al.*[23] showed evident tumour progression in oropharynx carcinomas during the waiting time for radiotherapy. This finding was based on tumour progression measured from the diagnostic to the planning CT scan in a median time period of 35 days, range 12-47, which is comparable with the referral delay in this study. Furthermore, in most cases, having a sore throat or dysphagia was no reason to suspect a tumour, nor was it an indication for early referral. This is probably due to the fact that for most patients seen in primary care with a sore throat or dysphagia, the cause is usually benign, such as an infection, and seldom a tumour. This is also reflected in the high number (61%) of the patients with a sore throat who were initially treated with medication.

Patients whose complaints lasted for more than 30 days were referred significantly more frequently at the first visit than patients who had symptoms for a shorter period. Particularly, patients with a glottic carcinoma were more often referred at the first consultation. In the Netherlands, patients are generally referred to a specialist when hoarseness persists for more than three weeks to exclude causes other than an infection or

voice abuse. Although a tumour was suspected in only 24% of the patients with hoarseness, more hoarse patients (33%) were referred at the first visit.

Patients who smoke more than 20 cigarettes a day seem to have more delay in the referral process. This is probably due to the fact that GPs and dentists attribute the patients' complaints to their smoking behaviour. Extra attention should be given to this high-risk population, even although some patients with a squamous cell carcinoma in the head and neck region have never smoked or used alcohol.[24] Overall, GPs/dentists tended to consider the possibility of a tumour sooner when a patient drank >4 units per day and smoked >20 cigarettes per day. Suspicion of a tumour would probably arise earlier if every patient were asked about his or her alcohol use and smoking habits.

We can conclude from this study that it is often difficult for GPs and dentists to recognize symptoms as potentially emanating from carcinomas in the head and neck region. Delayed referral and inappropriate treatment caused by misinterpretation of symptoms, either by the GP or the patient, should be prevented. Therefore we, the professional specialists, should advise the clinicians in primary care, who are our gatekeepers, not to hesitate to refer patients to a specialist for further examination. The recently developed guidelines (Table 3) will probably facilitate referral.[25;26]

Table 3. Referral guidelines for suspected head and neck cancer

1.	Hoarseness persisting for >3 weeks
2.	Sore throat
3.	Pain in oral cavity
4.	Referred pain (for example otalgia)
5.	Blood or mucus in oral cavity
6.	Dysphagia
7.	Complaints of teeth or prosthesis
8.	Ulcer
9.	White or red patches of the oral mucosa
10.	Neck mass

Note: referral is more urgent when symptoms persist >3 weeks or have an unusual course.

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Chapter 7

Professional delay in head and neck cancer patients: Analysis of the diagnostic pathway

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Submitted

Chapter 7

Professional delay in head and neck cancer patients: Analysis of the diagnostic pathway

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Abstract

Background. The aim of this study was to identify which factors are related to professional delay and to determine the length of the diagnostic pathway in head and neck cancer patients.

Methods. Three hundred and six patients with a carcinoma of the larynx, pharynx and oral cavity were included in the study. Logistic regression analysis was used to identify risk factors for professional delay.

Results. Large (T3-T4) tumours showed significantly less professional delay than small (T1-T2) tumours (p=.045, odds ratio [OR] = 0.6). Pharyngeal (p=.00, OR=02) and oral carcinomas (p=.00, OR=0.2) had less professional delay than glottic carcinomas. Hoarseness was associated with prolonged professional delay (p=.00, OR=5.9). Heavy drinking in combination with smoking (p=.005, OR=0.3), a sore throat (p=.02, OR=0.4) or having a lesion (p=.03, OR=0.2) showed a shorter diagnostic period. The duration of the diagnostic process in a general hospital ranged from 0-570 days, with a median of 14 days. Only a small group of patients met the ideal management standards in our head and neck clinic.

Conclusions. Although prolonged delay was associated with small (glottic) tumours, the diagnostic process takes a fairly long time. The results indicate that continued educational programs for professionals are warranted.

INTRODUCTION

The incidence of head and neck tumours has been rising over the past few decades. The increase is particularly marked for advanced stage tumours.[1-3] One important contributing factor in late stage disease is patient delay.[4;5] Several studies found that professional factors contributed to a prolonged diagnostic interval in 30% of the cases.[6-8] Some studies reveal an association between professional delay and advanced tumours at diagnosis [9-12] while others do not.[7;13-19] The study by Wildt *et al.*[8] on oral cancer shows that a relatively high proportion of patients with small tumours had a professional delay of more than 45 days.

Measures to minimize diagnostic delay can lead to diagnosis at an earlier stage of the disease, which usually results in a better prognosis.[20;21] We therefore examined the total length of the diagnostic process. It starts with the referral by the GP or dentist and ends with the final diagnosis in our hospital and the first day of treatment, being either surgery or radiotherapy. In addition, we evaluated the patient- or tumour-related factors that could influence the diagnostic process.

In the Netherlands, most head and neck cancer patients are seen in a general hospital before being referred to a specialized head and neck clinic. By then, most patients have already had an endoscopy and/or histopathological diagnosis. All referred patients undergo a diagnostic and staging panendoscopic examination under general anesthesia in our clinic. In addition, all patients get a chest X-ray, an echo with fine needle aspiration cytology and a CT or MRI scan. The results are then presented at a weekly multidisciplinary tumour conference to determine a treatment proposal according to the Dutch head and neck cancer guidelines.[22;23] The proposed treatment may involve surgery, radiotherapy or a combined chemo-radiotherapy.

PATIENTS AND METHODS

Patients were eligible to take part in this study if they had newly diagnosed squamous cell carcinoma of the oral cavity (ICD-O 141, 143-145), the oropharynx or hypopharynx (ICD-O 146,148) or larynx (ICD-O 161) and had no previous or synchronous malignancies in the head and neck region. Patients with cognitive impairment or who did not understand the

Dutch language were excluded from the analysis. From 2000 to 2002, patients who had been diagnosed at the Department of Otorhinolaryngology or Oral and Maxillofacial Surgery at UMC Utrecht were sent a letter inviting them to participate. Their GP and/or dentist were sent a questionnaire asking about the date of the first visit, the duration of the symptom mentioned by the patient and the date of referral to a hospital.

One hundred sixty-nine patients with a laryngeal carcinoma, 85 patients with a pharyngeal carcinoma and 173 patients with an oral cavity carcinoma were eligible for this study during the accrual period. Fifty-two patients (37%) with a laryngeal carcinoma, 30 patients (35%) with a pharyngeal carcinoma and 39 patients (23%) with an oral cavity carcinoma refused the invitation to participate. Their main reasons were lack of motivation (29%), too much trouble (22%), and poor physical/mental health (30%). There were no differences between the participants and those patients who refused to participate with respect to localization, tumour stage, sex or age. Our analyses were based on data for 117 patients with a laryngeal carcinoma, 55 patients with a pharyngeal carcinoma and 134 patients with an oral cavity carcinoma.

