Prognostic Models in Head and Neck Oncology
Predictors and dynamics

M.P. van der Schroeff

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Predictoren en dynamiek

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Copromotor:	Dr. M.H. van den Brink-Wieringa

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Part I

INTRODUCTION

Chapter 1

General introduction

Head and neck malignancies originating from the mucosal lining of the upper aero-digestive tract (head and neck squamous cell carcinoma's: HNSCC's) and the salivary glands make up nearly 5% of the total number of malignant tumours in the Netherlands. Variation of incidence trends between sites exist[1], the general incidence of HNSCC's is 17/100,000; the incidence of malignant salivary gland tumours 0.7/100,000 (Netherlands Cancer Registry). In this thesis we discuss prognostics in both types of cancer, although we focus on HNSCC's. Once diagnosed with head and neck cancer, the prognosis (likely outcome of the disease) plays an enormous role in choosing treatment options and informing patients. Generally, survival rates for patients vary depending on the type and the stage (extent) of the cancer involved. The five-years survival rate of patients (the percentage of patients who survive at least five years after the cancer is detected) with HNSCC is around 50%. For those with salivary gland cancer this figure is highly dependent on the type of tumour and differs between 30% to nearly 100%. The prognosis at the time of diagnosis of cancer is taken into account in the choice of treatment. When it comes to informing patients about their prognosis, physicians also incorporate events such as staying free for cancer or the occurrence of a non related health event (eg. myocardial infarction) during follow up. The methods of determination of prognosis, the way prognosis changes over time and the way in which prognosis should be discussed with patients are the central themes of this thesis. This introduction aims to explore the concept of prognosis, the fallibility of prognostic factors, the statistical methods used when working with prognostic factors and the role prognosis plays in the process of decision-making. Finally, we will state the central hypotheses for this thesis.

Prognosis is a key concept in patient care: it concerns the future course in the sense of utilities such as life expectancy and disease free survival. In general, the prognosis of a specific condition differs from the prognosis of a patient with this specific condition: the first denotes global risk (natural history of disease, modified by treatment), the latter an individualized prediction conditional on the patients' characteristics and medical intervention. In contrast to etiological research, prognostic studies aim to predict rather than to explain. All causal factors are prognostic factors, not all prognostic factors are causal. If for example blue eye colour predicts survival in head and neck cancer patients, 'blue eyes' could be a suitable prognostic factor. In reality however we use variables considered to be of influence on prognosis, but not necessarily with a causal relation to it. The most commonly used prognostic factor is the TNM classification in which local tumour spread (T), regional lymph node involvement (N) and presence of distant metastases (M) are combined.

When dealing with prognostic factors, one must realise that most prognostic factors have a limited explanatory value. No prognostic model (a combination of prognostic factors) is perfect, and usually in time better predictors become apparent. Because "the facts" change over time, truth is relative. Medical knowledge, as any science, progresses via a series of theories (paradigms) that are held to be true until they are replaced by a better approximation of reality.[2] For example, the half-life of medical knowledge (period of time it takes for a medical 'truth' to be recognized as such by only half of the number of doctors, a measure of decay) appears to be approximately 40-45 years.[3,4] However, the half-life effect is mainly applicable to therapy and prognosis, certain etiologic and diagnostic relationships will remain as true as they are today. This calls for regularly updating our knowledge on prognostic factors and possible adjustments in treatment choices. Besides temporal limitations, uncertainty is a problem too. Most prognostic studies and presented prognostic factors or models estimate up to 80% of observed survival. This leaves 20% of unpredicted course of disease, possibly explained by factors we have not yet identified.

So, estimating prognosis is difficult and leaves room for uncertainty. Physicians and the media generally opt to present a positive view on that uncertainty. An analysis of proportion of articles reporting about cancer survival, cancer death and dying, aggressive cancer treatment, cancer treatment failure, adverse events of cancer treatment, and end-of-life palliative or hospice care in 8 large readership newspapers and 5 national magazines in the US showed interesting bias.[5] It seemed that of a total of 436 articles, 140 (32.1%) reported cancer survival, in contrast to 33 (7.6%) dealing with cancer death. In general, cancer survival and aggressive cancer treatment were discussed most frequently. Only a few articles discussed cancer death and dying, cancer treatment failure, adverse events of cancer treatment, and end-of-life palliative or hospice care. These portrayals of cancer care in the news media may give patients an inappropriately optimistic view of cancer treatment, outcomes and prognosis. This is also true for predictions made by physicians.[6-8]

In order to optimize predictions on survival and to present patients with a realistic presentation on their future we can only rely on statistics. In most malignant tumours, the prognosis is influenced by a variety of variables (factors), and there are several interactions of varying strength among the different variables. In order to identify those variables that have an independent influence on outcome, we use multivariate biometric methods that enable an estimation of the relative risk associated with each prognostic variable. For studies of prognostic factors, univariate analysis alone is not sufficient; multivariate techniques are indispensable.[9,10] This thesis uses various multivariate survival models. The issue at hand is the time to death or censoring (an observation is called censored if we cannot measure it precisely but know that it is beyond some time limit). The models

can be viewed as consisting of two parts: the underlying hazard function, often denoted $h_0(t)$, which describes how the hazard (risk) changes over time at baseline levels of covariates; and the effect parameters, which describes how the hazard varies in response to prognostic covariates. Sir David Cox (born 1924, Birmingham, England) observed that if the proportional hazards assumption holds, then it is possible to estimate the effect parameter(s) without any consideration of the hazard function. This approach to survival data is called application of the Cox proportional hazards model, sometimes abbreviated to Cox model. The Cox model can be written as:

$H(t,X)=h_0(t)*\exp^{(B1X1+B2X2+\ldots+BnXn).}$

The baseline hazard reflects the risk of dying for the individual patient at a certain point in time when all variables are equal to zero (the 'reference value/category'). Therefore, H(t,X) is the resultant hazard or cumulative hazard and is based on the impact of each model variable of the respected individual (bnXn) multiplied by the baseline hazard. The X is the covariate vector and b is the regression coefficient. The regression coefficients of each categoric variable reflect the additional risk for death (of all causes) adjusted for their reference category to which the risk is set to 1.0. The reference category is generally the category with the best prognosis. The Cox model assumes that the predictors have the same effect on the hazard function at all values of t.[11]

Now that we understand the concept of prognosis, the limited explanatory value of prognostic factors and the statistical way in which we address analysis of prognostic factors, we should look at the way prognosis influences decision making. Physicians deal with a variety of unique patients and limited treatment options. Their treatment choices are driven by the urge to maximize future life (years or quality) for patients. In the classical decision theory the physician assesses the probability of each outcome (eg 5-years survival) based on patient characteristics and treatment. This is done for every possible treatment, as well as investigating the benefit of each outcome. Then, benefits are combined with treatment specific prognoses so as to obtain treatment specific expected utilities. The treatment of greatest expected utility is chosen and the associated treatment-specific prognosis is communicated to the patient and his relatives.[12] In daily practice however, physicians generally reduce the treatment options to a concise set (often described in a protocol), ignoring the variety of outcomes and outcome utilities. Also, the technical optimal treatment in decision theory may be rejected by physician or patient if for instance it implies a long period of uncertainty as to whether the patient will in fact be cured completely.[13] For example, a patient might prefer surgery over chemoradiation therapy because it is a quick and seemingly decisive treatment. This makes treatment decisions even harder to make, especially in the palliative setting. The value patients place on quality of life in the end-of life phase differ considerably to patients in a curative

setting. The first may refuse treatment in order to optimize quality of life whereas the latter in general choose maximal treatment. In general, clinical prediction models may provide the evidence-based input for shared decision-making by providing estimates of the individual probabilities of risks and benefits.[14]

This thesis covers a variety of clinical prediction models in head and neck cancer. We explore the prognostic effect of various patient and tumour characteristics in salivary gland cancer (**chapter 3 and 4**) and squamous cell carcinoma (**chapter 5, 6, 7, 8, and 9**). The focus of this thesis is dynamics of prognostication (**chapter 5 and 6)**. What happens with predicted survival during follow-up when classically stationary co-variables change over time? These dynamic aspects of prognosis are relatively new to head and neck scientific research. After attempting to produce an accurate, up to date and individualized prognosis the next challenge is how to convey the message. Communicating prognosis in a way that is satisfactory for both patient and doctor is difficult. We finish with some recommendations on this topic (**chapter 11**).

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chapter 2

Staging and prognosis in head and neck cancer

Marc P. van der Schroeff, Robert J. Baatenburg de Jong

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Abstract

Head and neck malignant tumors are classified according to the TNM staging system. The TNM system is a universally accepted, widely used, staging method. Its goals are to help clinicians and researchers to choose from treatment options, to give patients an estimate of their prognosis and to compare results of treatment. In this paper we discuss the history and daily usage of the TNM system and some pros and cons. In the field of prognostic estimations, particularly for the individual patient, the TNM system could be upgraded with other prognostic indicators. We discuss insights into enhanced usage of the TNM system and the possibilities of comprehensive and dynamic staging models.

Introduction

TNM history

The first attempt to categorize malignant tumors into different stages was made in the early years of the 20th century. Steinthal (1905) and later Paterson (1940) created a staging system for breast cancer. Between 1943 and 1952, Pierre Denoix, a Parisian oncologic surgeon, chairman of the 'Institute Gustave-Roussy' and the International Union Against Cancer (UICC), introduced the well-known TNM-system.[1] Both the American Joint Committee on Cancer (AJCC) and the UICC used this system, but with different staging rules. It was not until 1982, at the 13th International Cancer Congress, that the AJCC and the UICC agreed to join hands in a single TNM staging system (fourth edition TNM), which after extensive deliberation was published in 1987.[2] Revisions have been based on better assessment of the extent of tumors and better insights in the tumor characteristics at specific head and neck sites. In head and neck oncology there have been two major modifications: in the third edition (1987) nodal status was measured according to nodal size instead of fixation or mobility. In the sixth edition (2002) stage IV disease was divided in IV a, b and c according to resectability of the T4 lesion and N2 or N3 nodal stage.[3] There are now seven distinct stages for head and neck cancer from mucosal origin (0, I, II, III, IVa, IVb, IVc).

Tumor staging in head and neck cancer

Head and neck malignant tumors are classified according to the TNM system too (tables 1a–d); the most recent (sixth) edition of the UICC TNM classification[4] is identical to that published by the AJCC.[5] Tumors are stratified into at least 32 (4*4*2) possible combinations of local tumor spread (T1-4), regional lymph node involvement (N0-3) and presence of distant metastases (M0-1). Tumors, within a particular head and neck site and of specific histology, who share the same TNM combination, are thought to have similar behavior. This stratification helps clinicians and researchers to choose from treatment options, to give patients an estimate of their prognosis and helps to compare results of treatment. For purposes of simplification, the 32 possible T, N and M combinations can be reduced to clustered stages: I, II, III and IVa, b, c which are meant to reflect homogeneous survival and interstage discrimination. A different staging system is used in the SEER database, a frequently used source in cancer literature. The SEER (Surveillance, Epidemiology and End Results) database groups clinical stages; in situ, localized, regional or distant. These categories originate from the Summary Staging Guide[6], published in 1977. In situ is defined as; intraepithelial, non-invasive, noninfiltrating. The localized stage represents invasive tumors confined to the organ of origin. A neoplasm extending beyond the organ of origin by direct extension to adjacent organs and/or regional lymph nodes is classified as regional. Finally, the distant stage is defined as tumors spreading to non-adjacent

organs or tissues by direct extension, discontinuous metastasis or lymphatic pathways. For some tumor sites the AJCC/IUCC staging system is available in the SEER database, unfortunately not for head and neck tumors.

Basic TNM

The two most widely used TNM classifications are cTNM and pTNM. The cTNM is based on clinical examination as well as ancillary techniques such as imaging. The pathological stage (pTNM), derived from the histopathological examination of the tumor specimen, is generally used for decision making on adjuvant treatment and more accurate estimation of prognosis. The pTNM is considered superior to the cTNM. When the treatment is non-surgical pathologic staging is by definition not available.

Detailed TNM

The UICC and AJCC have supplemented the basic TNM with more detailed information. This supplementary information is coded by prefixes. These are meant to address and incorporate factors that are thought to affect prognosis and help describing the tumor in more detail. Unfortunately, their use is not universally accepted. The r and R symbols are used to indicate recurrent tumor (r) or residual tumor (R); the latter reflects the effect of treatment. The C-factor, or certainty factor, reflects the validity of classification according to the diagnostic methods employed.[4] This C-factor ranges from C1, with usage of standard diagnostic means, to C5 when the TNM stage is derived from autopsy. Usage of for example MRI, gives a C2 classification whereas pathological examination of the resected specimen yields a C4 classification. Histopathological grading can be done using the G prefix: G1 stage indicates a well-differentiated tumor; G4 stage an undifferentiated tumor. Lymphatic and venous invasion are staged using L and V symbols.

Pros and cons of the TNM system

The purpose of the TNM system is to facilitate treatment planning, prognosis, uniform evaluation of treatment results and research. Especially in the field of inter-physician communication and research, the purpose is well served. The TNM staging system is an anatomically based, user-friendly, universally applicable, indicator of tumor burden. The TNM system therefore is a major contribution to cancer care and research. However, important limitations do exist:

(a) The TNM stage groupings were created on the basis of presumed prognosis: no prospective, multivariate analysis was performed to create the four stage groups from the various combinations of T, N and M.[7]

(b) The assessment of the tumor in different medical centers is subject to differences in diagnostic tools, availability of these tools and inter- and intra-observer variability.

Table 1a. T-classification according to anatomical site.4 *ICD WHO International Classification of Diseases for Oncology.[20]

Lip, oral cavity (ICD-O C00, C02-C06*)	
T1	≤ 2cm
T2	> 2 to 4cm
T3	> 4cm
T4a	lip: through cortical bone, inferior alveolar nerve, floor of mouth, skin oral cavity: through cortical bone, deep/extrinsic muscle of tongue, maxillary sinus, skin
T4b	masticator space, pterygoid plates, skull base, internal carotid artery
Pharynx (ICD-O C01, C05.1, 2, C09, C10.0, 2, 3, C11-13*)	
Oropharynx	
T1	≤ 2cm
T2	> 2 to 4cm
T3	> 4cm
T4a	larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, mandible
T4b	Lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base, carotid artery
Hypopharynx	
T1	≤ 2cm and limited to one subsite
T2	> 2 to 4cm or more than one subsite
T3	> 4cm or with hemilarynx fixation
T4a	thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartment soft tissue
T4b	prevertebral fascia, carotid artery, mediastinal structures
Nasopharynx	
T1	nasopharynx
T2	soft tissue a: oropharynx/nasal cavity without parapharyngeal extension b: tumour with parapharyngeal extension
T3	bony structures, paranasal sinuses
T4	intracranial extension, cranial nerves, infratemporal fossa, hypopharynx, orbit, masticator space
Larynx (ICD-O C32.0, 1, 2, C10.1*)	
Supraglottis	
T1	one subsite, normal mobility
T2	mucosa of more than one adjacent subsite; without fixation
T3	cord fixation or invasion postcricoid area, pre-epiglottic tissues, paraglottic space
T4a	through thyroid cartilage
T4b	prevertebral space, mediastinal structures, carotid artery

Table 1a. (continued)

Glottis	
T1	limited to vocal cord(s), normal mobility a: one cord, b: both cords
T2	supraglottis, subglottis, impaired cord mobility
T3	cord fixation, paraglottic space, thyroid cartilage erosion
T4a	through thyroid cartilage
T4b	prevertebral space, mediastinal structures, carotid artery
Subglottis	
T1	limited to subglottis
T2	extends to vocal cord(s), with norm,al/impaired mobility
T3	cord fixation
T4a	through cricoid or thyroid cartilage
T4b	prevertebral space, mediastinal structures, carotid artery
Nasal cavity and paranasal sinuses (ICD-O C30.0, 31.0, 1*)	
maxillary sinus	
T1	mucosa
T2	bone erosion/destruction, hard palate, middle nasal meatus
T3	posterior bony wall maxillary sinus, subcutaneous tissues, floor/medial wall orbit, etmoid sinus
T4a	anterior orbit, cheek skin, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid/frontal sinus
T4b	orbital apex, dura, brain, middle cranial fossa, cranial nerves other then V_2, nasopharynx, clivus
nasal cavity and etmoid sinus	
T1	one subsite
T2	two subsites or adjacent naso-etmoidal site
T3	medial wall/floor orbit, maxillary sinus, palate, cribriform plate
T4a	anterior orbit, skin, anterior cranial fossa, pterygoid plates, sphenoid/frontal sinuses
T4b	orbital apex, dura, brain, middle cranial fossa, cranial nerves other then V_2, nasopharynx, clivus
Thyroid gland (ICD-O C73*)	
Papillary, follicular and medullary carcinoma	
T1	≤ 2cm, intrathyroidal
T2	> 2 to 4cm, intrathyroidal
T3	> 4cm or minimal extension
T4a	subcutaneous, larynx, trachea, oesophagus, recurrent laryngeal nerve
T4b	prevertebral fascia, mediastinal vessels, carotid artery

Table 1a. (continued)

Anaplastic/undifferentiated carcinoma	
T4a	tumour limited to thyroid
T4b	tumour beyond the thyroid capsule
Salivary glands (ICD-O C07, C08*)	
T1	≤ 2cm, without extraparenchymal extension
T2	> 2 to 4cm, without extraparenchymal extension
T3	> 4cm and/or extraparenchymal extension
T4a	skin, mandible, ear canal, facial nerve
T4b	skull, pterygoid plates, carotid artery

Table 1b. N-classification according to anatomical site.[4]

N-stage for all sites except nasopharynx and thyroid	
N1	ipsilateral single ≤ 3cm
N2	a: ipsilateral single > 3cm to 6cm b: ipsilateral multiple ≤ 6cm c: bilateral, contralateral ≤ 6cm
N3	> 6cm
N-stage for nasopharynx	
N1	unilateral node(s) ≤ 6cm, above supraclavicular fossa
N2	bilateral node(s) ≤ 6cm, above supraclavicular fossa
N3	a: > 6cm b: in supraclavicular fossa
N-stage for thyroid	
N1a	level VI
N1b	other regional

Table 1c. M-classification.[4]

M-stage	
M0	no distant metastasis
M1	distant metastasis

(c) Stage migration, a problem to any staging system, is the result of either a change in the staging system itself or a change in technology. The introduction of a new diagnostic tool could improve assessment of tumor spread and therefore lead to movement of patients from one stage to another. The Will Rogers phenomenon occurs when a patient in stage group A is moved to stage group B, giving both groups a better prognosis. For example: a patient initially classified as T1, is, due to improved assessment, up-staged to T2. If the restaged patient has a below average prognosis in the T1 stage group, removing him or her will, by definition, raise the average prognosis in the T1 stage group. If the patient who now enters the T2 stage group has an above the average prognosis in this stage group, consequently the average prognosis is raised. Of course stage migration itself is a non-differential effect (it works both ways). For example a patient with T2 stage disease is moved to stage T1 disease because of better, more accurate assessment or a change in TNM staging itself. This could lead to a worse prognosis for both stage groups if the patient had an above average prognosis in the T2 stage group and a below average prognosis in the T1 group.
(d) The present TNM system of head and neck cancer classification is based solely on tumor morphology and does not consider patient-based prognostic factors such as age, gender and co-morbidity, nor factors such as biological and molecular markers. Therefore, the current TNM staging system is not fully equipped to supply an individualized prognosis.

Table 1d. Staging according to anatomical site.[4]

All sites except nasopharynx and thyroid			
stage 0	Tis	N0	M0
stage I	T1	N0	M0
stage II	T2	N0	M0
stage III	T1, T2	N1	M0
	T3	N0, N1	M0
stage Iva	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
stage IVb	any T	N3	M0
	T4b	any N	M0
stage IVc	any T	any N	M1
Nasopharynx			
stage 0	Tis	N0	M0
stage I	T1	N0	M0
stage IIa	T2a	N0	M0

Table 1d. (continued)

All sites except nasopharynx and thyroid			
stage IIb	T1	N1	M0
	T2a	N1	M0
	T2b	N0, N1	M0
stage III	T1	N2	M0
	T2a, T2b	N2	M0
	T3	N0, N1, N2	M0
stage IVa	T4	N0, N1, N2	M0
stage IVb	any T	N3	M0
stage IVc	any T	any N	M1
Thyroid gland: papillary or follicular, under 45 years			
stage I	any T	any N	M0
stage II	any T	any N	M1
Thyroid gland: papillary or follicular, 45 years and older and medullary			
stage I	T1	N0	M0
stage II	T2	N0	M0
stage III	T3	N0	M0
	T1, T2, T3	N1a	M0
stage IVa	T1, T2, T3	N1b	M0
	T4a	N0,N1	M0
stage IVb	T4b	any N	M0
stage IVc	any T	any N	M1
Thyroid gland: anaplastic/undifferentiated			
stage IVa	T4a	any N	M0
stage IVb	T4b	any N	M0
stage IVc	any T	any N	M1

Enhanced TNM

Besides the AJCC/UICC TNM staging system there are alternative systems based on the TNM: e.g. TANIS, and systems developed by Hall et al., Hart et al., Berg, and Kiricuta.[8–13] These alternative systems were extensively discussed by Lydiatt et al.[14] and Groome et al.[15] e.g. TANIS transforms the TNM-score into different staging groups by adding the T and N integer values to produce a score from 1 to 7. TANIS is based on the assumption that T and N are equally important and independent predictors of prognosis.[10] For example, a T1N2M0 tumor yields a score of 3, whereas a T3N1M0 tumor yields a score of 4. When tested on hazard consistency, hazard discrimination, outcome prediction and balanced

distribution of patients these alternative staging systems proved to be superior to the AJCC/UICC TNM staging system in oral cavity carcinomas.[15] Figure 1 gives the different stage grouping schemes (adopted from Groome[15]). The two TANIS schemes are the result of several studies on this staging scheme whereby different clustering-schemes of TANIS scores were proposed. TANIS-3 clusters all integer values into 3 different stages. (For example: all integer values from 1 to 3 are clustered into a comprehensive score of 1). TANIS-7 does not cluster the integer scores but uses the original 7 stages. Although these alternative systems may be excellent staging systems, the fact is that TNM staging remains the most used system in general practice.

Figure 1. TANIS staging. Adapted from Groome et al.[15]

TNM UICC/AJCC

	T1	T2	T3	T4	M1
N0	1	2	3	4a	4c
N1	3	3	3	4a	
N2	4a	4a	4a	4a	
N3	4b	4b	4b	4b	

TANIS-7

	T1	T2	T3	T4	M1
N0	1	2	3	4	7
N1	2	3	4	5	
N2	3	4	5	6	
N3	4	5	6	7	

TANIS-3

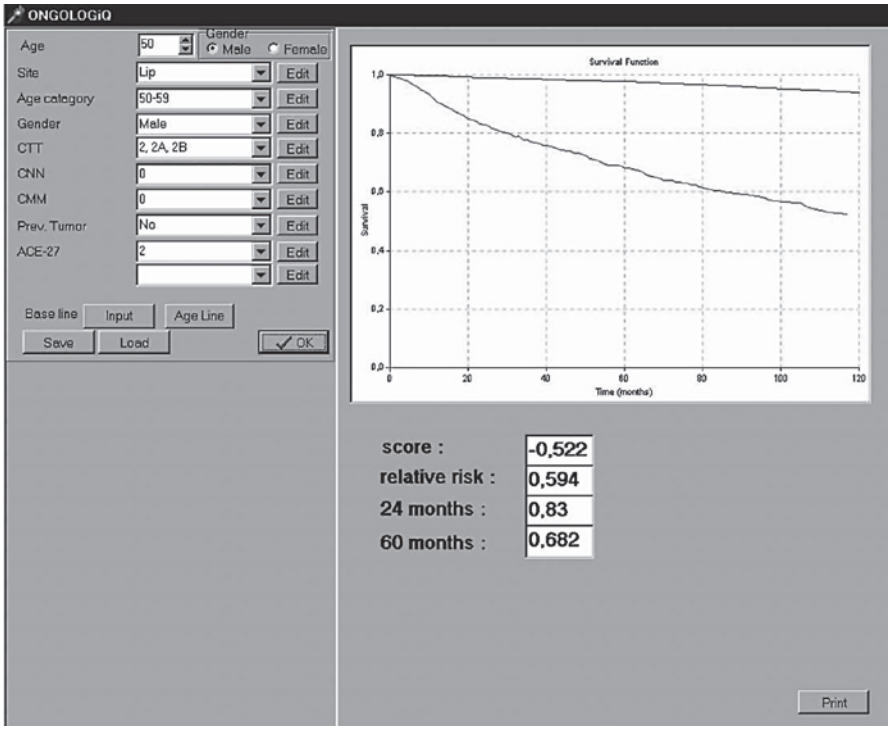
	T1	T2	T3	T4	M1
N0	1	1	1	2	3
N1	1	1	2	3	
N2	1	2	3	3	
N3	2	3	3	3	

Comprehensive models

The present TNM system of head and neck cancer classification (as well as the alternative staging systems mentioned) lacks biological and molecular markers and general patient-based prognostic factors, such as co-morbidity. In recent years more and more multivariate analyses are done, yielding unbiased relative risks of prognostic factors, including non-tumor characteristics (e.g., Ribeiro et al.[16]). These studies could lead to a more comprehensive staging system using all relevant patient and tumor characteristics. A fine example to stage the patient and not only the tumor was given by Pugliano et al.[17], who in 1999 performed a multivariate analysis on 23 cancer symptoms in 1010 cancer

patients. Dyshagia, otalgia, neck lump and weight loss were analyzed to be predictors of survival. These cancer symptoms were evaluated as one composite biologic index (none-mild-moderate-severe). When entered in a proportional-hazards model along with TNM stage, co-morbidity, age, and alcohol use this index proved an independent predictor of survival. In 2001, Baatenburg de Jong et al. published a comprehensive model making use of data on site of the primary tumor, TNM, age at diagnosis, gender and prior malignancies.[18] Recently, co-morbidity was established as an independent prognostic factor and it was added to the model. All patients with HNSCC of the oral cavity, the pharynx, and the larynx diagnosed in the Leiden University Medical Center between 1981 and 1998 were included. The prognostic model, based on a multivariate analysis, produced individualized prognosis based on historical data from daily clinical practice in a single referral centre. An example is given in Figure 2.

Figure 2. A 50-year old male with a T2N0M0 carcinoma of the lip with no previous malignancy and an ACE-27 score 2, has a predicted 5-years survival of 68%.



*ACE-27: Adult Co-morbidity Evaluation-27 [21]
*red line: predicted survival for this specific patient.
*blue line: predicted survival for general population, matched on age and gender.

Dynamic prognosis

When it comes to prognostic estimates, the TNM staging system is limited to a static prognosis at diagnosis (cTNM) or after surgery (pTNM). However, a prognosis is not static: all prognostic estimates change when during follow-up a patient develops a tumor recurrence or metastasis. But when the patient remains tumor-free his or her prognosis will change too: the prognosis of cancer patients who survive e.g. the first two years improves. This is caused by the fact that they survived the first critical period. Of interest in this field of research is the work done by Janssen-Heijnen et al.[19] who showed that the prognosis for patients with cancer in general improved with each year survived, using population-based conditional 5-year relative survival rates. There are variations in excess mortality between different tumor sites. For example: patients with colorectal cancer show hardly any excess mortality after 3–15 years. There were no head and neck patients in their cohort, it would be interesting to see whether these patients' survival, perhaps due to co-morbidity, remains poorer than for the general population.

Conclusion

The TNM system is simple and therefore easy to use and adhere to. More importantly, it is universally accepted. The introduction of prefixes (e.g. c, p, r, R, C, G) to the TNM-score is a step forward in more detailed description of tumor characteristics and yields transparency as to how the information was gathered. We would strongly recommend adding this detailed information to the TNM. New improvements of the TNM should include the possibility to include other relevant factors, such as age and co-morbidity. In addition, a new system should allow the inclusion of parameters from molecular biology as well.

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Part II

PROGNOSIS IN SALIVARY GLAND CARCINOMA

Chapter 3

The prognostic role of comorbidity in salivary gland carcinoma

Chris H. J. Terhaard, Marc P. van der Schroeff, Kim van Schie,
Simone E. J. Eerenstein, Herman Lubsen, Johannes H. A. M. Kaanders,
Ludwig E. Smeele, Fred R. Burlage, Piet L. van Den Ende,
Robert J. Baatenburg de Jong.

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Abstract

Patients with head and neck cancer are prone to develop significant comorbidity mainly because of the high incidence of tobacco and alcohol abuse, both of which are etiologic and prognostic factors. However, to the authors' knowledge little is known regarding the prognostic relevance of comorbidity in patients with salivary gland cancer. A retrospective cohort of 666 patients with salivary gland cancer was identified within the Dutch Head and Neck Oncology Cooperative Group database. For multivariate analysis, a Cox proportional hazards model was used to study the effect of comorbidity on overall survival and disease-specific survival. According to the Adult Comorbidity Evaluation-27 (ACE-27) index, 394 patients (64%) had grade 0 comorbidity, 119 patients (19%) had grade 1 comorbidity, 71 patients (12%) had grade 2 comorbidity, and 29 patients (5%) had grade 3 comorbidity. In multivariate analysis for overall survival, the ACE-27 comorbidity grade was a strong independent prognostic variable. The hazards ratio (HR) of death, including all causes, was 1.5 (95% confidence interval [CI], 1.1-2.1) for patients with ACE-27 grade 1 comorbidity versus grade 0 comorbidity ($P < .007$). The HR was 1.7 (95% CI, 1.2-2.5) for grade 2 comorbidity ($P = .003$) and 2.7 (95% CI, 1.5-4.7) for grade 3 comorbidity versus grade 0 comorbidity ($P = .001$). In the current analysis, ACE-27 comorbidity grade was not an independent prognostic factor for disease-free survival. To the authors' knowledge, this is the first study concerning the prevalence and relevance of the prognostic comorbidity variable ACE-27 grade in patients with salivary gland cancer. Overall survival, but not disease-free survival, was correlated strongly with ACE-27 grade. Compared with other studies that investigated the effect of comorbidity on patients with head and neck cancer, patients with salivary gland cancer had less comorbidity. Their comorbid status appeared to be reasonably comparable to that of patients with other nonsmoking-and nonalcohol-related cancers.

Introduction

Patients with head and neck cancer are prone to have significant comorbidity mainly because of the high incidence of tobacco and alcohol abuse, both of which are etiologic and prognostic factors. The associated medical problems are most pronounced in the respiratory and cardiovascular systems. These conditions have direct impact on the care of the patient, selection of initial treatment, and evaluation of treatment effectiveness.[1-3] It has been demonstrated that comorbidity is an important prognostic factor for overall survival[4] and, in some studies, for locoregional control[5] in patients with malignant tumors of the head and neck area. Comorbidity may influence the choice of treatment, eg, leading to a more conservative approach to prevent possible postoperative complications.

Several comorbidity indices have been developed, such as the Kaplan-Feinstein Index[6] and the Adult Comorbidity Evaluation-27 (ACE-27), which is a modification of the Kaplan-Feinstein Index.[6] In recent years, the ACE-27 has become a common method for scoring comorbidity. The ACE-27 adds several important comorbid conditions, such as acquired immunodeficiency syndrome and diabetes mellitus. Modification of the Kaplan-Feinstein Index into the ACE-27 was done based on expert opinion and a review of the medical literature.[1] The ACE-27 grades specific comorbid conditions into 1 of 4 levels of comorbidity -none, mild, moderate, or severe- according to the severity of individual organ decompensation and prognostic impact.[7] The overall comorbid score, or ACE-27 ranking, is based on the highest ranked single ailment. Patients with 2 or more moderate ailments in different organ systems or disease groupings are graded as severe. The ACE-27 is a comprehensive tool that has been modified previously and validated[8] and is of common use in head and neck cancer literature.

Whether comorbidity is a prognostic factor in salivary gland carcinomas is not known: Because of the absence of an etiologic correlation between salivary gland carcinomas and tobacco and alcohol abuse, a prognostic significance in theory may be questionable. The objective of this study was to evaluate the prevalence and the prognostic importance of comorbidity in a group of patients who were treated for salivary gland cancer. To our knowledge, in the literature, no such study has been published to date.

