S. MAK-KREGAR — STAGING, SUBSITE AND PROGNOSIS IN OROPHARYNGEAL CARCINOMA

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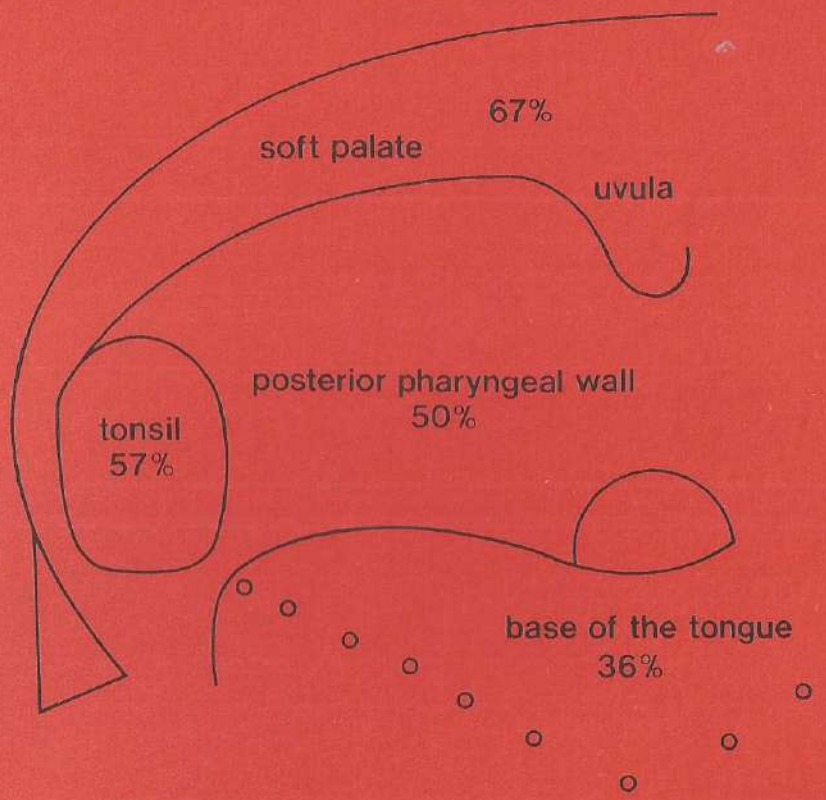

S. MAK-KREGAR

STAGING, SUBSITE AND PROGNOSIS IN OROPHARYNGEAL CARCINOMA

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To my parents

To Keka and Mirna,
my friends in Croatia who had to face the war.

Cover illustration: oropharyngeal carcinoma; the probability of 5-year tumor control per subsite.

Lay-out: E.E. Mak & S. Mak-Kregar

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CONTENTS

PREFACE

Similar to other uncommon tumors, squamous cell carcinomas of the oropharynx pose a complex problem to medical teams and to investigators: optimal management is still debated upon, resulting in ambiguous recommendations for treatment, whereas own experience in single institutions often reflects a long-standing preference for certain treatment modalities.

Specific problems in the majority of oropharyngeal carcinomas rise from the natural history, the growth being asymptomatic and leading to late diagnosis, and from the characteristics of the patients population, being old and often in poor general condition. Furthermore, when the oropharynx is seen as one oncological entity, treatment results regarding tumor control, quality of life and survival are poor.

Many analyses of possible prognostic factors in carcinomas of the oropharynx confirmed the leading role of the extent of the disease in predicting tumor control and survival. Interestingly, the term 'oropharyngeal carcinoma' is being more often replaced by specific subsites in the recent literature, despite the fact that the prognostic role of the subsite has not been demonstrated in comparative studies. Reviewing the literature on the two most frequent subsites, i.e. the tonsillar region and the base of the tongue, the treatment results and survival seem generally to be worse in base of the tongue tumors. Comparison of treatment results and prognostic factors from different studies is hampered by differences in selecting, staging and treating of patients, methodology of research, and due to incomplete reporting of these.

This study was therefore conducted in a single institutional group of patients in order to address three issues possibly related to the prognosis of carcinomas of the oropharynx:

1. The role of different treatment modalities,
2. The effect of the UICC(1987) classification system on prognosis of tumor control, and
3. The role of subsites in prognosis.

The thesis is divided into 8 chapters. The introductory part *(Chapter 1)* includes a global approach to carcinomas in all oropharyngeal subsites, and overall results that were achieved in our patients. The two most common subsites are presented with respect to treatment modalities, classification and prognostic factors *(Chapters 2, 3 and 5)*, and with particular attention to similarities and differences between the subsites *(Chapters 4 and 6)*. The two sporadic tumor subsites, i.e. soft palate and posterior wall, are presented together *(Chapter 7)*. Finally, these papers are discussed in *Chapter 8.*

CHAPTER 1

General introduction

1. Squamous cell carcinoma of the oropharynx

Anatomy and physiology of the oropharynx

The oropharynx is situated posteriorly to the oral cavity, between the nasopharynx above and the hypopharynx below, communicating widely with these 3 cavities. The boundaries are as follows:

superiorly - the projection of the soft palate in the horizontal position (while swallowing) on the lateral and posterior pharyngeal walls;
inferiorly - the basis of the epiglottis and the pharyngoepiglottic folds;
anteriorly - the base of the tongue (till papillae circumvallatae) and the isthmus faucium;
laterally - the tonsillar pillars, the tonsillar fossa and the lateral pharyngeal wall, and
posteriorly - the mucosal wall at the level of the 2nd and 3rd cervical vertebrae (40).

Functionally, the oropharynx forms the junction of respiratory and alimentary tract, and is therefore crucial in several vital functions and in the proper coordination of these. The tongue and the soft palate are actively involved in the voluntary phase of the deglutition, when the bolus is forced from the oral cavity into the pharynx. Next, contractions of the musculus palatoglossus prevent reflux of food into the oral cavity, prior to further pushing of the bolus towards the esophagus. In this -pharyngeal- phase of deglutition, the epiglottis closes off the distal parts of the respiratory tract, enabling the food passage to the esophagus and protecting the larynx from choke-like irritations (14).

Adjacent to the oropharynx is the parapharyngeal space, which contains several structures of vital interest (cranial nerves V, X, XI and XII, both carotid arteries, the jugular vein and sympathetic ganglia), and the internal pterygoid muscles with important masticatory functions (40).

Histology and histopathology

Squamous cell carcinoma is the most frequent malignancy in the oropharynx, comprising 75% of the cases. Other epithelial tumors are undifferentiated carcinomas of the nasopharyngeal type in 5% and salivary

gland tumors in another 5% of patients. The remaining malignant tumors are lymphomas (39). In general, squamous cell carcinomas of the oropharynx are known to be biologically more aggressive than those in the oral cavity (35).

Oncology (clinical pathology)

Strictly to the rules of the TNM classification of malignant tumors formulated by the International Union Against Cancer (43), the oropharynx is a site in the region pharynx, that can be further divided into 10 subsites: base of tongue, vallecula, lateral wall, tonsil, tonsillar fossa, tonsillar pillars, glossotonsillar sulci, posterior wall, inferior surface of the soft palate and uvula. However, these subsites are regularly grouped into 5 clusters, that are practically managable: tonsillar region, base of the tongue (including the vallecula), posterior wall, lateral wall and the soft palate-uvula complex.

Clinically, carcinomatous lesions can have a superficial, exophytic, submucous, ulcerative of infiltrative aspect, the first two being associated with less aggressive growth (35).

Lymphatic drainage to the cervical nodes involves first the subdigastric echelon (level II (33)) in the majority of the tumors. Further spread depends upon the localisation of the lesion: anteriorly located lesions metastasize to the midjugular nodes (level III), whereas posteriorly localized tumors prefer to drain to retropharyngeal nodes. Midline lesions can metastasize bi- and contralaterally at an earlier stage of the disease (35).

Etiology and epidemiology

Three factors are associated with the initiation of malignant alteration in the oropharynx: irritation with aromatic hydrocarbons from tobacco, consumption of alcohol (combination of these is often), and ionizing radiation (35).

Carcinomas of the oropharynx account for 0.3-0.5% of all malignancies (21, 25). Traditionally, men are predominantly affected, the male:female ratio varying in different subsites from 13:1 to 2:1 (17, 18, 23, 38). However, a trend towards relatively more women developing this disease has been signalized (7, 38). Persons in the 6th and 7th decade are affected more often than others (41).

Symptomatology and diagnostics

Most of the oropharyngeal tumors are asymptomatic in their early stages. When present, the initial complaints are mainly pain, dysphagia or

a mass in the neck. Moreover, the patient's and/or the physician's delay may postpone the diagnosis for 6 months on the average, after the first symptoms had been signalized.

Besides ENT mirror examination, the diagnostic work-up must include a meticulous examination of the complete head and neck region under general anaesthesia, even in case of small lesions. Not only the primary tumor and regional metastases should be assessed in full extent; synchronous second primaries need to be excluded as well (46). Also a general physical examination should be performed (35). Biopsy specimens of the tumorous lesion should be taken in order to prove the diagnosis histologically.

TNM classification and staging

The results of the diagnostic procedures in oncology should be compiled by allocating the TNM classification and stage of the disease to the specific tumor. The purpose of the classification is to provide standard means of communication about the patients populations. Staging, as the executive form of classification should direct the choice of therapy and predict the prognosis (2, 26). In combination, TNM classification and stage grouping reflect the anatomic extent of the disease, which is a function of the natural history and duration of the specific malignant disease (5).

Presently, two classifications and stage grouping systems are used in Europe: the UICC proposal from 1978/1982 [1] and the version from 1987 (43). The differences between them, as far as oropharyngeal subsites are concerned, are as follows:

1. relocation of the subsite 'lingual surface of the epiglottis' from the oropharynx (UICC 1982) to the larynx (UICC 1987), and
2. redefinition of the N^+ categories, as shown in Table 1.1.

	UICC(1982)	UICC(1987)
N1	movable and ipsilateral	single and ipsilateral and < 3 cm
N2	movable and contra- or bilateral	single and ipsilateral and 3 - 6 cm, or multiple and ipsilateral and < 6 cm, or bi- or contralateral, and < 6 cm
N3	fixed	> 6 cm

Table 1.1 Redefinition of the N^+ categories according to the UICC(1987) classification and staging system, in comparison to the UICC(1982) system.

[1] In 1982, an enlarged and revised edition of the classification from 1978 (42) was published. The categories in the oropharyngeal carcinoma are identical in both versions. In this thesis, the term UICC 1982 will be used.

For the completeness of the records, the data related to categorizing the neck nodes in both classification systems, i.e. size, number, lateralization and fixation of suspected lymphnodes, need still to be recorded (27).

Treatment and sequelae of treatment

Depending on the extent of the tumor on admission, the general condition of the patient, age, the patient's attitude towards treatment, histopathological grading of the tumor, facilities and skills of the medical team, one of the following treatment modalities is available: radiotherapy, surgery, combination of these, chemotherapy, and no specific treatment. Generally, the first three forms represent radical therapy with a curative intent. The last two belong to the sphere of palliation, and are applicable on approximately 20% of patients on first admission (39).

Treatment with a curative intent is thus applied in the majority of patients, provided there is still only local or locoregional disease, that they can cope with sequelae of the rather intense treatment, and that they agree to do so. Modern concepts of management of the carcinomas of the oropharynx include treatment of both the primary site and the regional nodes. In stages I and II either radiotherapy or surgery are succesfully applied. In stages III and IV, the combination of both treatment modalities is thought to be more succesful than either alone. The rationale of the combined treatment is based on the observations of failures after single modalities. Surgery tends to fail at the margins of the excision, whereas radiotherapy cannot always control the center of tumors. Their combination should provide benefit from both: removal of large tumoral masses by surgery, and eradication of the residual microscopic disease by radiotherapy (11).

Radiotherapy can cause complications such as osteonecrosis, xerostomy, fibrosis of subcutaneous tissues and orocutaneous fistula (8, 12). Complications of surgery include orocutaneous fistula, haemorrhage and shoulder drop after radical neck dissection (35).

Major problems after treatment regard nutrition and deglutition, self-care consideration, altered speech communication and disfigurement (6). Xerostomia and dental problems causing bone exposure and osteomyelitis are the most distressing intraoral sequelae of irradiation. In order to minimalize the latter problem and preserve teeth, a prophylactic dental program is required. Such a program should include sanation of the dentition and extractions prior to radiotherapy, fluorid application, regular brushings and oral lavage during the course of radiotherapy and frequent follow-up in the post-radiation period (9, 34). Some patients suffering

from xerostomia benefit from artificial saliva, deposed in a saliva-containing denture, or applied directly on the oral mucosa (37, 45, 47). Also with the application of post-irradiation prostheses made of thermoplastic denture material that is resilient at body temperature, favorable results were noted (10).

An increased rate of complications and treatment-related problems are expected in patients who undergo combined surgical and radiotherapeutical treatment (24, 29).

Tumor control and survival

When all subsites of the oropharynx are considered, 5-year overall survival rates of approximately 40% are obtained (13, 16, 19-21, 44, 48), without striking differences between treatment modalities. Incidentally, poorer (15-25% (31)) or better results (62-64% (1, 32)) are reported.

Tumor control rates, being particularly prone to variation in methods of calculation and presenting the end results, range from 50-66% (13, 19, 32). Some authors prefer reporting in terms of local control rates, that range widely from 46-80% (1, 13, 21, 30, 44, 48). There are also papers where the effect of treatment is expressed as locoregional control, showing values between 50 and 60% (15, 20). An overview of these papers, including the sample size, tumor stage and therapy is shown in Table 1.2.

Prognosis and prognostic factors

Two different groups of patients with respect to prognosis should be distinguished:

1. Patients who can be submitted to primary treatment with curative intent, having generally a better prognosis with respect to tumor control and survival, and
2. Patients with advanced local and/or regional disease, patients in a very poor general condition, and patients with evidence of distant metastasis on admission, who are receiving only palliative treatment, and have *a priori* a poor prognosis for both tumor control and survival. Some patients with a recurrent local and/or regional disease can still have a fair prognosis if submitted to treatment with curative intent; however, they are regularly presented separately.

In literature, analyses of prognostic factors are usually performed on the first group. Prior to treatment, extension of the disease is undoubtedly the leading clinical prognostic factor in oropharyngeal carcinoma (16, 36): the more limited the disease, the better the tumor control and survival.

Author	N	T/Stage	Therapy	Tcontrol	Survival
Ang e.a.(1)	72	86% T2-3	RT(acc)	74% L-2yr	64% 2yr
Geoffray e.a.(13)	90	92% T2-3	(C)+S+RT	75% L-3yr 60% T-3yr	43% 5yr
Hamberger e.a. (15)	54	all T3-4	S+RT	59% LR-2yr	?
Jesse e.a.(19)	384	70% III-IV	RT,S(comb)	49% T-5yr	39% 5yr
Johansen,J e.a. (20)	105	equally over T1-4	RT	52% LR-2yr	44% 5yr
Johansen,LV e.a. (21)	213	85% T2-3	RT	48% L-10yr	40% 10yr
Pierquin e.a. (30)	86	all 3-5 cm	RT hd vs ld	46% vs 79% L-3yr	43% 3yr
Pinto e.a.(31)	112	80% T3	RT (hf vs cf)	?	25% vs 15% 2yr
Rabuzzi e.a. (32)	58	80% III-IV	RT+S	66% T-3yr	62% 3 yr
Viani e.a.(44)	221	50% T1-2	RT	73% L-5yr	47% 5yr
Weller e.a.(48)	305	old TNM	RT	46% L-2yr	35% 5yr (act)

Tcontrol = tumor control
RT(acc) = radiotherapy (accelerated)
C = chemotherapy
S = surgery
hd, ld = high dose, low dose
hf, cf = hyperfractionation, conventional fractionation
act = actuarial
comb = combination

Table 1.2. Overview of papers dealing with oropharyngeal carcinoma, including the sample size(n), global distribution by the T category or the stage of the disease, therapy, tumor control (T-, alternatively local L-, or locoregional control LR-), and survival.

Some controversy seems to exist as to which parameter related to extension of the disease, i.e. T (13), N, stage (21) or some other feature, provides more accurate prediction of the outcome after treatment.

The possible prognostic impact of treatment will not be discussed in this chapter.

Of the posttreatment parameters, regression rate after treatment and tumor status early in the follow-up are important in prognosis of the ultimate tumor control (3, 4, 19). In predicting survival, also second primaries need to be considered, as they may occur in up to 37% of patients during the follow-up (19, 46).

2. Patients treated in the Netherlands Cancer Institute in the period 1966-1984

Materials and methods

Methodology

Selection of patients

To all patients who are admitted to the Netherlands Cancer Institute, an unique patient's record number is allocated. All data related to a particular patient are consequently filed under that number and kept in the archives. Possible new admissions of the same patient, even many years later, are added to the same record. Selected data-sets of all patients, blinded for personal identification and containing the diagnosis, global information about the treatment and a yearly update of the follow-up are also stored in the Hospital Cancer Registry. In this way, a complex network of information with a continuity over more than 70 years has been built. For illustration, over the past 15 years representing the period of computerized data-handling, over 55000 patients were entered in the database in the described way (28). From this database, (sub)groups of patients can be extracted, according to investigators' specifications.

For the purposes of this study, all patients who were admitted to the Institute between January 1st 1966 and December 31st 1984, and in whom a squamous cell carcinoma of the oropharynx was diagnosed, corresponding to the ICD-0 codes 141.0 (base of the tongue), 145.3 (inferior surface of the soft palate), 145.4 (uvula), and 146 (oropharynx, all other subsites) (49), were selected. Rationale of the choice of the study period was the introduction of megavoltage equipment in the Institute (1966), and minimal follow-up of 3 years at the time the study was designed (1984 and 1987, respectively).

Study design and creation of the database

In order to review all patients selected for the study, a standardized checklist covering a total of 195 items was designed. This checklist (protocol) and the related manual, containing the values that could be adjaced to each variable, are shown in Appendix A. Next, a database including 204 variables was programmed in Scientific Information Retrieval (SIR), version 2.2, installed on an IBM personal computer AT. The discrepancy in the number of variables used on the checklist and in the database exists due to 9 sort-identification variables that were programmed with the purpose to facilitate later queries. Taking into account the specific

characteristics of the SIR database system, and the quantity of repeated events c.q. measurements in the studied patients population, a 5-record database was initially designed, with the following records: 'Patient', 'Histology', 'Recurrence', 'Reconstructions' and 'Multiple primaries'. The first record ('Patient') contained data related to measurements or events that were not expected to be repeated during the course of the study: sociodemografic information, patient's history, diagnosis on admission, initial treatment and sequelae, and the summary of the follow-up. In the remaining records, where multiple data of the same type could be expected (recurrences, reconstructions and second primaries), a flexible entry-system with respect to potentially repeating events was created. Record 'Histology' was expected to store a second data-set after revision of all slides. By the time of revision, however, also additional assessment methods were employed. For that purpose, a new record called 'Revision of histology' was later added to the database (Appendix B).

Data entry

All data required in the protocol that were available from the patients records, were entered into the database using Forms, the interactive entry-system of SIR 2.2. Data-verification was executed through:

1. On-line checks that were programmed in SIR-Forms (all patients),
2. Double-data entry in the 'verify' mode of SIR-Forms (at random in 40 patients), and
3. Matching the print-outs with original records (all patients).

Where ambiguous interpretation of the texts in records was possible, the responsible medical specialists were consulted. In cases where the measurements of the tumor, necessary for staging, were missing, the T category was determined from the textual descriptions and drawings in the records by two independent investigators.

Statistical analysis

Simple queries and descriptive statistics were performed in SIR, using either Sequential Query Language (SIR-SQL) or Programming Query Language (SIR-PQL). For other analyses the SPSS/PC+ package was used.

Tumor-free interval (disease-free interval or tumor-free period) is defined as the period between the start of treatment and first evidence of recurrence or metastasis. The term tumor control, that corresponds to the rate of patients having no evidence of disease in a given tumor-free interval,

is used alternatively. Recurrence is a renewed manifestation of tumor in an area that was treated before. Tumor manifestation out of the previous treatment field, that is found during the follow-up, is considered a (locoregional) metastasis. Lesions, not disappearing after the initial treatment, irrespective of time, are considered as residual tumor.

Patients were followed for at least 3 years, or untill death, and were censored if they died without tumor or were lost to follow-up before the end of that period.

Survival curves were calculated by the Kaplan-Meyer method (22), beginning from the first day of treatment. Only in patients who were not treated, the admission date is equal to the starting point for calculation of the survival. In determination of the survival all deaths were included, regardless of tumor status.

Patients

In the studied period, 217 consecutive patients with squamous cell carcinoma of the oropharynx were recorded in the Hospital Cancer Registry. The distribution by subsite is shown in Table 1.3. However, due to the alterations introduced by the UICC(1987) classification and staging

Tonsil and tonsillar fossa	91
Tonsillar pillars	9
Lateral pharyngeal wall *	3
Base of the tongue	81
Soft palate and uvula	18
Posterior oropharyngeal wall	10
Total	212 **

* these 3 patients with tumors originating from the lateral pharyngeal wall, and involving grossly the tonsillar region were added to the tonsillar region in this study.
** according to the UICC(1987) version of the TNM Classification and Staging system (43), the lingual surface of the epiglottis was relocated to (supraglottic) larynx, and therefore 5 patients are excluded from the analysis of oropharyngeal carcinomas.

Table 1.3. 212 patients with carcinoma in the oropharynx; distribution by subsite.

system, the lingual surface of the epiglottis is now considered to be a subsite of the larynx, instead of the oropharynx. Therefore, 5 patients were in retrospect excluded from this study.

Median age of 212 patients, 165 males (78%) and 47 females (22%), was 65 (31-91) years.

Second primaries were recorded in 49 (23%) patients; they had a total of 68 other malignancies some time during their life. Split up by incidence of occurrence, 34 patients (16% of the total) had one other tumor, 12 (6%) had two other tumors, 2 patients had 3 tumors, whereas one patient presented with 4 simultaneous tumors in the head and neck region.

Split up by the time of occurrence (Table 1.4), 28 (41%) of all tumors were diagnosed prior to the oropharyngeal carcinoma, 33 (49%) developed metachronously to the studied disease, 6 (9%) were seen synchronously with the carcinoma in the oropharynx, whereas in one patient with prostatic carcinoma the year of diagnosis could not be traced in the records. In terms of patients having multiple tumors, 23 (47%) had only metachronous tumors, 16 (33%) had tumors only in history, 6 (12%) before and after the oropharyngeal cancer, 2 simultaneously, one simultaneously and after and

	Tumors	Patients
Metachronously	33 (49%)	23 (47%) *
Previously	28 (41%)	16 (33%) *
Synchronously	6 (9%)	2 (4%) *
Time unknown	1 (1%)	*
Total	68 (100%)	41 (84%) *

* excluding patients with the following combinations:
6 (12%) patients with previous and metachronous tumors,
1 (2%) patient with a synchronous and a metachronous tumor, and
1 (2%) patient with a metachronous and an unknown tumor (regarding year of diagnosis).

Table 1.4. Multiple primaries; occurrence in time.

one after and unknown when. Of the totally 22 patients having tumor in history, 17 had the earlier tumor diagnosed longer than 3 years before the oropharyngeal malignancy.

The most frequent localizations of the multiple primaries were the head and neck region (26, or 38%), the digestive tract (15, or 22%) and the lung (10, or 15%) (Table 1.5).

Fourty-six patients (22%) were in poor general condition on admission due to other disorders; in only one patient this was due to a synchronous malignant disease (tumor in the lung). Other disorders are shown in Table 1.6.

Head and neck region (excluding the skin)		26	(38%)
i.e.	oral cavity	20	
	larynx	4	
	hypopharynx	1	
	nose	1	
Digestive tract		15	(22%)
i.e.	esophagus	8	
	distal localizations	7	
Lung		10	(15%)
Skin (including basalioma)		5	(7%)
Breast		3	(4%)
Prostate		3	(4%)
Gynaecological tumors		2	(3%)
Thyroid gland		2	(3%)
Osteosarcoma		1	(1.5%)
Unknown		1	(1.5%)
Total		68	(99%)

Table 1.5. Multiple primaries, localization.

	Tonsil	Base of tongue	Soft palate	Posterior wall	Total
Cardiovascular	5	8	0	2	15
Respiratory	5	2	2	2	11
Haematological	0	4	0	0	4
Endocrinol/metabolic	3	4	0	0	7
Alimentary	2	3	1	0	6
Locomotory	0	1	0	0	1
Neurological	1	0	0	0	1
Total	16	22	3	4	45*

* excluding one patient with synchronous tumor in the lung.

Table 1.6. Other disorders on admission.

Tumors

According to the principles of the TNM classification and staging system, only previously untreated patients can be staged. Of 212 patients, 197 were previously untreated. Four of these patients had distant metastases on admission [1] and were excluded from further analysis. Of the remaining previously untreated 193 patients with local or locoregional disease in whom the staging was feasible, the vast majority (80%) had advanced disease, i.e. stage III-IV. The extent of the disease according to the TNM classification and staging system is presented in Table 1.7. [2]

All patients were suspected to have squamous cell carcinoma; this could be confirmed on biopsy specimens of the primary tumor in 205 patients. The remaining 6 patients in whom the diagnosis was based on clinical assessments only, and one patient in whom only the biopsy specimen of the suspected lymphnode was obtained were excluded from the subsite-specific analyses, but are presented in this chapter.

	T1	T2	T3	T4	Total
N0	14 (7)	24 (12)	25 (13)	22 (11)	85 (44)
N1	11 (6)	26 (13)	19 (10)	20 (10)	76 (39)
N2	0 (0)	1 (0)	6 (3)	4 (2)	11 (6)
N3	1 (0)	4 (2)	8 (4)	8 (4)	21 (11)
Total	26 (13)	55 (28)	58 (30)	54 (28)	193 (100)

Stage I	14 (7)
Stage II	24 (12)
Stage III	81 (42)
Stage IV	74 (38) *

* four other patients, with distant metastases on admission (stage IV) are not presented in this table.

Table 1.7. Distribution by the T and N category of 193 patients with local or locoregional tumor, who were submitted for the primary treatment. Figures in the parentheses are percentages.

[1] TN stages in these patients were: T2N3, T4N2, T4N0 and T2N0. In case of the last patient, a possibility of having had a second primary in the lungs instead of a metastasis should be considered in retrospect.