Professional delay was calculated from the date of the first consultation with a specialist until the date of the histopathological diagnosis. Just before surgery, the patients were interviewed about their symptoms, treatment and date of referral. Those receiving radiotherapy and/or chemotherapy were interviewed just before or during the first treatment sessions. To verify their answers, a questionnaire was sent to a close relative. The date of the first medical contact was derived from the information given by the GP or dentist. The date of the first consultation with a specialist in a general hospital and the date of endoscopy for histopathological diagnosis were obtained from the referral letter. First visit to our hospital, date of endoscopy for staging of the tumour, the date of determining a treatment proposal by the multidisciplinary tumour conference, and the date of treatment and the characteristics of the tumour, such as T stage and localization, were obtained from the medical records. The tumours were registered according to the International Classification of Diseases for Oncology (ICD-O) and the TNM classification.[24]

Statistical analysis

All analyses were carried out with SPSS statistical software for Windows, version 12.0. Odds ratios and 95% confidence intervals were estimated by logistic regression analysis. The chi-square test was used to analyse categorical data.

RESULTS

The study population consisted of 306 patients, 210 of whom were male and 96 female. The patients' ages ranged from 34 to 89 years, with a mean of 62 years. Two hundred and seven patients were diagnosed with a small (T1-T2) tumour and 97 patients with a large (T3-T4) tumour.

The duration of the diagnostic process, calculated from the first visit to a specialist until the diagnosis was made at a general hospital, ranged from 0 to 570 days, with a median of 14 days (Table 1). At our department, the work-up for staging of the tumour took another 21 days, and the waiting time for treatment was 47 days. Altogether, the median duration was 44 days from the first visit to a specialist at a general hospital until a treatment proposal was made at the multidisciplinary tumour conference. There was hardly any delay in referral to our department by the GP/dentist and the specialist.

Table 1. Diagnostic delay (in days) from making an appointment with a specialist after referral by a GP/dentist to the final diagnosis of cancer and treatment in our hospital. With maximum standards (workdays) of the NWHHT.

Stage	No. patients	Mean	Median	Range	Standards[a]
Making appointment – first visit ENT	302	10	7	(0-74)	1
ENT - endoscopy	219	24	7	(0-563)	
First visit ENT - diagnosis	269	31	14	(0-570)	
Diagnosis – first visit at our department	270	8	6	(0-51)	
First visit at our department - endoscopy	304	17	14	(0-309)	10
First visit at our department – diagnosis[b]	305	25	21	(0-440)	17
First visit at our department - treatment	302	49	47	(5-476)	30

[a] according to the ideal standard for management of head and neck cancer

[b] the date of determination of a treatment proposal by the multidisciplinary tumour conference.

Table 2. Odds Ratios (OR) with 95% Confidence Interval (CI) for professional delay according to tumour and social variables (delay ≥2 months from first visit to specialist until diagnosis in our hospital)

	No	Yes			
	No. patients (%)	No. patients (%)	*p*-value	OR	(95% CI)
T classification					
T1-T2	134 (64)	73 (76)		1.0	(referent)
T3-T4	74 (36)	23 (24)	0.045	0.6	(0.3-1.0)
Localization					
glottic	35 (17)	43 (45)		1.0	(referent)
supra-/ subglottic	18 (9)	21 (22)	0.90	1.0	(0.4-2.1)
pharynx	45 (22)	9 (9)	0.00	0.2	(0.1-0.4)
oral cavity	110 (53)	23 (24)	0.00	0.2	(0.1-0.3)
N classification					
0	145 (70)	74 (77)		1.0	(referent)
≥1	63 (30)	22 (23)	0.18	0.7	(0.4-1.2)
Duration complaint					
<30 days	83 (41)	39 (41)		1.0	(referent)
≥30 days	119 (59)	56 (59)	0.99	1.0	(0.6-1.6)
Age					
≤65 year	131 (64)	53 (56)		1.0	(referent)
>65 year	75 (36)	42 (44)	0.20	1.4	(0.8-2.3)
Sex					
male	144 (69)	66 (69)		1.0	(referent)
female	64 (31)	30 (31)	0.95	1.0	(0.6-1.7)
Comorbidity					
yes	57 (31)	33 (38)		1.0	(referent)
no	129 (69)	55 (63)	0.26	0.7	(0.4-1.3)
Smoking					
never	20 (10)	10 (10)		1.0	(referent)
stopped	55 (26)	33 (34)	0.68	1.2	(0.5-2.9)
0-20 cigarettes/day	71 (34)	34 (35)	0.92	1.0	(0.4-2.3)
>20 cigarettes/day	62 (30)	19 (20)	0.30	0.6	(0.2-1.5)
Alcohol intake					
drinker	123 (59)	52 (54)		1.0	(referent)
none/ not daily	85 (41)	44 (46)	0.42	1.2	(0.8-2.0)
Alcohol and smoking					
≤4 drinks/day	151 (73)	80 (83)		1.0	(referent)
>4 drinks/day and stopped	7 (3)	7 (7)	0.25	1.9	(0.6-5.6)
>4 drinks/day and smokes	50 (24)	9 (9)	0.005	0.3	(0.2-0.7)

Note: 'duration of complaints' data of 6 patients was missing. Comorbidity includes hypertension, heart failure, chronic obstructive pulmonary disease and diabetes and was based on data of 276 patients.

Patients with large (T3-T4) tumours had significantly less professional delay than patients with small (T1-T2) tumours (Table 2). The professional delay was also significantly less among patients with oral and oro- or hypopharyngeal tumours than among those with glottic laryngeal tumours. Professional delay was not associated with patient delay, comorbidity or other tumour characteristics. When analyzed separately, neither alcohol use nor smoking was associated with diagnostic delay, but the combination of heavy drinking and smoking did show significantly less delay.

Professional delay was not associated with sociodemographic variables. These include age, sex, marital status (married or divorced/widowed), living situation (alone or with family) and income (less or more than modal).

The association between hoarseness and prolonged diagnostic delay was significant (Table 3). The diagnostic period was significantly shorter for patients with a lesion or a sore throat.

DISCUSSION

The length of professional delay that we found fell within the same range as that reported in the literature. The professional delay varies from 4 days to 3.5 months, depending on the localization and size of the tumour.[8;10;12;13;25-30]

The period between consulting a specialist and being diagnosed at a general hospital was 25 days for laryngeal, 10 days for pharyngeal and 7 days for oral cancer. In the Netherlands, nearly every patient diagnosed with a head and neck tumour in a general hospital is referred to a specialized head and neck clinic for staging of the tumour and treatment. Including a median referral period of 6 days, the staging process for patients with laryngeal cancer was accomplished after 62 days, for patients with pharyngeal cancer after 43 days and for patients with oral cancer after 34 days.