Patients and methods

On the basis of 565 patients in a dataset from the Dutch Head and Neck Oncology Cooperative Group (NWHHT) concerning general results in patients with salivary gland cancer,[9] the role of radiotherapy[10] and the importance of facial nerve palsy in parotid cancer[11] have been published. An update of the NWHHT salivary gland cancer database has been performed, including the variable comorbidity. In this article, we present the results from those 565 patients and from an additional 101 patients with malignant salivary

gland tumors, including up to date follow-up data and information on comorbidity. Thus, the dataset has been extended to 666 patients who were treated between 1985 and 1994. The median follow-up of patients who were alive at last follow-up was 125 months.

Table 1. Distribution of clinical stage according to the 2002 American Joint Committee on Cancer Staging classification.

Stage	Criteria	Patients, %
I	Tumor ≤2cm (T1), N0, M0	19
II	Tumor >2cm to ≤ 4cm (T2), N0, M0	29
III	Tumor >4cm (T3), N0, M0 or T1-3, N1, M0	24
Iva	T1-3, N2, M0 or T4a*, N0-N2, M0	22
IVb	T4b, Ƀ N0-N2, M0 or any T, N3, M0	1
IVc	Any T, any N, M1	4

T indicates tumor classification; N, lymph nose status; M, metastatic status.
* Tumor invades the skin, mandible. Ear canal, and/or facial nerve.
Ƀ Tumor invades the skull base and/or pterygoid plates and/or encases the carotid artery

Clinical characteristics

The mean patient age was 59 years (range, 8-100 years). Fifty-two percent of patients were men. Pain was a complaint in 27% of patients. Clinical tumor invasion of the skin was noted in 7% of patients. The salivary gland cancer was located in the parotid gland in 56% of patients, in the submandibular gland in 13% of patients, in the oral cavity in 26% of patients, and in the pharynx/larynx in 5% of patients. Facial nerve function was intact in 79% of patients with parotid gland cancer, partially impaired in 13% of patients; and, in 8% of patients, complete facial paralysis was noted before treatment. Comorbidity Scoring Using the ACE-27 Index In this analysis, we used the ACE-27 index for scoring comorbidity. Data about comorbidity were derived from the medical record in 92% of patients. The number of patients with ACE-27 grade 0, 1, 2, and 3 comorbidity was 394 patients (64%), 119 patients (19%), 71 patients (12%), and 29 patients (5%), respectively.

Staging

The TNM staging was used for both major and minor salivary gland cancers according to the 2002 American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[12] Four percent of patients had M1 disease, and 15% had positive lymph nodes at first presentation. Distribution of T classification was 24%, 40%, and 35% for patients with T1, T2, and T3/T4, respectively. According to the 2002 AJCC manual, staging for facial nerve tumor invasion of the skin, mandible, ear canal, and/or facial nerve is staged as T4a. Table 1 shows the distribution of clinical disease classification according to the 2002 AJCC manual.

Treatment

Surgery alone was undergone by 141 patients (22%) and was combined with postoperative radiotherapy in 444 patients (67%). Radiation alone was received by 47 patients (7%), and no treatment or chemotherapy alone was received by 34 cases (5%).

Histologic data

Histology was reviewed and classified according to the 1972 World Health Organization classification. Adenoid cystic carcinoma was diagnosed most frequently (27%), followed by mucoepidermoid carcinoma (16%), acinic cell carcinoma (14%), carcinoma expleomorphic adenoma (8%), undifferentiated carcinoma (7%), and squamous cell carcinoma (5%). Twenty-one percent of tumors were diagnosed as adenocarcinoma, not otherwise specified. Sixteen patients (2%) were missing information on histology. Including data derived from the resection specimen of the primary tumor (n = 585) and neck dissection (n = 228), the distribution according to pathologic AJCC stages I, II, III, and IV was 27%, 21%, 16%, and 35%, respectively. Resection of the tumor was incomplete in 36% of patients and close (<5 mm) in 21%. Bone and skin were invaded in 8% and 5% of patients, respectively. Perineural invasion was diagnosed in 30% of patients; however, information about perineural invasion was lacking in 21% of patients.

Statistical analysis

For univariate analysis, version 10.0 of the SPSS/PC software program was used. Statistical significance was calculated by using the chi-square test and the Mann-Whitney test. To determine independent risk factors for ACE-27, binary regression analysis was performed. For actuarial curves, the method of Kaplan Meier was used along with the log-rank test for computing statistical significance. For multivariate analysis, a Cox proportional hazards model was used. A comparison between the occurrence of comorbidity in patients with salivary gland carcinomas and in patients with other head and neck cancers is presented in Table 2. Statistical significance was calculated by using the Kruskal-Wallis test, because there is an ordering in the ACE-27 scores.

Results

Correlation between ACE-27 comorbidity and possible prognostic factors

ACE-27 grade was correlated significantly with age ($P < .001$) (see Figure 1). ACE-27 comorbidity grades 1 through 3 were diagnosed in 30% of women versus 41% of men ($P = .02$). The ACE-27 grade was not correlated with pain, facial nerve function, tumor localization, or clinical AJCC 2002 stage. Among the patients who had clinical skin invasion, 52% had ACE-27 comorbidity grades 1 through 3 compared with 34% among patients without clinical skin invasion ($P = .02$). For all histologic subtypes, the distribution

according to ACE-27 grade was equal, except for squamous cell carcinoma. Approximately 66% of patients with squamous cell carcinoma had ACE-27 comorbidity grades 1 through 3 compared with approximately 33% of all other patients. Patients who had ACE-27 grade 3 comorbidity received radiotherapy alone significantly more often compared with other patients. Conversely, if patients underwent surgery, then postoperative radiotherapy was received less frequently in this group (see Figure 2). The mean delay between surgery and postoperative radiotherapy was equal for patients with ACE-27 grade 0 through 2 comorbidity; however, the delay was significantly prolonged for patients with ACE-27 grade 3 comorbidity (6.5 weeks vs 9 weeks, respectively; P 5.005). No correlation was observed between the ACE-27 comorbidity grade and any histopathologic variable derived from the resection specimen. The completeness of resection and the ACE-27 grade or age were not related. ACE-27 grade was related to 2002 AJCC pathologic stage: ACE-27 grade 0 comorbidity occurred in 79%, 64%, 61%, and 59% of patients with AJCC stage I, II, III, and IV, respectively (P = .001). Independent risk factors for ACE-27 (grade 0 comorbidity vs grade 1-3 comorbidity) were age, with an increased relative risk (RR) of 1.05 (95% confidence interval [CI], 1.04-1.06) per year, and sex, with an RR for men versus women of 1.7 (95% CI, 1.2-2.5).

Figure 1. This chart illustrates the distribution of Adult Comorbidity Evaluation-27 comorbidity grade and age.

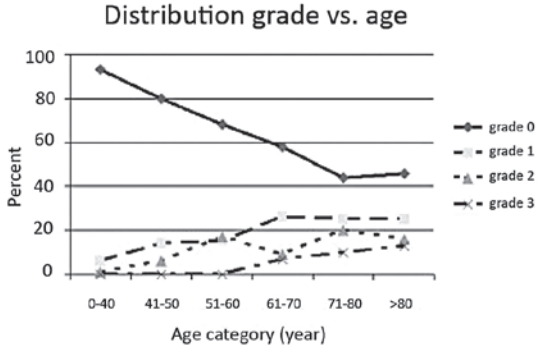


Figure 2. This chart illustrates the correlation between Adult Comorbidity Evaluation-27 comorbidity grade and treatment performed. S indicates surgery; RT, radiotherapy.

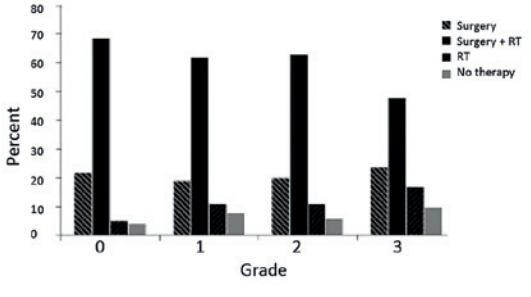
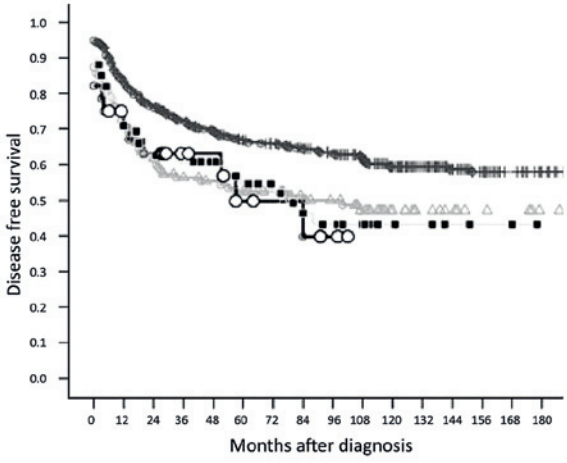


Figure 3. Disease-free survival is illustrated according to the Adult Comorbidity Evaluation-27 index. Crosses indicate grade 0 (390 patients); triangles, grade 1 (119 patients); squares, grade 2 (67 patients); circles, grade 3 (28 patients; P 5.003).



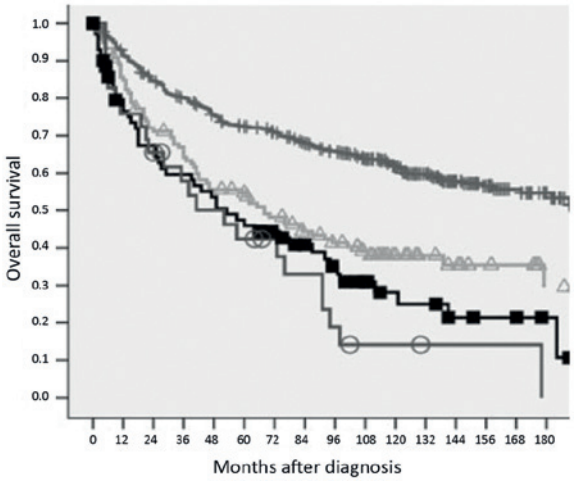
Disease-free survival

The actuarial 10-year disease-free survival rate for grade 0, 1, 2, and 3 comorbidity was 59%, 47%, 43%, and 40%, respectively (P = .003; log-rank test) (see Figure 3). Because disease-free survival was determined by 3 different events (local control, regional control, and distant metastases), these 3 events were analyzed separately. No significant difference was observed between ACE-27 comorbidity grade and actuarial regional control or distant metastases-free survival. The 10-year actuarial local recurrence-free survival rate was 81%, 68%, 75%, and 65% for grade 0, 1, 2, and 3 comorbidity, respectively (P =.005; logrank test). In a multivariate analysis with disease-free survival as the endpoint, variables that were significant in the univariate analysis were included. Inclusion of clinical AJCC 2002 stage resulted in loss of significance of the variables tumor classification, lymph node status, metastasis stage, facial nerve invasion, and skin invasion. Independent factors were clinical AJCC 2002 stage, pain, sex, and age. In this analysis, ACE-27 comorbidity grade was not an independent prognostic factor for disease-free survival. Because treatment performed may influence disease-free survival, this was also included in the analysis. Treatment was an independent factor. Compared with surgery alone, combined surgery and radiotherapy resulted in significantly better locoregional control, and radiation alone in resulted significantly worse results consistent with our previous report.[10] For the patients who underwent surgery, the relevance of the histologic parameters derived from the specimen also was analyzed. The status of the resection margins (patients with incomplete or close margins fared worse) and the pathologic lymph node status also were independent factors for disease-free survival.

Overall survival

The 10-year actuarial overall survival rate was 62%, 38%, 25%, and 14% for ACE-27 grade 0, 1, 2, and 3 comorbidity, respectively (log-rank test; P < .0001) (see Figure 4). In a multivariate analysis of overall survival, ACE-27 comorbidity grade was a strong independent prognostic variable. The hazard ratio (HR) of death, including all causes, was 1.5 (95% CI, 1.1-2.1) for ACE-27 grade 1 comorbidity versus grade 0 comorbidity (P <.007). The HR was 1.7 (95% CI, 1.2-2.5) and 2.7 (95% CI, 1.5-4.7) for grade 2 comorbidity and for grade 3 versus grade 0 comorbidity, respectively (P 5 .003 and P 5 .001, respectively). In addition to ACE-27 grade, pain, age, clinical AJCC 2002 stage, localization of the salivary gland tumor (patients with oral cavity tumors had the best survival), and histologic subtype (patients with acinic cell tumors fared best) were independent factors for overall survival. For the patients who underwent surgery, the significant histologic variables derived from the specimen were pathologic lymph node status, bone invasion, and pathologically verified invasion of the skin.

Figure 4. Overall survival is illustrated according to the Adult Comorbidity Evaluation-27 index. Crosses indicate grade 0 comorbidity (394 patients); triangles, grade 1 comorbidity (119 patients); squares, grade 2 comorbidity (71 patients); circles, grade 3 comorbidity (29 patients; P < .0001).



Comparison of comorbidity in salivary gland carcinoma versus head and neck squamous cell carcinoma

The results from a comparison between comorbidity in patients with salivary gland carcinomas and comorbidity in patients with other head and neck cancers are presented in Table 2. The chi-square test statistics from the reports by Ferrier et al,[13] Borggreven et al,[14] Rogers et al,[15] Sanabria et al,[4] and Piccirillo et al.[7] were 22.6 (P <.0005), 83.4 (P <.0005), 21.6 (P < .0005), 136.9 (P < .0005), and 8 (P = .046), respectively. Because, in our dataset,

Table 2. Comparison between comorbidity in salivary gland carcinoma and other head and neck carcinomas.

		No. of patients (%)						
Study	**Type of tumor**	**Total No.**	**ACE grade 0**	**ACE grade 1**	**ACE grade 2**	**ACE grade ≥2**	**ACE grade 3**	**Chi-square***
Ferrier 2005[13]	HNSCC: sinus, lip, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx	117	48 (41.0)	35 (29,9)	-	34 (29.1)	-	22.6Þ
Borggreven 2003[14]	HNSCC: oral cavity, oropharynx	100	17 (17)	36 (36)	34 (34)	-	13 (13)	83.4Þ
Rogers 2006[15]	HNSCC: oropharynx, hypopharynx, larynx	157	74 (47)	57 (36)	-	26 (17)	-	21.6
Sanabria 2007[4]	HNSCC: nasopharynx, nose/ paranasal, oral cavity, oropharynx, hypopharynx, larynx	309	77 (25)	141 (46)	48 (15)	-	43 (14)	136.9Þ
Piccirillo 2004[7]	HNSCC: lip, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, thyroid gland	341	188 (55)	82 (24)	53 (16)	-	18 (5)	8.0Þ
Current study	Salivary gland	613	394 (64)	119 (19)	71 (12)	-	29 (5)	

ACE indicates Adult Comorbidity Evaluation-27 comorbidity index; HNSCC, head and neck squamous cell carcinoma.
* Test statistic using the Kruskal-Wallis test (comparing the current study with the article cited in each row).
Þ P<.05

the only 2 factors that were related significantly to the ACE-27 comorbidity grade after adjusting for all other factors were age and sex, we checked to determine whether the distribution of age in the articles mentioned above were in reasonable concordance with our data. We also examined the sex distribution over the different articles and observed no significant differences (data not shown). The significant test statistics suggest that the comorbidity distribution is different in patients with salivary gland cancer compared with the comorbidity distribution in patients with head and neck squamous cell carcinoma. The distribution shown in Table 2 indicates that patients with salivary gland cancer have less comorbidity.

Comparison of comorbidity in salivary gland carcinoma versus other nonsmoking- and nonalcohol-related cancer

We know of only 1 article in which the ACE-27 score was determined for patients with non head and neck cancers.[1] We compared the ACE-27 scores from our cohort of salivary gland cancer patients with the scores from patients who had prostate cancer patients to compare with another nonsmoking- and nonalcohol-related form of cancer. The results are presented in Table 3. The Kruskal-Wallis test indicated that there was a significant correlation (chi-square statistic, 14.6; P =.002). This implies that the comorbidity distribution does deviate from the distribution among patients with prostate cancer, as it does in Table 2.

Table 3. Comparison between comorbidity in salivary gland carcinoma and another nonsmoking- and nonalcohol-related cancer.

			No. of patients (%)				
Study	**Type of tumor**	**Total No.**	**ACE grade 0**	**ACE grade 1**	**ACE grade 2**	**ACE grade 3**	**Chi-square***
Piccirillo 2000[1]	Prostate cancer	1110	698 (63)	283 (25)	101 (9)	28 (3)	14.6Þ
Current study	Salivary glands	613	394 (64)	119 (19)	71 (12)	29 (5)	

ACE indicates Adult Comorbidity Evaluation-27 comorbidity index.
* Test statistic using the Kruskal-Wallis test (comparing the current study with the article cited in each row).
Þ P<.05

Discussion

To our knowledge, very few reports published to date have provided the results of multivariate analysis on prognostic indicators performed on a large group of patients that included tumors of all major and minor salivary glands.[16-18] Most reports deal exclusively with either tumors of the major salivary glands (submandibular and parotid glands combined), or tumors of the minor salivary glands,[19-24] or tumors of the parotid gland only.[25-34] We performed an update of the database of the NWHHT concerning all salivary gland cancers irrespective of site and histology. This analysis, which was based on data from all head and neck centers in the Netherlands, included comorbidity scores. Compared with the report published in 2004,[9] the current database has been extended from 565 patients to 666 patients with malignant salivary tumors who were treated between 1985 and 1994. The median follow-up of the patients who remained alive at last follow-up was extended from 99 months to 125 months. In particular, this appears to be important for the patients with adenoid cystic carcinomas (27%; 180 of 666 patients), which can behave in an indolent way and, thus, require a long follow-up. Overall, the extension of the follow-up did result in only a few instances of disease recurrence 10 years after treatment. In the current analysis, we used the ACE-27, a commonly used tool in head and neck cancer literature. If it is used retrospectively, then the information needed to score the ACE-27 is collected through, for example, the medical chart, nursing notes, referral letters from general practitioners, anesthetic sheets, and laboratory investigations. Comorbidity scoring with the ACE-27 using trained cancer registrars in the US reportedly has produced valid information.[8] Paleri and Wight[35] studied the applicability of the ACE-27 by using notes extraction in a cohort of patients in the UK with head and neck cancer. Those authors concluded that, along with difficulties regarding (confidential) human immunodeficiency virus status, retrospective data collection and the completion of a comorbidity index is feasible. In another study by Paleri and Wight,[36] they compared the information obtained from a review of notes alone with information that was available after a structured patient interview. They observed that a retrospective review of notes was an accurate and reliable technique for grading comorbidity. However, in a feasibility study of the ACE-27 among patients with head and neck cancer, Rogers et al.[37] identified several problems regarding the retrospective use of the ACE-27 index. Not all items mentioned in the ACE-27 are recorded in the actual charts and, if mentioned, are not always detailed enough. Items in the ACE-27 index such as immunologic disorders are included infrequently when taking a patient's history. In addition to the comorbid conditions that are included in the ACE-27 index, there are other theoretic prognostic comorbid conditions, such as anemia and hypercholesterolemia. In our study, ACE-27 scores were related significantly to age and sex. The first appears to be a consequence of deteriorating health in the elderly, and the latter appears to be a presumed difference in

lifestyle. Comorbidity in our study was independent of histologic tumor type, except for squamous cell carcinoma, which has a significant correlation with comorbidity and, thus, reflects the known relation between comorbidity and head and neck squamous cell carcinoma. On the basis of these findings, it may be argued that squamous cell carcinomas are a different entity among all salivary gland carcinomas. Comorbidity, and specifically comorbidity scored by the ACE-27 index, in head and neck cancer is reportedly a significant prognostic factor.[1,4,13-15,38] Comparison of comorbidity in salivary gland carcinoma and the head and neck cancer studies mentioned above indicated that there were consistent and significant differences. Recently, in a retrospective cohort study of 310 patients with head and neck cancer aged >70 years (average age, 76 years) who had a median follow-up of 22.5 months, Sanabria et al.[4] reviewed the effect of comorbidity on overall and cancer-specific survival. They reported an HR of 1.72 (P =.002) in a multivariate analysis of moderate comorbidity and severe comorbidity (ACE-27 grade 2 and 3 comorbidity) compared with no comorbidity and mild comorbidity (ACE-27 grade 0 and 1 comorbidity) on overall survival. In the current study, multivariate analysis indicated that the prognostic effect of comorbidity on overall survival also was strong. The HR for ACE-27 grade 1, 2, and 3 comorbidity was 1.5, 1.7, and 2.7, respectively (reference, ACE-27 grade 0 comorbidity). A different measure of survival was used by Allareddy and Konety in 2006[39] in a retrospective analysis from the US of a nationwide inpatient sample for the years 2000 through 2003 consisting of 24,803 patients with head and neck cancer, including salivary gland cancers. Instead of overall survival, as a proxy for assessing clinical outcomes, those authors used in-hospital mortality as the primary outcome (the overall in-hospital mortality rate was 5.18%; n = 1284 patients). Specific comorbid conditions, such as congestive heart failure, renal failure, liver disease, and coagulopathy, had increased risks of in-hospital mortality. That analysis was done on the basis of a multivariate analysis that included the variables sex, comorbid conditions, complications, health insurance status, hospital bed size, hospital localization, and hospital teaching status. The analysis did not include, for example, tumor size and, thus, was uncorrected for disease stage. Noteworthy is a study done by Park et al.[40] indicating that prediagnosis smoking and heavy alcohol use not only are precursors for comorbidity and etiologic factors in head and neck cancer but also are significant prognostic factors on alone. Several other authors have reported that therapy is dependent on comorbidity[41,42] In our cohort, patients with grade 3 comorbidity received significantly less than gold-standard treatment (surgery or surgery with postoperative radiotherapy) (see also Figure 2), had a longer delay between surgery and postoperative radiotherapy, and received more primary radiotherapy. In our cohort, comorbidity was not a relevant prognostic factor for disease-free survival. Neither univariate analysis nor multivariate analysis revealed a significant difference between ACE-27 comorbidity grade and actuarial regional control or distant metastases-free

survival. This concurs with the report by Rogers et al. in head and neck squamous cell carcinoma,[15] who observed no significant correlation between comorbidity and disease-free survival. Sanabria et al.[4] reported a nonsignificant HR (P =.11) in multivariate analysis for the ACE-27 index grade in relation to cancer-specific survival. An observational prospective cohort of 17,712 patients with cancer in the US, including disease locations in head and neck and also the prostate, lung, breast, digestive system, and gynecologic and urinary systems, revealed that 5058 patients (28.5%) developed disease recurrence.[7] The odds ratios of developing recurrence for increasing levels of comorbidity, after adjusting for extent of disease and treatment, with the category 'none' as the referent, were 1.18 (95% CI, 1.07-1.30) for mild comorbidity, 1.37 (95% CI, 1.22-1.53) for moderate comorbidity, and 1.54 (95% CI, 1.31-1.80) for severe comorbidity. We compared comorbidity in patients with salivary gland cancer with comorbidity in patients with other head and neck cancers. Because these data were not matched on age or sex, a valid comparison may be hindered. In analyzing at the comorbidity distribution, it appears that patients with salivary gland cancer have significant less comorbidity. A second analysis in which we tried to compare the comorbidity in our database and the comorbidity in cohort of patients with prostate cancer indicated that there were many similarities, although the distributions were not statistically similar. In conclusion, to our knowledge, this is the first study concerning the prevalence and relevance of the prognostic comorbidity variable ACE-27 in patients with salivary gland cancer. For this selected group of patients, the ACE-27 index was correlated with age and sex. The treatment performed was influenced by ACE-27 comorbidity only in patients with grade 3 comorbidity. Overall survival was correlated strongly with the ACE-27 index; however, disease-free survival was not. Comparison with other studies in which the effect of comorbidity on head and neck cancer was studied indicated that patients with salivary gland cancer have less comorbidity. Their comorbid status appeared to be reasonably comparable to that among patients with other non-smoking and nonalcohol-related cancers. In a future article, we plan to use the current data to construct predictive models for overall survival.

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Chapter 4

Cytology and histology have limited added value in prognostic models for salivary gland carcinomas

Marc P. van der Schroeff, Chris H.J. Terhaard, Marjan H. Wieringa,
Frank R. Datema, Robert J. Baatenburg de Jong

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Abstract

Univariate analyses on malignant salivary gland tumors report a strong relation of histological subtypes and prognosis. However, multivariate analyses with sufficient patients and reflecting the broad spectrum of putative prognostic factors are rare. In order to study the prognostic value of cytology and histology in salivary carcinoma we performed multivariate analyses on 666 newly diagnosed patients. In multivariate analyses sex, tumor size, N- and M-staging, localization, comorbidity, skin involvement and pain were independent predictors of survival. Histology was an independent prognostic factor, mainly because acinic cell carcinoma acted differently from the other histological subtypes. However, a simple prognostic model without cytology and/or histology has similar predictive power compared to more elaborate models. The added prognostic value of cytology and/or histology factors in salivary carcinoma is limited, largely due to the combined prognostic value of other prognostic factors such as tumor size, N- and M-classification and comorbidity.

Introduction

Malignant salivary gland tumors are rare (1–3% of all head and neck cancers), histological and biological diverse neoplasm's. Reportedly, this diverse group of tumors has variable outcomes with respect to different measures of survival, such as disease free survival and overall survival. Probably because of its rarity, there are no published prospective studies available. In general, its insidious clinical course necessitates studies with long follow up. Known important prognostic risk factors are stage[1–7] and positive cervical lymph nodes.[4,7–12] The histopathological diversity of malignant salivary gland tumors and its relation to prognosis has been subject to relatively few retrospective studies. Van der Poorten et al.[11] and Carrillo et al.[13] investigated the prognostic value of various possible prognostic factors in parotid tumors including histopathology in prognostic models on disease free survival, and in both studies histopathology did not seem to be relevant as it was not incorporated in the final models.

Table 1. Multivariate analysis (cox proportional hazards model) in model A, B and C. Presented hazard ratios (HR) are used to build the prognostic models.

		Analysis A (model A)		Analysis B (model B)		Analysis C (model C)	
	N (%)	HR	95% CI	HR	95% CI	HR	95% CI
Sex							
Female (referent)	323 (49)						
Male	343 (51)	1.4	1.2-1.7	1.4	1.2-1.7	1.4	1.2-1.6
Missing	0						
Age (continuous, mean 59 years)	666	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0
Missing	0						
Tumor size							
<2cm (referent)	134(20)						
2-4cm	225 (34)	1.1	0.8-1.4	1.1	0.8-1.4	1.1	0.7-1.4
4-6cm	125 (19)	1.2	0.8-1.5	1.2	0.8-1.5	1.2	0.9-1.6
>6cm	73 (11)	2.0	1.6-2.4	2.0	1.6-2.4	1.5	1.1-1.9
Missing	109 (16)						
N-classification							
N0 (referent)	555 (83)						
N1	31 (5)	1.3	0.9-1.8	1.3	0.8-1.8	1.2	0.7-1.7
N2	59 (9)	2.2	1.9-2.5	2.0	1.7-2.4	1.8	1.5-2.1
N3	7 (1)	3.6	2.8-4.3	3.1	2.4-3.9	1.6	0.8-2.4
Missing	14 (2)						

Table 1 (continued)

		Analysis A (model A)		Analysis B (model B)		Analysis C (model C)	
	N (%)	HR	95% CI	HR	95% CI	HR	95% CI
M-classification							
M0 (referent)	638 (96)						
M1	25 (3)	4.4	3.9-4.9	4.6	4.1-5.1	2.8	2.3-3.4
Missing	3 (1)						
Localisation							
Gl. parotis (referent)	372 (56)						
Gl. submandibularis	86 (13)	1.1	0.8-1.4	1.2	0.8-1.5	1.2	0.8-1.5
Accessory glands: mouth	175 (26)	0.6	0.3-0.9	0.6	0.3-1.0	0.6	0.3-1.0
Accessory glands: other	33 (5)	0.9	0.4-1.3	0.9	0.4-1.4	0.6	0.1-1.2
Missing	0						
ACE-27							
ACE 27 0 (referent)	394 (59)						
ACE-27 1	119 (18)	1.4	1.1-1.6	1.3	1.0-1.6	1.3	1.0-1.6
ACE-27 2	71 (11)	1.6	1.3-1.9	1.7	1.3-2.0	1.7	1.4-2.0
ACE-27 3	29 (4)	1.9	1.5-2.4	2.0	1.5-2.5	1.9	1.5-2.4
Missing	53 (8)						
Skin involvement							
No (referent)	594 (89)						
Yes	46 (7)	1.7	1.4-2.1	1.7	1.3-2.1	1.5	1.2-1.9
Missing	26 (4)						
Pain							
No (referent)	465 (70)						
Yes	169 (25)	1.7	1.5-1.9	1.8	1.5-2.0	1.8	1.5-2.0
Missing	32 (5)						
Cytology							
Acinic cell ca. (referent)	27 (4)						
Mucoepidermoid ca.	21 (3)			1.0	0.4-1.6		
Adenoid cystic ca.	46 (7)			0.9	0.4-1.4		
Adeno ca.	74 (11)			1.3	0.8-1.8		
Squamous cell ca.	20 (3)			1.0	0.4-1.6		
Undifferentiated	27 (4)			1.1	0.5-1.6		
Other	68 (10)			1.0	0.5-1.5		
Not malignant	39 (6)			0.9	0.3-1.4		
Missing	344 (52)						

Table 1 (continued)

		Analysis A (model A)		Analysis B (model B)		Analysis C (model C)	
	N (%)	HR	95% CI	HR	95% CI	HR	95% CI
Treatment							
Surgery (referent)	141 (21)						
Surgery and radiotherapy	444 (67)					1.1	0.8-1.5
Radiotherapy and/or chemotherapy	47 (7)					3.1	2.6-3.6
No therapy	34 (5)					3.4	2.9-4.0
Missing	0						
Histology							
Acinic cell ca. (referent)	91 (14)						
Mucoepidermoid ca.	105 (16)					2.1	1.6-2.6
Adenoid cystic ca.	181 (27)					1.7	1.2-2.2
Adeno ca.	140 (21)					2.5	2.0-3.0
Ca. ex-pleomorfic adenoma	55 (8)					2.1	1.5-2.6
Squamous cell ca.	34 (5)					2.4	1.8-3.0
Undifferentiated	44 (7)					2.8	2.2-3.3
Missing	16 (2)						

The aim of this study is to perform multivariate analyses on a broad range of putative prognostic factors available, and to look at the prognostic value of cytology and histology in particular. We constructed prognostic models based on relevant prognostic factors to aid the clinician in decision making and counseling. We used overall survival as prognostic endpoint, because this, in our view, represents the most relevant entity at the time of diagnosis and initial treatment for individual patients.

Patients and methods

Based on a dataset of the Dutch Head and Neck Cooperative Group (NWHHT) concerning salivary gland cancer general results,[14] the role of radiotherapy,[15] and the importance of facial nerve palsy in parotid cancer[16] have already been published. We performed an update of the database of the NWHHT concerning salivary gland cancer from all subsites, including the variable comorbidity, and including the results of all eight tertiary referral centers in The Netherlands. The database has been extended to 666 cases treated between 1985 and 1994. Median follow-up time of patients alive at the last follow-up is 125 months. Clinical characteristics and analysis of disease free survival have been reported recently.[17] The cytology report stated 'not malignant' in 39 (6%) cases (Table 1). These patients were nevertheless operated on for other reasons than cytology and shown to have a histological

malignancy. All pathology reports were reviewed. Most slides were analyzed previously by experts in salivary gland pathology, and if the remaining reports were considered questionable, slides were reviewed as well. Of all malignant salivary tumors (n = 666), 34 were diagnosed as squamous cell carcinoma. Because this percentage (5.1%) seemed rather high in comparison to most published studies,[18] we examined and excluded the possibility of a primary tumor of the mucosa or skin in the head and neck region meticulously. Squamous cell carcinomas were found in the parotid and submandibular gland only. These patients did not receive radiation therapy to the ipsilateral neck and Waldeyer's ring. However, we cannot totally exclude to possibility of an unknown primary with regional metastasis in the salivary gland, although during follow-up no primary tumor was found in these patients.