[2] In this chapter, that should give a global impression of the studied patients, only the UICC(1982) classification is applied. The effect of the UICC(1987) system is discussed in Chapters 2 (tonsillar region) and 3 (base of the tongue).

Treatment

Previously treated patients

Of 212 patients, 15 (7%) were referred for recurrent or residual disease. Of these, 4 patients were not submitted to further treatment because of advanced recurrent disease and one patient received palliative radiotherapy. The remaining 10 patients received a secondary treatment with curative intent: radiotherapy (7 patients), surgery (2 patients) and combination of these (1) (Table 1.8).

Previously untreated patients

From the remaining 197 patients, 4 were not treated with a curative intent due to evidence of distant metastases. These patients were not recorded further and are considered as 'not treated'. Another 3 patients, who could not be submitted to any radical treatment due to a poor general condition, died before any treatment was given. Five patients were treated palliatively, 4 of them receiving radiotherapy to the primary tumor and one only to the neck nodes.

One hundred eighty-five patients were finally scheduled for primary treatment with intention to cure. Of these, 10 patients were submitted to surgery, whereas 15 received also planned postoperative radiotherapy. The vast majority, 160 patients, were scheduled for external radiotherapy (Table 1.8).

		modality		
		RT	surgery+RT	surgery
None	11 *			
Palliative	6 **	(6)		
Secondary (curative int.)	10	(7)	(1)	(2)
Primary (curative intent)	185	(160)	(15)	(10)
Total	212	(173)	(16)	(12)

* i.e. 4 patients who were referred with advanced recurrent disease, 4 patients with distant metastasis, and 3 patients in poor general condition.

** i.e. one patient who was referred with recurrence, and 5 patients who were treated palliatively in the frame of the primary treatment.

Table 1.8. Distribution of patients by treatment and (modality).

Results

Tumor control

Previously treated patients

The 4 patients who were not treated and one patient who was treated palliatively died with tumor during the first year of the follow-up. Of the 10 patients who were submitted to secondary treatment with curative intent (Table 1.9), tumor recurred within one year, or was not eradicated in 7 patients, leading to death with uncontrolled disease in the first 2 years of the follow-up in 6 patients. One patient (nr. 10 in Table 1.9), who

Pt.	Sub-site	Previous therapy	Therapy NCI	Effect	Tfree	Follow-up	Vital status
1	bt	surg	RT	LRR	7	9	DOD
2	bt	RT	RT	LR	4	20	DOD
3	to	RT	RT	LR	7	12	DOD
4	sp	surg	RT	NED	11	11*	NED
5	bt	RT	RT	NED	60	60	NED
6	bt	RT	surg	LRes	0	6	DOD
7	bt	RT	surg	DPO	0	0**	DOD
8	to	urg	RT	NED	115	115	NED
9	pw	RT	RT	RR	8	16	DOD
10	to	s+RT	s+RT	RM	12	60***	DNED

NCI = The Netherlands Cancer Institute
Tfree = tumorfree interval (in months)
L.fup = length of the follow-up (in months)
bt = base of the tongue
to = tonsillar region
sp = soft pallate
pw = posterior wall
s,surg = surgery (in NCI: commando-like procedure or laryngectomy)

RT = radiotherapy
LRR = locoregional recurrence
LR = local recurrence
RR = regional recurrence
RM = regional metastasis
NED = alive, no evidence of disease
DPO = dead, postoperative
DNED = dead, no evidence of disease
DOD = dead of disease

* patient nr. 4 was lost to follow-up after 11 months.
** patient nr. 7 underwent a commando procedure with a partial resection of the base of the tongue and a supraomohyoidal neck dissection ipsilaterally. Postoperatively, he developed a choke-pneumonia and died. On autopsy tumor was found in the primary site.
*** patient nr. 10 developed a contralateral neck node metastasis after 1 year, underwent surgery and survived tumorfree for 4 following years.

Table 1.9. Patients receiving secondary treatment for recurrence after primary treatment elsewhere.

developed a contralateral metastasis in the neck was operated and lived free of tumor for another 4 years. Ultimate tumor control was also achieved in the remaining 3 patients; one of them was lost to follow-up after one year, whereas 2 other patients survived 5 years or longer.

Previously untreated patients

Of the 8 patients who were treated palliatively or not treated at all, 7 patients died during the first year, and one patient was lost to follow-up. The remaining 185 patients were scheduled for primary treatment with curative intent. Tumor control after primary treatment was achieved in 83 patients, but only 54 of these survived for 3 years or longer. Five-year tumor control was 50% (Figure 1.1). Split up by the subsite, the corresponding figures were 66%, 57%, 43% and 37% for the soft palate, tonsillar region, posterior oropharyngeal wall and base of the tongue, respectively. Differences between subsites are statistically significant ($p<0.05$).

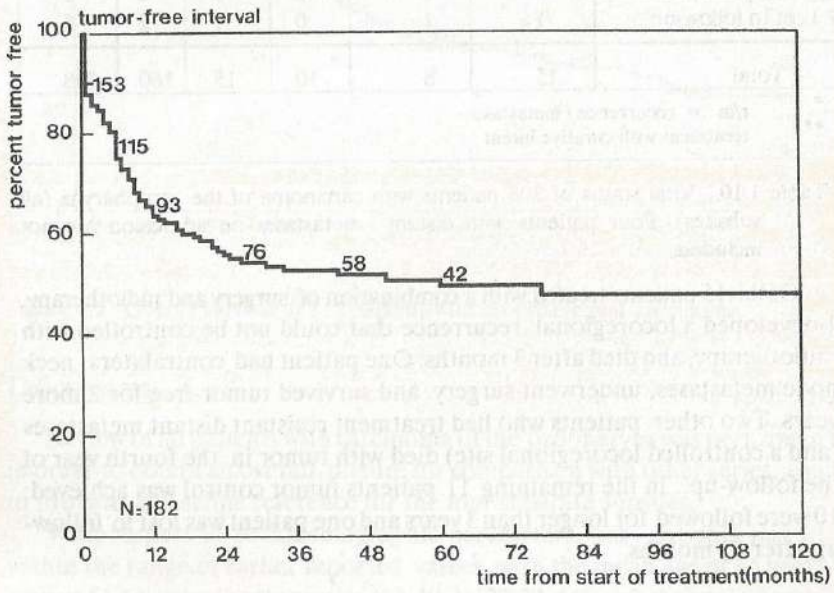

Figure 1.1. Tumor-control in 182 patients treated with curative intent. Of the 185 patients who were scheduled for treatment, tumor was not proven histologically in 3; these are excluded from the curve.

Patients treated with radiotherapy only (160) are presented *in extenso* in chapters dealing with separate subsites. Of the 10 patients treated with surgery, one patient developed a local recurrence after 6 months, received chemotherapy that appeared to be without effect, underwent subsequently a commando resection and remained tumorfree for 6 years thereafter. Of the remaining patients, 4 died with no evidence of disease during the first 3 years of the follow-up, whereas 5 survived tumor-free for 6 years or longer (Table 1.10).

	Secondary treatment**	Palliation	Primary treatment**			Total
			surg	s+RT	RT	
Alive, NED	2	0	5	10	54	1
Dead, NED	0	0	4	0	22	26
Alive, NED after r/m*	0	0	1	1	2	4
Dead, NED after r/m	1	0	0	0	6	7
Alive, with tumor	0	0	0	0	9	9
Dead, with tumor	11	7	0	3	64	85
Dead, postoperatively	0	0	0	0	1	1
Lost to follow-up	1	1	0	1	2	5
Total	15	8	10	15	160	208

* r/m = recurrence / metastasis
** treatment with curative intent

Table 1.10. Vital status of 208 patients with carcinoma of the oropharynx (all subsites). Four patients with distant metastases on admission are not included.

Of the 15 patients treated with a combination of surgery and radiotherapy, 1 developed a locoregional recurrence that could not be controlled with radiotherapy, and died after 3 months. One patient had contralateral neck node metastases, underwent surgery and survived tumor-free for 2 more years. Two other patients who had treatment resistant distant metastases (and a controlled locoregional site) died with tumor in the fourth year of the follow-up. In the remaining 11 patients tumor control was achieved; 10 were followed for longer than 3 years and one patient was lost to follow-up after 11 months.

Survival

The vital status of the 212 patients is shown in Table 1.10. Five-year overal survival was 32% (Figure 1.2). Split up by the subsite, the following 5-year rates were calculated: 40% in the tonsillar region, 36% in the soft palate, 33% in the posterior wall and 22% in base of the tongue carcinomas. These curves do not differ significantly.

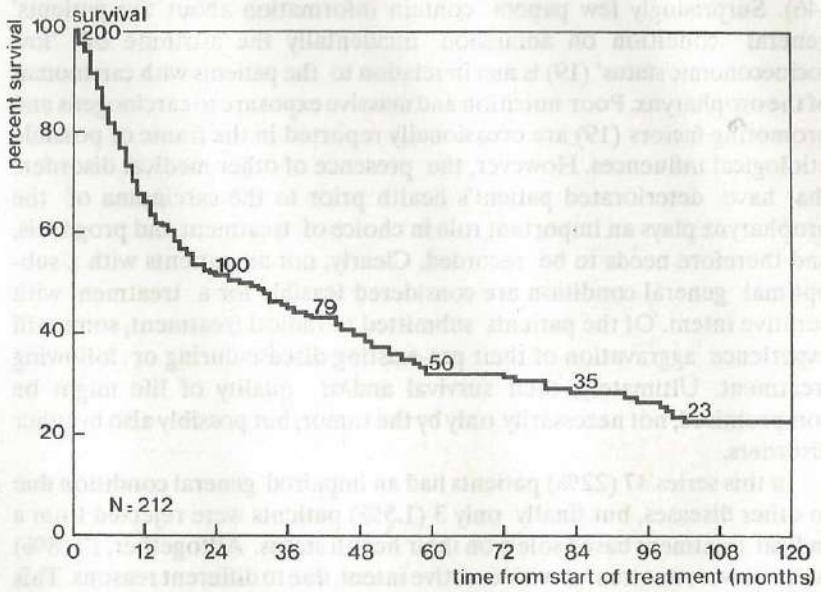

Figure 1.2. Overall survival in 212 patients with oropharyngeal carcinoma.

Discussion

Review of all patients with carcinoma of the oropharynx was performed in order to obtain an overall picture for comparison with other series, and to provide a baseline reference for the four separate subsites.

With respect to sociodemographic parameters, our patients just fit within the range of earlier reported values, with the mean age of 65 years (versus 51-64 years in other series (13, 19-21, 30-32, 44)) and the male:female ratio of 3.5:1 (2:1 till 10:1 in other series (19-21, 30-32)). It is interesting to notice that two Danish series (20, 21), that are similar to our patients in the population size, geographically, and with respect to studied period, also

reveal a trend towards a higher age (62 and 64 years) and relatively more females (2:1).

Noteworthy, our patients seem to have had more often T4 (28%) tumors than in other series (1, 13, 20, 21, 31, 44), where groups T2-T3 were particularly pronounced. The stage grouping, however, shows regularly advanced tumors (stage III-IV) in at least 70% of patients in practically all series.

The rate of multiple primaries is similar to the reports in the literature (46). Surprisingly few papers contain information about the patients' general condition on admission. Incidentally the attribute of 'low socioeconomic status' (19) is met in relation to the patients with carcinomas of the oropharynx. Poor nutrition and massive exposure to carcinogens and promoting factors (19) are occasionally reported in the frame of possible etiological influences. However, the presence of other medical disorders that have deteriorated patient's health prior to the carcinoma of the oropharynx plays an important role in choice of treatment and prognosis, and therefore needs to be recorded. Clearly, not all patients with a sub-optimal general condition are considered feasible for a treatment with curative intent. Of the patients submitted to radical treatment, some will experience aggravation of their pre-existing disease during or following treatment. Ultimately, their survival and/or quality of life might be compromised, not necessarily only by the tumor, but possibly also by other disorders.

In this series 47 (22%) patients had an impaired general condition due to other diseases, but finally only 3 (1.5%) patients were rejected from a radical treatment based solely on their health status. Alltogether, 17 (8%) patients were not treated with curative intent, due to different reasons. This figure might seem low in comparison to the 20% of patients who are '...not treatable with any prospect of success...' as published by Stell (39). However, '...the question of untreatability of carcinoma is inevitably coloured by personal philosophy...'(39); in surgeon's view tighter criteria need to be applied, surely leading to a higher rate of untreatable patients than in our patients. For the sake of completeness, also the not-curatively-treated patients are presented in this chapter, but they are not included in the later analyses of prognostic factors.

Recognizing that the allocation of treatment to patients treated with curative intent was sometimes arbitrary, or at least not well documented, we have chosen not to analyze the treatment results with respect to different modalities. It is well known from the literature and daily practice (4), that patients who undergo surgery must be in a better general condition, and therefore do not match the non-selected group of patients receiving

radiotherapy. Having seen that an unexpectedly high rate of patients received only radiotherapy, we readily decided to analyze those patients separately.

The results in our patients with respect to tumor control (50% at 5 years) approach the figures published by other authors (Table 1.2.), as far as any comparisons are feasible. A relatively high rate of patients with locally advanced tumors in our series can perhaps give some explanation for tumor control rates being on the low side. Noteworthy, when split up by the subsite the tumor control rates differ significantly (37%, 43%, 57% and 66%, $p<0.05$).

Overall survival in our patients is on the low side of the published results as well; a somewhat higher mean age might be partially responsible for this outcome. Survival rates in separate subsites range from 22%-40%, the differences not being statistically significant. The difference between the tumor control and survival is particularly large in case of soft palate tumors. This reflects the sensitivity of small groups to events in individual patients on the one side, and the risk of developing other diseases after being cured for the index tumor on the other side, the latter being consistent to pessimistic predictions of Jesse already made in 1976 (19).

In the following chapters the subsites will be assessed through the patient and tumor characteristics, staging, treatment and prognosis, calculated on those patients who were submitted to a treatment with curative intent.

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CHAPTER 2

Carcinoma of the tonsillar region: comparison of two staging systems and analysis of prognostic factors

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Abstract

Between 1966 and 1985, 92 patients with local or locoregional tonsillar carcinoma were treated in the Netherlands Cancer Institute. Treatment consisted of radiotherapy in 79 patients, combination of surgery and postoperative radiotherapy in 10 patients, and surgery alone in 3 patients.

The 5-year crude survival is 43% and the disease-free interval 57%.

Patients were classified according to the UICC 1982 and the UICC 1987/AJCC 1988 criteria. The changes in the lymph node classification proposed in UICC 1987 lead to inversion in sizes of N1 and N2 groups, and of stages III and IV.

The most important prognostic factor for disease-free interval is T stage (p=0.03). Prognosis is significantly worse in stage IV (UICC 1982) compared to stages I to III (41% vs. 65% respectively, p=0.03). Crude survival is lower in males (p=0.031) and in patients who smoked (p=0.019).

Keywords: *tonsillar carcinoma, classification, prognostic factors, treatment results*

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Introduction

The purpose of tumor classification is to provide standard means of communication about patient populations regarding tumor extension and treatment results. Staging, as a condensed form of classification, should indicate the choice of therapy and predict prognosis (2, 13).

Currently, two tumor classifications are widely used: the TNM system of UICC from 1982 (20)[1] and UICC 1987/AJCC 1988 (1, 21) [2]. The latter system resulted from cooperation between both committees in providing a standard classification and stage grouping of high prognostic value (12, 21).

In both systems, T categories for tonsillar carcinoma are identical. The differences are in criteria for the N category. In the 1982 system, the criteria for lymph node involvement are the side and fixation of affected nodes. The size, number, and side of affected nodes are the basis for the N classification in the 1987 version. A staging system based on these parameters has been used by the AJCC since 1977, and appeared to be significantly more discriminative in comparison to the UICC 1982 system (12).

Several prognostic factors have been reported for tonsillar carcinoma in the literature. Extension of the disease expressed by the T and the N category (6, 7, 14, 16, 17, 22), T category alone (4, 5), N category alone (8, 11, 15) or stage grouping (3, 9) were predictive for disease-free survival. Infiltration in the tongue and the base of the tongue is predictive for treatment failures in irradiated patients (3, 4, 7, 10, 16, 23). Considerable treatment delay (8), age above 60 years (3), male sex (6, 16) and performance status of 2 or more (16, 18) were prognostic indicators for low survival rates.

A retrospective study of all patients with tonsillar carcinoma treated in The Netherlands Cancer Institute between 1966 and 1985 was performed. The effects of the new staging systems on the distribution of patients and on the prognosis were evaluated. Other possible prognostic factors were analyzed.

Materials and methods

In this paper 103 patients with tonsillar carcinoma are described. They are derived from a population of 217 patients with carcinoma of the oropharynx. All records were reclassified according to the UICC 1982 and UICC 1987/AJCC 1988 classification, shown in Table 2.1.

[1] In 1982, an enlarged and revised edition of the classification from 1978 (19) was published. All categories in tonsillar carcinoma are identical in both versions.

[2] In this paper, term UICC 1987 will be used.

	UICC 1982	UICC 1987 / AJCC 1988
T1	< 2 cm	
T2	2 - 4 cm	
T3	> 4 cm	
T4	extension to bone, muscle, skin, neck, etc.	
N0	none	
N1	movable, ipsilateral	single, ipsilateral, < 3 cm
N2	movable, contra-, or bilateral	a) single, ipsilateral, 3-6 cm b) multiple, ipsilateral, < 6cm c) bi- or contralateral, < 6cm
N3	fixed	> 6 cm

	All classifications		
Stage I	T 1	N 0	M 0
Stage II	T 2	N 0	M 0
Stage III	T 3	N 0	M 0
	T 1-3	N 1	M 0
Stage IV	T 4	N 0-1	M 0
	Any T	N 2-3	M 0
	Any T	Any N	M 1

Table 2.1. TNM classifications and stage grouping according to the system of the UICC 1982 and UICC 1987/AJCC 1988.

In cases where the size of the primary tumor was missing, the T category was determined by two independent investigators from descriptions and drawings in the records. The choice between T2 and T3 category sometimes had to be arbitrary for tumors approximately 4 cm in size, that did not invade adjacent tissues as defined in T4.

The sizes of the affected neck nodes were missing in 7 patients, and the determination of the N category (UICC 1987) could not be performed because of less accurate descriptions and fewer anatomical references in the neck. This lead to exclusion of 7 patients from the UICC 1987 system.

Survival curves were calculated by the Kaplan-Meier method. Tumor-free interval is defined as the time between start of treatment and recurrence (or metastasis). Patients were followed-up for at least 3 years or until death. Only one patient was lost to follow-up. Patients who died without recurrence were censored at the time of death. Comparisons were made using the score test. Possible prognostic factors were analyzed using the Cox's proportional hazard model.

Patients

There were 103 patients with carcinoma of the tonsillar region: 91 with tumor in the tonsillar fossa or the tonsil, 9 in the tonsillar pillars and 3 had tumor originating from the lateral pharyngeal wall, grossly involving the tonsillar region.

Eleven patients were excluded from the analysis for the following reasons: uncertain histopathology (2) synchronous second primary in the lungs (1), secondary treatment (5), lung metastases on admission (1), and death before initiation of curative treatment (2). The last two patients were included in the calculation of the crude survival.

Ninety-two patients remained for the analysis of the disease-free intervals: 71 men and 21 women with ages ranging between 34 and 88 years. Median age was 64 years. Seventy-one percent of the patients had a positive smoking history, and 61% consumed alcohol regularly. Patient delay was less than 4 months in 61% of the patients. The rate of multiple malignancies was 23%, which was equally distributed over the period before and after the tonsillar carcinoma. One patient had a synchronous second primary tumor.

Treatment

Ninety patients were treated with curative intention, while in 2 patients the intention was unclear in retrospect. Of these 90 patients, 77 (84%) were treated with radiotherapy alone. The tumor dose was equivalent to 60 to 70 Gy in 6 to 7 weeks. Three patients were managed by surgery alone and, in 10 other patients, surgery was followed by planned postoperative irradiation.

Regional neck nodes were treated simultaneously with the primary tumor in 80 patients, whereas treatment was limited to the primary tumor site in 10 patients. Of the 56 patients treated for clinically positive neck nodes, 42 received radiotherapy, 2 underwent surgery and in 12 patients a combination of surgery and postoperative radiotherapy was given. Of the 24 patients receiving elective treatment, 23 were irradiated and 1 was treated surgically.

Prognostic factors

The following tumor and host characteristics were tested for prediction of the tumor-free interval: extension of the primary tumor, involvement of adjacent sites, involvement of neck nodes, stage of disease, smoking habits, and sex. Patient's delay, smoking habits, and sex were tested for prognostic value in crude survival.

Results

Classification of tumors

Distribution of the primary tumor according to the T classification was as follows: T1 (15%), T2 (32%), T3 (26%) and T4 (27%). The incidence of tumor invasion to adjacent sites is schematically presented in Figure 2.1. The faucial arch complex and the base of the tongue were the sites most frequently involved.

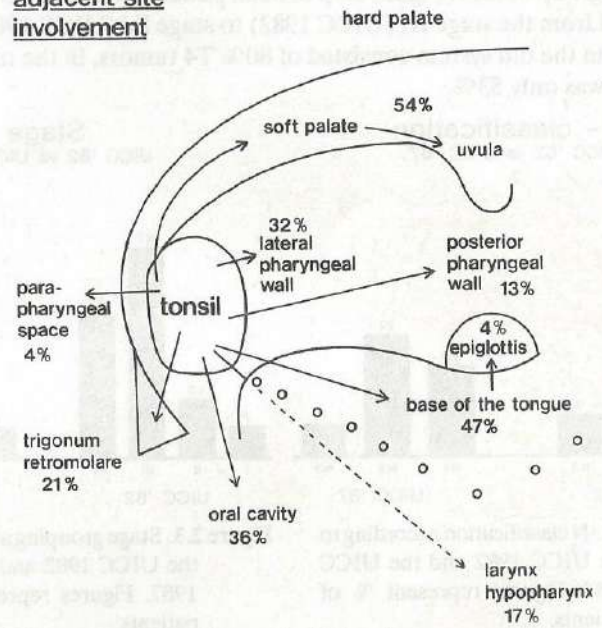

Figure 2.1. Frequency of the adjacent site(s) involvement.

Clinically positive neck nodes were present in 56 patients (61%) before the onset of the treatment. In this group, the subdigastric and high jugular nodes were involved in three fourths of the patients. Single node involvement was present in 59%, whereas the remainder of the patients had multiple nodes. The vast majority of the positive nodes were localized ipsilaterally. Only 2 patients had bilateral nodes, both in combination with a mobile convoluted mass on the ipsilateral side of the neck. Fixed nodes were present in 9% of the patients.

Distribution of the N category according to the UICC classifications of 1982 and 1987 is shown in Figure 2.2. Seven patients (7%), all N1 in UICC 1982, could not be reclassified according to the 1987 criteria because the diameter of the involved node(s) was not recorded.

Redistribution of patients occurs mainly in the N1 group of UICC 1982. From the 39 N1 patients who could be regrouped, 19 patients had to be classified as N2, 2 became N3, and 18 remained N1 in the new classification.

Due to the altered distribution of the patients with affected neck nodes in the UICC 1987 classification, an inversion in the size of stage III and stage IV-group occurs (Figure 2.3). Sixteen patients, all T1 to T3 N+, were relocated from the stage III (UICC 1982) to stage IV (UICC 1987). While stage IV in the old system consisted of 80% T4 tumors, in the new system the rate was only 53%.

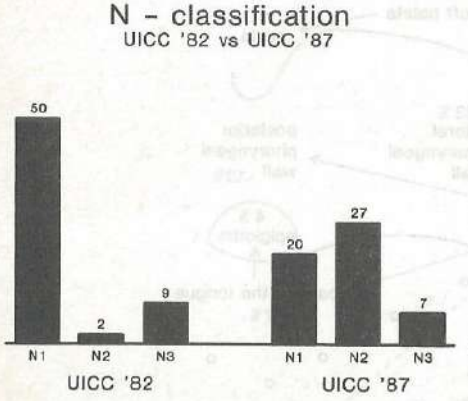

Figure 2.2. N classification according to the UICC 1982 and the UICC 1987. Figures represent % of patients.
* classification in retrospect not possible in 7% of patients.

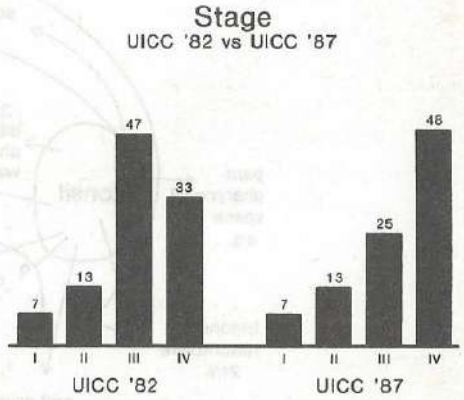

Figure 2.3. Stage grouping according to the UICC 1982 and the UICC 1987. Figures represent % of patients.
* classification in retrospect not possible in 7% of patients.

Tumor control

Following initial treatment, tumor control was achieved in 56 patients. Two patients died with tumor during radiotherapy, 14 patients had residual tumor, 10 patients developed local and/or regional recurrences and distant metastases were the first site of failure in 10 patients.

Treatment results by stage (UICC 1982) and modality are presented in Table 2.2. The group of surgically treated patients was too small for comparison with the patients managed by radiotherapy alone.

Treatment	Stage I	Stage II	Stage III	Stage IV	Total
Radiotherapy	5 (3)	11 (8)	32 (22)	31 (13)	79 (46)
Surgery (+ RT)	1 (1)	1 (1)	11 (8)	- -	13 (10)
Total	6 (4)	12 (9)	43 (30)	31 (13)	92 (56)

Table 2.2. Number of patients and (patients with no evidence of disease) by stage and modality.

Survival

Crude survival at 5 years was 43%. The disease-free interval for this period was 57%. The vital status is summarized in Table 2.3.

Alive, tumor-free; no recurrence	20
Dead; tumor-free	35
Alive, tumor-free; after recurrence	1
Dead, tumor-free; after recurrence	4
Dead; with cancer	31
Unknown; lost to follow-up	1
Total	92

Table 2.3. Vital status.

Prognostic factors

In the multivariate analysis the T classification is the single most important prognostic factor. The disease-free interval according to T classification is shown in Figure 2.4.