In 2004, an ideal standard for the management of head and neck cancer patients was developed in the Netherlands.[31] To meet this standard, the period from the first visit to a specialized head and neck clinic until treatment should not exceed 30 workdays. For an endoscopy, the period should be no more than 10 workdays, and the maximum wait for a

Table 3. Odds Ratios (OR) with 95% Confidence Interval (CI) for professional delay according to different tumour symptoms (delay ≥2 months from first visit to specialist until diagnosis in our hospital)

Variable	Category	No	/Yes	*p*-value	OR	(95% CI)
Hoarseness	not reported	168	/40		1.0	(referent)
	yes	40	/56	0.00	5.9	(3.5-10.0)
Dyspnoe	not reported	207	/94		1.0	(referent)
	yes	1	/2	0.23	4.4	(0.4-49.2)
Dysphagia	not reported	193	/92		1.0	(referent)
	yes	15	/4	0.31	0.6	(0.2-1.7)
Sore throat	not reported	168	/88		1.0	(referent)
	yes	40	/8	0.02	0.4	(0.2-0.9)
Neck mass	not reported	198	/91		1.0	(referent)
	yes	10	/5	0.88	1.1	(0.4-3.3)
General symptoms	not reported	205	/94		1.0	(referent)
	yes	3	/2	0.69	1.5	(0.2-8.8)
Otalgia	not reported	205	/95		1.0	(referent)
	yes	3	/1	0.78	0.7	(0.1-7.0)
Mass in throat	not reported	205	/96		1.0	(referent)
	yes	3	/0	1.00	0.0	-
Lesion	not reported	184	/93		1.0	(referent)
	yes	24	/3	0.03	0.2	(0.1-0.8)
Mass	not reported	197	/94		1.0	(referent)
	yes	11	/2	0.22	0.4	(0.1-1.8)
Irritation	not reported	196	/94		1.0	(referent)
	yes	12	/2	0.17	0.3	(0.1-1.6)
Painful lesion	not reported	193	/92		1.0	(referent)
	yes	15	/4	0.31	0.6	(0.2-1.7)
Pain (no lesion)	not reported	183	/90		1.0	(referent)
	yes	25	/6	0.13	0.5	(0.2-1.2)

diagnosis was set at 17 workdays. In our study, the standard for the diagnostic period was met in 54% of the patients with laryngeal carcinomas, in 56% of those with pharyngeal carcinomas and in 72% of those with oral carcinomas. The goal of starting treatment within 30 days was reached in 19% of the cases for laryngeal, 26% for pharyngeal and 68% for oral carcinomas.

Patients with large (T3-T4) tumours had less professional delay than those with small (T1-T2) tumours. This result is in accordance with that of Wildt *et al.*[8], who found that patients with small tumours had more professional delay. One possible explanation is that diagnosis is easier when the tumours are larger because they are visible and cause more complaints. We found the most professional delay for glottic tumours. Obviously, it was hard to tell if the hoarseness or voice change had been caused by a carcinoma. This difficulty was also noted by Merletti *et al.*[17]; in their study, patients with dysphonia had a longer professional delay than patients without these symptoms. Another explanation could be that some patients experiencing persistent hoarseness were eventually diagnosed with a glottic laryngeal carcinoma at a pre-malignant stage of the disease. Although the complete history was not known for every patient, malignancy was preceded in 14 cases by a benign lesion (dysplasia, hyperplasia, chronic laryngitis, not malignant). This hypothesis arises in the study by Alvi *et al.*[32] Regarding patients who seek medical care for early symptoms, they conclude that the diagnosis is often delayed because the condition is considered benign. Patients with a sore throat or a lesion had less professional delay. This finding concurs with the results of a study by Allison *et al.*[33] in which painless mucosal lesions had reduced odds of professional delay. These lesions occur most frequently in the oral cavity, which is easily accessible for examination. This is also confirmed by our data, which show that having oral cancer lowers one's odds of having professional delay.

In contrast to our findings, Carvalho *et al.*[10] demonstrated that professional delay actually increased the risk of being diagnosed with advanced head and neck tumours. Also the study by Allison *et al.*[9] showed a higher risk of being diagnosed with late-stage disease in upper respiratory tract cancer when the professional delay exceeds one month. A study by Teppo *et al.*[12] showed increased risk of having advanced-stage laryngeal carcinomas and a poorer chance of survival when professional delay occurred. An explanation could be that in these studies professional delay included referral delay in primary care. These authors defined professional delay as the period from the first consultation with a healthcare professional until the histopathological diagnosis is made[10;12] or until a consultation with the treating specialist

takes place.[9] More delay, and thus larger tumours, probably occurred during the referral process and not during the diagnostic process in the hospital. This is confirmed in a study we conducted on referral delay, whereby the most delay was incurred for larger tumours (Brouha, internal report). Other studies found no relationship between professional delay and the stage of the disease.[13;14;16;27]

We did not find an association between comorbidity and professional delay. In the study by Allison *et al.*[33], a tendency was shown for comorbidity to increase the odds of professional delay in head and neck cancer patients. The only shortcoming of that study is that comorbidity was not clearly defined. In a study by Singh *et al.*[34], comorbidity was not associated with the stage of the disease at presentation or with the localization of the tumour. The absence of significant association between age and professional delay in our study is consistent with the findings from other studies.[26;35;36] Neither education nor sex was associated with professional delay. In this regard, our study differs from Allison's, which showed that patients with higher education had less professional delay.[33] Wildt *et al.*[8] showed that old age and being female increased the risk of having professional delay in a cohort of oral cancer patients. The combination of heavy drinking and smoking was associated with reduced odds of professional delay. Most studies have not analysed the combination of drinking alcohol and smoking, but two studies did show less diagnostic delay among smokers.[27;36] Other studies showed no relation between professional delay and either smoking or alcohol consumption.[12-14]

In conclusion, the significant prolonged professional delay found in our study was related to small glottic tumours, and only a small group of patients met the ideal management standards. Although small tumours have a better prognosis of survival, a delay in diagnosis is often frustrating for the patients. Our goal of facilitating diagnosis should focus on education and screening to prevent/minimize patient delay, since previous studies have shown that patient delay contributes to larger tumours.[4;5] General practitioners and dentists should also be educated to prevent delayed referral. Furthermore, we should prevent prolonged diagnostic pathways leading up to the first day of therapy, be it in the form of surgery or radiotherapy. Therefore, as hypothesized in the discussion, we would advise specialists to follow up on patients who have been diagnosed with a pre-malignant disease. The reason is that some lesions eventually become malignant, especially in patients who continue smoking and drinking alcohol. Finally, we strongly advocate that doctors should discourage all of their patients from smoking and drinking excessively.

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Chapter 8

General discussion

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General discussion

Introduction

The incidence of head and neck cancer has been rising the last decades.[1] An explanation for an increasing incidence of cancer in the Netherlands could be an aging population[2] and an increase of cancer in women.[3] More women have shown risk behaviour of smoking and alcohol consumption. Not only the incidence of head and neck cancer increased, but also surprisingly, the percentage of large (T4) tumours increased.[4;5] Linear regression analyses estimated an increase of the percentage of T4 tumours of 0.9% every year at the University Medical Centre Utrecht (Chapter 1). An explanation could be that the composition of head and neck tumours changed over the years in favour of an increased number of oral cavity tumours in women and pharynx cancer in men and women, at the cost of the number of larynx carcinomas in men. While advanced stage disease is more common in oral and pharynx cancer than in larynx cancer this may explain the increased percentage of T4 tumours (Chapter 1).[1]

This increasing number of advanced stage disease poses clinicians with a huge problem since treatment of advanced head and neck cancer needs more extensive and expensive treatment and is accompanied with increased morbidity and mortality. Despite optimized treatment protocols for head and neck cancer, the prognosis of patients with advanced disease is still modest and treatment has still a major impact on quality of life. Survival in general has only been little improved since the last 30 years.[6-8] Therefore, early detection of head and neck cancer becomes more and more important to improve prognosis and quality of life.