Models and statistical analysis

The prognostic impact of the different variables on overall survival was first studied univariately by Kaplan–Meier curves. Statistical significance was assessed using the log-rank tests (data not shown). Because of missing values (Table 1), especially concerning cytology and tumor size, we performed a multiple imputation.[19,20] This is a well established technique for dealing with missing values. The missing values are filled in after which the completed data set can be analyzed. We used the regression imputation method: a regression model is fitted for each variable with missing values, with the previous variables as covariates. Based on the resulting model, a new regression model is then simulated and is used to impute the missing values for each variable. Inference on the imputed model is superior to its alternative, a complete case analysis. Multivariate analysis was done using the Cox proportional hazards or regression model. The additivity assumption of the Cox regression model was tested using interaction terms. The usage of interaction terms yielded no significantly better fit. Therefore, we did not include interaction terms in our models. We tested the proportional hazards assumption for a Cox regression model fit: the assumption was deemed reasonable. Initially, three prognostic models were constructed based on the multivariate analysis. The first model (A) included all pretreatment putative prognostic factors but without cytology or histology. The second model (B) included the same pre-treatment factors with the inclusion of cytology. The third and final model (C, post-treatment) again used all pre-treatment factors, but now also included the type of treatment and, if collected, histology. To investigate the separate effect of histology we also constructed a fourth (post-treatment) model in which treatment was left out (data not shown). The discriminative power of all models was measured through the c-statistic; this indicates the proportion of all pairs of patients who can be ordered such that the patient with the higher predicted survival is the one who survived longer.[21] The c-statistic can be regarded as a generalization of the area under the Receiver Operating Characteristic (ROC) curve. A value of 0.5 indicates no predictive value and 1.0 indicates perfect separation

of patients with different outcomes (longer vs. shorter survival). In order to quantify potential overfitting of the model we used bootstrapping techniques.[22,23] In this way the entire dataset is used for model development. In order to assess whether the model would have a decreased performance in future patients we created regression models in each bootstrap sample and tested them on the original sample. This procedure was repeated 50 times to obtain stable estimates of optimism of the model. Bootstrapping provides nearly unbiased estimates of predictive accuracy that are of relatively low variance.[24] On the basis of the discriminative power (c-statistic) we then chose the optimal model. For the statistical analyses we used SPSS®, version 13.0 and R.[25,26]

Table 2. Usage of putative prognostic factors in various models and c-statistic for each model.

	Model A	Model B	Model C
Cytology		x	
Histology			x
Treatment			x
Other putative prognostic factors	x	x	x
c-statistic	7.7	7.7	7.8

Results

Model A used all pre-treatment putative prognostic factors (predictors) without cytology or histology. The factors included were age, sex, tumor size, N- and M-classification, tumor localization, ACE-27 comorbidity score, skin invasion and pain. All factors were independent predictors of overall survival, except age. The impact of independent prognostic factors in model A is shown in Figure 1. The c-statistic of model A was 7.7. (A graphic illustration representing this statistic is given in Figure 2 in the form of a Receiver Operating Characteristic (ROC) curve.) Model B is a pre-treatment model, similar to model A, but with the addition of cytology. Cytology appeared to be no significant independent predictor of survival (Table 1). All other predictors showed roughly stable HR's in comparison with model A. Model B also yielded a c-statistic of 7.7. In the post-treatment model C, we found that treatment and histology were significant and independent predictors of overall survival (Table 1). This model yields only a little higher c-statistic of 7.8 than the previous models (both 7.7). A post-treatment model with only histology showed a c-statistic of again 7.7 (data not shown). The usage of putative prognostic factors in various models, and the c-statistic for each model is given in Table 2. The formulas of the full models are reported in the Appendix, which could easily be translated into a more practical, desktop, application, offering individual survival estimates.

Figure 1. Hazard ratio's of prognostic factors in salivary carcinoma. Based upon multivariate analysis of all pre-treatment variables, except cytology (model A). gl. subm. = gl. submandibularis; acc. other = accessory glands; other, mouth = accessory glands; mouth.

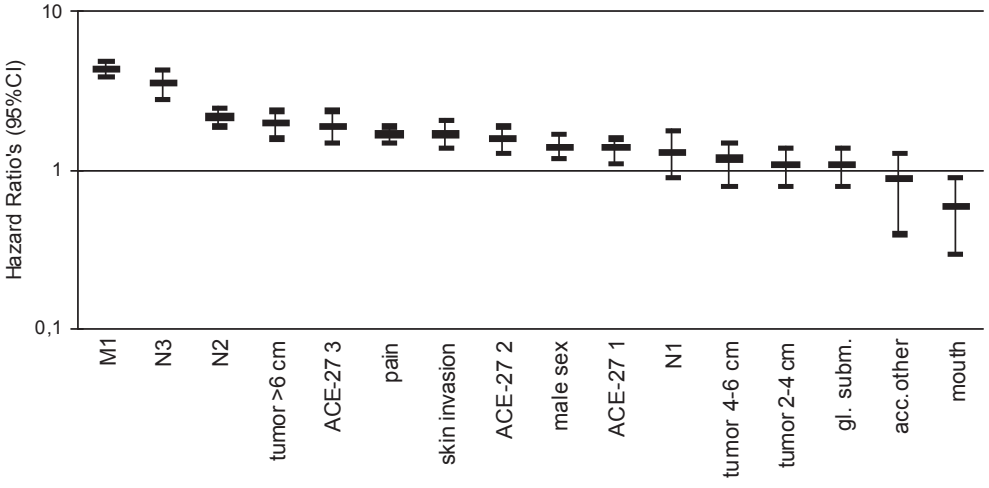
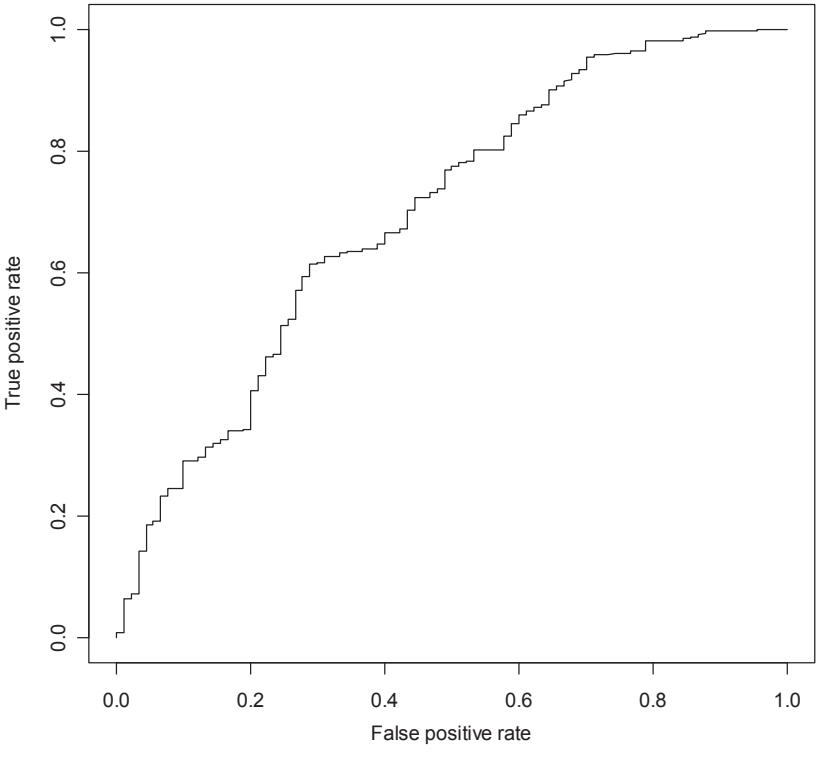


Figure 2. Receiver Operating Characteristic curve of model A. The area under the curve represents a c-statistic of 7.7.



Discussion

Very few publications give the results of multivariable analysis on prognostic factors of survival performed on large groups of patients and including tumors of the major and minor salivary glands.[4,9,27] Most deal exclusively with either tumors of the major or minor salivary glands,[1,2,28–31] or only tumors of the parotid gland.[5,7,11,13,32–37] In recent years two prognostic models have been published, both concerning parotid gland tumors. Carrillo et al.[13] reported 127 parotid-gland cancer patients between 1981 and 2004 with a minimal follow-up of 18 months en a mean age of 53 years. They performed a logistic regression on tumor-recurrence and found tumor classification, facial nerve palsy, grade of tumor differentiation, age and surgical margins to be recurrence associated markers. Their presented model identifies three postoperative risk groups: high, intermediate and low. Histology was analyzed as a prognostic factor in multivariate analysis but showed no significant effect and was consequently not incorporated in their prognostic model. The other publication (Van der Poorten et al.[11]) presented a pre- and post-treatment model based upon data from 151 parotid-gland cancer patients, collected between 1973 and 1994 with a median follow-up of 37 months and a median age of 63 years. Their prognostic models were also based on the risk of tumor recurrence. The pre-treatment model consisted of age, pain, T- and N-classification, skin invasion and facial nerve dysfunction. Cytology and incisional biopsy were tested in multivariate analysis, but not included in this model. The post-treatment model was complemented with factors from the pathology report, but not with treatment itself. Therefore their final posttreatment model included age, T- and N-classification, skin invasion and facial nerve dysfunction and extended with following predictors of the pathology report: perineural growth and positive surgical margins. Histology (high vs. low graded tumors), extracapsular growth and no nodes in neck dissection specimen were also tested in a multivariate analysis, but again not included in the final (post-treatment) model, due to lack of additional prognostic power. The studies reported by Van der Poorten et al.[11] and Carrillo et al.[13] were structured to model disease free survival and tumor recurrence in parotid malignancies. We used overall survival as prognostic endpoint, because this, in our view, represents the most relevant entity at the time of diagnosis and initial treatment. Besides parotid malignancies we included other salivary gland subsites as well. These structural differences might explain variation in strength of specific prognostic factors such as age; both Van der Poorten and Carrillo report age as an independent predictor for recurrence, whereas in our study age was no predictor. In our analysis we used tumor type as histological entity because the determination of tumor grade (high vs. low) is a somewhat subjective exercise. Individual pathologists may apply different criteria which lead to poor interobserver reproducibility.[38] The value of grading for the prognosis of salivary gland tumors remains limited,[1,39] however in mucoepidermoid tumors grade is proven to

be an independent prognostic factor.[38,40] In the current study, with long-term follow-up (particularly important for patients with adenoid cystic carcinomas which can behave in an indolent way and, thus, require a long follow-up) and a large study population including all subsites, we investigated three models on overall survival in salivary gland carcinoma. Sex, tumor size, N- and M-classification, tumor localization, ACE-27 comorbidity score, skin invasion, pain, treatment and histology all showed to be independent prognostic factors. Cytology is paramount in differentiating between malignant and benign lesions, but once determined, the classification into cytological subcategories adds little prognostic value. This is probably caused by competing prognostic factors (e.g. TNM classification) in the multivariate analysis. Histology on the other hand does act as an independent prognostic factor. Especially the differentiation between acinic cell carcinoma vs. all other sub-categories is a relevant factor. These tumors, not evidently treated different (Table 3), seem to represent an intermediate risk profile between benign lesions and the group of other malignant tumors.

Table 3. Cross tabulation of histology and therapy. Pierson Chi-square = 0.06.

	Acinic cell carcinoma	Other histological subtypes
Surgery	24 (27%)	113 (20%)
Surgery and radiotherapy	63 (69%)	370 (66%)
Radiotherapy with/without chemotherapy	1 (1%)	45 (8%)
No therapy	3 (3%)	31 (5%)
Total	91 (100%)	559 (100%)

However, when we compare our three prognostic models, the differences in discriminative power are small (c-statistic 7.7, 7.7 and 7.8). A simple model with the least predictors is more stable than a more elaborated model. For an estimate of the prognosis, which is most relevant in the pre-treatment phase, the simplest model (model A) therefore seems to be the most useful. Inclusion of cytology or histology adds only very modest discriminative power, as reflected in the c-statistic. In conclusion, in multivariate analysis, acinic cell carcinoma is associated with a more favorable outcome compared to other malignant salivary subtypes, which have a similar prognosis. When complementing prognostic models on malignant salivary gland tumors in which tumor size, N- and M-classification (or AJCC tumor stage) and other clinical prognostic factors are already included, the added prognostic effect of cytology, histology and treatment factors wane. A model based on readily available clinical pretreatment parameters seems therefore most appropriate.

Appendix A

Model A formula (reflecting the additional risk on overall survival in comparison with a reference patient) = 1.4*male sex + age + 1.1*tumor size 2–4 cm + 1.2*tumor size 4–6 cm + 2.0*tumor size > 6 cm + 1.3*N1 + 2.2*N2 + 3.6*N3 + 4.4*M1 + 1.1*location in gl. submandibularis + 0.6*location in accessory glands of the mouth 0.9*location in accessory glands elsewhere + 1.4*ACE-27 score 1 + 1.6*ACE-27 score 2 + 1.9*ACE-27 score 3 + 1.7*skin involvement + 1.7*pain.

Model B formula (reflecting the additional risk on overall survival in comparison with a reference patient) = 1.4*male sex + age + 1.1*tumor size 2–4 cm + 1.2*tumor size 4–6 cm + 2.0*tumor size > 6 cm + 1.3*N1 + 2.0*N2 + 3.1*N3 + 4.6*M1 + 1.2*location in gl. submandibularis + 0.6*location in accessory glands of the mouth 0, location in accessory glands elsewhere + 1.3*ACE-27 score 1 + 1.7*ACE-27 score 2 + 2.0*ACE-27 score 3 + 1.7*skin involvement + 1.8*pain + 1.0*mucoepidermoid ca.(cytology) + 0.9*ad.cystic ca. (cytology) + 1.3*adeno ca. (cytology) + 1.0*squamous cell ca. (cytology) + 1.1*undifferentiated ca. (cytology) + 1.0*other (cytology) + 0.9*not malignant (cytology).

Model C formula (reflecting the additional risk on overall survival in comparison with a reference patient) = 1.4*male sex + age + 1.1*tumor size 2–4 cm + 1.2*tumor size 4–6 cm + 1.5*tumor size > 6 cm + 1.2*N1 + 1.8*N2 + 1.6*N3 + 2.8*M1 + 1.2*location in gl. submandibularis + 0.6*location in accessory glands of the mouth 0.6*location in accessory glands elsewhere + 1.3*ACE-27 score 1 + 1.7*ACE-27 score 2 + 1.9*ACE-27 score 3 + 1.5*skin involvement + 1.8*pain + 1.1*surgery/PORT + 3.1*RT ± CT + 3.4*no therapy + 2.1*mucoepidermoid ca.(histology) + 1.7*ad.cystic ca. (histology) + 2.5*adeno ca. (histology) + 2.1*ca.ex.pleo.ca. (histology) + 2.4*squamous cell ca. (histology) + 2.8*undifferentiated ca.
(histology).

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Part II

PROGNOSIS IN HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)

Chapter 5

Conditional relative survival in head and neck squamous cell carcinoma: permanent excess mortality risk for long-term survivors

Marc P. van der Schroeff, Saskia A.M. van de Schans, Jay F. Piccirillo, Ton P.M. Langeveld, Robert J. Baatenburg de Jong, Maryska L.G. Janssen-Heijnen

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Abstract

Dynamic predictions on head and neck cancer survival could offer, besides improved patient counseling, insight into long-term effects of tumor- and patient-based characteristics on survival. Theoretically, there could be a certain time period after diagnosis after which the patient returns to a population risk on survival. In all, 7255 patients with a primary head and neck squamous cell carcinoma (HNSCC) aged 25 to 90 years, diagnosed between January 1980 and January 2004 in The Netherlands, were included. Conditional 5-year relative survival for every additional year survived was computed. The overall conditional relative prognosis reached a plateau after approximately 4 years; a permanent 20% to 25% excess mortality for long-term HNSCC survivors remained. Conditional 5-year relative survival for patients with HNSCC remains poorer compared to age- and sex-matched counterparts in the general population, even when alive at 15 years after diagnosis. We assume that this is caused by an excess comorbidity in these patients, mainly due to smoking and alcohol abuse.

Introduction

In general, prognostic modeling is based on patient characteristics known at the time of diagnosis. However, the 5-year prognosis of cancer patients who, for example, survived the first 2 years is conceivably better than 7-year survival at diagnosis would predict. This is caused by the fact that they have already survived the first critical period. Prognosis is a dynamic concept not fully appreciated in classic and static estimates at the time of diagnosis. Patients who have survived a certain period after being diagnosed with head and neck squamous cell carcinoma (HNSCC) are often interested in their up to-date prognosis. In addition, a dynamic prognosis may be of value when a cancer patient is faced with a new event, such as a recurrence. Theoretically, there could be a certain time period after diagnosis with HNSCC after which the patient returns to a (sex- and age-matched) population risk on 5-year survival. A more dynamic prediction would offer, besides improved patient counseling on prognosis, insight into long-term effects of tumor- and patient-based characteristics on survival. Conditional survival estimates, that precondition having survived a certain period of time, are probably the best way to give insight into this kind of dynamic prognosis.[1] In recent years, various types of tumors have been subject to conditional survival studies, most of them only reporting until 5 years after diagnosis. These studies included lung,[1–3] breast, prostate cancer,[2,4–6] and gastrointestinal malignancies.[2,7–10] In the field of HNSCC, to our knowledge, only 2 publications on conditional survival exist. Fuller et al.[11] reported an increased excess risk for patients with HNSCC resulting from noncancer-related causes up to 10 years from the time of diagnosis. Yang et al.[12] studied conditional survival in buccal and tongue cancer. Our aim was to provide conditional survival estimates for Dutch cancer patients up to 15 years after diagnosis and to identify the magnitude of excess mortality compared with the underlying general population.

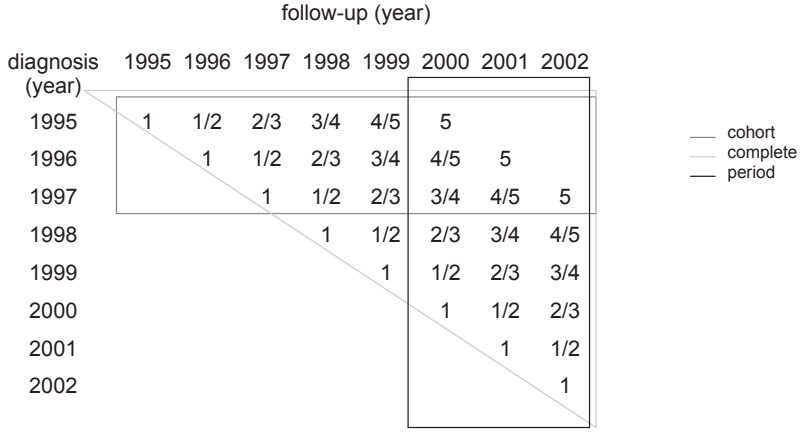
Patients and methods

Data were derived from the Leiden University Medical Centre (LUMC) and from the long-standing Eindhoven Cancer Registry (ECR). The LUMC data were retrieved from the Leiden hospital-based cancer registry system (ONCDOC). Trained oncological data managers store all patient, treatment, and follow-up data. The database consists of 2829 consecutive patients with a primary HNSCC, diagnosed at the LUMC between January 1980 and January 2004, aged 25 to 90 years. The ECR has collected data on all patients with newly diagnosed cancer in the southern part of the Netherlands since 1955 (completeness >95%[13]). The registry now serves a population of 2.3 million inhabitants. The area offers good access to specialized medical care in 10 general hospitals and 2 large radiotherapy institutes. In addition to passive follow-up via the hospitals, date of death is also retrieved from the

Municipal Personal Records Database (GBA). Patients diagnosed with primary HNSCC, between 1980 and 2004 aged 25 to 90 years, were included (n = 4426). We combined the LUMC and ECR data to achieve more power (n = 7255). We excluded double records (patients from the region of the ECR who had been diagnosed or treated in LUMC, n = 10).

Conditional relative survival was calculated as the 5-year relative survival for every additional year survived up to 15 years, conditional on being alive at that moment. We calculated 5-year conditional relative survival rates for the follow-up period 1980 to 2004 with period analysis.[14–16] Period analysis provides the most up-to-date survival estimates because all observations included in the analyses are left truncated at the beginning of the period of interest, in addition to being right-censored at its end. Therefore it exclusively reflects the survival experience of patients within some most recent calendar period, such as the most recent calendar year(s) for which mortality follow-up is available. An illustration of this concept is given in Figure 1.

Figure 1. Illustration of years of diagnosis and years of follow-up included in cohort and period analyses of 5-year relative survival of patients in fictive time period 1995 to 2002.



Period analysis enables the early detection of changes in survival trends and better predicts long-term survival of concurrently diagnosed and treated patients than survival estimates derived by traditional methods.[16] It requires a long and complete follow-up, especially when studying the conditional 5-year relative survival for every additional year during a long period of time since diagnosis. Relative survival is an estimation of disease-specific survival. It is calculated as the absolute survival rate among patients with cancer divided by the expected survival rate of a comparable group from the general population with the same sex and age structure in the same period (derived from Statistics Netherlands), according to the Ederer II method.[17] Therefore most competing causes of

death are accounted for. We stratified the analyses on localization of tumor and stage. Only conditional relative survival proportions with a standard error ≤ 5% of the survival proportion were presented. There is no excess mortality for patients when conditional 5-year relative survival has reached 100%. Survival is then similar to that of the general population. Calculations were performed with the SAS computer package (SAS Institute Inc., Cary, NC, 1999).

Table 1. Baseline characteristics and numbers of patients available for conditional period survival analysis after 5 and 10 years after diagnosis.

			No. of patients available for conditional survival, after year:	
Tumor	**No. of patients at diagnosis**	**Reliable estimates up to year**	**5**	**10**
HNSCC	7255	14	1130	455
Stage I	2086	12	512	218
Stage II	1259	7	229	87
Stage III	985	3	116	45
Stage IV	1760	4	112	37
Unknown stage	1165	-	-	-
Oral cavity	1967	6	213	55
Pharynx	1327	3	103	55
Glottis	1653	11	405	177
Supraglottis	839	4	130	50
Other	1469	-	-	-

Results

Baseline characteristics are shown in Table 1, as well as the number of patients at specific time points during follow-up (5 and 10 years) available for conditional survival estimates. Mean follow-up in the combined dataset was 61 months (5 years, 1 month), with a maximum of nearly 26 years. Figure 2 shows 5-year relative survival at diagnosis and conditional 5-year relative survival for each additional year survived after diagnosis of HNSCC. Five-year relative survival at diagnosis was 60%. Although conditional 5-year relative survival increased with each additional year survived up to 3 years after diagnosis, a considerable excess mortality remained after 3 years (conditional 5-year relative survival did not exceed 84%). Figure 3 shows that differences in conditional survival between stage groups became smaller, but remained present over time. After having survived for 4 years, conditional 5-year relative survival was 92% for stage I, 83% for stage II, and only 69% for stages III and IV. Tumors of the glottis offer a much better prognosis at diagnosis

compared with other tumor sites (Figure 4). This favorable prognosis for glottic cancer persisted over time; conditional 5-year relative survival for this tumor type increased to 94% after having survived at least 3 years, whereas conditional survival for the other tumor types did not exceed 80%.

Figure 2. Conditional 5-year relative survival rates for each additional year survived for patients with head and neck squamous cell carcinoma (HNSCC) and 5-year relative survival at diagnosis.

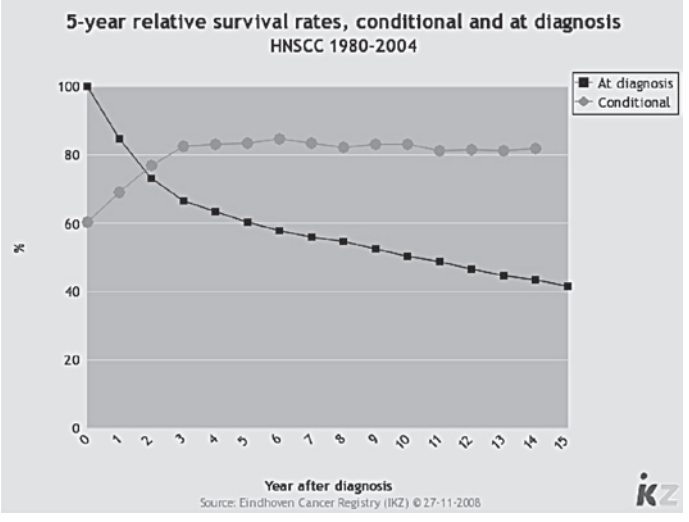


Figure 3. Conditional 5-year relative survival rates for each additional year survived for patients with HNSCC and 5-year relative survival at diagnosis, by stage.

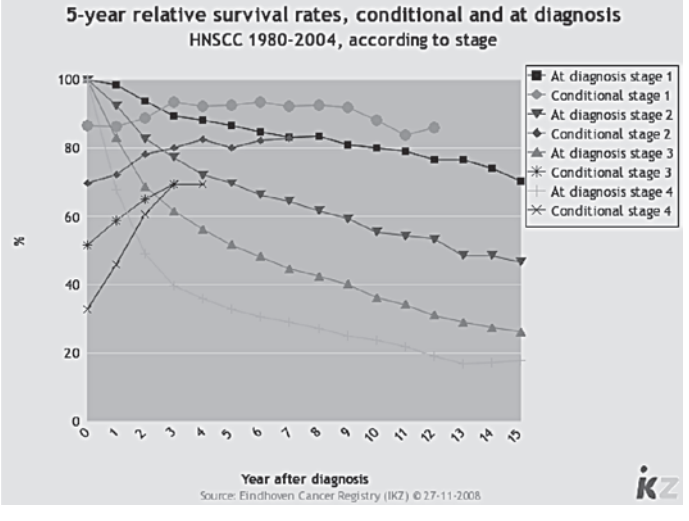
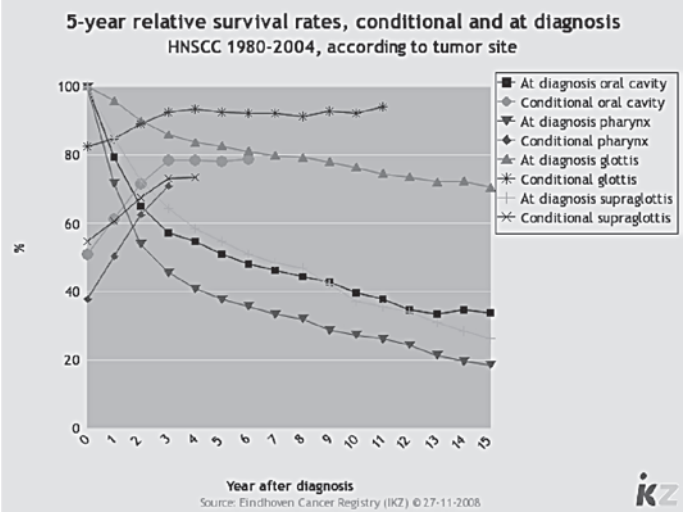


Figure 4. Conditional 5-year relative survival rates for each additional year survived for patients with HNSCC and 5-year relative survival at diagnosis, by tumor site.



Discussion

This is the first study that presents conditional relative survival of unselected patients with HNSCC up to 15 years after diagnosis, which could be very useful for both cancer survivors and health professionals for planning remaining life and optimal surveillance. Our study shows that conditional 5-year relative survival for HNSCC patients remains poorer compared with their age- and sex-matched counterparts in the general population, even when alive at 15 years after diagnosis. Worse conditional survival for patients with HNSCC was also shown in a previous (United States) population-based study[11]; Fuller et al.[11] reported conditional survival estimates up to 10 years after diagnosis for 76,181 HNSCC patients, identified from the Surveillance, Epidemiology, and End Results (SEER) Program, diagnosed between 1973 and 1998. Fuller et al used 3 survival concepts: the expected conditional survival (ECS), the observed conditional survival (OCS), and the relative conditional survival (RCS), all reflecting a 5-year survival estimate. The difference between the OCS and ECS reflects the excess risk for patients with HNSCC of not surviving another 5 years at a given time point. This excess risk stabilizes at approximately 20% after 3 to 4 years after diagnosis. They also showed that the RCS and ECS converge after approximately 6 years. This implies that the excess risk for HNSCC is the result of non–cancer-related causes (such as chronic obstructive pulmonary disease [COPD] in smoking patients with HNSCC). These reports concur with our results that show an overall conditional relative prognosis plateau after approximately 4 years, after which a 20% to 25% excess

risk remained. This means that there seems to be a permanent excess risk for long-term cancer survivors relative to the general population. Hypothetical causative factors of the increasing excess risk after 3 years from diagnosis might be secondary primaries and/or late recurrences, or comorbidity. We will discuss these possible causative factors in more detail. A possible explanation of the increasing excess mortality is the development of a second primary cancer or local recurrence. Second primaries are common (7.5% to 17%) in head and neck cancer follow-up.[18–24] They typically occur in the head and neck, lung, and esophagus. A theoretical explanation for the occurrence of second primaries is given in the classic "field cancerization" model[25]: multiple precancerous lesions exist adjacent to the index tumor. They share the (continued) exposure to smoke and alcohol. Recurrences predominantly occur within the first 3 years; second primaries usually present within 2 to 4 years from initial diagnosis.[18,24,26] The latter probably represent a group of patients with slightly more favorable index tumor (and patient) characteristics because they have already survived the first few years. Since most second primaries and recurrences are relatively "early events," they cannot fully account for the stable excess mortality up to 15 years from index tumor diagnosis. If one survives up to 15 years from diagnosis of the index tumor, the effects of possible recurrences and/or second primaries on conditional relative survival will probably be minimal. Comorbidity acts as a long-term risk factor for mortality and seems to be a more prominent problem in patients with HNSCC compared with the general population.[27] In head and neck oncology, there is a strong etiological relationship between smoking and alcohol abuse and the occurrence of HNSCC.[28–30] Besides acting as a major etiologic factor in HNSCC, smoking is thought to be partly responsible for substantial comorbidity (eg, COPD and cardiovascular disease [CVD]),which in turn significantly influences cancer survival.[31,32] Alcohol abuse acts in a similar way; it not only causes HNSCC, but also is a major source of comorbidity, such as esophagitis, gastritis, and liver disease.[28,33,34] Furthermore, the combined etiologic effect of alcohol and smoking might be multiplicative.[33,35] Indeed, in HNSCC, the prevalence of smoking and alcohol-related comorbidity is high, and comorbidity is reported to be a significant prognostic factor.[27,36–41] Our results show glottic cancer to have a distinct conditional survival plateau: 94% at 3 years after diagnosis, compared with <80% for the other subsites. A possible explanation could be the relatively weak association with alcohol abuse and therefore differences in the prevalence of comorbidity compared with the other subsites.[30] A large pooled analysis of individual data from 15 case-control studies that included over 10,000 subjects with head and neck cancer and over 15,000 controls reported no statistical difference in the risk of laryngeal cancer among never users of tobacco between never and ever alcohol consumption.[42] The difference between glottic localization and the other subsites therefore may be a reflection of less alcohol-associated comorbidity in this group. The remaining excess mortality (6%) in patients with

glottic cancer is probably attributable to tobacco related comorbidity. Tumor stage has an impact on conditional relative survival. As can be seen in Figure 2, during the first 3 years the different tumor stages have considerable impact on the conditional relative survival, but the effect decreases after having survived 3 years. This is reflected in the convergence of the conditional survival curves around 70% to 80% (see Figure 2). This can be explained by the fact that many patients with a very poor prognosis in the more advanced stages die within the first few years after diagnosis, leaving those with a relatively favorable prognosis. In conclusion, conditional 5-year relative survival for patients with HNSCC remains poorer compared with their age- and sex-matched counterparts in the general population, even when alive at 15 years after diagnosis. We assume that this is largely caused by an excess comorbidity in these patients, mainly as a result of smoking and alcohol abuse. Information on conditional relative survival is very useful for both cancer survivors and health professionals for planning remaining life and optimal surveillance.

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Chapter 9

Prognosis: a variable parameter Dynamic prognostic modeling in Head and Neck Squamous Cell Carcinoma

Marc P. van der Schroeff, Ewout W. Steyerberg, Marjan H. Wieringa,
Ton P.M. Langeveld, Jan Molenaar, Robert J. Baatenburg de Jong.

