Surgical Treatment with Microvascular Reconstruction of Oral and Oropharyngeal Cancer

Prognostic Factors and Outcome

The research described in this thesis was performed at the Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands.

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de Vrije Universiteit Amsterdam,
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door

Pepijn Anton Borggreven

geboren te Nijmegen

promotor: prof.dr. C.R. Leemans

copromotor: dr. I.M. Verdonck-de Leeuw

To my parents

To Inger and Piet Hein

Contents

Chapter 1

Introduction

1. Head and Neck Cancer

1.1 Epidemiology and staging

Head and neck cancer generally refers to tumors that arise from the mucosal linings of the oral cavity (including lip), oropharynx, nasopharynx, hypofarynx and larynx. More than 95% of these are squamous cell carcinomas.[1,2] Development of squamous cell carcinomas of the head and neck is strongly associated with risk factors as tobacco use and excessive alcohol consumption.[3,4] Other risk factors are the oncogenic human papillomavirus (HPV), certain diets (e.g., salted meat), betel quid chewing and industrial pollution.[5-10] Worldwide the estimated incidence of head and neck cancer exceeds 600.000 new cases annually.[1,2] There is geographical variation in incidence (e.g., in some parts of Asia and South-America the incidence is higher).[11] In The Netherlands the total incidence of squamous cell carcinomas of the head and neck in 2002 was more than 2300 according to the national cancer registry.[12] In the last decade, an increase in incidence of the various head and neck tumors is noted. This is especially the case in females because of changes in tobacco and alcohol habits during recent decades.[12,13] The male versus female ratio in The Netherlands is approximately 2.5:1.[12] Squamous cell carcinomas of the head and neck are rarely seen in people younger than 40 years, and the incidence peaks between 55 and 75 years.[12,14] Classification and staging of the head and neck squamous cell carcinomas is performed according to the TNM system of the Union Internationale Contre le Cancer (UICC).[15] The TNM classification system describes the anatomical extent of the primary tumor, the status of the regional lymph nodes, and the presence or absence of distant metastases. The recent edition also incorporates the potentials for cure.[15-17]

1.2 Oral and oropharyngeal cancer

The oral cavity is divided in buccal mucosa, upper alveolus and gingiva, lower alveolus and gingiva, hard palate, the anterior two thirds of the tongue, and the floor-of-mouth. In The Netherlands, approximately 32% of the newly diagnosed head and neck tumors occur in the oral cavity.[12] In the period between 1989-2002 in more than 7000 patients an oral cavity squamous cell carcinoma was diagnosed, with a male versus female ratio of 1.5:1. Within this same period the amount of patients increased annually with 3.5%. This can be explained mainly by changes in the Dutch population distribution; for males the incidence did not change, for females there was an increase between 45-74 years. The incidence for age did not change in this period, although in some studies there is evidence for an increase of incidence in younger patients (less than 40 years) on global scale.[18-20]

The pharynx is anatomically divided into the nasopharynx, oropharynx and hypopharynx. The oropharynx is divided in base-of-tongue and vallecula, tonsillar fossa and tonsil, posterior wall, soft palate and uvula. In The Netherlands, approximately 22% of the newly diagnosed head and neck tumors occur in the oropharynx.[12] In the period between 1989-2002 in more than 3900 patients an oropharyngeal squamous cell carcinoma was diagnosed, with a male versus female ratio of 2:1. Within this same period the amount of patients increased annually with 5%; for males this increase was mainly in patients between 45-59 years and for females this was mainly between 60-74 years.

2. Treatment of Oral and Oropharyngeal Cancer

2.1 General aspects

Treatment of T1 and early T2 oral cavity or oropharynx carcinomas consists of primary surgery or radiotherapy. Advanced oral cavity or oropharynx carcinomas are often treated by a combination of surgery and radiotherapy.

Surgery of advanced oral cavity or oropharynx carcinomas generally encompasses excision of the primary tumor with en bloc ipsilateral or bilateral neck dissection. If the tumor encroaches on the mandible, a marginal mandibulectomy will be performed. In case of T4 tumors which invade the mandible, a segmental mandibulectomy will be performed. In oropharyngeal carcinomas a paramedian mandibular swing approach is frequently used. Indications for postoperative radiotherapy include positive or close surgical margins, T3-T4 tumors, perineural tumor spread, multiple positive nodes or extranodal spread. Generally, the clinical target volume of the initial field includes the entire surgical bed. The primary tumor area and neck nodes will be irradiated using 2 Gy per fraction to a dose of 46 Gy. An additional boost will be given at the primary site up to a total dose of 56 Gy (2 Gy per fraction, 5 times/week). In case of positive surgical margins or extranodal spread an additional boost will be given to a total dose of 66 Gy (2 Gy per fraction, 5 times/week).

Surgery of the head and neck results in defects of soft tissues, sometimes in combination with bone and skin. To reconstruct these defects after surgery several techniques have been developed for restoring functional and cosmetical features. These are primary closure, skin grafts, local transpositions of skin, mucosa or muscle, regional flaps and free vascularized flaps. Primary closure cannot strictly be categorized as a reconstructive technique, however this closure plays a prominent role for relatively small oral cavity and oropharynx tumors. The functional status after primary closure is acceptable.[21,22] Nonvascularized skin grafts [23] are a good alternative for primary closure when there is a well vascularized wound bed. Lingual flaps as a local transpostion [24] have largely been discarded because of their inferior functional results. A major step forward was the development of the deltopectoral flap in the 1960s.[25] Currently regional flaps, i.e., the pectoralis major flap [26], lattisimus dorsi flap [27], trapezius flap [28,29], and temporalis muscle flap [30], still play an important role in reconstruction of larger defects. The pectoralis major flap proved to be a “work horse flap” in many institutions in the 1980s and 1990s.[26,31,32] Because of the ‘bulky’ and pedicled structure of the locoregional flaps, with consequent frequently unsatisfactory functional results, free vascularized flaps have gained almost uniform popularity during the last decade.

2.2 Free vascularized flaps

Microsurgically revascularized skin flaps to the head and neck were first described in 1973.[33] Vascularized flaps encompasses soft tissue free flaps and bony free flaps. Soft tissue flaps can be classified as fasciocutaneous and myocutaneous flaps. The success of microvascular free tissue transfer depends upon the properties of the patient and the technical perfection of the microsurgeon. For reconstruction of oral cavity and oropharyngeal defects, fasciocutaneous and myocutaneous free flaps have proven to be very reliable and an average flap survival rate of 95% is usually achieved in experienced hands.[34,35] In the last two decades many major centers in the world have shifted from pedicled flaps to revascularized reconstruction flaps for reconstruction of defects after surgery for advanced oral and oropharyngeal tumors. This, mainly because of an observed better outcome in terms of function, cosmetics and thus probably a better quality of life.[36-40] A comparison of different reconstructive procedures for a given primary tumor has never been carried out in a randomized manner. Only scarce retrospective studies about comparison between flaps can be found in literature.[41]

2.2.1 Soft tissue flaps

2.2.1.1 Fasciocutaneous flaps

Fasciocutaneous flaps include the radial forearm flap [42,43], ulnar forearm flap [44], lateral arm flap [45], deltoid flap [46], and anterolateral thigh flap.[47] The radial forearm free flap (RFFF) is one of the most widely used and versatile fasciocutaneous free flaps in head and neck reconstruction because of its qualities; the consistent vascular anatomy, the thin and pliable nature, and the minimal donor site morbidity.[48] The radial forearm flap was first described in the early 1980s [42,43] and Soutar et al. were the first who described intra-oral usage.[42] The flap is created at the distal ventral aspect of the forearm and skin and subcutaneous tissues are harvested, as well as the radial artery and its superficial venous drainage. The flap is sutured into the defect and microsurgically anastomosed to the arterial and venous systems of the neck. The donor site on the forearm often requires a split-thickness skin graft for coverage.[48]

2.2.1.2 Myocutaneous flaps

If a more bulky reconstruction is necessary, for example in case of a total glossectomy, myocutaneous free flaps are preferred. Examples of these are the rectus abdominis free flap [49] and the latissimus dorsi musculocutaneous free flap.[50] The rectus abdominis flap is the most widely used myocutaneous flaps. One of the distinct advantages of this flap is that the volume of the muscle and fatty tissue attached to a given skin paddle can be readily adjusted to suit individual requirements. This flap has proven particularly useful for complex or large tissue defects in the head and neck region. The flap, based on the deep inferior epigastric vessels, is versatile in terms of skin island design, thickness and length of the pedicle. As with the forearm free flap, the inferior rectus abdominis has the advantage of offering the possibility of simultaneous excision and reconstruction. The area of skin that can be transferred is probably the largest of all flaps presently in use.

2.2.2 Bony flaps

Development of free vascularized free flaps enabled functional and esthetical reconstruction after resection of large tumors, especially when there is bone invasion. Well-vascularized bone and soft tissues can be used to repair any kind of oromandibular defects and many of the morphological and functional goals of mandibular reconstruction can now be achieved. The ideal flap should provide vascularized bone of sufficient length and height, easily shaped to match the original mandible with a thin, abundant soft tissue component.

Examples of these flaps are the fibula flap [51], scapula flap [51], and iliac crest flap.[52-54] Particularly in extensive defects, there may be no single flap which combines sufficient bone stock with thin, pliable, soft tissue. By combining two free flaps, the best osseous and soft tissue elements may be independently selected, to yield a result superior to that achievable with one free flap alone.[55]

3. Prognostic Factors of Oral and Oropharyngeal Cancer

Several prognostic factors have been identified that contribute to oncological outcome. Some of these factors are more prominent than others and described below.

3.1 Gender and age

Several studies did not find significant differences in the prognosis for oral or oropharyngeal cancer when gender was analyzed while other studies reported higher survival rates for the female gender.[56,57] The reason for this possible prognostic difference between males and females is still unclear. Regarding age, the prognosis of older patients might be worse than that of younger patients as reported by some studies.[14,58] However, the type and intensity of treatment for elderly patients may affect prognosis just as comorbidity does.[14,59,60]

3.2 Comorbidity

Patients with head and neck cancer often have other diseases, illnesses, or conditions in addition to their index cancer. These other conditions are generally referred to as comorbidities.[61,62] Several different indices, e.g., the Kaplan-Feinstein Comorbidity Index (KFI) [63], have been developed and utilized to classify different comorbid ailments and quantify the severity of overall comorbid condition. Piccirillo et al. have modified the KFI into the Adult Comorbidity Evaluation 27 (ACE-27) test.[64] Particularly for patients with head and neck cancer, the modified KFI has proven to be a very useful system to score the severity of comorbid conditions.[65] Frequent comorbid conditions in patients with oral or oropharyngeal cancer are related to their life-style (i.e., alcohol usage and smoking) and to the fact that the majority of patients are in the age category (50-70 years) in which comorbidities are often present.[12,14,66,67] Although not a feature of the cancer itself, comorbidity is an important attribute of the patient and seems to play an important role in the prediction of prognosis.[68] Comorbidity also has direct impact on the care of patients and selection of treatment (e.g., surgery versus radiotherapy).[69,70] When reporting statistical survival data, hospital-based and national cancer registries do not routinely take into account these coexisting medical ailments. Patients with comorbid conditions seem to have worse outcome [71-73] and thus the addition of comorbidity might refine the prediction of treatment outcome for head and neck patients.[68]

3.3 TNM staging system

Tumor stage, as defined by the TNM staging system, is considered to be the most important prognostic indicator for patients with oral or oropharyngeal cancer.[15,16] Patients with early stages (T1-T2), who do not have regional spread, experience high cure rates, whereas the late stages (T3-T4) often fail localregional or at distant sites. In a study by de Cassia et al. these differences for stage were clearly described. They investigated a total of 530 patients with oral or oropharyngeal carcinomas and found a 5-year survival rate of 76.7% for stage I, 64.4% for stage II, 44.8% for stage III, and 25.5% for stage IV.[74] It is important to realize that the TNM staging system describes only an anatomical expansion. Biological parameters as aggressiveness or patient factors as comorbidity are not included and might have a considerable influence on patients' prognosis.[75]

3.4 Sites and subsites

Differences between tumor (sub)sites can also influence oncological outcome. For example in patients with oral cavity tumors, those with tumors arising from the buccal mucosa and retromolare trigone have a poorer outcome compared to similarly staged patients with tumors arising from other subsites within the oral cavity.[76] Patients with oropharyngeal tumors have better outcome when the tumor is localized in the tonsil or soft palate than patients with a tumor localized in the base-of-tongue or posterior pharyngeal wall.[77,78]

3.5 Surgical margins

Surgical margins are a clear prognostic factor for a possible locoregional recurrence and thus for survival.[79] Patients with tumor-free margin status (more than 5mm) show a better survival than those with close (1-5mm) or involved margins; an overall 5-years locoregional recurrence percentage between 53% (involved margin) and 74% (tumor-free margin) is reported.[76]

4. Outcome Parameters and Results of Oral and Oropharyngeal Cancer

To determine how head and neck cancer patients prioritize potential treatment effects in relationship to each other and to survival List et al. investigated a group of 131 patients pretreatment. They found that being cured was ranked top priority by 75% of patients; another 18% ranked it second or third. Living as long as possible and having no pain were placed in the top three by 56% and 35% of patients, respectively. They concluded that, at least pretreatment, survival is of primary importance to patients, although results also highlighted individual variability and warnings were made against making assumptions about individual patients' attitudes. Other important issues were related to functional outcome and health related quality of life (HRQOL).[80]

4.1 Traditional outcome parameters

4.1.1 Overall survival

The American Cancer Society Facts & Figures 2003 reports a 5-years survival of 56% for oral cavity and pharynx tumors, representing the total group of both tumor sites.[81] The literature with a broad variety of oral and oropharyngeal cancer patients and with different treatment modalities reports overall 5-years survival percentage ranging from 38% to 77%.[78,82-84] During the last decades a change in survival rates for different (sub)sites is noticeable. Carvalho et al. analyzed the site-specific data collected in the Surveillance, Epidemiology, and End Results-SEER Public-Use Database 1973-1999.[85] Trend analysis was carried out on 96,232 cases. Site-specific analysis of survival from 1974-1997 showed significant improvements in 5-year survival rates for cancers of the oropharynx 36.3% to 49.1%. On the other hand, the prognosis for oral cavity cancer patients declined during 1983-1997 (49.2% to 43.8%). Reasons for these survival improvement and worsening are probably multifactorial but unclear.

4.1.2 Complications

A globally accepted postoperative scoring system for complications in surgical treatment of head and neck cancer patients does not exist. Whereas some authors use broad categories of clinically important complications, others use a much more detailed scoring system that includes every minor deviation from the normal course.[86,87] In general, a postoperative major complication rate of 15% - 23% is reported among patients treated for oral cavity and oropharyngeal cancer.[87,88]

Especially the use of microvascular free tissue transfer has allowed the reconstruction of increasingly complex defects in high risk patients after head and neck cancer resections. However, the combination of these factors also results in a higher risk of complications, e.g., pulmonal problems due to aspiration or problems related to the microvascular reconstruction. Complications of microvascular free tissue transfer may occur at the recipient site or at the donor site. Complications occurring at the recipient site are largely a result of vessel thrombosis. Eckardt et al. described postoperative complications in 500 patients; surgical exploration because of flap problems occurred in 8%.[89] Other recipient site complications as fistula forming or wound infection are less frequent in microvascular free tissue transfer reconstruction as compared to reconstruction by regional flaps.[90] Complications occurring at the donor site may result from many causes, ranging from infection to those related to the harvesting of the flap. Chen et al. described in 37 patients reconstructed with a RFFF, donor site complications including partial loss of skin graft (11%), abnormal sensations (26%), poor appearance (8%), and reduced grip strength (11%).[91] De Bree et al. described that the objective morbidity of a RFFF harvest procedure seems to be negligible, but a number of patients have subjective complaints when asked. Elaborate presurgical counseling can probably reduce these complaints.[48]

Irrespective of the site of the complication, it is essential that complications be recognized and addressed early in their course to prevent or minimize devastating consequences.[92] Variables that might affect postoperative complications are well described in the literature, such as comorbidity, age and prolonged hospital stay.[87]

4.2 Non-traditional outcome parameters

4.2.1 Functional status

After oral and oropharyngeal cancer treatment, a significant number of patients encounter speech deterioration and swallowing limitations.[93,94] Although long-term cures have been achieved for locally advanced squamous cell carcinomas of the head and neck, longitudinal data reveal that swallowing and speech problems continue to exist.[95,96]

Speech outcome is assessed by using indicators of speech production (oral function and articulation tests, aerodynamic and acoustical analyses), speech perception (intelligibility and acceptability), and self-reported speech adequacy in every-day-life situations (questionnaires). There are numerous methodological differences between studies on speech quality of patients treated for oral or oropharyngeal cancer.[97-101] Also, various methods are used to evaluate swallowing function including clinical evaluation (oral sensomotoric assessment and observing symptomatic aspiration), objective evaluation (fiberoptic examination, videofluoroscopic swallowing study (VFSS), scintigraphy, manometry) and questionnaires on swallowing problems. VFSS and scintigraphy are currently the preferred objective assessment methods in most institutions.[21,96,102] Due to this methodological variety, results as reported in the literature are difficult to compare. Nevertheless, some general statements can be made. Regarding surgical treatment, the preservation of speech and swallowing function is the primary goal when reconstructing soft tissue defects in the oral cavity or oropharynx. The type of reconstructive procedure used should be based on outcome data examining speech and swallowing function; yet, there is a paucity of such information.[21,103-106] There is evidence that speech and swallowing problems are related with tumor stage and with larger resections resulting in more functional status problems.[107] Furthermore, tumor localization might also play a role in the severity of functional status problems after surgical therapy. Speech outcome seems to be better for patients with base-of-tongue defects as compared to those with tumors of the mobile tongue and/or floor-of-mouth.[108,109] Swallowing scores of patients with mobile tongue, floor-of-mouth, and tonsillar primaries seem superior to those of patients with base-of-tongue lesions.[104,110] Postoperative radiotherapy may also have a negative influence on functional status, especially during short-term follow-up; these functional problems seems to diminish on the long-term, although there is no consensus in the literature.[110-112]

4.2.2 Health related quality of life

Beside survival, complications, and functional outcome, HRQOL is an important outcome parameter. Quality of life issues in head neck cancer have been portrayed increasingly in the medical literature in recent decades. A literature search (PubMed) revealed a total of more than 7000 papers with quality of life as a title-word in the past 5 years. For HRQOL and head and neck cancer related articles this was up to 300. In contrast, in 1970 only six papers had HRQOL as a key word. Unfortunately, many of the HRQOL studies on head and neck patients are cross-sectional rather than longitudinal and most are retrospective.

HRQOL contains four basic components or dimensions which are generally considered to provide the core elements of the conceptual framework of HRQOL research: physical state, psychological well-being, social relations and functional capacity.[113] Additional, an overall global quality of life is often recommended to be obtained as well as subcomponents as such as self-esteem, economic status, sexuality or spirituality.

Baseline studies reveal that HRQOL, although better than after treatment, is often deteriorated already before treatment.[114-119] Funk et al. showed that HRQOL of life is poor at diagnosis compared to a normative population sample as assessed by the standard version of the Medical Outcomes Study 36-Item, Short-Form Health Survey.[120] Hammerlid et al. found in their study on 135 head and neck cancer patients that for the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire only females scored worse (on some scales) compared to a normative population.[121] Regarding the EORTC head and neck cancer module QLQ-H&N35 results, patients in that study scored worse on the majority of scales and single items as compared with normative population values.

De Graeff et al. described in their prospective study on patients with oral cavity (84%) and/or oropharyngeal tumors a significant deterioration of physical functioning, fatigue, appetite loss (EORTC QLQ-C30), and trismus, dry mouth, sticky saliva, taste/smell, social eating, swallowing, speech and sexuality (EORTC QLQ-H&N35) after 6 months follow-up. All symptoms improved after 12 months follow-up, but most were still significantly worse compared with baseline.[115] Kessler et al. found in their prospective study (12 months follow-up) on 53 patients with oral cavity carcinomas comparable results (as de Graeff et al.) for both EORTC QLQ-C30 and QLQ-H&N35 items; they also found a significant worsening of the item "global quality of life".[116] Other prospective follow-up studies on patients treated for oral cavity tumors also found most items significant worse after 12 months as compared to baseline.[118,122,123]

Regarding patients with pharyngeal cancer, especially problems with nutrition and pain complaints are reported at time of diagnosis [124] while after one year follow-up, patients with pharyngeal cancer in general reported worse HRQOL compared with the other groups and did not reach pretreatment values in several domains.[122] Deleyiannis et al. found in their study on patients with advanced oropharyngeal tumors, treated by surgery combined with radiotherapy, after one year follow-up a worsening of chewing, swallowing and speech by using the University of Washington Quality of Life questionnaire.[125]

Results as reported in the literature on HRQOL of patients with oral cavity or oropharyngeal carcinomas are difficult to compare because of the diversity of stage, (sub)site and treatment modalities. A worse HRQOL seems to be associated with higher stage [124,126,127], although not always found.[128,129] Some authors reported that patients with oropharyngeal tumors have a worse HRQOL than those with oral cavity tumors [122,124,127], while others found no significant differences in tumor subsites.[130,131]

The use of combined treatment might have a negative impact on quality-of-life scores.[132] Also, the type of resection, for example comparison between marginal and segmental mandibular resection as described by Rogers et al., is found to be associated with HRQOL.[117]

5. Aim of the Study

Oral and oropharyngeal reconstruction represents one of the greatest challenges in the surgical rehabilitation of patients with head and neck cancer. Insight has been obtained into the role of reconstructive surgery on improved functional status and HRQOL in the broad population of head and neck cancer patients.

However, prospective longitudinal studies on functional status and HRQOL in a selected group of patients undergoing reconstructive surgery for oral and oropharyngeal cancer are scarce and inconclusive. Also, little is known about factors as age and gender, comorbiditiy, and tumor site and stage on oncological and functional outcome and HRQOL.

Therefore, the aim of this study is twofold: 1) To investigate the role of several prognostic factors on outcome parameters, and 2) To gain more insight in long-term functional status and HRQOL. The data on functional speech and swallowing status and HRQOL, that are described in this thesis, can serve as benchmark for future evaluations of treatment modalities.

Part one (Chapter 2 and 3) focuses on comorbidity in relation to traditional outcome (i.e., complications and survival), whereas in part two (Chapter 4, 5, 6, and 7) non-traditional outcome (i.e., functional status and HRQOL) is described in relation to several prognostic factors.

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Chapter 2

Comorbid Condition as a Prognostic Factor for Complications in Major Surgery of the Oral Cavity and Oropharynx with Microvascular Soft Tissue Reconstruction

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Abstract

Identification of factors, especially comorbidity, which affect the incidence and severity of complications in head and neck cancer patients.

One hundred patients with an oral/oropharynx carcinoma undergoing composite resection and microvascular soft tissue transfer were analyzed. Patient data and tumor and treatment factors were recorded. Comorbidity was graded by a Adult Comorbidity Evaluation 27 (ACE-27) test. Postoperative complications were scored according to their severity.

Comorbidity score ACE-27 grade 2 or higher was present in 47% of patients, whereas 33% developed a clinically important complication. A comorbidity score of ACE-27 grade ≥ 2 was a strong predictor for complications ($p < 0.001$). There were no other predictors for postoperative complications.

Comorbidity is of great importance for prediction of postoperative complications in head and neck cancer patients, especially an ACE-27 grade ≥ 2. It may be concluded from these results that prevention of complications should focus on comorbidities.

Introduction

Comorbidity can be defined as one or more medical ailments subservient to the primary medical illness. Even though the literature about cancer treatment has generally not paid much attention to the effects of comorbidities, more insight has been obtained about their role in various oncologic diseases.[1-5] Especially in patients with head and neck cancer, who often have significant comorbid conditions and undergo extensive surgical treatments such conditions may have a profound effect on several outcome factors.[6-9] Until now there is a lack of studies which emphasize the importance of comorbidity with regard to complications in microvascular reconstruction of head and neck defects.[10]

Current microvascular reconstructive techniques offer the best choice for reconstruction of defects after major oncologic surgery in head and neck patients.[11-13] For reconstruction of oral and oropharyngeal defects, fasciocutaneous and musculocutaneous free flaps have proven to be very reliable and an average flap survival rate of 95% is usually achieved in experienced hands.[13]

To classify different comorbid ailments and quantify the severity of overall comorbid condition, several instruments have been developed and utilized, such as the Kaplan-Feinstein Comorbidity Index (KFI) [14], Charlson Comorbidity Index [15], National Cancer Institute/ National Institutes of Aging Index [16] and Index of Co-existent Disease.[17] The KFI as modified by Piccirillo et al.[18] provides an excellent staging tool for comorbidity and has been shown to be a useful predictor for outcome factors in head and neck cancer.[7,19,20]

The objective of this study is to define the predictive value of comorbidity on postoperative complications in a well-defined head and neck cancer patient population.

Materials and Methods

The medical records from the department of Otolaryngology/Head and Neck Surgery of the VU University Medical Center, Amsterdam, The Netherlands, were reviewed to extract a consecutive group of patients who underwent composite resections for advanced oral or oropharyngeal squamous cell carcinoma with microvascular soft tissue transfer (i.e., radial forearm and rectus abdominis flaps) for the reconstruction of their surgical defects, between January 1, 1995 and December 31, 1998. Patients with a history of prior treatment for head and neck cancer were included as were recurrent tumors. The study population comprises one hundred patients.