No relation was found between the prognosis and the extension of the primary tumor to any of the adjacent sites shown in Figure 2.1. Patients with palpable neck nodes had a lower disease-free interval than patients without nodal involvement (54% vs. 61%), but this difference was not statistically significant. There was no association between the different N categories and the disease-free interval in any of the classifications tested, nor was the difference in disease-free interval between N0-N1 group and N2-N3 group statistically significant.

The 5-year disease-free interval staged according to the UICC 1982 classification was 53% for stage I, 67% for stages II and III, and 41% for

stage IV. In this classification, stage IV has a significantly worse prognosis then stages I, II and III together (65%). This is mainly due to residual tumor, rather than to recurrences during follow-up, as shown in Figure 2.5.

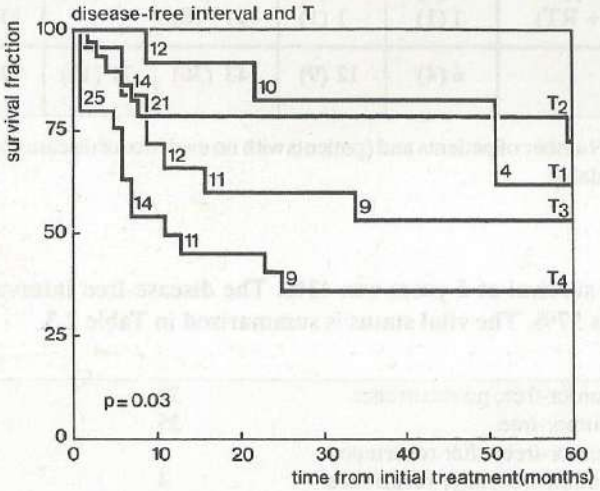

Figure 2.4. Disease-free interval according to the T classification.

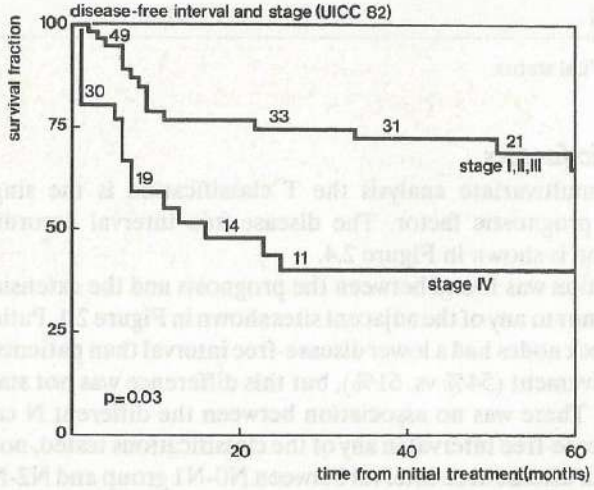

Figure 2.5. Disease-free interval according to the stage grouping UICC 1982 (I-III vs. IV).

No notable difference in disease-free interval by stage (I-III vs. IV) was found using the classification of 1987. However, the same holds true if the 7 patients with affected nodes of unknown size, excluded from the 1987 classification, are subtracted from the 1982 system as well. The difference in disease-free intervals in the reduced latter group was no longer significant.

Women had a better prognosis than men. The crude survival was 56% and 33% ($p = 0.031$) respectively. There was no difference in stage between men and women at first presentation. Differences exist, however, in pretreatment smoking habits. The majority of men (83%) were smoking, in contrast to only about one fourth of the women (29%). The 5-year crude survival in non-smokers was 68%, compared with 32% in patients who had a positive smoking history ($p=0.019$). However, using the Cox's proportional hazard model, it was not possible to determine which was the dominant prognostic factor: smoking habits or sex. In addition, these factors had no prognostic value for the disease-free interval.

Finally, no relation was found between age and survival, or between delay in treatment and survival.

Discussion

The influence of the new classification (UICC 1987) on the redistribution of patients over the N categories in this series was obvious. Nevertheless, the study of its prognostic value presented two problems in our material: exclusion of 7 patients in this classification, and the subordinate role of nodal involvement to the T category in the prognosis.

The study of the prognostic value of stage grouping, which is a combination of the T and the N category, meets the same problems. Stage IV reflects a significantly worse prognosis than the other stages combined in UICC 1982, but not in UICC 1987. Possibly this was due to restructuring of stages III and IV in the new classification, where stage IV consisted of more patients with limited local disease (T1 to T3) and neck nodes (N2-N3). Compared to the old classification, stage IV (UICC 1987) was enlarged, and a substantial group of patients had a better prognosis due to a lower T stage. This did not contribute to separation into prognostically more distinct groups. On the other hand, the reduced number of patients in the system from 1987 makes the results less significant.

Better survival in women has been reported previously (6, 16). In one study, better survival could be explained by the lower stage at first presentation in women (16). In our patient population, only differences in smoking habits could partially explain the better survival in women.

In conclusion, comparison of two staging systems with regard to their prognostic value was, in this small series, only possible if the discriminating category, in this case the N stage, had a clear prognostic value. Due to the dominant influence of the T stage, identical in both classifications, it was difficult to draw conclusions with regard to the changes in the UICC 1987 proposal. The new staging system did not seem to improve separation of tonsillar carcinoma into prognostically distinct groups in this series. Obviously, this new classification will hamper comparison of treatment results in tonsillar cancer with studies using the old staging system.

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CHAPTER 3

Staging and prognostic factors in carcinoma of the base of the tongue

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Abstract

During the period 1966-1985, 66 patients were submitted for curative treatment of a carcinoma of the base of the tongue in the Netherlands Cancer Institute. Treatment consisted of radiotherapy (59 patients), surgery and postoperative radiotherapy (4 patients) and surgery alone (3 patients).

Patients were staged according to the UICC(1982) and UICC(1987)/ AJCC(1988) criteria. Regrouping by the latter system caused enlargement of the N2-group and of stage IV.

The crude 5-year survival was 22%, the 5-year tumor control was 36% and the locoregional control was 47%. The most important prognostic factors for the tumor-free interval are the T category ($p=0.01$) and stage grouping (UICC 1982) ($p=0.022$). The same factors predict the locoregional control ($p=0.005$ and 0.02 respectively). Crude survival is lower in smokers, and in patients in poor general condition ($p=0.04$ and 0.007 respectively).

Keywords: *carcinoma of the base of the tongue, staging, prognostic factors, treatment results*

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Introduction

At the time of diagnosis, many patients with squamous cell carcinoma of the base of the tongue are elderly, in poor general condition and with advanced disease (18). Treatment of these patients should provide adequate tumor control and acceptable quality of life. Radical surgery consists of a total or partial glossectomy and occassionally a total or a supraglottic laryngectomy with a neck dissection. However this method is indicated in only a small number of patients who are in reasonable general condition, have resectable tumors and can be expected to cope with the morbidity after surgery. Combined treatment (surgery and radiotherapy) can control large resectable tumors (2, 12, 16, 20), but produces even more severe psychological and social problems in adaptation to the effects of treatment (13). Radiotherapy often remains the only possible approach (1, 7). High doses (75 Gy in 7.5 weeks or more) should be delivered to the deeply infiltrating, probably anoxic lesions in order to obtain high control rates (19). In general, the prognosis with respect to tumor control and survival is poor (1,7, 9, 16).

Most authors agree upon the prognostic role of the extent of the primary tumor (2, 10, 11, 15, 19). However, the T-classification is often found to be inadequate in distinguishing between T2 and T3 tumors (11, 19); a result of clinical understaging of diffusely infiltrative cancers in this region (15).

The prognostic role of nodal invasion depends on the treatment. In surgical series, pathological staging of cervical lymph nodes correlates with the outcome of the disease (2, 9, 15, 20), but in patients treated with irradiation the prognostic role of neck node metastases is subordinate to the extent of the primary tumor (3, 4, 10, 19). This discrepancy is partially caused by different assessment of regional lymph nodes: palpation before radiotherapy, possibly incorrect in as many as 40% (8), versus analysis of specimen after surgery, which provides reliable information about nodal invasion.

Stage of the disease is also a prognostic factor, i.e. increasing stage predicts decreasing cure rates (1, 15, 23). Nevertheless, inversion of cure rates between stages II and III has been observed (1, 10).

Recent changes in the TNM classification system for carcinoma of the base of the tongue influence only the staging of lymph node metastasis (21, 22). An effect is expected in the regrouping of patients with palpable cervical nodes, i.e. categories N1, N2 and N3 and in stages III and IV of the disease (6, 14). The impact on prognosis has yet to be explored.

Black and Gluckman conducted a study of 898 patients in order to evaluate UICC (1982) and AJCC systems with regard to survival and found no difference between the two systems (6). In a large series of patients with

cancer of oropharynx and pharyngolarynx, Bernier and Bataini found the UICC (1987) system slightly superior to the UICC (1982) system in predicting nodal control, distant spread and disease-free survival (4, 5).

In this paper, the results of a retrospective study of patients with carcinoma of the base of the tongue treated in the Netherlands Cancer Institute are presented. UICC (1982) and UICC (1987) classification systems are evaluated, and factors possibly influencing tumor control and survival rates are analyzed.

Materials and methods

Patients

In the period 1966-1984, 81 patients with squamous cell carcinoma of the base of the tongue were admitted to our hospital. Thirteen patients are excluded from the analysis because of previous treatment (6), distant metastases on admission (3), unclear or missing histopathology (2) and lack of follow-up information (2).

The age of the patients ranged from 31 to 91 years, with a median of 67 years. Fifty-three patients were men and 15 were women. Forty-nine patients (72%) were known to be smokers; 44 of these were men. Thirty-eight patients (56%) drank alcohol regularly, and 36 patients (54%) both drank and smoked. Four patients (6%) had a history of irradiation to the head and neck for other reasons. Seventeen patients (25%) had other malignancies: previous in 4 patients, concurrent in 2, and subsequent in 11 patients. Nineteen patients (28%) (16 men and 3 women), had other severe chronic disorders on admission: cardiovascular (6), haematologic (4), endocrine (4), gastrointestinal (3), respiratory (1) and musculoskeletal (1).

The most common presenting symptoms were pain (38%), dysphagia (22%) and a mass in the neck (15%). Delay by the patient was less than 4 months in 35 patients (51%).

Classification

The records were restaged according to the UICC 1982[1] and UICC 1987/AJCC 1988[2] systems. The determination of the T category, which is identical in both systems, was possible in all patients. Descriptions and drawings in the records provided references for classification where the exact size of the primary tumor was missing. In cases of doubt between T2

[1] In 1982, an updated version of the classification from 1978 was published by the UICC. All categories in carcinoma of the base of the tongue are identical in both versions. In this paper, the term UICC 1982 will be used

[2] In 1988 UICC and AJCC published a standard classification system. In this paper, the term UICC 1987 will be used.

and T3, the higher category was chosen. The N category and stage grouping were obtained in all patients using the UICC 1982 system. In UICC 1987, 9 patients (13%) had to be excluded because of the unknown size of the affected node(s).

Treatment

Megavoltage irradiation was the treatment of choice, delivered from opposed lateral fields either with Co60 equipment (1966-1973) or 8 MeV linear accelerator (1972-1984). From 1976-1978, a few patients were managed with fast neutron beams.

Patients in a good condition were occasionally submitted to surgery, provided that a radical resection of the tumor would compromise neither the vascularization of the residual tongue, nor the closure of the defect. Postoperative radiotherapy was given for positive margins and/or extensive nodal metastasis (more than 2 positive nodes and/or extracapsular spread).

Prognostic factors

In order to identify the tumor and host characteristics of prognostic value, T and N category and stage grouping according to both classifications, delay, sex, general condition, smoking habits and treatment method were tested.

Minimal follow-up was 3 years, or until death. Patients who died without tumor are censored at the time of death. Tumor-free interval is defined as the time between start of treatment and first evidence of recurrence or metastasis. Recurrence is a new local and/or regional manifestation of tumor in a previously treated area. Tumor found in an area that was not treated before is considered metastatic. Residual tumor is defined as a lesion not eradicated by the initial treatment. In this paper, only the first failures after the initial treatment are reported.

Survival was calculated by the Kaplan-Meyer method. Comparisons are made using the score test. Possible prognostic factors were tested by Cox's proportional hazard model on 66 patients who were treated with curative intent.

Results

Classification

The distribution of patients by the T and the N category is presented in Table 3.1. The distribution of 36 patients with clinically positive neck nodes according to the UICC systems from 1982 and 1987 is shown in Figure 3.1. Stage grouping according to both systems is depicted in Figure 3.2.

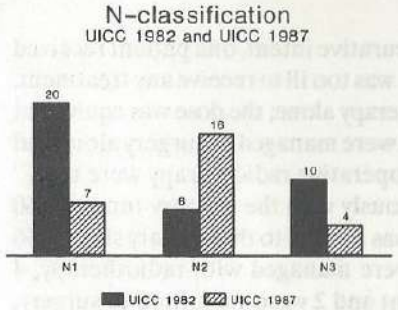

Figure 3.1. N classification according to the UICC 1982 and the UICC 1987*.
* classification in retrospect was not possible in 9 patients.

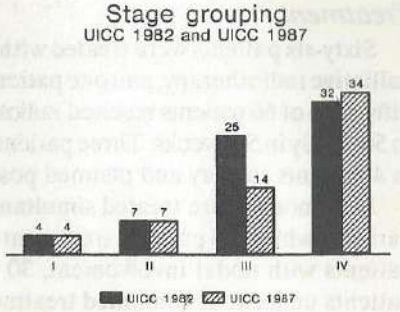

Figure 3.2. Stage grouping according to the UICC 1982 and the UICC 1987*.
* classification in retrospect was not possible in 9 patients.

	T1	T2	T3	T4	Total
N0	4 (4) I	7 (7) II	11 (11)	10 (10	32 (32)
N1	3 (0)	7 (2)	4 (1) III	6 (4)	20 (7)
N2	0 (0)	0 (2)	4 (10)	2 (4)	6 (16)
N3	0 (1)	2 (1)	4 (0)	4 (2) IV	10 (4)
Total	7 (5)	16(12)	23 (22)	22 (20)	68 (59) *

Stage I	4 (4)	patients.
Stage II	7 (7)	patients.
Stage III	25 (14)	patients.
Stage IV	32 (34)	patients.

* classification in retrospect not possible in 9 patients.

Table 3.1. Distribution of patients by the T and the N category and the stage of the disease according to UICC 1982 and (UICC 1987) staging system.

Treatment

Sixty-six patients were treated with curative intent, one patient received palliative radiotherapy, and one patient was too ill to receive any treatment. Fifty-nine of 66 patients received radiotherapy alone; the dose was equivalent to 50-70 Gy in 5-7 weeks. Three patients were managed by surgery alone and in 4 patients surgery and planned postoperative radiotherapy were used.

Neck nodes were treated simultaneously with the primary tumor in 60 patients, while in 6 patients treatment was limited to the primary site. Of 36 patients with nodal involvement, 30 were managed with radiotherapy, 4 patients underwent combined treatment and 2 were submitted to surgery. Of 24 patients who received elective treatment of the neck, 20 were treated with radiotherapy and 4 with surgery.

Treatment results

Table 3.2 shows the results of treatment. The distribution of patients by the stage of the disease and treatment modality with related results of initial treatment are shown in Table 3.3.

Follow-up

Of the 23 patients with local and/or regional failure, 11 were submitted to salvage treatment. Ultimate tumor control was achieved in 4 of these patients; they survived for 6 months, 2, 4 and 10 years after salvage. The vast majority (80%) of patients with uncontrolled local and/or regional disease died within 2 years. Distant metastases occurred in 7 patients, in whom

Locoregional control	36	(54%)			
Died during radiotherapy	2	(3%)			
Residual tumour	11	(17%)			
			6	(9%)	local
			5	(8%)	local+regional
Recurrence *	12	(18%)			
			9	(14%)	local
			3	(4%)	regional
Lymphnode metastasis *	5	(8%)			
Total	66	(100%)			

* only the local and/or regional failures as first sign of tumor recurrence after the initial treatment are reported.

Table 3.2. Treatment results.

Treatment	Stage I	Stage II	Stage III	Stage IV	Total
Radiotherapy	3 (2)	7 (5)	21(13)	28(11)	59(31)
Surgery (+RT)	1 (1)	-	4 (3)	2 (1)	7 (5)
Total	4 (3)	7 (5)	25(16)	30(12)	66(36)

Table 3.3. Number of patients treated with curative intent and (patients with locoregional control after initial treatment) by stage (UICC 1982) and modality.

locoregional disease was controlled by radiotherapy. They all died of tumor within 4 years. Ultimate tumor control was achieved in 33 patients (49%). The outcome is summarized in Table 3.4.

Alive, NED after the initial treatment	5	(7%)
Alive, NED after recurrence / metastasis	1	(2%)
Dead, with tumour	35	(52%)
Dead, NED after the initial treatment	24	(35%)
Dead, NED after recurrence / metastasis	3	(4%)
Total	68	(100%)

Table 3.4. Vital status.

Prognosis and survival

Tumor control

In 66 patients treated with curative intent, the 5-year tumor control rate was 36% (Figure 3.3). Distribution by the Tcategories provides prognostically separate groups ($p=0.01$) (Figure 3.4).

The five-year tumor control rate in patients without lymph node involvement is 41%. In N1 (UICC 1982) this is 44%, in N2 0 and in N3 28% ($p=0.15$). Five-year tumor control rates according to the stage of the disease (UICC 1982) are shown in Figure 3.5. The difference is significant at $p<0.025$. The results according to UICC (1987) system are biased by the reduced number of available patients.

In 59 patients treated with radiotherapy, 5-year tumor control rate of 32% was achieved; in 7 patients submitted to surgery, this was 71% . The groups are not comparable because of the small number of patients treated by surgery and because of selection.

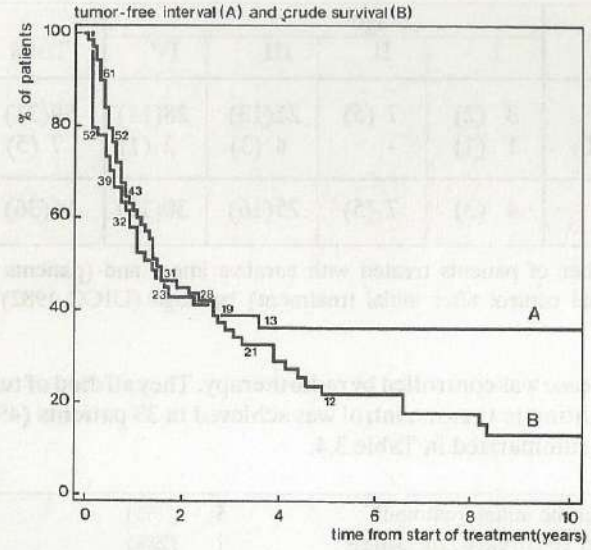

Figure 3.3. Tumor-free interval (A) and crude survival (B).

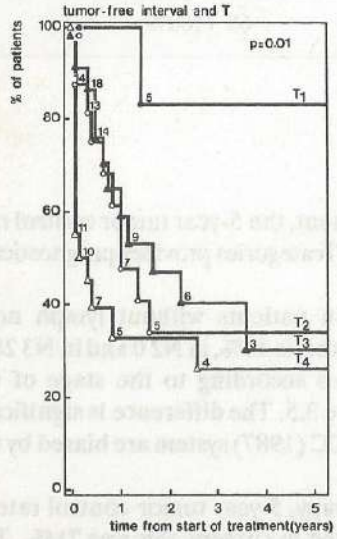

Figure 3.4. Tumor-free interval by the T categories.

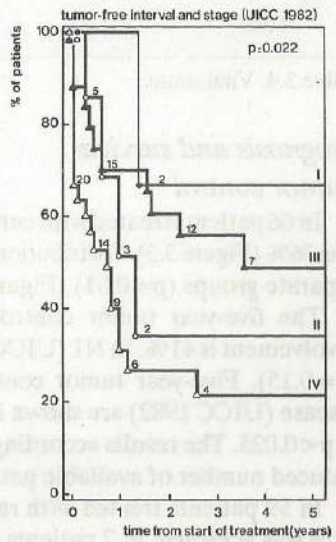

Figure 3.5. Tumor-free interval by stage (UICC 1982).

No relation was found between tumor control and general condition, sex, age, smoking habits or delay. In the multivariate analysis, T category correlates best with tumor control ($p=0.01$). Stage grouping alone ($p=0.67$) does not add prognostic value to the T category.

Loco-regional control

At 5 years, loco-regional control of 47% was obtained. Also in this case, the T category and stage grouping give prognostically distinct groups ($p<0.01$ and <0.025 respectively). In multivariate analysis, T category appears to be the single most important prognostic factor ($p=0.005$).

Crude survival

Twenty-two percent of patients were alive 5 years after the onset of treatment (Figure 3.3). In 17 patients who had other severe disorders, survival was 8%, versus 28% in 49 patients with a better general condition. This difference is significant ($p<0.01$).

Non-smokers had a 5-year survival of 55%, but in patients who had been smoking up to 20 cigarettes daily the survival was 29%, and in heavy smokers (>20 cigarettes) it was only 24% ($p<0.05$).

T category is highly predictive for crude survival ($p<0.01$), results at 5 years being 57% in T1, 29% in T2, 17% in T3 and 15% in T4. Smoking habits ($p<0.05$), general condition ($p<0.01$) and the T category ($p<0.01$) are three independent prognosticators of the crude survival.

Survival is 51% in women and 17% in men. This difference was not statistically significant ($p=0.07$). No difference in survival is seen when patients are split up by the length of the delay.

Discussion

Restaging according to the UICC (1987) system leads in this series to an enlargement of the N2 group. Groups N1 and N3 decrease in number of patients to the level where further analysis is hampered. Subtraction of 13% of patients is possibly contributing to the problem. Missing assessment of size of the affected nodes is likely to reduce the numbers of available patients in many reviews where the new classification system will be applied.

Stage grouping (UICC 1982) reveals a significant correlation with the tumor control, though less accurately than the T category alone. This indicates a negative effect of the N stage on the predictive value of stage grouping. A better 5-year tumor control in stage III compared to stage II

(49% and 34% respectively) can be explained with deficient N staging in this series.

Separation between T2 and T3 tumors posed a dilemma in the retrospective determination of the extent of the primary tumor. According to General Rules of the TNM-classification and stage grouping, the lower category should be chosen in case of doubt. Observations by other authors suggest that many tumors staged as T2 presumabely exceed 4 cm, but cannot be assessed for their full extent by palpation. As reported by Spanos et al. (19), control rates in T2 and T3 lesions after radiotherapy were not significantly different.

Gelinas and Fletcher (11) noticed the same overlap, where an obvious cause of failure could not be found in 74% of cases. They associated this outcome with the problematic staging by size in cancers of the base of the tongue. Parsons et al. (15) found the same local control in T2 and T3 tumors, but better results followed external radiotherapy, when compared to interstitial therapy. The outcome was explained by inadequate coverage of cancer extensions by the implant, due to understaging.

Strict application of General Rules leads to excessive understaging in tongue base tumors causing collapse of the T2 and T3 categories into one group. Significantly different prognoses in T2 and T3 lesions demonstrated in this study, support the choice of the higher category in cases of doubt.

Interaction of tumor and host characteristics is reflected in the crude survival. Clearly, tumor is the principal cause of death during the first 2 years of follow-up, when the vast majority of failures occur. Other factors determine survival after that time. A similar observation was reported by Rollo et al., with the turning point at 5 years (17).

The role of smoking habits and serious chronic diseases could be demonstrated in our group of patients. Metachronous malignancies and advanced age certainly contribute to deaths observed later in the follow-up.

In conclusion, control of the disease in patients with carcinoma of the base of the tongue treated by radiotherapy is accurately predicted by the T category. Allocation of the higher category in staging of tumors where doubt between T2 and T3 exists is recommended.

Palpation of the neck is unreliable. The degree of nodal involvement determined by palpation can have negative effects on prognostic value of the stage of the disease. Comparison of UICC(1982) and UICC(1987) systems, that differ only in the N categories, is not always justified in patients treated mainly by radiotherapy.

Crude survival rate of cancers of the base of the tongue is determined by the extent of the disease in the primary site, by smoking habits, and by the general condition of the patient.

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CHAPTER 4

Carcinoma of the oropharynx: is subsite a prognostic factor?

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Abstract

A comparative study of 92 patients with squamous cell carcinoma of the tonsillar region and 68 patients with a base of the tongue carcinoma was conducted, in order to study the prognostic role of localisation (subsite) within the oropharynx.

All patients were submitted to the Netherlands Cancer Institute from 1966-1984, for treatment with curative intent. Significantly different results in terms of tumor control (5-years tonsillar tumors 57%, base of tongue 36%; $p=0.007$) and crude survival (5-years in tonsillar tumors 43%, base of tongue 22%; $p=0.004$) were obtained. We now analyzed the distribution of 12 parameters related to host and tumor characteristics with respect to the subsite. The two subsites did not differ significantly in distribution of patients by age and sex, intoxications (smoking and alcohol), frequency of previous irradiation to the head and neck region, incidence of second primaries, distribution by T and by the stage of the disease, neither was there difference in treatment modalities or prognostic factors. The groups differed significantly in 2 parameters: other severe diseases on admission (14% of patients with tonsillar tumors vs 28% in base of the tongue; $p<0.05$) and patient delay (mean delay in tonsillar tumors 3 months, in base of tongue 4,5 months; $p=0.02$). These results suggest that two comparable groups of patients responded substantially different to similar treatment. Provided that the radiotherapy (that was given to the vast majority of patients in both subsites) did not differ with respect to relevant parameters, tumor subsite within oropharynx can be seen as an independent prognostic factor for tumor control and survival.

Keywords: *oropharyngeal carcinoma, subsite, prognostic factors*

Introduction

Reviewing the papers that report upon local control achieved with radiotherapy in carcinomas of the tonsillar region (Table 4.1) (2, 3, 10, 13-15, 18, 20, 25) and carcinomas of the base of the tongue (Table 4.2) (1, 6, 12, 15, 16, 21, 23, 28, 31), the impression rises that two different oncological entities exist within one anatomical region. However, a comparison of results from different papers is not possible because of the wide variation in methods of selecting, staging and treating patients, analyzing and reporting of results, and due to incomplete recording of the above.

After having studied all our patients with carcinomas of the tonsillar region (20) and of the base of the tongue (21), we conducted a comparative clinical study of these patients, in order to appraise the possible prognostic value of tumor subsite within the oropharynx.