An impeding factor for early detection of head and neck cancer is delay in diagnosis. Delay can occur at different stages in the diagnostic process. The patient, the doctor or both could be responsible for delay. Many studies have investigated diagnostic delay in head and neck cancer patients, but not as extensive as in this study. Regarding the different stages of delay, we asked the patients what they thought had caused their first symptoms and when they had first inferred illness. Furthermore, we asked the patients why they had consulted a general practitioner or dentist, and explored the reasons why they had postponed medical consultation. In addition, this study takes into account the data from the general practitioner and the partner when establishing the possible causes of diagnostic delay. The high response rate enhances the reliability of the findings regarding the different stages of delay.

Patient, referral and diagnostic delay

Patients eventually diagnosed with a head and neck carcinoma wait fairly long before deciding to consult a general practitioner. For example, only 14% of the patients with hoarseness, and about 30% of the patients with dysphagia or a sore throat made an appointment with their general practitioner within 3 weeks. Even one quarter of the patients postponed seeking medical care for more than 3 months. This is probably due to ignorance of the patient. Our study (Chapter 3 and 4) showed that most of the patients attributed their symptoms to something innocuous such as an infection or common cold. This is also confirmed in the fact that when we asked the patients when they inferred illness, almost 80% referred to the period after the visit to a general practitioner or specialist. Thus, most of the patients did not consider themselves ill before they sought medical help. Patients with an oral carcinoma often attributed their symptom to problems with their prosthesis or to complaints of dental origin. Many patients had absolutely no idea what had caused their symptom, not to mention a malignant tumour. This was also seen in the study of Fabian *et al.*[9] In this study more than 85% of the patients diagnosed with head and neck cancer were unaware of the causative factors of their tumour, which in turn contributes to late presentation.[10] Probably, because of the seemingly harmless nature of the symptoms, most patients postponed consultation of a general practitioner or dentist, until symptoms worsened or persisted for a fairly long time. Also, earlier studies showed that the less specific the symptoms, the longer the appraisal delay.[11;12] This, in sharp contrast to patients who had a neck mass as first symptom. A neck mass is probably alarming to most patients and, therefore a reason to consult a general practitioner without delay (Chapter 4).

Excessive drinking and smoking was quite common in our study population and was associated with prolonged patient delay and advanced disease at diagnosis (Chapter 5). In other studies, advanced disease was related to tobacco use[13;14], drinking alcohol[15] or the combination of drinking alcohol and smoking tobacco.[16;17] This particular patient population ignore symptoms or were probably not convinced that their general practitioner could help them or did not want to bother the doctor with their complaint. This was also concluded in the study of Cunningham *et al.*[18] in which the authors suggested that heavy drinkers may not be so concerned about health issues and tend to ignore early warning signals.

Prolonged referral delay was associated with advanced tumours (Chapter 6). Although a large number of patients (38%) eventually diagnosed with a head and neck tumour were referred after the first visit, the referral period took a fairly long time. In our study the median referral delay for the total number of patients was nearly one month with a range of 0 to 25 months. When there was no tumour suspicion at first visit, referral delay increased fairly to 8 weeks for patients who presented themselves with hoarseness or dysphagia to 11 weeks for patients with a sore throat. Patients with an eventually diagnosed T4 tumour were less frequently referred at the first visit than patients with a T1 tumour. One of the explanations could be that quite a few of the T4 tumours were located in the oropharynx and hypopharynx, which is less accessible for examination. Another explanation could be that tumour progression occurred during the referral period. Accelerated referral by general practitioners and dentist could probably lead to diagnosis in an earlier stage of the disease. Most patients with large tumours have an oropharynx or hypopharynx carcinoma. This is not only due to prolonged patient delay (Chapter 4), but it seems that symptoms appear late. While these tumours are difficult to examine for GPs/dentists it is not surprising that these patients are least frequent referred at the first visit and treated with medication or got a wait and see policy (Chapter 6). Another reason could be that most patients seen in primary care with a sore throat or dysphagia have benign causes such as an infection and seldom a tumour. Referral guidelines for suspected head and neck cancer are developed to facilitate diagnosis (Chapter 6). These guidelines stated that referral is more urgent, when symptoms persist for more than three weeks or symptoms have an unusual course. Furthermore, when there is no tumour suspicion at first visit, patients should be followed up or advised to return if symptoms persist after treatment to prevent delay. Heavy smokers are less frequent referred at the first visit than patients who never smoke. Probably general practitioners think that symptoms are just due to the patients' smoking behaviour and not caused by a tumour. On the other hand general practitioners and dentist considered more earlier a tumour when patients drank >4 U/day in combination with heavy smoking. It is therefore possible that referral could be accelerated by asking every patient about their alcohol and smoking habits.

The period from first visit to a specialist in a general hospital until diagnosis ranged from 0 to 81 weeks, with a median of 2 weeks (Chapter 7). Patients with a glottic larynx carcinoma had the longest professional delay. This finding is also confirmed by the finding that patients with hoarseness are significantly associated with prolonged diagnostic delay. An explanation could be that some patients with hoarseness present with a pre-malignant lesion,

but were not adequately followed up. So their initial management is justified, but aftercare should be improved. Specialists are familiar with the risk factors of head and neck cancer in contrast to general practitioners or dentist; heavy drinkers who also smoke, show significantly less diagnostic delay than patients who consume only a few drinks a day.

Possible methodological limitations

During the two year accrual period of this study, 427 patients were eligible of which 306 actually participated. There were no differences detected regarding age, sex, tumour characteristics between participants and those patients who refused to participate. However, we do not know if there is selection bias regarding diagnostic delay. There might be an under representation of those who themselves delayed seeking medical care and did not want to discuss or be confronted with this topic. We tried to minimize this selection bias by not explicitly referring to delay in diagnoses in the information letter, but by stating that we are investigating in more general terms, factors related to seeking diagnoses for head and neck cancer.

Furthermore, due to the retrospective nature, the data regarding diagnostic delay may be subject to recall bias. To minimize recall bias, we interviewed patients just after diagnosis and before treatment. In addition, to enhance reliability we collected complementary information from the patients' general practitioner or dentist and from the patients' partner. However, the patients' interview was used primarily, since the partner could only give information about possible patient delay once symptoms became perceptible or were discussed openly.

On the other hand we do not think that patients underreport delay because in this study we found that prolonged patient delay was associated with more advanced stage of the disease.

Practical implications: towards prevention of advanced tumours

The present study revealed that prolonged patient delay was associated with late-stage disease for patients with pharyngeal cancer and for patients with oral cancer (Chapter 4). Patients with glottic tumours on the other hand showed the longest delay before deciding to consult their general practitioner (Chapter 3). But most patients were diagnosed in an early stage of the

disease, probably due to the early onset of symptoms and the slow growing nature of the tumour. Supraglottic tumours, probably more related to pharyngeal cancer, were often diagnosed in late-stage disease. Attempts to reduce patient delay in seeking medical care are therefore extremely important to reduce the number of patients with advanced tumours. This may have important effects in reducing the morbidity, mortality and the costs of treatment and rehabilitation. Due to a lack of knowledge about specific tumour symptoms accompanying head and neck cancer and the potential risk factors, an information campaign to alert the general public could be beneficial in accelerating tumour detection. For example, we could also think of specific health warnings on every pack of cigarettes. In addition, preventive measures aimed at reducing risk behaviour are probably more beneficial and cost effective than screening, because of the low incidence of head and neck tumours in the Netherlands.