Data extraction forms were used to collect data on patient, tumor and treatment factors. Patient factors include age, gender, tobacco use, previous treatment (particularly previous radiation) and comorbidity. Classification for comorbidity factors was achieved by using the Adult Comorbidity Evaluation 27 (ACE-27) test, which was especially designed for cancer patients and developed by Piccirillo based on the modified KFI.[14,18,21] The ACE-27 test includes 27 different cogent comorbid ailments composed of various organ systems (such as cardiovascular, respiratory, gastro-intestinal, renal, endocrine, neurological, and immunological), disorders at the psychiatric and rheumatological level, previous or co-existent malignancy, alcohol abuse and body weight. Comorbidity is divided into a 3-category severity system defined as severe, moderate or mild. For example severe comorbidity for hypertension is defined as a diastolic blood pressure (DBP) $\geq$ 130 mmHg, moderate as a DBP of 115-129 mmHg and mild as a DBP of 90-114 mmHg or a DBP $<$ 90 mmHg while taking antihypertensive medications. An overall comorbidity score is determined according to the highest single scoring ailment, except when two or more grade 2 ailments are present. In this situation, the overall comorbidity score is designated grade 3.

Tumor and treatment factors include tumor site, TNM classification (according to UICC 1997), operative procedures, histopathological findings and postoperative course.[22] Operative time was determined as the period between the time of entering the operating room and the time of departure. Hospital stay was defined as the number of days between operative procedure and discharge. Discharge took place when wounds were healed or needed minor care and adequate oral intake was possible or secured by nasal or gastrostomy tube feeding. Postoperative complications were recorded as mild, moderate and severe. Severe complications were those that were life threatening or required return to the operating room. Complications of moderate severity included those with a substantial impact on the patient's postoperative course. Mild complications included those that resolved with minimal intervention. As one patient can have multiple postoperative complications, every patient was categorized according to most severe recorded complication. For example a patient with two severe complications, one moderate and two mild complications recorded, was categorized as a patient who developed a severe complication.

Relations between preoperative comorbidity and post-operative complications were analyzed in 2 by 2 tables with Fisher's Exact Test and odds ratio's and their confidence intervals. Significance levels were set at $p = 0.05$ and confidence interval was taken at 95%.

The role of demographic and diagnostic predictors on treatment outcome was calculated by using logistic regression. In the tables for logistic regression the initial and final p values (and generating approximate chi-square values) are presented to illustrate the univariate and multivariate influence of the diverse predictors. For all logistic regression analyses the stepping process was stopped after the first step, due to residual non-significance or instability of further models. Statistical analyses were done with the statistical software package BMPD.[23] Data summaries and graphical presentations were created with SPSS.[24]

Results

The ages of the 100 patients included in this study ranged from 39 to 84 years (median 58 years). Sixty-one were male and 39 female. Seventy-eight patients were current moderate or heavy smokers, whereas 13 were former smokers and 9 never smoked. Oral cavity tumors represented 47% of cases, whereas 53% were located in the oropharynx. Mobile tongue, floor-of-mouth, tonsil, and base-of-tongue were the most common subsites, with 18, 14, 26, and 18%, respectively. Ninety-six patients underwent a free radial forearm flap (RFFF) and 4 patients a rectus abdominis flap reconstruction. Operative time varied from 6.5 to 13.5 hours (median 8 hours). Tumor stage distribution for the 89 previously untreated patients was 48.3% T2, 47.2% T3, and 4.5% T4. There were 37% N0, 17% N1, 8.9% N2a, 29.2% N2b, 6.8% N2c, and 1,1% N3. Eleven patients were operated for a recurrent tumor after previous surgery (n=2) or radiotherapy (n=2) or both (n=7). In these patients the rTNM stage was used. The admission time ranged from 12 to 83 days (median 18 days). An overall success rate of 96% for free flap reconstruction was achieved. One patient (1%) died in hospital because of abdominal problems.

A distribution of the comorbid ailment scoring according to the ACE-27 test is shown in Table 1. The most frequent categories were cardiovascular, respiratory, previous or co-existent malignancy and substance abuse. The presence of the overall comorbid condition revealed 13% severe (grade 3), 34% moderate (grade 2) and 36% mild (grade 1) cases, while 17% of the patient population had no comorbidity.

Table 1. The distribution of comorbid ailments scoring according to the ACE-27 test

Cogent comorbid ailment \ Score	Grade 3	Grade 2	Grade 1
Cardiovascular system	1	12	52
Respiratory system	0	6	18
Gastrointestinal system	0	2	6
Renal system	0	0	0
Endocrine system	0	1	4
Neurological system	0	1	6
Psychiatric	0	1	0
Rheumologic	0	0	1
Immunological system	0	0	0
Malignancy	0	12	5
Substance abuse	0	20	15
Body weight	2	5	0
Total	3	60	107

ACE-27 test: Adult Comorbidity Evaluation 27 test

The frequency of clinically important complications (i.e., moderate or severe complications) is shown in Table 2. In total 32 severe and 19 moderate complications were recorded. Fifty percent of the severe complications were systemic complications. The remaining 50% were recipient site complications, which occurred in 16 patients. These patients had to be brought back to the operation room for re-exploration of the microvascular anastomosis (n=8), wound hematoma and/or dehiscence (n=7) or chyle leakage (n=1). After recording the complications every patient was categorized. Twenty percent of the patients developed a severe complication, 13% a moderate complication and 32% a mild complication (e.g., minor recipient site and donor site problems, prolonged trachea canula insertion (> 14 days), urinary tract infection or bedsores). Thirty-five percent had an uneventful postoperative course.

Table 2. Frequency of clinically important (i.e., moderate or severe) complications

Complication	n
Severe (n=32)	
Systemic	
Cardiac arrest (myocardial infarction confirmed on ECG or by serum enzyme elevation)	1
Respiratory insuffiency requiring ventilatory assistance for > 12 hours	5
Pulmonary embolism	1
Cerebrovascular accident	1
Sepsis	3
Intensive care unit admission due to circulatory, respiratory or other life-threatening problems	4
Death	1
Recipient site	
Return to the operating room because of e.g., flap problems, hematoma, wound dehiscence and chyle leakage	16
Moderate (n=19)	
Systemic	
Cardiac insuffiency (clinical and radiologic diagnosis) requiring diuretics, oxygen and/or cardiotonics	11
Respiratory tract infection: positive sputum culture or abnormal chest x-ray requiring treatment with antibiotics	5
Recipient site	
Chyle leakage conservatively treated	2
Fistula formation	1

Table 3 shows the patient population according to their ACE-27 grade relative to clinically important complications. Patients with none or grade 1 comorbidity score developed a severe complication in 4% of cases (2 of 53). For patients with advanced comorbidity (ACE-27 grade ≥ 2) this was 38% (18 of 47) and for patients with ACE-27 grade 3 this was 46% (6 of 13). Patients with advanced comorbidity score developed a clinically important complication in 55% of cases.

Table 3. The patient population according to their ACE-27 grade relative to clinically important complications

ACE-27 \ Complications	Moderate (n=13)	Severe (n=20)
None (n=17)	2 (12%)	1 (6%)
Grade1 (n=36)	3 (8%)	1 (3%)
Grade2 (n=34)	8 (24%)	12 (35%)
Grade 3 (n=13)	0 (0%)	6 (46%)

ACE-27: Adult Comorbidity Evaluation 27

Table 4 is a 2 by 2 table for comorbidity associated with complication development as outcome. A strong indication for postoperative complications could be found if the ACE-27 scored at least a moderate (grade 2) comorbidity. This relation existed at any chosen level of severity, which was used to indicate a postoperative complication, but was stronger for increasing severity.

Logistic regression was performed to determine the impact of age, gender, tobacco use, preoperative radiotherapy, ACE-27 scoring, tumor site, TN classification and operative time on clinically important complications (Table 5). Tumor site was dichotomized between patients with tongue or base-of-tongue tumors (n=36) and the other sites (n=64), because tongue resections may have an impact on swallowing and thus postoperative complications, particularly those due to aspiration. No significant difference between these groups existed. Dichotomization of flap reconstruction (i.e., RFFF and rectus abdominis) did not produce significant differences and was therefore not added to the table. Having at least a moderate comorbidity turned out to be a strongly significant determinant (p = 0.001). Age, gender and severity of tobacco usage as well as TN classification, preoperative radiotherapy and prolonged operative time were not associated with postoperative complications. Entering of the ACE-27 score into the model did not produce any obvious changes in the other (non) significances.

Table 4. Two by two table of comorbidity associated with complication development as outcome

ACE-27 \ Complications	At least a moderate (n=33)	Severe (n=20)
Grade ≥ 1	p = 0.167 OR = 2.6 CI (0.7-9.9)	p = 0.182 OR = 4.8 CI (0.6-38.1)
Grade ≥ 2	p < 0.001 OR = 8.1 CI (3.1-21.7)	p < 0.001 OR = 15.8 CI (3.4-73.2)
Grade 3	p = 0.346 OR = 1.9 CI (0.6-6.2)	p = 0.021 OR = 4.5 CI (1.3-15.3)

ACE-27: Adult Comorbidity Evaluation 27

p: p Value (Fisher's exact test)

OR: Odds Ratio

CI: 95% Confidence Interval

Table 5. Logistic regression of variables associated with clinically important complications

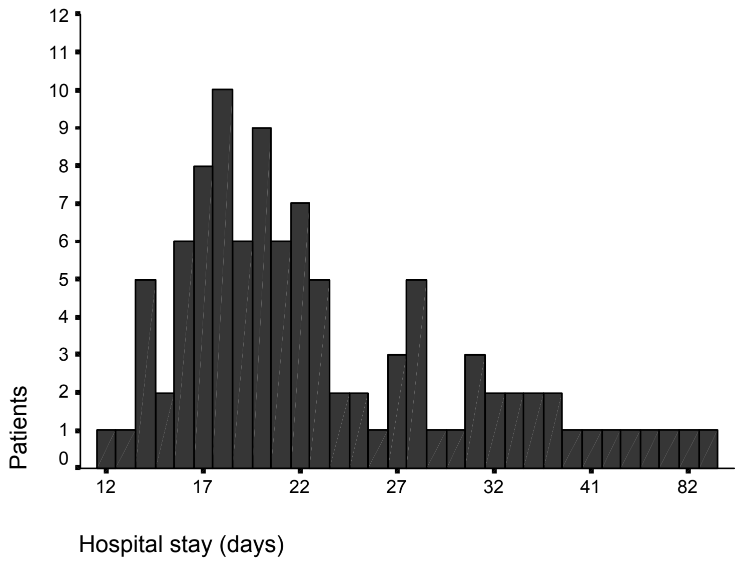
	Initial		After entering ACE-27	
Variables	Approximate chi-square value	p value	Approximate chi-square value	p value
Age	0.82	0.365	0.26	0.614
Gender	0.67	0.412	0.72	0.396
Tobacco use	0.14	0.707	0.01	0.939
Preoperative irradiation	0.15	0.701	1.19	0.275
ACE-27 grade ≥ 2	20.8	0.001	-	-
Tumor site *	0.00	0.960	0.22	0.642
T score	0.05	0.821	0.16	0.690
N score	2.22	0.136	1.26	0.261
Operative time	1.56	0.211	3.37	0.066

ACE-27: Adult Comorbidity Evaluation 27

*Tumor site dichotomized in tongue and none-tongue sites

A histogram of hospitalization time showed a bimodal distribution, leading to a possible division into two groups (Figure 1). The first group ('normal' length of hospital stay) represented 68% of the patients who were discharged within 25 days after operation (median 18 days). The remaining 32% ('extended' hospital stay patients) had a maximum admission time of two and a half months. Analyses showed that for ACE-27 grade 0 and 1 patients 21% experienced an extended hospital stay, for grade 2 patients this was 38% and for grade 3 patients 61%. Stepwise logistic regression was performed for the prolonged hospitalization group and possible predictive factors (Table 6). Some factors seemed to be of marginal significant importance, whereas postoperative complications showed a clearly statistical significance. As expected, when this factor was entered into the model ACE-27 lost all significance since this index is strongly related to complications.

Figure 1. Hospital admission for all cases



To evaluate the relationship between the above factors and ACE-27 grade ≥ 2 score, further logistic regression was performed (Table 7). It appeared that only age might be a predictive parameter ($p = 0.027$). When age was entered into the model none of the other variables reached a statistical significance.

Table 6. Logistic regression of variables associated with an extended hospital stay (> 25 days)

	Initial		After entering Complications	
Variables	Approximate chi-square value	p value	Approximate chi-square value	p value
Age	2.85	0.091	4.78	0.029
Gender	0.10	0.749	0.02	0.877
Tobacco use	3.37	0.066	2.07	0.150
Preoperative irradiation	0.55	0.457	0.52	0.473
ACE-27 grade ≥ 2	6.54	0.010	0.98	0.323
Tumor site*	0.11	0.739	0.91	0.340
T score	6.49	0.011	4.64	0.031
N score	0.55	0.450	0.01	0.903
Operative time	2.75	0.098	2.07	0.150
Complications	16.47	0.001	-	-

ACE-27: Adult Comorbidity Evaluation 27

*Tumor site dichotomized in tongue and none-tongue sites

Table 7. Logistic regression of variables associated with a ACE-27 grade ≥ 2

	Initial		After entering Age	
Variables	Approximate chi-square value	p value	Approximate chi-square value	p value
Age	4.91	0.027	-	-
Gender	0.32	0.569	0.54	0.461
Tobacco use	2.36	0.125	0.98	0.322
Preoperative irradiation	3.56	0.060	2.50	0.114
Tumor site*	1.60	0.207	0.44	0.507
T score	0.01	0.997	0.12	0.734
N score	0.59	0.442	0.59	0.377
Operative time	0.26	0.609	0.04	0.837

ACE-27: Adult Comorbidity Evaluation 27

*Tumor site dichotomized in tongue and none-tongue sites

Discussion

The role of comorbidity on complications in head and neck cancer patients undergoing extensive ablative and reconstructive surgery was investigated in a group of 100 consecutive patients with identical histopathological diagnoses, tumor origin in the oral cavity or oropharynx and soft tissue reconstruction only. The ACE-27 test was used for scoring comorbidity. The relationship between comorbidity and postoperative complications could thus be established.

In the present study, 83% of the patients had some form of comorbidity whereas 47% had advanced comorbidity. The majority of comorbidities were within the cardiovascular, respiratory, previous or co-existent malignancy, or substance abuse categories, which is well explicable by the life style of the head and neck patient population. Funk et al. report similar overall and advanced comorbidity scores of 75% and 45% respectively in a population of 73 oral cavity cancer patients.[25] In a group of young patients only (mean 41 years, maximum 45 years old) with various anatomical sites of head and neck squamous cell carcinomas, Singh et al. found an advanced comorbidity score of 30%.[26]

The 33% incidence of clinically important complications in the present series was comparable to our earlier experience.[27] Major complications occurred in 20% of our patient group. Others, who used different classifications, report a major complication rate of 15% - 23%.[10,28] Postoperative complication rates among different studies are somewhat difficult to compare. An ideal and universally accepted postoperative scoring system for complications in surgical treatment of head and neck cancer patients does not exist. Whereas some authors use broad categories of clinically important complications, others use a much more detailed scoring system that includes every minor deviation from the normal course.[10,28,29] Such minor complications can probably be omitted because no relation with comorbid ailments has ever been shown.

Patients with advanced comorbidity developed a clinically important complication in 55% of cases. Advanced comorbidity was a clear prognostic factor for complications. The relation between life threatening complications and advanced comorbidity has also been demonstrated by others.[25,30] Singh et al. also found a relationship between comorbidity and postoperative complications after major resections of head and neck cancer and free flap reconstruction. However, they evaluated a heterogeneous group of defects, an array of reconstructive microvascular methods and used a different comorbidity index.[10] Only thirteen percent of patients with none or mild (grade 1) comorbidity developed a clinically important complication and there was no difference between these two groups. After analyses mild comorbidity was not a prognostic factor for postoperative complications. In the present study, no additional factors (such as age, gender, tobacco use, previous treatment, tumor site, TNM stage and operative time) besides comorbidity, turned out to be significant predictors for complications in a multivariate analysis. This clearly points to comorbidity as the dominant independent influence on postoperative complications.

Logically, an association between complications and duration of hospital admission was found in our analysis. Comorbidity did impact through its effect on complications. Therefore, it may be concluded from these results that prevention of complications (and an associated extended hospital stay) should focus on comorbidities.

There is controversy as to the relationship between advanced age and complications after microvascular reconstructive surgery.[31-34] In our study, age had a slight impact on comorbidity, whereas age as such seemed to be of no relevance as regards to complications. Any possible influence of age on complications therefore is be explained by its indirect impact through comorbidity rather than by a direct effect. Advanced age by itself is not to be considered a contraindication to microvascular reconstructive surgery.

This study demonstrates the relation between comorbidity and postoperative complications within a specific group of patients. Patients with advanced comorbidity generally had a prolonged postoperative course due to complications and the influence of age on complications could be explained by its indirect effect through comorbidity. Despite relatively high comorbidity scores (and associated complications), our study population of one hundred patients showed a free flap survival of 96%, an expected hospital stay for more than two-third of the population and minimal residual morbidity even for those who were discharged after an extended hospital stay. Naturally the question arises, when will comorbidity be a contraindication in major surgery? In general restrictive guidelines for surgery on the basis of comorbidity are hard to define. This study aims at giving some insight into this question. Patients with the highest comorbidity score (e.g., grade 3) experienced a severe complication ratio of almost 50%. Therefore we believe that for some of these patients, that have e.g., unstable angina, COPD with dyspnea at rest despite treatment, portal hypertension or severe dementia requiring full support for activities for daily living, refraining from major surgery should be considered, especially when reasonable treatment alternatives are available [35,36] and also keeping in mind that these patients seem to have a decreased survival.[37-39] In general, however, comorbidity should not be a restriction for major surgery.

The information of our study helps to fill the gap of knowledge about the prognostic value of comorbidity on postoperative complications in the head and neck cancer patient. With this knowledge better patient selection, counceling, preparation and vigilance as to complications may be possible.

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Chapter 3

Severe Comorbidity Negatively Influences Prognosis in Patients with Oral and Oropharyngeal Cancer after Surgical Treatment with Microvascular Reconstruction

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Abstract

The aim of the study was to investigate the possible impact of comorbidity on survival of patients undergoing composite resection and microvascular reconstruction for oral/oropharyngeal cancer.

Patient, tumor and treatment data were recorded. Comorbidity was graded by the Adult Comorbidity Evaluation (ACE-27) test. Survival and statistics were calculated.

Comorbidity score ACE-27 grade ≥ 2 was present in 47% of patients, for ACE-27 grade 3 this was 13%. The median follow-up was 50 (3 - 87) months. Thirty-eight patients died, 32 developed a recurrence. Comorbidity score ACE-27 grade 3 turned out to be a clear predictor for overall survival ($p < 0.05$). For ACE-27 grade 3 (n=13) 5-years survival was 29%, for ACE-27 grade ≤ 2 (n=87) this was 64%. No multivariate influences on the effects of comorbidity were found.

Improved knowledge of the effect of comorbidity on survival may lead to better patient selection and counseling for major surgery and microvascular reconstruction.

Introduction

Medical ailments that accompany a primary oncologic illness, defined as comorbidity, may have a significant impact on outcome.[1-4] Patients with head and neck cancer frequently have severe comorbidity which may be related to their survival.[5,6] Ablative surgical treatment with microvascular reconstruction is the most common therapeutic option for advanced oral and oropharyngeal cancer. Literature has only marginally emphasized the prognostic importance of comorbidity on survival in these patients. The current TNM staging system, which describes the anatomic extension of the oncologic disease, predicts prognosis best but has inherent shortcomings.[7] Other factors, next to the TNM staging system, which are linked to prognosis have been increasingly reported in literature.[8,9] Especially the addition of comorbidity might refine the prediction of treatment outcome for head and neck patients.

Several different indices (e.g., the Kaplan-Feinstein Comorbidity Index (KFI) [10], Charlson Comorbidity Index [11], National Cancer Institute/National Institutes of Aging Index [12]) have been developed and utilized to classify different comorbid ailments and quantify the severity of overall comorbid condition. Piccirillo et al.[13,14] have modified the KFI into the Adult Comorbidity Evaluation 27 (ACE-27) test. Particularly for patients with head and neck cancer, the modified KFI has proven to be a very useful system to score the severity of comorbid conditions.[4,15]

Reconstruction of complex defects in the head and neck after major oncologic surgery has been revolutionized over the past two decades by the advent and refinement of microvascular tissue transfer.[16] Using these free vascularised flaps more complex tumor resections can be performed safely with an average flap survival rate of 95% or more in experienced hands.[17]

In a previous publication we analyzed the relation between comorbidity and postoperative complications.[18] It was shown that severe comorbidity negatively impacts on the clinically important complication rate. The purpose of the current study is to determine the prognostic impact of comorbidity on postoperative survival in the same well-defined head and neck cancer patient population. Implementation of the results should possibly realize a better selection of patients and better counseling.

Materials and Methods

A study cohort was drawn from the medical records from the department of Otolaryngology-Head and Neck Surgery of the VU University Medical Center, Amsterdam, The Netherlands. The study population comprised one-hundred consecutive patients with advanced oral or oropharyngeal squamous cell carcinoma who underwent major surgery with microvascular free soft tissue transfer for surgical defect reconstruction from January 1, 1995 to December 31, 1998. All patients were followed-up at least 5 years. Patient (gender and comorbidity), tumor (site and stage) and treatment data (margin status, complications, postoperative radiotherapy and survival) were collected.

Patients' comorbidity was classified according to the ACE-27 test. Table 1 shows the distribution for each scored cogent comorbid ailment. Comorbidity is divided into a 3-category severity system (severe, moderate or mild). For example severe comorbidity for the cardiovascular system is defined as a recent myocardial infarction, moderate as a myocardial infarction longer than 6 months ago and mild as an old myocardial infarction diagnosed by ECG only. The overall comorbidity score is established by the highest-scoring illness, except when two or more grade 2 ailments are present, in which the grade is 3. Tumor data include tumor site (i.e., oral cavity or oropharynx) and stage according the TNM classification (according to UICC 1997).[19] Complications were classified as mild, moderate or severe as previously described.[18] Indications for postoperative radiotherapy included T3-4 tumors, irradical margins, perineural tumor spread, multiple positive nodes or extranodal spread. Generally, the target volume of the initial field included the entire surgical bed (primary tumor and ipsilateral neck) and contralateral neck nodes level IB-IV/V. The tumor bed and upper neck nodes were irradiated with two parallel-opposed photon 6 MV photon fields, while an oppositional anterior 6 MV photon field was used to treat the lower neck nodes, using 1.8 to 2.5 Gy per fraction to a dose of 40 to 50 Gy. In case the total dose was 50 Gy, the spinal cord was shielded after 40 Gy. An additional boost was given to the sites in the neck with residual disease to a cumulative dose varying from 50 to 70.5 Gy. Overall survival was determined as the period of time between the day of surgery to the date at last follow-up. For patients who died, the cause of death was recorded. The date and site of the first recurrence were also noted. Kaplan-Meier survival curves were estimated to allow maximum use of censored observations. To minimize the effect of complications on comorbidity (as documented before [18,20]), stratification for complications was performed. Disease-free survival was determined as the period between the day of surgery and date of first recurrence. For disease free survival censoring was performed when a local recurrence, regional recurrence or distant metastasis was not diagnosed or when a patient survived more than 5 years. For tumor specific survival observations were censored for patients who were lost to follow-up during the study, who died of causes unrelated to cancer, or who survived at least 5 years.

Table 1. Distribution of comorbid ailment scoring grades according to the Adult Comorbidity Evaluation 27 test. An overall comorbidity score can be esthablished by the highest scoring grade (except when 2 or more grade 2 ailments are present, in wich the overall score is 3)

Score / Comorbid ailment	Mild Grade 1	Moderate Grade 2	Severe Grade 3
Body weight	0	5	2
Cardiovascular system	52	12	1
Substance abuse	15	20	0
Malignancy	5	12	0
Respiratory system	18	6	0
Gastrointestinal system	6	2	0
Neurological system	6	1	0
Endocrine system	4	1	0
Psychiatric	0	1	0
Rheumologic	1	0	0
Renal and Immunological system	0	0	0
Total	107	60	3

Fisher's Exact Test was performed for exact nonparametric inference in contingency tables. Log rank (Mantel-Cox) test was used for statistical comparison of survival curves. Cox regression analysis was performed to study the association between comorbidity and survival. The influence of possible confounding by patient, tumor and treatment variables was studied by adding these into the Cox model. Whenever appropriate a trend variant was used. Statistical significance was defined as a two-tailed p value less than or equal to 0.05. Statistical analyses were done with the statistical software package BMPD.[21] Data summaries and graphical presentations were created with SPSS.[22]

Results

Patient, tumor, and treatment data are shown in Table 2. The median age was 58 years (range, 39 to 84), thirty-nine were female (39%) and 61 male (61%). The distribution of comorbid ailment scoring revealed 13% severe (grade 3), 34% moderate (grade 2) and 36% mild (grade 1) cases, while 17% of the patient population had no comorbidity. Forty-seven percent of cases were located in the oral cavity, whereas oropharyngeal tumors represented 53%. The majority of tumors were located in the following subsites; tonsil (26%), base-of-tongue (18%), mobile tongue (18%) and floor-of-mouth (14%). Tumor stage distribution was 22% stage II, 33% stage III and 45% stage IV. Eleven patients were operated for a recurrent tumor after previous surgery (n=2), radiotherapy (n=2) or both (n=7). In these patients the rTNM stage was used. Most patients (96%) underwent a free fasciocutaneous radial forearm flap, while the remaining patients (4%) underwent a myocutaneous rectus abdominis flap reconstruction. An overall success rate of 96% for free flap reconstruction was achieved. One patient (1%) died in hospital because of an ileus. Eighty-two patients (82%) had a tumor-free margin status. Eighty-five patients (85%) received postoperative radiotherapy. Fifteen patients (15%) did not receive radiotherapy; 10 patients (10%) because there was no indication, 4 patients (4%) because previous radiotherapy did not allow for a second course, and 1 patient (1%) refused postoperative radiotherapy. The median follow up was 50 months (range 4 to 87 months). Thirty-two patients (32%) developed a recurrence, 38 died (38%), and 3 patients (3%) were lost during the follow-up. For 28 of the 38 patients who died death was tumor-associated, whereas 10 patients died without evidence of disease (NED): pneumonia (n=3), bronchogenic carcinoma (n=2), cardiac arrest, pulmonary embolism, sepsis, ileus and traffic accident. Of the 32 recurrences, 17 patients developed a locoregional recurrence, 9 distant metastases and 6 both a locoregional recurrence and distant metastases.