Materials and methods

Patients

All patients were presented into detail before (20, 21); in this paper, only the figures necessarry for comparison of tumors in both subsites will be repeated.

Authors and year	Local control(%) in all patients	Patients by T(%)			
		T1	T2	T3	T4
Dubois e.a.(1983)	37	23	39	38	*
Johansen e.a.(1990)	56	13	51	34	2 **
Fayos & Morales(1983)	62	10	45	29	16 ***
Perez e.a.(1982)	63		****		
Garrett e.a.(1985)	63	13	43 *****		44
Bataini e.a.(1989)	64	8	20	37	35
Baris e.a.(1983)	65	17	36	41	6
Gelinas & Fletcher(1973)	82	12	26	46	16

* UICC (1962) classification
** oropharynx carcinoma (not only tonsil)
*** including retromolar trigone and soft palate
**** a modified T classification
***** UICC (1974) classification
Minimal follow-up was 2 years (Garrett et al.), 3 years (Baris et al.) or 5 years (all other authors).

Table 4.1. Review of the literature; local control and distribution by the T category in patients with tonsillar carcinoma treated with radiotherapy.

Author(s) and year	Local control(%) in all patients	Patients by T(%)			
		T1	T2	T3	T4
Jaulerry e.a.(1991)	47	13	28	39	20
Riley e.a.(1983) *	47	20	40	20	20
Blumberg e.a.(1979)	48	13	37	40	10
Parsons e.a.(1982)	48	12	24	34	30
Baris e.a.(1985)	59	12	22	49	17
Fayos(1981)	61	15	21	36	28 **
Spanos e.a.(1976)	69	18	28	37	17
Gelinas & Fletcher(1973)	75	18	23	38	21

* all patients, not only the ones treated with radiotherapy
** a modified (descriptive) T classification

Minimal follow-up was 2 years (Blumberg et al., Parsons et al., Riley et al.), 3 years (Jaulerry et al.) or 5 years (all other authors).

Table 4.2. Review of the literature; local control and distribution by the T category in patients with carcinoma of the base of the tongue treated with radiotherapy

One hunderd sixty-two patients with disease limited to local or locoregional site, who were admitted for primary treatment and followed for at least 3 years or til death, are analyzed. They all had squamous cell carcinoma, 94 patients in tonsillar region and 68 patients in base of tongue. The most relevant patients' characteristics, split up by the subsite, are summarized in Table 4.3.

	Tonsil (n=94)	Base of tongue (n=68)
Age (range)	34-88	31-91
Median age	64	67
Men:women (%)	78:22	78:22
Smokers (%)	71	72
Smokers & regular drinkers(%)	56	54
Previous RT to head & neck(%)	6	6
Other malignancies (%)	23	25
Other severe disorders (%) *	14	28
Delay (months) *	3	4.5

* $p<0.05$

Table 4.3. Carcinoma of the tonsillar region and the base of the tongue: patients' characteristics.

The distribution over the T and N categories and stage grouping according to UICC(1982) classification and staging system (32) in both subsites are shown in Table 4.4 and Table 4.5.

	T1	T2	T3	T4	Total
N0	6 (6%)	12 (13%)	10 (11%)	8 (8%)	36 (38%)
N1	7 (8%)	16 (17%)	12 (13%)	13 (14%)	48 (52%)
N2	-	-	1 (1%)	1 (1%)	2 (2%)
N3	1 (1%)	1 (1%)	3 (3%)	3 (3%)	8 (8%)
Total	14 (15%)	29 (31%)	26 (28%)	25 (26%)	94 (100%)

Stage I	6 (6%)
Stage II	12 (13%)
Stage III	45 (48%)
Stage IV	31 (33%)

Table 4.4. Carcinoma of the tonsillar region: distribution of patients by T, N and stage of the disease in absolute figures and (percentages).

	T1	T2	T3	T4	Total
N0	4 (6%)	7(10%)	11(16%)	10(15%)	32 (47%)
N1	3 (4%)	7(10%)	4 (6%)	6 (9%)	20 (29%)
N2	-	-	4 (6%)	2 (3%)	6 (9%)
N3	-	2 (3%)	4 (6%)	4 (6%)	10 (15%)
Total	7 (10%)	16(23%)	23(34%)	22(33%)	68(100%)

Stage I	4 (6%)
Stage II	7 (10%)
Stage III	25 (37%)
Stage IV	32 (47%)

Table 4.5. Carcinoma of the base of tongue: distribution of patients by T, N and stage of the disease in absolute figures and (percentages).

Treatment

The vast majority of patients, i.e. 81 (86%) with carcinoma of the tonsillar region and 61 (90%) with carcinoma of the base of the tongue, were scheduled for external radiotherapy, as single modality treatment.

Surgery with planned postoperative radiotherapy was applied in 13 (14%) of patients with tonsillar- and in 7 (10%) of patients with base of tongue carcinoma. Treatment modality by stage of the disease are presented in Figures 4.1 and 4.2.

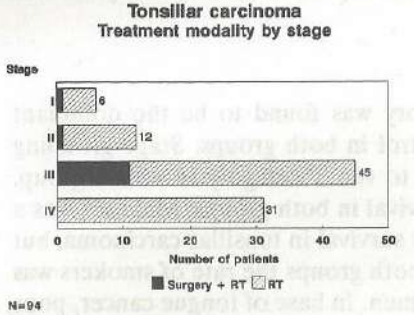

Figure 4.1. Treatment modality by stage in tonsillar carcinoma.

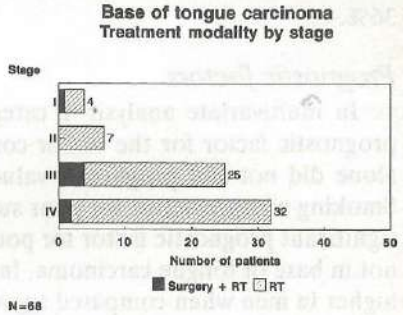

Figure 4.2. Treatment modality by stage in base of tongue carcinoma.

Definitions and statistical analysis

Minimal follow-up was 3 years or until death. Patients who died without tumor were considered lost to follow-up. Tumor-free interval is defined as the time between the start of treatment and first evidence of failure in local, regional or distant site.

Survival and the tumor-free interval were calculated by the Kaplan-Meyer method (19). Comparisons were made using the score test, or with analysis of contingency tables (26). Possible prognostic factors were analyzed in the Cox's proportional hazard model (8).

Results

Tumor control and survival

In patients with carcinoma of the tonsillar region 3-year tumor control was 61% (Figure 4.3). Split up by the T stage the following tumor-control rates were achieved: 83% in T1, 79% in T2, 53% in T3 and 36% in T4. Overall survival at 3 years was 58% (Figure 4.4).

In carcinoma of the base of the tongue 3-year tumor control was 39%; in T1 83%, T2 34%, T3 40% and T4 26%. Overall survival at 3 years was 36%.

Prognostic factors

In multivariate analysis T category was found to be the dominant prognostic factor for the tumor control in both groups. Stage grouping alone did not add prognostic value to the T category in either group. Smoking was predictive for poor survival in both groups. Male sex was a significant prognostic factor for poor survival in tonsillar carcinoma, but not in base of tongue carcinoma. In both groups the rate of smokers was higher in men when compared to women. In base of tongue cancer, poor general condition on admission due to other diseases was predictor of short survival. Review of all prognostic factors that were previously tested on these groups is shown in Table 4.6.

Host characteristics

Tonsillar region- and base of tongue group of patients were compared with respect to age on admission, sex, intoxications, previous radiotherapy, rate of second primaries, other chronical diseases on admission and patients delay (Table 4.3). Groups were similar with respect to the first 7 parameters on the list. Significant difference was found in case of two parameters: general condition on admission and patients delay. In tonsillar carcinoma-group 14% of patients were in poor general condition due to other chronical diseases, versus 28% in base of tongue-group ($p<0.03$). Mean delay was 3 months in patients with tonsillar carcinoma, versus 4.5 months in base of tongue patients ($p<0.02$).

Tumor characteristics and treatment

Two groups were compared with regard to TNM classification and stage of the disease. There was no significant difference in distribution between the groups. In considering application of different treatment modalities in whole groups and split up by stage, no relevant differences were found between the two subsites.

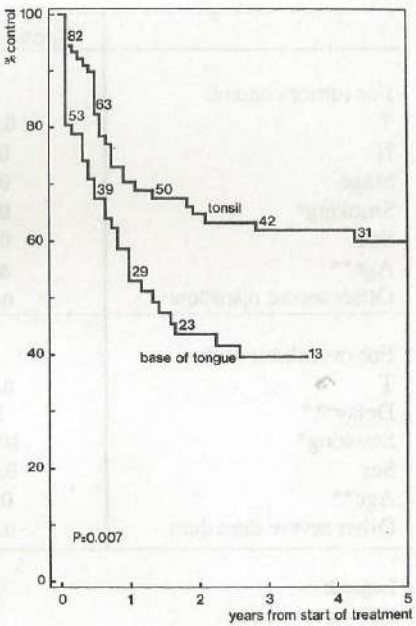

Figure 4.3. Tumor control in tonsillar- and base of the tongue carcinoma.

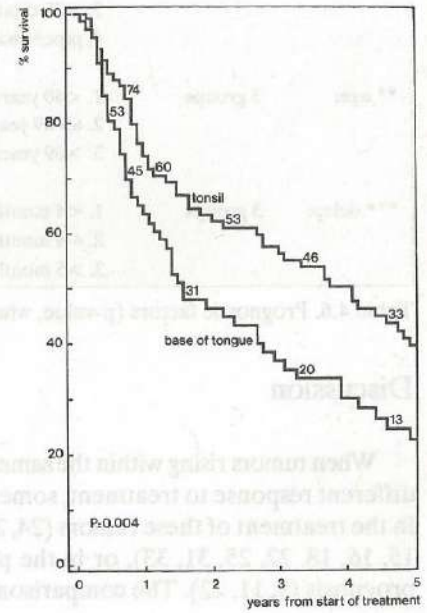

Figure 4.4. Overall survival in tonsillar- and base of the tongue carcinoma.

	Tonsillar region	Base of tongue
For tumor control:		
T	0.03	**0.01**
N	0.1	0.15
Stage	0.2	**0.02**
Smoking*	0.6	0.9
Sex	0.2	0.4
Age**	n.a	0.5
Other severe disorders	n.a.	0.7
For overall survival:		
T	n.a.	**0.008**
Delay***	1.	0.65
Smoking*	**0.04**	**0.04**
Sex	0.03	0.07
Age**	0.3	n.a.
Other severe disorders	n.a.	**0.007**

Legend:
n.a. = not assessed

* smoking:	4 groups	1. never 2. <21 cigarettes daily, 3. >20 cigarettes daily and 4. pipe/tobacco
** age:	3 groups	1. <60 years 2. 60-69 years 3. >69 years
*** delay:	3 groups	1. <4 months 2. 4-6 months 3. >5 months

Table 4.6. Prognostic factors (p-value, where <0.05 printed in boldface).

Discussion

When tumors rising within the same anatomic region display a significantly different response to treatment, some differences are expected to be found in the treatment of these tumors (24, 27), in stage of the disease (3, 7, 9, 12, 15, 16, 18, 22, 25, 31, 33), or in the presence of other features related to prognosis (9, 11, 22). The comparison of prognostically distinct tumors of

the tonsillar region and of the base of the tongue in our patients, with respect to these features, did not reveal a satisfactory explanation for the observed difference in prognosis. Of all the parameters under comparison, i.e. patients' age (2), sex (9, 22), carcinogenic intoxications (30), rate of second primaries (17), general condition on admission (22), patient's delay (11), T, N and stage of the disease and treatment modality, only patient's delay and proportion of patients in poor general condition appeared to differ signifficantly between the subsites. Of these, only the poor general condition due to other diseases than the oropharyngeal tumor, correlated with low survival rate in base of the tongue tumors. The difference in tumor control, however, cannot be explained by this correlation.

Longer delay in patients with carcinoma of the base of the tongue would perhaps offer an explanation, if it had been associated with a higher tumor stage. However, this is not the case; longer delay probably indicates a slower growth and less abundant symptoms than in tonsillar tumors. Empirically, slow tumor growth has been associated with poor respons to radiotherapy, but this observation was not yet satisfactory explained. Studies of potential doubling time in head and neck tumors (4) will hopefully provide a better insight in this phenomenon.

The fact that the two subsites did not differ with respect to treatment modalities does not exclude possible variations in radiotherapy, that was delivered to the vast majority of our patients. The features known for prognostic significance, i.e. overall treatment time (3-5, 18), target volume (14), and dose (5, 29) need to be analyzed in both subsites and compared.

In addition, the presented material can be assessed through a morphologic and immunohistochemical study with techniques applicable to formaline-fixed, paraffin-embedded biopsy specimens. The obtained results might contribute to a better understanding of different biologic behaviour of tumors in these subsites.

In conclusion, comparison of tumors of the tonsillar region and the base of the tongue with respect to 12 parameters related to host- and tumor characteristics and treatment modalities could not provide a satisfactory explanation for significantly different tumor control rates in these subsites. Under the assumption that the radiotherapy did not differ with respect to overall treatment time, dose and target volume, the subsite within the oropharynx can, as far as the two most frequent occurring tumors are concerned, be considered as a separate factor in predicting the outcome after treatment in individual patients.

Acknowledgments

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CHAPTER 5

Radiotherapy of tonsillar and base of the tongue carcinoma. Prediction of local control.

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Oral Oncol, Eur J Cancer (in press)

Abstract

One hundred and nineteen patients with squamous cell carcinoma of the tonsillar region (68) and the base of the tongue (51), who received external radiotherapy with curative intent between 1966 and 1984, are analyzed with respect to overall treatment results, local tumor control and prognostic factors. Radiation doses were equivalent to 60-70 Gy in 6-7 weeks, with a mean fraction dose of 2.4 Gy on the Cobalt 60 equipment and 2 Gy on the linear accelerator.

Significant differences were found between both oropharyngeal subsites. Three-year overall survival was 57% in tonsillar carcinoma and 38% in base of the tongue ($p=0.006$); disease-specific survival was 70% and 47% respectively ($p=0.005$); and local control rates were 82% and 61% ($p=0.02$). Late damage to normal tissues, like persistent dysphagia and osteomyelitis, were seen in 11% of patients. Patients with large tumors in the tongue base developed significantly more complications ($p=0.04$).

T-stage and tumor subsite predict local control independently before start of the treatment ($p=0.02$ in both cases). A significant nonlinear correlation between Normalized Total Dose (using an α/β ratio of 15 Gy) and local control rate was found ($p=0.006$), the middle range having the worst prognosis. The size of radiation field and overall treatment time did not correlate with local control in either site. Response at the end of radiotherapy and 6 weeks later have additional prognostic value for local control, irrespective of the initial stage or subsite ($p=0.0004$ and <0.001, respectively).

Keywords: *tonsillar carcinoma, base of the tongue carcinoma, external radiotherapy, local control, prognostic factors*

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Introduction

The tonsillar region and the base of the tongue are the two most frequent subsites of origin in cancers of the oropharynx. Radiotherapy appears to be more effective for the tonsillar region than for the base of the tongue. For carcinoma of the tonsillar region a local control rate of approximately 65% (3, 5, 18, 22, 37), or incidentally lower (16, 28) is reported. For base of tongue carcinoma, the local control rate fluctuates around 50% in most studies (11, 27, 35, 39), although some higher values have been noted (2, 17, 42). In 1973 Gelinas and Fletcher reported on remarkably good results having 82% and 75% local tumor control, for the tonsillar region and base of the tongue, respectively (24).

In oropharyngeal tumors, control of the primary site emerges as the crucial parameter for the success of the therapy (28). A reliable prediction of the control for the primary tumor before the start of radiotherapy can be based upon T stage, as confirmed in many studies (5, 12, 16, 17, 24, 27, 28, 35, 37, 42, 47), N stage (16, 17, 42, 47) and infiltration of tonsillar tumors in base of the tongue correlate with local control, the latter being a poor prognostic sign (3, 5, 16, 22, 48). Of the treatment parameters, increasing target volume (22, 23) and decreasing overall treatment time (5, 8, 10, 28) were found predictive for improved local control rates. A dose-response relationship is still disputed; it could be demonstrated in some studies (10, 28, 40), but not in others (5, 16, 22). In fact is the mechanism of repopulation during radiotherapy, with respect to overall treatment time and dose as important factors, presently debated (21, 43). Regression of tumor during radiotherapy and total clearance following treatment are as can be expected reliable predictors of tumor control (4, 6, 15, 27, 41). Finally, age above 60 (3) and male sex (14, 32, 34) correlate with low survival rates, but not with local control.

Radiotherapy to the oropharyngeal region can lead to xerostomia and dysphagia, and in a small number of patients severe nutritional problems will follow (37). Late damage to normal tissues leading to fibrosis, soft tissue and mandibular bone necrosis, or cervical spine myelitis are reported to occur in 10%-35% of the patients (36, 37, 49). Generally, more complications are expected after high-dose treatment (40).

In our previous papers we have studied the prognostic factors for the tumor control in tonsillar carcinoma (32) and carcinoma of the base of the tongue (33). Of the tested parameters (T and N category and the stage of the disease according to UICC 1982 and UICC 1987 systems and extension of the tonsillar tumors to adjacent sites), the T category appeared to be the single most important prognostic factors in both subsites. In each subsite

the majority of patients was treated with radiotherapy, and significantly better tumor control and survival were reported in tonsillar carcinoma. In this paper we continue the study focussing upon those patients who were treated with radiotherapy only. The efficacy of treatment is evaluated in terms of local control and survival. Late damage to normal tissues, and significance of tumor and treatment parameters for prediction of late damage were studied. Dose-effect and time factor are tested in relation to local control in our patients. The impact of tumor subsite on effects of treatment was studied in particular; therefore the results are presented separately for tonsillar carcinoma and base of the tongue carcinoma.

Materials and methods

Patients

One hundred thirty-three consecutively treated patients were registered. Fourteen patients were excluded from the analysis of treatment. These include two patients who did not complete radiotherapy, 2 patients treated with an implant only and 10 patients treated only with fast neutrons. For the remaining 119 patients (68 with tonsillar carcinoma and 51 with base of the tongue carcinoma) all data was available, except for the response at the end of radiotherapy in 7 patients and the response 6 weeks after the end of radiotherapy in 6 patients. All patients had histologically proven squamous cell carcinoma.

In patients with tonsillar carcinoma, 55 (81%) were male and 13 (19%) female; median age was 66 (42-89) years. In the tongue base carcinoma group, 39 (76%) patients were male and 12 (24%) female; median age was 67 (43-81) years. In both groups, about 80% of patients had tumors in stage III or IV on admission (Table 5.1 and Table 5.2).

Treatment

Megavoltage radiotherapy was delivered through opposing lateral fields either with Cobalt 60 equipment (1966-1973) or a 8 MV linear accelerator (1972-1984). From 1966-1975, 250 kilovoltage radiotherapy and electron beams were incidentally applied in the treatment of tonsillar carcinoma (3 patients and 1 patient, respectively). The total dose was equivalent to 60-70 Gy in 6-7 weeks. Fraction doses ranged from 1.8 to 3.1 Gy, but were generally higher in the early period when Co60 was used (mean 2.4 Gy) than in the later period (mean 2 Gy). To take into account the biological effect of the dose per patient, Normalized Total Doses (NTD)(31) were calculated in all patients both for tumor control and for late damage, according to the equation

$$NTD = nd\{1+d/(\alpha/\beta)\} / \{1+2/(\alpha/\beta)\}$$

where n is equal to the number of fractions, d is the dose per fraction in Gy and α/β is 15 Gy (31) for local tumor control (NTD_{15}) and 2 Gy for late damage to normal tissue (NTD_2) (7, 19).

	T1	T2	T3	T4	Total
N0	5 (8)	11 (16)	7 (10)	6 (9)	29 (43)
N1	2 (3)	8 (12)	10 (15)	11 (16)	31 (46)
N2	-	-	1 (1)	-	1 (1)
N3	1 (1)	1 (1)	3 (5)	2 (3)	7 (10)
Total	8 (12)	20 (29)	21 (31)	19 (28)	68 (100)
Stage I	5 (8) patients				
Stage II	11 (16) patients				
Stage III	27 (40) patients				
Stage IV	25 (37) patients				

Table 5.1. Carcinoma of the tonsillar region. Distribution of patients by the T and the N categories and the stage of the disease according to UICC(1982) staging system (46) in absolute figures and (percentages).

	T1	T2	T3	T4	Total
N0	2 (4)	7 (14)	7 (14)	5 (10)	21 (41)
N1	3 (6)	6 (12)	3 (6)	5 (10)	17 (33)
N2	-	-	3 (6)	2 (4)	5 (10)
N3	-	2 (4)	2 (4)	4 (8)	8 (16)
Total	5 (10)	15 (29)	15 (29)	16 (31)	51 (100)
Stage I	2 (4) patients				
Stage II	7 (14) patients				
Stage III	19 (37) patients				
Stage IV	23 (45) patients				

Table 5.2. Carcinoma of the base of the tongue. Distribution of patients by the T and the N categories and the stage of the disease according to UICC(1982) staging system (46) in absolute figures and (percentages).

In the 68 patients with tonsillar carcinoma, the mean NTD_{15} was 58 Gy. In 26 patients (38%) NTD_{15} was less than 60 Gy, in 18 (27%) equal to 60-65 Gy and in 24 (35%) higher than 65 Gy. In the 51 patients with base of the tongue carcinoma, mean NTD_{15} was 61 Gy. The NTD_{15} was less than 60 Gy in 20 patients (39%), equal to 60-65 Gy in 16 (31%) and higher than 65 Gy in 15 (30%). No significant differences were observed with respect to NTD_{15} between different T stages.

Overall treatment time in tonsillar carcinoma was 25-73 days (mean 37 days), 28 patients (41%) having had radiotherapy for 34 days or shorter, 23 (34%) patients for 35-48 days, and 17 (25%) patients for 49 days or longer. In base of the tongue carcinoma patients, the mean overall treatment time was 38 days (22-53). Twenty-two patients (43%) had radiotherapy over 34 days or shorter, 19 patients (37%) for 35-48 days and 10 patients (20%) for more than 48 days.

In tonsillar carcinoma the largest radiation field size was smaller than 70 cm^2 in 18 patients (26%), 70-120 cm^2 in 23 (34%), while in the remaining 27 patients (40%) the largest field was larger than 120 cm^2. In base of the tongue cancer the largest field was smaller than 70 cm^2 in 18 patients (35%), 70-120 cm^2 in 20 (39%) and larger in 13 patients (25%). In case shrinking fields or boosts were used, the calculations were based on the largest radiation field.

Responses were estimated by routine ENT examinations and palpation. In case of recurrent, residual and/or metastatic disease, the possibilities for secondary treatment were evaluated individually, based on the patient's general condition and tumor extent. Treatment consisted of surgery, chemotherapy or radiotherapy, depending on the individual situation.

Definitions and statistical analysis

Minimal follow-up was 3 years or until death. Patients who died without tumor were considered lost to follow-up. Time to local recurrence is defined as the time from start of treatment until the first evidence of failure in the primary site. Recurrence is a renewed manifestation of the tumor in the area that was previously irradiated. Tumor manifestation outside the radiation treatment field found during follow-up is considered as a metastasis. Lesions, not disappearing after the initial treatment, irrespective of time, are considered as residual tumor.

In testing the prognostic value for local control, the following variables were used: age, sex, tumor subsite, T stage, size of the radiation treatment field, the NTD_{15}, overall treatment time, response at the end of treatment and response 6 weeks later (Table 5.3).

For possible prediction of late normal tissue damage, the following variables were tested: age, sex, tumor subsite, T stage, radiotherapeutic equipment, the NTD_2 and radiation field size.

Survival curves were calculated using the product-limit method of Kaplan and Meyer (29). In determination of overall survival, all deaths were included, regardless of tumor status. Calculation of disease specific survival is based only on those patients who died with cancer. Cox's proportional hazard regression analysis (13) was used to estimate and test the independent contribution of multiple variables to prognosis in a forward stepwise manner. At each step we tested linearity of variables and interaction between all variables and the subsite of primary tumor. In cases where the association of variables had to be analyzed, the Chi-square test for contingency tables was performed for nominal and ordinal variables and the Kruskall-Wallis test for ordinal and interval variables.

Logistic regression was used for the analysis of complications at 1 year. Patients not surviving for 1 year or longer were not included in this analysis, regardless of their status, with respect to complications. Both for inclusion and exclusion a p-value of 5% was used.

Results

Response to radiotherapy

Response of the primary tumor at the end of radiotherapy was recorded in 62 of 68 patients with tonsillar carcinoma as follows: no evidence of disease (NED) in 37%, unclear whether there was residual tumor or scar tissue in 40%, residual tumor in 23% of the patients. For base of the tongue carcinoma response at the end of treatment was known in 50 of 51 patients: NED in 16%, unclear in 42%, residual tumor in 42%.

Response to treatment 6 weeks after completion of therapy was recorded in 64 of 68 patients suffering from tonsillar carcinoma: NED in 91%, unclear in 8% and residual tumor in 1% of the patients. For base of the tongue group, the response at this time was known in 49 of 51 patients: NED in 76%, unclear in 14% and residual tumor in 10%.

All patients with no evidence of disease at the end of the radiotherapy were controlled in the primary site at 6 weeks follow-up as well. From the patients with residual tumor or unclear tumor status at the end of treatment, 87% were tumor-free at the primary site at 6 weeks for tonsillar carcinoma and 70% for base of the tongue carcinoma. At both evaluation points the response of the primary tumor to treatment was significantly better in tonsillar carcinoma than in base of tongue cancer (p=0.005 and 0.02,

Variable	Category	N
Sex	men	94
	women	25
Age	<=59	41
	60-74	50
	>=75	28
Subsite	tonsil	68
	base of tongue	51
T stage	T1	13
	T2	35
	T3	36
	T4	35
Field size	<70 cm^2	36
	70-119.9 cm^2	43
	>=120 cm^2	40
NTD_{15}	<=60 Gy	46
	60.1-65 Gy	34
	>65 Gy	39
Overall treatment time	<35 days	50
	35-48 days	42
	>48 days	27
Response end RT*	NED	31
	unclear	46
	residual tumor	35
Response at 6 weeks**	NED	95
	unclear	12
	residual tumor	6

* missing values in 7 patients
** missing values in 6 patients

Table 5.3. Variables, related categories and numbers of patients per category, that were used in the analysis of the local control.

respectively). In none of the patients with residual tumor at 6 weeks after completion of radiotherapy local control was reached later during the follow-up.