Another important conclusion of this study was that patients interpreted the symptoms as a minor disorder and not suspected cancer (Chapter 3 and 4). As a consequence, the general public should not only be informed about the nature of the symptoms, but also about the duration of the symptoms. Tumour symptoms persist or may worsen over time and should therefore be a reason to consult a general practitioner. Furthermore when symptoms persist or do not improve after initial management of the general practitioner or dentist, people should not hesitate to return to their health care practitioner for referral to a specialist for further examination.

Delay was not only caused by patients, but delay occurred also in primary care (Chapter 6). In this study referral of patients with head and neck cancer took a fairly long time. This is probably due to inappropriate treatment by the general practitioner caused by misinterpretation of the symptoms. Education could be meaningful to prevent delayed referral, while we showed that prolonged delay was associated with more advanced disease. Recent developed guidelines for suspected head and neck cancer will probably facilitate referral. Furthermore, when there is no tumour suspicion at first visit, we think that to prevent delay, evaluation of therapy and follow up of at risk patients is extremely important. In the case of tumour suspicion we recommend the health care professionals to make themselves an appointment for the patient with the appropriate specialist to speed up diagnosis. Furthermore, health care professionals and specialists could play a preventative role by discouraging every patient to smoke or drink excessively. The risk for tobacco-related cancers of the alimentary tract declines among ex-smokers after 5 years, and is said to approach the risk of nonsmokers after 10 years of abstention.[19]

Some delay is due to the specialist, especially in those who are diagnosed with a pre-malignant stage of the disease. These patients should be adequately followed up, while some lesions become eventually malignant, especially in patients who continue smoking and drinking alcohol. Therefore, professionals should advice patients about head and neck tumour symptoms and discourage risk behaviour.

Ideal, no delay should occur in diagnosis and treatment when patients are referred to a specialist in a hospital. To shorten waiting times for medical examination and treatment in general, the government and hospital directors should provide sufficient capacity while recent prognostications show an increase of 40% of cancer in the year 2015, particularly due to an aging population (KWF).[20]

In conclusion of our study to prevent delay in seeking a diagnosis, we have the following recommendations:

1. The general public should be better informed about the potential risk factors and specific tumour symptoms accompanying head and neck cancer and the benefit of early detection.

2. General practitioners should ask about the patients' smoking and drinking behaviour in the case of unknown complaints such as hoarseness and a sore throat.

3. General practitioners should schedule at risk patients for a follow up appointment.

4. In case of persistent symptoms, general practitioners should not hesitate to refer patients to a specialist.

5. To prevent referral delay, we recommend the health care professional to make themselves an appointment for the patient in the case of tumour suspicion.

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Chapter 9

Summary

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Summary

Summary

The incidence of patients diagnosed with squamous cell carcinomas in the head and neck region has been rising in the past few decades. Especially the incidence of advanced-stage tumours has increased. This increasing number of advanced-stage disease poses clinicians with a huge problem since treatment of advanced head and neck cancer needs more extensive and expensive treatment and is accompanied with increased morbidity and mortality. Despite optimized treatment protocols for head and neck cancer, the prognosis of patients with advanced disease is still modest and treatment has still a major impact on quality of life. Survival in general has only been little improved the last 30 years. Therefore, early detection of head and neck cancer becomes more and more important to improve prognosis and quality of life. An impeding factor for early detection of head and neck cancer is delay in diagnosis. Delay can occur at different stages in the diagnostic process. The patient, but also the doctor could be responsible for delay. Therefore, a distinction is often made between patient and professional delay. Patient delay is defined as the period between experiencing symptoms and the first medical consultation. Professional delay is defined as the period between first medical consultation for tumour-related symptoms and the definite diagnosis or treatment. Delay can also occur during the time period between the first visit to a health care professional and referral to a specialist in a hospital. Literature show conflicting results regarding delay and either the stage of the disease at diagnosis or survival. In this thesis we analysed which patient, doctor and tumour-related factors contributed to the different stages of delay.

In **chapter 1** we describe the results of previous studies about delay and which factors contribute to delay. Furthermore, a stage model developed by Anderson and Cacioppo, which distinguishes various steps in the care seeking process, was used to explore the different stages of patient delay. This model describes the following stages of delay: (1) appraisal delay, represents the period from unexplained symptoms until the moment he/she considers to be ill; (2) illness delay, describes the number of days from the time an individual concludes to be ill to the decision to seek medical help; (3) behavioural delay, is the time elapsed between the decision to seek medical help and making an appointment with a health care practitioner; (4) scheduling delay, is the time elapsed between making an appointment and first receiving

medical attention; (5) referral delay, is the time between first medical consultation with the general practitioner/dentist and the first visit to a medical professional in the hospital; (6) medical specialist delay, which is the time which elapses between the first consultation with the medical specialist and the definitive diagnosis; and (7) management delay, which is the time between diagnosis and the treatment.

From 2000 to 2002, 306 patients diagnosed with a head and neck tumour at the University Medical Centre Utrecht participated in our study: 117 patients with a laryngeal carcinoma, 55 patients with a pharyngeal carcinoma, and 134 patients with an oral cavity carcinoma. There were 210 men and 96 women aged 34 to 89 years (mean, 62 years). Two hundred seven patients were diagnosed with a small (T1-T2) tumour and 99 with a large (T3-T4) tumour. Regarding the clinical stage, 172 patients were diagnosed with early stage (I-II) disease and 134 patients with advanced stage (III-IV). To the best of our knowledge, there are no studies that used information from the partner or a close relative to verify the data on diagnostic delay. The partner was asked about the care seeking process, the visits to the healthcare professional until the start of treatment. The response rate for the partners of the patients was 76%. Also information of the general practitioner and/or referring dentist was collected. They were sent a questionnaire asking about the policy from the first visit of the patient for tumour-related symptoms until the referral to a medical specialist. The response rate for the general practitioners and/or dentists was 94%.

In **chapter 2** we describe the retrospective analyses of more than 3000 patients diagnosed in the period 1980 to 2000 at the UMC Utrecht. In the early 1980s the percentage of T4 tumours was 12% and increased to 25% in the late 1990s. Using linear regression analysis, it was estimated that every year an increase of 0.9% of T4 tumours occur. This observed increase of T4 tumours shows up in figures from the regional (Netherlands Regional Cancer Registry) and national (National Cancer Registration) cancer database.

In **chapter 3** we analysed delay in a cohort of patients diagnosed with a laryngeal carcinoma. Patients diagnosed with a laryngeal carcinoma showed no significant difference in the length of delay between early- and late-stage disease. Only tumour site was significantly associated with patient delay. Although patients with a glottic tumour showed significantly longer delay than those with a supraglottic tumour, most of them were diagnosed with a lesion at an early

stage of the disease. This is probably due to the early onset of symptoms in glottic carcinomas and the long symptom-free period characteristic of supraglottic tumours.