Table 2. Patient, tumor and treatment data of patients

Age	39 - 84 (median 58) years
	n
Gender	
- male	61
- female	39
Overall comorbidity score	
- ACE-27 grade 0	17
- ACE-27 grade 1	36
- ACE-27 grade 2	34
- ACE-27 grade 3	13
Tumor site	
- oral cavity	47
- oropharynx	53
Tumor stage	
- II	22
- III	33
- IV	45
Tumor-free margin status	82
Postoperative radiotherapy	85
Recurrence (5-years follow-up)	32
Death (5-years follow-up)	38

ACE-27= Adult Comorbidity Evaluation 27 test

Table 3 shows the distribution of survival, death and lost during follow-up relative to comorbidity. Patients were divided into patients with no, mild, or moderate comorbidity (i.e., ACE-27 grade ≤ 2 score, n=87) and patients with severe comorbidity (i.e., comorbidity ACE-27 grade 3, n=13). Among patients with ACE-27 grade 3, significantly more patients died without evidence of disease as compared among those with ACE-27 grade ≤ 2 relative to survival (p=0.012).

Table 3. Distribution of death, survival and lost during 5-years follow-up for divided comorbidity groups

	ACE-27 grade ≤ 2 (n=87) n (%)	ACE-27 grade 3 (n=13) n (%)
Death		
-tumor related	23 (26%)	5 (38%)
-NED	6 (7%)	4 (31%) #
Survival	55 (63%)	4 (31%)
Lost during follow up	3 (4%)	0

ACE-27= Adult Comorbidity Evaluation 27 test
# Fisher's Exact Test p-value = 0.012
NED= no evidence of disease

Table 4 shows the analyses of overall 5-year survival for different variables. Besides tumor stage (p=0.0004) and margin status (p=0.019), comorbidity (p=0.039) was shown to be a statistically important prognostic factor for survival. Further analyses by calculating log rank tests for all comorbidity groups separately (i.e., comparing patients with no comorbidity, an ACE-27 score 1, 2 or 3) showed no statistically significant difference for survival. Analyses of advanced comorbidity groups (i.e., ACE-27 grade ≥ 2) compared to patients with no or grade 1 comorbidity did also show no significant difference.

Table 4. Statistical comparison of overall 5-years survival per variable (Log rank (Mantel-Cox) test)

Variables	overall survival (%)	Generalized Savage	p-value
Gender		0.07	0.792
- males	60		
- females	64		
Comorbidity *		4.27	0.039
- Ace-27 grade ≤ 2	64		
- Ace-27 grade 3	29		
Tumor site		1.14	0.285
- oral cavity	58		
- oropharynx	65		
Tumor stage		15.79	0.0004
- II	91		
- III	67		
- IV	44		
Margin status		5.45	0.019
- tumor-free	67		
- not tumor-free	38		
Postoperative radiotherapy		2.19	0.139
- yes	59		
- no	80		

* Stratified for complications

Figure 1 demonstrates the Kaplan-Meier survival curve by tumor stage. The 5-years overall survival is significantly decreased (p=0.0004) for the tumor stage IV (44 % survival) compared to stage III and II (67 % and 91% survival, respectively). The overall 5-years survival was 64% for the patient group with a comorbidity ACE-27 grade ≤ 2 score, whereas for patients with an ACE-27 grade 3 score the 5-years survival (29%) was statistically worse (p=0.039, Figure 2). Concerning disease-free survival, no significant difference was found between the ACE-27 grade ≤ 2 and ACE-27 grade 3 group (p=0.21, figure not shown). For tumor-specific survival, again no significant difference was found between the ACE-27 grade ≤ 2 and ACE-27 grade 3 group (p=0.34, Figure 3).

Figure 1. Kaplan-Meier overall survival by tumor stage (p = 0.0004)

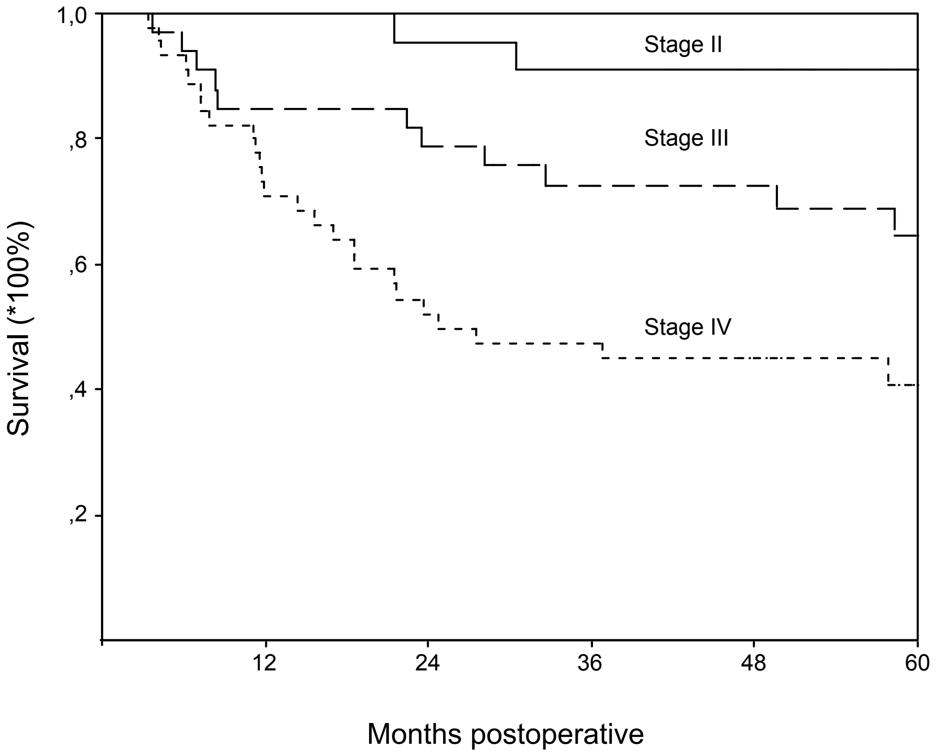


Figure 2. Kaplan-Meier overall survival by comorbidity (p = 0.039)

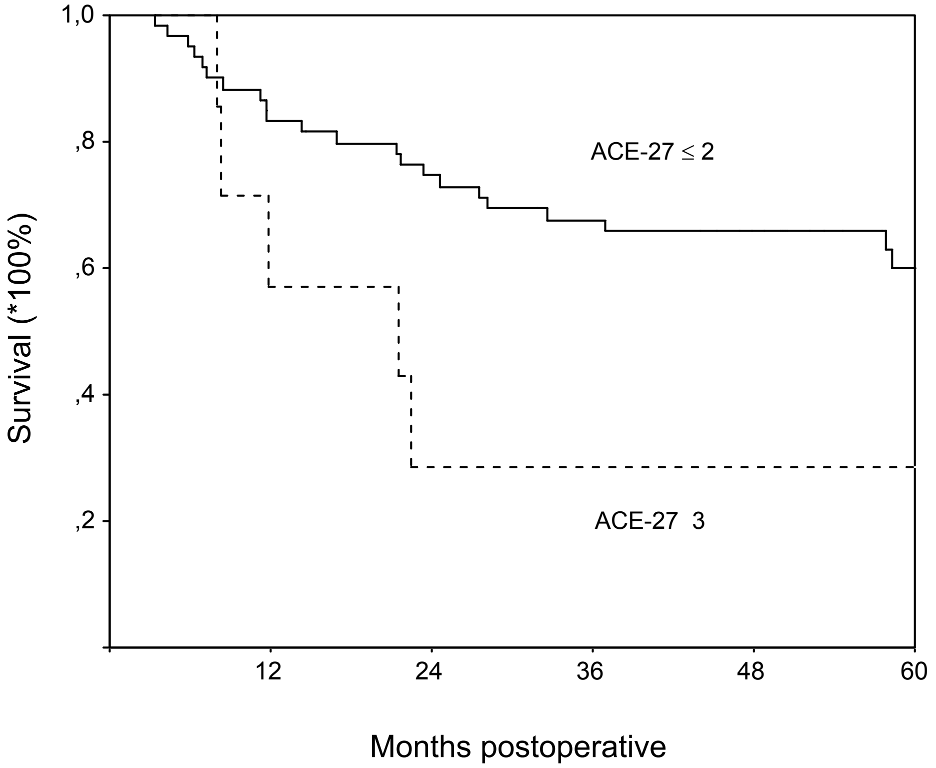
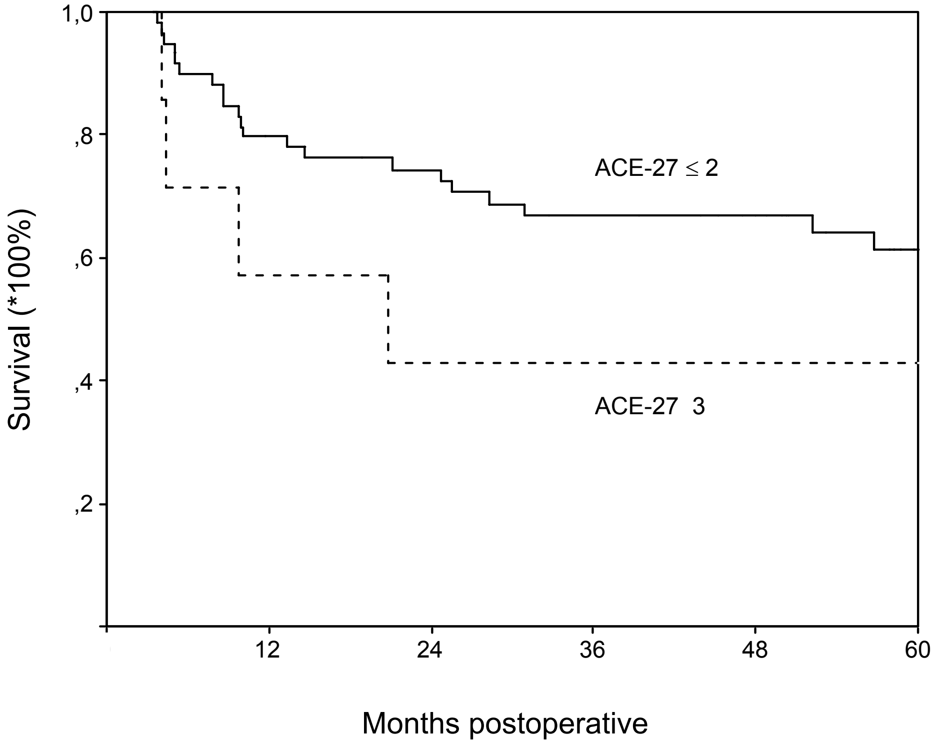


Figure 3. Kaplan-Meier tumor specific survival by comorbidity (p = 0.34)



For multivariate analysis Cox regression was done to study the possible confounding effect of gender (female versus male), tumor site (oral versus oropharynx), tumor stage (II, III, IV dichotomized), margin status (tumor-free versus not tumor-free), postoperative radiotherapy (yes or no) and complications (mild, moderate, severe dichotomized) on the association between comorbidity and survival. None of the factors significantly influenced this relationship.

Discussion

This study analysis the impact of comorbidity on survival of head and neck patients. Using the ACE-27 test, we were able to demonstrate a negative impact in a homogeneous and well-defined head and neck patient population. All tumors were localized within a limited number of two sites within the head and neck (the oral cavity and oropharynx) and patients were treated within a 4-year period in which treatment policy (as to indications for surgery, reconstruction and radiotherapy) remained unchanged.

Comorbidity was present in 83% of the patients, including 47% that had an advanced comorbidity score (i.e., moderate and severe comorbidity) and 13% with a severe comorbidity. Comparable comorbidity scores are reported in the literature. In a cost analysis study of 73 oral cancer patients, Funk et al. reported comparable overall and advanced comorbidity scores of 75% and 45%, respectively.[23] In a study by Pugliano et al., 8% of the investigated patients showed a severe comorbidity, while Paleri et al. reported an incidence of 21%.[15,24]

The American Cancer Society Facts & Figures 2003 reports a 5-years survival of 56% for oral cavity and pharynx tumors.[25] This percentage represents an overall tumor stage. In our study the overall 5-years survival was 62 %: for oral cavity this was 58% for oropharynx 65%. In other studies, with broad variety of oral/oropharyngeal cancer patients and with different treatment modalities, an overall 5-years survival percentage between 38% and 77% is reported.[24,26-28]

The TNM staging system, based on anatomical extension only, is considered the most important and reproducible prognostic indicator.[19,29] Piccirillo et al. and others have described the prognostic importance of comorbidity in different scoring systems on the survival of surgically treated oncologic patients.[7,8,30] In the present study, as expected, tumor stage showed a strong statistical influence on overall survival. Furthermore patients with tumor-free margin status showed a significant better survival (67%) than those without tumor-free margin status (38%). Patel and Shah described a similar outcome.[31] However, another important significant predictor for survival without multivariate confounding effect of other variables was comorbidity as assessed by the ACE-27 system. This confirms the important role of comorbidity within surgically treated patients with oral and oropharyngeal carcinoma.

Patients with severe comorbidity (ACE-27 grade 3) showed a statistically significant lower survival rate than patients with an ACE-27 grade ≤ 2; 29% versus 64%, $p=0.039$.

Further analysis of the comorbidity groups separately did not reveal any significant differences. This emphasizes the important role of especially severe comorbidity. Severe comorbidity was not a significant prognostic factor for cause-specific and disease free survival. Singh et al. described a significant influence of comorbidity on disease free survival in a similar patient group.[6] They stated that the reason for this influence was unclear but postulated that this might be because of a lower level of anti-tumor activity in patients with advanced comorbidity.

Within the comorbidity ACE-27 grade 3 patient group, the cause of death was roughly equally divided into tumor related death (38%) and death without evidence of disease (31%). For patients with an ACE-27 grade ≤ 2 there were only 6 out of 87 (7%) patients who died without evidence of disease. This difference was statistically significant. Although some report a poorer tumor specific survival for patients with severe comorbidity [32], our results shows a clear impact on survival by NED death. These results implicate that comorbidity plays an important role in survival for the head and neck patient, but this influence is mainly related to the comorbidity itself and probably not to the cancer.

Our study contributes in two ways to the generally accepted idea that comorbidity should get a more prominent role in the management of cancer patients. The main reason is that survival estimates in head and neck cancer might be improved by addition of comorbidity to the current TNM staging system. The second reason is that patients with the highest comorbidity score (e.g., grade 3) showed a poor 5-years survival of 29 %. Refraining from major surgery for this group of patients, particularly in oropharyngeal cancer, should be considered when reasonable treatment alternatives are available.[33] Based on information of the current study, patient counseling may improve. Moreover, inclusion of comorbidity in a prognostic staging system may result in a more balanced choice of treatment.

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Chapter 4

Quality of Life and Functional Status in Patients with Cancer of the Oral Cavity and Oropharynx: Pretreatment Values of a Prospective Study

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Submitted

Abstract

Background: In this study we investigated the pretreatment health-related quality of life (HRQOL) and functional status of patients with advanced oral and oropharyngeal cancer.

Methods: Eighty patients were investigated. HRQOL was assessed by EORTC QLQ-C30/QLQ-H&N35 questionnaires. Functional status assessment comprised speech and oral function tests.

Results: The results indicated that a wide range of HRQOL and functional deficits were present before treatment. HRQOL appeared to be related to some extent to tumor site (patients with oral tumors reported more pain ($p<.05$) than patients with oropharyngeal tumors) and tumor classification (patients with T3-T4 tumors reported more trouble opening the mouth ($p<.05$) and felt more ill ($p<.05$) than patients with T2 tumors). Comorbidity appeared to have a major impact. Patients with comorbidity had significantly worse scores ($p<.05$) on several scales/items of both the EORTC questionnaires. Functional deficits were related to tumor site, classification and comorbidity. Patients with oral cavity tumors (versus oropharyngeal tumors), patients with T3-T4 tumors (versus T2 tumors), and patients with comorbidity (versus without comorbidity) scored significantly worse ($p<.05$) on several speech and oral function tests. Impaired speech and oral function appeared to be clearly related to global quality of life (QLQ-C30) and self-reported speech (QLQ-H&N35).

Conclusions: Many patients with advanced oral and oropharyngeal cancer have compromised HRQOL and functional status before the start of treatment. In addition to tumor site and tumor classification, comorbidity appears to have a major impact on HRQOL and functional status. Knowledge of pretreatment HRQOL and functional status levels is useful for better understanding the impact of treatment on these outcomes over time.

Introduction

The most important outcome for cancer patients is overall survival. However, the disease and its treatment often have a major impact on health-related quality of life (HRQOL) and functional status, which may hamper coping with the disease.[1] Therefore, HRQOL and functional status are important outcomes to consider in the evaluation of the treatment of patients with head and neck cancer.[2] To interpret outcomes following treatment, it is necessary to assess HRQOL and functional status following diagnosis, but before the start of treatment.[3,4]

Studies of pretreatment HRQOL [2,3,5-8] and functional status [9-12] often include heterogeneous groups of head and neck cancer patients. However, there are substantial differences between patient groups that are related to tumor site and stage.[13] Patients with advanced oral or pharyngeal cancer, for example, often have the poorest HRQOL and functional status.[8,14,15] The pretreatment levels of HRQOL among patients with oral or oropharyngeal cancer is often compromised, although it tends to be better than that observed following treatment.[16-21] There is also evidence that functional status, including oral function, speech and swallowing abilities is significantly deteriorated before treatment.[4,22-27] Comorbidity is another important factor that can vary substantially among subpopulations of patients, and can have a significant influence on the choice of initial treatment, the care that patients receive, and on treatment outcomes.[28] It is thus important to take comorbidity into consideration when evaluating the HRQOL of patients, both at time of diagnosis, and over the course of treatment.[29-31]

The primary objective of this study was to describe pretreatment HRQOL and functional status in relation to tumor site, tumor classification and comorbidity, in a well-defined group of patients with advanced oral and oropharyngeal cancer.

Patients and Methods

Patients

Between January 1998 and December 2001, 92 consecutive patients diagnosed with stage II-IV oral or oropharyngeal squamous cell carcinomas were asked to participate in the study. The planned treatment was composite resection with microvascular soft tissue transfer (i.e., radial forearm free flap) for the reconstruction of surgical defects, and radiotherapy on indication. Exclusion criteria were age greater than 75 years, serious cognitive impairment and lack of basic fluency in the Dutch language. Twelve patients declined to participate in the study, resulting in a final sample of 80 patients (response rate = 87%). All patients were treated at the Department of Otolaryngology-Head and Neck Surgery of the VU University Medical Center, Amsterdam, The Netherlands.

Data collection and study measures

All data were collected prior to the start of treatment. This included sociodemographics (age and gender), disease stage [32], comorbidity, and HRQOL. Comorbidity was established by review of medical records and on the basis of self-report, and was noted when a patient had one or more relevant medical ailments that accompanied their primary medical illness. These comorbid conditions were cardiovascular, respiratory, gastro-intestinal, renal, endocrine, neurological, and immunological disorders, previous malignancy and considerable weight loss or alcohol abuse. For example; cardiovascular problems such as a myocardial infarct or hypertension, respiratory problems such as restrictive lung disease or COPD, or endocrine disorders such as diabetes mellitus with insulin usage were defined as relevant comorbid conditions.

HRQOL was assessed with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (version 2.0) [33] and the EORTC head and neck cancer module QLQ-H&N35.[34] The QLQ-C30 is composed of multi-item scales and single items assessing 5 areas of functioning (physical, role, emotional, cognitive, and social), fatigue, pain, emesis, dyspnea, insomnia, appetite loss, constipation, and diarrhea. Overall quality of life and the perceived financial impact of the disease and treatment are also assessed. The head and neck cancer-specific QLQ-H&N35 module comprises 7 symptom scales: pain, swallowing, senses, speech, social eating, social contact, and sexuality. There are 11 additional, single items covering problems with teeth, opening the mouth wide, dry mouth, sticky saliva, cough, feeling ill, weight loss, weight gain, use of nutritional supplements, feeding tubes, and painkillers. The scores of both the QLQ-C30 and of the QLQ-H&N35 are linearly transformed to a scale of 0 to 100, with a higher score indicating a higher (i.e., more positive) level of functioning or global HRQOL, or a higher (i.e., more negative) level of symptoms or problems.

To place the HRQOL results in a broader perspective, the QLQ-C30 data of the patients were compared with published normative data from the general population of Norway (no such population-based data are available for The Netherlands).[35] Comparisons were made with that part of the normative sample that corresponded as closely as possible to the age and gender distribution of the patient sample (i.e., normative subsample with age range of 50-59 years and 48% female). The QLQ-C30 results were also compared with EORTC "reference values" derived from a large, international sample of head and neck cancer patients.[36] The QLQ-H&N35 results were compared with reference values derived from a randomly selected sample of the Swedish general population that had participated in a study of dysphagia (again no such population-based data are available for The Netherlands).[14]

Speech and oral functional status

Speech analyses were performed according to a standardized speech assessment protocol. Speech recordings of a read aloud text were performed in a sound-treated room and digitized using Cool Edit PRO 1.2 (Adobe Systems Incorporated, San Jose, California, USA) with 22 kHz sample frequency and 16-bit resolution. Recording level was adjusted for each speaker to optimize signal-to-noise ratio. All recordings were made with a mouth-to-microphone distance of 30 cm. A computer program was developed to perform blinded randomized speech evaluation and to score overall intelligibility, and quality of articulation and nasal resonance. Overall intelligibility was assessed on a 10-point scale ranging from poor to excellent by 2 trained speech therapists. Scores below 6 were defined as insufficient intelligibility (according to the Dutch educational system). To obtain more insight into the cause of decreased intelligibility, evaluation of the quality of articulation and nasal resonance was performed by the same two speech therapists on a 4-point scale ranging from deviant (score 1-3) to normal (score 4). Speech rate was measured by calculating words per minute on a read aloud standardized text.

Oral function was evaluated by a trained investigator according to a protocol described by Teichgraeber et al.[37] All assessments were based on 5-point scales ranging from poor to excellent (transformed scores ranging from 0-100). The oral function evaluation included three tests; 1) tongue mobility (mean score of tongue straight out, elevation of tongue tip, elevation of the base of the tongue, tongue deviation left and right, symmetry left and right, and tongue withdrawal), 2) lip mobility (mean score of general movement, spreading and rounding, symmetry left/right, lip closure without speech, and lip closure during speaking), and 3) diadochokinesis (mean score of repetitive motion ability concerning tongue movement left/right, up/down, and in/out, and repeating the syllables /ta/ /cha/, and /ka/). Tongue and lip strength were quantified by a calibrated digital voltameter. To measure tongue strength the patient was asked to push the tongue against a metallic disc with the lips positioned around a cylinder, and to resist the force. To measure lip strength, the patient was asked to keep his lips around a button with a string attached to it on which the examiner pulled. Scores ranged from 0 (no strength) to 0.5 mV (normal strength).

Statistical analyses

Chi-square tests were used to assess associations between the independent variables tumor site, classification and comorbid condition. Student's t-tests were performed to test for statistically significant differences between the patient sample and the normative or reference samples. These tests were based on the mean scores of the study sample, the mean scores of the reference sample and the standard deviations of the study sample only, because no standard deviations of reference samples were available. Student's t-tests (HRQOL) and Mann-Whitney tests (functional status) were performed to determine the impact of tumor site (oral versus oropharyngeal), tumor classification (T2 versus T3-T4) and comorbidity (yes or no). Spearman correlation coefficients (r) were calculated to investigate the association between self-reported HRQOL (i.e., the QLQ-C30 global quality of life scale and the QLQ-H&N35 speech scale) and speech and oral functional status. Statistical significance was defined as a p-value less than or equal to .05.

Results

Sample description

Patient characteristics are shown in Table 1. The patients' age ranged from 23 to 74 years (mean = 58 years). Forty-one percent of the sample was female. One patient was operated on for a recurrent tumor after prior transoral excision (1 year earlier) in which the rTNM stage was used, and one patient had undergone previous radiotherapy (3 years earlier) for a neck node of an unknown primary. Four patients had a synchronous second primary tumor, and in these cases the stage of the largest tumor was used. An equal percentage (50%) of patients had a tumor originating on the left or right side, and in the majority of patients (73%) the tumor did not extend over the median line. All 80 patients completed the EORTC questionnaires, speech rate tests (word count) and oral function tests (mobility and strength). For one patient the speech recording could not be done due to logistical problems, and for 3 patients speech recordings were inadequate for interpretation due to technical problems. Thus speech quality analyses could be performed on 76 patients. Presence of comorbid conditions and tumor classification were significantly associated. Significantly more patients with comorbidity were diagnosed with a larger tumor (χ^2 =10.37, p<.01). No other significant associations were observed between tumor site, tumor classification, age, gender and comorbidity.

Health-related quality of life

The results pertaining to the EORTC QLQ-C30 and QLQ-H&N35 questionnaires are reported in Table 2. The patient sample scored significantly worse than the general population reference sample on 5 (out of 15) scales or single items of the QLQ-C30: role functioning (p=.000), emotional functioning (p=.000), pain (p=.026), insomnia (p=.016) and appetite loss (p=.003). Conversely, patients scored significantly better than the general population reference sample on 4 (out of 15) scales or single items of the QLQ-C30: social functioning (p=.009), fatigue (p=.030), emesis (p=.001), and diarrhea (p=.001).