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Abstract

In general, the estimated prognosis of cancer patients is based on patient characteristics known at the time of diagnosis and presented as if a lifetime verdict. However, the prognosis of cancer patients who survive the first critical years changes, as well as the prognosis for those with local or regional recurrences or distant metastases. This study concerns 2927 patients with a primary head and neck squamous cell carcinoma (HNSCC). We developed prognostic models after initial treatment and at different time points during follow-up. The developed models show the effects of survival time, recurrences and distant metastasis during follow-up. The C-statistics ranged from 0.76-0.69. Prognosis is dynamic: the passage of time and the occurrence of life-events change the predicted probabilities of survival. The models enhance our insight in the effect of recurrences and metastasis during follow-up and could be used for better patient counseling.

Introduction

Prognoses in head and neck cancer, but also in cancer generally, are based on characteristics known at the time of diagnosis and presented as if a lifetime verdict. However, when a cancer patient survives the first year his or her prognosis is conceivable better than at time of diagnosis. This is caused by the fact that they survived the first critical period and the passing away of those with similar tumor features but shorter survival. Furthermore, no one would argue that a patient with a local or regional recurrence or distant metastasis during follow-up has an altered (worse) prognosis as well. This illustrates that there is need for a more dynamic prognosis during follow-up. A prognostic model that would take into account the survival time and recurrences or metastases during follow-up would probably better predict. Therefore, the purpose of this study was to design prognostic models for patients with HNSCC, taking into account the passage of time and incorporating recurrences and delayed metastases.

Table 1. Baseline characteristics and univariate analysis.

Covariable	N	KM-estimate* 5-years	KM-estimate* 10-years
Sex			
male	2220 (75.8%)	50.6%	34.0%
female	707 (24.2%)	48.9%	33.3%
Age	8-100 (mean 63 years)		
T-status**			
T1	913 (34.4%)	73.5%	53.4%
T2	692 (26.1%)	49.6%	31.2%
T3	443 (16.7%)	39.3%	24.5%
T4	608 (22.9%)	25.0%	15.5%
missing	271		
N-status**			
N0	1868 (68.6%)	61.3%	42.3%
N1	293 (10.8%)	36.0%	22.1%
N2	442 (16.2%)	25.6%	15.4%
N3	122 (4.50%)	10.2%	5.50%
Missing	202		
M-status**			
M0	2681 (98.2%)	52.0%	35.5%
M1	50 (1.80%)	0%	0%
Missing	196		

table 1 (continued)

Covariable	N	KM-estimate* 5-years	KM-estimate* 10-years
Comorbidity**			
ACE 27: 0	481 (45.3%)	57.9%	41.4%
ACE 27: 1	278 (26.2%)	50.7%	32.5%
ACE 27: 2	210 (19.8%)	44.3%	23.3%
ACE 27: 3	93 (8.80%)	25.0%	9.50%
Missing	1865		
Site**			
Hypopharynx	269 (9.20%)	27.6%	12.8%
Larynx glottic	769 (26.3%)	67.8%	49.0%
Larynx supraglottic	351 (12.0%)	46.5%	28.9%
Lip	224 (7.70%)	71.5%	52.3%
oral cavity	557 (19.0%)	42.0%	27.1%
nasopharynx	73 (2.50%)	54.3%	33.1%
oropharynx	501 (17.1%)	36.8%	22.8%
other	183 (6.30%)	41.7%	26%
Degree of differentiation**			
good	397 (25.4%)	61.1%	43.0%
moderate	853 (54.6%)	47.6%	31.0%
bad	312 (20.0%)	37.6%	24.9%
missing	1365		
Treatment**			
surgery	550 (18.8%)	60.7%	42.9%
radiotherapy	1362 (46.5%)	53.5%	36.4%
surgery + radiotherapy	636 (21.7%)	48.0%	30.7%
radiotherapy + chemotherapy	186 (6.40%)	41.8%	22.8%
chemotherapy	19 (0.60%)	0%	0%
other treatment	38 (1.30%)	48.3%	27.1%
No treatment	136 (4.60%)	0.80%	0%

* Kaplan-Meier estimate: cumulative proportion surviving 5 and 10 years respectively
**Log-rank test significant, p-value <0.05

Table 2. follow-up data at different time points

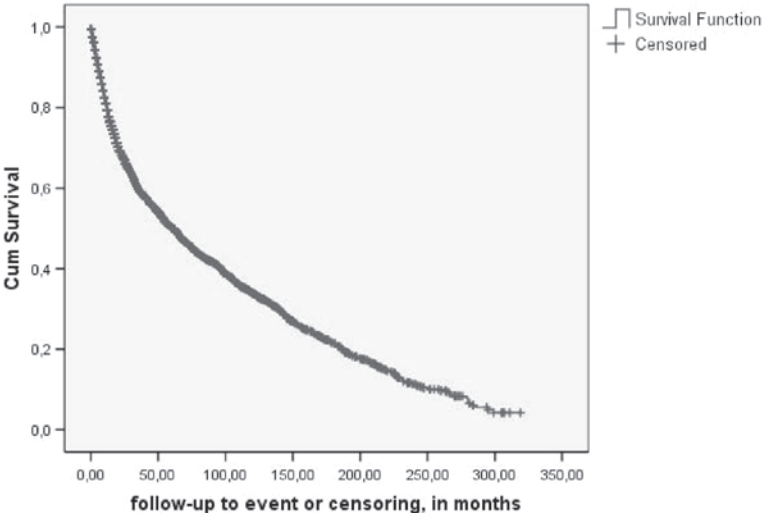
	After initial treatment	≤3 m	3 m	>3 m ≤6 m	6 m	>6 m ≤12 m	12 m	>12 m ≤24 m	24 m	>24 m ≤60 m	60 m	>60 m
Number of patients	2927		2736		2536		2229		1754		1044	
Deaths (total=1828)		114		151		269		345		410		539
Deaths per model at time t	1828		1714		1563		1294		949		539	
Number of local recurrences (n=485)		4		52		167		122		96		44
Number of regional recurrences (n=282)		11		53		83		81		45		9
Number of distant metastasis (n=320)		11		33		92		87		62		35

m' represents the number of months
'n' represents the number of patient at each point in time
'deaths' represents the number of patients who died in each time-frame
'deaths per model at time t' represents the number of deaths or events after the specific point in time. This is the number of events still available for analysis.

Patients and methods

The data were retrieved from the hospital-based cancer registry system ("oncological documentation" or ONCDOC) of the Leiden University Medical Center (LUMC). Trained data-managers store all patient, treatment and follow-up data. These data are retrieved from the patient's file and hospital-based data system. ONCDOC also performs an independent and active follow-up. When patients are lost to follow-up ONCDOC will contact the family physician and/or the Dutch Registry of Births, Deaths, and Marriages. In this way follow-up is as complete as possible. The database consists of 2927 consecutive patients with a primary HNSCC, diagnosed at the LUMC between January 1980 and November 2006. Baseline characteristics and univariate analysis are shown in table 1. Follow-up ranged from 0 to 319 months, with a median of 34 months. Follow-up data are shown in table 2. Overall 5-year survival was 50.2%. Table 2 and figure 1 show overall survival, the number of deaths of all causes (n = 1828, 62.5%) and the numbers of recurrences and metastases during follow-up (n = 1087, 37.1%).

Figure 1. Kaplan Meier curve, overall survival.



Covariables

We considered the following covariables as prognostic factors: age, sex, T-status, N-status, M-status, site of the tumor, degree of differentiation, comorbidity and treatment. The covariable age was tested in a continuous version versus two dichotomized versions (> 50 years and >65 years). The model with age as a continuous variable (compared to a dichotomized version) produced the largest difference in -2 log likelihood or X-square (compared to a basic model with just an intercept). T-, N- and M-status were retrieved from the hospital-based cancer registry system (ONCDOC). Degree of differentiation was classified as good, moderate or bad. For comorbidity we used the Adult Comorbidity Evaluation-27 (ACE-27), which is a modification of the Kaplan-Feinstein index.[1] In contrast to all other covariables the ACE-27 score was collected retrospectively (in a subset of patients for another study) by studying the patients' medical record. The ACE-27 grades specific comorbid conditions into 1 of 3 levels of comorbidity, mild, moderate or severe, according to decompensation and prognostic impact.[2] The overall comorbid score, or ACE-27 ranking, is based on the highest ranked single ailment, where patients with two or more moderate ailments in different organ systems or disease groupings, are graded as severe. The ACE-27 is a comprehensive tool, has been previously modified and validated and is of common use in head and neck cancer literature.

Multivariate analysis

Multivariate analysis was done using the Cox proportional hazards or regression model. The additivity assumption of the Cox regression model was tested using interaction terms. We tested the proportional hazards assumption for a Cox regression model fit.[3]

Time-intervals and dynamic covariables

In order to investigate follow-up time dependent effects and to incorporate local and regional recurrences as well as delayed distant metastases we produced five follow-up models at three and six months after diagnosis as well as after one, two and five years after diagnosis. Only those patients that were alive and still in follow-up at those time points were used to build these follow-up models. Because of smaller numbers, the variance in successive follow-up models increased. All tumor characteristics were kept identical to the initial model at diagnosis. Comorbidity was kept identical as well, because of lack of data on comorbidity developing during the course of the disease. The covariable age was adjusted to the length of follow-up: the actual age at time of follow-up was used. All (follow-up) models besides the initial model at diagnosis included local and regional recurrence and metastasis.

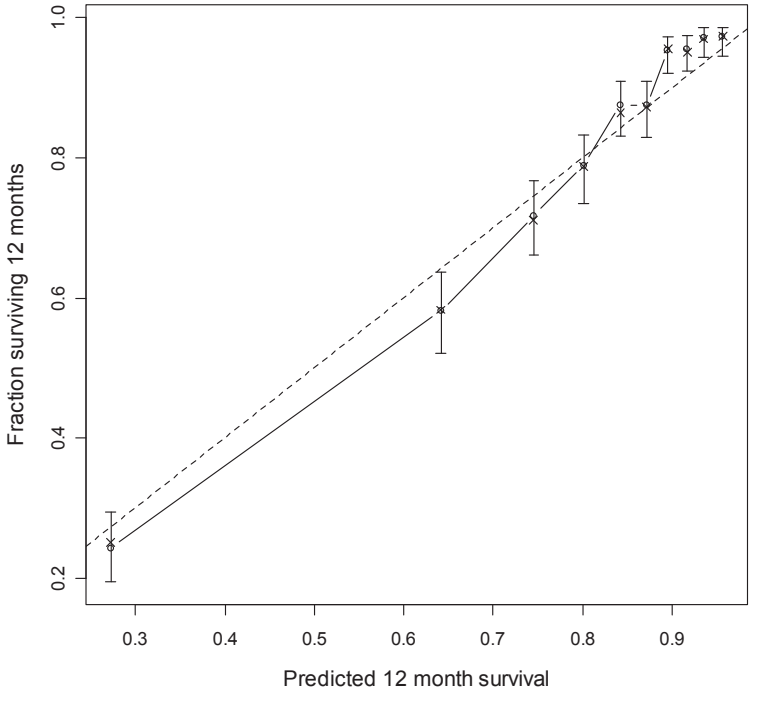
Multiple imputation

Because of substantial missing values (table 1), especially concerning comorbidity and degree of differentiation, we performed a multiple imputation.[4,5]

Validation

The model's ability to separate patients with different outcomes, or discriminative power, was measured through the c-statistic.[6] A value of 0.5 indicates no predictive value and 1.0 indicates perfect separation of patients with different outcomes. In order to quantify potential overfitting of the model we used bootstrapping techniques.[7,8] In this way the entire dataset is used for model development. In order to assess whether the model would have a decreased performance in future patients we created regression models in each bootstrap sample and tested them on the original sample. This procedure was repeated 50 times to obtain stable estimates of optimism of the model. Bootstrapping provides nearly unbiased estimates of predictive accuracy that are of relatively low variance.[9] The calibration plot of actual 12 month survival versus predicted is shown in figure 2.

Figure 2. Internal validation, calibration.



Software

For the statistical analyses we used SPSS®, version 13.0 and R.[10,11]

Results

We excluded sex and degree of differentiation on basis of their small contribution (X-square of 7.37, p-value 0.08, and 11.82, p-value 0.05, respectively) to a full model with all covariables (X-square full model: 1686). The usage of interaction terms yielded no significantly better fit. Therefore, we did not include interaction terms in our models. The proportional hazards assumption for a Cox regression model fit[3] was tested and showed a global p-value < 0.01, indicating a time-dependent effect. The final presented models consisted therefore of: age, T-status, N-status, M-status, site of the tumor, comorbidity, treatment (model after initial treatment) and local recurrence, regional recurrence and metastasis (follow-up models). All hazard ratio's and 95% confidence intervals of the various models are listed in table 3.

The resulting models are best illustrated using an example. Figure 3 shows the 1-, 2-, 5- and 10-years predicted prognosis of a 60-years old patient with a T3N1M0 SCC of the larynx, treated with surgery and radiotherapy. The patient has an ACE-27-score of 1, indicating mild comorbidity. The predicted 5-year survival after initial treatment is 60.4%. Figure 4 shows the effect for this patient of being alive up to 2 years after the initial treatment. The predicted 5-year survival at that point of time (=7 years after initial treatment) is increased to 75.9%. For means of comparison: the predicted 3-year survival (=5 years after initial treatment) is 84.2% (not shown in figure 4). Figure 5 shows the effect of being alive up to 2 year after the initial diagnosis but with development of a regional recurrence: the predicted 5-year survival falls to 66,4% (3-year survival: 77,5%). The difference of developing a regional recurrence 'late' versus 'early' is illustrated by comparing figure 5 and 6. A regional recurrence within 1 year after diagnosis drops the predicted 5-year survival (=6 years after initial treatment) down to 46,8%. The predicted 4-year survival (=5 years after initial treatment) is 53,8% (not shown in figure 6).

Figure 3. The 1-, 2-, 5- and 10-years predicted prognosis of a 60-years old patient with a T3N1M0 SCC of the larynx, treated with surgery and radiotherapy after initial treatment.

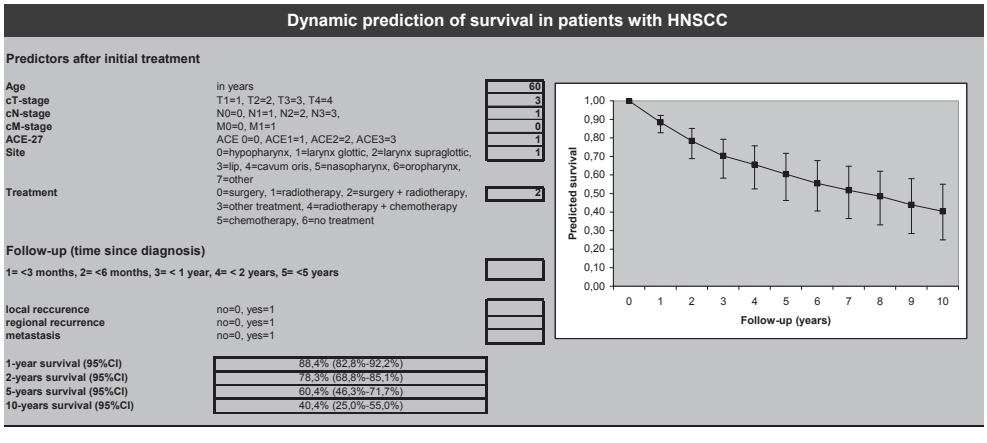


Table 3. Hazard ratio's and 95% Confidence Intervals in various models at different time points.

	HR (t=0)*	95% CI	HR (t=0.25)*	95% CI	HR (t=0.5)*	95% CI	HR (t=1)*	95% CI	HR (t=2)*	95% CI	HR (t=5)*	>95% CI
Age	1.03	1.03-1.04	1.03	1.03-1.04	1.03	1.03-1.04	1.04	1.03-1.04	1.04	1.04-1.05	1.06	1.05-1.07
T-stage (ref:cT1)												
cT2	1.38	1.25-1.52	1.36	1.22-1.50	1.38	1.25-1.52	1.52	1.37-1.66	1.38	1.22-1.55	1.22	1.01-1.43
cT3	1.92	1.75-2.08	1.86	1.702.03	1.74	1.56-1.91	1.77	1.58-1.97	1.18	0.94-1.42	1.10	0.78-1.42
cT4	2.48	2.32-2.64	2.47	2.31-2.64	2.45	2.28-2.61	2.14	1.95-2.33	1.64	1.38-1.89	1.13	0.79-1.48
N-stage (ref:N0)												
cN1	1.42	1.26-1.58	1.37	1.20-1.53	1.39	1.22-1.56	1.32	1.13-1.51	1.31	1.06-1.56	1.03	1.68-1.37
cN2	1.94	1.79-2.08	2.04	1.89-2.19	1.93	1.77-2.09	1.70	1.51-1.89	1.49	1.23-1.75	1.23	0.82-1.63
cN3	2.57	2.36-2.78	2.73	2.51-2.96	2.56	2.32-2.81	1.89	1.57-2.22	1.58	1.12-2.04	0.53	0.00-1.42
M-stage (ref:M0)												
cM1	2.37	2.04-2.69	1.94	1.49-2.38	1.47	0.94-2.00	4.84	3.99-5.68	0.57	0.00-2.59	*	*
ACE 27 score (ref: ACE 27: 0)												
ACE 27: 1	1.22	1.11-1.34	1.18	1.06-1.30	1.18	1.05-1.31	1.11	0.97-1.25	1.09	0.92-1.26	0.98	0.76-1.20
ACE 27: 2	1.39	1.26-1.51	1.44	1.31-1.56	1.39	1.26-1.52	1.38	1.24-1.53	1.73	1.56-1.90	1.64	1.41-1.86
ACE 27: 3	1.68	1.51-1.84	1.71	1.53-1.88	1.72	1.53-1.90	1.44	1.23-1.66	1.64	1.36-1.92	2.40	1.97-2.82
Site (ref: hypopharynx)												
Larynx glottic	0.48	0.28-0.67	0.44	0.24-0.65	0.47	0.25-0.68	0.49	0.26-0.73	0.57	0.26-0.87	0.41	0.00-0.83
Larynx supraglottic	0.64	0.45-0.83	0.63	0.43-0.83	0.62	0.41-0.83	0.64	0.40-0.87	0.81	0.51-1.12	0.67	0.25-1.08
Lip	0.54	0.29-0.79	0.52	0.27-0.78	0.60	0.33-0.87	0.54	0.25-0.83	0.64	0.28-0.99	0.46	0.00-0.93
Oral cavity	0.87	0.68-1.05	0.86	0.67-1.06	0.88	0.67-1.09	0.78	0.54-1.02	0.72	0.40-1.05	0.58	0.12-1.03
Nasopharynx	0.47	0.12-0.83	0.45	0.07-0.82	0.46	0.06-0.85	0.51	0.05-0.96	0.80	0.24-1.36	0.80	0.04-1.57
Oropharynx	0.71	0.53-0.88	0.73	0.54-0.92	0.76	0.56-0.96	0.78	0.55-1.02	0.88	0.57-1.19	0.76	0.32-1.20
Other	0.57	0.34-0.80	0.65	0.41-0.88	0.71	0.45-0.96	0.72	0.43-1.01	0.76	0.18-1.35	0.66	0.16-1.16

table 3 (continued)

	HR (t=0)*	95% CI	HR (t=0.25)*	95% CI	HR (t=0.5)*	95% CI	HR (t=1)*	95% CI	HR (t=2)*	95% CI	HR (t=5)*	>95% CI
Treatment (ref: surgery)												
Radiotherapy	1.16	1.00-1.33	1.33	1.15-1.50	1.39	1.21-1.56	1.13	0.93-1.32	0.98	0.75-1.21	1.00	0.69-1.30
Surgery + radiotherapy	0.73	0.54-0.92	0.8	0.60-0.99	0.95	0.75-1.14	0.90	0.68-1.11	0.89	0.62-1.15	0.99	0.63-1.35
Oth er	0.75	0.31-1.20	0.81	0.36-1.26	0.91	0.43-1.39	0.73	0.22-1.25	0.80	0.15-1.45	1.56	0.71-2.42
Radiotherapy + chemotherapy	0.84	0.57-1.11	0.94	0.66-1.22	1.01	0.72-1.30	1.03	0.70-1.37	0.80	0.34-1.25	0.90	0.12-1.69
Chemotherapy	2.20	1.65-2.76	2.27	1.61-2.92	3.02	2.31-3.72	1.23	0.00-2.48	1.48	0.00-3.50	*	*
No treatment	6.19	5.94-6.45	5.15	4.84-5.46	5.18	4.79-5.57	2.73	2.08-3.39	1.79	0.61-2.96	0.89	0.00-2.90
Follow up												
Local recurrence	*	*	10.84	9.79-11.9	1.78	1.44-2.12	1.55	1.35-1.75	1.34	1.11-1.57	0.97	0.69-1.25
Regional recurrence	*	*	2.14	1.34-2.93	1.75	1.41-2.10	1.76	1.50-2.02	1.48	1.18-1.79	0.93	0.50-1.36
Distant metastasis	*	*	6.99	6.23-7.74	10.5	10.1-11.0	9.37	9.05-8.69	8.88	8.50-9.27	6.84	6.10-7.59

*t=0: model after initial treatment of index tumor, t=0.25: model at 3 months of follow-up, , t=0.5: model at 6 months of follow-up, t=1: model at 1 year of follow-up, t=2: model at 2 years of follow-up , t=5: model at 5 years of follow-up.

Figure 4. The 1-, 2-, 5- and 10-years predicted prognosis of a 60-years old (at time of diagnosis and treatment) patient with a T3N1M0 SCC of the larynx, treated with surgery and radiotherapy, 2 years after the initial treatment.

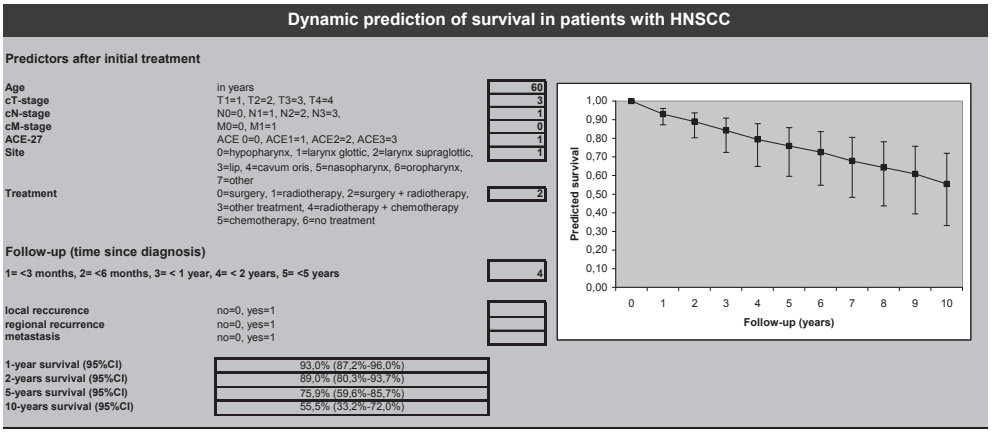
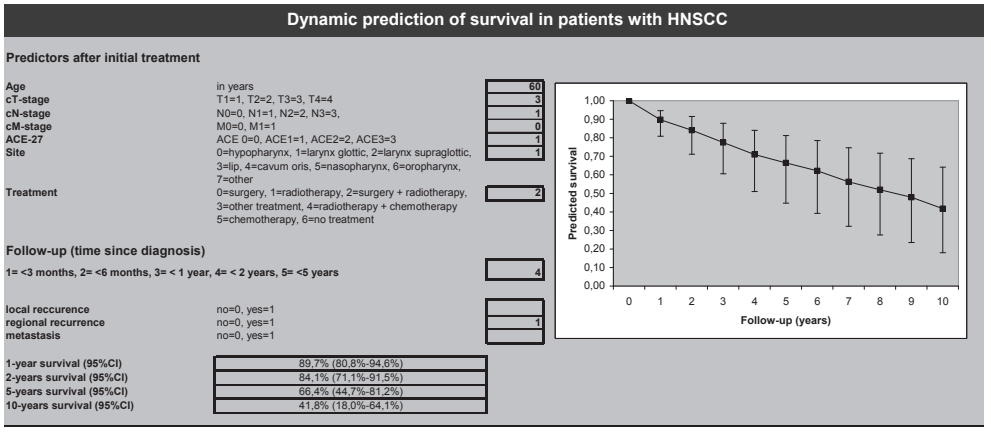
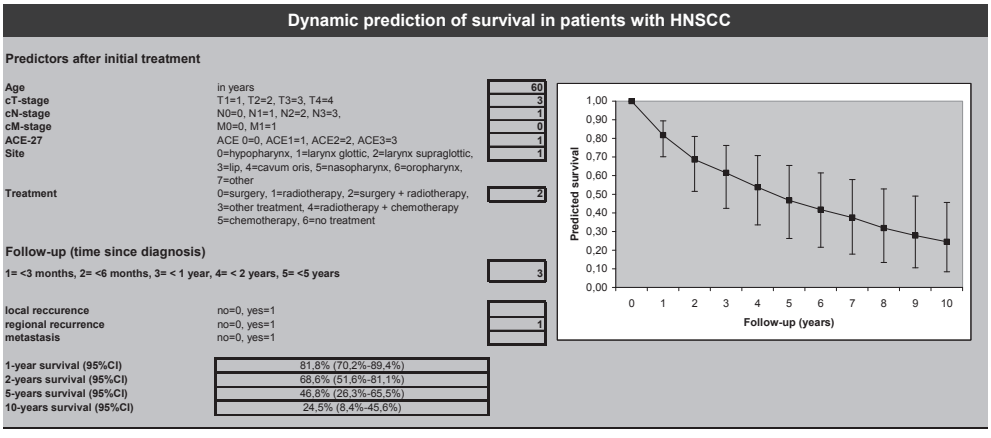


Figure 5. The 1-, 2-, 5- and 10-years predicted prognosis of a 60-years old (at time of diagnosis and treatment) patient with a T3N1M0 SCC of the larynx, treated with surgery and radiotherapy, 2 years after the initial treatment with development of a regional recurrence.



The successive models showed decreasing discriminative performances. In the first model, after initial treatment, the c-statistic was 0.76, indicating moderate discriminative performance. The model at 5-years after diagnosis showed a c-statistic of 0.69. We found little difference in the c-statistic after using bootstrapping techniques, hardly any optimism was found. The expected shrinkage was 0.96, indicating that only about 0.04 of the model fit can be considered as noise. A calibration plot with observed versus predicted 12 months survival of this initial model, shows reasonable fit (Figure 4).

Figure 6. The 1-, 2-, 5- and 10-years predicted prognosis of a 60-years old (at time of diagnosis and treatment) patient with a T3N1M0 SCC of the larynx, treated with surgery and radiotherapy, 1 year after the initial treatment with development of a regional recurrence.



Discussion

Prognostic factors occurring during follow-up after initial treatment are generally not integrated in prognostic models. We showed that incorporating these changeable factors, such as surviving the first critical years, developing age or the presence of recurrence or metastasis indeed have a tremendous effect in the prognosis of an individual patient with HNSCC.

Besides TNM-classification, prognosis is also dependent on factors such as prior malignancies[12], comorbidity[2,13-15], perinodal spread[16] and for example age[17-19]. More recently, also molecular prognostic factors were found, such as: vascular endothelial growth factor[20]. This is thought to cause angiogenesis, presumably an important biological process in cancer. Prognostic factors on the molecular level in general are subject to intensive study[21-31], the independent effect on survival is however not clear. These results are nonetheless promising and genetic aberrations in HNSCC's will probably prove to be useful independent prognostic factors. This field of study could complement existing prognostic models especially when using high-resolution genetic analysis techniques such as micro array technology. However availability and costs might hamper widespread usage in prognostic models. Therefore we choose to focus our prognostic models using only clinically available covariables, rather then to incorporate these promising but difficult to obtain factors such as vascular endothelial growth factor. For univariate and multivariate analysis we used sex, age, T-status, N-status, M-status, site, degree of differentiation, treatment and comorbidity. Our overall 5-year survival of 50.2% is in agreement with most reported survival rates in HNSCC.

Prognostic models in which various prognostic factors are combined are scarce in HNSCC literature. In general, multivariate analyses are done to demonstrate independent effects of the factors under study. In such cases it is possible to calculate a risk score by combining the reported patient and tumor characteristics with the given regression coefficients, but interpretation is difficult. We know of only one presented model in which these factors are integrated in dedicated software, published in 2001.[12] In other fields of cancer research models are more frequently presented.[32-36]

A prognosis is not static. During follow-up there are various factors that might change from the situation at diagnosis, the easiest example being age. All prognostic estimates change when during follow-up a patient develops a tumor recurrence or metastasis. But when the patient remains tumor-free his prognosis will change as well: the prognosis of cancer patients who survive e.g. the first two years will improve. This is caused by the fact that they survived the first critical period. Because most prognostic models are based on patient and tumor characteristics at the time of diagnosis, or after initial treatment, these meaningful events are not taken into account. In this paper we present dynamic models after initial treatment, 3 and 6 months follow-up and 1,2 and 5 years follow-up. We chose to do this stepwise analysis because we wanted to study the effect of changing prognosis when those who die early are excluded from further analysis and to look at the effect of possible events during follow-up. There are two possible problems with this approach. The first is that of power. Because of smaller numbers the variance in successive follow-up models increases. However, because of our large database with ample events we discarded this possible problem. The second concerns the hazard ratio's in the various models. These hazard ratio's are the mean hazard of that particular covariable during the follow-up from that moment in time. It could however be that some covariables behave in a non-proportional way. In particular the short term predictions, e.g. 1-year survival predictions, are thus subject to possible bias. Alternatively one could make just one initial model with time-dependent variables, but in our opinion this would make the results more difficult to interpret.

Besides age, recurrences and metastases, comorbidity is likely to change from the moment of diagnosis. An optimal model would incorporate changing comorbidity scores in case of, for example, a myocardial infarction. We could not use comorbidity other than the comorbidity at diagnosis because of lack of relevant follow-up data. In the future we hope to have better records on comorbidity during follow-up. An alternative method for calculating dynamic predictions on head and neck cancer survival is the usage conditional relative prognosis. We published the results of such an approach which showed the overall conditional relative prognosis (of 7255 patients with a primary HNSCC) to reach a plateau after approximately 4 years; a permanent 20-25% excess mortality (compared to age- and gender-matched counterparts in the general population) for long-term HNSCC survivors remained.[37]

The presented prognostic models are not made or tested for use outside our institution. It is therefore unclear whether our data may be generalized. On the other hand, the prognosis of primary HNSCC's is generally the same in the western world. There is no good reason for recurrences to behave otherwise. We hope this study might offset further investigations into the impact on prognosis of recurrent HNSCC.

In conclusion, dynamic prognostic models, taking into account follow-up time, (local and regional) recurrences, delayed distant metastases and age at moment of follow-up, show us the dynamics of prognosis during follow-up. The presented models enhance our insight into prognostic factors in general and specifically into the effect of recurrences and metastasis. This information could be used for better patient counseling.

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Chapter 7

Prognosis of recurrent head and neck cancer

Marc P. van der Schroeff, Robert J. Baatenburg de Jong

to be published in book 'Management of Recurrent Head and Neck Cancer'

Abstract

Optimal counselling and treatment of patients with recurrent head and neck cancer require an accurate estimate of their prognosis. Patients need up-dated prognostic information to balance the burden of the new treatment against the possible gain in life expectancy and quality of life. Recurrence rates depend on initial tumor stage, localisation, histological markers, treatment and bio- and genomic-markers. The occurrence and timing of recurrences influence prognosis heavily. Dynamic, multivariate prognostic models could offer accurate and individualized estimates of prognosis in recurrent disease.

Introduction

Optimal counselling and treatment of patients with recurrent head and neck cancer require an accurate estimate of their prognosis. Patients need up-dated prognostic information to balance the burden of the new treatment against the possible gain in life expectancy and quality of life. In addition, they need to re-organize their lives and to adapt to the new situation. As clinicians we need prognostic information to assist our patients in these important decisions. In primary head and neck cancer, a lot of research is devoted to the identification of prognostic factors, and numerous papers on this subject are published every month. Unfortunately, information on determinants of prognosis in recurrent cancer is scarce. In this chapter we aim to present an overview of available information on this topic. In addition, we will present an instrument to integrate available information and their corresponding hazard ratios into an individualized prognosis for the patient with recurrent cancer.