Hoarseness was the most commonly mentioned symptom for both glottic and supraglottic cancer. Some patients complained about a sore throat or dysphagia. Most patients attributed their symptoms to something innocuous such as a common cold or an infection and some patients had no idea about the cause. A malignant tumour was rarely suspected. Because symptoms were interpreted as innocuous/benign or the symptom was thought not to be serious enough, medical attention was often postponed. Ultimately, the main reason to visit the general practitioner was the persistent hoarseness or the duration of the dysphagia or sore throat. The patients also consulted the general practitioner if symptoms got worse.

In **chapter 4** we analysed delay in a cohort of patients diagnosed with a pharyngeal or an oral cavity carcinoma. Prolonged patient delay was associated with late-stage disease for patients with pharyngeal cancer. Patients with an oral cavity carcinoma were more often diagnosed in early-stage disease than in advanced-stage, but patients with oral cancer with advanced-stage disease showed significantly more delay than those diagnosed in early-stage disease.

Appraisal delay was different for the tumour-related symptoms. The delay was longer among patients with pharyngeal cancer whose first symptom was a sore throat than among patients with dysphagia or a neck mass. Patients with oral cancer with dysphagia, a sore throat, a neck mass, irritation, or a painful lesion showed a shorter appraisal delay than patients with a lesion, a mass, or pain without a visible lesion. Most patients attributed their symptoms to a common cold or an infection. More patient delay was found among patients who attributed their symptoms to their prosthesis or dental problems and among patients who had no idea of the cause. Patients postponed medical attention because they thought the symptom was harmless or because it did not bother them. Other patients reported that they do not go to the doctor quickly or ignored their symptom. Reasons to visit a general practitioner were the persistence of a symptom or worsening of a symptom. Also developing a new complaint such as a neck mass and otalgia were reasons to see a general practitioner.

In **chapter 5** the association between patient delay and alcohol and smoking habits are investigated. This study showed that excessive drinking and smoking was not only associated with prolonged patient delay, but also with advanced disease at diagnosis. This study showed

also that all of the heavy drinkers were smokers or had been smoking before being diagnosed with a tumour. Most of the heavy drinkers smoked more than 20 cigarettes a day.

Furthermore, younger patients (<65 years) drank and smoked significantly more than elderly patients. The importance of a health education campaign to reduce incidence and to improve survival is discussed. This campaign should focus on the patient population who drink and smoke excessively and should include information about the risk factors of head and neck cancer.

In the study described in **chapter 6**, we analysed delay in referral by the general practitioner and dentist. This study showed that prolonged referral delay was associated with advanced-stage tumours at diagnosis. Although about one third of the patients was referred after the first visit, the referral period took a fairly long time. When there was no tumour suspicion at the first visit, referral delay increased to eight weeks for patients who presented themselves with hoarseness or dysphagia and to eleven weeks for patients with a sore throat.

There was significantly more tumour suspicion at the first visit when the tumours occurred in either the pharynx or the oral cavity compared with tumours situated in the larynx. This was also the case when symptoms persisted for more than 30 days. Patients who reported dysphagia or a sore throat were least frequent referred at the first visit. They were initially treated with medication or got a wait-and-see policy. Also, heavy smokers seem to be less frequently referred at the first visit than patients who have never smoked. Probably general practitioners think that symptoms are just due to the patients' smoking behaviour and not caused by a tumour. The results are discussed, and suggest that in primary care it is often difficult to decide when to refer a patient to a specialist. Referral guidelines are presented for suspected head and neck cancer to prevent delayed referral.

The study described in **chapter 7** identifies which factors are related to professional delay and determines the length of the diagnostic pathway in head and neck cancer patients. Patients with large tumours showed significantly less professional delay than patients with small tumours. For specialists, diagnosis of a large tumour in general is less complicated. Patients with a glottic tumour showed a long professional delay. Also patients with hoarseness showed a prolonged diagnostic delay. Patients who drink and smoke excessively showed significantly less delay in diagnosis of their tumour. Furthermore, we analysed the total work up in our department for staging of the tumour. The analyses showed that it took a median of 21 days

for staging of the tumour according to the TNM classification and a median period of 47 days to treatment. There was hardly any delay in referral from both the GP/dentist and specialist to our department.

In the **general discussion**, we discussed the results of the previous studies. In addition, we discussed the possible methodological limitations (e.g. recall bias) and gave practical implications of this study towards prevention of advanced-stage tumours. Because of the unacquaintance of the potential risk factors, the general public should be better informed about the risk factors and specific tumour symptoms accompanying head and neck cancer. Furthermore, patients should be educated about the benefit of early detection. To enhance early diagnosis general practitioners should ask about the patients' alcohol and smoking behaviour and pay extra attention to this risk group by scheduling them for a follow up appointment. General practitioners and dentists should not hesitate to refer patients to a specialist for further examination. The recently developed guidelines for suspected head and neck cancer will probably facilitate referral.

In conclusion, patient and referral delay is common among head and neck cancer patients and affects tumour size at diagnosis. This is particularly due to a lack of knowledge of the risk factors and specific tumour symptoms accompanying head and neck cancer. It is recommended that the general public and in particular the high risk individuals of the heavy smokers and drinkers, are educated about the nature and duration of the symptoms associated with head and neck cancer, the risk factors, and the benefits of early detection.

Chapter 10

Samenvatting

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De incidentie van patiënten gediagnosticeerd met een kwaadaardige tumor in het hoofd-halsgebied is de laatste decennia gestegen. Met name de incidentie van tumoren in een vergevorderd stadium is toegenomen. Deze toename van grote tumoren vormt een steeds groter probleem voor artsen, aangezien de behandeling van grote tumoren veel uitgebreider en kostbaarder is. Ondanks geoptimaliseerde behandelingsprotocollen voor hoofd-halskanker is de prognose voor tumoren in een vergevorderd stadium nog niet veel belovend en heeft de behandeling een grote invloed op de kwaliteit van leven. Overleving in het algemeen is de laatste 30 jaar maar weinig verbeterd. Het is daarom belangrijk om hoofd-halstumoren vroegtijdig op te sporen om de prognose en de kwaliteit van leven te kunnen verbeteren. Een factor die vroege detectie verhindert, is vertraging in de diagnostiek van de tumor. Vertraging in de diagnostiek van de tumor kan optreden in verschillende stadia van het diagnostisch traject. De patiënt, maar ook de arts kan verantwoordelijk zijn voor vertraging in diagnostiek en behandeling. Vaak wordt onderscheid gemaakt tussen vertraging veroorzaakt door de patiënt zelf en vertraging veroorzaakt door de arts. Patiëntvertraging is gedefinieerd als de periode tussen het gewaarworden van de symptomen en het eerste bezoek aan een arts. Professionele vertraging wordt gedefinieerd als de periode tussen het eerste medische consult voor de tumor gerelateerde symptomen en de definitieve diagnose of behandeling. Vertraging in de diagnostiek kan ook optreden in de periode tussen het eerste bezoek aan de huisarts of tandarts en de verwijzing naar de specialist. Onderzoeken in de literatuur laten tegenstrijdige resultaten zien tussen vertraging en het stadium van de tumor bij diagnose en ook tussen de vertraging en de kans op overleving. In dit proefschrift wordt geanalyseerd in welke mate de patiënt, de arts en de tumor gerelateerde factoren bijdragen tot de verschillende stadia van vertraging.