Table 1. Characteristics of 80 patients included in this study

Age		
Range	23 – 74	yrs
Mean	58	yrs
	n	%
Gender		
Male	47	(59)
Female	33	(41)
General condition		
Comorbidity	48	(60)
No comorbidity	32	(40)
Tumor site		
Oral cavity	38	(47)
Oropharynx	42	(53)
T		
2	35	(44)
3	42	(52)
4	3	(4)
N		
0	24	(30)
1	16	(19)
2a	2	(3)
2b	30	(38)
2c	6	(7)
3	2	(3)

For the QLQ-H&N35, the patient sample scored significantly worse on 7 (out of 10) scales or single items, compared to the general population reference sample: pain (p=.000), swallowing (p=.000), senses (p=.050), social eating (p=.000), teeth (p=.009), opening the mouth wide (p=.000) and sticky saliva (p=.005). Conversely, the patients scored significantly better than the reference sample on 2 items: coughing (p=.002) and feeling ill (p=.025). Comparison regarding the remaining scales and single items of the QLQ-H&N35 could not be made, because these data were not reported in the paper by Hammerlid et al.[14]

Table 2. EORTC QLQ-C30 and QLQ-H&N35 mean scores of patients with oral/oropharyngeal cancer (this study) and normative population scores as reported in literature * #

	This study	Reference *	
	Mean (SD) n=80	Mean n=298	p ‡
EORTC QLQ-C30			
Physical Functioning	87.0 (19.4)	85.3	.487
Role Functioning	81.7 (22.6)	92.5	**.000**
Cognitive Functioning	88.1 (18.8)	86.3	.448
Emotional Functioning	71.1 (24.0)	83.6	**.000**
Social Functioning	90.4 (18.7)	84.2	**.009**
Global quality of life	75.9 (20.2)	73.1	.272
Fatigue	21.7 (23.3)	28.1	**.030**
Emesis	1.5 (4.7)	3.5	**.001**
Pain	31.7 (30.2)	23.2	**.026**
Dyspnea	8.8 (18.9)	12.8	.094
Insomnia	33.3 (37.9)	21.8	**.016**
Appetite loss	14.2 (28.0)	3.5	**.003**
Constipation	13.3 (29.3)	11.2	.570
Diarrhea	5.4 (13.5)	11.4	**.001**
Financial impact §	5.4 (17.1)	--	**--**
	This study	**Reference #**	
	Mean (SD) n=80	Mean n=270	
EORTC QLQ-H&N35			
Pain	35.7 (23.7)	3	**.000**
Swallowing	20.3 (22.9)	3	**.000**
Senses	7.7 (18.9)	3	**.050**
Social eating	22.3 (27.0)	1	**.000**
Teeth	23.8 (35.3)	12	**.009**
Opening mouth	18.3 (32.7)	1	**.000**
Dry mouth	19.6 (27.9)	17	.460
Sticky saliva	17.9 (30.4)	7	**.005**
Coughing	11.3 (19.1)	19	**.002**
Feeling ill	5.8 (14.8)	10	**.025**

* Hjermstad M, et al. [35] Part of the sample of general Norwegian population

\# Hammerlid E, et al. [14] Randomly selected population of Sweden inhabitants

‡ The result of the t-test (p-value) was based on the mean score of the study sample, the mean score of the reference sample and the standard deviation of the study sample

§ Comparison of financial impact was not made as this is not a relevant question for the general population

A number of statistically significant differences were found when comparing the QLQ-C30 data for the current sample with those derived from the EORTC reference values for patients with oral cavity and (oro)pharynx tumors (Table 3). Specifically, the current sample of patients with oral cavity tumors reported significantly more pain (p=.015), but significantly less emesis (p=.020) and dyspnea (p=.003) than those in the EORTC reference values sample. Patients in the current study with oropharynx tumors reported a significantly better global quality of life (p=.043) and less emesis (p=.001), dyspnea (p=.014) and financial difficulties (p=.001) than the patients with (oro)pharynx tumors from the EORTC reference values sample.

Table 3. EORTC QLQ-C30 scores for tumor site of patients in this study and EORTC Reference Values *

	Tumor site			**Tumor site**		
	Oral cavity this study	**Oral cavity EORTC QLQ-C30 Reference Values ***		**Oropharynx this study**	**(Oro)pharynx EORTC QLQ-C30 Reference Values ***	
	Mean(SD) n=38	Mean n=279	p ‡	Mean(SD) n=42	Mean n=72	p ‡
EORTC QLQ-C30						
Physical Functioning	88.9 (18.4)	87.0	.552	85.2 (20.3)	86.4	.714
Role Functioning	78.9 (24.1)	84.3	.200	84.1 (21.1)	84.0	.981
Cognitive Functioning	88.2 (19.3)	87.0	.719	88.1 (18.5)	85.7	.506
Emotional Functioning	70.8 (24.9)	68.8	.643	71.4 (23.5)	70.1	.776
Social Functioning	89.0 (19.1)	84.8	.184	91.7 (18.5)	85.1	.063
Global quality of life	73.7 (20.4)	68.6	.149	78.0 (20.1)	70.0	**.043**
Fatigue	24.3 (26.3)	25.9	.725	19.3 (20.2)	26.1	.086
Emesis	1.8 (5.2)	3.9	**.020**	1.2 (4.3)	4.0	**.001**
Pain	39.5 (32.5)	25.7	**.015**	24.6 (26.3)	22.5	.682
Dyspnea	6.1 (15.2)	14.0	**.003**	11.1 (21.7)	21.6	**.014**
Insomnia	36.8 (39.4)	29.1	.259	30.2 (36.7)	31.9	.812
Appetite loss	14.0 (32.5)	17.7	.511	14.3 (23.4)	21.1	.137
Constipation	12.3 (26.2)	8.5	.402	14.3 (32.2)	12.2	.738
Diarrhea	6.1 (13.1)	4.7	.537	4.8 (13.9)	8.6	.162
Financial impact	7.9 (19.7)	11.4	.305	3.2 (14.4)	12.7	**.001**

* Fayes P, et al. [36] EORTC “reference values” derived from a large, international sample of head and neck cancer patients

‡ The result of the t-test (p-value) was based on the mean score of the study sample, the mean score of the reference sample and the standard deviation of the study sample

The association between tumor site and HRQOL is shown in Table 4. In general, the QLQ-C30 results were comparable between oral cavity and oropharynx cancer patients. Only the pain score was significantly worse (p=.027) for patients with oral cavity tumors as compared to patients with oropharynx tumors. Results from the QLQ-H&N35 indicate that patients with oral cavity tumors had significantly more pain (p=.002) and problems with their teeth (p=.001), and tended to report more problems with a dry mouth (p=.074) and sticky saliva (p=.063) than patients with oropharynx tumors.

Table 4. EORTC QLQ-C30 and QLQ-H&N35 scores for tumor site

	Tumor site		
	Oral cavity	**Oropharynx**	
	Mean (SD) n=38	Mean (SD) n=42	p
EORTC QLQ-C30			
Physical Functioning	88.9 (18.4)	85.2 (20.3)	.396
Role Functioning	78.9 (24.1)	84.1 (21.1)	.309
Cognitive Functioning	88.2 (19.3)	88.1 (18.5)	.988
Emotional Functioning	70.8 (24.9)	71.4 (23.5)	.913
Social Functioning	89.0 (19.1)	91.7 (18.5)	.533
Global quality of life	73.7 (20.4)	78.0 (20.1)	.347
Fatigue	24.3 (26.3)	19.3 (20.2)	.346
Emesis	1.8 (5.2)	1.2 (4.3)	.598
Pain	39.5 (32.5)	24.6 (26.3)	**.027**
Dyspnea	6.1 (15.2)	11.1 (21.7)	.243
Insomnia	36.8 (39.4)	30.2 (36.7)	.434
Appetite loss	14.0 (32.5)	14.3 (23.4)	.968
Constipation	12.3 (26.2)	14.3 (32.2)	.762
Diarrhea	6.1 (13.1)	4.8 (13.9)	.650
Financial impact	7.9 (19.7)	3.2 (14.4)	.221
EORTC QLQ-H&N35			
Pain	44.1 (21.6)	28.2 (23.1)	**.002**
Swallowing	20.2 (20.7)	20.4 (25.0)	.960
Senses	3.5 (10.4)	11.5 (23.7)	.059
Speech	12.3 (16.9)	10.8 (15.8)	.696
Social eating	23.0 (22.9)	21.6 (30.5)	.819
Social contact	4.0 (6.5)	3.0 (6.5)	.484
Sexuality	20.1 (30.4)	12.9 (22.2)	.245
Teeth	36.8 (40.1)	11.9 (25.3)	**.001**
Opening mouth	16.7 (29.8)	19.8 (35.4)	.667
Dry mouth	25.4 (32.4)	14.3 (22.3)	.074
Sticky saliva	24.6 (33.5)	11.9 (26.4)	.063
Coughing	7.9 (16.3)	14.3 (21.0)	.136
Feeling ill	5.3 (12.3)	6.3 (16.8)	.745

No statistically significant differences were observed for any of the QLQ-C30 scores as a function of tumor classification (T2 versus T3-T4; data not shown). For the QLQ-H&N35, patients with T3-T4 tumors scored significantly worse on opening the mouth (p=.009) and reported feeling more ill (p=.035) than patients with T2 tumors. No other significant differences were observed between patients on the basis of tumor classification.

Table 5. EORTC QLQ-C30 and QLQ-H&N35 scores for comorbidity

	Comorbidity		
	No	**Yes**	
	Mean (SD) n=32	Mean (SD) n=48	p
EORTC QLQ-C30			
Physical Functioning	95.0 (12.4)	81.7 (21.4)	**.002**
Role Functioning	85.4 (18.3)	79.2 (24.9)	.228
Cognitive Functioning	89.6 (18.3)	87.2 (19.2)	.574
Emotional Functioning	69.5 (23.4)	72.2 (24.6)	.626
Social Functioning	93.2 (13.3)	88.5 (21.5)	.275
Global quality of life	82.6 (19.6)	71.5 (19.7)	**.016**
Fatigue	13.9 (20.0)	26.9 (24.1)	**.014**
Emesis	1.6 (4.9)	1.4 (4.7)	.874
Pain	22.4 (25.3)	37.8 (31.8)	**.024**
Dyspnea	6.3 (19.7)	10.4 (18.4)	.338
Insomnia	36.5 (36.3)	31.3 (39.1)	.550
Appetite loss	7.3 (20.3)	18.7 (31.4)	.072
Constipation	5.2 (20.9)	18.7 (32.9)	**.042**
Diarrhea	1.0 (5.9)	8.3 (16.1)	**.017**
Financial impact	2.1 (8.2)	7.6 (20.9)	.157
EORTC QLQ-H&N35			
Pain	27.1 (17.6)	41.5 (25.5)	**.007**
Swallowing	14.6 (22.6)	24.1 (22.6)	.068
Senses	6.3 (14.5)	8.7 (21.5)	.577
Speech	9.4 (14.1)	13.0 (17.5)	.336
Social eating	14.6 (25.3)	27.4 (27.1)	**.036**
Social contact	3.1 (7.0)	3.7 (6.1)	.674
Sexuality	16.1 (24.9)	16.3 (27.6)	.981
Teeth	13.5 (26.6)	30.6 (38.8)	**.034**
Opening mouth	7.3 (20.3)	25.7 (37.2)	**.013**
Dry mouth	15.6 (26.8)	22.2 (28.6)	.303
Sticky saliva	12.5 (29.0)	21.5 (31.1)	.196
Coughing	6.3 (13.2)	14.6 (21.6)	.055
Feeling ill	0 (0)	9.7 (18.1)	**.003**
	% Yes	% Yes	
Pain medication	50.0	75.0	**.022**

The association between comorbidity and HRQOL is shown in Table 5. Patients with one or more comorbid conditions scored significantly worse on physical functioning (p=.002), global quality of life (p=.016), fatigue (p=.014), pain (p=.024), constipation (p=.042) and diarrhea (p=.017) than patients without comorbidity. Additionally, based on the QLQ-H&N35 data, patients with comorbidity reported significantly more pain (p=.007), trouble with social eating (p=.036), teeth problems (p=.034), problems with opening the mouth (p=.013) and feeling ill (p=.003). The use of pain medication was significantly higher among patients with than those without comorbidity (75% versus 50%; p=.025).

Speech and oral functional status

Abnormal scores were observed in 17% of the patients for overall intelligibility, in 25% for nasality and in 37% for articulation. Functional results in relation to tumor site, classification and comorbidity are shown in Table 6. Patients with oral cavity tumors were rated significantly worse on intelligibility (p=.015), articulation (p=.039), nasality (p=.040), tongue and lip mobility (p=.000, p=.009), diadochokinesis (p=.004), and tongue strength (p=.001) than patients with oropharyngeal tumors. No significant differences as a function of tumor site were found for speech rate or lip strength.

Table 6. Functional status tests for tumor site, tumor stage and comorbidity

	Tumor site			**Tumor stage**			**Comorbidity**		
	Oral cavity	**Oropharynx**		**T2**	**T3-T4**		**No**	**Yes**	
	Mean (SD) n=37	Mean (SD) n=39	p	Mean (SD) n=32	Mean (SD) n=44	p	Mean (SD) n=29	Mean (SD) n=47	p
Intelligibility:									
-(0-10)	6.0 (1.3)	6.7 (1.0)	**.015**	6.8 (1.0)	6.0 (1.2)	**.011**	6.6 (1.0)	6.2 (1.3)	.132
Articulation:									
-(0-4)	3.4 (0.8)	3.7 (0.6)	**.039**	3.8 (0.4)	3.3 (0.8)	**.003**	3.8 (0.4)	3.4 (0.8)	**.043**
Nasality:									
-(0-4)	3.6 (0.6)	3.8 (0.4)	**.040**	3.8 (0.4)	3.7 (0.6)	.911	3.7 (0.4)	3.7 (0.5)	.771
	n=38	n=42		n=35	n=45		n=32	n=48	
Rate:									
-Words p/minute	183 (31.6)	182 (38.5)	.988	189 (33.8)	178 (35.8)	.201	189 (31.4)	179 (38.1)	.233
	n=38	n=42		n=35	n=45		n=32	n=48	
Oral functions:									
Mobility:									
-Tongue (0-100)	82.3 (20.0)	96.4 (5.4)	**.000**	96.0 (5.8)	84.8 (19.3)	**.001**	93.9 (9.9)	89.9 (14.4)	.209
-Lip (0-100)	87.4 (5.7)	99.7 (0.9)	**.009**	99.4 (2.0)	98.0 (5.1)	.140	99.3 (2.2)	98.5 (3.9)	.239
-Diadoch.(0-100)	87.4 (20.7)	97.2 (6.1)	**.004**	97.5 (5.0)	88.7 (19.6)	**.012**	97.4 (5.1)	91.5 (15.4)	**.026**
Strength:									
-Tongue (0-0.5)	0.2 (0.2)	0.4 (0.2)	**.001**	0.4 (0.2)	0.3 (0.2)	**.021**	0.4 (0.2)	0.2 (0.2)	**.045**
-Lip (0-0.5)	0.3 (0.1)	0.4 (0.2)	.328	0.4 (0.2)	0.3 (0.1)	**.018**	0.4 (0.2)	0.3 (0.1)	.370

Patients with T3-T4 tumors were rated significantly worse on intelligibility (p=.011), articulation (p=.003), tongue mobility (p=.001), diadochokinesis (p=.012), and tongue and lip strength (p=.021, p=.018) than patients with T2 tumors. No statistically significant associations were observed between tumor classification and nasality, speech rate or lip mobility. Patients with comorbidity were rated significantly worse on articulation (p=.043), diadochokinesis (p=.026), and tongue strength (p=.045) as compared to patients without comorbidity. No statistically significant associations between comorbidity and intelligibility, nasality, speech rate, tongue, or lip mobility and strength were observed.

Correlations between self-report and observer rated data

Significant correlations (p<.01) were observed between self-reported global quality of life scale (QLQ-C30) and observer ratings of intelligibility (r=.41) and articulation (r=.36) (Table 7). Additionally, statistically significant (p<.05) but relatively low correlations were found between self-reported speech (QLQ-H&N35) and observer ratings of intelligibility (r=-.28), articulation (r=-.24), nasality (r=-.27), and diadochokinesis (r=-.28).

Table 7. Correlations between functional status tests and QLQ-C30 global quality of life scale / QLQ-H&N35 speech problems

	Scales			
	QLQ-C30 global quality of life		**QLQ-H&N35 speech problems**	
	Correlation coefficient (r) n=76	p	Correlation coefficient (r) n=76	p
Speech:				
Intelligibility:	.411	**.000**	-.285	**.013**
Articulation:	.355	**.002**	-.242	**.035**
Nasality:	.152	.190	-.270	**.019**
	n=80		n=80	
Rate:	.129	.267	-.142	.221
	n=80		n=80	
Oral functions:				
Mobility:				
-Tongue	.078	.490	-.188	.095
-Lip	.157	.164	-.176	.119
-Diadochokinesis	.109	.337	-.280	**.012**
Strength:				
-Tongue	.188	.095	-.175	.121
-Lip	.056	.624	-.049	.665

Discussion

In this study, pretreatment HRQOL and functional status were investigated in a well-defined sample of patients with advanced oral and oropharyngeal cancer. Deteriorated HRQOL and functional status before treatment have been reported in earlier studies, albeit for less well defined patient groups.[16-26] The results of this study indicate that a wide range of HRQOL and functional deficits were present in patients with advanced oral and oropharyngeal cancer before treatment. Impaired speech and oral function, as assessed objectively, were associated significantly with self-reported global HRQOL and speech problems, which is in accordance with the conclusions of Rogers et al. and Karnell et al.[25,38]

Compared to the general population, patients scored significantly worse on 5 of 15 scales or items of the EORTC QLQ-C30 but, conversely, they scored significantly better on 4 others. Regarding the QLQ-H&N35, patients scored significantly worse on most scales or items but significantly better on coughing and feeling ill. The significantly better scores for patients compared to the reference groups on some scales or items may be explained by the fact that people from the general population may have (other) chronic conditions as well. Alonso et al. reported that, 55% of the general population has one chronic health condition, and 30% has more than one chronic condition.[39] They also found that comorbidity can have a substantial impact on HRQOL, and that the presence of comorbidity limits the ability to attribute HRQOL deficits to one specific disease (e.g., to head and neck cancer).

In head and neck cancer patients, comorbidity has proven to be an important factor associated with complications and mortality rates.[40-44] Studies of the impact of comorbidity on functional status in head and neck cancer patients are lacking, and those that have examined the impact of comorbid status on HRQOL are scarce, have yielded conflicting results, and have examined the post-treatment period only. Pourel et al. found no significant association between comorbidity and HRQOL in 113 long-term survivors 2 years after treatment of oropharynx carcinomas.[29] Similarly, Taylor et al. found no impact of comorbidity on work-related disability among 384 patients after treatment for head and neck cancer.[45] However, Terrel et al., in a study of the HRQOL of 570 head and neck cancer patients after treatment, reported a clear effect of comorbidity for patients with 2 or more comorbid conditions.[31] In our study of patients with oral or oropharynx carcinomas before treatment, comorbidity was present in 60% of the patients, and was found to have a major impact on HRQOL and functional status. Patients with comorbidity had significantly worse scores on several items and scales of both EORTC QLQ-C30 and QLQ-H&N35 and scored significantly worse on speech and oral function tests than patients without comorbidity.

HRQOL was found to have only a relatively modest association with tumor site and classification, with patients with oral cavity tumors reporting more pain, and patients with T3-T4 tumors reporting more trouble opening the mouth and feeling more ill. With regard to tumor site, comparisons with earlier studies are difficult because most studies have investigated patients with oral cavity tumors only or heterogeneous samples not stratified by (sub)sites.[6,16-21] Other studies have reported worse HRQOL for patients with higher tumor classifications and stages before treatment.[3,19,27]

Tumor site and classification were found to have a clear impact on functional status. Patients with oral cavity tumors (versus oropharynx tumors) and patients with T3-T4 tumors (versus T2 tumors) had worse speech and oral function scores, which is in accordance with the results of earlier studies.[4,11,23,25,46]

In conclusion, we observed compromised HRQOL and functional deficits among patients with advanced oral and oropharyngeal cancer before the start of treatment. In addition to the impact of tumor site and classification, comorbidity had a major impact on HRQOL and functional status. Prospective studies are needed to better understand the effect of pretreatment HRQOL and functional status on outcome after treatment, and the relationship between changes in HRQOL and functioning over time and tumor site, tumor classification, and comorbid conditions.

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Chapter 5

Speech Outcome after Surgical Treatment for Oral and Oropharyngeal Cancer: A Longitudinal Assessment of Patients Reconstructed by a Microvascular Flap

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Abstract

Background: The aim of the study is to analyze speech outcome for advanced oral/oropharyngeal cancer patients treated with reconstructive surgery and adjuvant radiotherapy.

Methods: Speech tests (communicative suitability, intelligibility, articulation, nasality and consonant errors) were performed in a control group, before (n=76), and 6 (n=51) and 12 (n=42) months after treatment.

Results: Speech tests were significantly worse for patients, before and after treatment, as compared to the controls. Speech did not improve between 6 and 12 months. After treatment, patients with T3-T4 tumors showed a significantly worse score for communicative suitability, intelligibility and articulation than patients with T2 tumors. No significant differences were found for subsites after treatment, although patients with mobile tongue tumors showed the best results.

Conclusion: Speech difficulties are significant and with the knowledge of this study better counseling and vigilance as to speech difficulties may be possible in patients undergoing treatment for oral/oropharyngeal cancer.

Introduction

Head and neck cancer and its treatment may negatively affect the patient's functional status. Shortly following treatment, a significant number of patients encounter speech deterioration, swallowing limitations, facial appearance changes and psychological problems.[1-5] Longitudinal data reveal that quality of life after treatment only gradually improves during the first year,[6-8] but swallowing and speech difficulties continue to exist.[9-11] Oral and oropharyngeal cancer patients are especially prone to speech difficulties.[12]

Speech outcome is dependent on residual mobility of structures in the oral cavity and oropharynx. The past 20 years have shown an improvement in the technical possibilities of replacing ablated tissues in the oral cavity and oropharynx by regional or distant flaps. Free fasciocutaneous flaps, such as the radial forearm free flap (RFFF), have become the preferred method of reconstruction for larger soft tissue defects in the oral cavity and oropharynx because of their reliability and improved functional characteristics of dynamic structures such as the tongue and pharynx.[13-15]

Speech outcome is assessed by using indicators of speech production (oral function and articulation tests, aerodynamic and acoustical analyses), speech perception (intelligibility and acceptability), and self-reported speech adequacy in every-day-life situations (questionnaires). There are numerous methodological differences between studies on speech quality of patients treated for oral or oropharyngeal cancer.[16-20] Nevertheless, it can be concluded that speech difficulties are highly dependent on tumor size and site. Expectantly, patients undergoing resection of larger tumors have more speech difficulties. After resection of oral carcinomas, patients encounter articulation problems due to tissue loss, structure alteration, or tongue mobility impairment. Target sounds may be distorted, substituted, or omitted leading to decreased intelligibility. Speech production problems of patients with oropharyngeal defects include nasal resonance problems due to velopharyngeal inadequacy. In case of tissue loss or mobility impairment, air will escape through the nose, vowels sound nasal and insufficient pressure can be build up in the oral cavity to produce stops and fricatives. In case of continued velopharyngeal closure, the air stream cannot escape through the nose and the nasal consonants are denasalized.

The aim of this study is to investigate speech outcome by means of a multidimensional speech assessment protocol in a well-defined head and neck cancer patient population reconstructed with up-to-date methods, in order to obtain insight in speech difficulties in relation to tumor stage and site.

Materials and Methods

Speakers

Seventy-nine patients who underwent composite resections for advanced oral or oropharyngeal squamous cell carcinoma with microvascular soft tissue transfer (i.e., RFFF) for the reconstruction of their surgical defects, operated between January 1998 and December 2001, were included in the study after written informed consent. The study population was treated at the department of Otolaryngology-Head and Neck Surgery of the VU University Medical Center. Exclusion criteria were age more than 75 years or inability to participate in functional tests. Patients were operated by means of composite resections including excision of the primary tumor with en bloc ipsilateral or bilateral neck dissection. If the tumor encroached on the mandible, a marginal mandibulectomy was performed transorally or by using a cheek flap. In oropharyngeal carcinomas a paramedian mandibular swing approach was used. Indications for postoperative radiotherapy included T3-T4 tumors, positive surgical margins, perineural tumor spread, multiple positive nodes or extranodal spread. Generally, the clinical target volume of the initial field included the entire surgical bed. The primary tumor area and neck nodes were irradiated using 2 Gy per fraction to a dose of 46 Gy. An additional boost was given at the primary site up to a total dose of 56 Gy (2 Gy per fraction, 5 times/week). In case of positive surgical margins or extranodal spread an additional boost was given to a total dose of 66 Gy (2 Gy per fraction, 5 times/week).

Patient data (age and gender), tumor data (TNM stage [21] and tumor site) and treatment data (postoperative radiotherapy and rehabilitation) were registered. Collection of speech data for patients was performed at three points in time; before treatment, 6 months after treatment and 12 months after treatment. Identical speech tests were performed for an age and gender matched control group of 18 persons (controls).

Speech assessment

Speech analyses were performed according to a standardized speech assessment protocol. Speech recordings of a standardized read aloud text and a subset of Dutch consonants were performed in a sound-treated room and digitized using Cool Edit PRO 1.2 (Adobe Systems Incorporated, San Jose, California, USA) with 22 kHz sample frequency and 16-bit resolution. Recording level was adjusted for each speaker to optimize signal-to-noise ratio. All recordings were made with a mouth to microphone distance of 30 cm. A computerized program was developed to perform blinded randomized speech evaluation. Communicative suitability is defined as the speaking-dependent adequacy of speech as judged by naïve listeners.[22] Communicative suitability (judged by a panel of 13 naïve listeners) and overall intelligibility (judged by a panel of 2 trained speech therapists) was assessed on a 10-points scale (ranging from poor to excellent: the 10-point grading scale is commonly used in the Dutch educational system in which 5 or less is judged as insufficient and 6 or more as sufficient). Interrater reliability scores (Cronbach's alpha) on communicative suitability and intelligibility were high, 0.98 and 0.86, respectively. Intrarater agreement (percentage within one scale value between the first and second, repeated speech fragment) were equally high, ranging from 50-100% for the naïve raters on communicative suitability, and ranging from 40-90% for the experts on intelligibility.