Head and neck squamous cell carcinoma (HNSCC) invades locally and tends to metastasize to regional lymph nodes. Locoregional control is paramount in the optimisation of disease-free and overall survival. In order to improve local and regional control in early-stage and locally advanced HNSCC, new treatment modalities have been developed and implemented. In recent years, e.g. laser surgery, intensity-modulated radiation therapy (IMRT), chemoradiation and biologicals were introduced. These changes in treatment modalities make recurrence-rates over longer periods of time difficult to interpret. However, in general 15 to 50 percent of all HNSCC patients will recur.[1-6] Recurrence rates depend on initial tumor stage, localisation, histological markers and treatment. In addition, tumor-volume, bio- and genomic-markers (such as DNA copy number variation and loss of heterozygosity) have been shown to be associated with recurrence of HNSCC.[7-9] Up to 50 percent of the patients who die from HNSCC have locoregionally recurrent disease as the sole site of failure.[10] Treatment options for locally recurrent disease are of course dependent on the extent of disease and previous treatment.

Impact on prognosis

Prognosis in head and neck cancer, but also in cancer generally, is based on characteristics known at the time of diagnosis. However, the prognosis is not static. During follow-up there are various factors that might change from the situation at diagnosis, such as age (obviously patients get older during follow-up), developing comorbidity (especially in comorbidity prone patients such as head and neck cancer patients) and the occurrence of recurrences. Dynamic predictions of head and neck cancer survival can be done using conditional relative prognosis. We published the results of such an approach which

showed that the overall conditional relative prognosis of 7255 patients with primary HNSCC reached a plateau after approximately 4 years: long term HNSCC survivors exhibited a permanent 20-25% excess mortality (compared to age- and gender-matched counterparts in the general population).[11]

Table 1. cohort characteristics.

	Cohort (n=2927)	Recurrence (n=838)	KM-estimate* 5-years	no recurrence (n=2089)	KM-estimate* 5-years
gender (n,%)					
female	707 (24)	199 (24)	30.0%	508 (24)	57.8%
male	2220 (76)	639 (76)	30.2%	1581 (76)	60.0%
age (mean, in years)	63	61		64	
localisation (n,%)					
larynx, glottic	769 (26)	182 (22)	48.6%	587 (28)	74.1%
larynx, supraglottic	351 (12)	110 (13)	34.2%	241 (11)	52.2%
hypopharynx	269 (9.2)	99 (12)	9.80%	170 (8.1)	38.6%
oropharynx	501 (17)	146 (17)	16.0%	355 (17)	48.3%
nasopharynx	73 (2.5)	21 (2.5)	21.5%	52 (2.5)	67.0%
oral cavity	557 (19)	190 (23)	25.3%	367 (18)	52.0%
lip	224 (7.7)	31 (3.7)	62.8%	193 (9.2)	72.4%
other	183 (6.3)	59 (7.0)	24.7%	124 (5.9)	50.5%
initial treatment					
surgery	550 (19)	127 (15)	41.3%	423 (20)	66.4%
radiotherapy	1362 (46)	398 (47)	37.6%	964 (46)	61.3%
surgery with radiotherapy	636 (22)	219 (26)	14.6%	417 (20)	67.2%
radiotherapy with chemotherapy	186 (6.4)	65 (7.8)	21.4%	121 (5.8)	46.5%
chemotherapy	19 (0.6)	9 (1.1)	-	10 (0.5)	-
other treatments	174 (5.9)	13 (1.6)	-	154 (7.4)	70.6%
time to local recurrence (mean, in months)		29			
time to regional recurrence (mean, in months)		47			
time to distant recurrence (mean, in months)		57			

*Kaplan-Meier estimate: cumulative proportion surviving 5 years respectively

The single most important event during follow-up is the occurrence and timing of local, regional or distant recurrence. It is common knowledge that these adverse events greatly influence prognosis.[12] Little is published about the effect on actual survival and the natural course of recurrent head and neck cancer. Obviously, a study on the natural course of recurrent disease is unethical if treatment is considered beneficiary. Most studies examine the effect of (novel) cytotoxic agents or salvage surgery. Effectiveness differs with patient selection (eg. previous treatment, tumor localization). In 2000, Goodwin published a meta-analysis on salvage surgery in recurrent HNSCC.[13] It contained 32 published reports with 1,080 patients from 28 different institutions. The weighted average of 5-year survival was 39%. No comparison can be made with a group of patients who refused treatment and therefore serve as a reflection of natural history. Goodwin also reported on a prospective review of 109 consecutive patients undergoing salvage surgery for the treatment of recurrent squamous cell carcinoma of the upper aerodigestive tract.[14] Survival time was strongly dependent on the TNM stage of recurrent disease at the time of surgical salvage and weakly dependent on the site of disease. An (yet unpublished) analysis of our own patients data is in line with the data published by Goodwin (table 1). Our database consists of 2927 consecutive patients with a primary HNSCC, diagnosed between January 1980 and November 2006. Follow-up ranged from 0 to 319 months, with a median of 34 months. Overall 5-year survival was 50.2%. The number of recurrences and metastases during follow-up was 1087 (37.1%), occurring in 838 patients (table 1). Glottic and oral cancer were associated with the highest incidence of recurrence, 22 and 23% respectively. Interestingly, chances of surviving a recurrence of glottic cancer was nearly 50%, which is favorable compared to all other subsites, except recurrence of lip cancer. Five-year survival rate for a recurrence of lip cancer was as high as 62.8%. These results are probably biased by treatment of the primary tumor: Both early glottic and lip cancer may be treated by irradiation or limited surgery providing the possibility of salvage treatment. Other subsites are more likely to have received multimodality treatment with limited possibilities for salvage treatment. Indeed, in our series of patients, 5 year survival rates of patients treated with single modality compared favorably with patients treated with a combination of radiation and surgery or radiation and chemotherapy (figure 1). In local recurrence, other predictors of survival, e.g. tumor size and age, may play a role too (figure 2 and 3). Treatment of the index tumor, not the recurrence, influences treatment options when diagnosed with a recurrence. These univariate survival analyses after the diagnosis of recurrence produce probable, but no definite, predictors of length of survival. Multivariate analysis would account for confounders but requires larger numbers of patients. Salvage rates are shown in table 2.

Figure 1. Univariate survival analysis (Kaplan Meier) on therapy, after occurrence of local recurrence

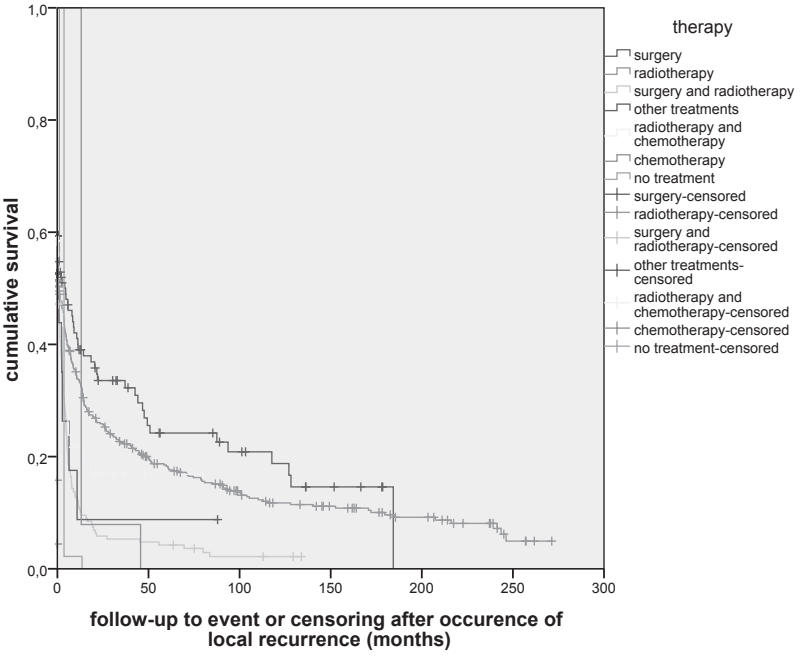


Figure 2. Univariate survival analysis (Kaplan Meier) on T-stage, after occurrence of local recurrence.

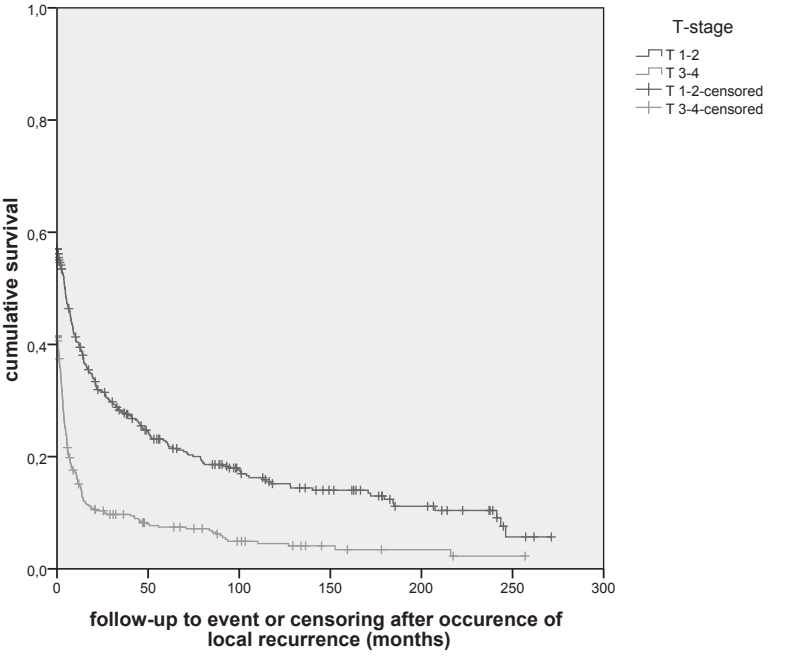


Figure 3. Univariate survival analysis (Kaplan Meier) on age, after occurrence of local recurrence.

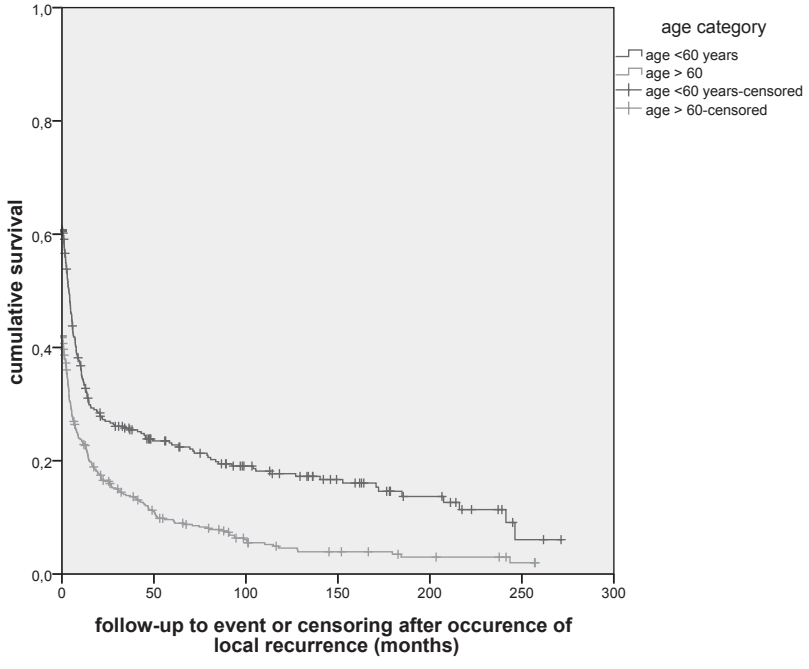


Table 2. salvage rates.

	1 year survival	2 years survival	5 years survival
local recurrence	54%	41%	29%
regional recurrence	38%	27%	14%
locoregional recurrence	41%	25%	12%
distant metastasis	13%	4.3%	1.8%

Timing and time-dependent effects

In addition to the occurrence of recurrent cancer, its timing is of prognostic importance. Approximately 80 to 90 percent of all recurrences will occur within the first two to four years after curative intent treatment.[15,16] In general the prognosis for a group of HNSCC patients improves after surviving the first few critical years after treatment of the index tumor. This is caused by the fact that patients with a very poor prognosis, possibly in the more advanced stages of the disease, die early, leaving those with relatively favorable prognosis.[11] At an individual level, early failures of control might reflect a more aggressive index tumor. In table 1, the mean time to recurrence is shown for our cohort: 29 months for

a local, 47 months for a regional and 57 months for a recurrence at a distant site. Figure 4 shows the distribution of occurrences during follow-up. A steep curve is seen up to 1 year after treatment of the index tumor and is then followed by a gradual decline afterwards.

We performed a period analysis in which we studied those patients who had a recurrence and the predictors of length of survival after this diagnosis. Figure 5 displays the effect on predicted survival of a locoregional or distant recurrence, the first showing a better prognosis. In figure 6, the difference in effect on survival between an early versus late local recurrence is illustrated, the latter showing better prognosis.

Figure 5. Univariate survival analysis (Kaplan Meier) on type of recurrence.

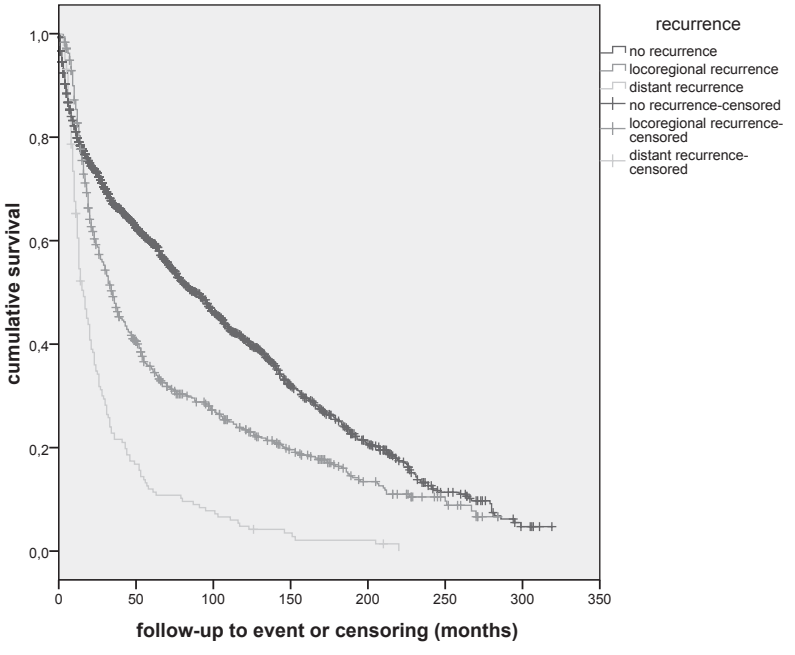
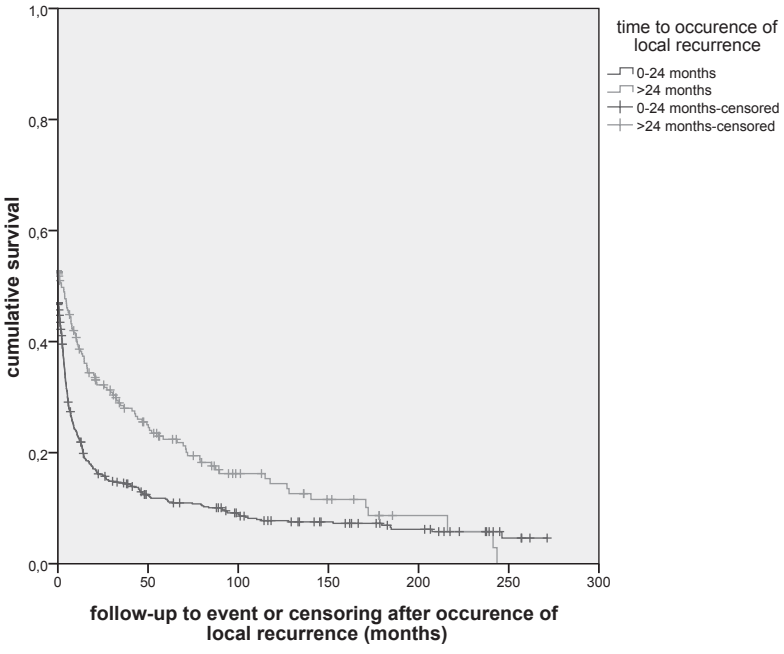


Figure 6. Univariate survival analysis (Kaplan Meier) on timing of recurrence.



Individualized prognosis in recurrent HNSCC

A predictive model based on a multivariate analysis using the Cox proportional hazards model was build. In order to investigate follow-up time dependent effects and to incorporate local and regional recurrences as well as delayed distant metastases we produced further follow-up models at different time points after initial diagnosis and treatment.[17] This stepwise approach allows for dynamic predictions taking into account only those patients still alive at certain time points, the progression of age and the occurrence of locoregional and distant recurrences. The final models were incorporated into a desktop interface (figure 7-10) For example: a 65 years old patient with a T2N0M0 glottic laryngeal carcinoma treated with radiotherapy and known with mild comorbidity (ACE-27[18] score 1) has an estimated 5 years overall survival of 62.7% (95% confidence intervals 50.3%-72.5%). When still alive after 2 years of follow-up the predicted 5-years overall survival increases to 68.9% (95% confidence intervals 52.0%-80.5%). This improved predicted prognosis is caused by the survival of the first two critical years. On the other hand, the effect is muted by advancing age. If a regional recurrence has occurred after 2 years of follow-up, the estimated 5-years overall survival drops to 56.0% (95% confidence intervals 34.5%-73.7%). If this particular patient had have experienced an early recurrence (for example within 3 months) the predicted 5-years overall would be even worse (42.5%). The broad 95% confidence intervals indicate uncertainty of estimation, a question of power.

Figure 7. Desktop interface showing survival estimates for a 65 years old patient with mild comorbidity and a T2N0M0 glottic carcinoma treated with radiotherapy. No follow up data at this point in time.

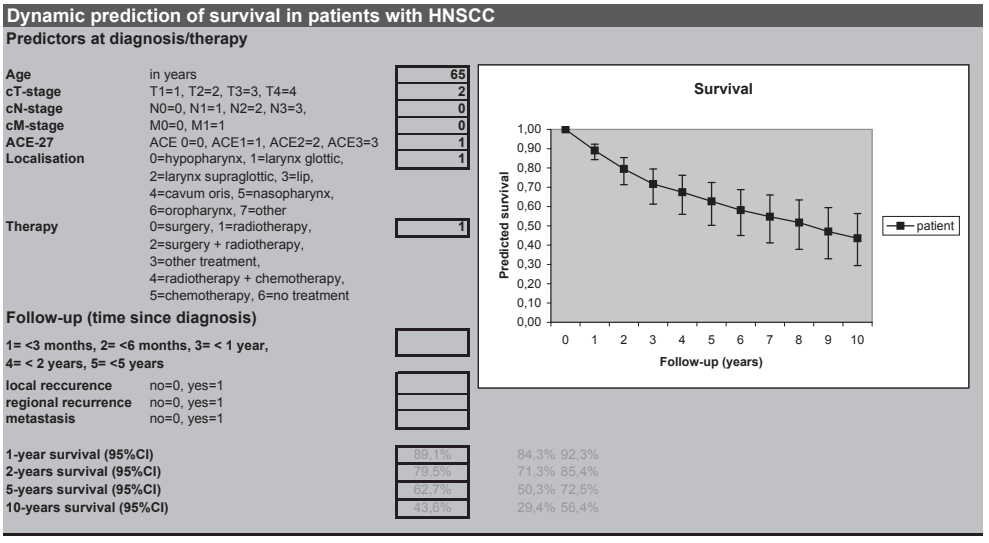


Figure 8. Desktop interface showing survival estimates for a 65 years old patient with mild comorbidity and a T2N0M0 glottic carcinoma treated with radiotherapy. No recurrence up to 2 years of follow up.

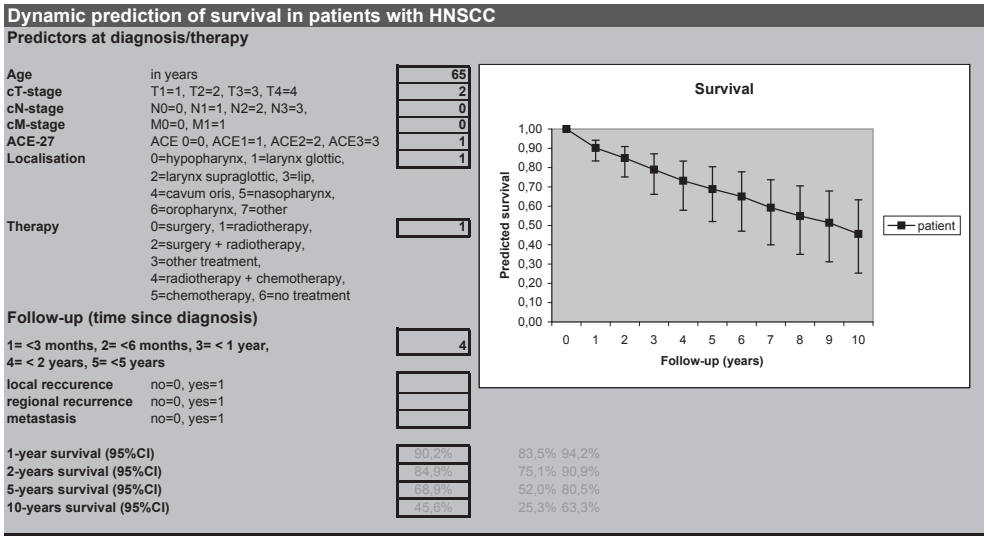


Figure 9. Desktop interface showing survival estimates for a 65 years old patient with mild comorbidity, a T2N0M0 glottic carcinoma, treated with radiotherapy and a regional recurrence within 2 years of follow up.

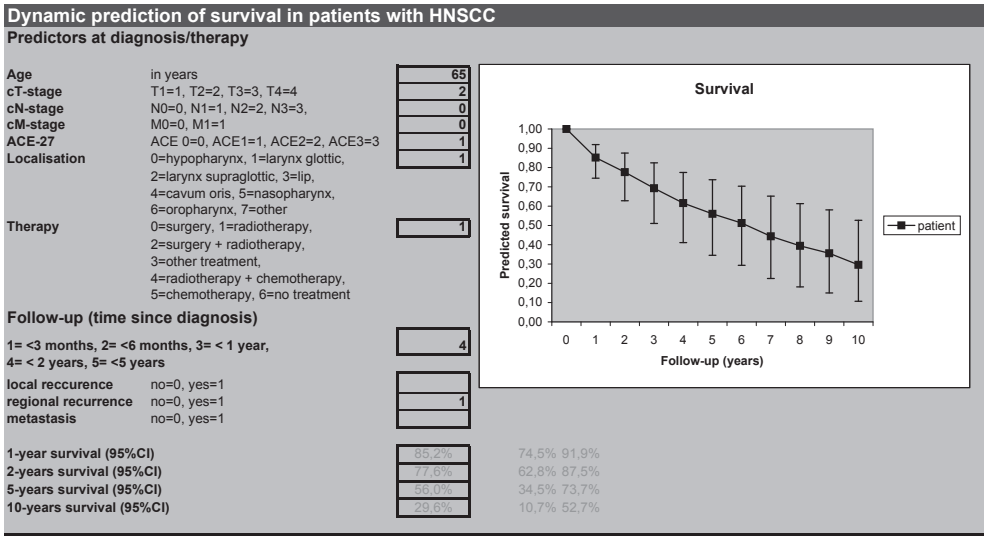
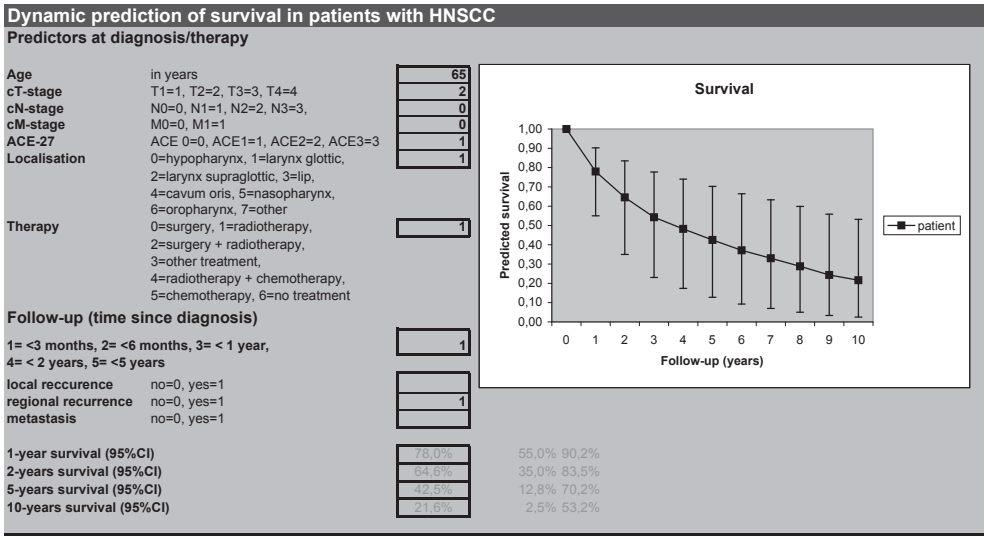


Figure 10. Desktop interface showing survival estimates for a 65 years old patient with mild comorbidity, a T2N0M0 glottic carcinoma treated with radiotherapy and a regional recurrence within 3 months of follow up.



Routine follow-up and recurrent disease

A Norwegian study on recurrence-rates during follow-up showed the overall recurrence "pick-up rate" of 1 recurrence in 36 consultations.[15] This concerned 661 consecutive and previously untreated patients with confirmed squamous cell carcinoma of the head and neck, considered "free of disease" 6 weeks after the completion of the therapy. Ritoe et al. studied the effect of routine follow-up after treatment of laryngeal cancer on life expectancy and mortality.[19] Their simulation model showed only slight gains in life expectancy when discovering recurrences at an asymptomatic stage during routine follow-up compared to no follow-up. The lead time, estimated to be less then two months,[19, 20] produced a gain in life expectancy in the range of 0.3 years to 1.5 years that decreased with advancing age. Routine follow-up seems therefore not very effective in the detection of recurrences. However, a very modest improvement of life expectancy may be expected.

Conclusion

In contrast to primary tumors, prognostic research into recurrences is scarce. Commonly used adages on the detrimental effect of recurrences could benefit from more statistical founding. In general, recurrences worsen prognosis, the earlier the recurrence the worse the prognosis. Dynamic, multivariate prognostic models could offer accurate and individualized estimates of prognosis in recurrent disease.

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Chapter 8

The effect of age on survival and quality of life in elderly head and neck cancer patients: a long-term prospective study

Marc P. van der Schroeff, Wynia Derks,
Gerrit Jan Hordijk, Rob J. de Leeuw

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Abstract

Little is known about long-term treatment outcome of elderly head and neck cancer patients and their quality of life (QOL). One hundred and eighteen older (≥70 years) and 148 younger (45–60 years) patients with head and neck cancer were followed up for 3–6 years. In the long-term follow-up 33 younger and 24 older patients completed the EORTC QLQC30 and H&N35 and a questionnaire about depression. The survival rate after 3–6 years for younger patients was 36%, as compared to 31% in the older patient group. Higher tumour stages, more co-morbidity and non-standard treatment showed to be independent prognostic factors for mortality. No independent prognostic value of age could be found. The global QOL score remains roughly comparable. Even up to 6 years after treatment, we found no significant differences in survival or overall QOL between older and younger head and neck cancer patients.

Introduction

The prolongation of life expectancy results in an increasing number of elderly patients with cancer. Aging is associated with a variety of declining physiological functions and for a long time these older patients were not considered to be good candidates to receive extensive (surgical) treatment. In 1986, the first study documented inadequate cancer treatment in the elderly.[1] Several studies concerning head and neck cancer patients showed that older patients are less likely to receive potentially curative treatment than younger patients.[2-6] Though in many cases an exact reason to treat the elderly patient less intensive is not documented, co-morbidity is thought to be an important factor. Yet, as we recently showed, even the elderly with no or mild co-morbid conditions were less likely to receive standard treatment.[5] However, most studies showed that radical surgical treatment can be performed safely in elderly patients without a significant increase in the overall complication rate, provided there is no severe co-morbidity.[7-9] Besides co-morbidity, surgeons' motives to treat the elderly less intensively can be based on personal opinions about treatment tolerance and complications. Genden et al.[10] recently proposed that it is not uncommon for the patient and the family to refuse surgery. Psychological aspects tend to be neglected although these factors have a significant impact on the course of the disease. It has been suggested that older head and neck cancer patients have a lower overall survival.[3,4,7,11] However, it remains unclear whether this is due to age or co-morbid conditions and less intensive treatment. Co-morbidity is common among head and neck cancer patients and forms an important determinant of survival.[11-16] Remarkably, several studies were not able to show a relationship between age and survival after correction for co-morbidity.[6,14-17] Assumptions on the lack of social support and diminished quality of life (QOL) after treatment could also play a role in determining why surgeons decide to treat elderly patients less intensively.[18] However, several studies showed that age does not influence QOL up to one year after treatment.[18-21] Up to now, little is known about long-term QOL in elderly head and neck cancer patients. This prospective study was designed to evaluate and compare treatment outcome and QOL of older and younger head and neck cancer patients. We have already described the QOL of younger and older patients up to 12 months after diagnosis. At that time no significant differences between both groups were found.[19] In the present study, we describe the results of a follow-up measurement of these patients 3–6 years after diagnosis. This is one of the first long-term prospective studies on survival and QOL in elderly patients with head and neck cancer.

Patients and methods

Patients

Patients aged 70 years or older (referred to as older patients) and patients aged between 45 and 60 years (referred to as younger patients) with newly diagnosed squamous cell carcinoma of the oral cavity (American Joint Committee on Cancer stage > II), oropharynx and hypopharynx (stage > II), or larynx (stage > III) without distant metastasis were eligible for inclusion at the start of this study. These criteria for tumour stage were set, because we wanted to study the effects of major treatment on QOL. During the inclusion period (December 1998–December 2001) 266 patients met these criteria. In total, 105 of 148 (71%) younger and 78 of 118 (66%) older patients agreed to participate in the original QOL-study and were enrolled at the time of diagnosis. Only patients participating in this original QOL-study were asked to participate in the present long-term QOL-study. All 266 patients were followed up in February 2005 (further referred to as 'the long-term follow-up') to get information about survival. We recorded the follow-up medical data of these patients, including death, recurrence, metastases and 2nd primaries. All 266 patients were followed up in February 2005 for gathering information regarding survival. The median follow-up in February 2005 was 56 months (4.7 years), the maximum follow-up was 76 months (6.3 years) and the minimum follow-up 39 months (3.3 years). There was no loss to follow-up. All 266 patients were treated at the University Medical Centre Utrecht, The Netherlands. For each patient a treatment proposal was presented at the weekly multidisciplinary tumour conference. In Utrecht, the standard treatment protocol for head and neck cancer is based on guidelines published by the Comprehensive Cancer Centre of the Middle Netherlands (IKMN). Standard treatment varies from radiotherapy, surgery, and surgery with postoperative radiotherapy to combined chemo/radiotherapy depending on the site and stage of the tumour. Surgical procedures included local excision (transoral resection, partial glossectomy) and extensive procedures (e.g. commando procedure, laryngectomy, partial maxillectomy) with or without neck dissection. Co-morbidity was classified according to the Kaplan–Feinstein index.[22] The original index was modified to incorporate diabetes mellitus and consisted of 13 categories, such as cardio-vascular disease or respiratory disorders. All ailments were rated individually on a 4-point scale (0 = no, 1 = mild, 2 = moderate, 3 = severe co-morbidity). Subsequently, the overall comorbidity index was based on the highest ranked single ailment or, in the case of two grade 2 individual ailments, the overall index was upgraded to grade 3. Within the long-term follow-up period (3–6 years) 62% (66/105) of the younger and 64% (50/78) of the older patients participating in the original QOL-study died. Three younger patients failed to complete the follow-up questionnaires because their condition had deteriorated, and 3 younger and 4 older patients no longer wanted to participate. In total, 33 younger and 24 older patients completed a questionnaire before treatment, at 12 months after the start

of treatment and in the long-term follow-up. The crude compliance rate at 3–6 years was 31% in both age groups. Adjusted for death, this compliance rate was 85% in the younger and 86% in the older group. The patient characteristics of the total eligible cohort and the long-term QOL-study cohort are shown in Table 1. Tumour site, tumour stage, the severity of co-morbid conditions and the type of treatment differed significantly between the age groups in the total cohort. Within the long-term QOL-study there are no significant differences regarding these variables.