Treatment results and follow-up

Tonsillar region

For tonsillar carcinoma, NED was observed in 65 patients in a period following radiotherapy, whereas 3 patients had residual disease (local, regional or both, see Table 5.4) that did not resolve later in the follow-up.

Of the 65 patients with NED, 14 developed a local and/or regional recurrence and another 8 patients distant metastases. Forty-three patients never had a relapse, but 11 patients died of other causes in the first 3 years of follow-up resulting in 32 patients being at risk for recurrence after 3 years.

Residual tumors are included: 1 locoregional and 2 regional in tonsillar carcinoma and 6 local, 2 locoregional and 2 regional residual tumors in base of the tongue carcinoma.

In total 25 patients had a relapse at some site; and secondary treatment was given to 15 (60%) of these patients. Median survival after diagnosis of failure was 10 months in patients who received secondary treatment, versus 2.5 months in the non-treated group. Tumor control was achieved in 3 patients, but 2 of them died from intercurrent disease within 6 months.

Base of the tongue

In this group of 51 patients, NED in a period following radiotherapy was reached in 41 patients, while 10 patients had permanent residual cancer at some site (Table 5.4). Fourteen of these 41 patients had local and/or regional failure during the follow-up. Seven patients had distant metastases with controlled locoregional site. Of the 20 patients who remained tumor-free after radiotherapy, 9 patients died of other causes during the first 3 years of follow-up and 11 patients were still at risk.

Of the 31 patients who failed radiotherapy, 11 (35%) were submitted to secondary treatment. In this group mean survival after diagnosis of failure was 9.5 months, versus 4 months in patients who were not treated any

	Tonsil	Base of tongue	Total
Tumor control	43	20	63
Local failure	4	13 (1)*	16
Regional failure	6 (1)*	7 (3)**	12
Local & regional failure	7	4	13
Distant metastasis	8	7	15
Total	68	51	119

* of these patients, one had recurrence at the margin of the field.
** of these patients, two had recurrence at the margin of the field and one had metastasis low in the neck.

Table 5.4. Crude treatment results (i.e. figures are not corrected for the length of the follow-up). The first sites of failure are reported.

further. The tumor was controlled in 2 patients, who survived 22 months and more than 10 years after relapse, respectively.

Local control

In the total group of 119 patients, a 3 year local control rate of 73% was achieved. Failure to control tumor at the primary site occurred in 29 patients, all within 26 months after onset of treatment.

Pretreatment parameters in relation to local control

For 68 patients with tonsillar carcinoma, local control at 3 years was 82% while for 51 patients with base of the tongue carcinoma, there was only a 61% local control rate (Figure 5.1). The significant difference between these results ($p=0.02$) exists mainly because 8 patients had local or locoregional residual tumor in the tongue base, versus only one patient with local residual disease in the tonsillar region. After exclusion of these patients, the 3-year local control rates are no longer significantly different (82% versus 72%).

Despite small numbers of patients in T1 group in both subsites (8 in tonsillar- and 5 in base of the tongue carcinoma), a significant difference in local control by T stage was found in each subsite ($p=0.02$),(Figure 5.2).

No relation was found between local control and patients' sex or age.

Treatment parameters in relation to local control

A statistically significant nonlinear correlation ($p=0.006$) between NTD_{15} and local control was found, with the middle range (60-65 Gy) showing the worst results. Three-year local control rate by NTD_{15} for tonsillar tumors was as follows: NTD_{15} lower than 60 Gy was 82%, NTD_{15} equal to 60-65 Gy was 69%, NTD_{15} higher than 65 Gy was 93%. Corresponding values for the base of the tongue tumors were 71%, 34% and 78% respectively.

In an attempt to explain this significant nonlinear relation, the association of NTD_{15} with the following variables was analyzed: sex, age, subsite, T stage, field size, overall treatment time and radiotherapeutic device. An association with the field size ($p<0.0001$), overall treatment time ($p<0.0001$) and radiotherapeutic device ($p<0.0001$) was found. However, these cannot explain the nonlinear relation between NTD_{15} and local control as the main difference is observed between the high dose group ($NTD_{15} > 65$ Gy) and the other two, and not between the low and the middle dose groups.

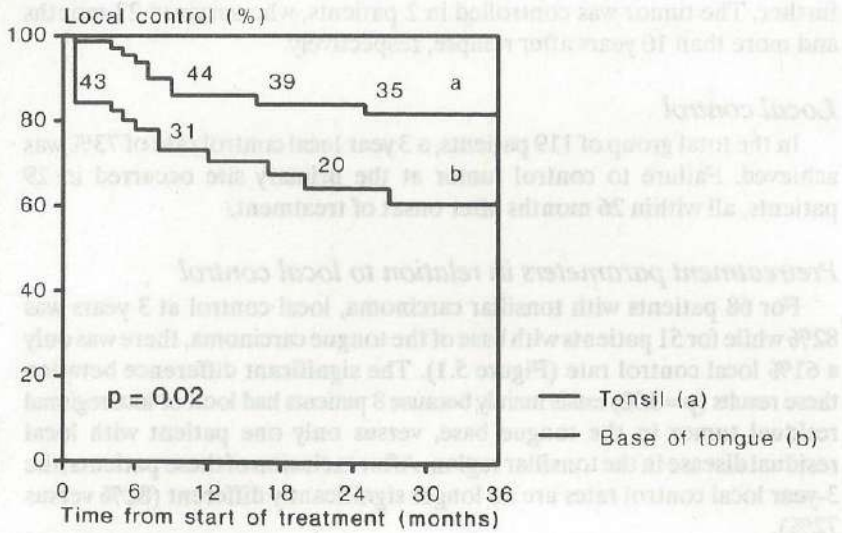

Figure 5.1. Local control in tonsillar region and in base of the tongue.

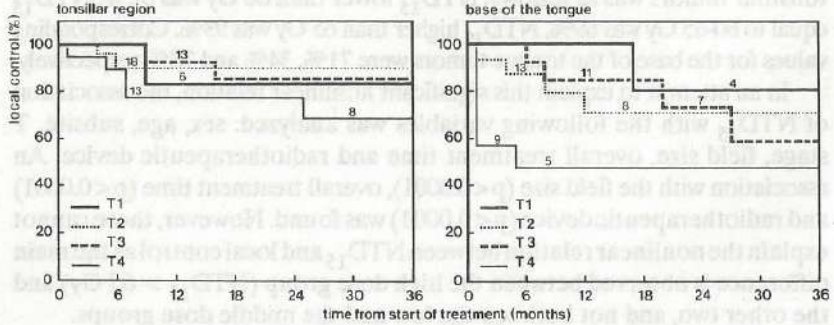

Figure 5.2. Local control by T stage in tonsillar and in base of tongue carcinoma (p=0.045).

Posttreatment parameters in relation to local control

After the relation of pretreatment and treatment factors to local control was assessed, relation of response to treatment and local control was studied. Strong correlation between lasting local control and response to treatment at the end of radiotherapy (p=0.0004) and 6 weeks later (p<0.0001) was found in both subsites.

The prognostic value of all these variables was tested using Cox's proportional hazard regression model. In the multivariate analysis of pretreatment and treatment parameters, all variables were controlled for the tumor subsite, T stage, and NTD_{15}. Tumor subsite and T stage have prognostic value for local recurrence, i.e. tonsillar region and small tumors are predictive for higher local control rates (p=0.0005 and 0.03, respectively). The nonlinear relation between NTD_{15} and local recurrence remained significant (p=0.004).

Responses to radiotherapy at the end of treatment and 6 weeks later, when controlled for the initial tumor stage, subsite and NTD_{15}, have additional prognostic value for local recurrence (p=0.03 and <0.0001, respectively). When controlled for the response at 6 weeks, the only significant parameter in the multivariate analysis remains the NTD_{15} (Table 5.5).

Late damage to normal tissue

Of 83 patients (50 with tonsillar carcinoma and 33 with base of the tongue carcinoma) who were still alive after one year of follow-up, 9 patients (11%) had severe late damage secondary to the radiotherapy. In the tonsillar carcinoma group, 6 patients (12%) developed the following sequelae: persistent dysphagia with (1) or without (2) pain, osteomyelitis (2) and myelopathy (1). In base of the tongue carcinoma group, late damage was observed in 3 patients (9%): persistent dysphagia in one patient and osteomyelitis of the mandibula in a further two patients.

All complications were entered in the logistic regression model. Univariately, only a site-dependent relation between T stage and complications was observed (p=0.04) in patients with extensive tumors in base of the tongue having a higher complication rate. Controlling for this factor, no other variable attained statistical significance.

	Univariately	Multivariately[1]	
		step 1[2]	step2[3]
Sex	NS[4]	NS	NS
Age	NS	NS	NS
Subsite	0.02	0.0005	NS
T stage	0.02	0.03	NS
NTD_{15}	0.006[5]	0.004[5]	0.0002[5]
Field size	NS	NS	NS
Overal treat.time	NS	NS	NS
Response end RT	0.0004		NS
Resp. at 6 weeks	<0.0001		<0.0001

1 in multivariate analysis all variables were controlled for site, T stage and NTD_{15}
2 multivariate analysis of pretreatment and treatment variables
3 multivariate analysis controlled for response to radiotherapy at 6 weeks
4 not significant
5 including nonlinearity

Table 5.5. P-values of stepwise proportional hazard regression analysis of prognostic factors for local control.

Survival

Overall survival and disease-specific survival were significantly higher in tonsillar carcinoma than in base of the tongue carcinoma. Three-year rates for the two subsites were 57% and 38% respectively (p=0.006) in case of overall survival (Figure 5.3). Disease specific survival at 3 years was 70% in the tonsillar region and 47% in the base of the tongue (p=0.005)(Figure 5.4).

Discussion

The 3-year local control rate achieved in patients with tonsillar carcinoma was 82% in this series. Compared to other published results (3, 5, 16, 18, 22, 24, 28, 37), and taking into account that the majority of the patients had advanced disease, this is a favorable result. The 3-year local control for base of the tongue carcinoma group was 61%. These results, even though higher than in many other series (2, 11, 17, 27, 35, 39, 42), are less satisfactory. The significant difference between local tumor control rates in the two subsites could not be explained from different treatment parameters. Thus, basically the same treatment, i.e. external radiotherapy with doses equivalent to 60-70 Gy in 6-7 weeks, controls effectively the primary site in tonsillar tumors,

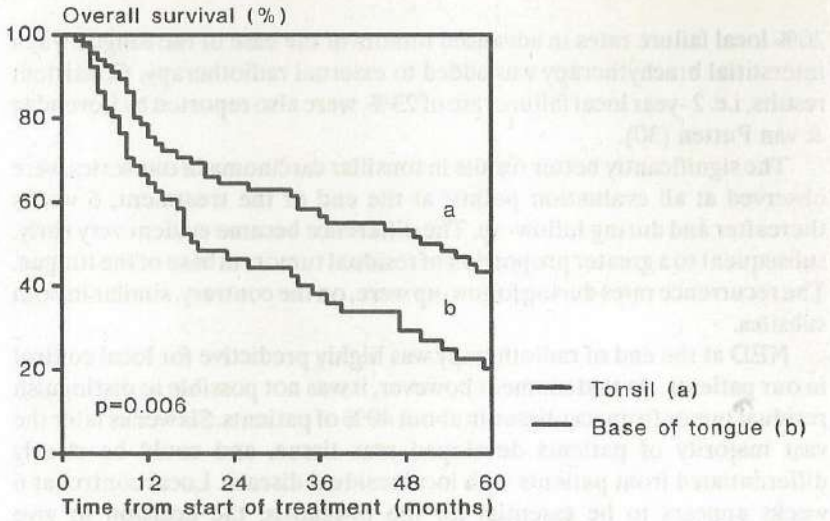

Figure 5.3. Overall survival of 119 patients split up by tumor site.

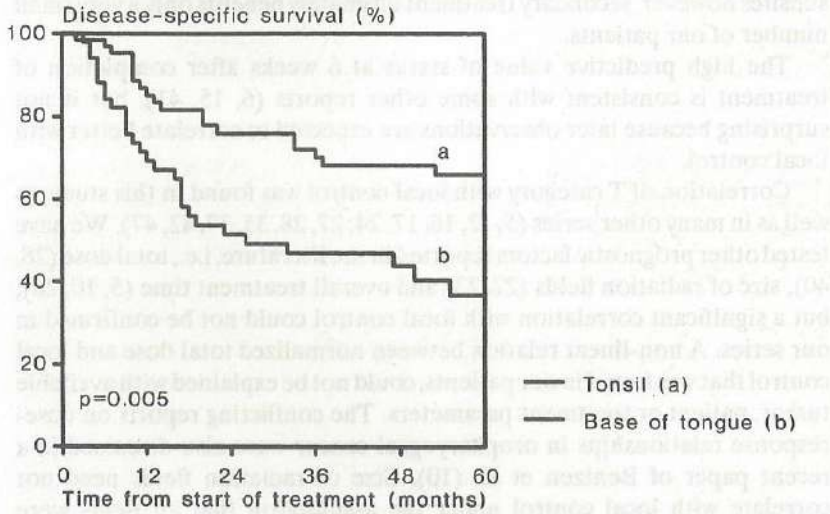

Figure 5.4. Disease-specific survival of 119 patients split up by tumor site.

but not in base of the tongue tumors. Possibly, accelerated regimes (1, 26, 44) or combination with interstitial radiotherapy (25, 30, 38) could yield better results in this subsite. Hoffstetter et al. (25) observed improvement in local control of T1 and T2 tumors after combination of external radiotherapy and interstitial brachytherapy. Puthawala et al. (38) reported on only 10-

20% local failure rates in advanced tumors of the base of the tongue when interstitial brachytherapy was added to external radiotherapy. Consistent results, i.e. 2-year local failure rate of 23%, were also reported by Levendag & van Putten (30).

The significantly better results in tonsillar carcinoma in our series were observed at all evaluation points: at the end of the treatment, 6 weeks thereafter and during follow-up. The difference became evident very early, subsequent to a greater proportion of residual tumors in base of the tongue. The recurrence rates during follow-up were, on the contrary, similar in both subsites.

NED at the end of radiotherapy was highly predictive for local control in our patients. At that moment however, it was not possible to distinguish residual tumor from scar tissue in about 40% of patients. Six weeks later the vast majority of patients developed scar tissue, and could be clearly differentiated from patients with local residual disease. Local control at 6 weeks appears to be essential for the prognosis; the decision to give secondary treatment should therefore be made at that point. At both subsites however, secondary treatment ultimately benefits only a very small number of our patients.

The high predictive value of status at 6 weeks after completion of treatment is consistent with some other reports (6, 15, 41), but is not surprising because later observations are expected to correlate better with local control.

Correlation of T category with local control was found in this study, as well as in many other series (5, 12, 16, 17, 24, 27, 28, 35, 37, 42, 47). We have tested other prognostic factors reported in the literature, i.e., total dose (28, 40), size of radiation fields (22, 23) and overall treatment time (5, 10, 28); but a significant correlation with local control could not be confirmed in our series. A non-linear relation between normalized total dose and local control that was found in our patients, could not be explained with available tumor, patient or treatment parameters. The conflicting reports on dose-response relationships in oropharyngeal cancer were also discussed in a recent paper of Bentzen et al. (10). Size of radiation fields need not correlate with local control under the assumption that all fields were designed as to cover the tumor sufficiently. The low incidence of recurrences at the margin of the field in our patients suggests the fields were large enough as to cover the complete tumor.

Based on results presented in this study and in our earlier papers (32, 33), we conclude that tumor subsite is a separate early prognostic factor when the two most frequently involved subsites of oropharyngeal cancer are compared. The literature does not confirm this conclusion, although there

is certainly enough evidence of poorer results for base of the tongue tumors (2, 11, 17, 27, 35, 39, 42), when compared to tumors of the tonsillar region (3, 5, 16, 18, 22, 24, 28, 37). Studies of tumor-host relationship, potential doubling time (8, 9, 20, 45) and of histological and histochemical aspects of these tumors might contribute to more accurate determination of prognosis for the individual patient with a tonsillar or base of tongue carcinoma.

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CHAPTER 6

Squamous cell carcinoma of the tonsillar region and the base of the tongue. A morphologic and immunohistochemical comparative pilot study.

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Abstract

Sixteen squamous cell carcinomas of the tonsillar region and 13 carcinomas of the base of the tongue were studied in a search for significant differences between the tumors of these two oropharyngeal subsites, which are known to carry a significantly different prognosis. The characteristics of the tumor cells and the tumor-host relationship were scored on HE-stained slides, as well as on slides stained with a panel of antibodies. The obtained results were crosstabulated and analyzed with respect to the subsite. Ten variables were tested: cytonuclear pleomorphism, mitotic activity, the presence of atypical mitoses, keratinization, tumor grade, presence of eosinophils, severity of inflammatory response, and the expression of keratin 10, blood group antigens and collagen IV. When split-up by site, only cytonuclear pleomorphism revealed a significant difference, tonsillar carcinomas more often exhibiting marked pleomorphism ($p=0.04$).

Despite having some prognostic relevance for squamous cell carcinomas of the head and neck, the variables tested could not provide an explanation for the difference in biological behavior of the tumors we studied.

Keywords: *tonsillar carcinoma, base of the tongue carcinoma, tumor grade, immunohistochemistry*

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Introduction

The oropharynx has often been considered to embody one single anatomical and physiological entity. Oncologically, however, this is questionable: of the five subsites that are recognized in oropharynx, i.e. the posterior wall, lateral wall, soft palate and uvula, the tonsillar region and the base of the tongue, the latter two host as many as 95% of oropharyngeal tumors (35). Interestingly, cancers of these two subsites differ widely in clinical outcome, treatment results and survival rates generally being more favorable in tonsillar carcinomas (5, 6, 13-15, 17, 26) than in carcinomas of the base of the tongue (4, 13, 15, 17, 23, 27). In the recently published material from our institute (26, 27), these differences could not be explained by differences in patient characteristics, macroscopic features or treatment aspects (25).

To gain further insight into the biologic behavior of tumors of these two subsites, we decided to investigate several histopathological parameters which presumabely have prognostic significance in head and neck carcinomas: cytonuclear pleomorphism (16, 22), mitotic activity (1, 22, 30), presence of atypical mitoses (16, 30), keratinization (7), peritumoral inflammatory response (1) and the mode of tumor invasion (1, 16, 22). We also wanted to study the histological grade, which is considered an important indicator of the biologic behavior of the tumors (2, 7, 8, 16, 24, 28-30), despite the fact that tumor grades are not well standardized, and therefore prone to intra- and inter-observer variability. In an attempt to overcome these shortcomings, we have reviewed the slides using a standardized checklist for all the above mentioned characteristics.

The development of monoclonal antibody technology (Mabs) and diagnostic immunohistochemistry has provided new possibilities in tumor diagnosis (31, 34). In stratified epithelia and in some squamous cell carcinomas, early keratinization can be visualized with monoclonal antibodies to cytokeratin-10 (K_{10}). Expression of K_{10} is thus expected to correlate to some extent to the differentiation grade of squamous cell carcinoma (10, 18). Loss of expression of blood group (A, B and H) antigens has been associated with increased tumor aggressiveness in malignancies of several sites, such as the urinary bladder (33) and oral mucosa (12). Collagen IV staining can be employed to demonstrate the basement membrane that separates normal epithelia and the underlying surrounding mesenchymal tissue; discontinuity or even complete loss of basement membrane is seen in some carcinomas.

Since many monoclonals and antisera are applicable on formalin-fixed, paraffin-embedded material (19, 32), the previously obtained clinical results

and archival material (biopsy specimens) can be approached from a new viewpoint.

The presented pilot study was conducted to explore the possibilities of relating retrospectively collected clinical data with histological findings using reevaluated HE and immunohistochemically stained slides. In addition, we attempted to assess morphological differences between the tumors in the two oropharyngeal subsites, that may possibly be related to their known different biological aggressiveness.

Materials and methods

Patients

This pilot study is based on a group of 29 patients (16 with tonsillar and 13 with base of the tongue carcinoma), out of totally 162 patients (94 with tonsillar and 68 with base of the tongue carcinoma), who were admitted for primary treatment to the Netherlands Cancer Institute between 1966 and 1985 and followed for minimally 3 years or till death. A detailed description of all patients, classification methods and treatment was published previously (25-27). In summary, the vast majority of patients in both groups was treated with external radiotherapy (86% and 90% respectively). The 94 patients with tonsillar carcinomas had a significantly higher tumor control rate (61% at 3 years) and overall survival (58%) than the 68 patients with base of the tongue carcinomas (3-year tumor control: 39% and survival: 36%, $p=0.007$ and 0.004, respectively (27)). The two groups of patients were similar with respect to possible prognostic factors: age, sex, intoxications, previous radiotherapy, TNM classification, radiation dose, size of radiation fields and overall treatment time (25). Significant differences between the two subsites were found only in the mean patient delay (3 months in tonsillar carcinoma versus 4.5 months in base of the tongue carcinoma, $p<0.05$) and in the incidence of patients with other severe disorders on admission (14% versus 28%, respectively, $p<0.05$). However, it seems unlikely that these parameters alone would account for the difference in tumor control rates, because they did not correlate significantly with the tumor size on admission, or with the choice of therapy (25-27).

This study is based on 29 patients in whom the pretreatment biopsy specimens of the primary tumor were readily available for a complete histopathological and immunohistochemical analysis. This subgroup has comparable patient characteristics, macroscopic tumor features and treatment as we reported in our former papers (25-27).

Twenty-two patients were males and 7 were females, with the median age of 70 (31-87) years. The T classification was as follows: 5 T1, 7 T2, 12 T3

and 5 T4 tumors (UICC 1982 classification and staging system) (37). Half of the tumors were ulcerating lesions, 8 were predominantly infiltrative, 3 submucous, whereas the remainder was exophytic or mixed with red or white precancerous lesions.

Histopathological studies

Formalin-fixed, paraffin-embedded sections of biopsy specimens were available in all instances. The slides were stained with haematoxylin and eosin, or according to routine immunohistochemical techniques. The following antibodies were used: polyclonal anti-collagen IV (Eurodiagnostics, 1:1000), a cocktail of monoclonal antibodies to bloodgroup A, B and H antigen (Dakopatts, 1:25) (Figure 6.1) and a monoclonal antibody recognizing keratin 10 (19) (K_{10}, kindly provided by Dr. D. Ivanyi, NKI, Amsterdam, 1:10) (Figure 6.2).

The following morphologic features were assessed semiquantitatively, using a standard scoring form: cytonuclear pleomorphism, mitotic activity, presence of atypical mitoses, keratinization, pattern of invasion, stromal eosinophilia, inflammatory infiltrate, tumor grade, expression of keratin 10, blood group antigens and collagen IV. All scores were reviewed by the first two authors (SMK and WJM) without prior knowledge of site and size of the primary lesion.

Statistical analysis

The morphological scores obtained on HE and immunostained slides were tabulated and cross-tabulated. Each variable was also analyzed with respect to the subsite. Of the macroscopic tumor characteristics, the T category and macroscopic growth pattern (infiltrative, submucous, exophytic or ulcerating) were taken into account. P-values were calculated using the corrected chi-square test, and considered significant when <0.05.

Results

The morphological features and their scores are listed in Table 6.1. The tumor cell populations in the two subsites were similar with respect to mitotic activity, the presence of atypical mitoses, and keratinization. Cytonuclear pleomorphism was more marked in tonsillar carcinoma.

Compact invading strands of tumor were seen in all instances. Perineural tumor growth and angioinvasion were detected only incidentally. Some stromal eosinophilia was found in 2 cases in each site.

In the immunohistochemical tests, a number of cases did not yield a clear staining pattern, and were discarded from the statistical analysis.

	Tonsillar region	Base of tongue	Total
Cytonuclear pleomorphism * :			
mild	0	3	3
moderate	14	6	20
strong	2	4	6
Mitotic activity:			
low	6	4	10
moderate	4	4	8
high	6	5	11
Atypical mitoses:			
none	4	5	9
sporadic	8	7	15
few	4	1	5
many	0	0	0
Keratinization ** :			
none	2	2	4
trace	5	4	9
moderate	4	3	7
marked	4	4	8
Inflammatory infiltrate:			
none	1	0	1
sparse	5	2	7
moderate	5	8	13
heavy	5	3	8
Stromal eosinophilia:			
absent	14	11	25
present	2	2	4
Tumor grade:			
undifferentiated	1	0	1
poorly differentiated	4	5	9
moderately differentiated	7	7	14
well differentiated	4	1	5

* p=0.04 (between the subsites)
** 1 missing value in tonsillar carcinoma

Table 6.1. Tabulation of the tumor characteristics tested on HE-stained slides. Figures represent numbers of patients.

A difference by site was seen only in case of collagen IV, which was more often positive in tumors of the base of the tongue (Figure 6.3) than in those of the tonsillar region (Figure 6.4), (Table 6.2) .

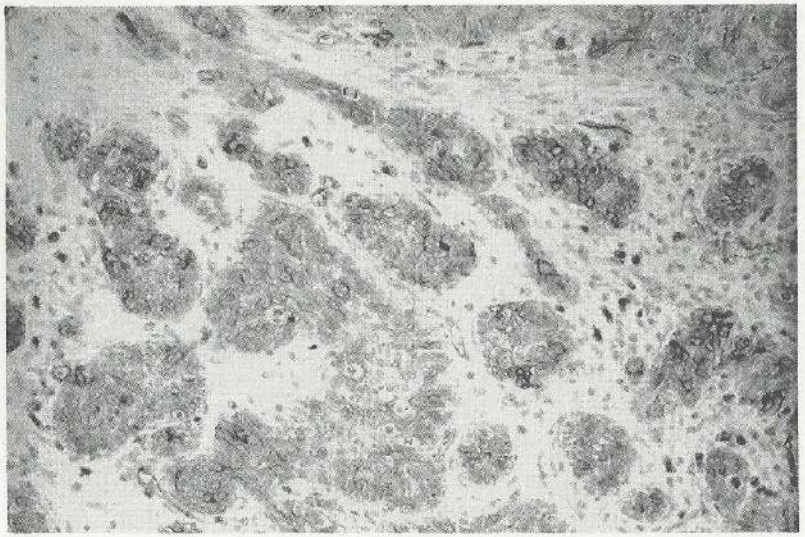
	Tonsillar region	Base of tongue	Total
K_{10}:			
++	4	1	5
focally +	3	6	9
sporadic positive cells	1	0	1
no staining	4	6	10
missing	4	0	4
Collagen IV:			
continuous BM staining	2	6	8
focally strongly posit.	1	2	3
focally weakly positive	7	2	9
no staining	1	1	2
missing	5	2	7
ABH:			
+++	5	5	10
positive	3	4	7
weakly positive	2	3	5
no staining	2	1	3
missing	4	0	4

Table 6.2. Tabulation of the tumor characteristics tested on Mabs-stained slides.