To obtain more insight in the cause of decreased intelligibility, evaluation of the quality of articulation and nasal resonance was performed by the same panel of speech therapists agreeing consensus on a 4-point scale ranging from normal to increasing deviant. Intrarater agreement was high with 100% equal scores between the ratings on the first and second, repeated speech fragments on articulation and nasality. Furthermore, consonant error rate was assessed. Patients were asked to repeat 5 times the consonant-vowel (CV) syllables *ta*,*da*,*na*,*sa*,*xa*,*ka*, and *la*. In a computerized listening experiment, all Dutch consonants were presented on a computer screen. The CV-syllables with the 7 target consonants were presented in random order to a panel of 5 naïve raters, who were asked to click with the mouse on the consonant they recognized in each CV-syllable. Consonant error rate was assessed by the percentage incorrect target consonant.

Statistical analyses

To test multiple group differences, groups in time (controls, patients tested before treatment and patients tested 6 and 12 months after treatment) and groups regarding tumor site (mobile tongue, floor-of-mouth, retromolare trigone, tonsil, base-of-tongue and soft palate) analyses of variance (ANOVA F-test) were carried out on intelligibility and communicative suitability; in case of significant F-tests, posthoc tests were performed to test which groups differed from each other. Kruskal-Wallis H-tests were used to test group differences regarding articulation and nasality scores. Independent t-tests (intelligibility and communicative suitability) and Mann-Whitney U-tests (articulation, nasality) were performed to determine the impact of tumor stage (T2 versus T3-T4). The influence of tumor stage and tumor site on consonant error rate was tested by chi-square tests. To investigate relations between overall intelligibility and detailed speech outcome (articulation and nasal resonance scores), Spearman's correlation rho (r) coefficients were calculated. On patients who were tested at all points of time (i.e., before, and 6 and 12 months after treatment), comparable paired tests (ANOVA F-test with repeated measures, Friedman chi-square test) were performed.

Table 1. Characteristics of 79 patients included in the study

	n	(%)
Gender		
Male	46	(58)
Female	33	(42)
Tumor site		
Oral cavity	37	(47)
Mobile tongue	18	(23)
Floor-of-mouth	15	(19)
Retromolare trigone	4	(5)
Oropharynx	42	(53)
Tonsil	24	(30)
Base-of-tongue	11	(14)
Soft palate	7	(9)
T		
2	35	(44)
3	41	(52)
4	3	(4)
N		
0	24	(30)
1	15	(19)
2a	2	(3)
2b	30	(38)
2c	6	(7)
3	2	(3)

Results

Patient characteristics

Patient characteristics are shown in Table 1. The ages of the 79 patients included in this study ranged from 23 to 74 years (mean 56 years). In the majority of patients (73%) the tumor did not extend over the median line. One patient was operated on a recurrent tumor after prior transoral excision (1 year before) in which the rTNM stage was used, and one patient received previous radiotherapy (3 years before) for a neck node with unknown primary. Four patients had a synchronous second primary tumor and in these the T of the largest tumor was used. In total 73 patients (92%) received postoperative radiotherapy. Only 2 patients were rehabilitated by speech therapy, which precluded statistical analyses.

For a total of 76 patients tested before treatment speech tests could be analyzed, while for patients tested 6 and 12 months after treatment this was possible for 51 and 42 patients respectively. For 38 patients speech tests could be analyzed on all points in time (i.e., patients tested before, and 6 and 12 months after treatment). After treatment there were no patients with retromolare trigone tumors. Drop-out was caused by tumor recurrence, distant metastases, death, patients refusal, due to technical problems, or by the fact that patients were lost to follow-up.

Overall speech outcome

Based on intelligibility scores, none of the control speakers were deviant, while 17% of the patients before treatment, and 71% of the patients after treatment had deviant scores. Analyses of variance revealed significant differences regarding communicative suitability ($F=51.26$, $p<0.01$) and intelligibility ($F=46.57$, $p<0.01$). Posthoc tests showed significant differences ($p<0.05$) between controls on the one hand and patients tested before, and 6 and 12 months after treatment on the other hand, both regarding communicative suitability and intelligibility (Figure 1). The differences between patients tested before treatment on the one hand and patients tested 6 and 12 months after treatment on the other hand were statistically significant for both communicative suitability and intelligibility. No significant differences were found between patients tested 6 and 12 months after treatment. Repeated analyses of variance on the 38 patients who underwent assessment at all points in time, revealed the similar results: patients tested before, and 6 and 12 months after treatment were significantly less communicative suitable ($F=36.23$, $p<0.01$) and less intelligible ($F=55.79$, $p<0.01$) compared to controls, patients tested before treatment were significantly better than patients tested 6 and 12 months after treatment, and no significant differences were found between patients tested 6 and 12 months after treatment.

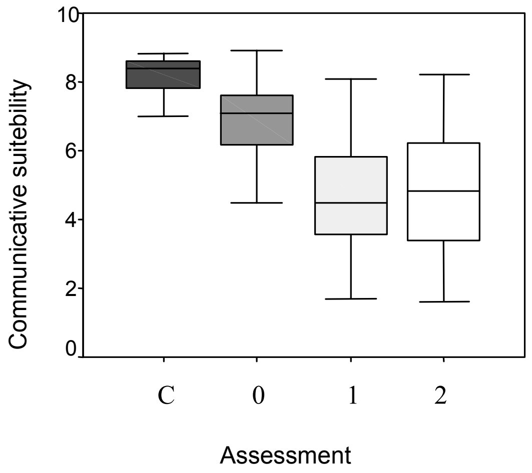


Figure 1a

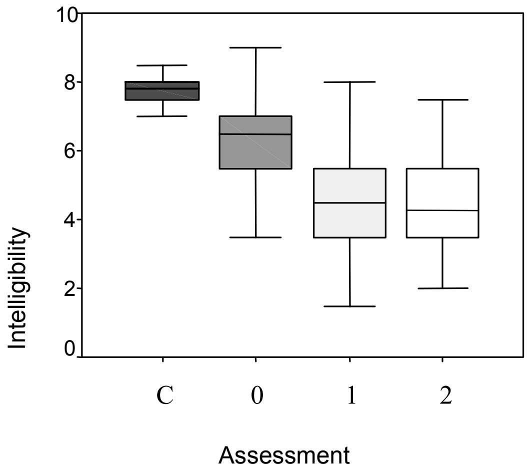
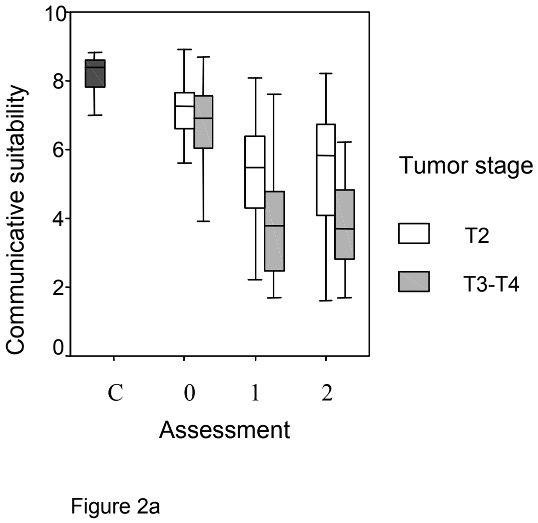


Figure 1b

Figure 1: Box-plots of the mean scores (range 25th and 75th percentile) of communicative suitability (1a) and intelligibility (1b) for controls (C), patients tested before treatment (0) and 6 months (1) and 12 months (2) after treatment

Regarding tumor stage, patients were divided into patients having T2 tumors and patients having T3-T4 tumors. Before treatment, 32 patients (42%) had T2 tumors and 44 patients (58%) T3-T4 tumors. Six months after treatment this was 26 (51%) and 25 (49%) and 12 months after treatment this was 24 (57%) and 18 (43%) respectively. A significant difference between patients with T2 tumors and patients with T3-T4 tumors was found on communicative suitability and intelligibility (Figure 2), before treatment ($t=2.03$, $p<0.05$ and $t=2.68$, $p<0.01$, respectively), 6 months after treatment ($t=3.84$, $p<0.01$ and $t=3.03$, $p<0.01$, respectively) and 12 months after treatment ($t=3.22$, $p<0.01$ and $t=3.41$, $p<0.01$, respectively).
Regarding tumor site, there were no significant differences between patients on communicative suitability tested before, and 6 and 12 months after treatment, but statistical significant differences were found for intelligibility in patients tested before treatment ($F=2.67$, $p<0.05$; Figure 3). Posthoc tests revealed that, before treatment, intelligibility was significantly worse in patients with tumors of the mobile tongue (mean intelligibility score 5.72) compared to patients with tumors of the base-of-tongue (mean intelligibility score 7.22). For patients tested 6 and 12 months after treatment, no significant differences between tumor sites were found regarding intelligibility, but patients with mobile tongue tumors showed best scores on both communicative suitability and intelligibility.



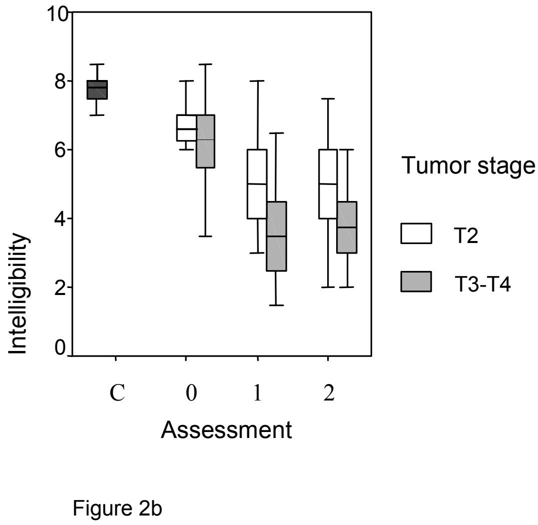


Figure 2. Box-plots of the mean scores (range 25th and 75th percentile) of communicative suitability (2a) and intelligibility (2b) for tumor stage for controls (C), patients tested before treatment (0) and 6 months (1) and 12 months (2) after treatment

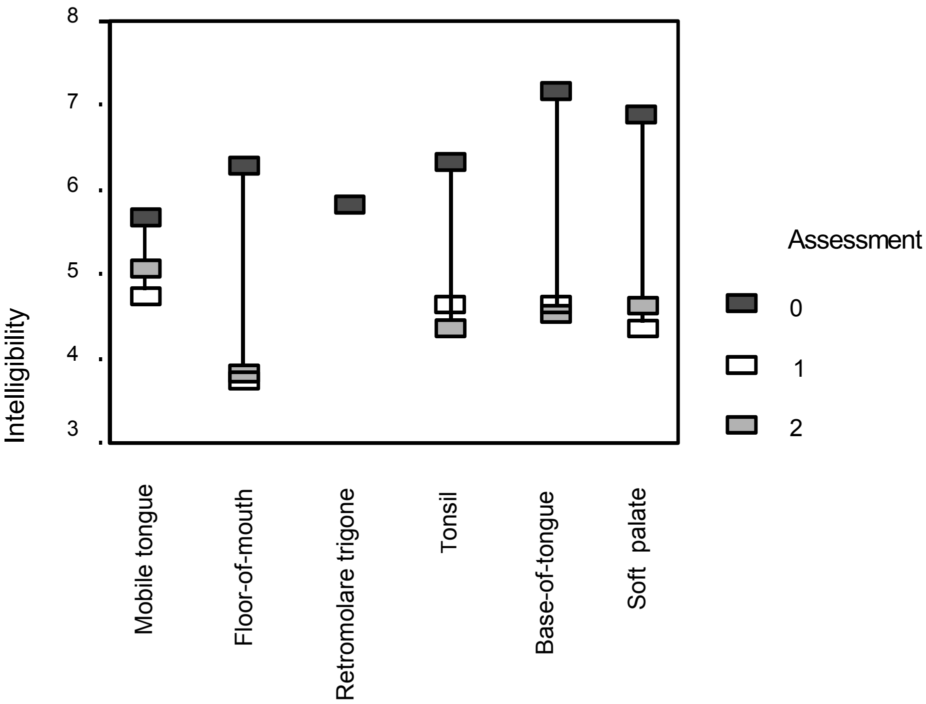


Figure 3. Intelligibility scores for tumor sites for patients tested before treatment (0) and 6 months (1) and 12 months (2) after treatment

Detailed speech outcome

To obtain more insight in the causes of deviant communicative suitability and intelligibility of patients, detailed evaluation was carried out on articulation and nasal resonance. Significant differences between controls and patients tested before, and 6 and 12 months after treatment were found for both articulation ($H=62.63$, $p<0.01$) and nasality ($H=47.75$, $p<0.01$) (Figure 4). Regarding articulation, 94% of controls had normal scores, while for patients tested before treatment this was 63%, for those tested 6 months after treatment this was 14% and for patients tested 12 months after treatment this was 24%. Regarding nasality, no controls showed deviant scores, while 25% of patients tested before treatment, 67% of patients tested 6 months after treatment and also 67% tested 12 months after treatment showed deviant nasality scores. The same trend was found in the 38 patients who underwent assessment at all points in time regarding both articulation (Friedman chi-square ≥ 44.77, $p<0.01$) and nasal resonance (Friedman chi-square ≥ 25.26, $p<0.01$).

Articulation was significantly worse for patients with T3-T4 tumors than for patients with T2 tumors tested before treatment ($U=466$, $p<0.01$) and tested 6 months after treatment ($U=183$, $p<0.01$), but not for those tested 12 months after treatment ($U=144$, $p=0.06$). No significant differences appeared between patients with T2 versus T3-T4 cancer regarding nasal resonance. Regarding tumor site, no statistically significant results were found on articulation. Nasality scores revealed significant differences ($H=14.36$, $p<0.01$) for patients tested 6 months after treatment. Patients with floor-of-mouth tumors showed the best nasality scores, while patients with tonsil or soft palate tumors showed the worst overall scores.

Spearman correlations between intelligibility on the one hand, and articulation and nasal resonance on the other (all evaluated by the same panel of trained raters) revealed that intelligibility is more prominently correlated to articulation scores than to nasality scores for patients tested before treatment ($r=0.64$, $r=0.44$, respectively), tested 6 months after treatment ($r=0.68$, $r=0.36$, respectively) and tested 12 months after treatment ($r=0.69$, $r=0.45$, respectively).

In order to obtain more insight in the rate and type of articulation problems, consonant errors were assessed. Comparisons were made between controls and patients after treatment. For the patients the latest assessment was chosen and in total 52 measurements of patients were analyzed. Consonant error rate appeared to be low for controls (2% error rate) and significantly higher for patients (17% error rate) (chi-square=91.9, $p<0.01$). Patients with T3-T4 tumors showed significantly more consonant errors (25%) than patients with T2 tumors (9%) (chi-square=78.67, $p<0.01$). Tumor site appeared to affect consonant error rate (chi-square=9.79, p<0.05). Patients with base-of-tongue tumors made the fewest consonant errors (11%), while patients with tonsil tumors made the most consonant errors (19%), compared to patients with other tumor sites (17%). The type of consonant errors appeared to be diffuse, but a few clear observations can be extracted. The target consonants *k* (velair), and *s*, *d*, and *t* (alveolair) were the most difficult consonants to produce correctly. The velair *k* was often confused with the velair *g*, which was observed in all patient groups, except for patients treated for base-of-tongue tumors. The alveolair consonants were often nasalized (*d* confused with *n*) in case of patients treated for oropharyngeal tumors (tonsil or soft palate) or retracted (*s* confused with *sj* (as in sheep), *t* with *tj* (as in chill) in patients treated for mobile tongue tumors.

Figure 4a

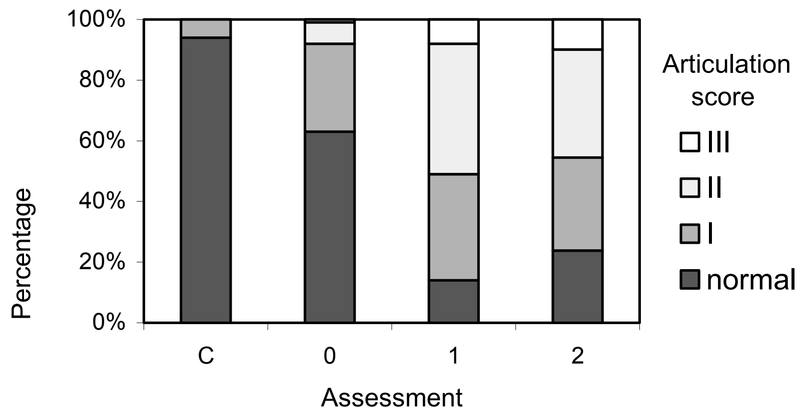


Figure 4b

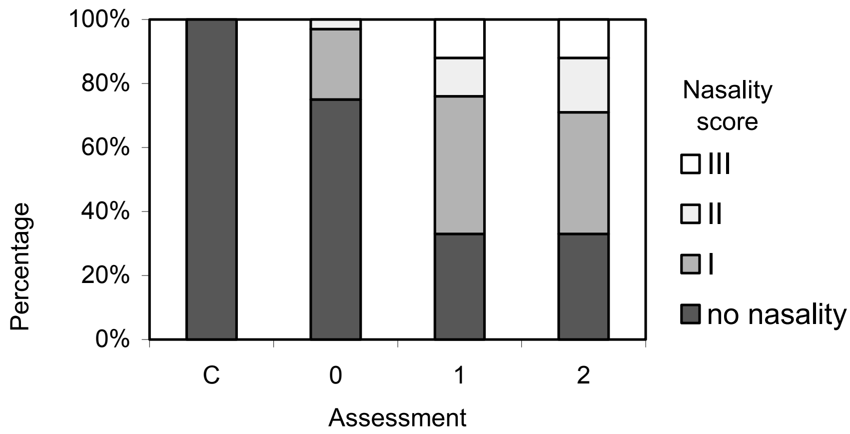


Figure 4. Percentages of scores for articulation (normal to deviant (I-III)) (4a) and nasality (no nasality to deviant (I-III)) (4b) for controls (C), patients tested before treatment (0) and 6 months (1) and 12 months (2) after treatment

Discussion

The outcome of speech in head and neck cancer patients undergoing extensive ablative and reconstructive surgery was investigated in a fairly homogenous group of 79 patients. Speech was examined on the level of communicative suitability and intelligibility, which were considered to be influenced by nasality, articulation, and consonant errors. Speech before treatment and speech outcome were assessed relative to tumor stage and site. As expected, all aspects of speech both before and after treatment turned out to be significantly worse for patients compared to controls. Furthermore, patients scored significantly more consonant errors than controls. McKinstry and Perry also found impaired speech in 20 patients with various head and neck cancers before treatment compared to a control group.[20] The present study also shows that speech was significantly worse 6 and 12 months after treatment than before treatment. This effect after treatment is caused by the inevitable anatomical and functional alterations of surgery and radiotherapy. Currently, optimal functional results are observed with the application of free flaps and, in the oral cavity and oropharynx, the best outcome is obtained by the use of thin pliable fasciocutaneous flaps, such as the RFFF and anterolateral thigh flap.[23,24] Su et al. reported better speech function after reconstruction with RFFF than with the more bulky pectoralis major flap.[25] Intelligibility was also found to be improved for patients who underwent reconstruction by RFFF compared to those who underwent a somewhat thicker lateral upper arm flap as described by Hara et al.[13] Seikaly et al. reported that the use of the RFFF is presently the best reconstructive option, especially when the created defect takes up multiple anatomical sites.[15]

Tumor stage and size plays an important role in speech. In this study, patients with advanced primary tumors did significantly worse than patients with smaller tumors in the assessments before and after treatment concerning communicative suitability, intelligibility, articulation and consonant errors. Speech was minimally impaired in patients with T2 tumors before treatment, a finding also shown by Schonweiler et al.[26] These objective speech data are in concordance with patient’s self-assessment in which patients with smaller tumors assessed their speech before treatment significantly better than those with larger tumors.[27] Although Colangelo et al. found no stage effect in the phase before treatment, a clear influence was observed after treatment, as shown in the present study.[28] However, irrespective of tumor stage, speech deteriorates after treatment and has no real tendency to improve after 12 months.

A statistical difference in communicative suitability as assessed by naive listeners between patients with different tumor subsites could not be established. Assessment before treatment by expert listeners, however, regarding intelligibility and articulation revealed a clear difference between tumor subsites. On the two extremes of the spectrum were patients with mobile tongue and base-of-tongue tumors: the latter doing significantly better than the first. Speech in all its aspects deteriorates markedly after treatment for all subsites. Although it seemed that communicative suitability, intelligibility and articulation was somewhat better after treatment for an oral cavity cancer than for an oropharyngeal cancer and site analyses pointed to distinct problems for different subsites, there were no statistical differences. Communicative suitability and intelligibility were most markedly preserved in patients who were treated for mobile tongue lesions, whereas articulation problems and nasality (significantly) were especially present in patients with tonsil and soft palate cancers. In contrast Haughey et al., who investigated speech for 43 patients with tongue or floor-of-mouth carcinomas who also underwent fasciocutaneous flap reconstruction, found improved intelligibility for patients with base-of-tongue defects as compared to those with tumors of the mobile tongue.[29] This study, however, included 51% of patients who had undergone prior treatment (partial glossectomy, radiation therapy, or chemotherapy), which may have influenced their results. Colangelo et al. reported significantly worse speech in T3-staged patients with oral cavity tumors compared to those with cancer of the oropharynx, whereas this difference was absent in the same dichotomized site groups with T1-T2 or T4 tumors.[28] In this study average results for the assessments before and (3 months) after treatment were analyzed.

Whereas, as expected, particularly patients with larger tumors make significantly more consonant errors than the control group or patients with smaller tumors, patients with base-of-tongue tumors showed the least consonant errors after treatment. Similar findings were reported by Haughey et al.[29]

When articulation scores after treatment were compared to consonant errors no clear pattern could be found. The reason for this was unclear, but personal articulation strategies and tumor stage might influence both articulation and consonant errors. Analyses of type of consonant errors showed that for all tumor sites, pronunciation of the *k* was the most abnormal. In a study by Pauloski et al. this was also reported, but most markedly for patients with base-of-tongue tumors.[30]

It is obvious that in any patients group treated for cancer longitudinal follow-up is often inadequate. Factors such as marked comorbidity, alcohol abuse, depression and a relatively high recurrence rate are typical of head and neck cancer patients and a certain bias because of selective drop out seems therefore inevitable.[31-34] In our patient cohort, the initial fraction of patients with a T3-T4 tumor was 58%, whereas this dropped to 49% and 43% at 6 and 12 months, respectively. Likewise, patients with mobile tongue and floor-of-mouth tumors, as well as those who scored worse at baseline dropped out more frequently. The possible effect of speech rehabilitation is another matter of consideration in outcome analyses such as the present. Although speech rehabilitation can be beneficial in improving speech intelligibility, reference rates in clinical practice are low.[17,18,20] This also counts for the present study; only 2 patients received speech rehabilitation on their own request. Regarding the objective speech deterioration, it might be recommended to analyze the objective and subjective effect of speech rehabilitation in a future study. In literature although, information on efficacy of speech rehabilitation is scarce. Only one study was found, demonstrating a positive effect of speech rehabilitation on 27 patients after glossectomy.[19]

This study presents an inventory of speech performance before and after treatment in a well-defined head and neck patient group. Overall speech quality in patients before treatment was approximately 20% worse than in controls, while 6-12 months after treatment this was approximately 75%. No evident improvement was seen between 6 and 12 months after treatment. Worse postoperative overall speech quality was demonstrated for patients with larger tumors. Patients with mobile tongue tumors showed a worse overall speech quality than those with base-of-tongue tumors at baseline. Patients with mobile tongue tumors tended to better speech outcome as compared to those with tumors at other subsites, albeit without significant difference. Speech rehabilitation might be beneficial for these patients, but further research on its efficacy is clearly needed. The results of this study could assist in improved patient counseling and vigilance as to speech difficulties in patients who are treated for oral cavity and oropharynx cancer.

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Chapter 6

Swallowing after Major Surgery of the Oral Cavity or Oropharynx: A Prospective and Longitudinal Assessment of Patients Treated by Microvascular Soft Tissue Reconstruction

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Abstract

Background: The aim of the study was to analyze swallowing outcome in advanced oral/oropharyngeal cancer patients treated with microvascular reconstructive surgery and adjuvant radiotherapy.

Methods: Eighty patients were included. Patient, tumor and treatment factors were assessed. Postoperative videofluoroscopic swallowing studies (VFSS) and scintigraphy tests were performed at 6 (n=54 vs n=44) and 12 (n=32 vs n=37) months. Swallowing parameters as the oropharyngeal swallow efficiency (OPSE) and the Penetration/Aspiration Scale were analyzed.

Results: Impaired swallowing status was found at 6 months which remained stationary at 12 months. Comorbid condition, larger tumors (T3-T4 vs T2) and resections of the base-of-tongue and soft palate combined (vs defects of other dynamic structures) were associated with most profound swallowing problems ($p<.05$).

Conclusion: Swallowing difficulties are relatively frequent and can to a large extent be predicted. With the knowledge of this study better counseling and vigilance as to swallowing difficulties may be possible.