Table 1. Baseline characteristics of the total patient cohort and the characteristics of the older and younger patients participating in the long-term (3–6 years) QOL-study.

	Total cohort			Long-term QOL-study[a]		
	45-60 years (n=148)	≥70 years (n=118)	P(χ^2 test)	45-60 years (n=33)	≥70 years (n=24)	P(χ^2 test)
Gender						
Male	109 (72%)	72 (61%)	0.06	28 (85%)	16 (67%)	0.11
Female	43 (28%)	46 (39%)		5 (15%)	8 (33%)	
Tumor site						
Oral cavity	56 (37%)	58 (49%)	<0.01	17 (52%)	12 (50%)	0.20
Pharynx (oro/hypopharynx)	81 (53%)	31 (26%)		12 (36%)	5 (21%)	
Larynx	15 (10%)	29 (25%)		4 (12%)	7 (29%)	
Stage (AJCC)						
II	26 (17%)	30 (26%)	0.04	12 (36%)	8 (33%)	0.11
III	29 (19%)	31 (26%)		6 (18%)	10 (42%)	
IV	97 (64%)	57 (48%)		15 (46%)	6 (25%)	
Co-morbidity						
No	48 (32%)	30 (26%)	<0.01	14 (42%)	10 (42%)	0.41
Mild	71 (47%)	33 (28%)		17 (52%)	10 (42%)	
Moderate	26 (17%)	43 (36%)		2 (6%)	4 (16%)	
Severe	7 (4%)	12 (10%)		-	-	
Standard treatment						
Yes	132 (87%)	73 (62%)	<0.01	31 (94%)	23 (96%)	0.75
No	20 (13%)	45 (38%)		2 (6%)	1 (4%)	
Treatment						
No treatment	10 (7%)	16 (14%)	<0.01	-	-	0.26
Surgery + RT	80 (53%)	34 (29%)		20 (61%)	10 (42%)	
Surgery	14 (9%)	38 (32%)		7 (21%)	7 (29%)	
RT	16 (10%)	27 (23%)		3 (9%)	6 (25%)	
Chemotherapy + RT	32 (21%)	3 (2%)		3 (9%)	1 (4%)	

RT: radiotherapy. a: patients alive and willing to participate in the present QOL-study, 3–6 years after diagnosis.

Questionnaires

QOL was measured with the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ-C30).[23] This is a general cancer-specific questionnaire consisting of 30 items grouped into five functional scales (physical, role, cognitive, emotional, and social functioning), three symptom scales (fatigue, pain, nausea/vomiting), a global quality-of-life-scale, and six single questions (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The EORTC Head and Neck Cancer Quality of Life Questionnaire (H&N35)[24], which was designed for use in combination with the QLQ-C30 questionnaire, consists of six symptom scales (pain, swallowing, senses, speech, social eating, and social contacts) and six single items (teeth problems, problems opening the mouth, dry mouth, sticky saliva, cough, and feeling ill). In the present study, only results of the functioning and symptom subscales of the QLQ-C30 and QLQ-H&N35 questionnaires are presented. The scores are linearly transformed into a score from 0 to 100. A high score for a functional scale and for the global QOL scale represents a better level of functioning, while a high score for a symptom scale or a single-item scale denotes a high level of symptoms/problems. Depressive symptoms were measured with the Centre for Epidemiological Studies Depression Scale(CES-D)[25]. This is a questionnaire of 20 items developed to measure depressive symptoms in the general population. A high score reflects a high level of depressive symptoms. A score of ≥16 is an indication for a clinical depression. The questionnaires were extended with two questions concerning the impact of the disease and treatment on daily life. We asked whether their illness preoccupied them and whether they would make the same treatment choice again.

Statistical analysis

Data were analyzed with the statistical package SPSS 12.0 for Windows. The survival analysis is based on all 266 eligible patients. The QOL-analysis is based on 57 patients who completed all questionnaires. Chi-square tests were performed to compare diVerences in categorical data between the older and younger patients, and non-parametric Mann–Whitney test were used to compare continuous data. Statistical significance was assumed when $P \leq 0.05$ was achieved. Cox regression analysis was performed to detect whether tumor stage, co-morbidity, standard treatment and age group were predictive of mortality.

Table 2. 3–6 years survival in relation to the patients characteristics at baseline.

	45-60 years (n=148)			≥70 years (n=118)		
	Dead (n=94)	Alive (n=54)	P(χ^2 test)	Dead (n=81)	Alive (n=37)	P(χ^2 test)
Tumor site						
Oral cavity	32 (57%)	24 (43%)	0.21	39 (67%)	19 (33%)	0.94
Pharynx (oro/hypopharynx)	54 (70%)	23 (30%)		22 (71%)	9 (29%)	
Larynx	8 (53%)	7 (47%)		20 (69%)	9 (31%)	
Stage (AJCC)						
II	9 (35%)	17 (65%)	<0.01	14 (47%)	16 (53%)	<0.01
III	19 (65%)	10 (35%)		18 (58%)	13 (42%)	
IV	66 (71%)	27 (29%)		49 (86%)	8 (14%)	
Co-morbidity						
No	25 (53%)	22 (47%)	0.09	14 (47%)	16 (53%)	<0.01
Mild	46 (65%)	25 (35%)		20 (61%)	13 (39%)	
Moderate	16 (70%)	7 (30%)		35 (81%)	8 (19%)	
Severe	7 (100%)	-		12 (100%)	-	
Standard treatment						
Yes	82 (62%)	50 (38%)	0.31	42 (56%)	32 (44%)	<0.01
No	12 (75%)	4 (25%)		40 (89%)	6 (11%)	
Tumor follow-up						
No tumor	11 (20%)	43 (80%)	<0.01	23 (46%)	27 (54%)	<0.01
Recurrence, progression or metastases	70 (96%)	3 (4%)		48 (89%)	6 (11%)	
2nd primary	13 (62%)	8 (38%)		9 (69%)	4 (31%)	

Results

Three to six years after diagnosis the survival rate did not differ significantly between the two age groups. The survival rate for the younger patients was 36% (54/148), as compared to 31% (37/118) in the older patient group ($P = 0.38$). Most patients died within the first two years after diagnosis (Figure 1). Tumour-stage was a significant prognostic factor for mortality for the younger as well as for the elderly patients (Table 2). Co-morbidity, according to the Kaplan–Feinstein index, was a significant prognostic factor for mortality solely for older patients; e.g. 81% of the older patients with a moderate co-morbidity died compared to 47% of the older patients without comorbidity. In the older age group, where 40 of the 45 patients not treated according to the treatment protocol died, deviation of standard treatment was a significant prognostic factor for mortality. In the younger patient

group 75% of the patients who were not treated according to protocol died, compared to 62% of the patients who were given standard treatment. During the 3–6 years follow-up a substantial number of patients developed progression or recurrence of the primary tumour, metastases or a 2nd primary. These events were a significant prognostic factor for mortality. Older patients more frequently died without tumour; 46% of the deceased older patients died without tumour compared to 20% in the younger age group. A Cox regression analysis of the entire cohort showed higher tumour stages, more co-morbidity and non-standard treatment to be independent prognostic factors for mortality. No independent prognostic value of age could be found. Table 3 shows the mean scores of the symptom and functioning scales of the QLQ-C30 and H&N35 questionnaires at baseline,12 months after treatment and at long-term follow-up. These results refer to the 57 patients who completed all questionnaires. At 12 months after treatment and in the long-term follow-up, 3–6 years after diagnosis, the older patients scored significantly worse on physical functioning, swallowing and speech. Throughout the follow-up the global quality of life score remains roughly comparable between the age groups. The mean CES-D scores of participating patients in the present QOL-study, before treatment, at 1 year after treatment and in the long-term follow-up, and the proportion of patients with a score ≥16, did not differ significantly between the older and younger patients (Table 3). The longitudinal relationship between the variables physical functioning, global quality of life, swallowing and speech are shown in Figure 2. These figures are based on data collected from participating patients in the QOL-study who completed all five questionnaires (n = 57). The two additional questions revealed that after 3–6 years 90% of younger patients would once again choose the same way of treatment, compared to 65% in the older age group. At one year after diagnosis these percentages for those who survived up to the long-term follow-up were 90 and 94%, respectively. There were no significant differences in the way their illness preoccupied the two age groups.

Figure 1. Survival analysis of 148 younger (45–60 years) and 118 older (≥70 years) patients

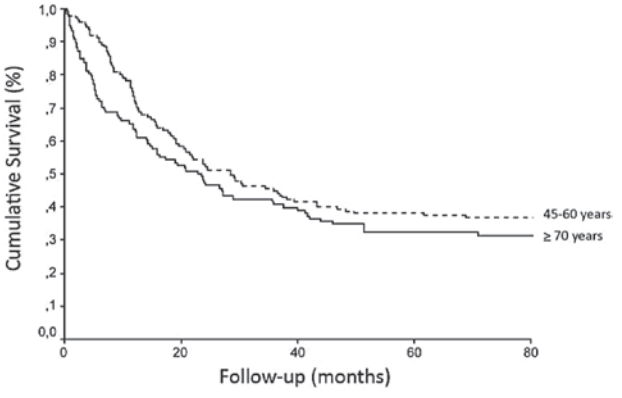


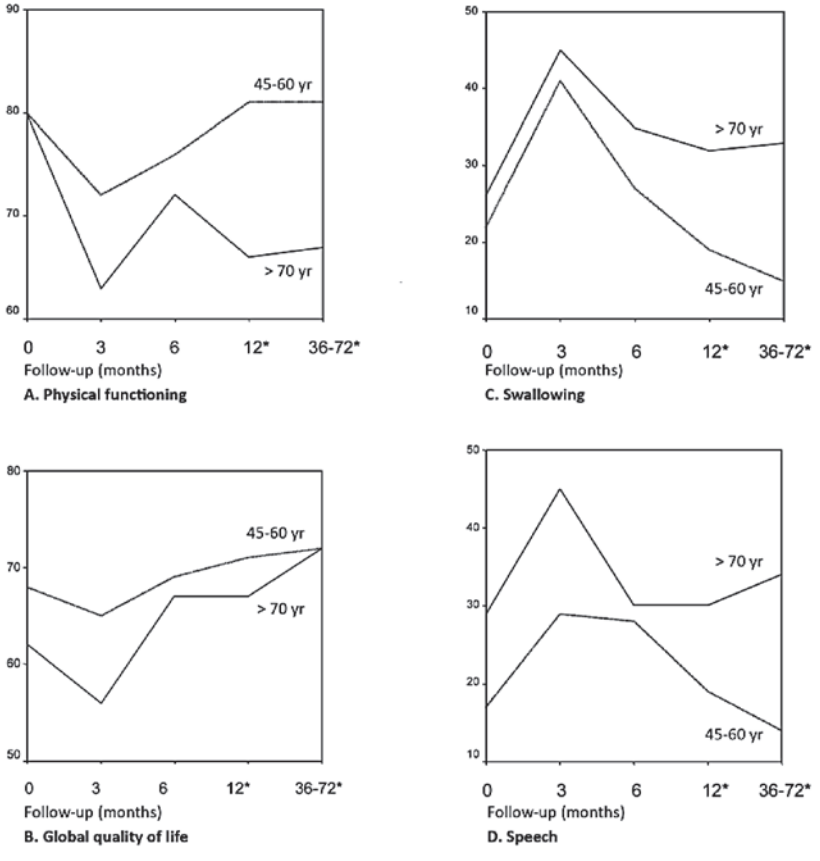
Table 3. Comparison of mean scores of quality of life for participating older (*n* = 24) and younger patients (*n* = 33) before and 12 months after treatment and at long-term follow-up (3–6 years)

	Baseline		12 months		3-6 years FU	
	45-60 years	≥70 years	45-60 years	≥70 years	45-60 years	≥70 years
EORTC QLQ-C30						
Functioning scales						
Physical functioning	80	80	81	66*	81	67*
Social functioning	84	83	85	83	89	79
Role functioning	78	78	73	70	78	69
Emotional functioning	67	69	77	77	78	82
Cognitive functioning	87	79	81	78	87	78
Global quality of life	69	62	70	67	72	72
Symptom scales						
Fatigue	28	26	30	35	25	35
Nausea and vomiting	7	4	6	4	4	6
Pain	27	24	21	20	16	17
EORTC H&N35[a]						
Symptom scales						
Social eating	16	22	23	43*	18	37
Social contact	4	10	8	17	9	23
Pain	34	34	20	25	18	20
Swallowing	22	26	19	32*	15	33*
Senses (taste/smell)	9	16	25	34	24	28
Speech	17	29	19	30*	14	34*
CES-D						
Mean score	12	13	12	14	11	14
% ≥16[b]	21%	29%	30%	43%	23%	30%

Nonparametric Mann–Whitney test. a: a high score for functioning scales and the global QOL scale represents a higher level of function, whereas a high score for a symptom scale represents more problems. b: X^2 test; no significant differences

**P ≤ 0.05*

Figure 2. Longitudinal scores for patients completing the study (33 younger and 24 older patients) for selected scales and single items from the EORTC QLQ-C30 and QLQ-H&N35. The assessment points shown are at diagnosis, 3 months, 6 months, 12 months and 3–6 years follow-up.



**P ≤ 0.05; Nonparametric Mann–Whitney test*

Discussion

Though there is cumulative evidence that age is not a limiting factor for treatment, there is lack of evidence on long-term survival and QOL in the elderly treated for head and neck cancer to support this statement. This is one of the first long-term prospective studies on survival and QOL in elderly people. Our follow-up data showed a 3–6 years overall survival rate of only 34%. One must bear in mind that this figure concerns both younger and older patients with higher stages of head and neck cancer. There was no significant difference in survival between older and younger patients. This in contrast to some retrospective studies which have reported that overall survival is much lower in older than in younger

patients with head and neck cancer.[3,4,7] However, others have found that differences in the death rate are due to co-morbid conditions and not due to age.[14,15,17,26-28] In a case-control study by Bhattacharyya, 2,508 cases of squamous cell carcinoma of the larynx, tongue and tonsil in patients older then 70 years and 2,508 controls (50–69 years of age) were extracted from the Surveillance, Epidemiology and End Results (SEER) database.[29] These controls were randomly matched for gender, year of diagnosis, cancer stage, extent of surgery and radiation therapy. Survival analysis showed no significant cancer-specific differences except for stage I and IV glottic tumours. We found that co-morbidity was a significant prognostic factor in the older age group. This seems to be associated with a large number of older patients with intercurrent non-cancer related deaths. Younger patients more frequently died as a result of the tumour. This is in concordance with the differences in tumour stage at baseline; 64% of younger patient had a tumour stage IV, compared to 48% of older patients. Tumour stage was a significant prognostic factor for survival in both age groups. Elderly patients often receive less intensive treatment, and this can affect the survival rate. Our study showed that receiving non-standard treatment was a significant prognostic factor in the older age group. Eighty-nine percent of elderly patients not treated according to the treatment protocol died. A few publications have reported that if older patients receive standard treatment, the survival rate, adjusted for deaths due to causes other than cancer, is similar in older and younger patients.[27-29] In this prospective study, we found no significant differences in survival, even without correction for standard treatment. Though the majority of the QLQ-C30 scores did not differ significantly between the two age groups, there was a pattern of poorer physical functioning in elderly patients. At the long-term follow-up the older patients scored significantly worse on swallowing and speech. This might be the result of poorer physical health and revalidation in the elderly. Our results show no difference in depressive symptoms between the two age groups 3–6 years after the start of treatment. Our results are comparable with a prospective study with 107 patients on the quality of life in patients with head and neck cancer by de Graeff et al.[30], in which the only significant difference between patients younger and older than 60 years was on psychical functioning. In reaction to the question whether, 3–6 years after diagnosis, patients would make the same treatment choice again, 65% of the elderly patients responded positively. This in contrast to 90% of the younger age group, and in remarkable contrast to the results at one year after diagnosis, when 94% of the elderly patients who survived up to the long-term follow-up responded positively. A large group of elderly long-term survivors changed their way of thinking about the treatment. This might also be associated with the fact that elderly people are often very aware of the inevitability of the deterioration of their quality of life. When we compare the results of this study with earlier publications on survival en QOL 1 year after diagnosis[19], there are some remarkable differences in the QOL-scores. These differences however are

probably caused by selection of those who survive up to our long-term follow-up. While in the original cohort a significant difference in physical functioning between the age groups was found at baseline, the older and younger patients participating in the long-term follow-up study had the same mean score on physical functioning at that time. In conclusion, even up to 6 years after the start of treatment for head and neck cancer, we found no significant differences in survival, general quality of life or depressive symptoms between older and younger head and neck cancer patients. At long-term follow-up the elderly patients scored significantly worse on physical functioning, and they experienced more problems with swallowing and speech. Therefore more attention should be paid to swallowing and speech revalidation in the elderly age group. Nonetheless, according to these results, there seems to be no reason to treat elderly patients differently from younger patients if no severe comorbid conditions exist. This seems to be in concordance with recent reviews by Bernardi et al.[6] and Genden et al.[10] in which they compare head and neck cancer treatment modalities and outcome between younger and older patients. The choice of treatment should always be based on a thorough medical assessment and the preferences of the patient, and not on chronological age. Elderly patients like patients of any age, need full information concerning their disease and its potential treatment, and they need to participate in the decision making process. In our study, a relatively large group of elderly long-term survivors however, wouldn't make the same treatment choice again. This asks for further investigation about the reasons why.

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chapter 6

Survival of palliative head and neck cancer patients

Quirine C.P. Ledeboer, Marc P. van der Schroeff,
Jean F.A. Pruyn, Maarten F. de Boer,
Robert J. Baatenburg de Jong,
Lilly-Ann van der Velden

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Abstract

The purpose of this study was to describe patient characteristics and prognostic factors for survival in the palliative stage of patients with head and neck cancer. Since November 2003, all patients with palliative head and neck cancer treated in our hospital have been recorded in a central database. In total, 262 deceased patients were included in this retrospective study. The reasons for palliation were inoperability, distant metastases, refusal of curative treatment, or poor condition. The mean palliative phase lasted 5.3 months for patients with squamous cell carcinomas. Involvement of a specialized nurse was significantly related with the number of admissions and place of dying. Multivariate analysis showed comorbidity and treatment to be independent predictors of survival in the palliative phase. Comorbidity and palliative interventions are possible prognostic factors for survival. The involvement of a specialized nurse might be associated with an improved quality of life.

Introduction

Palliative care is defined by the World Health Organization as "an approach that is aimed at improving the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."[1] In our department, this palliative phase is considered to start at the moment of diagnosis of an incurable head and neck tumor, or rejection of curative treatment, and lasts until death. During this phase, the patient can still undergo treatment aimed at symptom control, such as surgery, radiotherapy, or chemotherapy. Knowledge about the palliative phase of head and neck cancer is limited. An extensive literature search only yielded 6 articles published since September 2003.[2–7] The overall 5-year survival of head and neck cancer is between 34% and 77%, depending on the localization and stage.[8] A large percentage (59%) of these patients die as a consequence of their disease, whereas approximately 18% die due to comorbidity.[9] To reduce physical and psychosocial symptoms in these patients, systematic screening, follow-up, and support are necessary. Multidisciplinary teams are mandatory in the care of patients with head and neck cancer, especially during the palliative phase.[10] Better support can increase the probability that both patient and family will be able to achieve the best possible outcome and quality of life.[4] In studies in the curative setting, survival time seems to be related to improvements in quality of life.[11] In The Netherlands, the incidence of head and neck carcinomas is less than 5% of all malignant tumors. Therefore, the treatment of head and neck cancer is concentrated in academic head and neck centers, because expertise in regional hospitals and in general practice is insufficient.[12] Our Expert Center of Palliative Care for Head and Neck Cancer (hereinafter Expert Center) was set up at the Erasmus Medical Center Rotterdam in 2005. The team consists of head and neck surgeons, specialized nurses, psychologists, speech therapists, a pain team of anesthesiologists, a dietitian, social workers, and clergymen. The objectives of the expert center are to improve symptom control, to improve consultation toward other caregivers in home-based palliative care, create targeted information, and provide structural support of patient, family, and research. A joint clinic was realized with 2 specialized palliative care nurses on a staff of 8 head and neck surgeons. These nurses handle social support, pain management, wound care, information, and consultation.[13] On average, besides having an introductory consultation, the patients were contacted by the nurse every 6 weeks, or more frequently if needed. Within the center, questions were raised about the palliative phase, such as what are the patient characteristics of this group; which factors influence survival time, and does specialized nurse involvement indeed reduce palliative symptoms and admissions. Because most patients prefer to spend the palliative phase at home, we considered admission to be a surrogate marker for quality of life. Patient characteristics

and clinical aspects may be useful in the prediction of survival time per individual palliative patient. These prognoses are essential for better education and support of patient, family, and caregivers. Estimations of life expectancy may also be important to patients, affecting their choices in palliative treatment. The purpose of this retrospective study was to describe the characteristics of the patients with palliative head and neck cancer and to explore which characteristics and other factors (tumor, treatment, laboratory, and quality of life) are related to their survival.

Table 1. Patient and index tumor characteristics (n=262)

Characteristics	No. of patients (%)
Sex	
male	193 (73.7)
female	69 (26.3)
Comorbidity	
ACE 27: 0	76 (29.0)
ACE 27: 1	77 (29.4)
ACE 27: 2	83 (31.7)
ACE 27: 3	25 (9.5)
missing	1 (0.4)
Tumor stage	
stage I	16 (6.1)
stage II	23 (8.8)
stage III	36 (13.7)
stage IV	179 (68.3)
not applicable	8 (3.1)
Histology	
squamous cell carcinoma	235 (89.7)
other	27 (10.3)
Degree of differentiation	
well differentiated	27 (10.3)
moderately	124 (47.3)
poorly	33 (12.6)
undifferentiated	10 (3.8)
unknown (eg. biopsies)	68 (26.0)

Table 1. Patient and index tumor characteristics (n=262) (continued)

Characteristics	No. of patients (%)
Tumor localisation	
oral cavity	58 (22.1)
oropharynx	79 (30.2)
hypopharynx	30 (11.5)
nasopharynx	6 (2.3)
larynx	45 (17.2)
nasal cavity and paranasal sinuses	21 (8.0)
salivary glands	1 (0.4)
lip	1 (0.4)
skin	15 (5.7)
unknown primary	6 (2.3)
Treatment in curative phase	
none	90 (34.4)
surgery	12 (4.6)
radiotherapy	19 (7.3)
chemotherapy	1 (0.4)
surgery and radiotherapy	90 (34.4)
chemotherapy with radiotherapy and/ or surgery	50 (19.1)
Prior malignancies	
no	189 (72.1)
yes	73 (27.9)
Localisation of prior tumor	
head and/or neck	38 (14.5)
other	33 (12.6)
both	2 (0.8)
Marital status	
living alone	98 (37.4)
married, living together	164 (62.6)

Patients and methods

Patients.
As of late 2003, socio-epidemiological and tumor data of all patients with palliative head and neck cancer in our clinic were recorded in a central database. In total 262, deceased patients with head and neck cancer were also included in this database until October 2006. Part of these patients were included before the realization of the expert center (2005), part were included after its realization. Therefore, not all patients have had specialized nurse involvement. Data on comorbidity, treatment, and laboratory investigations were retrospectively collected through the (electronic) medical records. When the exact date of entering the palliative phase is unknown, the median day of the month was used. All patient and index tumor-related baseline characteristics upon entering the palliative phase are given in table 1. Table 2 denotes all palliative phase characteristics.

Descriptive statistics.
All patient characteristics were analyzed for correlation using the chisquare statistic and linear regression models. Only correlations with a $p \leq .05$ are discussed in our results.

Survival analysis.
The prognostic value of the different variables on survival was first tested univariately by Kaplan–Meier curves. Statistical significance was assessed using the log-rank tests. Multivariate analysis was done using the Cox regression analysis.

Results

In total, 262 deceased patients with palliative head and neck cancer have been included in our study. A specialized head and neck oncology nurse was involved with two-thirds of these patients. Since the realization of our Expert Center, almost all patients (89%) have been supported by our specialized nurse. The mean age at time of entry in the palliative phase was 64 years old. Two-thirds of these patients were married or living together, whereas one-third were living alone. All patients' status were discussed in a multidisciplinary tumor-consulting group, where they were staged and their treatment was planned. Two-thirds of the patients (68.3%) had a stage IV tumor at first diagnosis, and onethird (34.4%) became palliative at that point in time. The majority of patients (85%) who became palliative at first presentation had a stage IV tumor. The largest part of this group (40%) presented with an oropharyngeal tumor. Further sociodemographic data can be found in table 1.

Table 2. Palliative phase characteristics (n=262).

Characteristics	No. of patients (%)
Cause of palliation	
inoperability of head and/or neck tumor	139 (53.1)
distant metastasis	78 (29.8)
refusal of curative treatment	25 (9.5)
frailty, condition does not permit curative treatment	19 (7.3)
missing	1 (0.4)
Treatment in palliative phase	
none	155 (59.2)
surgery	5 (1.9)
radiotherapy	70 (26.7)
chemotherapy	10 (3.8)
surgery and radiotherapy	6 (2.3)
chemotherapy with radiotherapy	12 (4.6)
chemotherapy with radiotherapy and surgery	2 (0.8)
chemotherapy with surgery	1 (0.4)
photodynamic therapy	1 (0.4)
Specialized nurse involvement	
no	92 (35.1)
yes	170 (64.9)
Number of hospital admissions	
0	101 (38.5)
1	94 (35.9)
> 1	67 (25.6)
Cause of admission	
treatment	41 (15.6)
head and neck symptoms	86 (32.8)
general symptoms	30 (11.5)
missing	105 (40.1)
Cause of death	
natural	100 (38.2)
terminal sedation	44 (16.8)
euthanasia	14 (5.3)
missing	104 (39.7)
Location of death	
at home	108 (41.2)
hospital	62 (23.7)
nursing home	40 (15.3)
hospice	6 (2.3)
missing	46 (17.6)
Other palliative treatment	
pain team	65 (24.8)
tracheotomy	11 (4.2)
gastric tube	71 (27.1)

The mean length of the palliative phase was approximately 6 months (177 days), with a maximum of 3 years 4 months (1196 days). The mean length of the palliative phase for patients with mucosal squamous cell carcinoma (excluding skin, unknown primary, nasopharyngeal, and salivary gland tumors) was 5.4 months. In half of the cases (53.1%), the reason for palliation was inoperability of the tumor. Additionally, distant metastases (29.8%), refusal of curative treatment (9.5%), and poor condition (7.3%) were reasons for refraining from administering curative treatment. The reason for palliation had significant impact on the number of admissions ($p = .005$). Patients with inoperability of the head and neck tumor or with distant metastases were more frequently admitted to our hospital. More than half of the palliative patients (59.2%) did not receive interventions such as surgery, radiotherapy, or chemotherapy. When patients did receive interventions, this had a significant effect on the number of times the patient was admitted to the hospital ($p < .001$). There was an average of 1.3 admissions (range, 0–13) in our hospital per palliative patient, of which one-third was because of head and neck symptoms (eg, dyspnoea, swallowing difficulties, and bleeding). Other reasons for admission were palliative treatment (15.6%) and general palliative symptoms (11.5%), such as pain and malaise. Patients with more than 1 hospital admission were generally admitted for treatment (eg, chemotherapy, tracheotomy). The study found no relationship between the number of hospital admissions and the marital status of the patient. In one-fourth of the patients, the pain team was consulted because pain relief was insufficient. Eleven patients (4.2%) needed a tracheotomy at some point in the palliative stage because of upper airway obstruction due to edema or tumor progression.

Most patients died at home (41%) or in the hospital (23.7%), mainly of natural causes (38.2%). The location of the deaths was significantly associated with marital status ($p = .001$). Patients who were married more often died at home. Involvement of a specialized nurse was significantly related to the location of death ($p = .011$); patients who had been treated by a specialized nurse were more likely to die at home or in a hospice instead of the hospital. Moreover, when a specialized nurse was involved, the number of admissions was diminished ($p = .012$). The specialized nurses had no role in decisions concerning the patients' end of life. However, on request they did inform patients and families about their ability to influence this process. Overall, in 44 of the palliative patients (16.8%), the process of dying was eased by palliative sedation, in 14 patients (5.3%) active euthanasia was performed.

To investigate the relation between various patient and tumor characteristics and the duration of the palliative phase, univariate and multivariate analyses were performed using possible prognostic factors. Only characteristics apparent at the beginning of the

Table 3. Laboratory characteristics at entry of palliative phase.

Characteristics	No. of patients (%)
Hemoglobin	
low (3.9-6.7)	45 (17.2)
low-intermediate (6.7-7.4)	47 (17.9)
intermediate-high (7.4-8.4)	47 (17.9)
high (8.4-10.7)	67 (25.6)
not analyzed	56 (21.4)
Albumin	
low (23-31)	33 (12.6)
low-intermediate (32-36)	33 (12.6)
intermediate-high (37-39)	32 (12.2)
high (40-48)	70 (26.7)
not analyzed	94 (35.9)
Leukocytes	
low (3.6-7.5)	35 (13.4)
low-intermediate (7.6-9.2)	40 (15.3)
intermediate-high (9.3-12.3)	40 (15.3)
high (12.4-39)	64 (24.4)
not analyzed	83 (31.7)

palliative phase were included in these analyses. First, Kaplan–Meier curves were created for all putative factors (mentioned in tables 1 and 2). This univariate analysis showed comorbidity (Figure 1), index tumor histology, localization and degree of differentiation, palliative therapy (Figure 2), and laboratory characteristics (Table 3) to significantly affect the length of survival after entry in the palliative phase. Index tumor stage, cause of palliation, and specialized nurse involvement did not affect the duration of the palliative phase. Multivariate analysis (Cox regression analysis) was performed using variables known at the beginning of the palliative phase and factors relating to the terminal phase were excluded. Also, variables with considerable amounts of missing values (eg, laboratory characteristics: >19% missing values) were left out. The final analysis (n = 252) showed only ACE 27 score 3 (severe comorbidity) and almost all palliative interventions (all except surgery combined with radiotherapy and photodynamic therapy) to be independent predictors of length of survival in the palliative phase. Severe comorbidity shortened whereas palliative treatment elongated the length of this phase. All other factors did not qualify as independent predictors (Table 4).

Figure 1. Kaplan–Meier curve: ACE 27-score.

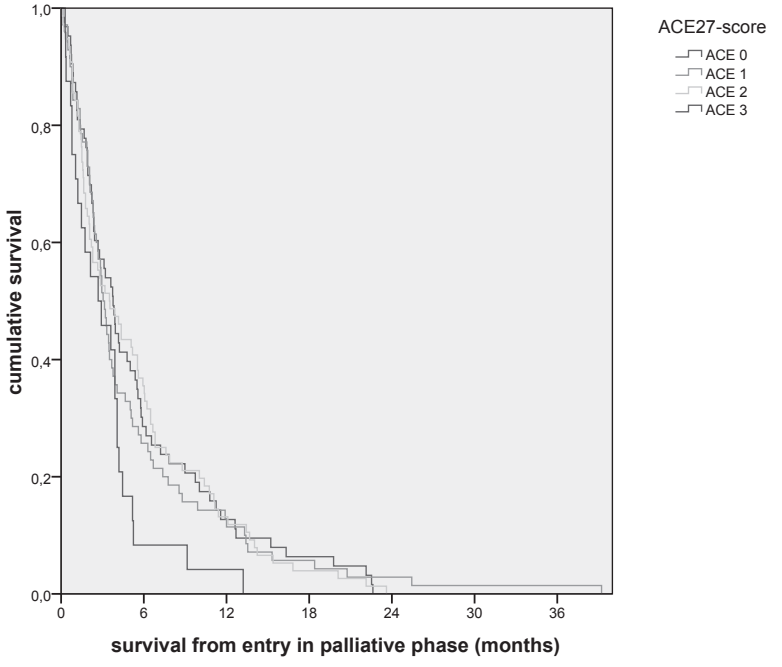

Figure 2. Kaplan–Meier curve: Palliative treatment.