In **hoofdstuk 1** worden de resultaten beschreven van voorgaande studies over vertraging en welke factoren daartoe bijdragen. Tevens wordt het model, ontwikkeld door Andersen en Cacioppo dat verschillende stappen onderscheidt in het zoeken van medische hulp, gebruikt om de verschillende stadia van patiëntvertraging te kunnen onderzoeken. Het model beschrijft de volgende stadia: (1) 'appraisal delay' geeft de periode van onverklaarbare symptomen tot aan het moment dat men zich realiseert ziek te zijn weer; (2) 'illness delay' beschrijft het

aantal dagen vanaf de tijd dat men zich realiseert ziek te zijn tot aan de beslissing om medische hulp te zoeken; (3) 'behavioural delay' is de periode tussen de beslissing om medische hulp te zoeken en het maken van de afspraak met de huisarts of tandarts; (4) 'scheduling delay' is de tijd tussen het maken van de afspraak en het plaatsvinden van het consult; (5) 'referral delay' is de tijd tussen de eerste medische consultatie met de huisarts of tandarts en de eerste afspraak met de specialist in een ziekenhuis; (6) 'medical specialist delay' is de tijd tussen het eerste bezoek bij de medisch specialist tot aan de definitieve diagnose; en (7) 'management delay' is de tijd tussen diagnose en het begin van de behandeling.

Van 2000 tot 2002 hebben 306 patiënten, gediagnosticeerd met een tumor in het hoofd-halsgebied in het Universitair Medisch Centrum Utrecht, geparticipeerd in ons onderzoek: 117 patiënten met een kwaadaardige tumor van het strottenhoofd, 55 patiënten met een kwaadaardige tumor in de keelholte en 134 patiënten met een tumor in de mondholte. Er waren 210 mannen en 96 vrouwen in de leeftijd van 34 tot 89 jaar met een gemiddelde leeftijd van 62 jaar. In totaal waren er 207 patiënten gediagnosticeerd met een kleine (T1-T2) tumor en 99 patiënten met een grote (T3-T4) tumor. Bij 172 patiënten werd de tumor in een klinisch vroeg (I/II) stadium ontdekt en bij 134 patiënten in een laat (III/IV) stadium.

In ons onderzoek hebben wij, om de gegevens van de patiënt te kunnen verifiëren, aan de partner vragen gesteld met betrekking tot de diverse stadia van vertraging en over de bezoeken aan de huisarts en de specialist. De respons van de partners van de patiënten was 76%. Naar ons beste weten is er geen studie die informatie van de partner of een naaste heeft gebruikt. Ook werd er informatie opgevraagd bij de verwijzend huisarts en/of tandarts. Zij kregen een vragenlijst opgestuurd waarin het beleid vanaf het eerste bezoek van de patiënt voor tumor gerelateerde symptomen tot aan de verwijzing werd gevraagd. De respons van de huisarts/tandarts was 94%.

In **hoofdstuk 2** wordt een retrospectieve analyse van meer dan 3000 patiënten uit het Universitair Medisch Centrum Utrecht, gediagnosticeerd in de periode 1980 tot 2000, beschreven. In het begin van de jaren tachtig was het percentage T4 tumoren 12%. Aan het einde van de jaren negentig was dit 25%. Op basis van de analyse van onze resultaten is een jaarlijkse voortzetting van de stijging van T4 tumoren te verwachten van 0.9%. Selectieve

verwijzing is onwaarschijnlijk, omdat de toegenomen incidentie van T4 tumoren overeenkomt met die van de regionale en landelijke kankerregistratie.

In **hoofdstuk 3** worden patiënten geanalyseerd die gediagnosticeerd zijn met een tumor in het strottenhoofd. De duur van de vertraging tussen tumoren gediagnosticeerd in een vroege en late fase van de ziekte vertonen geen significant verschil. De vertraging veroorzaakt door de patiënt zelf hangt wel sterk af van de lokalisatie van de tumor. Patiënten met een tumor van de stembanden vertoonden een significant langere vertraging dan patiënten met een tumor boven de stembanden. Maar de meeste patiënten met een tumor van de stembanden werden gediagnosticeerd met een laesie in een vroege fase van de ziekte. Dit wordt waarschijnlijk veroorzaakt doordat stembandtumoren in een vroege fase van de ziekte al klachten geven in tegenstelling tot tumoren die direct boven de stembanden ontstaan.

Heesheid was het meest gerapporteerde symptoom voor zowel stembandtumoren als tumoren welke zich boven de stembanden bevinden. Enkele patiënten klaagden over een zere keel of slikklachten. De meeste patiënten dachten dat hun klacht veroorzaakt werd door iets onschuldigs zoals een verkoudheid of een infectie. Sommige patiënten hadden absoluut geen idee wat de oorzaak van hun klachten zou kunnen zijn. Een kwaadaardige tumor werd zelden vermoed. Omdat de symptomen geïnterpreteerd werden als iets onschuldigs of niet ernstig genoeg, werd het zoeken van medische hulp vaak uitgesteld. De voornaamste reden dat patiënten uiteindelijk toch de huisarts bezochten was de persisterende heesheid of de tijdsduur van de pijnlijke keel of de voortdurende slikklachten. Patiënten consulteerden ook de huisarts wanneer de klachten verergerden.

In **hoofdstuk 4** worden patiënten met een kwaadaardige tumor in de keel- of mondholte geanalyseerd. Bij patiënten gediagnosticeerd met een tumor in de keelholte is er een duidelijk verband tussen vertraging veroorzaakt door de patiënt en het stadium van de tumor. Patiënten met een mondholte tumor werden vaker gediagnosticeerd in een vroeg stadium van de ziekte.

'Appraisal delay', de periode van onverklaarbare symptomen tot de patiënt zich realiseert ziek te zijn, hing erg af van de verschillende klachten. De vertraging was langer onder patiënten met een keelholte tumor, wier eerste symptoom bestond uit een zere keel dan onder patiënten met slikklachten of een zwelling in de hals. Patiënten met een mondholte tumor met slikklachten, een zere keel, een zwelling in de hals, irritatie of pijnlijke afwijking vertoonden een kortere vertraging dan patiënten met een laesie, een zwelling of pijn zonder

een zichtbare afwijking. De meeste patiënten dachten dat hun klacht veroorzaakt werd door iets onschuldigs zoals een verkoudheid of een infectie. De meeste vertraging werd gezien onder patiënten, die dachten dat hun symptomen werden veroorzaakt door hun prothese of door problemen van de tanden. Ook patiënten die absoluut geen idee hadden waardoor hun klachten werden veroorzaakt, vertoonden vaker een vertraging. Patiënten stelden vaak een medisch consult uit, omdat ze dachten dat de symptomen onschuldig waren of omdat het symptoom hen niet irriteerde. Andere patiënten vertelden dat ze niet gauw naar een dokter gingen of ze vertelden dat ze hun klacht hadden genegeerd. Evenals bij patiënten met strottenhoofdtumoren was het persisterende karakter van de symptomen of het verergeren van een symptoom aanleiding om uiteindelijk een arts te bezoeken. Ook het krijgen van een nieuwe klacht, zoals een zwelling in de hals of oorpijn, was een reden om de huisarts te bezoeken.