Introduction

Oral and oropharyngeal cancer and its treatment often causes functional impairment, most notably speech and swallowing problems.[1-3] When surgical resection is the treatment of choice, an optimal reconstruction of the affected area is mandatory to reduce postoperative impairment. Current microvascular techniques offer excellent reconstructive methods of major defects in head and neck cancer patients.[4,5] For reconstruction of oral cavity and oropharyngeal defects, fasciocutaneous and musculocutaneous free flaps have proven to be very reliable with an average flap survival rate of 95% [3] and quite acceptable or good functional speech and swallowing outcome.[6-9]

Regarding swallowing impairment, various methods are used to evaluate swallowing function, including clinical evaluation (oral sensomotoric assessment and observing symptomatic aspiration), objective evaluation (fiberoptic examination, videofluoroscopic swallowing study (VFSS), scintigraphy, manometry) and questionnaires on swallowing problems. VFSS and scintigraphy are currently the preferred objective assessment method in most institutions.[10-13] The swallowing sequence is usually divided into the oral, pharyngeal, and esophageal phase. Studies on swallowing after combined treatment including surgery and radiotherapy for oral or oropharyngeal cancer reveal that swallowing impairment is common; any of the swallowing phases can be compromised dependent on tumor site and size.[14-21] In general, patients treated for extended tumors have more swallowing problems; patients with resection of the mobile tongue and floor-of-mouth experience problems in the oral phase while patients after resection of base-of-tongue encounter swallowing dysfunction in the pharyngeal phase.[15-17,21-23]

Information on swallowing outcome in patients treated by the use of free flaps for advanced oral or oropharyngeal cancer is limited and contradictory. Excellent functional results are reported by Sinha et al. and Moerman et al.[24,25] Others found that most of the patients had normal diets, were reasonably rehabilitated but still experienced dysphagia complaints [18,26,27], whereas some investigators found significant swallowing impairment for the majority of patients.[16,28,29] Information on the impact of tumor or treatment factors, such as tumor site, tumor stage, size or localization of the subsites resected is limited and long-term follow-up is scarce.

The aim of this study is to investigate longitudinal swallowing function in patients after treatment for oral or oropharyngeal cancer and reconstructed by radial free forearm flaps (RFFF), in relation to patient characteristics (age, gender, and comorbid status), tumor characteristics (tumor site and stage), and treatment characteristics (localization of subsite defect and cranial nerve sacrifice). This information will provide better insight in postoperative outcome of patients which can be helpful for better patient counseling and rehabilitation.

Materials and Methods

Patients

Between January 1998 and December 2001, 92 consecutive patients diagnosed with stage II-IV oral or oropharyngeal squamous cell carcinoma were asked to participate in the study. The planned treatment was composite resection with microvascular soft tissue transfer for the reconstruction of surgical defects, and radiotherapy on indication. Exclusion criteria were age greater than 75 years, serious cognitive impairment, and no ability to participate in swallowing tests. Twelve patients declined to participate in the study, resulting in a final sample of 80 patients. All patients were treated at the Department of Otolaryngology/Head and Neck Surgery of the VU University Medical Center, Amsterdam, The Netherlands. Patients were operated by means of composite resections including excision of the primary tumor with en bloc ipsilateral or bilateral neck dissection. If the tumor encroached on the mandible, a marginal mandibulectomy was performed transorally or by using a cheek flap. In posteriorly located lesions a paramedian mandibular swing approach was used. All patients underwent free flap reconstruction (i.e., RFFF) by a separate team. Indications for postoperative radiotherapy included T3-T4 tumors, positive or close surgical margins, perineural tumor spread, multiple positive nodes, or extranodal spread. Generally, the clinical target volume (CTV) of the initial field included primary tumor with a 1.0 cm margin, the cervical neck node areas on both sides and the entire surgical bed. For the planning target volume (PTV), an extra margin of 0.5 cm surrounding the CTV was taken. The primary PTV was irradiated using 2 Gy per fraction to a total dose of 46 Gy. An additional boost was given at the primary site up to a total dose of 56 Gy (2 Gy per fraction, 5 times/week) in case of negative surgical margins. In case of positive surgical margins or extranodal spread an additional boost was given to a total dose of 66 Gy (2 Gy per fraction, 5 times/week). Patient data (age, gender, and comorbidity), tumor data (site and TNM stage, according to UICC 1997) and treatment data (localization of subsite defect, cranial nerve sacrifice, and postoperative radiotherapy) were registered. Collection of swallowing data for patients was performed at two points in time: 6 and 12 months after treatment.

Data collection and study measures

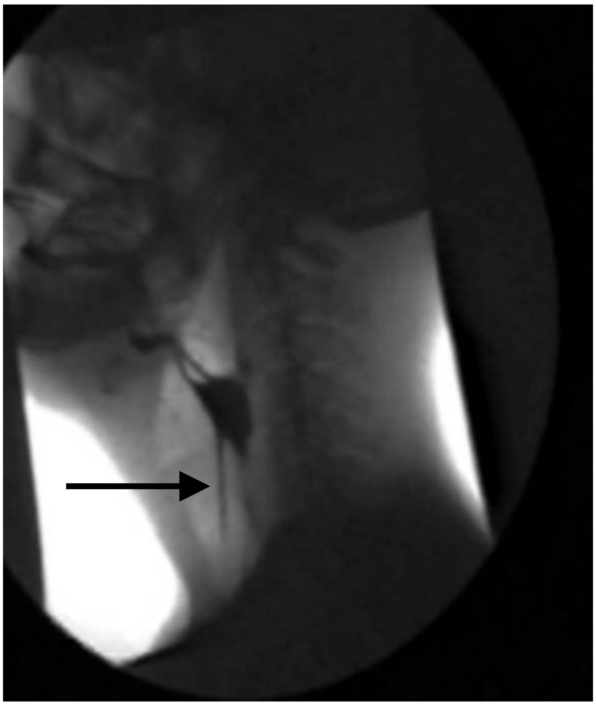
Comorbidity was assessed by review of medical records and on the basis of self-report, and was noted when a patient had one or more relevant medical ailments that accompanied their head and neck cancer. These comorbid conditions were cardiovascular, respiratory, gastro-intestinal, renal, endocrine, neurological, and immunological disorders, previous malignancy, and considerable weight loss or alcohol abuse. For example: cardiovascular problems such as a myocardial infarct or hypertension, respiratory problems such as restrictive lung disease or COPD, or endocrine disorders such as diabetes mellitus with insulin usage were defined as relevant comorbid conditions.

For each subsite (mobile tongue, floor-of-mouth, base-of-tongue, tonsillar fossa, and soft palate) the resection was noted. The patient cohort was divided into 3 groups that underwent resection of a dynamic structure; I resection of the mobile tongue, II resection of the base-of-tongue in combination with resection of the mobile tongue, and III resection of the base-of-tongue in combination with resection of the soft palate (and tonsillar fossa). Because of the small numbers, patients with resection of the base-of-tongue only, the soft palate only, and resection of the mobile tongue in combination with resection of the base-of-tongue and the soft palate were left out in the analyses. Cranial nerve status was defined whether the hypoglossal nerve and lingual nerve were intact after the operation.

Swallowing tests

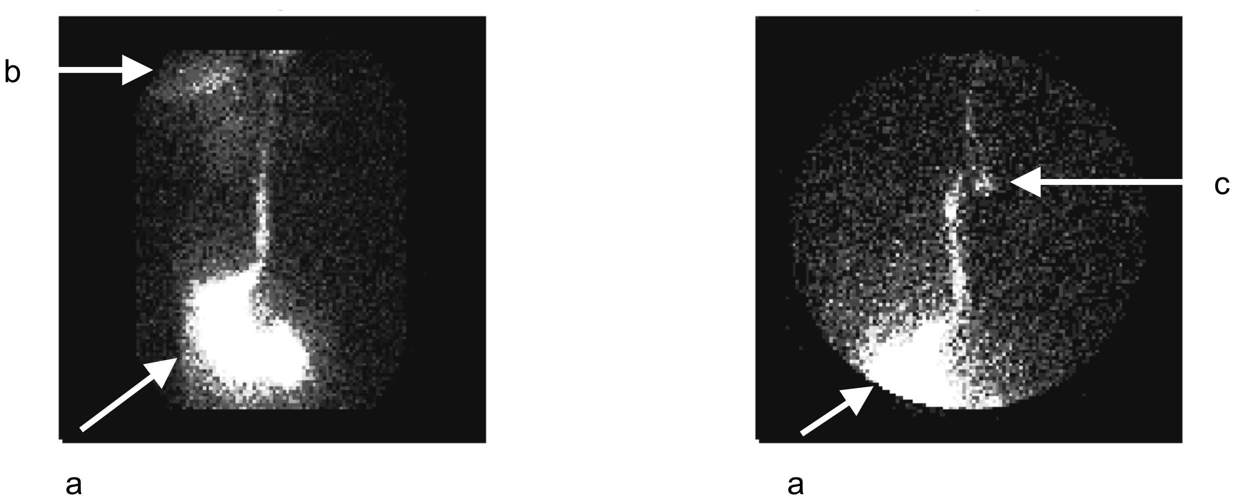
Swallowing was assessed by means of VFSS and scintigraphy. VFSS recordings were performed by modified isovist swallowing. A video-recorder with frame-by-frame and slow-motion analysis capabilities was used for recording. During the VFSS, subjects stood upright and were viewed in anterior/posterior and in the lateral position. The fluoroscopic tube was focused on the nasopharynx superiorly and the lower end of the cervical esophagus inferiorly. Each subject was asked to swallow two swallows each of 10 mL liquid isovist, two swallows each of 10 mL thick liquid isovist and two half-teaspoon amounts of one fourth of a cookie coated with isovist paste. Anterior/posterior and lateral views of the oral cavity, pharynx and upper part of the esophagus were then observed as the patients swallowed (see Figure 1). If the patient aspirated on any of the swallows, various postures and manoeuvres were employed in an attempt to eliminate the aspiration. If these were not successful, not all swallows of a given consistency were presented. Video recordings were digitized (Adobe Premiere Pro 1.5) and evaluations were performed on swallowing liquids of all patients presented in random order by 2 raters (an otolaryngologist and a phoniatrician) who were blinded for the clinical data. Swallowing evaluation included oral transit time (time it takes the food to move through the oral cavity), pharyngeal transit time (time it takes the food to move through the pharynx), oral residue (approximate percent oral residue after the first swallow) and pharyngeal residue (approximate percent pharyngeal residue after the first swallow), and the oropharyngeal swallow efficiency (OPSE).[30] OPSE is calculated by measuring the percentage of bolus swallowed into the esophagus divided by the total (oral and pharyngeal) transit time. The OPSE scores typically range from 75 to 125 in normal subjects, meaning that 100% of the bolus is swallowed in 0.8 s to 1.3 s. In patients, the OPSE often drops below 60, as the percentage of bolus swallowed reduces and the time increases.[1,21,31] Additionally to the OPSE analyses, global evaluations were performed of the oral phase (normal versus deviant), the pharyngeal phase (normal versus deviant), contact base-of-tongue to posterior pharyngeal wall (yes/no) and nasopharyngeal regurgitation (yes/no). Finally, evaluations using the penetration-aspiration scale were performed.[32] This scale encompasses an 8-point, equal-appearing interval scale to describe penetration and aspiration events.

Figure 1. Example of a lateral video-still VFSS projection of a patient at a moment of aspiration (arrow) of liquid isovist



Scintigraphic recordings were preceded by training with plain water. After this, all patients were asked to drink approximately 10 ml of water with 20 MBq 99mTechnetium-Hepatate and to keep this for 10 seconds in the mouth. Then they were asked to swallow. A gamma camera was positioned laterally of the head at the operated site and acquisition was performed with 1 sec frames, during 1 min. After the study, a static posterior/anterior image was obtained from the thorax, after drinking a glass of plain water to empty the esophagus. Evaluation was performed by an otolaryngologist regarding pre-swallowing leakage, total amount of swallowed bolus, and aspiration. Pre-swallowing leakage was defined as involuntary leakage of the liquid to the pharynx region or the esophagus before patients were asked to swallow. The total amount of the oral-pharyngeal bolus 5 seconds before swallowing (or shorter time when pre-swallowing leakage to esophagus within these 5 seconds periods occurred) was recorded. For all patients, a swallowing time of 2 seconds was allowed as the time that the bolus could be swallowed. After these 2 seconds, the total amount of the oral-pharyngeal bolus for 5 seconds (or shorter time when uncontrolled swallowing in this 5 seconds periods occurred) was recorded and defined as the oral-pharyngeal residue bolus. The total swallowed amount could thus been calculated (bolus before swallowing – residue bolus / bolus before swallowing (*100%)). Aspiration could not be objectified on lateral recordings but was analyzed by the posterior/anterior image (see Figure 2).

Figure 2. An example of a static posterior/anterior image of two patients who aspirated a part of the volume of water with 20 MBq 99mTechnetium-Hepatate. In the lower part of both images, the stomach is visible (a). On the left image, aspiration is seen in the upper lobe of the left lung (b). On the right, aspiration is seen into the right bronchus (c)



Statistical analyses

Intrarater reliability was tested and proved to be good with Pearson test-retest correlations ranging from .61 (oral residue) to .89 (OPSE) to over .95 (oral and pharyngeal transit time and residue) (all VFSS tests) to .99 (percentage swallowed bolus (scintigraphy)), Spearman correlation of .87 for the penetration/aspiration scale, and kappa´s of .78 for pre-swallowing leakage (scintigraphy)) to 1 (100% equal scores) for oral and pharyngeal phase, contact base-of-tongue to posterior pharyngeal wall, nasal regurgitation (all VFSS), and aspiration (scintigraphy).

Student's t-tests (continuous variables) and chi-square tests (binomial variables) were carried out to test longitudinal swallowing status (paired t-tests on patients tested 6 and 12 months after treatment) and group differences regarding gender (male/female), comorbidity (yes/no), tumor site (oral/oropharyngeal), tumor stage (T2/T3-T4), and the cranial nerve status. One-way analysis of variance (ANOVA) (continuous variables) and chi-square tests were carried out to test group differences regarding localization of subsite resection (tongue only/tongue combined with base-of-tongue/base-of-tongue combined with soft palate). Correlation tests (Pearson or Spearman) were used to assess the relation between the various swallowing parameters and age.

Results

Sample description

The ages of the 80 patients included in this study ranged from 23 to 74 years (mean 58 years). Forty-seven patients (59%) were male and 33 (41%) female. Relevant comorbid condition was present in 60% (48 patients) while 40% (32) of the patient population had no comorbidity. One patient was operated upon for a recurrent tumor after transoral excision (1 year earlier) and for this patient the rTNM stage was used, and one patient had undergone previous radiotherapy for a neck node of an unknown primary. Four patients had a synchronous second primary oral or oropharyngeal tumor, which was also resected, and in these cases the stage of the largest tumor was used. Oral cavity tumors represented 47.5% (n=38) of the cases, whereas in 52.5% (n=42) of the patients, the tumor was located in the oropharynx. Tonsil, mobile tongue, floor-of-mouth, and base-of-tongue were the most common subsites, with 30%, 23%, 20%, and 14%, respectively. For 71 patients (89%), the hypoglossal nerve was intact after operation and regarding the lingual nerve this was for 41 patients (51%). An equal percentage (50%) of patients had a tumor origin on left or right side, and for a majority of the patients (73%) the tumor did not cross the median line. Tumor stage included T2 (44%), T3 (52%), and T4 (4%). Regarding node stage, there were 30% N0, 20% N1, 3% N2a, 38% N2b, 7% N2c, and 3% N3. In total 74 patients (93%) received postoperative adjuvant radiotherapy. Postoperative VFSS tests could be performed in 54 patients at 6 months after treatment and in 32 patients at 12 months after treatment. Postoperative scintigraphy tests were performed in 44 patients at 6 months after treatment and in 37 patients at 12 months after treatment. Drop-out was caused by tumor recurrence, death, noncompliance, due to technical problems (e.g., problems with VFSS or scintigraphy recording), or by the fact that patients were lost to follow-up. Complete longitudinal data, i.e., swallowing tests completed at both 6 and 12 months after treatment, were collected for 32 patients regarding VFSS and for 35 patients regarding scintigraphy. Regarding the different resection groups, the number of patients at 6 months were; group I (n=13), group II (n=11), and group III (n=21). Two patients, who underwent swallowing tests at 6 months, received a percutaneous endoscopic gastrostomy tube insertion later. Information on rehabilitation at some point post treatment for 8 patients (10%) who received speech therapy (n=2) and/or swallowing therapy (n=8), was incomplete. Because of this and the small numbers no further analyses were performed in these patients.

Longitudinal swallowing status

Mean results regarding oral transit time (OTT), pharyngeal transit time (PTT), oral residue (OR), pharyngeal residue (PR), and OPSE, as well as percentages normal scores of the oral phase (OP), pharyngeal phase (PP), contact base-of-tongue to posterior pharyngeal wall (CTP), and nasal regurgitation (NR) at 6 months and 12 months post treatment are presented in Table 1. Percentages of the penetration/aspiration scale (P/A) at 6 and 12 months are shown in Table 2. Percentage patients with pre-swallowing leakage, total swallowed amount percentage and percentage patients with aspiration based on scintigraphy at 6 months and 12 months are shown in Table 3.

Most patients had impaired swallowing status both at 6 and 12 months after treatment. Nasal regurgitation and oral transit time were the least frequent problems and observed in 6% (6 months) - 13 % (12 months) of the patients. Pharyngeal transit time and especially oral and pharyngeal residue were often abnormal, inducing abnormal OPSE values in almost all patients. Deviancy in the oral or pharyngeal swallowing phase was observed in more than half of the patients as was insufficient contact between the base-of-tongue and the posterior pharyngeal wall. Based on the scintigraphy, 66% (6 months) - 69% (12 months) of the total liquid oral-pharyngeal bolus was swallowed (irrespective of aspiration) and pre-swallowing leakage either to the pharynx or into the esophagus occurred in 66% (6 months) - 70% (12 months) of the patients. Penetration (P/A scale 2,3,4 and 5 cumulated) was observed in 34% (6 months) - 39% (12 months) of the patients by means of VFSS; aspiration (P/A scale 6,7 and 8 cumulated) was observed in 25% (6 months) - 34% (12 months) of the patients by means of VFSS and in 10% (6 months) - 21% (12 months) by means of scintigraphy.

Table 1. Overview of mean (s.d.) results and percentages normal score* (OTT,PTT,OR,PR,OPSE) and normal percentages (OP,PP,CTP,NR) at 6 months (n=54) and 12 months (n=32) post treatment

	6 months		12 months	
OTT	.56 (.38) s	92 % *	.52 (.48) s	91 % *
PTT	1.04 (.41) s	64 %	1.09 (.48) s	53 %
OR	16.22 (18.99) %	28 %	15.63 (13.54) %	25 %
PR	20.28 (26.24) %	11 %	21.40 (15.67) %	9 %
OPSE	44.09 (21.71) %/s	6 %	44.46 (21.31) %/s	4 %
OP	43 %		34 %	
PP	44 %		44 %	
CBP	48 %		47 %	
NR	87 %		94 %	

OTT: oral transit time, PTT: pharyngeal transit time, OR: oral residue, PR: pharyngeal residue, OPSE: oropharyngeal swallow efficiency, OP: oral phase, PP: pharyngeal phase, CBP: contact base-of-tongue to posterior pharyngeal wall, NR: nasal regurgitation

* normal scores according to Pauloski et al., 2004 [16] : OTT<1s, PTT<.6 s, OR<3%, PR<2%, OPSE between 75-125 %/s

Table 2. Percentages of penetration/aspiration (P/A) scale scores at 6 months (n=54) and at 12 months (n=32)

P/A scale	6 months	12 months
1 doesn't enter airway	28 %	34 %
2 above TVC, ejected	29 %	31 %
3 above TVC, not ejected	0 %	0 %
4 contacts TVC, ejected	9 %	7 %
5 contacts TVC, not ejected	0 %	3 %
6 below TVC, ejected	4 %	3 %
7 below TVC, not ejected	6 %	16 %
8 below TVC, no effort to eject	24 %	6 %

TVC: true vocal volds

Table 3. Overview of scintigraphic results: percentage patients with pre-swallowing leakage, total swallowed amount percentage and percentage patients with aspiration based on scintigraphy at 6 months (n=44) and at 12 months (n=37)

	6 months	12 months
Pre-swallowing leakage		
none	34 %	30 %
pharynx	34 %	46 %
esophagus	32 %	24 %
Total swallowed amount		
	66 %	69 %
Aspiration		
none	79 %	87 % *
possible	9 %	5 %
evident	12 %	5 %

* at 12 months, for 1 patient no static posterior/anterior image was obtained from the thorax because of technical problems

No significant differences (p>.05) were found on any of the swallowing parameters (as assessed by means of VFSS or scintigraphy) at 6 months between patients who completed both assessments at 6 and 12 months compared to drop-outs. Furthermore, no significant differences (p>.05) were found on any of the swallowing parameters between assessments at 6 or 12 months in the patient group who completed both assessments, indicating that swallowing status at 12 months remains the same as at 6 months.

Impact of patient, tumor and surgical related characteristics

The swallowing data at 6 months were used to investigate the impact of several patient, tumor, and surgical factors on the various swallowing parameters. For this purpose, the P/A scale was reduced to a binomial scale (normal (score 1) versus penetration or aspiration (score >1)), as was the pre-swallowing leakage parameter (normal versus pre-swallowing leakage, either to the pharynx or esophagus). The results are summarized in Table 4.

Age, gender and comorbidity

There was no statistical significant impact of age or gender on any of the swallowing parameters. Comorbidity on the other hand appeared to have a significant impact. Patients with comorbidity performed worse compared to patients without comorbidity on the percentage of oral residue (mean score 24 vs 5; p<.01), OPSE (mean score 37 vs 55; p<.01), deviancy of the oral phase (percentage deviant 75 vs 32; p<.01), pre-swallowing leakage (percentage leakage 74 vs 53; p<.05), and total amount of swallowed bolus (mean score 58 vs 79; p<.01).

Tumor site and stage

Patients with oropharyngeal cancer had more often laryngeal penetration or aspiration (percentage penetration or aspiration 88 vs 50; p<.05), more pharyngeal residue (mean score 24 vs 14; p<.05), more often pharyngeal deviancy (percentage deviant 72 vs 32; p<.01), and insufficient contact between base-of-tongue and the pharynx wall (percentage insufficient 69 vs 27; p<.01) as compared to those with oral cancer. Patients with larger tumors (T3-T4) as compared to patients with smaller (T2) tumors had significant longer pharyngeal transit times (mean score 1.18 vs 0.90; p<.05), more oral residue (mean score 22 vs 11; p<.05), and more often nasal regurgitation (percentage regurgitation 22 vs 4; p<.05) and pre-swallowing leakage (percentage leakage 79 vs 50; p<.01).

Table 4. Overview of significant impact (indicated by a cross) of patient (age, gender, comorbidity), tumor (stage (T2 vs T3-T4), site (oral vs oropharynx)), and surgical related characteristics (localization of subsite resection (tongue vs tongue + base-of-tongue vs base-of-tongue + soft palate) and spared (yes/no) lingual nerve)) on swallowing parameters regarding VFSS (OTT,PTT,OR,PR,OPSE,OP,PP,CTP,NR,P/A) and scintigraphy (pre-swallowing leakage (none vs pharyngeal or esophageal), TSA, aspiration (none vs possible or evident))

	OTT	PTT	OR	PR	OPSE	OP	PP	CBP	NR	P/A	leakage	TSA	aspiration
Age													
Gender													
Comorbidity			x		x	x					x	x	
Tumor stage		x	x						x		x		
Tumor site				x			x						
Resection							x	x		x			
Lingual n.													

OTT: oral transit time, PTT: pharyngeal transit time, OR: oral residue, PR: pharyngeal residue, OPSE: oropharyngeal swallow efficiency, OP: oral phase, PP: pharyngeal phase, CBP: contact base-of-tongue to posterior pharyngeal wall, NR: nasal regurgitation, P/A: penetration/aspiration, TSA: total swallowed amount

Surgery

Subsite localization of resection appeared to influence several swallowing parameters in which a trend could be observed that resection of the mobile tongue (group I) induced the least swallowing problems, followed by resection of the tongue in combination with base-of-tongue (group II), while resection of the base-of-tongue in combination with the soft palate lead to the most prominent swallowing problems (group III). This trend proved to be statistically significant regarding contact of the base-of-tongue with the posterior pharynx wall (percentage deviant 73 vs 45 vs 21; $p<.01$), pharyngeal phase (percentage deviant 68 vs 46 vs 29; $p<.05$), and penetration/aspiration (percentage penetration or aspiration 86 vs 64 vs 50; $p<.05$). Sacrifice of the lingual nerve was of no significant importance on swallowing parameters. Because of the small number of patients in which the hypoglossal nerve needed to be sacrificed (n=5) at 6 months no statistical analyses were performed.

Discussion

Swallowing status at 6 and 12 months post treatment was investigated in a group of patients after surgical resection with reconstruction by a fasciocutaneus flap. All patients had squamous cell carcinomas and tumor origin in the oral cavity or oropharynx. The majority of the patients in the present study showed impaired swallowing status 6 months after treatment which remained the same at 12 months. Based on VFSS, pharyngeal transit time and especially oral and pharyngeal residue was often abnormal, inducing abnormal OPSE values in almost all patients. Deviancy in the oral or pharyngeal swallowing phase was observed in more than half of the patients. Penetration was observed in 34-39% and aspiration in 25-34% of the patients. Based on scintigraphy 66-69% of the total liquid oral-pharyngeal bolus was swallowed and pre-swallowing leakage either to the pharynx or into the esophagus occurred in 66-70% of the patients. Aspiration was observed in 10-21% of the patients.