Relation between the obtained scores

All tested parameters were crosstabulated (Table 6.3). A proportional increase in frequency of mitoses and of the presence of atypical mitoses was observed ($p=0.01$). Mitotic activity was significantly higher in less differentiated tumors ($p=0.01$). Low mitotic activity was associated with strong keratinization ($p=0.04$). Atypical mitoses were more common in less keratinizing tumors ($p=0.03$). More keratinization was seen in better differentiated tumors ($p=0.04$). A higher K_{10} expression was found in the better differentiated tumors ($p=0.01$). In tumors with no K_{10} expression a trend towards higher mitotic activity was observed; focally strong K_{10} expression was associated with low mitotic activity ($p=0.009$). Expression of collagen IV was higher in cases of more pronounced peritumoral inflammation ($p=0.03$).

Crosstabulation with macroscopic features of the tumors, i.e. the clinical aspect of lesions and the T category did not reveal association with any of the variables tested.



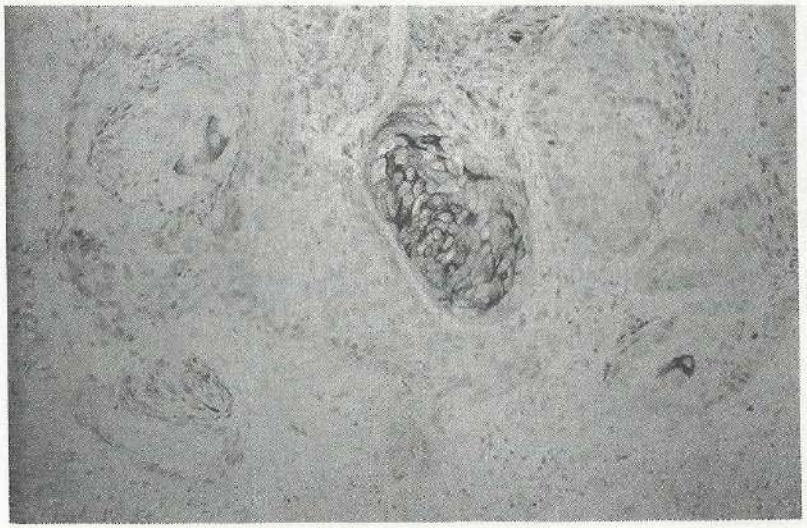
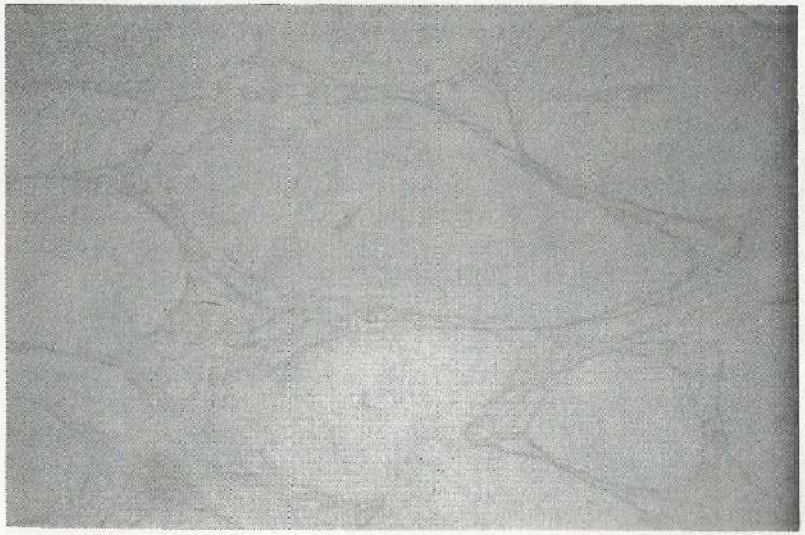


Figure 6.1. (above) Squamous cell carcinoma, base of tongue. Blood group immunostaining, showing strong positivity of all tumor cells.

Figure 6.2. (below) Squamous cell carcinoma, base of tongue. K_{10} immunostaining, showing focal positivity in tumor cell nests.



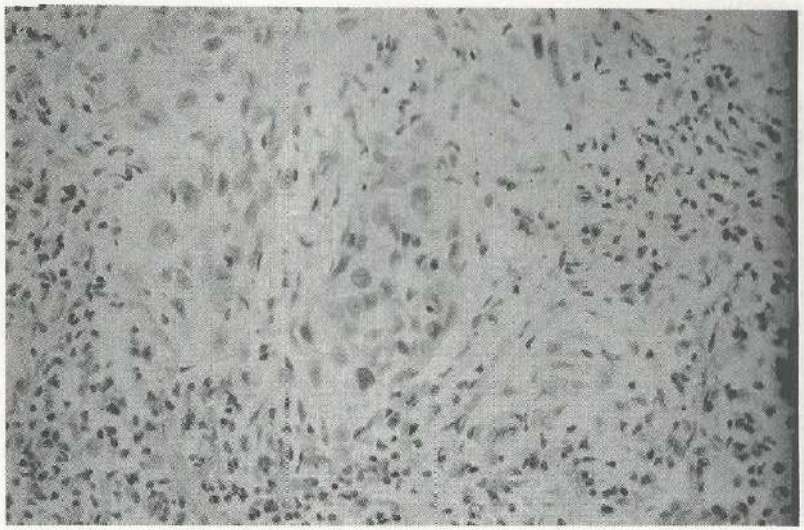


Figure 6.3. (above) Squamous cell carcinoma, base of tongue. Collagen IV immunostaining, showing an almost continuing basement membrane surrrounding large nests of tumor cells.

Figure 6.4. (below) Squamous cell carcinoma, tonsil. Collagen IV immunostaining, showing absence of basement membrane around tumor cell nests.

	Mitoses				
Atyp.mitoses	0.01	Atyp.mitoses			
Keratinizat.	0.04	0.03	Keratinizat.		
Tumor grade	0.01	NS	0.04	Tumor grade	
K_{10}	0.009	NS	NS	0.01	Inflam.
Collagen IV	NS	NS	NS	NS	0.03

Table 6.3. Crosstabulation of the tested parameters. Only the p-values < 0.05 are presented (NS=not significant).

Discussion

In a number of previous papers on head and neck carcinomas, the morphologic parameters tested in this study were demonstrated to correlate to each other (21, 22), to outcome after treatment (7, 8, 16), or to survival rates (2, 24, 28-30). However, these features have not yet been standardized in a system of distinct categories of tumor differentiation, that would allow a reliable comparison of results from different studies. Several semi-quantitative grading systems employing these factors have been proposed (1, 22, 24), but none of them has become widely accepted. Tumor grading remains a relatively subjective matter, difficult to reproduce by other investigators (3, 9, 11, 16, 36).

In analyzing the errors occurring with the use of Jakobsson's grading system (21, 22), Anneroth and Hansen identified 3 main sources of error: the absence of a clear definition of morphological parameters, possible interactions between the used variables, and technical shortcomings (1). We have attempted to standardize the categories and related scores in order to overcome the first error. We feel that a consistent use of a standardized checklist (possibly employing additional parameters), may generate relevant data in larger series to support our clinical findings, despite the fact that in this limited number of patients insufficient evidence was obtained. The second problem, of technical shortcomings however, remained unsolved. For example, the material sometimes precluded the assessment of some

parameters associated with the tumor-host relationship: perineural growth and angioinvasion of tumor are more likely to be detected on surgical specimens than on biopsy material. Stromal eosinophilia, that was suggested to carry a favorable prognostic significance by Goldsmith et al (16), was present only incidentally in our material, and was never massive.

Crosstabulation of the tested parameters revealed some expected outcomes in this study: correlation between a high mitotic activity and the presence of atypical mitoses, keratinization, and the tumor differentiation, respectively, as well as between K_{10} expression and tumor differentiation. Absence of correlation between keratinization and K_{10} expression was consistent with some observations in early stages of vulvar squamous cell carcinoma, as reported by Ivanyi et al. (20). The authors suggested the irregular expression of K_{10} during the tumor development, as possible explanation for their results.

The relevance of the parameters tested has not yet been demonstrated specifically for the subsites of oropharyngeal carcinoma, possibly due to the relatively low incidence of these tumors. Therefore, we attempted to assess the morphological difference between tonsillar carcinomas and carcinomas of the base of the tongue. The only significant difference between the subsites, i.e. the degree of cytonuclear pleomorphism, does not appear to provide sufficient explanation for the observed different biologic behaviour of these tumors. Some difference in expression of collagen IV was seen between the subsites, but this did not reach the level of significance in this series, possibly due to the small sample size and the high rate of non-evaluable slides (25%). However, studies of the basal membrane might appear more promissing in obtaining additional prognostic tumor characteristics. Other methods, such as flow cytometric DNA ploidy measurements, which have been shown to have prognostic value in T1 glottic carcinoma (38), should be evaluated with respect to substantiating the different biologic aggressiveness of these two most frequent tumors in the oropharynx.

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CHAPTER 7.

Sporadic lesions in the oropharynx: Clinical and therapeutic aspects of carcinoma of the soft palate and the posterior pharyngeal wall

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Abstract

From 1966-1984, 14 patients with carcinoma of the soft palate and 8 patients with posterior oropharyngeal wall carcinoma were submitted for primary treatment with curative intent to the Netherlands Cancer Institute. In the soft palate group, the majority of patients (10) had small tumors (T1-T2); the median patient's delay was 1 (0-5) month(s). Eleven patients were treated with radiotherapy and 3 with surgery, as single treatment modalities. Tumor control was achieved in 10 patients following the initial treatment. Five-year results for tumor control and overall survival were 67% and 41%, respectively.

In the posterior wall group all patients had advanced tumours (T3-T4), after a median patient's delay of 4 (0-6) months. Six patients were treated with radiotherapy, one with surgery only and one with a combination of these. Following the initial treatment, tumor control was achieved in half of the patients. Five-year tumor control was thus 50%, overall survival at 5 years was 38%.

In conclusion, the tumors in these two sporadic subsites of the oropharynx differ significantly in the extent of the primary tumor ($p<0.01$), posterior wall tumors being more advanced on first admission, after a significantly longer history of complaints ($p<0.01$).

Keywords: *carcinoma of the soft palate, carcinoma of the posterior oropharyngeal wall, tumor control, survival*

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Introduction

Carcinomas of the oropharynx count for 0.3-0.5% of all malignancies (17, 20), whereas only 5-20% of them rise from the soft palate/uvula or the posterior wall (17, 19, 34, 39). Tumors in these uncommon subsites are often included in studies of head and neck carcinoma (3, 5, 7, 9, 10, 12, 15-17, 29, 34), but are only occasionally specified in the results (9, 10). A limited number of papers have dealt particularly with soft palate cancers (1, 8, 13, 14, 19), whereas the posterior wall of the oropharynx is regularly combined with the hypopharyngeal posterior wall (25, 27, 38), and never specified in the results. We have demonstrated the prognostic value of subsite within the oropharynx, when the tonsillar region and the base of the tongue are considered (21-24). Therefore, we feel that the results of treatment in the more sporadic oropharyngeal subsites should be presented separately as well.

The optimal treatment in these rare tumors has not been agreed upon. Management of carcinoma of the soft palate involves surgery (8, 13), radiotherapy (1, 8-10, 13, 14, 19, 31), or a combination of both (8, 13), with an obvious prevalence of papers on radiotherapy. Generally, 5-year survival rates are about 40%, regardless of treatment modalities.

Treatment of tumors of the posterior wall is troublesome because of the close anatomical relation to the cervical vertebrae and the spinal cord, limiting the extent and margins of both radical surgery and radiotherapy. Poor survival rates due to uncontrolled tumor in the locoregional site seem thus inevitable (27, 36).

Materials and methods

From 1966 till 1985, 212 patients with squamous cell carcinoma of the oropharynx were admitted to the Netherlands Cancer Institute. Of these, 18 (8%) patients had carcinoma of the soft palate/uvula and 10 (5%) patients had carcinoma of the posterior pharyngeal wall. Of the patients with carcinoma of the soft palate, 3 were referred for recurrent disease after treatment elsewhere and one patient received only palliative radiotherapy to massive neck nodes. Of the patients with the carcinoma of the posterior wall, 1 was referred for a recurrence after radiotherapy elsewhere.

Fourteen patients with histologically proven squamous cell carcinoma of the soft palate/uvula and 8 of the posterior pharyngeal wall, who were scheduled for primary treatment with curative intent, will be presented in this paper.

Patients

Carcinoma of the soft palate and uvula

The median age of 14 patients (11 men and 3 women), was 68 (46-83) years. Thirteen (93%) patients were known as smokers, 9 (64%) also for drinking alcohol. One patient received radiotherapy for a carcinoma in the oral cavity prior to the current disease. One patient was in poor general condition on admission due to other disorders. Of the 6 (43%) patients with second primaries (2 in history and 4 metachronously to the carcinoma of the soft palate), 4 had cancers in the oral cavity, one in the oesophagus and one in the prostate. The median delay was 1 (0-5) month(s). The most frequent presenting symptoms were pain (6) and dysphagia (4 patients).

Carcinoma of the posterior oropharyngeal wall

The median age of the 8 patients (7 men and 1 woman) was 67 (44-82) years. Six patients (75%) were recorded as smokers; 6 (75%) had a history of alcohol abuse. One patient received radiotherapy for glottic carcinoma prior to the current disease. Five patients (63%) were in poor general condition due to other diseases on admission. The median delay was 4 (0-6) months. Te most frequent presenting symptom was dysphagia (4 patients).

Treatment

In the study period, megavoltage radiotherapy delivered through two opposing lateral fields with Cobalt 60 equipment or an 8 MV linear accelerator was the treatment of choice in both subsites. Usually, the total dose was 70 Gy delivered in 2 Gy fractions. No interstitial radiotherapy was given in this period. From 1975-1978, facilities for treatment with fast neutrons were available for experimental therapy (2); this was given to one patient from this series. Occasionally, patients in good general condition and with small tumors were submitted to surgery (local excision for tumors confined to primary site, or a composite resection with radical neck dissection in case of lymphnode metastases), with or without postoperative radiotherapy. The defects were closed with split skin grafts and maxillary resectional prostheses in the palatal site.

Methodology

All but one patients were followed for minimally 3 years, or untill death; one patient was lost to follow-up at 30 months. Tumor-free interval is defined as the time between the start of treatment and the first evidence of recurrence or metastasis. Recurrence is a new manifestation of tumor in a

previously treated area. Tumor found in an area that was not treated before is considered metastatic. Residual tumor is defined as a lesion not completely disappearing after the initial treatment.

Patients were compared with analysis of contingency tables, or with the two-sample t-test (28). Overall survival and tumor-free interval were calculated using the Kaplan-Meyer method (18).

Results

Carcinoma of the soft palate/uvula

Staging and treatment

All 14 patients were staged according to the UICC classification from 1982 (37) (Table 7.1). Eight patients had small tumors confined to the primary site (T1-T2). Eight patients had ulcerating lesions. Concomitant premalignant changes in the oral and/or oropharyngeal mucosa were not seen. Regional metastases were palpated in only 2 patients.

Eleven patients received radiotherapy to the primary site and high jugular/subdigastric lymphnodes. Three patients were submitted to surgery as a single treatment modality.

Tumor control

Following the initial treatment, tumor control was achieved in 10 patients (71%). In one patient residual tumor was persisting at the primary site. One patient developed a local recurrence. Two patients developed contralateral regional metastases. Distant metastases were not found. All failures occurred within 2 years after radiotherapy. An overview of all patients with regard to extension of the disease, treatment, effect of treatment and follow-up is presented in Table 7.2.

	T1	T2	T3	T4	Total
N0	4 / 0	4 / 0	2 / 2	2 / 2	12 / 4
N1	1 / 0	1 / 0	0 / 2	0 / 0	2 / 2
N2	0 / 0	0 / 0	0 / 1	0 / 0	0 / 1
N3	0 / 0	0 / 0	0 / 1	0 / 0	0 / 1
Total	5 / 0	5 / 0	2 / 6	2 / 2	14 / 8

Stage I	4 / 0	patients
Stage II	4 / 0	patients
Stage III	4 / 4	patients
Stage IV	2 / 4	patients

Table 7.1. Distribution of patients with carcinoma of the soft palate/posterior pharyngeal wall by the T and the N category and the stage of the disease according to UICC (1982) staging system.

Complications of treatment

In this series one patient (nr. 13 in Table 7.2) developed osteomyelitis of the mandible that required additional surgical treatment.

Patient	TNM	Treatment	Effect	Tumor -free	Follow up	Vital status
1	T2N0	RT	L res.	0	8	DOD
2	T1N0	Lex	NED	11	11	DNED
3	T1N0	RT	NED	4	4	DNED
4	T3N0	RT	NED	207	207	DNED
5	T2N0	RT	NED	45	45	DNED
6	T4N0	RT	NED	188	188	ANED
7	T1N0	RT	NED	51	51	ANED
8	T4N0	RT	R met.	3	22	DOD
9	T2N0	RT	NED	30	30	DNED
10	T1N1	RT	R met.	23	30	ANED
11	T3N0	RT	NED	20	20	DNED
12	T2N0	Lex	NED	79	79	ANED
13	T2N1	Com	NED	78	78	ANED
14	T1N0	RT	L rec.	21	31	DNED

Legend:

Tumor-free	=	tumor-free interval (in months)
Follow-up	=	length of the follow-up (in months)
RT	=	radiotherapy
Lex	=	local excision
Com	=	composite resection (primary tumour and ipsilateral neck nodes)
L res.	=	local residual tumour
NED	=	no evidence of the disease
L rec.	=	local recurrence
R met.	=	regional metastasis
DOD	=	dead of disease
ANED	=	alive, no evidence of disease
DNED	=	dead, no evidence of the disease

Table 7.2. Extension of the disease, treatment, and follow-up of 14 patients with carcinoma of the soft palate.

Follow-up and survival

The patient with residual tumor was not treated further and he died 8 months after the onset of initial treatment. Of the 2 patients with contralateral lymphnode metastasis, one died with locoregional tumor after 22 months despite aggressive salvage therapy, whereas in the other patient the tumor was controlled with curative radiotherapy to the contralateral neck nodes. In the patient with local recurrence tumor control was achieved after a composite resection and postoperative radiotherapy. In this subsite, tumor was ultimately controlled in 12 of 14 patients (86%).

The 2 year tumor control rate was 67% (Figure 7.1). Overall survival was 49% and 41% at 3 and 5 years, respectively (Figure 7.2).

Carcinoma of the posterior oropharyngeal wall

Staging and treatment

All patients had advanced tumors, T3 (6 patients) and T4 (2 patients). The aspect of the lesion was ulcerous (5 patients), exophytic (2 patients) and infiltrative (1 patient). In 2 cases also concomittant leukoplakia was present. Half of the patients had lymphnode metastasis on admission (Table 7.1).

Of the 6 patients who were scheduled for radiotherapy, 2 discontinued the treatment due to poor condition. One patient was treated with fast neutrons. In one patient a local excision was performed, and another patient underwent a composite resection and planned postoperative radiotherapy.

Tumor control

Of the 6 patients who completed the treatment, tumor control was achieved in 4. Of the remaining 2 patients, 1 had residual tumor in the primary site, and 1 developed lung metastases 6 months after the start of therapy. Overview of all patients with regard to extension of the disease, treatment, effect of treatment and follow-up is presented in Table 7.3.

Complications of treatment

During the course of radiotherapy one patient (nr. 7 in Table 7.3) developed edema that caused fatal respiratory insufficiency, despite emergency-tracheotomy. Another patient (nr. 5 in Table 7.3), who was in poor general condition on admission died 6 months after the end of radiotherapy due to deterioration of his preexisting respiratory disease. One patient (nr. 8 in Table 7.3) who was treated with surgery and postoperative radiotherapy developed a mild fibrosis in the neck.

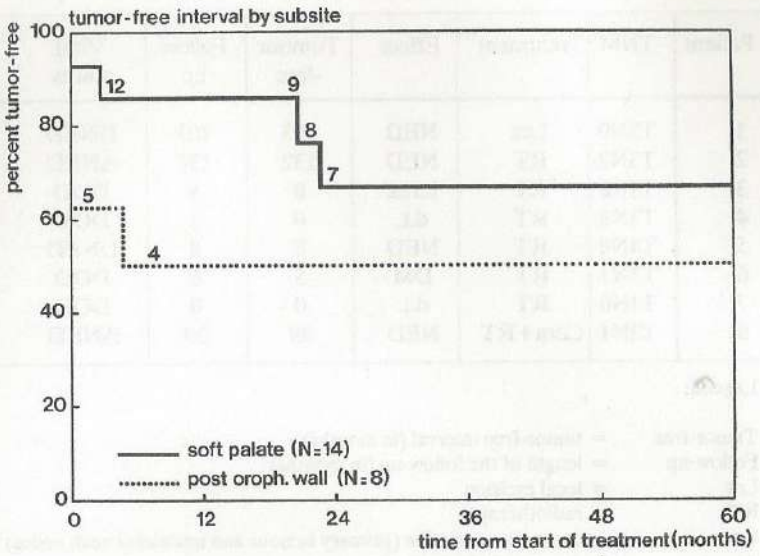

Figure 7.1. Tumor-free interval in 14 patients with carcinoma of the soft palate and 8 patients with posterior wall carcinoma.

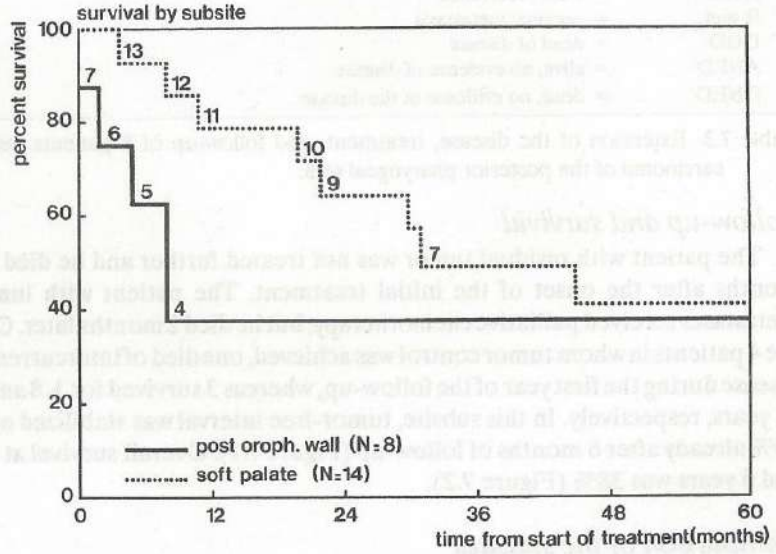

Figure 7.2. Overall survival of 14 patients with carcinoma of the soft palate and of 8 patients with posterior wall carcinoma.

Patient	TNM	Treatment	Effect	Tumour -free	Follow up	Vital status
1	T3N0	Lex	NED	103	103	DNED
2	T3N2	RT	NED	132	132	ANED
3	T3N0	RT	L.res.	0	5	DOD
4	T3N3	RT	d.t.	0	2	DOD
5	T4N0	RT	NED	8	8	DNED
6	T3N1	RT	DM	5	8	DOD
7	T4N0	RT	d.t.	0	0	DOD
8	T3N1	Com+RT	NED	39	39	ANED

Legend:

Tumor-free	= tumor-free interval (in months)
Follow-up	= length of the follow-up (in months)
Lex	= local excision
RT	= radiotherapy
Com	= composite resection (primary tumour and ipsilateral neck nodes)
d.t.	= discontinued treatment
L res.	= local residual tumour
NED	= no evidence of disease
DM	= distant metastases
L rec.	= local recurrence
R met.	= regional metastasis
DOD	= dead of disease
ANED	= alive, no evidence of disease
DNED	= dead, no evidence of the disease

Table 7.3. Extension of the disease, treatment, and follow-up of 8 patients with carcinoma of the posterior pharyngeal wall.

Follow-up and survival

The patient with residual tumor was not treated further and he died 5 months after the onset of the initial treatment. The patient with lung metastases received palliative chemotherapy, but he died 2 months later. Of the 4 patients in whom tumor control was achieved, one died of intercurrent disease during the first year of the follow-up, whereas 3 survived for 3, 8 and 11 years, respectively. In this subsite, tumor-free interval was stabilized on 50% already after 6 months of follow-up (Figure 7.1). Overall survival at 3 and 5 years was 38% (Figure 7.2).

Comparison of the subsites

The subsites were compared with respect to patient's delay, tumor stage, tumor control and survival. There was no difference in age and male:female ratio. Distribution by both the T category and stage of the disease appeared significantly different ($p<0.01$ in both cases), posterior wall tumors being in a higher stage. The delay was significantly longer in patients with with posterior wall tumors ($p<0.01$). A comparison of the tumor-free interval and crude survival between the two subsites did not reveal a statistically significant difference.

Discussion

Addressing the problem of an uncommon disease, the literature on carcinomas of the oropharynx and its subsites inevitably suffers from limited numbers of patients. In attempts to cope with ambitious scientific questions, head and neck tumors are often considered to be one oncological entity. Relatively large groups of patients that are obtained and analyzed, may deliver statistically significant answers, but the resuls are not directly applicable to small subgroups in the total patients population. Also in recently published large reports on incidence, treatment and survival of patients with head and neck cancer, the data related to these oropharyngeal subsites are merged with other head and neck regions (4, 15).

Unlike tumors in other subsites of the oropharynx, carcinomas of the soft palate can, due to their localization and interference with normal functions, be diagnosed at an early stage. Often these tumours cause pain and disorders in deglutition, and when asymptomatic, they still can be seen by the patient or the physician, particularly if located around the midline (13). In this series 70% of the patients with soft palate tumors had T1-T2 lesions, a distribution similar to other reports (1, 8, 14). For comparison, the proportion of patients with T1-T2 tumors in carcinoma of the tonsillar region and the base of the tongue in the same period was only 47% and 34%, respectively (22, 24).