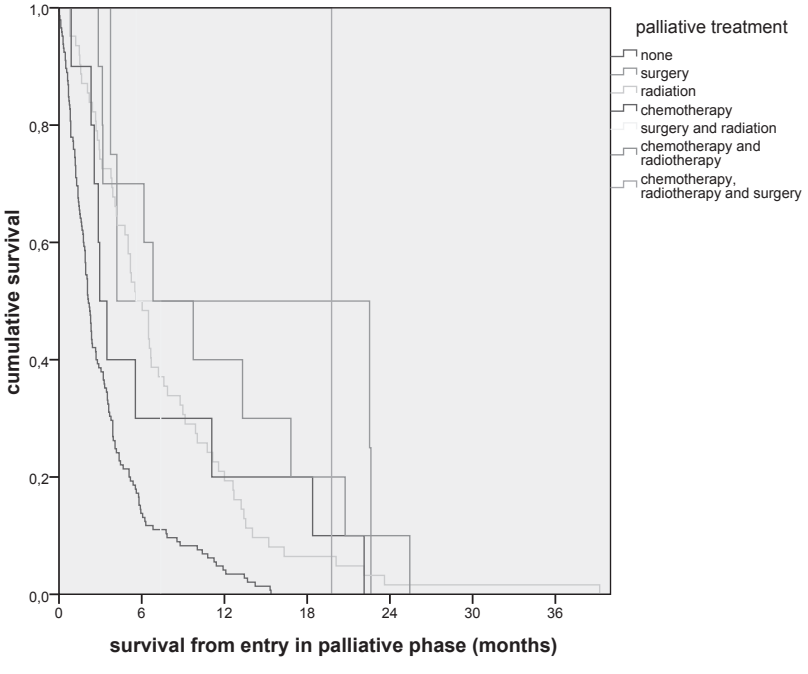

Table 4. Multivariate analysis (Cox) of predictors on length of palliative phase.

Prognostic factor	HR	95% CI
Sex		
male	referent	
female	1.4	1.0-1.9
Age at entry in palliative phase		
Δ year	1.0	1.0-1.0
Marital status		
living alone	referent	
married, living together	1.4	1.0-1.9
Comorbidity		
ACE 27: 0	referent	
ACE 27: 1	0.9	0.6-1.3
ACE 27: 2	0.7	0.5-1.1
ACE 27: 3	1.8	1.1-3.1
Tumor stage		
stage I	referent	
stage II	0.9	0.4-1.8
stage III	0.8	0.4-1.7
stage IV	1.0	0.5-1.9
Histology		
squamous cell carcinoma	referent	
other	0.4	0.2-1.0
Tumor localisation		
oral cavity	referent	
oropharynx	1.0	0.6-1.4
hypopharynx	1.4	0.9-2.3
larynx	0.8	0.5-1.2
nasal cavity and paranasal sinuses	1.0	0.4-2.8
salivary glands	21	2.0-213
skin	1.7	0.9-3.5
unknown primary	2.2	0.9-5.6
nasopharynx	3.0	0.9-9.6
lip	0.5	0.1-4.9
Previous malignancy		
no	referent	
yes	1.1	0.8-1.6

Table 4. Multivariate analysis (Cox) of predictors on length of palliative phase. (continued)

Prognostic factor	HR	95% CI
Treatment in curative phase		
none	referent	
surgery	1.0	0.4-2.3
radiotherapy	0.6	0.3-1.1
chemotherapy	3.6	0.3-47
surgery and radiotherapy	1.2	0.8-1.7
chemotherapy with radiotherapy and/ or surgery	0.9	0.6-1.5
Cause of palliation		
inoperability of head and/or neck tumor	referent	
distant metastasis	1.0	0.7-1.4
refusal of curative treatment	1.1	0.7-1.4
frailty, condition does not permit curative treatment	1.5	0.8-2.7
Treatment in palliative phase		
none	referent	
surgery	0.2	0.1-0.6
radiotherapy	0.4	0.3-0.5
chemotherapy	0.4	0.2-0.9
surgery and radiotherapy	0.4	0.1-1.0
chemotherapy with radiotherapy and/ or surgery	0.2	0.1-0.4
photodynamic therapy	0.1	0.0-1.1
Specialized nurse involvement		
no	referent	
yes	0.8	0.6-1.1

Abbreviations; HR: hazard ratio, CI; confidence interval, ACE; adult comorbidity evaluation.

Discussion

The mean duration of the palliative phase is approximately 6 months (177 days).[1] This offers many opportunities for patient and family counseling. Not all patients (35%) have had specialized nurse involvement because part of these patients were included before the realization of the Expert Center in 2005. Since then, almost all patients (89%) have been supported by our specialized nurses. When a specialized nurse is involved, the number of hospital admissions per patient is lower. General practitioners consult specialized nurses to improve home-based palliative care. Because most patients wish to spend the palliative phase at home, fewer hospital admissions possibly augments the quality of life. Currently, patients more often have palliative sedation at the end of their life. This probably is the result of the introduction of the national guideline for palliative sedation in The Netherlands in December 2005.[14] Besides the improvement of the quality of palliative sedation, a major target of this guideline is to improve the patient's contribution in the decision-making process.[15] The Dutch Euthanasia Act of 2002 was followed by a modest decrease in the rates of euthanasia and physician-assisted suicide, probably because of improved palliative care and the increased application of palliative sedation.[16] The specialized nurse plays an important role in informing patients about the various possibilities available. Additionally, patients with specialized nurse involvement more often die in a nursing home and less often in our hospital. One of the aims of our center is to better inform the patients and family about end of life care. This could be reflected in the way and place of dying. Although specialized nurse involvement does not influence survival, it may, however, influence the quality of life during the palliative phase. This could be tested in further prospective studies. More than one-third of our patients with palliative head and neck cancer live alone: 58 men (34%) and 31 women (50%). The average age of our palliative patient group is 64 years old. The percentage of people of this age living alone in the general population is approximately 14% in men and 21% in women.[17] Single patients have more stage IV tumors at first diagnosis. This avoidance of care could be the result of reduced social control. The mean survival time in this group is 4.7 months compared with 6 months in the overall group. Our specialized nurse plays an important role for this considerable group of single patients. Two-thirds of our patient group had a stage IV tumor at first presentation. Of patients who become palliative at first presentation, the majority (85%) had a stage IV tumor. In The Netherlands, the number of patients with head and neck cancer diagnosed with an advanced stage carcinoma (T4) had increased during the last decades.[18] Because of this increasing incidence, and the complexity of care needed for these patients with advanced-stage tumors, a growing group of patients will need support by multidisciplinary teams and specialized nurses.

Survival data may be used for better guidance for patients and their families. Almost all palliative patients seem interested in being informed about their life expectancy. Personal data of palliative patients (pilot study, n = 9) indicate that the foremost reasons are uncertainty, the wish to spend time with their family, and possible plans for the near future. However, the pilot study also found that the knowledge of their prognosis would not alter patients' plans for the future or change the possible palliative treatment strategies. This pilot study was ended prematurely, because medical doctors considered questioning about life expectancy to be inappropriate. ACE 27 score 3 (severe comorbidity) and all palliative interventions (except surgery combined with radiotherapy and photodynamic therapy) are shown to be independent predictors of survival in the palliative phase. Piccirillo et al.[19] previously demonstrated the impact of severity of comorbidity on survival. The efficacy of palliative treatment is hard to assess, as indications for therapy are highly correlated with the patient's prognosis. On the other hand, severe comorbidity, which shortens life expectancy, may be targeted for extensive attention and possible intervention. Univariate analysis shows lower levels of albumin to significantly affect the length of survival after entry in the palliative phase. Low albumin levels can be a sign of cachexia, a possible prognostic factor on cancer survival,[20] or related to the anorexia-cachexia syndrome. This is a constellation of symptoms including malnutrition, weight loss, muscular weakness, acidosis, and toxemia. Because of this syndrome, affected patients have an increased risk of surgical complications and infections.[21] Results of this study could help us with patient counseling, but we should not confuse these results as indicators of treatment. Because of the retrospective analysis, confounding by indication could be an issue, although dealt with in multivariate analysis. A larger prospective study started as of September 2008, in which all successive palliative patients in our center will be asked to participate. With an accurate prognostic model, we could better inform and support patients and families and provide consultation to caregivers during the last stage of life. Survival rates may help caregivers to adjust the palliative treatment. Medical doctors are trained to cure patients and tend to be too optimistic about their life expectancy. Before 2005, treatment stopped in our clinic when patients were incurable. Currently, more attention is paid to palliative treatment and supportive care aimed at a better quality of life for the patient and their family. In our opinion, every oncologic head and neck surgeon should not only be trained in surgery but also in palliative care. In conclusion, this study enables us to look at various patient, environmental, and tumor characteristics of the palliative phase. In addition, its prognostic factors are highlighted. As this study was done retrospectively, we should be careful not to interpret the hazard ratios of the various palliative treatments as an indicator of treatment efficacy. The second independent prognostic factor on survival, namely severe comorbidity, should be subject to extensive attention and could cause adjustment of intervention.

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Part IV

ADDENDUM

Chapter 10

Model-assisted predictions on prognosis in HNSCC: do we learn?

Marc P. van der Schroeff, Kim van Schie,
Ton P. M. Langeveld,Caspar Looman,
Robert J. Baatenburg de Jong

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Abstract

Dedicated software packages incorporating prognostic models are meant to aid physicians in making accurate predictions of prognosis. This study concerns 742 predictions of 5-year survival on consecutive newly diagnosed patients with head- and neck squamous cell carcinoma. The 5-year survival predictions made by the physicians are not compared with actual survival, but with a prediction made by OncologIQ, a dedicated software package. We used a linear regression and a linear mixed effects model to look at absolute differences between both predictions and possible learning effects. Predictions made by the physicians were optimistic and inaccurate. Using the linear regression and linear mixed-effects models, the physicians' learning effect showed little improvement per successive prediction. We conclude that prognostic predictions in general are imprecise. When given feedback on the model's predicted survival, the accuracy increases, but only very modestly.

Introduction

Prognostication remains a difficult aspect of daily medicine and oncology in particular. Due to the uncertainty of future events, physicians are often unable to give cancer patients an accurate assessment of their prognosis. This may result in non-optimal patient counselling and over- and undertreatment. In oncology the prognosis is classically based on the TNM-classification. However, it is clear that, besides TNM-classification, a variety of covariables play a role in the prognosis. The combination of factors, however, poses a difficult equation to the daily practice. Most physicians will combine their own experience and knowledge on prognostic factors in order to prognosticate. However, it is questionable how accurate these assessments are. In 2000, Christakis and Lamont[1] reported only 20% of predictions done by doctors were to be considered as accurate (predicted survival within plus or minus 33% of actual survival). This concerned 343 doctors providing survival estimates for 468 terminally ill patients admitted to five outpatient hospice programmes in Chicago during 130 consecutive days in 1996. The direction of the inaccuracy of predictions is often to the positive side, doctors are optimistic on survival prognosis.[1-3] In order to improve predictions, spreadsheets and dedicated software which present prognostic models are developed and published in literature, based on large datasets on which multivariate survival analyses are done. These programs can help physicians with patient counselling and deciding on treatment options. We hypothesise that when the clinical predictions are supported by such prognostic models, the prediction error would decrease in time. The aim of this study is to evaluate the differences between a 5-year survival prediction done by a physician on a newly diagnosed head- and neck oncology patient compared to the one done by a dedicated software package. We also studied a possible learning effect in the assessment of the physician if supported by this computerised prediction.

Patients and methods

This study concerns 742 predictions done by 33 physicians and the dedicated software package. The average number of predictions done by individual physicians was 22.5 (range 1–88). All 742 predictions were done on consecutive newly diagnosed patients with head- and neck squamous cell carcinoma, who were discussed in the Leiden Head and Neck Oncology Cooperative Group. The patient and tumour characteristics are given in Table 1. All participating members (otolaryngologists, radiologists, plastic surgeons, etc.) of the group were asked to make a 5-year survival prediction based on all available patient and tumour data at hand at that time. Simultaneously, these data were entered in 'OncologIQ', which produces a 5-year survival prediction as well. We looked at the difference between these two assessments. After each prediction the physicians were given the results of the model's prediction in order to give them feedback. We must stress that the predictions made by the physicians are not compared with actual survival, but with a prediction made by OncologIQ.

Table 1. Baseline characteristics of head- and neck oncology patients on which the predictions were made. Shown are the data entered in OncoligIQ.

	n
Gender	
male	532
female	201
missing	9
Age (years)	
<50	89
50-59	230
60-69	274
>60	137
missing	12
cT-stage	
cT1	202
cT2	224
cT3	210
cT4	95
missing	11
cN-stage	
cN0	460
cN1	63
cN2	147
cN3	53
missing	19
cM-stage	
cM0	652
cM1	8
missing	82
Localisation	
nasopharynx	4
oral cavity	125
oropharynx	264
hypopharynx	72
larynx glottic	205
larynx supraglottic	61
missing	11
Prior malignancies	
yes	85
no	612
missing	45

OncologIQ is a dedicated software package, which we presented in 2001.[4] This program is based on a Cox regression analysis on 1,396 head- and neck oncology patients. This program takes not only TNM-classification into account, but all available and relevant covariables of survival time in the Cox regression analysis. The prognostic model consists of TNM-classification, gender, age, localisation of the tumour and the absence or presence of a prior tumour. We analysed the data in two different ways. First, we looked at absolute differences between both predictions ('absolute residuals'). The possible decline of these differences, as a measure of a possible learning effect, was analysed using a linear regression model. Second, we analysed the data with a linear mixed-effects model [5], in which individual physicians were declared as random factors in the model. The OncologIQ-score served as predictor, the physicians' prediction as outcome and we used no intercept. This model then simply estimates the mean physicians' prediction as a percentage of the OncologIQ prediction. A next step is to add the interaction of the number of successive predictions per physician and OncologIQ-score: this leads to the change in percentage over- or underestimation as a (linear) function of the successive predictions per physician. A last step sought is to differentiate these changes in time between patients with different characteristics as used to build up the OncologIQ-score. For data analysis we used linear regression models in S-Plus®, version 6.

Results

Figure 1 shows the difference in predictions between the physician and OncologIQ as a function of successive predictions. The absolute difference between both predictions is on average 11%, with a range from 0 to 52%. When we consider a difference of ≤10% (maximum deviation from 5-year survival prediction made by OncologIQ of 6 months) as accurate, only 277 out of 742 (37.3%) predictions classify as accurate. Predictions made by the physicians were optimistically relative to the OncologIQ's prediction; 459 out of 742 (61.9%) predictions made by the physicians are in absolute percentages higher than that of the program (Figure 1). The decline in absolute difference between the physicians prediction and that of OncologIQ was 3.6% (95% CI 0.1%, 7.1%) per successive prediction (Figure 2). In other words, a learning effect was that the variability between physicians and OncologIQ decreases with successive predictions. Using the linear mixed-effects model (Figure 3), predictions from physicians were on average 4.5%, too optimistic (95% CI 2.6, 6.4%). Per successive prediction the difference between the physicians' prediction and that of OncologIQ is declined by 0.1% (p value 0.024). A physician with more than 45 successive predictions had on average no optimism in his/her predictions compared to OncologIQ. The last step sought is to differentiate changes in time between patients with different characteristics as used to build up the OncologIQ-score. This analysis showed no significant interactions (no data shown).

Figure 1. The difference in predictions between the 5-year survival predictions made by the physicians and OncologIQ (reference) as a function of successive predictions. The fitted lines represent the boundaries of the 'accurate' prediction (6 months, 10%).

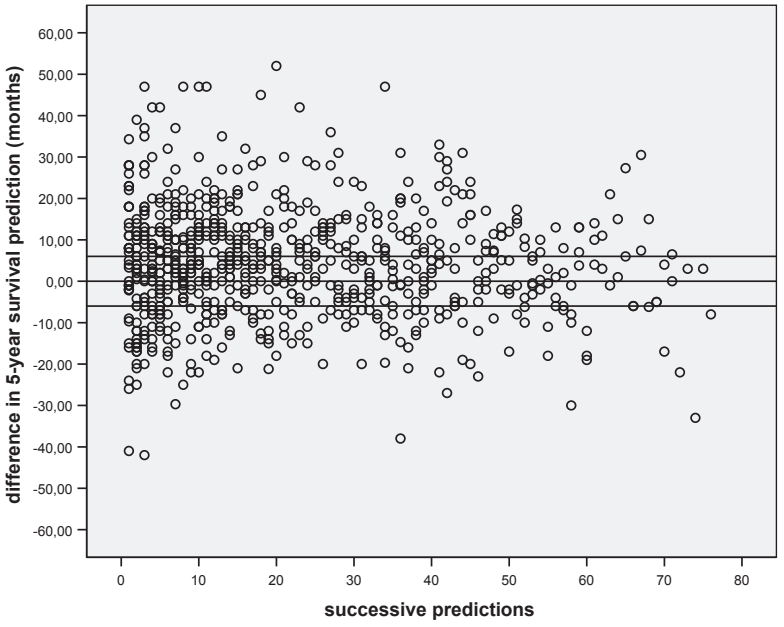


Figure 2. The absolute difference between predictions made by physician and OncologIQ ('absolute residuals') as a function of successive predictions with a fitted linear regression line.

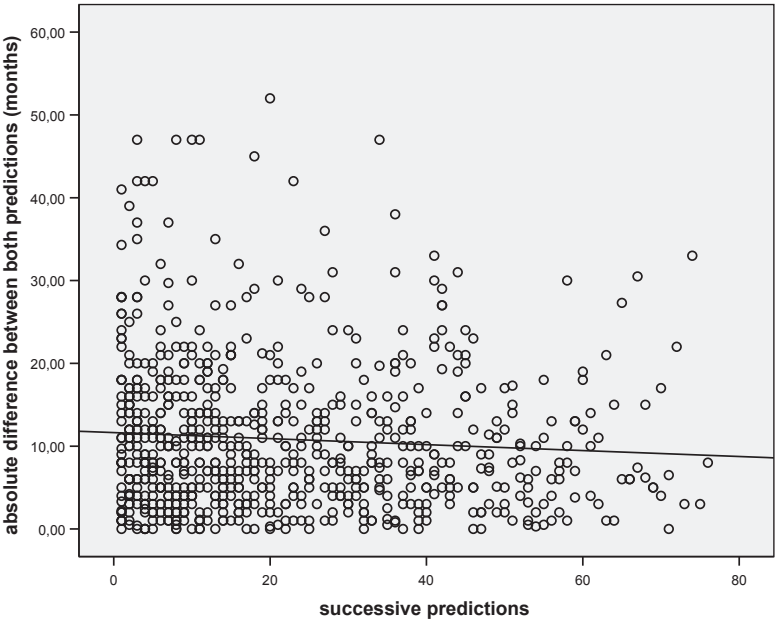
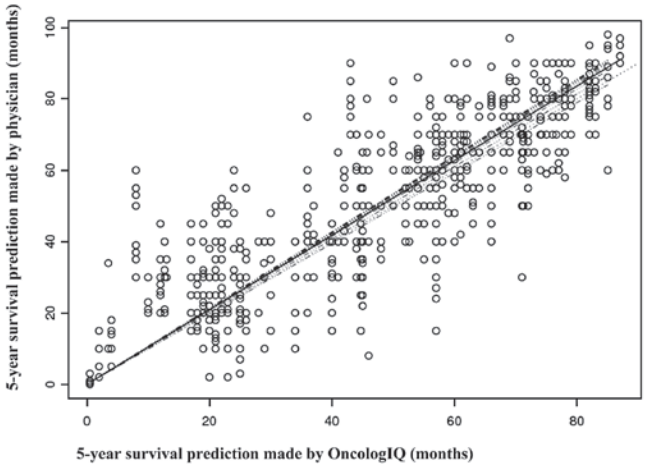


Figure 3. The black line represents the beta of the difference in average predictions (beta 1.045). The dotted red lines represent beta's for successive predictions. A physician with just one prediction produces a beta larger than 1.045, indicating more than average optimism. A physician with more than 45 successive predictions produces a beta around 1, indication no optimism.



Discussion

Most previous studies on prognostication in oncology concern the prediction of survival of terminally ill cancer patients by the physician compared with actual survival time and relative optimism or pessimism. Chow et al.[2] examined the accuracy of 739 survival predictions by six palliative radiation oncologists in 2004. It concerned cancer patients with metastatic disease with most common primary cancer sites being the lung, breast and prostate. The median survival of the 739 patients was 15.9 weeks. It showed that the predictions of survival tended to be too optimistic with a –12.3 weeks difference between the actual survival and the clinically predicted one. Vigano et al.[3] showed that in their study the clinical estimation of survival had a low sensitivity in terminally ill cancer patients (primary cancer sites: breast, lung, gastrointestinal and prostate) and a tendency to overestimate survival. These data concur with those of Christakis and Parkes[1,6] who also describe inaccurate and systemically optimistic predictions. Stockler et al.[7] studied the predicted survival in 102 newly referred patients with incurable cancer (various primary cancer sites) and found these predictions to be imprecise (29% were within 0.67–1.33 times the actual survival), but not over optimistic (35% were >1.33 times the actual survival) or pessimistic (39% were <0.67 times the actual survival). Median survival time was 12 months. Muers described 196 consecutive patients diagnosed and managed as non-small cell lung cancer, who did not receive curative treatment.[8] Physicians correctly predicted within 1 month, the survival of only 19 patients (10%). However, almost 59% (115/196) of patients had their survival predicted to within 3 months. Mackillop and

Quirt asked doctors to estimate the probability of cure for 98 cancer patients undergoing outpatient treatment and the duration of survival for 39 incurable patients.[9] These patients had various primary cancer sites, including head and neck. In conclusion, the doctors were able to discriminate quite well between curable and incurable patients (area under the ROC-curve 0.91), but performed less when the duration of survival was concerned. Differences in accuracy and optimism or pessimism between these studies might be due to differences in primary cancer sites, mean length of survival and experience of the physicians. To our knowledge there has been no study published concerning the prediction of survival comparing physicians and dedicated software. At the moment the patients in our study were discussed at the Head and Neck Oncology Cooperative Group, the data entered in OncologIQ were probably not exactly the same as the information available to the physicians. It is conceivable that some physicians (especially the one who presents the patient to the other members of the group) were aware of certain covariables that are not in the OncologIQ program. Noteworthy is the result presented by Muers, that a prognostic model for prediction of survival in non-small cell lung cancer patients in which the physicians' prediction of survival is incorporated showed better discriminative performance in comparison with a model without.[8] This would also suggest that physicians are not using exactly the same factors as the prognostic model and must be using additional information. This additional knowledge, however, does not always have to be beneficial in prediction making; it could theoretically also blur the sight on more important prognostic factors. To our best knowledge there has been no publication in which the physician's prediction is compared with that of a dedicated software program based on a multivariate survival analysis. In this way we do not compare with actual outcome (survival time), but with a maximised prediction based on the knowledge of all relevant covariables at the time of presentation of these patients. We know from previous studies that the clinical estimation of survival is consistently imprecise. That is one of the reasons to develop these multivariable prognostic models. Our results show only 37.3% of the predictions to be accurate (maximum of 10% difference considered as accurate). We hypothesised that when the clinical prediction was supported by such a model the prediction error would decrease in time. This is, however, not that clear cut. In general, we showed little, but significant, improvement in deviation from the model's prediction with successive predictions. We therefore conclude that prognostic predictions in general are imprecise. When supported by feedback, the accuracy increases, but only very modestly. In other words we do learn, but not spectacularly. In order to maximise the patient counselling and treatment decision-making we should rely on a combination of experience and prognostic models.

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Chapter 11

Predicting survival: what about the right side of the curve? -thoughts on communicating prognosis-

Marc P. van der Schroeff, Marinella P. Offerman, Robert J. Baatenburg de Jong

submitted

Abstract

When diagnosed with cancer, patients as well as their families are concerned with the prognosis. The way in which this information is given however poses numerous challenges. We studied our own database to illustrate the message given when using statistical averages in communicating prognosis. The group under study is 824 patients with a primary head- and neck squamous cell carcinoma, diagnosed between January 1980 and December 1989. We discuss the effect of censoring and skewness on survival distributions, as well as optimism in predictions and patients' preferences when it comes to disclosure of prognosis. Medical statistics in general are not useful for indicating the prognosis of the individual patients. This may result in sub-optimal patient counseling. Perhaps a carefully prepared, more detailed and graphic illustration of statistical averages and variations would allow the patient a better understanding of the uncertainties involved.

Introduction

After being informed of the diagnosis, oncology patients as well as their families are concerned with the prognosis. The way in which this information is given however poses numerous challenges. Frequently used terms as median, mean and modus survival offer insight in probability distribution for groups of patients, but are inadequate for informing the individual patient about their personal future. Most communication in the literature has focused on bringing bad news; however, little guidance is available for clinicians in communicating prognosis.[1] Prognostication itself remains a difficult factor in daily medicine and prognosis is an undervalued feature of the art of medicine. Due to the uncertainty of future events, the possibility of unknown but relevant prognostic factors and the complexity of statistical analysis involved, physicians are often unable to give oncology patients an exact assessment of their prognosis. Inaccurate prognostication may lead to over and under treatment.[2] Most health professionals tend to either withhold information or to be reticent to disclose prognosis.[3] Reasons of this reticence include fear of negative impact on the patient, uncertainty about estimating illness trajectory, request from family members to withhold information and a feeling of inadequacy or hopelessness regarding the unavailability of further curative treatment. This may result in sub-optimal patient counseling.

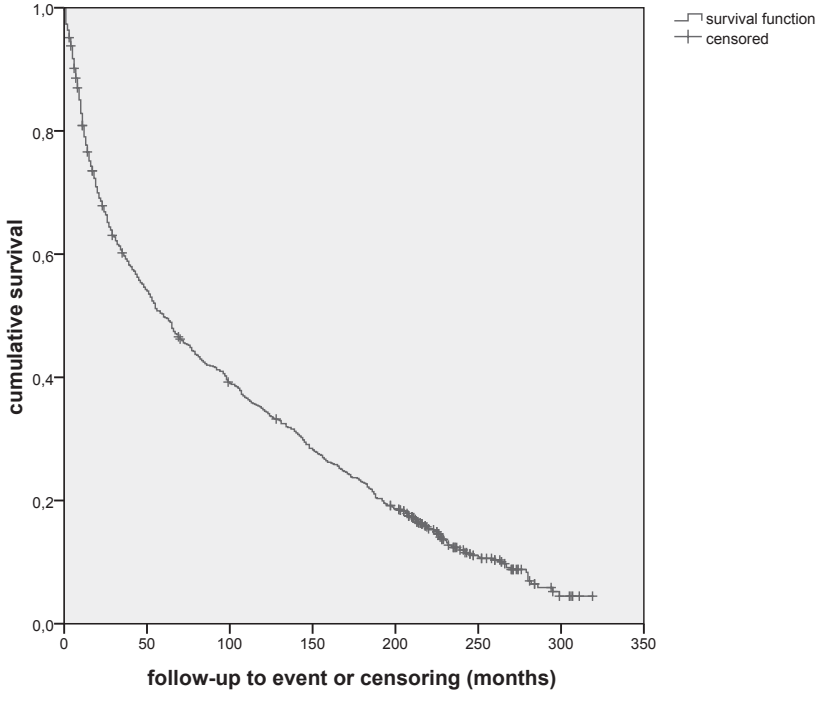
Gould and Brel

Stephan Jay Gould, the essayist and evolutionary biologist was diagnosed with abdominal mesothelioma in 1982. Being one of the most noted scientific writers of our day, he naturally published several stories about his illness; about the way his doctors informed him about his prognosis and the usefulness or relevance of the statistics employed. "In short, we view means and medians as the hard "realities," and the variation that permits their calculation as a set of transient and imperfect measurements of this hidden essence... But all evolutionary biologists know that *variation itself is nature's only irreducible essence*. Variation is the hard reality, not a set of imperfect measures for a central tendency. Means and medians are the abstractions. Therefore, I looked at the mesothelioma statistics quite differently- and not only because I am an optimist who tends to see the doughnut instead of the hole, but primarily because I know that variation itself is the reality. I had to place myself amidst the variation."[4] Gould died in 2002 from a metastatic adenocarcinoma of the lung, unrelated to his abdominal mesothelioma, though possibly associated with its treatment. Jacques Brel, the Belgian singer, returned to Paris from Hiva Oa, French Polynesia, in 1977 and recorded his well-received final album 'les Marquises', after being diagnosed with lung cancer in 1974. He died in 1978 at age 49, well beyond his initially predicted prognosis.

Head and Neck example

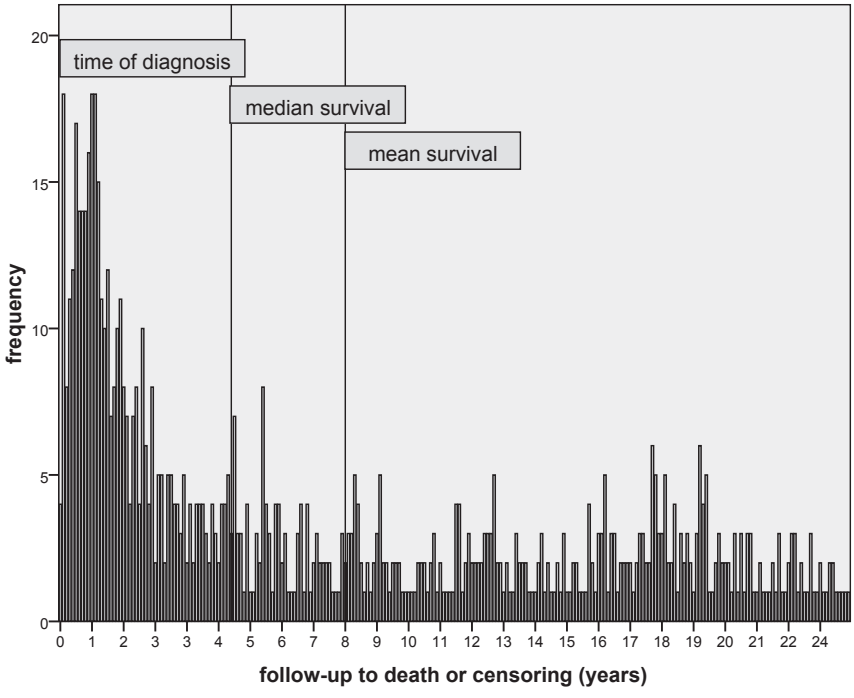
We studied our own database to illustrate the point made by these two patients. The group under study is 824 patients with a primary head- and neck squamous cell carcinoma, diagnosed between January 1980 and December 1989. This timeframe allows for long term follow-up. The 5-years survival rate was 50.3% (Figure 1). The mean survival was 92 months, the median survival 56 months (Figure 2). The minimal survival-time was less than one month, the maximum survival time 319 months (26 years and 7 months).

Figure 1. Kaplan Meier curve; the 5 years survival of head- and neck squamous cell carcinoma patients is 50%.



When informing a patient with a primary head- and neck squamous cell carcinoma about his or her prognosis, the physician might use any of the statistical terms mentioned above but will frequently choose mean survival. While this is entirely valid the whole group of patients, it may not be adequate for the particular patient you are talking to. Though for example, the statistical probability of pulmonary metastasis may be 4% for a head and neck tumor which has a 5 year survival rate of over 50%, the patient who does develop pulmonary metastases is likely to be 100% deceased before the 5 years are up.

Figure 2. Skewed survival-time distribution to the right: a long tail.



The first line represents the median, the second the mean survival.

Statistical phenomena

When discussing statistical information about prognosis with patients, two important statistical phenomena are invoked: skewness and censoring. Distributions of survival are invariably skewed. Skewness measures the degree and direction of asymmetry. A symmetric or gaussian (normal) distribution has a skewness of 0, and a distribution that is skewed to the right, e.g. when the median is less than the mean, has a positive skewness. A right-skewed distribution with a long right-hand 'tail', as shown in figure 2 is true for most severe diseases. After all, the left of the distribution is truncated by the time of diagnosis. On the right side of the distribution there is much variation, due to many, perhaps unknown, factors. This implies that not all patients are rightfully represented by the mean or median. The second phenomenon is censoring. In almost all studies patients may be lost to follow-up. This can be differential or non-differential. It is probably reasonable to suggest that patients who do well might get lost to follow-up more easily than those doing less well and need more care. This leads to non-differential lost to follow-up, the distribution curve in reality is even more skewed to the right.