These results confirm findings as reported in the literature. Although Sinha et al. found excellent functional results in 12 out of 16 patients after treatment for oropharyngeal cancer by a folded radial free forearm flap, as did Moerman et al. who reported excellent results by RFFF reconstruction on 4 patients with oropharyngeal tumors, most studies report dysphagia in the majority of the patients.[24,25] Haughey et al. found that 85% of their 40 patients with oral cavity tumours had normal diets but with mild or moderate dysphagia.[26] Also Bodin et al. found that the majority of 100 patients had swallowing impairment after reconstructive RFFF surgery for oral and pharyngeal cancer.[28] Pauloski et al. found impaired swallowing in patients treated with a free flap.[16] McCombe et al. and Brown et al. reported on the limitations of the more static free flaps to reconstruct dynamic structures as the soft palate resulting in swallowing complaints.[23,29]

In our study a clear impact of tumor and treatment related characteristics on swallowing status was found. Regarding tumor site, particularly patients with oropharyngeal tumors showed more problems as compared to patients with oral cancer. This confirms the results as described by Skoner et al. and Winter et al. who reported reasonable swallowing in only half of their patients treated for oropharyngeal and base-of-tongue tumors respectively.[18,27] In the present study, patients with larger tumors (T3-T4) showed more swallowing impairment than those with smaller tumors (T2), which also confirms earlier research. A significant impact on swallowing outcome by tumor stage was shown by Schliephake et al. in their prospective study on 83 patients after reconstruction by several free flaps for oral or oropharyngeal cancer.[33] Su et al. found that patients after reconstruction for total glossectomy had worse results than patients after hemiglossectomy.[19]

Regarding treatment related factors, localization of subsite resection proved to influence swallow function. Resection of the mobile tongue only induced less swallowing problems compared to resection of the mobile tongue in combination with the base-of-tongue; patients after resection of the base-of-tongue in combination with the soft palate had the most swallowing problems, including penetration or aspiration. Furthermore, preservation of the lingual nerve was not of importance on swallowing status. Nicoletti et al. reported that localization and resection size had a clear impact on chewing and swallowing problems in 196 patients after treatment for oral cancer.[15] Analysis of subsite resection was found to be of importance on speech but less on swallowing outcome by Seikaly et al. in their cohort of 18 patients.[34] Hara et al. found swallowing impairment in their cohort of 25 oral cancer patients; anterior resection of the oral cavity proved to have a significant negative effect on swallowing function.[35] A worse swallowing for patients with base-of-tongue tumors as compared to those patients with resections limited to the floor of mouth was found by Jacobson et al. in a patient group reconstructed by the use of RFFF.[36] Also Pauloski et al. reported that combinations of percent base-of-tongue resected with other surgical variables had the strongest relationships with overall swallowing function.[16]

A new finding in the present study was the profound impact of comorbidity on swallowing function. It is most likely multicausal and it is a factor that should be taken into account in future outcome evaluations of treatment modalities, including functional swallowing analyses.

A drawback of the present study on patients with advanced oral and oropharyngeal cancer is that the known negative side-effects as fibrosis and xerostomia of radiotherapy on swallowing impairment could not be investigated, because almost all patients received additional radiation.[1,37,38] An interesting finding by Pauloski et al. was that patients who did not undergo radiotherapy demonstrated a steady improvement in swallowing efficiency between 3 and 12 months after surgery, in contrast to patients who were irradiated.[13] These results resemble our findings that no improvement was seen between swallowing status at 6 or 12 months. Although the exact role of either surgery or additional radiotherapy in these patients could not be explored separately it can be concluded that swallowing impairment for the majority of the patients described in the present study is a consequence of cancer treatment. This impairment must probably be accepted especially when reasonable available treatment alternatives are also linked with significant swallowing problems.[39,40]

Swallowing rehabilitation may help to reduce swallowing problems, but interventions studies are scarce.[1,12] Only one study was found on swallowing therapy one year after treatment for head and neck cancer with no effect, which was explained by the heterogeneous population and the late onset of rehabilitation.[41] It is clear that there is overwhelming evidence of swallowing limitations in patients treated for oral or oropharyngeal cancer and that information on efficacy of speech and swallowing rehabilitation is lacking. Studies on the efficacy of swallowing rehabilitation on homogeneous patient groups are therefore recommended.

Most of the patients in the present study had significant swallowing impairment after treatment which did not improve after 1 year follow-up. Swallowing problems in oral and oropharyngeal cancer are distinct and can be predicted to a large extent. The presence of comorbidity negatively influenced outcome. We also showed that patients with larger tumors and resections of the base-of-tongue in combination with soft palate had the most profound swallowing problems after treatment. These results helps to fill the gap of knowledge about swallowing problems in patients treated for oral and oropharyngeal tumors reconstructed by a free flap. With this knowledge better patient counseling may be possible. These data may also serve as benchmark for outcome in an era in which non-surgical treatment modalities, with surgery in reserve, are gaining popularity.

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Chapter 7

Quality of Life after Surgical Treatment For Oral and Oropharyngeal Cancer: a Prospective Longitudinal Assessment of Patients Reconstructed by a Microvascular Flap

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Submitted

Abstract

Background: The aim of this study was to document changes in health-related quality of life (HRQOL) over a one year period among advanced oral/oropharyngeal cancer patients treated with ablative and reconstructive surgery and adjuvant radiotherapy.

Methods: The HRQOL of 80 consecutive patients was assessed by means of the EORTC QLQ-C30 and QLQ-H&N35 questionnaires at 3 points in time, pretreatment (baseline), and 6 months and 12 months posttreatment.

Results: At 6 months posttreatment emotional functioning, pain and constipation improved ($p<.05$), while physical functioning, financial impact, swallowing, senses, social contact, teeth, mouth opening, dry mouth, sticky saliva and coughing worsened ($p<.05$). Between 6 and 12 months physical functioning, role functioning, swallowing, social eating and dry mouth improved ($p<.05$). Tumor site and stage and patients' comorbidity were found to be associated significantly with HRQOL outcomes. Patients with more extensive resections showed significantly more problems with teeth and dry mouth at 6 months follow-up ($p<.05$) and reported more problems with emotional functioning at 12 months ($p<.05$). Regression analyses after 6 months follow-up indicated that, not having a partner ($p=.017$) and older age ($p=.041$) were significantly related with lower global quality of life.

Conclusion: Mean HRQOL scores for most functioning domains remained unchanged after treatment, with exception of physical, role and emotional functioning. Many symptoms scales and single items improved over time, but sustained problems were observed for swallowing, senses, social contact, teeth, mouth opening, dry mouth, sticky saliva and coughing. These results, obtained in a homogenous group of patients, may serve as HRQOL benchmarks for future studies investigating surgical and other treatment modalities.

Introduction

Improvements in the management of patients with head and neck cancer are aimed not only at increasing the chances of cure, but also at improving or maintaining health-related quality of life (HRQOL) during and after treatment.[1-7] Prospective, longitudinal HRQOL studies among head and neck patients are diverse in nature and studies in well-defined groups of patients with advanced oral cavity and oropharyngeal cancer are scarce.[8-12]

Patients with advanced oral cavity and oropharyngeal cancer have to deal with the impact of the disease and its treatment on three major factors; the ability to eat, speech, and physical appearance, all of which influence HRQOL.[8-18] To maximize postoperative function, microvascular techniques are currently the preferred method for reconstruction of defects after major surgery.[19] For reconstruction of moderate soft tissue defects, fasciocutaneous free flaps (e.g., the free radial forearm flap, RFFF) have proven to be very reliable and an average flap survival rate of 95% is usually achieved in experienced hands.[20]

Whereas there are numerous reports on HRQOL after free flaps in head and neck cancer patients, prospective studies on longitudinal HRQOL in a large group of patients treated with a specific microvascular reconstructive technique are exceedingly rare. There is evidence that many of the generic and condition-specific HRQOL domains initially worsen after therapy, but that most return to the preoperative levels, or even exceed those levels at 1 year post-surgery.[21,22] In the case of large-volume defects, HRQOL is typically not restored to the same extent, and physical, functional, and social domains remain significantly impaired.[22]

We performed a prospective study on the HRQOL of a selected group of patients with advanced oral cavity or oropharyngeal squamous cell carcinomas treated with extensive microvascular reconstructive surgery and adjuvant radiotherapy. We have previously reported that, in this patient group, HRQOL is already compromised prior to the start of treatment, and that this appears to be related to tumor site and stage, and to the presence of comorbidity.[23] In the present paper we report on the HRQOL of these patients during the posttreatment period. The specific objective of the study was to describe changes in HRQOL over time among patients with oral cavity or oropharyngeal cancer reconstructed by a RFFF, and to relate these changes to a range of sociodemographic and clinical background variables, including age, gender, having a partner, tumor site and stage, comorbidity, pretreatment levels of HRQOL, and extent and site of resection.

Materials and Methods

Patients

Patients were eligible for the study if they had advanced squamous cell carcinomas of the oral cavity or oropharynx and were to be treated by composite resections with microvascular soft tissue transfer (i.e., RFFF) for the reconstruction of their surgical defects, supplemented by radiotherapy on indication. Exclusion criteria were age greater than 75 years, serious cognitive impairment and lack of basic fluency in the Dutch language. The study population was treated at the Department of Otolaryngology-Head and Neck Surgery of the VU University Medical Center, Amsterdam, The Netherlands.

Patients underwent composite resections including excision of the primary tumor with en bloc ipsilateral or bilateral neck dissection. If the tumor encroached on the mandible, a marginal mandibulectomy was performed transorally or by using a cheek flap. In posteriorly located lesions a paramedian mandibular swing approach was used.

Indications for postoperative radiotherapy included T3-T4 tumors, positive or close surgical margins, perineural tumor spread, multiple positive nodes and/or extranodal spread. Generally, the clinical target volume (CTV) of the initial field included the original primary tumor site with a 1.0 cm margin, the cervical neck node areas on both sides and the entire surgical bed. For the planning target volume (PTV), an extra margin of 0.5 cm surrounding the CTV was taken. The primary PTV was irradiated using 2 Gy per fraction to a total dose of 46 Gy. An additional boost was given at the original primary tumor site with a 0.5 cm margin up to a total dose of 56 Gy (2 Gy per fraction, 5 times/week) in case of negative surgical margins. In case of positive surgical margins or extranodal spread an additional boost was given to a total dose of 66 Gy (2 Gy per fraction, 5 times/week).

Data collection and study measures

Data collected included sociodemographics (age, gender, and marital status), diagnosis (tumor site and stage [24]), comorbidity, treatment (subsites resected and postoperative radiotherapy), and HRQOL. Comorbidity was assessed by review of medical records and on the basis of self-report, and included any of the following medical conditions: cardiovascular, respiratory, gastro-intestinal, renal, endocrine, neurological, and immunological disorders, previous malignancy, severe weight loss or alcohol abuse. For example; cardiovascular problems such as a myocardial infarct or hypertension, respiratory problems such as restrictive lung disease or COPD, or endocrine disorders such as diabetes mellitus with insulin usage were defined as relevant comorbid conditions.

Resection status was defined after treatment. The amount of oral cavity and oropharynx subsite (i.e., mobile tongue, floor-of-mouth, base-of-tongue, tonsillar fossa and soft palate) resections were indicated as 0 (no part to a quarter resected) or as 1 (more than a quarter resected). For each patient, the resected part for each subsite was calculated and cumulated (i.e., resection status) ranging from patients with a minimum (1) to those with a maximum resected (5).

HRQOL was assessed at pretreatment (baseline), and at 6 month and 12 month follow-up with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire (version 2.0) and the EORTC head and neck cancer module QLQ-H&N35.[6,25] The QLQ-C30 is composed of multi-item scales and single items assessing 5 areas of functioning (physical, role, emotional, cognitive, and social), fatigue, pain, emesis, dyspnea, insomnia, appetite loss, constipation, and diarrhea. Overall quality of life and the perceived financial impact of the disease and treatment are also assessed.

The head and neck cancer-specific QLQ-H&N35 module comprises 7 symptom scales: pain, swallowing, senses, speech, social eating, social contact, and sexuality. There are 11 additional single items covering problems with teeth, opening the mouth wide, dry mouth, sticky saliva, coughing, feeling ill, weight loss, weight gain, use of nutritional supplements, feeding tubes, and pain medication. The scores of both the QLQ-C30 and of the QLQ-H&N35 are linearly transformed to a scale of 0 to 100, with a higher score indicating a higher (i.e., more positive) level of functioning or global HRQOL, or a higher (i.e., more negative) level of symptoms or problems.

Statistical analyses

Paired Student's t-tests were used to assess change scores from pretreatment to 6 months follow-up and from 6 months to 12 months follow-up. Independent Student's t-tests were used to test differences in HRQOL change scores between: 1) patients with oral cavity versus oropharyngeal cancer; 2) patients with T2 versus T3-T4 tumor stage; and 3) patients with comorbidity versus without comorbidity. The relation between resection status and changes in quality of life was tested by regression analysis, with resection status as a continuous variable. A stepwise multiple regression analysis was performed to investigate the relationship between sociodemographic characteristics (age, gender, partner), comorbidity, clinical characteristics (tumor site, tumor stage, subsite resection), and changes in overall HRQOL as assessed by the two-item global quality of life scale of the QLQ-C30. For all statistical tests, significance was defined as a p-value less than or equal to .05.

Results

Sample description

Patient characteristics are shown in Table 1. During the inclusion period (January 1998-December 2001) 92 consecutive patients met the inclusion criteria. Twelve patients declined to participate in the study, resulting in a final sample of 80 patients (response rate = 87%). The patients' age ranged from 23 to 74 years (mean = 58 years). Forty-one percent of the sample was female. Fifty-four patients (67%) had a partner. One patient was treated for a recurrent tumor after transoral excision (1 year earlier) and for this patient the rTNM stage was used, and one patient had undergone previous radiotherapy for a neck node of an unknown primary. Four patients had a synchronous second primary oral cavity or oropharyngeal tumor which was also resected, and in these cases the stage of the largest tumor was used. An equal percentage (50%) of patients had a tumor originating on the left or right side, and in the majority of patients (73%) the tumor did not extend over the median line. Seventy-four patients (93%) received radiotherapy. Oral cavity tumors represented 47% (n = 38) of the cases, and oropharynx tumors the remaining 53% (n = 42). Tonsil, mobile tongue, floor-of-mouth, and base-of-tongue were the most common subsites (30%, 23%, 20%, and 14%, respectively). For all 80 patients, HRQOL questionnaires were completed before treatment. At 6 and 12 months follow-up questionnaires were completed by 55 and 45 patients, respectively. Drop-out was due to death without evidence of disease (n = 3), tumor recurrence and/or distant metastases (n = 19), noncompliance (n = 8), technical problems (n = 3) or patient loss to medical follow-up (n = 2). One patient completed the baseline and 12 month HRQOL questionnaires but not the 6 month assessment. This resulted in 44 patients for whom the HRQOL questionnaires were completed at all 3 points in time.

Table 1. Characteristics of 80 patients included in this study

Age		
Range	23 – 74 yrs	
Mean	58 yrs	
	n	%
Gender		
Male	47	(59)
Female	33	(41)
Partner	54	(67)
Yes	26	(33)
No		
General condition		
Comorbidity	48	(60)
No comorbidity	32	(40)
Tumor site		
Oral cavity	38	(47)
Oropharynx	42	(53)
T		
2	35	(44)
3	42	(52)
4	3	(4)
N		
0	24	(30)
1	16	(19)
2a	2	(3)
2b	30	(38)
2c	6	(7)
3	2	(3)

Health-related quality of life

Mean values of both the QLQ-C30 and QLQ-H&N35 questionnaires for the 44 patients with complete follow-up are shown in Table 2. At 6 months follow-up, significantly worse scores compared to pretreatment were found for physical functioning and financial impact. A significantly better score was found for emotional functioning, pain, and constipation. At 12 months, physical functioning returned to similar levels as pretreatment, and role functioning appeared to be improved significantly (QLQ-C30).

Regarding head and neck cancer specific symptoms (QLQ-H&N35), a significantly worse score was found for 8 of 13 scales and single items at 6 months follow-up compared to pretreatment. This included problems with swallowing, senses, social contact, teeth, opening mouth, dry mouth, sticky saliva and coughing. For pain a significant improvement was observed. At 12 months, problems with swallowing, social eating and dry mouth appeared to be reduced, although not returning completely to pretreatment levels.

Table 2. EORTC QLQ-C30 and QLQ-H&N35 mean scores for 44 patients with complete follow-up (pretreatment, 6 and 12 months after treatment)

	Pretreatment	**6 months**	**12 months**	**Significance**	
	Mean	Mean	Mean	$p_{P\text{-}6}$	$p_{6\text{-}12}$
EORTC QLQ-C30					
Functioning scales [a]					
Physical Functioning	87.7	80.5	85.9	**.005**	**.044**
Role Functioning	79.5	75.4	84.8	.237	**.005**
Cognitive Functioning	85.6	84.1	87.9	.685	.262
Emotional Functioning	70.3	86.0	84.7	**.000**	.602
Social Functioning	89.0	86.7	90.2	.486	.297
Global quality of life	75.9	76.3	80.7	.903	.064
Symptom scales or single items [b]					
Fatigue	24.7	23.0	18.9	.616	.136
Emesis	1.9	5.3	2.7	.071	.197
Pain	29.2	10.6	12.1	**.000**	.652
Dyspnea	10.6	12.1	7.6	.710	.160
Insomnia	36.4	23.5	17.4	.055	.221
Appetite loss	12.1	13.6	10.6	.772	.210
Constipation	13.6	3.0	3.0	**.046**	1.00
Diarrhea	6.8	5.3	5.3	.599	1.00
Financial impact	7.6	17.8	15.2	**.036**	.583
EORTC QLQ-H&N35					
Pain	33.0	21.8	19.5	**.010**	.443
Swallowing	18.9	35.4	25.8	**.001**	**.003**
Senses	4.2	17.8	19.7	**.000**	.452
Speech	9.1	11.4	9.7	.420	.518
Social eating	20.3	30.8	23.6	.050	**.023**
Social contact	3.9	6.9	5.9	**.029**	.542
Sexuality	19.3	22.1	24.0	.931	.673
Teeth	18.2	27.8	22.5	**.020**	.413
Opening mouth	19.7	37.9	33.3	**.018**	.360
Dry mouth	22.0	68.9	56.1	**.000**	**.005**
Sticky saliva	17.4	47.6	47.6	**.000**	.781
Coughing	11.4	23.5	24.2	**.001**	.855
Feeling ill	4.5	3.8	6.8	.660	.290

[a] A higher score indicating a higher (i.e.. more positive) level of functioning or global HRQOL

[b] A higher (i.e.. more negative) level of symptoms or problems

$p_{P\text{-}6}$: p-value for test effect pretreatment to 6 months follow-up

$p_{6\text{-}12}$: p-value for test effect 6 to 12 months follow-up

Changes in HRQOL at 6 month (n = 55) and 12 month (n = 44) follow-up in relation to tumor site are shown in Table 3. Patients with oropharyngeal tumors reported more emesis at 6 months compared to pretreatment than patients with oral cavity tumors. At 12 months, this difference diminished because emesis increased in oral cavity cancer patients and decreased in oropharyngeal cancer patients. Furthermore, patients with oral cavity cancer reported significantly more appetite loss at 12 months compared to their situation at 6 months than patients treated for oropharyngeal cancer (QLQ-C30).

Evaluation of the QLQ-H&N35 data indicated that patients with oral cavity tumors reported significantly less pain compared to patients with oropharynx tumors at 6 months compared to pretreatment. Problems with teeth, dry mouth and sticky saliva were significantly increased for patients with oropharynx tumors compared to patients with oral cavity tumors between pretreatment and 6 months follow-up. Between 6 and 12 months no significant differences between patients with oral cavity versus oropharyngeal tumors were found regarding changes over time on the QLQ-H&N35.

Changes in HRQOL after 6 and 12 months in relation to tumor stage are shown in Table 4. The results for the QLQ-C30 showed no significant differences in change scores between pretreatment and 6 months follow-up for patients with T2 tumors as compared to patients with T3-T4 tumors. Patients with larger (T3-T4) tumors reported significantly less fatigue at 12 months as compared to 6 months follow up (QLQ-C30). Evaluation of the QLQ-H&N35 data indicated that problems with teeth and sticky saliva were significantly greater at 6 months compared to pretreatment for patients with T2 tumors versus patients with T3-T4 tumors. At 12 months (compared to 6 months) follow-up, patients with T2 tumors reported less pain while patients with T3-T4 tumors reported more pain.

The impact of comorbidity on changes in HRQOL after 6 and 12 months follow-up appeared to be limited (data not presented in tabular form). Between pretreatment and 6 months follow-up, emesis (QLQ-C30) and speech problems (QLQ-H&N35) were significantly decreased for patients with comorbidity compared to patients without comorbidity. Between 6 and 12 months no significant differences in change scores between these two subgroups were observed.

Table 3. The impact of tumor site on the HRQOL difference scores of patients after 6 months follow-up versus pretreatment (n=55) and 12 versus 6 months follow-up (n=44)

	Difference score P-6			**Difference score 6-12**		
	Oral cavity	**Oropharynx**		**Oral cavity**	**Oropharynx**	
	Mean n=22	Mean n=33	p	Mean n=18	Mean n=26	p
EORTC QLQ-C30						
Functioning scales [a]						
Physical Functioning	-9.1	-4.8	.376	10.0	2.3	.153
Role Functioning	-5.3	-2.5	.680	12.0	7.7	.508
Cognitive Functioning	3.0	-5.1	.247	1.9	5.1	.635
Emotional Functioning	17.8	12.1	.166	0.5	-2.6	.562
Social Functioning	0	-8.6	.382	5.6	1.9	.587
Global quality of life	0.8	-4.3	.374	1.9	6.1	.369
Symptom scales or single items [b]						
Fatigue	0.5	-0.3	.897	8.6	9	.152
Emesis	0.8	-7.6	**.018**	-1.9	5.8	.063
Pain	23.5	8.1	.069	-3.7	0	.591
Dyspnea	-6.1	4.0	.154	11.1	0	.085
Insomnia	22.7	1.0	.078	3.7	7.7	.693
Appetite loss	3.0	-7.1	.303	-3.7	7.7	**.017**
Constipation	7.6	12.1	.610	0	0	1.000
Diarrhea	6.1	-2.0	.105	-1.9	1.3	.484
Financial impact	-7.9	-8.1	.986	11.8	-3.8	.069
EORTC QLQ-H&N35						
Pain	19.7	2.8	**.022**	-2.3	5.4	.197
Swallowing	-14.0	-21.0	.408	8.8	10.3	.820
Senses	-15.9	-8.6	.229	-0.9	-2.6	.751
Speech	-3.0	-2.0	.851	1.5	1.7	.975
Social eating	-12.3	-12.0	.972	8.7	5.7	.621
Social contact	-4.6	-2.8	.482	2.7	-0.3	.354
Sexuality	8.3	-6.9	.108	-2.4	0	.808
Teeth	3.3	-22.2	**.022**	-8.9	14.7	.107
Opening mouth	-10.6	-24.2	.296	-5.6	11.5	.088
Dry mouth	-31.8	-56.6	**.032**	20.4	7.7	.156
Sticky saliva	-4.5	-53.8	**.000**	-9.3	4.3	.250
Coughing	-12.1	-8.1	.508	-3.7	1.3	.559
Feeling ill	-1.5	3.0	.136	-1.9	-3.8	.733

[a] A negative change score is a deterioration in functioning. A positive change score an improvement

[b] A negative change score is an increase in symptoms. A positive change score is a decrease in symptoms

P-6 : Pretreatment to 6 months follow-up

6-12 : 6 to 12 months follow-up

Table 4. The impact of tumor stage on the HRQOL difference scores of patients after 6 months follow-up versus pretreatment (n=55) and 12 versus 6 months follow-up (n=44)

	Difference score P-6			Difference score 6-12		
	T2	**T3-T4**		**T2**	**T3-T4**	
	Mean n=27	Mean n=28	p	Mean n=24	Mean n=20	p
EORTC QLQ-C30						
Functioning scales [a]						
Physical Functioning	-2.2	-10.7	.067	2.5	9.0	.223
Role Functioning	-4.3	-3.0	.839	7.6	11.7	.534
Cognitive Functioning	4.3	-7.7	.076	-0.7	9.2	.143
Emotional Functioning	19.1	9.8	.141	-0.7	-2.1	.788
Social Functioning	-0.6	-9.5	.142	1.4	5.8	.500
Global quality of life	0.6	-5.1	.308	3.1	5.8	.562
Symptom scales or single items [b]						
Fatigue	4.1	-4.0	.202	-1.9	11.1	**.013**
Emesis	-3.1	-5.4	.520	2.8	2.5	.946
Pain	12.3	16.1	.658	-0.7	-2.5	.791
Dyspnea	-2.5	2.4	.489	9.7	-1.7	.074
Insomnia	6.2	13.1	.571	8.3	3.3	.616
Appetite loss	-7.4	1.2	.371	5.6	0	.249
Constipation	9.9	10.7	.924	1.4	-1.7	.536
Diarrhea	1.2	1.2	.993	-2.8	3.3	.163
Financial impact	-11.1	-4.9	.426	0	5.3	.541
EORTC QLQ-H&N35						
Pain	4.6	14.3	.191	8.0	-4.6	**.031**
Swallowing	-16.0	-20.2	.611	11.8	7.1	.455
Senses	-16.7	-6.5	.088	-3.5	0	.495
Speech	-0.8	-4.0	.549	3.2	-0.3	.493
Social eating	-11.7	-12.5	.932	9.7	3.1	.266
Social contact	-3.2	-3.9	.792	1.9	-0.3	.485
Sexuality	4.0	-8.3	.178	-2.5	1.2	.706
Teeth	-23.5	-1.3	**.042**	17.4	-9.8	.055
Opening mouth	-23.5	-14.3	.475	11.1	-3.3	.146
Dry mouth	-42.0	-51.2	.425	13.9	11.7	.803
Sticky saliva	-46.9	-19.2	**.023**	7.2	-13.0	.085
Coughing	-11.1	-8.3	.643	2.8	-5.0	.354
Feeling ill	-1.2	3.6	.107	-4.2	-1.7	.665

[a] A negative change score is a deterioration in functioning. A positive change score an improvement

[b] A negative change score is an increase in symptoms. A positive change score is a decrease in symptoms

P-6 : Pretreatment to 6 months follow-up

6-12 : 6 to 12 months follow-up

The impact of subsite resections appeared to be varied (Table 5, statistically significant results are shown together with explained variance). In these analyses, resection status was used as a continuous variable (with scores ranging from 1 to 4). Between pretreatment and 6 months follow-up no statistically significant association was observed between changes in the QLQ-C30 subscales and the resection status. For the QLQ-H&N35, patients with more extensive resections scored better on the variable "feeling ill" but reported more problems with dry mouth and teeth. Between 6 and 12 months, patients with more extensive resections reported significantly worse emotional functioning but reported significantly less pain (QLQ-C30). On the QLQ-H&N35 they reported less problems with opening the mouth, but more pain.