Soft palate is, together with the anterior tonsillar pillar, considered prone to field cancerization and multifocal tumor growth (9, 11, 33), a phenomenon that is probably related to excessive exposure to carcinogenes and promoting factors (11, 32). In this series, however, no multifocal tumors or premaignant mucosal changes were seen, despite the vast majority of patients having been exposed to carcinogenic effects of tobacco (93% and alcohol (64%). The incidence of metachronous primaries, that ranges from 15-21% in soft palate carcinomas (1, 14, 31), was somewhat higher in our series (28%). As expected, most of these second primaries were localized in the head and neck region.

Preference for radiotherapeutic management of soft palate cancer is based on the presumed multifocal growth, and on a better preservation of phonation and deglutition compared to surgery (14). In planning the treatment of the regional nodes however, both the nodal involvement and risk for second primaries need to be considered. Despite some discussion in the literature about the need for elective radiotherapy of the neck in all patients with cancer of the soft palate (1, 13), the neck problem seems less important in this site (19).

Absolute 5-year survival in patients with soft palate carcinoma treated with radiotherapy ranges from 32-50% (8, 9, 19, 31). In patients treated with surgery a 40% 5-years survival was reported (8), but surgery seems reserved for smaller unifocal lesions (8). In our limited series, a 41% 5-years survival was obtained on patients who were of a somewhat higher age than in other series (median age of 68 years, versus 57-61 years (1, 8, 14, 19, 31)). With external radiotherapy, local control rates of about 75% are feasible (14, 31). Interestingly, improvement up to 92% of local control that was achieved with interstitial application of Ir-192 (6, 26, 30) did not lead to a better 5-year survival; due to occurrence of fatal metachronous tumors this remained about 35%.

Most tumors of the posterior wall are advanced when diagnosed (27, 36). They tend to spread superficially and form large lesions, but remain limited in deep invasion by the prevertebral fascia, which seems to be an anatomical barrier. However, it is remarkable to observe that these large mucosal lesions give relatively few symptoms. Possibly, the poor sensory innervation of the posterior wall, with its passive role in deglutition, in contradistinction to the rich sensitive innervation of the palatal arch and its active role in deglutition, may explain the more 'silent' growth of tumors in this subsite.

All patients with posterior wall cancers in this series had T3-T4 tumors. In addition, half of our patients were suffering from other diseases on admission. These unfavorable host- and tumor factors, aggravated by limited possibilities for radical treatment due to the anatomical reasons mentioned earlier, pose a paramount problem in management of patients with tumors in this subsite. Following the treatment, complications like airway obstruction or pharyngocutaneous fistula were reported to follow in about half of the patients (25, 36).

Five-year survival rates reported in the literature range from 3%-32% (25, 27, 36, 38). However, in all previous series, the posterior wall of the hypopharynx, which is associated with a poorer survival, is included with the

oropharyngeal lesions. Our results, obtained on a very limited group of relatively old patients (median age of 67 years, versus 60-62 years reported by other authors in the literature (25, 27, 36, 38)), having all T3-T4 tumors, seem acceptable (38% at 5 years). Improvement of the local control is suggested by the use of peroral implants followed by megavoltage radiotherapy (35, 36). Son and Kacinski (35) obtained a remarkable 82% 5-year survival in 14 patients treated with either an Ir-192 ribbon looping method, or I-125 brachytherapy, both in combination with megavoltage radiotherapy (35).

When compared with the figures we reported from other oropharyngeal subsites, the 5-year survival in tumors of the soft palate (41%) and of the posterior wall (38%) approximate the results in the tonsillar region (43%) (22), and are substantially higher than in the base of the tongue (22%) (24). Based on the literature one would expect the results in the posterior wall cancer to be very poor, and closer to the figures obtained in base of the tongue tumors.

In conclusion, specific problems of different oropharyngeal subsites need to be addressed on the related patient populations, be it as subgroups in studies of head and neck cancers, or in separate reports. Recognizing the limitation of small series, we notice a trend towards favourable results in the two sporadic subsites of oropharyngeal carcinomas in comparison to our patients treated for other cancers in the oropharynx during the same period. External radiotherapy will remain the treatment of choice in both subsites.

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CHAPTER 8.

General discussion

As stated in the preface, this study was conducted in order to answer three questions:

1. What is the optimal treatment modality in carcinomas of the oropharynx,
2. Is the new classification and staging system (UICC 1987) an improvement with respect to prognosis of tumor control, and
3. Can the subsite be seen as an independent prognostic factor for tumor control in oropharyngeal carcinomas?

From 1966-1984, radiotherapy appears to have been the treatment of choice, delivered to 86% of our patients. The low rate of patients undergoing surgery hampers any meaningful comparison. In addition, the criteria for a specific treatment were not standardized or clearly recorded, which meant that some unspecified selection of patients must be considered in retrospect. With such a high risk of bias in case of comparison of these treatments, the only valid conclusion from this patient material remains that radiotherapy was the most frequently given treatment. The effects of different treatments in terms of tumor control and survival could not be compared in a meaningful manner.

Another effect of the obvious preference for radiotherapy in this series was seen in the staging of the disease. Whereas the primary tumor had to be histologically proven prior to treatment, the staging of the neck nodes was based on clinical assessments only. Knowing the marked inaccuracy of palpatory-based diagnosis in the neck (11, 14), and the importance of lymphnode involvement in prognosis of head and neck tumors (that has been demonstrated using *postsurgical* staging) (11, 12, 31), in combination with the fact that in none of the tested sites a relation could be seen between the N-stage and tumor control in this series, we consider the N-stages in this series unreliable in retrospect. This finding eliminated further possibilities to study the prognostic impact of the new classification in our patients. The interaction between treatment and staging in this series has also been discussed in a magisterial dissertation at the University of Zagreb. (33).

The prognostic value of the two staging systems has been studied previously in our Institute by Bartelink (5). He demonstrated that the

UICC(1978) and AJCC(1977) staging systems (the latter being almost identical to the UICC(1987) system we tested) had the same impact in patients with lymphnode metastasis from carcinoma in head and neck region. Noteworthy, that paper was based on 233 patients with regional metastasis from all head and neck sites, which is probably a more suitable model for studying staging systems that differ only in N categories.

Remarkable differences in results obtained in tonsillar and base of the tongue carcinoma, together with the leading role of the T category in prognosis of the tumor control in our patients, substantiated the feeling that the subsite may have a role in prognosis. As mentioned before, many published papers dealing with carcinoma of the tonsillar region, (4, 6, 15, 18, 20, 21, 30, 39), base of the tongue (3, 10, 17, 21, 28, 37, 43, 45), or oropharyngeal carcinomas in general (where results are split up by the subsite) (29, 40, 49), support these observations. Nevertheless, these papers address the two tumors separately, without further comparison of results with respect to the subsite. We have focussed on the similarities and differences between the patients, tumors, and treatment, in order to assess the effect of the subsite on the outcome after treatment. Having seen significant differences only in patients delay and rate of patients suffering from other diseases on admission, but not in any of the parameters directly related to tumor control neither in our patients nor in the literature, we could conclude that the subsite within the oropharynx has an independent role in prognosis.

Next step towards a better understanding of the results obtained up to that moment, was a histopathological assessment of these tumors. For several reasons a pilot study needed to be conducted first:

1. For the revision of the slides a new checklist was designed, which needed to be tested for feasibility and supplementary value compared to earlier procedures.
2. Because most antibodies used in the immunohistochemical analysis were not tested in these tumors before, baseline references had to be formulated first.

The checklist employing a semi-quantitative approach, that included histopathological parameters previously demonstrated to have a prognostic significance in head and neck tumors (2, 7, 22, 27, 42) in addition to customarily used histopathological grading, appeared to be useful for a consistent revision of slides. The benefit is expected in larger series, particularly if surgical specimens can be revised, leading to the accrual of better ordered data which will facilitate future analyses.

Some patterns in the antibody staining were identified, but their relevance in relation to macroscopic tumor aspects and prognosis has to be studied further. Some technical matters need to be solved also, before a meaningful study of parameters possibly explaining different biologic aggressiveness can be conducted. For example, the exact meaning of the absence of collagen IV staining around the tumor needs to be sorted out: is this a technical shortcoming of the staining procedure, or has the basement membrane been destroyed? In case of keratin 10 (K_{10}), the incongruence between the expression of K_{10} and keratinization as detected on HE slides over different phases of keratinization (26) needs to be fully understood before focussing on prognostic value of this method. For these reasons revision of the remaining biopsy specimens was discarded.

Thus, an intrinsic difference between the two most frequently involved subsites with respect to outcome after treatment could be demonstrated, but the substrate of their different behavior could not be identified. The interaction of unfavorable tumor and host characteristics, tumors often being advanced on first admission and patients having poor general health was in our series particularly pronounced in the base of the tongue group. Conventional radiotherapy -the treatment of choice- cannot provide a satisfactory local control, whereas surgery -a possible alternative- is often not feasible due to the advanced tumor requiring extensive resections and postoperative radiotherapy and because of patients' poor condition. The vicious circle seems closed; another, more efficient treatment is needed. Accelerated radiotherapy (1, 24, 47), or a combination of external and interstitial radiotherapy (23, 32, 41) might appear to be more suitable treatment modalities in this subsite. On the other hand, if more aggressive therapies are applied, a refinement in diagnostics and identification of patients with high risk of recurrence within a given T-stage, are mandatory. Studies of potential doubling time in tumor cell populations (8, 9, 19, 48), DNA-ploidy (50), and tumor thickness measurements (36, 46) might appear to be useful in identifying these patients.

Extrapolating the observations obtained on the frequently involved subsites to the sporadic ones, i.e. soft palate and posterior wall, we analyzed these two groups of patients separately as well. Interestingly, even on the small numbers of patients (14 versus 8), the stage of the disease on admission appeared to be significantly different between these subsites.

Specific problems following treatment in these two diseases are reported to be different as well: in early detected tumors of the soft palate reasonable curation rates are feasible, leading to an increased risk of death from

metachronous primaries (13, 16, 25, 35, 44). In patients with posterior wall tumors, second primaries do not play such an important role. The index tumor more often appears fatal (34, 38), 'preventing' patients from developing a second tumor; a reason to assess each of these sporadic diseases as an separate entity as well.

Guidelines for predicting tumor control in patients with a squamous cell carcinoma in the oropharynx

Based on the results from this study and from the literature, guidelines for a global prediction of tumor control in individual patients with a carcinoma in the oropharynx are tentatively formulated. The 4 groups with distinct probabilities of achieving and maintaining tumor control with external radiotherapy equivalent to 60-70 Gray in 6-7-weeks are defined based on the two dominant prognostic factors in our material, i.e. the T category and the subsite (Table 8.1). Ideally, additional features related to tumor control and survival, such as lymphnode metastases, other diseases, smoking and sex, will contribute to further prognostic refining in each patient.

Prognostic group	Subsite	T stage	Tumor control
I	tonsil base of tongue soft palate	T1-T2 T1 T1-T2	>=70%
II	tonsil soft palate posterior wall	T3 T3-T4 T3-T4	45-65%
III	tonsil base of tongue	T4 T2-T3	30-40%
IV	base of tongue	T4	=<25%

Table 8.1. The four distinct groups of patients with respect to tumor control. In individual patients also the N stage, presence of other disorders, smoking and sex should be taken into account, as to approximate their probability of survival with no evidence of the disease.

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SUMMARY

In this study, squamous cell carcinomas arising in the oropharynx were reviewed with respect to three prognosis-related issues, i.e. treatment, UICC(1987) classification, and the role of the subsite, as the central objective.

In *Chapter 1.* a general introduction to squamous cell carcinoma of the oropharynx is given along with an overview of all patients treated in the Netherlands Cancer Institute from 1966-1984 in relation to published series with respect to socio- demographic factors, tumor extent, treatment, tumor control and survival. Based on these parameters, the studied population appears to correspond well with other published series (5-year tumor control of 50% and overall survival of 32%).

In *Chapter 2.* the patients with carcinoma of the tonsillar region are presented. Radiotherapy was the treatment of choice during the whole study period, leading to a situation in which any meaningful comparison between treatment modalities becomes obsolete. This also affects the evaluation of the UICC(1987) classification with respect to prognosis: palpatory-based diagnostics of the regional lymphnodes and absence of pathological staging in the vast majority of patients does not provide a reliable basis for the N staging, or evaluation of its prognostic value. A 5-year tumor control rate of 57% was obtained, the overall survival in the same time was 43%; the T category emerges as the leading prognostic factor for tumor control.

In *Chapter 3.* the staging and prognosis in base of the tongue carcinomas are addressed. Again, the vast majority of patients has been treated with radiotherapy only. Similar to tonsillar carcinoma, the T category appears to be the single most important prognostic factor for tumor control, whereas N staging purely based on palpation must be considered unreliable in retrospect. The 5-year tumor control and overall survival are 36% and 22%, respectively.

In *Chapter 4.* a clinical comparative study of the two major oropharyngeal subsites, i.e. tonsillar region and base of tongue, is presented. There is no statistically significant difference in tumor and patient related parameters between both subsites, except for the length of the delay and the rate of patients in poor general condition on admission. However, these differences cannot provide a satisfactory explanation for the significant difference in tumor control rates, which appear to exist between the tonsillar region and base of the tongue.

An analysis of patients treated with radiotherapy (*Chapter 5.*) shows no significant difference with respect to the dose and overall treatment time in both subsites. Nevertheless, 3-year local control rates in the tonsillar region and the base of the tongue were significantly different (82% and 61%, respectively, p=0.04). T-stage and subsite were independent prognostic factors of local control before radiotherapy; response at the end and 6 weeks after the end of radiotherapy have additional prognostic value for local control, irrespective of the initial stage and subsite.

In *Chapter 6.* an attempt to assess morphologic differences between the two major oropharyngeal subsites is presented. The results obtained in a histopathological pilot study could not contribute to a further understanding of the difference in biologic aggressiveness of the tumors in these subsites. However, some insight in the patterns of expression of keratin 10 and collagen IV was achieved.

Chapter 7. contains reviews of the two sporadically involved subsites in the oropharynx, i.e. the soft palate and the posterior wall. Squamous cell carcinomas in these localizations appear to form separate entities with respect to their natural history, symptomatology and stage of the disease on admission. The 5-year tumor control (67% in the soft palate group and 50% in the posterior wall) and survival (41% and 38%, respectively) are not substantially different in these limited groups.

In *Chapter 8.* the presented papers are discussed. The issue of subsite in relation to the prognosis is readdressed, and tentative recommendations for categorizing oropharyngeal carcinomas with respect to the T category and the subsite are formulated.

SAMENVATTING

In dit proefschrift wordt een retrospectief onderzoek naar het plaveiselcelcarcinoom uitgaande van de oropharynx beschreven. In het bijzonder wordt ingegaan op de invloed van behandeling, UICC(1987) classificatie en tumorlokalisatie op de prognose.

Hoofdstuk 1 bevat een algemene inleiding tot het plaveiselcelcarcinoom van de oropharynx en een globaal overzicht van de patiënten die in de periode 1966-1984 behandeld zijn in Het Nederlands Kanker Instituut. De bestudeerde patiënten populatie blijkt, wat betreft sociodemografische factoren, tumoruitbreiding, behandeling, tumorcontrole en overleving, overeenkomstig te zijn met andere gepubliceerde series (een 5-jaars tumorcontrole van 50% en een ruwe overleving van 32%).

In *Hoofdstuk 2* worden de patiënten met het tonsilcarcinoom besproken. Dankzij het feit, dat radiotherapie de meest frequent toegepaste behandeling gedurende de gehele studieperiode was, is een vergelijking met andere therapeutische modaliteiten niet gerechtvaardigd. Dit weerspiegelt zich ook in de evaluatie van de prognostische waarde van de UICC(1987) classificatie: de diagnostiek van de halskliermetastasering door middel van palpatie alleen in de overgrote meerderheid van de patiënten (en derhalve het ontbreken van een histologische stadiering) leidt tot een minder betrouwbare N-stadiering en maakt een evaluatie van haar prognostische waarde moeilijk. De 5-jaars tumorcontrole is 57%, de 5-jaars ruwe overleving is 43%. Het T-stadium blijkt de dominante prognostische factor te zijn voor de tumorcontrole.

Hoofdstuk 3 beschrijft de stadiering en de prognose in het tongbasiscarcinoom. Ook in deze groep was de overgrote meerderheid van de patiënten behandeld met radiotherapie. Overeenkomstig het tonsilcarcinoom, blijkt het T-stadium de belangrijkste prognostische factor voor de tumorcontrole. De N-stadiering uitsluitend gebaseerd op palpatie wordt beschouwd als minder betrouwbaar. De 5-jaars tumorcontrole en ruwe overleving zijn respectievelijk 36% en 22%.

In *Hoofdstuk 4* wordt nader ingegaan op de twee meest voorkomende tumorlocalisaties in de oropharynx: het tonsilcarcinoom en het tongbasiscarcinoom. De resultaten van een vergelijkende klinische studie laten geen statistisch significant verschil zien tussen de patiënt- en tumor-

eigenschappen in de twee localisaties, behalve wat betreft de lengte van het delay en het percentage patiënten in slechte algemene conditie bij aanname. Echter, deze bevindingen zijn onvoldoende om de significante verschillen in de tumorcontrole in de twee localisaties te kunnen verklaren.

Ook de analyse van de dosis en totale behandelingsduur bij patiënten behandeld met radiotherapie laat geen significant verschil zien tussen de twee tumorlocalisaties (*Hoofdstuk 5*). Toch verschillen de 3-jaars resultaten met betrekking tot de lokale controle significant (82% en 61% voor het tonsilcarcinoom en het tongbasiscarcinoom, respectievelijk, $p=0.04$). Het T-stadium en de tumorlokalisatie zijn onafhankelijke prognostische factoren voor de lokale controle voorafgaand aan de radiotherapie. De klinische bevindingen aan het eind van de radiotherapie en 6 weken daarna hebben toegevoegde prognostische waarde voor de lokale controle, onafhankelijk van het T-stadium en de tumorlokalisatie.

In *Hoofdstuk 6* wordt een aanzet gegeven tot onderzoek naar morphologische verschillen tussen de twee belangrijkste tumorlocalisaties in de oropharynx. De resultaten van een histopathologische pilot-studie leverden geen bijdrage aan de waargenomen verschillen in het biologisch gedrag van de tumoren in de twee localisaties. Wel worden verdere inzichten in de expressiepatronen van de keratine 10 en collageen IV verworven.

In *Hoofdstuk 7* wordt aandacht besteed aan de twee sporadisch voorkomende tumorlocalisaties binnen de oropharynx: het palatum molle en de oropharynx achterwand. Ook in deze localisaties blijken de plaveiselcelcarcinomen aparte entiteiten te vormen, gelet op tumorgroei, symptomen en tumorstadium bij aanname. De 5-jaars resultaten in deze kleine groepen verschillen niet significant tussen de twee localisaties; de tumorcontrole is 67% en 50%, en de ruwe overleving is 41% en 38% in respectievelijk de palatum molle en oropharynx achterwandgroep.

In *Hoofdstuk 8* worden de beschreven resultaten besproken. De rol van localisatie en T-stadium in de prognose wordt samengevat en er wordt een indeling voorgesteld in prognostische groepen, rekening houdend met beide factoren.

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CURRICULUM VITAE

Sanja Kregar werd op 23 mei 1958 geboren te Zagreb. Na het Gymnasium (eindexamen 1976) en de studie Stomatologie aan de Universiteit te Zagreb (afgestudeerd in 1981) verbleef zij voor een stage aan de Subfaculteit der Tandheelkunde van de Vrije Universiteit te Amsterdam (1981-1982, staatsexamen in Zagreb 1982). Vanaf 1983 is zij werkzaam bij Het Nederlands Kanker Instituut, afdeling KNO / Hoofd-Halstumoren. Van 1984-1991 werkte zij ook bij de afdeling Wetenschappelijke Registratie en Trialbureau van Het Nederlands Kanker Instituut.

In 1984 begon zij aan de postacademische opleiding bij de Universiteit van Zagreb en rondde deze af met een proefschrift in 1990, waarmee zij de titel Magister in de Wetenschappen behaalde. Nadat haar in 1987 de vrijstelling Doctoraalexamen vrije studierichting Tandheelkunde verleend werd, begon ze aan dit (Nederlandse) proefschrift te werken.

Op dit moment is zij werkzaam als Clinical Research Associate bij Ferring Geneesmiddelen, en tevens verbonden aan Het Nederlands Kanker Instituut, afdeling KNO / Hoofd-Halstumoren.

Sanja Kregar is getrouwd met Ernst Edward Mak en zij hebben twee dochters, Felicia van 8 jaar en Cynthia van bijna 7.

APPENDIX A

Containing the protocol and related manual, that were used for data collection in study of squamous cell carcinoma of the oropharynx

PROTOCOL

SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX

patients treated in The Netherlands Cancer Institute /
Antoni van Leeuwenhoek hospital in the periode 1966-1984.

January 1987

S.Mak-Kregar

RECORD PATIENT

Sequential number	I/1-3
Record number	I/4-9
Date of birth	I/10-15
Sex	I/16
Smoking (daily consumption)	I/17
Number of years patient is no longer smoking	I/18-19
Alcohol abusus (daily)	I/20
Previous irradiation of the area	I/21
First symptom	I/22
Delay first symptoms-first consultation (months)	I/23-24
Month and year first admission elsewhere	I/25-28
Month and year first treatment elsewhere	I/29-32
Treatment elsewhere	I/33
WHO performance scale at admission AvL	I/34
Extension of the primary tumour	
Month and year first admission AvL	I/35-38
Localization of origin (subsite)	I/39
Side	I/40
Tonsil, tonsillar fossa and tonsillar pillars	I/41
Retromolar trigone	I/42
Soft palate and uvula	I/43
Lateral pharyngeal wall	I/43a
Base of the tongue	I/44
Epiglottis (lingual surface) and vallecula	I/45
Posterior pharyngeal wall	I/46
Oral cavity	I/47
Hypopharynx/larynx	I/48
Parapharyngeal space	I/49
Fixed to the mandible	I/50
Size of the lesion (mm)	I/51-52
Dominating aspect of the lesion	I/53
Praecancerous lesions	I/54
Localisation of the praecancerous lesions	I/55
T-classification	I/56

Regional disease

Lymphnodes (involved side)	I/57
Number of nodes	I/58
Diameter of the greatest (mm)	I/59-61
Most prominent localization	I/62
Level	I/63
Fixed	I/64
N (UICC) '82	I/65
N (UICC) '87	I/66
N (AJCC)	I/67

Distant metastases

M	I/68
Localization of the distant metastases	I/69-71
Stage grouping (UICC) '82	I/72
Stage grouping (UICC) '87	I/73
Stage grouping (AJCC)	I/74

First treatment of the locoregional disease

Date first treatment AvL	II/4-9

Surgery

Surgery of the primary tumour	II/10-12
Date	II/13-18
Surgeon's judgement	II/19
Surgery of the ipsilateral neck nodes	II/27
Date	II/28-33
Surgeon's judgement	II/34
Surgery of the contralateral neck nodes	II/46
Date	II/47-52
Surgeon's judgement	II/53

Irradiation

Irradiation of the primary tumour	III/4
Date of starting	III/5-10
Equipment	III/11
Tumour dosis (Gy)	III/12-13
Maximal dosis (Gy)	III/14-15
Split (days)	III/16-17
Fractions (number)	III/18-19
Date of ending	III/20-25
Size of the fields	III/26-28
	III/29-31
Number of fields	III/32
Other organs in fields	III/33
Booster : date of starting	III/34-39
equipment	III/40
total tumour dosis (Gy)	III/41-42
maximal dosis (Gy)	III/43-44
total fractions (number)	III/45-46
date of ending	III/47-52
Effect at the end of irradiation	III/53
Effect six weeks later	III/54

Irradiation of the neck

ipsilateral upper neck	III/55
lower neck	III/56
contralateral upper neck	III/57
lower neck	III/58
Date of starting	III/59-64
Localization booster	III/65-66
Total tumour dosis (Gy)	III/67-68
Maximal dosis (Gy)	III/69-70
Fractions (number)	III/71-72
Date of ending	III/73-78
Effect at the end of irradiation	III/79
Effect six weeks later	III/80

Complications

Complications		IV/7
Infection/fistule		IV/8
Necrosis of the flap		IV/9
Haemorrhage		IV/10
Fibrosis		IV/11
Myelopathy/myelitis		IV/12
Osteomyelitis		IV/13
Otherwise		IV/14

Recurrence/metastasis

Last date free of recurrence/metastasis (month and year only)	____	IV/15-20

Latest or last check-up

Month and year of the latest check-up	____	V/4-7
Condition		V/8-9
Date of death or last date alive	____	V/10-15
Autopsy		V/16-17
Cause of death		V/18

Permanent problems after treatment

Deglutition		V/29
Xerostomy		V/30
Speech		V/31
Choke-pneumonies		V/32
Dripping of saliva		V/33
Cosmetical problem		V/34
Hairy flap		V/35
Shoulder drop		V/36
Otherwise		V/37

RECORD HISTOLOGY

Histopathological grading of the primary tumour		I/75
Histopathological grading of the neck nodes		I/77
Analysis of the specimen of the primary tumour		II/20
Perineural growth		II/21
Angioinvasive growth		II/22
Carcinoma's in situ in the specimen		II/23
Atypical epithelium at the margines of the specimen		II/24
Histopathological grading		II/25
Analysis of the specimen ipsilateral neck nodes		II/35
Perineural growth		II/36
Angioinvasive growth		II/37
Carcinoma's in situ in the specimen		II/38
Atypical epithelium at the margines of the specimen		II/39
Rupture of the capsule		II/40
Great number of positive nodes (>=3)		II/41
Positive nodes low in the neck		II/42
Fixation on the skin and/or ulceration		II/43
Histopathological grading		II/44
Analysis of the specimen contralat. neck nodes		II/54
Perineural growth		II/55
Angioinvasive growth		II/56
Carcinoma's in situ in the specimen		II/57
Atypical epithelium at the margines of the specimen		II/58
Rupture of the capsule		II/59
Great number of positive nodes (>=3)		II/60
Positive nodes low in the neck		II/61
Fixation on the skin and/or ulceration		II/62
Histopathological grading		II/63
pTN (UICC) '82		II/65-66
pN (UICC) '87		II/67-68
pN (AJCC)		II/69-70