Optimism in predictions

Besides these variations in probabilities of survival-time, we must also recognize the fact that prognostication in general is hard. In oncology the prognosis is classically based on the TNM classification.[5] It is however self-evident and has been shown that, besides the TNM-classification, a variety of covariates play a role in the overall prognosis.[6-8] The combination of factors however poses an increasingly difficult equation for daily practice. On predicting prognosis, most studies concern the prediction of survival of terminally ill cancer patients by the doctor compared with actual survival time and relative optimism or pessimism. The direction of inaccuracy is often towards the positive side, doctors tend to be optimistic on survival prognosis.[9-12] Differences in accuracy and in optimism or pessimism between these studies may be due to differences in mean length of survival and experience of the physicians. In order to improve predictions dedicated software is being developed, based on multivariate survival analyses of large datasets.[13] These programs can help physicians with more personal patient counseling and help steer decisions on treatment options.

Patients' preferences

Another aspect of discussing prognosis with patients is the patient's preferences for the disclosure of prognosis. The majority of patients and their caregivers want the health professional to be honest when discussing prognosis, however, there are different views of what constitutes an honest approach.[14] This could be (a combination of) a straightforward approach, accurate information but without bluntness or a combination of honesty and optimism. In a study published by Lagarde[15], 74% of patients treated for esophageal cancer wanted to know the average time of survival, 93% wanted to know the average prognosis. Although preferences declined when information became more specific and more negative, around 70% still wanted to hear less positive information also. In the palliative setting most patients prefer realism and honesty from their professional team[16,17], but at the same time require room for optimism and hope.[18] In a review of research among women with metastatic breast cancer the need was highlighted to balance honesty with hope without encouraging unrealistic expectations. Health professionals may help patients to cope with their terminal prognosis by exploring and fostering realistic forms of hope (in broad aspects of life, not just the medical situation) that are meaningful for the particular patient and their family.[14] Where some advocate a broad indication of their prognosis[16], others prefer their doctor to acknowledge them as in individual when discussing prognosis.[17] Furthermore it is suggested that the way in which information is presented is as important as the actual content of the prognosis discussion. Emotional support and care to ensure patient understanding are vital points of a discussion about prognosis.[19] Additionally, differences in culture must be taken into account. Earlier research confirmed that cancer patients from Western cultures prefer knowledge on their diagnosis[20,21], however, this is not the preference of all cultures.[22]

If we return to our fictive head- and neck patient, we should, besides mentioning the statistical abstractions such as the mean survival, also discuss the variability in survival-time as shown in figure 2. It seems that there is a large group of patients who do not survive the first critical period. However, surviving this period increases the chances of an even longer survival. The mean and median survival however represent, due to their statistical definition (the mathematical average of all survival-time and the middle survival-time), the group instead of the individual patient. Who is to say where our specific patient is located on the curve?

Conclusions

Medical statistics in general are not useful for indicating the prognosis of the individual patient, but can indicate only trends in large populations of patients. Statistical averages are useful abstractions, but do not reflect the full range of variation. Few patients have sufficient understanding of statistics to be able to evaluate what the statistical statements made by doctors really mean. Furthermore, there is an increasing probability, due to the increasing complexity of the medical statistics and databases, that many physicians also lack the detailed knowledge required to be able to give the patient a clear explanation. Perhaps a carefully prepared, more detailed and graphic illustration of statistical averages and variations would allow the patient a better understanding of the uncertainties involved.

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chapter

12

General discussion

Prognostic factors occurring during initial treatment follow-up are generally not integrated in prognostic models. Most prognostic models aim to inform physicians and patients at or around the time of diagnosis of the index tumour. These prognostic models incorporate standard patient- and tumour characteristics known at that time such as: TNM stage, age and histological typing. They offer a static risk assessment at a fixed predictive moment. In **chapter 3, 4, 7, 8 and 9** we presented these kind of prognostic models for a variety of clinical settings such as patients with salivary gland cancer and those with incurable head and neck disease. In **chapter 5 and 6**, we showed that incorporating changeable factors, such as surviving the first critical years, advancing age or the occurrence of recurrence or metastasis have a tremendous effect on the prognosis of an individual patient with HNSCC. If the patient remains tumour-free his prognosis will change as well: for example, the prognosis of cancer patients who survive the first two years will improve. This is caused by the fact that they survived the first critical period. So, prognosis is not static. This may seem obvious, but in literature and daily practice prognosis is frequently presented as a lifelong verdict. Incorporation of changeable factors into prognostic models enhances our insight into dynamic processes during follow up. Instead of discussing chapter by chapter, we choose to discuss a set of central themes in this thesis: comorbidity, time dependent effects, missing values, generalizibility and counseling.

Comorbidity

In **chapters 3, 5, 8 and 9** the prognostic value of comorbidity status was paramount. The person largely responsible for the identification and acknowledgement of comorbidity as an important prognostic factor in HNSCC is Jay Piccirillo, the designer of the adult comorbidity evaluation (ACE)-27 score. Comorbidity acts as a long-term risk factor for mortality and, compared with the general population, seems to be a more prominent problem in patients with HNSCC.[1,2] In head and neck oncology, there is a strong etiological relationship between smoking and alcohol abuse and the occurrence of HNSCC.[3-5] Besides acting as a major etiologic factor in HNSCC, smoking is known to be partly responsible for substantial comorbidity (eg, COPD and cardiovascular disease), which in turn significantly influences cancer survival.[6,7] Alcohol abuse acts in a similar way: it not only causes HNSCC, but is also a major source of comorbidity, such as esophagitis, gastritis, and liver disease.[3,8,9] Furthermore, the combined etiologic effect of alcohol and smoking is multiplicative.[8,10] The impact of severe comorbidity (ACE 27 grade 3) is comparable to the impact of a T4 tumour or an N2 neck. Especially cardiovascular, respiratory and gastrointestinal comorbidity, and diabetes have been shown to influence survival time.[11] These findings have motivated us to have a greater sense of awareness of these diseases in the pre-treatment time period. In our department a doctor of internal medicine is added to the oncology staff to screen and treat newly diagnosed cancer patients for comorbidity. By incorporating this kind of

focus on comorbidity, we hope to see a positive effect on survival rates and quality of life for patients, as well as perhaps lower costs for the department.

Time dependent effects

The focus of any prognostic study is not on causality, as any plausible predictor will do for usage in prognostic models. It is the method in which the research is performed that is subject to discussion. In **chapter 6** we used a stepwise analysis because we wanted to study the effect of changing prognosis caused by those who die early being excluded from further analysis and to look at the effect of possible events during follow-up. In theory, there are two possible problems when using this approach. The first is that of power. Because of smaller numbers the variance in successive follow-up models increases. Despite our large database with ample events, confidence intervals widen in successive follow-up models. The second concerns the hazard ratios in the various models. These hazard ratios are the mean hazard of that particular covariable during the follow-up from that moment in time. It could however be that some covariables behave in a non-proportional way. In particular the short term predictions, e.g. 1-year survival predictions, are thus subject to possible bias. Alternatively one could make just one initial model with time-dependent variables, but in our opinion this would make the results more difficult to interpret. In **chapter 5** conditional relative survival was calculated as the 5-year relative survival for every additional year survived up to 15 years, conditional on being alive at that moment. We calculated 5-year conditional relative survival rates for the follow-up period 1980 to 2004 with period analysis.[12-14] Period analysis provides the most up-to-date survival estimates because all observations included in the analyses are left truncated at the beginning of the period of interest, in addition to being right-censored at its end. Therefore it exclusively reflects the survival experience of patients within some most recent calendar period, such as the most recent calendar year(s) for which mortality follow-up is available. Period analysis enables the early detection of changes in survival trends and better predicts long-term survival of concurrently diagnosed and treated patients than survival estimates derived by traditional methods.[14] It requires a long and thorough follow-up, especially when studying the conditional 5-year relative survival for every additional year during a long period of time since diagnosis. Relative survival is an estimation of disease-specific survival. It is calculated as the absolute survival rate among patients with cancer divided by the expected survival rate of a comparable group from the general population with the same sex and age structure in the same period (derived from Statistics Netherlands). Therefore most competing causes of death are accounted for. There is no excess mortality for patients when conditional 5-year relative survival has reached 100%. Survival is then similar to that of the general population. However, in our case, this 5-year relative survival only reached about 75-80% in patients with HNSCC

(chapter 5), most likely due to an excess comorbidity (see above). A recent study into the relative survival differences, or relative excess risk of death, for head and neck cancer in European populations (covered by population-based cancer registries) showed differences in survival even when corrected for subsite distribution. This may reflect differences in access to good treatment, the study lacks information on stage and comorbidity. The general European 5-year relative survival for all types of head and neck cancer increased from 1990-1994 to 1995-1999 and differences between countries decreased.[15]

Missing values and generalizibility

As is common in all retrospective studies we were confronted with missing values. To prevent is better than to cure, but retrospective research does not offer this possibility. Default statistical packages often perform a complete case analysis. All records with missing values are put aside, reducing the number of patients available for analysis and introducing possible bias. An example of this might be missing patient history and examination in sicker subjects producing a biased predictive value of patient history and examination predictors. Also the other way around might give problems with bias if the more healthy subjects had a full patient history and examination but lacked laboratory testing. When confronted with missing values, the aim should be to optimize unbiased (validity) and precise (precision) effect estimates. A suitable and statistically correct method of dealing with missing values is imputation.[16,17] Although there are several ways to do this, we used regression methods. In short, step one is to build a regression model for variables containing missing values on the basis of all the other predictors using patients without missing values. Step two is to use the model to 'predict' the missing value. Step three is to add an 'error' component. The imputed value does not need to be close to the true value, it should contain all relevant structural information conveyed in the data and a large enough error.

The presented prognostic models have not yet been made and have not yet been tested for use outside our institution (although in the near future we will publish an external validation). It is therefore unclear whether our data will be applicable to HNSCC patients outside our institution. On the other hand, the prognosis of HNSCC's is generally the same in the western world. There is no good reason for our patients to behave otherwise. The models as presented in this thesis can be used for counseling purposes. In general, multivariate analyses in HNSCC literature are done to demonstrate independent effects of the factors under study. In such cases it is possible to calculate a risk score by combining the reported patient and tumour characteristics with the given regression coefficients, although interpretation is difficult. The purpose of these reports seems to be more academic than practical; the translation to an individualized prognosis for patients is not the aim. In the field of HNSCC research, we know of only one presented model, published

in 2001, in which these factors are integrated in dedicated software.[18] In other fields of cancer research models are more frequently presented.[19-23] A well known example is Adjuvant Online![24], a web-based, thoroughly validated[25], program offering prediction models for breast, colon and lung cancer.

Counseling

After estimating the prognosis, the major challenge is to convey this statistical inference to the patient in a way that is satisfactory for both patient and physician. Physicians must emphasize that prognostic models are imperfect. They predict the likelihood that a population of similar patients will survive a defined period of time but not the certainty that this will occur.[26] In other words, on top of understanding probability, patient needs to understand uncertainty. "All of the estimates discussed here are associated with error; this fact should be transmitted to the patient should any estimate be given in a clinical setting".[27] In **chapter 11** we explored the distribution of uncertainty and try to condense useful methods to communicate probability and uncertainty of predicted survival.

Future research

We should be wary to interpret the results of the studies in this thesis as indicators of treatment. First of all, treatment itself is often used as covariable in the prognostic models (chapters 3, 4, 6, 7, 8 and 9). These models aim to make optimal predictions on prognosis, not to test treatment options. Secondly, because of the retrospective analysis, confounding by indication could be an issue. Treatment choices were made based on the prognostic factors at hand, in other words there were reasons to treat patients the way they were treated. This is a common confounding effect when trying to evaluate treatment effects from observational data. In my opinion, future research in prognostic models for head and neck oncology should aim at prospective designs in which a prognostic model is used for decision-making. The first and foremost prerequisite for this is a treatment decision where there is a real choice to make. In situations with one superior treatment modality, the 'treatment-choice' is easy. But when two different treatment modalities share equal overall effectiveness (predicted 5-years survival), prognostic models (incorporating more than just tumour-based characteristics) could offer individualized prognostic estimates and influence treatment choices. Also in situations where survival estimates are low, prognostic models and prognostic counseling could influence treatment choices. Nowadays, one of the central dogmas in treating head and neck cancer patients with poor prognosis, is that treatment with curative intent also offers optimal palliation. However, curative treatment in these patients is accompanied by extensive morbidity (e.g. impairment of swallowing and speech, cosmesis) while treatment outcome remains poor. The alternative could be e.g. hypofractionated radiotherapy with a total dose of 50Gy. This treatment is currently

only considered appropriate for patients deemed inoperable or incurable, or for patients with distant metastasis or second primary tumours. The morbidity of hypofractionated radiotherapy is lower (in contrast to curative treatment) and local control rates are quite reasonable.[28] Prognostic models could assist in identification of patients with poor prognosis and thus may help to decide whether to treat aggressively with curative intent or rather to aim for loco-regional control.

Could further research into prognostics factors make prognostic models for head and neck cancer patients better? At first glance this may seem obvious, but newly found clinical predictors of survival often are partly represented by already known and used variables. The added prognostic value therefore remains to be seen. Evaluating the incremental value of new risk factors is a sequential process for which area under the ROC-curve is a very suitable measure for a first impression about the improvement of the predictive performance of a model. When the area under the ROC-curve of an updated model does not differ markedly from the original model, further evaluations of reclassification, health impact, and cost-effectiveness are not warranted.[29] An illustration of this overlapping effect is shown in **chapter 4**. Recently the focus on prognostic research has shifted from clinical parameters to biomarkers. However, a single biomarker that would fill the gap between the combined prognostic power of models used today and perfect discrimination could well be fictitious.

Conclusion

The presented thesis aims to enhance our insight into prognostic factors in general and specifically into time dependent prognostic factors such as the passage of time itself and the occurrence of recurrences. This information should be used to improve patient counseling.

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Summary

To prognosticate is to estimate a prognosis for a particular set of patients with similar patient- or tumour characteristics or for an individual patient. The prognosis can be used for choosing between treatment options as well as informing the patient about the expected course of their disease. In this thesis we discuss prognostics and a variety of clinical prediction models for patients with head and neck squamous cell carcinoma's (HNSCC's) and salivary gland cancer, although we focus on HNSCC's. In **chapter 2** we introduce the most commonly used prognostic tool: the TNM system. **Chapter 3 and 4** deal with the prognostic relevance of comorbidity, cytology and histology in patients with salivary gland cancer. Afterwards, **chapter 5 and 6** aim to explore the dynamics of prognosis for patients with HNSCC, the central theme of this thesis. We study specific situations and prognostics in head and neck cancer care (recurrent disease, advancing age and palliation) in **chapter 7, 8, and 9**. The final **chapters (10 and 11)** deal with model-assisted predictions on prognosis in HNSCC and different aspects of communicating prognosis in general. In this summary, each consecutive chapter is summarized in more detail.

The TNM system is a universally accepted, widely used, staging method. Its goals are to help clinicians and researchers to choose from treatment options, to give patients an estimate of their prognosis and to compare results of treatment. In **chapter 2** ('staging and prognosis in head and neck cancer') the usefulness of the TNM staging system for head and neck cancer patients is investigated. We found that in the field of prognostic estimations, particularly for the individual patient, the TNM system could be upgraded with other prognostic indicators.

In **chapter 3 and 4** ('the prognostic role of comorbidity in salivary gland carcinoma' and 'cytology and histology have limited added value in prognostic models for salivary gland carcinomas') the prognostic relevance of comorbidity, cytology and histology in patients with salivary gland cancer is studied. A retrospective cohort of 666 patients with salivary gland cancer was identified within the Dutch Head and Neck Oncology Cooperative Group database. According to the Adult Comorbidity Evaluation-27 (ACE-27) index, 394 patients (64%) had grade 0 comorbidity (none), 119 patients (19%) had grade 1 comorbidity (mild), 71 patients (12%) had grade 2 comorbidity (moderate), and 29 patients (5%) had grade 3 comorbidity (severe). In multivariate analysis for overall survival, the ACE-27 comorbidity grade was a strong independent prognostic variable. Compared with other studies that investigated the effect of comorbidity on patients with head and neck cancer, patients with salivary gland cancer had less comorbidity. Their comorbid status appeared to be reasonably comparable to that of patients with other nonsmoking- and nonalcohol-related cancers. Histology was an independent prognostic factor, mainly because acinic

cell carcinoma acted differently from the other histological subtypes. However, a simple prognostic model without cytology and/or histology had similar predictive power compared to more elaborate models. The added prognostic value of cytology and/or histology in prognostic models for patients with salivary carcinoma is limited, largely due to the combined prognostic value of other prognostic factors such as tumour size, N- and M-classification and comorbidity.

In **chapter 5 and 6** ('prognosis: a variable parameter. dynamic prognostic modeling in head and neck squamous cell carcinoma' and 'conditional relative survival in head and neck squamous cell carcinoma: permanent excess mortality risk for long-term survivors') the dynamics of prognosis are explored. The prognosis of cancer patients who survive the first critical years changes, as well as the prognosis for those with local or regional recurrences or distant metastases. This first study concerned 2927 patients with a primary head and neck squamous cell carcinoma (HNSCC). We developed prognostic models after initial treatment and at different time points during follow-up. The developed models show the effects of survival time, recurrences and distant metastasis during follow-up. The C-statistics ranged from 0.76-0.69, indicating moderate discriminative performance. In the second study we focused on the overall conditional relative prognosis of 7255 patients (compared to age- and sex-matched counterparts in the general population). It reached a plateau after approximately 4 years; a permanent 20% to 25% excess mortality for long-term HNSCC survivors remained. Prognosis is dynamic: the passage of time and the occurrence of life-events change the predicted probabilities of survival. These models enhance our insight in follow-up effects and could be used for better patient counseling.

Chapter 7 ('prognosis of recurrent head and neck cancer') deals with prognosis of patients with recurrent HNSCC's. Optimal counseling and treatment of patients with recurrent head and neck cancer requires an accurate estimate of their prognosis. Patients need updated prognostic information to balance the burden of the new treatment against the possible gain in life expectancy and quality of life. In addition, they need to reorganize their lives and to adapt to the new situation. In contrast to primary tumours, prognostic research into recurrences is scarce. Commonly used adages on the detrimental effect of recurrences could benefit from more statistical founding. We found that recurrences worsen prognosis, the earlier the recurrence the worse the prognosis. We offered practical examples of dynamic, multivariate prognostic models that offer accurate and individualized estimates of prognosis in recurrent disease.

In **chapter 8** ('the effect of age on survival and quality of life in elderly head and neck cancer patients: a long-term prospective study') we discuss the long-term treatment outcome of elderly head and neck cancer patients and their quality of life (QOL). 118 older (≥ 70 years) and 148 younger (45-60 years) patients with head and neck cancer were followed up for 3-6 years. Higher tumour stages, more co-morbidity and non-standard treatment showed to be independent prognostic factors for mortality. No independent prognostic value of age could be found. The global QOL score remained roughly comparable.

Patient characteristics and prognostic factors for survival in the palliative stage of patients with head and neck cancer are described in **chapter 9** ('survival of palliative head and neck cancer patients'). Since November 2003, all patients with palliative head and neck cancer treated in our hospital have been recorded in a central database. In total, 262 deceased patients were included in this retrospective study. The reasons for palliation were inoperability, distant metastases, refusal of curative treatment or poor condition. The mean palliative phase lasted 5.3 months for patients with squamous cell carcinomas. Involvement of a specialized nurse was significantly related with the place of dying: patients who had been treated by a specialized nurse were more likely to die at home or in a hospice instead of the hospital. Moreover, when a specialized nurse was involved, the number of admissions was diminished. Multivariate analysis showed comorbidity and treatment to be independent predictors of survival in the palliative phase. The involvement of a specialized nurse might be associated with an improved quality of life.

An interesting question is whether physicians improve on making accurate predictions of survival when aided by a model. In **chapter 10** ('model-assisted predictions on prognosis in HNSCC: do we learn?') 742 predictions by physicians of 5-year survival on consecutive newly diagnosed patients with head- and neck squamous cell carcinoma are studied. The 5-year survival predictions made by the physicians were not compared with actual survival, but with a prediction produced by OncologIQ, a dedicated software package. We used a linear regression and a linear mixed-effects model to look at absolute differences between both predictions and possible learning effects. Predictions made by the physicians were optimistic and inaccurate. The physicians' learning effect showed little improvement per successive prediction. We conclude that prognostic predictions by a physician in general were imprecise. When given feedback on the model's predicted survival, the accuracy increased, but only very modestly.

After estimating the prognosis the major challenge is to convey this statistical inference to the patient in a way that is satisfactory for both patient and physician. In **chapter 11** ('predicting survival: what about the right side of the curve? thoughts on communicating prognosis') we try to explore the ways in which to do this. We also discuss the usefulness of medical statistics in general.

The presented thesis aims to enhance our insight into prognostic factors of head and neck oncology in general and specifically into time dependent prognostic factors such as the passage of time itself and the occurrence of recurrences. This information can be used to improve patient counseling. Future research should focus on prospective study designs and the usage of prognostic models in treatment decisions.

Samenvatting

Samenvatting

Prognosticeren is het voorspellen van een prognose voor een bepaalde groep patiënten met vergelijkbare patiënt- of tumorkenmerken of het voorspellen van een prognose voor een individuele patiënt. Deze prognose kan worden gebruikt voor het kiezen tussen behandelopties en voor het informeren van de patiënt over het te verwachten verloop van zijn of haar ziekte. In dit proefschrift wordt prognosticeren in het algemeen en de ontwikkeling en mogelijkheden van een aantal prognostische modellen voor patiënten met een maligniteit in het hoofd-hals gebied in het bijzonder besproken. Zowel de prognose van patiënten met een plaveiselcelcarcinoom als de prognose van patiënten met een maligniteit uitgaande van een speekselklier komen aan bod, de nadruk ligt op patiënten met een plaveiselcelcarcinoom. In **hoofdstuk 2** introduceren we het meest gebruikte prognostische middel: de TNM-classificatie. **Hoofdstuk 3 en 4** behandelen de prognostische relevatie van comorbiditeit, cytologie en histologie bij patiënten met een speekselklier maligniteit. Vervolgens richten we ons in **hoofdstuk 5 en 6** op het dynamische karakter van prognose voor patiënten met een plaveiselcelcarcinoom in het hoofd-hals gebied, het centrale thema van dit proefschrift. Specifieke situaties van patiënten met een maligniteit (terugkerende ziekte, voortschrijdende leeftijd en ongeneeslijke ziekte) en de daaraan gekoppelde prognose zijn onderwerp van studie in **hoofdstuk 7, 8 en 9.** De laatste **hoofdstukken (10 en 11)** behandelen het gebruik van prognostische modellen in de praktijk en verschillende aspecten van het communiceren van een prognose naar de patiënt. In deze samenvatting worden de achtereenvolgende hoofdstukken in meer detail samengevat.

Het TNM-classificatiesysteem is een universeel geaccepteerde en op grote schaal gebruikte stadierings-methodiek. De doelstellingen van dit systeem zijn clinici te helpen bij de keuze van behandeling, het geven van een inschatting van de prognose voor patiënten en het vergelijken van behandelresultaten. In **hoofdstuk 2** ('stadiering en prognose in de hoofd hals oncologie') wordt het nut van het TNM-systeem voor patiënten met een maligniteit in het hoofd-hals gebied onderzocht. Hieruit bleek dat op het gebied van prognostische schattingen, vooral voor de individuele patiënt, het standaard TNM-systeem kan worden verbeterd met andere prognostische indicatoren.

In **hoofdstuk 3 en 4** ('de prognostische rol van comorbiditeit bij speekselklier carcinomen' en 'cytologie en histologie hebben een beperkte toegevoegde waarde in prognostische modellen voor speekselklier carcinomen') bestuderen we de prognostische relevantie van comorbiditeit, cytologie en histologie bij patiënten met een maligniteit van een speekselklier. Een cohort van 666 patiënten werd verzameld binnen de Nederlandse Werkgroep Hoofd-Hals Tumoren. Volgens de 'Adult Comorbidity Evaluation-27 (ACE-27) index' hadden 394 patiënten (64%) graad 0 comorbiditeit (geen), 119 patiënten

(19%) graad 1 comorbiditeit (mild), 71 patiënten (12%) graad 2 comorbiditeit (matig) en 29 patiënten (5%) graad 3 comorbiditeit (ernstig). Patiënten met een maligniteit van een speekselklier hadden minder comorbiditeit in vergelijking met patiënten met een plaveiselcelcarcinoom. Hun comorbiditeit was vergelijkbaar met die van patiënten met bijvoorbeeld prostaatkanker, waarbij er ook geen etiologische relatie met alcohol- en tabakmisbruik is. Dit in tegenstelling tot patiënten met een plaveiselcelcarcinoom in het hoofd-hals gebied. In een multivariate analyse voor totale overleving komt de ACE-27 comorbiditeit score als een sterke onafhankelijke prognostische variabele naar voren. Histologie was een onafhankelijke prognostische factor, vooral omdat acinic cell carcinomen zich anders gedragen dan de andere histologische subtypes. Echter, prognostische modellen met en zonder cytologie en/of histologie hadden een vergelijkbare voorspellende kracht. De toegevoegde prognostische waarde van de cytologie en/of histologie bij prognostische modellen voor patiënten met een maligniteit uitgaande van een speekselklier was daarom beperkt. Dit was vooral het gevolg van de gecombineerde prognostische waarde van andere prognostische factoren zoals de grootte van de tumor, N- en M-classificatie en comorbiditeit.

In **hoofdstuk 5 en 6** ('prognose: een variabele parameter. dynamische prognostische modellen in hoofd en hals plaveiselcelcarcinoom' en 'conditionele relatieve overleving in hoofd en hals plaveiselcelcarcinoom: permanent overmatig sterfterisico voor lange termijn overlevers') wordt de dynamiek van prognosticeren verkend. De prognose van patiënten met een plaveiselcelcarcinoom in het hoofd-hals gebied veranderde als ze de eerste kritieke jaren na diagnose van de maligniteit overleefden. Dit gold eveneens voor de prognose van patiënten met lokale of regionale recidieven en metastasen op afstand. Deze eerste studie (**hoofdstuk 5**) was gebaseerd op 2927 patiënten met een primair plaveiselcelcarcinoom in het hoofd-hals gebied. Prognostische modellen werden ontwikkeld na de eerste behandeling en op verschillende tijdstippen tijdens de follow-up. De modellen toonden de effecten van de overlevingstijd, recidieven en metastasen op afstand tijdens de follow-up. De voorspellende waarde van de modellen, uitgedrukt in de oppervlakte onder de curve van een C-statistiek, varieerde van 0,76 tot 0,69, hetgeen matige discriminatie inhoudt. In de tweede studie (**hoofdstuk 6**) richten we ons op de voorwaardelijke relatieve overleving van 7255 patiënten met een plaveiselcelcarcinoom in het hoofd-hals gebied. We vergeleken deze groep met mensen van het zelfde geslacht en van dezelfde leeftijd uit de algemene bevolking. Deze relatieve overleving bereikte een plateau na ongeveer 4 jaar; wat betekent dat er een permanente 20% tot 25% oversterfte voor de lange termijn overlevenden bleef bestaan. We vonden dat de prognose dus dynamisch was: het verstrijken van de tijd en het optreden van life-events veranderden de voorspelde kansen op overleving. De gebruikte modellen hebben ons inzicht in de

dynamiek van follow-up vergroot en kunnen worden gebruikt voor betere counseling van patiënten.

Hoofdstuk 7 ("prognose voor de recurrente hoofd en hals kanker ') behandelt de prognose van patiënten met terugkerende maligniteiten in het hoofd-hals gebied. Optimale begeleiding en behandeling van patiënten met terugkerende ziekte vereist een nauwkeurige schatting van hun prognose. Patiënten hebben geactualiseerde prognostische informatie nodig om de lasten van de nieuwe behandeling af te wegen tegen de mogelijke winst in levensverwachting en kwaliteit van leven. Bovendien moeten zij hun leven reorganiseren en zich aanpassen aan de nieuwe situatie. In tegenstelling tot primaire tumoren is prognostisch onderzoek naar recidieven schaars. Veelgebruikte dogma's over de zeer slechte invloed van recidieven op de prognose zouden baat hebben bij een meer statistische onderbouwing. Uit de studie bleek dat recidieven de prognose verslechteren, hoe eerder het recidief optreedt des te schadelijker. We toonden met dynamische, multivariate prognostische modellen aan dat een nauwkeurige en geïndividualiseerde schatting van de prognose bij terugkerende ziekte gemaakt kan worden.

In **hoofdstuk 8** ('het effect van leeftijd op de overleving en kwaliteit van leven bij oudere hoofd-hals kanker patiënten: een prospectieve lange termijn studie') bespreken we de lange termijn resultaten van de behandeling van oudere patiënten met een plaveiselcelcarcinoom in het hoofd-hals gebied en hun kwaliteit van leven. Er werden 118 oudere (≥ 70 jaar) en 148 jongere (45-60 jaar) patiënten gevolgd gedurende 3-6 jaar. Hogere tumor stadia, meer comorbiditeit en geen standaardiseerde behandeling bleken onafhankelijke prognostische factoren voor sterfte, in tegenstelling tot leeftijd. De globale kwaliteit van leven score van beide groepen bleef ongeveer gelijk.

Kenmerken van patiënten en prognostische factoren voor overleving in de palliatieve fase van patiënten met een plaveiselcelcarcinoom in het hoofd-hals gebied worden beschreven in **hoofdstuk 9** ('overleving van palliatieve hoofd en hals kanker patiënten'). Sinds november 2003 zijn alle palliatieve patiënten in ons ziekenhuis opgenomen in een centrale database. Voor deze analyse maakten we gebruik van de gegevens van 262 overleden patiënten. De redenen voor palliatie waren inoperabiliteit, metastasen op afstand, weigeren van een curatieve behandeling of een slechte conditie. De gemiddelde palliatieve fase duurde 5,3 maanden. Als er een gespecialiseerde verpleegkundige betrokken was bij de palliatieve fase, bleken patiënten vaker thuis of in een hospice te overlijden in plaats van in het ziekenhuis en nam het aantal ziekenhuisopnames af. De multivariate analyse liet zien dat comorbiditeit en type behandeling onafhankelijke voorspellers van overleving in

de palliatieve fase waren. De betrokkenheid van een gespecialiseerde verpleegkundige zou de kwaliteit van leven van de palliatieve patiënten kunnen verbeteren.

Een interessante vraag is in hoeverre artsen er in slagen overleving nauwkeuriger te voorspellen als ze daarbij geholpen worden door een prognostisch model. In **hoofdstuk 10** ('model-ondersteunde voorspellingen van overleving van patiënten met een plaveiselcelcarcinoom in het hoofd-hals gebied: leren we?') zijn 742 voorspellingen door artsen van de 5-jaars overleving op opeenvolgende, nieuw gediagnosticeerde patiënten bestudeerd. De voorspelling van de 5-jaars overleving door artsen werd niet vergeleken met de werkelijke overleving, maar met een voorspelling van OncologIQ, een software pakket. De OncologIQ voorspelling werd gegenereerd op basis van een aantal tumor- en patiënt karakteristieken. We gebruikten verschillende methodieken (lineaire regressie en lineaire mixed-effects models) om te kijken naar absolute verschillen tussen beide voorspellingen en de mogelijke leereffecten. Over het algemeen waren de voorspellingen van artsen te optimistisch en onnauwkeurig. Ook het leereffect na terugkoppeling van successievelijke voorspellingen bleek gering.

Na inschatting van de prognose dient deze ook op een adequate manier te worden gecommuniceerd naar de patiënt. In **hoofdstuk 11** ('Het voorspellen van overleving: hoe zit het met de rechterkant van de curve? gedachten over het communiceren van prognose') hebben we geprobeerd verschillende manieren te bespreken. Hierbij bediscussieerden we ook het nut van medische statistiek in het algemeen.

Dit proefschrift probeert het inzicht in prognostische factoren van hoofd-hals kanker te vergroten. De nadruk wordt gelegd op dynamische factoren zoals het voortschrijden van de tijd na diagnose en het optreden van recidieven. Deze informatie kan gebruikt worden voor betere counseling van patiënten. Toekomstig onderzoek moet zich richten op prospectieve studies en het gebruik van prognostische modellen bij therapeutische beslissingen.

Dankwoord

Dankwoord

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