Table 5. The impact of resection status on the HRQOL difference scores of patients after 6 months follow-up versus pretreatment (n=55) and 12 versus 6 months follow-up (n=44)

	p	b	r^2
Difference score P-6			
EORTC QLQ-H&N35			
Teeth	.013	-.006	0.385
Dry mouth	.010	-.006	
Feeling ill	.000	.030	
Difference score 6-12			
EORTC QLQ-C30			
Emotional Functioning	.010	-.018	0.392
Pain	.008	.016	
EORTC QLQ-H&N35			
Pain	.024	-.018	
Opening mouth	.000	.017	

p : p-value

b : Beta coefficient

r^2 : Total explained variance

P-6 : Pretreatment to 6 months follow-up

6-12 : 6 to 12 months follow-up

Linear regression analyses were performed to investigate the association between a range of sociodemographic and clinical factors and HRQOL, in general. The global quality of life scale of the QLQ-C30 was employed as the dependent variable, and age, gender, marital status, comorbidity, tumor site, tumor stage and resection status as independent variables. After 6 months follow-up, not having a partner (p=.017) and older age (p=.041) were significantly related with (lower) global quality of life (R^2=0.16). After 12 months follow-up, no factors were found to be significantly related with the global quality of life scores.

Discussion

In this study we investigated longitudinal changes in HRQOL in a well defined sample of head and neck cancer patients. The results revealed that patients reported poorer head and neck cancer-specific (QLQ-H&N35) HRQOL at 6 months follow-up as compared to pretreatment, with an improvement in some HRQOL domains observed after 12 months of follow-up.

For the patient group that completed all three assessments, general physical functioning and financial impact (QLQ-C30) deteriorated 6 months after treatment. Physical functioning returned to pretreatment levels at 12 months follow-up. In contrast, patients reported improvement after treatment in emotional functioning, pain, and constipation. Based on earlier studies on HRQOL in patients with oral cavity and oropharyngeal cancer [12,16], we had expected that head and neck-specific symptoms would increase following treatment, but that the pattern of changes over time might be somewhat different due to the RFFF reconstruction. As expected, patients reported deterioration on the majority of the head and neck-specific symptoms (QLQ-H&N35) 6 months after treatment. Swallowing, senses, social contact, problems with teeth, opening the mouth, dry mouth, sticky saliva, and coughing were all worse and continued to be worse at 12 months follow-up. Pain was the only head and neck symptom that improved after treatment as compared to pretreatment. De Graeff et al. reported similar results in their prospective longitudinal study of patients with oral cavity and/or oropharynx tumors.[16] After 6 months follow-up they observed a significant deterioration on 8 out of 13 QLQ-H&N35 scales and items (i.e., swallowing, senses, speech, social eating, sexuality, problems with the opening mouth, dry mouth, and sticky saliva) and 3 of the 15 QLQ-C30 scales and items (i.e., physical functioning, fatigue, and appetite loss). All symptoms improved after 12 months follow-up, but most were still significantly worse compared with baseline. Our findings as well as those of de Graeff and colleagues underscore the value of a disease-specific questionnaire such as the QLQ-H&N35.

Other studies of the HRQOL of patients with oral cavity or oropharyngeal tumors have yielded similar results; a worsening in varied HRQOL domains (especially related to head and neck-specific issues) after 6 months and some improvement in the period thereafter. The present results, as well as those of previous longitudinal studies, suggest that HRQOL after treatment deteriorates, gradually improves during the first year, and then remains relatively stable thereafter.[12,26,27] This common, general conclusion is all the more striking given the variations across studies in patients groups, questionnaires, treatment, and follow-up interval. Conversely, differences in results between the current and earlier studies may be attributable, at least in part, to patients groups and treatment differences. For example, de Graeff et al. reported worse speech after 6 months follow-up, while this was not found in our study or in that of Hammerlid and colleagues.[16,27]

In an earlier study on pretreatment HRQOL we found a clear impact of tumor site, tumor stage and comorbidity on HRQOL and functional status.[23] In the present study, tumor site and stage, and to a lesser extent, comorbidity also appeared to influence HRQOL over time. These influencing factors may help to explain some of the contradictory results reported in the literature. For example, Bjordal et al. found that patients with pharyngeal cancer reported worse HRQOL as compared to patients with oral cavity cancer after one year follow-up.[12] Others found no significant HRQOL differences as a function of tumor site.[28,29] In the present study we found an increase in complaints of dry mouth and sticky saliva in patients with oropharyngeal tumors compared to patients with oral cavity tumors between pretreatment and 6 months follow-up. One would expect this might be due to radiotherapy, although there was a comparable amount of irradiated patients with oral cavity and oralpharyngeal tumors at six months.

Deteriorated HRQOL may be associated with higher stage [27,30,31], although this has not been reported consistently.[32] Deleyiannis et al., in their study of patients with advanced tumors, found a worsening of chewing, swallowing and speech after on year of follow-up.[33] De Graeff et al. did not find a significant association between stage and any of the scales of the QLQ-C30. However, tumor stage was found to be associated significantly with head and neck cancer-specific HRQOL problems. An explanation for this difference with our results might be that they also included stage I patients.[16]

Findings with regard to the impact of comorbidity on HRQOL are conflicting. Some workers have reported no clear influence of comorbidity before and after treatment on

HRQOL [34], whereas others have reported a significant impact on outcome.[35] We found that patients with comorbidity reported worse HRQOL both before and after treatment, and that during follow-up only minor changes take place. There is thus clearly a need to better define the impact of comorbidity on HRQOL in this patient population.

Acknowledging that stage had no major impact on HRQOL over time, we also investigated the role of the extent of the resection, as one would expect more HRQOL problems in patients with more extensive resections. However, deterioration HRQOL as a function of extent of resection was observed for only three scales; patients with larger resections reported more teeth and dry mouth problems at 6 months follow-up and poorer emotional functioning at 12 months compared to 6 months. Between 6 and 12 months pain also deteriorated (QLQ-H&N35) although an improvement was found regarding the QLQ-C30 results.

We found that well-known clinical factors such as disease stage and site, comorbidity and extent of resection were not associated significantly with overall quality of life. Advanced age and not having a partner were associated negatively with overall quality of life after 6 months follow-up, but these associations did not persist at 12 months. Derks et al. found that age only influenced physical functioning. However, in their study patients with larynx carcinomas were also included, and subgroup analyses showed that older patients with pharynx carcinomas seemed to have lower HRQOL.[36] Others have reported that elderly patients tend to report lower overall HRQOL than younger patients.[12,29] The relation between marital status and HRQOL has also been reported previously.[34] Interestingly, marital status may even be an independent predictor of recurrence and survival.[37]

In conclusion, in this well-defined patient group, we found that functional HRQOL tended to improve after treatment. Many symptoms improved or returned to baseline levels, but others, including with the exception of swallowing, senses, social contact, teeth, mouth opening, dry mouth, sticky saliva and coughing, persisted throughout the one year follow-up period. Hopefully, these data will serve as useful benchmarks for future HRQOL investigations of surgery and other treatment modalities used with this patient population.

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Chapter 8

Summary and General Discussion

Summary

Cancer of the oral cavity and oropharynx and its treatment has a profound and unique negative impact on the life of a patient. It affects three major domains; the ability to eat, speak and appearance. All of these factors influence the patients' health related quality of life (HRQOL). Surgery of head and neck cancers results in defects of soft tissues, sometimes in combination with bone and skin. To reconstruct these defects several techniques have been developed for restoring functional and cosmetic deficits. Modern microvascular reconstructive techniques offer the best choice for reconstruction after major oncologic surgery in patients with oral and oropharyngeal cancer. Several prognostic factors influence outcome. The interaction of these parameters is the subject of this thesis.

In Chapter 2, the relationship between comorbidity and postoperative complications in patients with oral cavity and oropharynx cancer was analyzed. The presence and severity of comorbid condition was determined, as well as the incidence of clinically important complications. We demonstrated that the presence of advanced comorbidity is a strong predictor for development of complications. Furthermore it was shown that patients with advanced comorbidity generally have a prolonged postoperative course due to complications. These findings assist in filling the gap of knowledge on the prognostic value of comorbidity on postoperative course in patients with oral cavity and oropharynx cancer. With this knowledge improved patient selection, counseling, preparation and vigilance as to complications may be possible.

In Chapter 3, the possible impact of comorbidity on survival of patients with oral or oropharyngeal cancer was investigated. The presence and severity of comorbid condition, as well as the overall 5-year survival for patients was determined. It was demonstrated that patients with severe comorbidity had a significantly lower survival rate than those with moderate, slight or no comorbidity. The results of the study indicate that survival estimates in head and neck cancer might be improved by addition of comorbidity to the current TNM staging system. Also, it is postulated that refraining from major surgery in patients with severe comorbidity should be considered when reasonable treatment alternatives are available.

Whereas in these first chapters the short term influence of comorbidity on postoperative complications and long term effect on patients' survival was analyzed retrospectively, we subsequently prospectively investigated the functional status and HRQOL in patients who had surgery for advanced oral cavity or oropharynx cancer.

In Chapter 4, HRQOL and functional status is described in patients with advanced oral and oropharyngeal cancer before treatment, in relation to tumor site, stage and comorbidity. HRQOL was determined using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire and the EORTC head and neck cancer module QLQ-H&N35. Functional status assessment comprised speech and oral function analyses. We demonstrated that patients had deteriorated HRQOL and functional status already before treatment, when compared with normative population values. Furthermore, it was found that in addition to tumor site and stage, comorbidity appeared to have a major impact on HRQOL and functional status. Impaired speech and oral function appeared to be clearly related to global quality of life and self-reported speech. With this knowledge of HRQOL and functional status in this population prior to treatment better interpretation of outcome measures is possible.

To investigate speech outcome in patients with advanced oral and oropharyngeal cancer, a follow-up study was done as described in Chapter 5. Patients were investigated before, and 6 and 12 months after treatment. Speech tests results were significantly worse for patients, before and after treatment, as compared to controls. Overall speech quality in patients before treatment was approximately 20% worse than in controls, while 6 and 12 months after treatment this was approximately 75%; speech did not improve between 6 and 12 months. Furthermore it was found that postoperative overall speech quality was worse for patients with larger tumors. From this study it was concluded that speech is deteriorated after treatment and rehabilitation might be beneficial for these patients, but further research on its efficacy is clearly needed.

Swallowing outcome for advanced oral and oropharyngeal cancer patients after treatment is described in Chapter 6. Patient, tumor and treatment factors were assessed and postoperative videofluoroscopic swallowing studies (VFSS) and scintigraphy tests were performed at 6 and 12 months. Swallowing parameters as the oropharyngeal swallow efficiency (OPSE) and the Penetration/Aspiration Scale were analyzed. Results revealed that impaired swallowing status was found at 6 months which remained stationary at 12 months. Comorbid condition, larger tumors and resections of the base-of-tongue and soft palate combined were associated with most profound swallowing problems. From this study it was concluded that swallowing difficulties are relatively frequent and can to a large extent be predicted. These data may also serve as benchmark for outcome in an era in which non-surgical treatment modalities with surgery in reserve, are gaining popularity.

In Chapter 7, insight in longitudinal long-term HRQOL for advanced oral and oropharyngeal cancer patients was obtained. HRQOL was assessed by EORTC QLQ-C30/QLQ-H&N35 questionnaires at 3 points in time, pretreatment (baseline), and 6 months and 12 months posttreatment. It was demonstrated that mean HRQOL scores for most functioning domains remained unchanged after treatment. Many symptoms scales and single items improved over time, but sustained problems were observed for swallowing, senses, social contact, teeth, mouth opening, dry mouth, sticky saliva and coughing. Tumor site and stage, patients' comorbidity and more extensive resections were found to be associated significantly with HRQOL outcomes. Not having a partner and older age were significantly related with lower global quality of life. These results in this population after treatment may serve as HRQOL benchmarks for future studies investigating surgical and other treatment modalities.

General Discussion

In recent years extensive outcome research related to function and quality of life has been performed in patients with a variety of head and neck squamous cell cancers. Unfortunately, only a minority of studies focus on well defined patient groups or specific treatment modalities, such as microvascular reconstruction.[1,2] Additionally, studies on prognostic factors and outcome focus on different aspects and are sometimes contradictory.[3,4] This thesis describes the relation between prognostic factors and outcome in a circumscribed head and neck patient group (patients with advanced oral or oropharyngeal cancer) that underwent standardized surgical treatment with microvascular soft tissue reconstruction and postoperative radiotherapy on indication.

The use of fasciocutaneous flaps, such as the radial free forearm flap (RFFF), is currently globally propagated for reconstruction of head and neck soft tissue defects. It offers an excellent choice for generating an optimal functional and anatomical reconstruction. In patients with advanced oral cavity or oropharyngeal tumors it is therefore a first choice method in soft tissue replacement.

Studies on comorbidity in head neck cancer have been portrayed increasingly in the medical literature in the recent decade. Comorbidity, however, is difficult to define and score. Disadvantages of an extensive scoring system are the time-consuming analyses and often the lack of input information. Currently, the ACE-27 index developed by Piccirillo is used mostly and has proven to be a very useful system to score the severity of comorbid conditions.[5,6] Other indices, such as the Charlson Comorbidity Index, are used less frequently.[7,8] The findings described in this thesis make it very clear that comorbidity plays an important role in tumor prognosis and outcome. Its exact role in treatment selection will undoubtedly become clearer and more prominent in the near future.

Severe complications, with direct profound consequences for the patient, must be avoided. There is as yet a lack in information about this. An ideal and universally accepted postoperative scoring system for complications in surgical treatment of head and neck cancer patients does not exist. Whereas some authors use broad categories of clinically important complications, others use a much more detailed scoring system that includes every minor deviation from the normal course.[9,10] It is therefore extremely difficult to compare results on complications and there is a need for a clear complication scoring system that focuses on the head and neck patient.

Speech tests are diverse, but execution and interpretation seems to be relatively accurate. Swallowing tests seem more complex and problems as estimating the bolus deviation in videofluoroscopy reporting and difficulty of aspiration detection in scintigraphic tests makes evaluation difficult. Further studies that strive for easy to perform and accurate measurements are needed.

There is no gold standard with respect to instruments which include all components which measure HRQOL. Rogers et al. give a brief description of 27 commonly used questionnaires in cancer research and describe guidelines for selecting a questionnaire.[11] A division can be made into two basic types of instruments: cancer specific and head and neck specific. Nowadays, leading cancer specific questionnaires are the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire and the Functional Assessment of Cancer Therapy (FACT), that is used in Northern America.[12,13] For head and neck specific instruments the mostly used questionnaires are the EORTC head and neck cancer module (QLQ-H&N35), the FACT head and neck supplement, and the University of Washington head and neck cancer questionnaire (UW-QOL).[14,15,16] The choice of the instrument is determined by the type of study, patients investigated, and by the experience of the investigators.

Tumor site and stage probably play a prominent role in HRQOL outcome.[17,18] We could demonstrate that site and stage indeed showed a clear effect on HRQOL before treatment, which was sustained in the follow-up phase. Moreover factors like older age and having a partner seemed also be related with postoperative HRQOL. Some authors found similar results [17], whereas others could not corroborate this finding.[19,20] Besides factors that influence quality of life as described in this thesis, it must be considered that psychosocial factors (such as social support and coping mechanisms) might also be associated with HRQOL differences. It has been described that social support might have a positive effect on HRQOL [21] and patients more able to cope with problems in life like stress show an improved HRQOL.[22] Some authors describe worse HRQOL in females, especially because of greater anxiety and depression.[23] It is clear that several factors influence HRQOL, and the quantity and diversity of these reflect the difficulty in comparing HRQOL results.

We and others found that prognostic factors have a more straightforward effect on objective functional status than on subjective HRQOL after treatment. A correlation between objective speech tests and subjective HRQOL before treatment is described in this thesis. The exact interactions between objective speech and swallowing and subjective HRQOL, although outside the direct focus of this work, remains an area of great interest for future study.

Conclusions

Based on the research described in this thesis the following can be concluded: 1) Comorbidity plays a prominent role in prediction of postoperative complications and long-term survival. 2) Speech and swallowing are deteriorated at 6 and 12 months after treatment as compared to pretreatment and normal values. 3) Head and neck specific HRQOL is deteriorated before treatment and is worsened at 6 months after treatment with a slight improvement on some scales after 12 months. 4) Factors as comorbidity, tumor site, and tumor stage affect speech and HRQOL before treatment, and speech, swallowing and HRQOL after treatment.

The results in this thesis are unique for this well defined patient group of patients with oral and oropharyngeal cancers. With the knowledge of this thesis improved patient selection, counseling and preparation in major surgical treatment is possible as well as vigilance as to complications. It may serve as benchmark for future studies that use other treatment modalities.

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Samenvatting

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Kanker van de mond- en keelholte alsmede de behandeling daarvan heeft een specifiek en negatief effect op het leven. Het betreft hierbij drie belangrijke onderdelen van het dagelijks functioneren; de mogelijkheid om te kunnen eten, te kunnen praten en het uiterlijk van de patiënt. Al deze factoren beïnvloeden de kwaliteit van leven. Chirurgische behandeling van tumoren in het hoofd-halsgebied resulteert in een defect van de weke delen, soms in combinatie met een bot- en/of huiddefect. Teneinde een dergelijk defect te kunnen reconstrueren zijn er verschillende chirurgische technieken ontwikkeld, waarbij getracht wordt om zo goed mogelijk de functie en cosmetiek te behouden. Voor de reconstructie na uitgebreide oncologische chirurgie bij patiënten met kanker van de mond- of keelholte bieden moderne microvasculaire reconstructieve technieken de beste keus. Verschillende prognostische factoren beïnvloeden de uitkomst na behandeling. De interactie tussen deze prognostische factoren en de uitkomst wordt onderzocht in dit proefschrift.

In hoofdstuk 2 wordt bij patiënten met kanker van de mond- of keelholte de relatie tussen comorbiditeit en postoperatieve complicaties geanalyseerd. Zowel de ernst van comorbiditeit alsmede klinisch relevante complicaties werden voor iedere patiënt genoteerd. Er kon worden aangetoond dat uitgebreide comorbiditeit een sterke voorspeller is voor het ontwikkelen van complicaties. Tevens bleek dat patiënten met uitgebreide comorbiditeit na de operatie langer opgenomen bleven als gevolg van complicaties. Deze bevindingen zijn van nut bij het bepalen van de prognostische waarde van comorbiditeit ten aanzien van postoperatieve complicaties bij patiënten met kanker van de mond- of keelholte. Met deze kennis is een betere patiënten-selectie, voorbereiding, begeleiding en waakzaamheid mogelijk met betrekking tot het ontwikkelen van postoperatieve complicaties.

In hoofdstuk 3 wordt de mogelijke invloed van comorbiditeit op de overleving van patiënten met kanker van de mond- of keelholte onderzocht. Zowel de ernst van de comorbiditeit als de vijf-jaars overleving werd voor iedere patiënt genoteerd. Het bleek dat patiënten met uitgebreide comorbiditeit een significant lagere overlevingskans hadden dan patiënten met een minder uitgebreide comorbiditeit of zonder comorbiditeit. De resultaten beschreven in deze studie duiden erop dat de voorspelling van overleving kan worden verbeterd door comorbiditeit toe te voegen aan het huidige TNM stadiërings-systeem. Tevens kan enige terughoudendheid in overweging worden genomen ten aanzien van grote chirurgische ingrepen bij patiënten met uitgebreide comorbiditeit, vooral wanneer redelijke alternatieven voor deze behandeling voorhanden zijn.

In de eerste twee hoofdstukken wordt de korte termijn invloed van comorbiditeit op postoperatieve complicaties en de lange termijn invloed van comorbiditeit op overleving retrospectief beschreven. In de volgende hoofdstukken wordt prospectief de kwaliteit van leven en functionele status onderzocht bij patiënten met kanker van de mond- of keelholte.

In hoofdstuk 4 wordt de preoperatieve kwaliteit van leven en functionele status beschreven in relatie tot tumor-localisatie, -grootte en comorbiditeit. De kwaliteit van leven werd bepaald aan de hand van de *European Organization for Research and Treatment of Cancer* (EORTC) QLQ-C30 vragenlijst en de EORTC hoofd-halskanker module QLQ-H&N35. De functionele status werd bepaald met behulp van spraak- en oralefunctie-testen. Er kon worden aangetoond dat patiënten reeds vóór de behandeling een verslechterde kwaliteit van leven en functionele status hadden vergeleken met een “normale” populatie. Tevens bleek dat tumor-localisatie, -grootte en met name comorbiditeit duidelijk van invloed zijn op de kwaliteit van leven en functionele status. Verminderde spraak en orale functies waren evident gerelateerd aan de scores voor globale kwaliteit van leven en problemen met het spreken. Met deze kennis over de kwaliteit van leven en functionele status vóór de behandeling is een betere interpretatie mogelijk met betrekking tot de uitkomst hiervan na de behandeling.

Om de uitkomst van spraak bij patiënten met kanker van de mond- of keelholte te onderzoeken werd een follow-up studie verricht welke is beschreven in hoofdstuk 5. De patiënten werden geanalyseerd middels diverse spraakonderzoeken vóór de behandeling en 6 en 12 maanden na de behandeling. De spraakfunctie bleek significant slechter vóór en na de behandeling vergeleken met een controle groep. Vóór de behandeling was de spraakfunctie enigszins slechter terwijl dit 6 en 12 maanden na de behandeling fors slechter was. De spraakfunctie veranderde dus niet tussen 6 en 12 maanden. Tevens bleek dat de spraakfunctie na de behandeling slechter was voor patiënten met een grotere tumor. Uit deze studie kan geconcludeerd worden dat de spraak verslechtert na de behandeling. Wellicht zou spraakrevalidatie een ondersteunende rol kunnen spelen.

In hoofdstuk 6 wordt de slikfunctie na de behandeling van patiënten met kanker van de mond- of keelholte beschreven. Patiënt-, tumor- en behandelingsfactoren werden bepaald en 6 en 12 maanden na de behandeling werden videofluoroscopische en scintigrafische slikstudies verricht. De slikfunctie werd onder andere aan de hand van de *oropharyngeal swallow efficiency* (OPSE) methode en de *Penetration/Aspiration Scale* geanalyseerd. Uit de resultaten bleek dat 6 maanden na de behandeling het slikken moeizaam ging en dat dit onveranderd bleef na 12 maanden. Comorbiditeit, grotere tumoren en een combinatie van tongbasis met palatum molle resectie bleken geassocieerd met de meeste slikproblemen. Op basis van deze studieresultaten kan worden geconcludeerd dat slikproblemen relatief frequent voorkomen en enigszins te voorspellen zijn. De resultaten van deze studie kunnen bijdragen aan toekomstig onderzoek naar de effectiviteit van slikrevalidatie. Tevens kunnen de slikfunctie-gegevens uit deze studie als standaard dienen voor toekomstige studies waarbij andere therapieën, met een chirurgische behandeling in reserve, worden toegepast.

Kwaliteit van leven op lange termijn bij patiënten met kanker van de mond- of keelholte wordt beschreven in hoofdstuk 7. Kwaliteit van leven werd bepaald middels de EORTC QLQ-C30 en QLQ-H&N35 vragenlijsten vóór de behandeling alsmede 6 en 12 maanden na de behandeling. Er kon worden aangetoond dat de gemiddelde kwaliteit van leven scores aangaande de functie-domeinen na de behandeling onveranderd bleven. Veel symptomen en items betreffende de kwaliteit van leven verbeterden na verloop van tijd, echter evidente problemen bleven er voor het slikken, de reuk en smaak, sociaal contact, problemen met het gebit, het kunnen openen van de mond, een droge mond, slijmstase en hoesten. Tumor-localisatie, -grootte, comorbiditeit en uitgebreidere resecties bleken significant geassocieerd met de kwaliteit van leven na de behandeling. De resultaten van de studie geven een duidelijker beeld van de verandering van kwaliteit van leven bij patiënten met kanker van de mond- of keelholte die behandeld zijn middels chirurgie, microvasculaire reconstructie en eventueel aanvullende radiotherapie. De resultaten kunnen dienen als standaard voor toekomstige studies waarbij zowel chirurgische als andere behandelingsmethoden met elkaar vergeleken worden.

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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 1 maart 1971 te Nijmegen. In 1989 behaalde hij zijn eindexamen VWO aan het Dominicus College te Nijmegen. Datzelfde jaar werd begonnen met de studie geneeskunde aan de Rijksuniversiteit Leiden. Tijdens de studie deed hij een wetenschappelijk onderzoek naar tuberculose bij kinderen aan de Universiteit van Stellenbosch te Kaapstad, Zuid-Afrika. Daarnaast was hij tijdens het grootste deel van zijn studie werkzaam als student-assistent bij de Thorax Intensive Care van het Leids Universitair Medisch Centrum. Het artsexamen werd behaald in 1998, waarna hij werkzaam was als assistent geneeskundige niet in opleiding bij de afdeling Heelkunde van het Bronovo ziekenhuis te Den Haag en vervolgens bij de afdeling Keel-, Neus- en Oorheelkunde van het VU medisch centrum Amsterdam. Vanaf 1 november 1999 tot 1 november 2004 werd hij opgeleid tot KNO-arts (opleiders prof.dr. G.B. Snow en prof.dr. C.R. Leemans) en gelijktijdig werd een aanvang gemaakt met het onderzoek beschreven in dit proefschrift. Een deel van de opleiding werd respectievelijk in het Ziekenhuis Hilversum (opleider dr. M.J. Middelweerd), in het Westfries Gasthuis Hoorn (opleider dr. H.F. Nijdam) en het Diakonessenhuis Utrecht (opleider dr. J.J. Quak) gevolgd. Vanaf 1 november 2004 is hij werkzaam als staflid bij de afdeling Keel-, Neus- en Oorheelkunde van het VU medisch centrum Amsterdam en vanaf 1 januari 2005 tevens als chef de clinique Keel-, Neus- en Oorheelkunde in het Ziekenhuis Hilversum.