RECORD RECURRENCE

Local recurrence

Local recurrence (month and year)	___	IV/21-24
Main localization	_	IV/25
Recurrence after irradiation (local,regional or locoregional)	_	IV/26
Histopathological grading (biopsy specimen) in records	_	IV/27
Therapy of the local recurrence	_	IV/29
Surgery	_	IV/30
Date	_	IV/31-36
Analysis of the specimen in records	____	IV/37
Chemotherapy	_	IV/38
Irradiation of the local recurrence	_	IV/39
Tumour dosis (cGy)	_	IV/40-41
Effect at the end of irradiation	_	IV/42
Effect six weeks later	_	IV/43

Regional recurrence

Regional recurrence	_	IV/48
Month and year	___	IV/49-53
Side	_	IV/54
Level	_	IV/55
Therapy	_	IV/56-57
Effect	_	IV/58

Distant metastases

Distant metastases during follow-up	_	IV/59
Month and year	___	IV/60-63
Localisation	___	IV/64-66
Therapy	_	IV/67-68
Effect	_	IV/69

RECORD RECONSTRUCTIONS

Reconstructions	_	IV/4
In how many terms	_	IV/5
Prosthetics	_	IV/6

RECORD MULTIPLE MALIGNANCIES

Year	___	V/19-23
Localization	___	V/24-28

MANUAL

FOR THE PROTOCOL SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX

(NCI/AvL 1966-1984)
January 1987

S.Mak-Kregar

RECORD PATIENT

I/1-3	Sequential number of this protocol, starts off at 001. For patients born outside the Netherlands starts off at 900	
I/4-9	Record identificational number AvL	
I/16	1	man
	2	woman
I/17	0	non-smoker
	1	1-10 cigarettes daily
	2	11-20 cigarettes daily
	3	over 20 cigarettes daily
	4	otherwise (pipe, cigars etc.)
	9	missing data
I/18-19	99	missing data
I/20	0	none
	1	1-3 units
	2	4-6 units
	3	over 6 units
	4	otherwise (note what)
	9	missing data
I/21	0	no
	1	yes
	9	missing data
I/22	0	no symptoms
	1	pain
	2	difficult swallowing
	3	mass in the neck
	4	1+2
	5	1+3
	6	2+3
	7	1+2+3
	8	otherwise
	9	missing data
I/23-24	99	missing data
I/25-28	9999	missing data
I/29-32	9999	missing data

I/33	0	no treatment
	1	a diagnostic procedure (exploration,biopsy,etc.)
	2	major surgery
	3	irradiation
	4	chemotherapy
	5	otherwise
	6	2 + 3
	9	missing data
I/34	0	fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
	1	restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example: light housework, office work (Karnofsky 70-80).
	2	ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50 % of waking hours (Karnofsky 50-60).
	3	capable of only limited self-care, confined to bed or chair 50 % or more of waking hours (Karnofsky 30-40).
	4	completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
	9	missing data

Extension of the primary tumour

I/39	0	none
	1	tonsil / tonsillar fossa
	2	tonsillar pillars
	3	soft palate / uvula
	4	base of tongue
	5	lingual surface of epiglottis / vallecula
	6	posterior pharyngeal wall
	7	lateral pharyngeal wall
	9	missing data
I/40	0	none
	1	left
	2	right
	3	middle
	9	missing data
I/41-49	0	free of tumour
	1	left
	2	right
	3	middle
	4	bilateral
	9	missing data

I/50	0	neither clinically nor on X-ray
	1	yes clinically but not on X-ray
	2	yes on X-ray but not clinically
	3	both clinically and on X-ray
	4	unclear
	9	missing data
I/51-52	99	missing data
I/53	1	superficial
	2	exophytic
	3	ulcer
	4	infiltrative lesion
	5	submucous
	6	otherwise
	9	missing data
I/54	0	none
	1	leukoplakia at admission
	2	erythroplakia at admission
	3	1+2
	4	leukoplakia during follow-up
	5	erythroplakia during follow-up
	6	4+5
	7	1+4
	8	2+5
	9	missing data
I/55	1	oropharynx
	2	oral cavity
	3	1+2
	4	larynx
	5	otherwise
	9	missing data
I/56	UICC '82 and '87, AJCC	
	0	T0 no evidence of primary tumour.
	1	T1 tumour 2 cm or less in its greatest dimension.
	2	T2 tumour more than 2 cm but not more than 4 cm in its greatest dimension.
	3	T3 tumour more than 4 cm in its greatest dimension
	4	T4 tumour with extension to bone, muscle, skin, antrum, neck, etc..
	5	Tis pre-invasive carcinoma (in situ).
	6	TX the minimum requirements to assess the primary umour cannot be met.
	9	missing data or treated before

Regional disease

I/57	0	no nodes
	1	ipsilateral nodes
	2	contralateral nodes
	3	bilateral nodes with ipsilateral dominating
	4	bilateral nodes with contralateral dominating
	5	bilateral nodes
	9	missing data
I/58	0-7	number of nodes
	8	convoluted mass in the neck
	9	missing data
I/59-61	999	missing data
I/62	1	submandibular
	2	subdigastric and high jugular
	3	mid-jugular
	4	supraclavicular
	5	posterior cervical triangle
	6	otherwise
	9	missing data
I/63	1	submental / submandibular region
	2	nodes palpable distal to level region 1 and con- firmed to the region above the skin crease or just below the level of the thyroid notch
	3	nodes palpable distal to level 2 and confirmed to the anterior cervical triangle including those deep to the sternocleidomastoid
	4	posterior cervical triangle, distal to level 3
	9	missing data
I/64	0	neither ipsilateral nor contralateral
	1	ipsilateral only
	2	contralateral only
	3	both ipsilateral and contralateral
	9	missing data
I/65	0	N0 no evidence of regional lymphnode involvement.
	1	N1 evidence of involvement of movable homolateral regional lymphnodes.
	2	N2 evidence of involvement of movable contralateral or bilateral regional lymphnodes.
	3	N3 evidence of involvement of fixed regional lymphnodes.
	4	NX the minimum requirements to assess the regional lymphnodes cannot be met.
	9	missing data or treated before.

I/66	0	N0 no regional lymph node metastasis
	1	N1 metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
	(2)	N2 metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
	3	N2a metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
	4	N2b metastasis in multiple ipsilateral lymphnodes, none more than 6 cm in greatest dimension
	5	N2c metastasis in bilateral or contralateral lymphnodes, none more than 6 cm in greatest dimension
	6	N3 metastasis in a lymph node more than 6 cm in greatest dimension
	9	missing data

Note : (2) should not be filled in

I/67	0	N0 no clinically positive node.
	1	N1 single clinically positive homolateral node 3 cm or less in diameter.
	(2)	N2 single clinically positive homolateral node more than 3 cm but not more than 6 cm in diameter or multiple clinically positive homolateral nodes, none more than 6 cm in diameter.
	3	N2a single clinically positive homolateral node more than 3 cm but not more than 6 cm in diameter.
	4	N2b multiple clinically positive homolateral nodes, none more than 6 cm in diameter.
	(5)	N3 massive homolateral node(s), bilateral nodes, or contralateral node(s).
	6	N3a clinically positive homolateral node(s), one more than 6 cm in diameter.
	7	N3b bilateral clinically positive nodes
	8	N3c contralateral clinically positive node(s) only
	9	missing data or treated before.

Note : (2) and (5) should not be filled in

Distant metastases

I/68	0	M0 no evidence of distant metastases.
	1	M1 evidence of distant metastases.
	2	MX the minimum requirements to assess the presence of distant metastases cannot be met.
	9	missing data or treated before.
I/69-71	ICD-O code	

I/72	1	Stage I	T1 N0 M0
	2	Stage II	T2 N0 M0
	3	Stage III	T3 N0 M0
			T1,T2,T3 N1 M0
	4	Stage IV	T4 N0,N1 M0
			Any T N2,N3 M0
			Any T Any N M1
	9	missing data or treated before.	
I/73	as above (I/72)		
I/74	as above (I/72)		

Surgery

II/10	main surgical procedure:	
	0	no surgery
	1	local excision
	2	commando
	3	supraglottic laryngectomy
	4	1+3
	5	2+3
	6	1+2
	7	1+2+3
	9	missing data
II/11-12	surgery (continued)	
	00	none
	01	partial resection of the tongue
	02	partial resection of the base of the tongue
	03	partial resection of the mandible
	04	partial resection of the maxilla
	05	partial resection of the soft palate
	06	partial resection of the tonsil
	07	partial resection of the lateral pharyngeal wall
	10	01+02+03+06+07
	99	missing data

Note: combinations of these will be specified later

II/19	1	radical
	2	dubious, probably microscopically not radical
	3	macroscopically not radical
	4	spill but otherwise radical
	9	missing data
II/27	0	no surgery
	1	radical neck dissection
	2	functional neck dissection
	3	suprahyoid neck dissection
	4	supraomohyoid triangle
	5	modified radical neck dissection
	9	missing data

II/46	0	no surgery
	1	radical neck dissection
	2	functional neck dissection
	3	suprahyoid neck dissection
	4	supraomohyoid triangle
	5	modified radical neck dissection
	9	missing data
II/53	1	radical
	2	dubious, probably microscopically not radical
	3	macroscopically not radical
	4	spill but otherwise radical
	9	missing data or no surgery

Irradiation

III/4	0	no irradiation
	1	intention to cure by irradiation only
	2	intention to cure by combined treatment (in combination with surgery)
	3	preoperative irradiation
	4	palliative treatment
	5	intention unclear
	9	missing data or no irradiation
III/11	1	Cobalt 60
	2	DT (250 kV)
	3	linear accellerator (8 MeV)
	4	fast neutrons
	5	implant (Ra or Ir)
	9	missing data
III/16-17	to be filled in only if due to patient's bad condition	
	000	no split
	999	missing data
III/26-28	horizontal dimensiom or diameter of the circle in mm.	
	999	missing data
III/29-31	vertical dimension	
	000	circle
	999	missing data
III/33	1	mandible with teeth
	2	mandible without teeth
	9	missing data
III/40	as above (III/11)	
III/41-42	sum of booster dosis and tumour dosis (III/12-13)	
III/43-44	sum of booster maximal dosis and maximal dosis (III/14-15)	

III/45-46	sum of number of fractions booster and fractions (III/18-19)	
III/53	1	NED
	2	residual tumour
	3	unclear
	9	missing data
III/54	as above (III/53)	
III/55	0	none
	1	elective
	2	selective
	3	2+booster
	4	palliative
	5	intention unclear
	9	missing data
III/56	as above (III/55)	
	6	only supraclav
III/57	as above (III/55)	
III/58	as above (III/55)	
	6	only supraclav
III/65	0	no booster
	1	ipsilateral
	2	contralateral
	3	1+2
	9	missing data
III/66	1	submandibular
	2	subdigastric and high jugular
	3	mid-jugular
	4	supraclavicular
	5	posterior cervical triangle
	6	otherwise
	7	upper neck
	9	missing data
III/67-68	booster included if applied	
III/69-70	as above (III/67-68)	
III/71-72	as above (III/67-68)	

		ipsilateral	contralateral
III/79	0	unclear	unclear
	1	unclear	NED
	2	unclear	residual tumour
	3	NED	unclear
	4	NED	NED
	5	NED	residual tumour
	6	residual tumour	unclear
	7	residual tumour	NED
	8	residual tumour	residual tumour
	9	missing data	

III/80 as above (III/79)

Complications

IV/7	0	none
	1	minor
	2	major
	3	fatal
	9	missing data

** NOTE ** IV/8 , 9 and 10 are occurring within 6 weeks after surgery

IV/8	0	no infection / fistula
	1	spontaneous healing / conservative surgery
	2	healing after minor surgery
	3	healing after surgical flap reconstruction
	4	no healing
	9	missing data
IV/9	0	no necrosis
	1	minor (less than 25 %)
	2	partial (about 50 %)
	3	major (skin 100 %)
	4	total (skin and muscle)
	9	missing data
IV/10	0	no haemorrhage
	1	minor
	2	major (requiring exploration)
	4	fatal
	9	missing data

IV/11 concearning fibrosis >= 1 year after having finished the treatment

0	none
1	yes
9	missing data

IV/12	0	none
	1	myelopathy within first 6 months
	2	myelitis (persisting longer than 6 months)
	9	missing data

IV/13 concearning osteomyelitis >=

0	none
1	minor (responding to conservative treatment)
2	major (requiring surgery)
3	extensive (requiring mandibulectomy)
9	missing data

IV/14 will be specified later

Latest or last check-up

V/8-9	01	NED
	02	local recurrence or residual tumour
	03	regional recurrence or residual tumour
	04	distant metastasis
	05	2+3
	06	2+4
	07	3+4
	08	2+3+4
	99	missing data
V/16-17	00	no autopsy done
	01	NED
	02	local recurrence or residual tumour
	03	regional recurrence or residual tumour
	04	distant metastasis
	05	2+3
	06	2+4
	07	3+4
	08	2+3+4
	99	missing data
V/18	0	patient is alive
	1	dead, free of tumour
	2	dead with tumour
	3	dead postoperative
	4	unknown, lost to follow up
	9	missing data

Permanent problems after treatment

V/29-36 Note: permanent problems occurring at the earliest 6 months after having finished treatment.

General frame :

1 minor
2 major (requiring treatment, hospitalization etc.)
9 missing data or none

V/29 2 major (requiring gastric fistula or permanent tube feeding

V/30 2 major (requiring saliva-containing denture or frequent drinking of liquids or saliva substitutes)

V/31
1 perfect speech
2 good understandable speech
3 difficult to understand
4 not understandable

V/32 2 major (requiring laryngectomy)

V/33 2 major, severe problem for patient

V/34 2 major, severe problem for patient

V/35 2 major, severe problem for patient

V/36
1 shoulder drop without pain
2 shoulder drop with pain

V/37 will be specified later

RECORD HISTOLOGY

I/75 0 grade of differentiation cannot be assessed
1 well differentiated
2 moderately differentiated
3 poorly differentiated
4 undifferentiated
5 carcinoma in situ
9 missing data

Note: if different grades of differentiation are met in the specimen, the lowest one should be filled in.

I/76 as above (I/75)

I/77 as above (I/75)

I/78 as above (I/75)

II/20
1 radical
2 dubious
3 not radical
9 missing data

II/21
1 yes
2 no
9 missing data

II/22 as above (II/21)

II/23 as above (II/21)

II/24 as above (II/21)

II/25
0 grade of differentiation cannot be assessed
1 well differentiated
2 moderately differentiated
3 poorly differentiated
4 undifferentiated
5 carcinoma in situ
9 missing data

Note: if different grades of differentiation are met in the specimen, the lowest one should be filled in.

II/35
1 radical
2 dubious
3 not radical
9 missing data

II/36
1 yes
2 no
9 missing data

II/37 as above (II/36)

II/38 as above (II/36)

II/39 as above (II/36)

II/40 as above (II/36)

II/41 as above (II/36)

II/42 fill in the level of the lowest positive node
0 none
1 submental / submandibular region
2 nodes palpable distal to level region 1 and con- firmed to the region above the skin crease or just below the level of the thyroid notch
3 nodes palpable distal to level 2 and confirmed to the anterior cervical triangle including those deep to the sternocleidomastoid
4 posterior cervical triangle, distal to level 3
9 missing data

II/43
1 yes
2 no
9 missing data

II/44
0 grade of differentiation cannot be assessed
1 well differentiated
2 moderately differentiated
3 poorly differentiated
4 undifferentiated
5 carcinoma in situ
9 missing data
Note: if different grades of differentiation are met in the specimen, the lowest one should be filled in.

II/53
1 radical
2 dubious
3 not radical
9 missing data

II/55
1 yes
2 no
9 missing data

II/56 as above (II/55)

II/57 as above (II/55)

II/58 as above (II/55)

II/59 as above (II/55)

II/60 as above (II/55)

II/61 fill in the level of the lowest positive node
0 none
1 submental / submandibular region
2 nodes palpable distal to level region 1 and con- firmed to the region above the skin crease or just below the level of the thyroid notch
3 nodes palpable distal to level 2 and confirmed to the anterior cervical triangle including those deep to the sternocleidomastoid
4 posterior cervical triangle, distal to level 3
9 missing data

II/62
1 yes
2 no
9 missing data

II/63
0 grade of differentiation cannot be assessed
1 well differentiated
2 moderately differentiated
3 poorly differentiated
4 undifferentiated
5 carcinoma in situ
9 missing data
Note: if different grades of differentiation are met in the specimen, the lowest one should be filled in.

II/65 UICC '82 and '87 , AJCC
0 T0 no evidence of primary tumour.
1 T1 tumour 2 cm or less in its greatest dimension.
2 T2 tumour more than 2 cm but not more than 4 cm in its greatest dimension.
3 T3 tumour more than 4 cm in its greatest dimension
4 T4 tumour with extension to bone, muscle, skin, antrum, neck, etc. .
5 Tis pre-invasive carcinoma (in situ).
6 TX the minimum requirements to assess the primary tumour cannot be met.
9 missing data or treated before

II/66
0 N0 no evidence of regional lymphnode involvement.
1 N1 evidence of involvement of movable homolateral regional lymphnodes.
2 N2 evidence of involvement of movable contralateral or bilateral regional lymphnodes.
3 N3 evidence of involvement of fixed regional lymphnodes.
4 NX the minimum requirements to assess the regional lymphnodes cannot be met.
9 missing data or treated before.

II/68
0 N0 no regional lymph node metastasis
1 N1 metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
(2) N2 metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
3 N2a metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
4 N2b metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
5 N2c metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
6 N3 metastasis in a lymph node more than 6 cm in greatest dimension
9 missing data
Note : (2) should not be filled in

II/70	0	N0 no clinically positive node.
	1	N1 single clinically positive homolateral node 3 cm or less in diameter.
	(2)	N2 single clinically positive homolateral node more than 3 cm but not more than 6 cm in diameter or multiple clinically positive homolateral nodes, none more than 6 cm in diameter.
	3	N2a single clinically positive homolateral node more than 3 cm but not more than 6 cm in diameter.
	4	N2b multiple clinically positive homolateral nodes, none more than 6 cm in diameter.
	(5)	N3 massive homolateral node(s), bilateral nodes, or contralateral node(s).
	6	N3a clinically positive homolateral node(s), one more than 6 cm in diameter.
	7	N3b bilateral clinically positive nodes
	8	N3c contralateral clinically positive node(s) only
	9	missing data or treated before.

Note : (2) and (5) should not be filled in

RECORD RECURRENCE

Local recurrence

IV/25	0	no recurrence
	1	tonsil / tonsillar fossa
	2	tonsillar pillars
	3	soft palate / uvula
	4	base of tongue
	5	lingual surface of epiglottis / vallecula
	6	posterior pharyngeal wall
	7	lateral pharyngeal wall
	8	origin of recurrence cannot be clearly established
	9	missing data
IV/26	0	no previous irradiation
	1	in the middle of the field
	2	at the border of the field
	3	outside field
	9	missing data
IV/27	0	grade of differentiation cannot be assessed
	1	well differentiated
	2	moderately differentiated
	3	poorly differentiated
	4	undifferentiated
	5	carcinoma in situ
	6	tumour could not be confirmed
	9	missing data

Note: if different grades of differentiation are met in the specimen, the lowest one should be filled in.

IV/29	0	no treatment
	1	intention to cure
	2	palliative treatment
	3	intention unclear
	9	missing data
IV/30	main surgical procedure:	
	0	no surgery
	1	local excision
	2	commando
	3	supraglottic laryngectomy
	4	1+3
	5	2+3
	6	1+2
	7	1+2+3
	9	missing data
IV/37	1	radical
	2	dubious
	3	not radical
	9	missing data
IV/38	0	no chemotherapy
	1	palliative
	2	adjuvant
	3	intention unclear
	9	missing data
IV/39	0	no irradiation
	1	intention to cure
	2	palliative treatment
	3	intention unclear
	9	missing data
IV/42	1	NED
	2	residual tumour
	3	unclear
	9	missing data
IV/43	as above (IV/42)	

Regional recurrence

IV/48	0	none
	1	yes
	2	dubious whether local or regional recurrence
	9	missing data

IV/54	0	no nodes
	1	ipsilateral nodes
	2	contralateral nodes
	3	bilateral nodes with ipsilateral dominating
	4	bilateral nodes with contralateral dominating
	5	bilateral nodes
	9	missing data
IV/55	1	submental / submandibular region
	2	nodes palpable distal to level region 1 and confirmed to the region above the skin crease or just below the level of the thyroid notch
	3	nodes palpable distal to level 2 and confirmed to the anterior cervical triangle including those deep to the sternocleidomastoid
	4	posterior cervical triangle, distal to level 3
	9	missing data
IV/56	0	no treatment
	1	intention to cure
	2	palliative treatment
	3	intention unclear
	9	missing data
IV/57	0	none
	1	surgery
	2	chemotherapy
	3	irradiation
	4	1+3
	9	missing data
IV/58	1	NED
	2	residual tumour
	3	unclear
	9	missing data

Distant metastases

IV/59	0	none
	1	yes
	9	missing data
IV/64-66	ICD-O code	
IV/67	0	no treatment
	1	intention to cure
	2	palliative treatment
	3	intention unclear
	9	missing data

IV/68	0	none
	1	surgery
	2	chemotherapy
	3	irradiation
	4	1+3
	9	missing data
IV/69	1	NED
	2	residual tumour
	3	unclear
	9	missing data

RECORD RECONSTRUCTIONS

IV/4	0	no reconstructions
	1	primary closure
	2	split skin grafting
	3	deltopectoral (Bahamian) flap
	4	myocutaneous flap
	9	missing data

Note : if any combination of 1-4 occurs, fill in the highest number.

IV/5	1	reconstruction at resection or number of reconstructions + 1
	9	missing data
IV/6	1	dentures
	2	resectional prostheses for maxilla
	3	obturator for soft palate defect
	4	saliva-containing dentures
	9	missing data

RECORD MULTIPLE MALIGNANCIES

V/24-28	ICD-O code

APPENDIX B

Containing the questionnaire for revision of slides, that was used for data collection in study of squamous cell carcinoma of the oropharynx

RECORD REVISION OF HISTOLOGY

QUESTIONNAIRE FOR REVISION OF THE SLIDES

Record number (clinic) _____
Record number (pathology) _____
Number of slide _____
Patient's name

quality of slide __ 1=good
2=moderate
3=bad

size of specimen __ 1=big
2=small

CHARACTERISTICS OF THE TUMOUR CELL POPULATION

cytonuclear pleomorphism __ 0=none
1=poor (<1/3 of cells)
2=moderate (<2/3 of cells)
3=strong (>2/3 of cells)

mitotic activity __ 0=none
1=poor (1-3 per field)
2=moderate (4-6 per field)
3=high (>6 per field)

atypical mitoses __ 0=none
1=sporadic (1 per field)
2=few (2-5 per field)
3=many (>5)

keratinization __ 0=very much
1=moderate
2=suggestion of
3=none

TUMOUR - HOST RELATIONSHIP

pattern of invasion __ 1=well defined borderline
2=cords
3=groups of cells
4=diffuse growth

stromal eosinophilia __ 0=none
1=5-10 per field
2=10-20 per field
3=>20 per field

inflammatory respons __ 0=none
1=poor
2=moderate
3=significant

ENDCONCLUSION AFTER REVISION

histopathological grade __ 0=not assessed
1=well
2=moderate
3=poor
4=undifferentiated

SURGICAL SPECIMENS

perineural growth __ 0=no
1=yes

angioinvasive growth __ 0=no
1=yes

ca in situ in specimen __ 0=no
1=yes

atypical epithelium at the margin of the spec. __ 0=no
1=yes

histopathological grade __ 0=not assessed
1=well
2=moderate
3=poor
4=undifferentiated

lymphnodes' differentiation compared to primary t. _ 1=better
2=equal
3=worse

rupture of the capsule __ 0=no
1=yes

HISTOCHEMICAL ANALYSIS

keratin 10 __ 0=very +
1=focally
2=1-3 cells
3=none

collagen 4 __ 0=continuously +
1=focally very +
2=focally weak +
3=none

cam __ 0=very +
1=focally very +
2=focally weak +
3=none

STELLINGEN

behorend bij het proefschrift

Staging, subsite and prognosis in oropharyngeal carcinoma

1. De localisatie van de primaire tumor in de oropharynx dient als een onafhankelijke prognostische factor beschouwd te worden. (dit proefschrift)

2. Van alle localisaties binnen de oropharynx, zijn bij de tongbasistumoren nieuwe diagnostische en therapeutische methoden het meest dringend nodig. (dit proefschrift)

3. Zelfs de sporadisch voorkomende tumorlocalisaties in de oropharynx dienen als aparte entiteiten te worden gezien. (dit proefschrift)

4. Bij patiënten met plaveiselcelcarcinomen in de oropharynx die behandeld zijn met radiotherapie, is het T-stadium de belangrijkste prognostische factor voor de tumorcontrole. (dit proefschrift)

5. Menige discussie omtrent prognostische factoren zou overbodig zijn wanneer de behandelingsmodaliteit vroegtijdig vermeld zou worden.

6. Nader onderzoek van botmetabolisme bij herhaalde toediening van GnRH-agonisten is een belangrijke voorwaarde voor verdere ontwikkeling van medicamenteuze behandeling van endometriose.

7. De opvatting, dat in het buitenland opgeleide tandartsen louter wegens gebrek aan handvaardigheid ook hun theoretische studie aan een Nederlandse universiteit dienen te herhalen, is strijdig met de beginselen van de universitaire opleiding en duidt op onwil.

8. Hoewel men de integratie van hoogbegaafde kinderen in het reguliere onderwijs tracht te bevorderen, blijft het belangrijk om ze met hun eenzaamheid te leren omgaan.

9. Niet het streven naar vrijheid en democratie, maar gretigheid naar geld en macht bepalen de prioriteiten in de wereldpolitiek.

10. In haar houding inzake de genocide van Kroaten en moslims in Kroatie en Bosnie, heeft de internationale gemeenschap een onvergeeflijke desinteresse getoond (en stelling 9 bewezen).

S.Mak-Kregar,

19 februari 1993