In **hoofdstuk 5** wordt het verband tussen patiëntvertraging en de rook- en drinkgewoonten onderzocht. Deze studie toont aan dat excessief drinken en roken niet alleen samenhangt met patiëntvertraging, maar ook met tumoren in een vergevorderd stadium van de ziekte. Ook bleek dat alle zware drinkers in de onderzoeksgroep roken of hebben gerookt voordat de diagnose van een kwaadaardige tumor werd gesteld. De meeste zware drinkers roken ook nog eens meer dan 20 sigaretten per dag.

Voorts toonden we aan dat jonge patiënten (<65 jaar) significant meer drinken en roken dan oudere patiënten. Het belang van een gezondheidscampagne om de incidentie te reduceren en het verbeteren van overlevingskansen wordt aan de orde gesteld. Deze campagne zou moeten focusseren op de patiëntenpopulatie die excessief drinkt en rookt en zou informatie moeten bevatten over de symptomen van hoofd-halstumoren en de risicofactoren.

In **hoofdstuk 6** analyseren we de vertraging van verwijzing door de huisarts en tandarts. Deze studie toont aan dat tumoren gediagnosticeerd in een vergevorderd stadium van de ziekte samenhangen met een vertraagde verwijzing. Over het algemeen duurde een verwijzing vrij lang; slechts ongeveer eenderde van de patiënten werd direct verwezen na het eerste bezoek. Wanneer er geen verdenking op een tumor bestond, werden patiënten die zich presenteerden met heesheid na gemiddeld 8 weken verwezen en patiënten met een zere keel pas na gemiddeld 11 weken.

Er was significant vaker een verdenking op een tumor wanneer deze ontstond in de keel- of mondholte, dan wanneer deze tumor in het strottenhoofd ontstond. Er was ook vaker een verdenking op een tumor indien de symptomen langer bestonden dan 30 dagen. Patiënten die zich presenteerden met slikklachten of een zere keel werden het minst frequent doorgestuurd tijdens het eerste consult. Deze groep patiënten werd in eerste instantie behandeld met medicijnen of kreeg een expectatief beleid. Ook zware rokers worden minder frequent doorgestuurd naar een specialist tijdens het eerste consult in vergelijking met patiënten die nooit hebben gerookt. Waarschijnlijk veronderstelt de huisarts dat de klachten veroorzaakt worden door het roken zelf en niet door een tumor. De resultaten worden bediscussieerd en suggereren dat het vaak moeilijk is voor een huisarts en tandarts om te beslissen wanneer ze een patiënt moeten verwijzen naar een specialist. Inmiddels zijn door de Nederlandse Werkgroep Hoofd-Halstumoren in 2000 richtlijnen voor tumoren van het strottenhoofd en in 2004 richtlijnen voor tumoren van de mond- en keelholte opgesteld om uitstel van verwijzing te voorkomen.

In **hoofdstuk 7** wordt de studie gepresenteerd waarin we factoren hebben geanalyseerd die gerelateerd zijn aan professionele vertraging. Tevens wordt het diagnostische tijdspad geanalyseerd voor hoofd-halskankerpatiënten. Patiënten met grote tumoren vertonen significant minder professionele vertraging dan patiënten met kleine tumoren. Dit komt omdat het diagnosticeren van een grote tumor over het algemeen eenvoudiger is. Ook bleken stembandtumoren, welke over het algemeen klein zijn als ze ontdekt worden, een lange professionele vertraging te vertonen. Het stellen van een diagnose van patiënten die zich presenteerden met heesheidsklachten duurde vaak erg lang. Patiënten die excessief drinken en roken vertoonden significant minder vertraging. Klachten van deze risicogroep worden waarschijnlijk eerder in verband gebracht met een hoofd-halstumor. Voorts werd het hele diagnostische traject in ons ziekenhuis in kaart gebracht. Uit analyse van de gegevens bleek dat het gemiddeld 21 dagen duurt om een tumor te stadiëren volgens de TNM-classificatie en een periode van gemiddeld 47 dagen tot aan de behandeling van de tumor. Er bleek vrijwel geen vertraging op te treden tussen het verwijzen van de patiënt door de huisarts/tandarts of specialist naar ons ziekenhuis.

In de **algemene discussie** worden de resultaten van de voorgaande studies in samenhang beschouwd. Daarnaast worden de mogelijke methodologische beperkingen (recall bias)

besproken en worden er praktische aanbevelingen van deze studie gegeven voor preventie van grote tumoren. Vanwege de onbekendheid van de potentiële risicofactoren zou de populatie met een verhoogd risico beter geïnformeerd moeten worden over de risicofactoren en specifieke tumorsymptomen van hoofd-halstumoren. Tevens is van belang dat patiënten op de voordelen van vroege detectie gewezen worden. Om de diagnose van een tumor te versnellen, zouden huisartsen en tandartsen naar het rook- en drinkgedrag moeten vragen en dienen ze de risicogroep een vervolgafspraak te geven. Tevens moeten ze niet aarzelen om een patiënt naar een specialist te sturen voor verder onderzoek. De recent ontwikkelde richtlijnen voor het diagnosticeren van hoofd-halstumoren zal het verwijzen naar de tweede lijn waarschijnlijk vergemakkelijken.

Geconcludeerd kan worden dat patiëntvertraging en vertraging in het verwijzen van een patiënt met hoofd-halskanker regelmatig voorkomt. Dit wordt voornamelijk veroorzaakt door onbekendheid met de risicofactoren en specifieke tumorsymptomen van hoofd-halskanker. Het verdient daarom aanbeveling om de bevolking en in het bijzonder de risicogroep van zware drinkers en rokers, voor te lichten over de symptomen veroorzaakt door hoofd-halskanker en het verloop en de duur ervan, de risicofactoren en de voordelen van vroege detectie.

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Curriculum Vitae

Xavier Brouha werd geboren op 7 november 1972 in Lieshout. Na het behalen van het Atheneum B diploma aan het Lorentz Lyceum te Eindhoven, studeerde hij in 1991 Geneeskunde aan de Katholieke Universiteit Leuven en vanaf 1992 Geneeskunde aan de Universiteit Utrecht. Na het behalen van het doctoraal examen werd onderzoek verricht aan de afdeling Plastic and Reconstructive Surgery van het University College London. De co-schappen werden ondermeer doorlopen in Bandung, Tunbridge Wells, Tilburg en Utrecht. In 1999 werd het artsdiploma behaald. In december 1999 werd begonnen met de opleiding tot KNO-arts in het Universitair Medisch Centrum Utrecht onder leiding van prof. dr. G.J. Hordijk. De B-opleiding werd gevolgd in de Gelre Ziekenhuizen, locatie Lucas te Apeldoorn onder leiding van dr. P.P.G van Benthem. Eind november 2005 wordt de opleiding afgerond, waarna de auteur werkzaam zal zijn in het Ziekenhuis Walcheren te Vlissingen.

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