



UvA-DARE (Digital Academic Repository)

Quality indicators in head and neck oncology

de Ridder, M.

Publication date

2017

Document Version

Final published version

License

Other

[Link to publication](#)

Citation for published version (APA):

de Ridder, M. (2017). *Quality indicators in head and neck oncology*. [Thesis, externally prepared, Universiteit van Amsterdam].

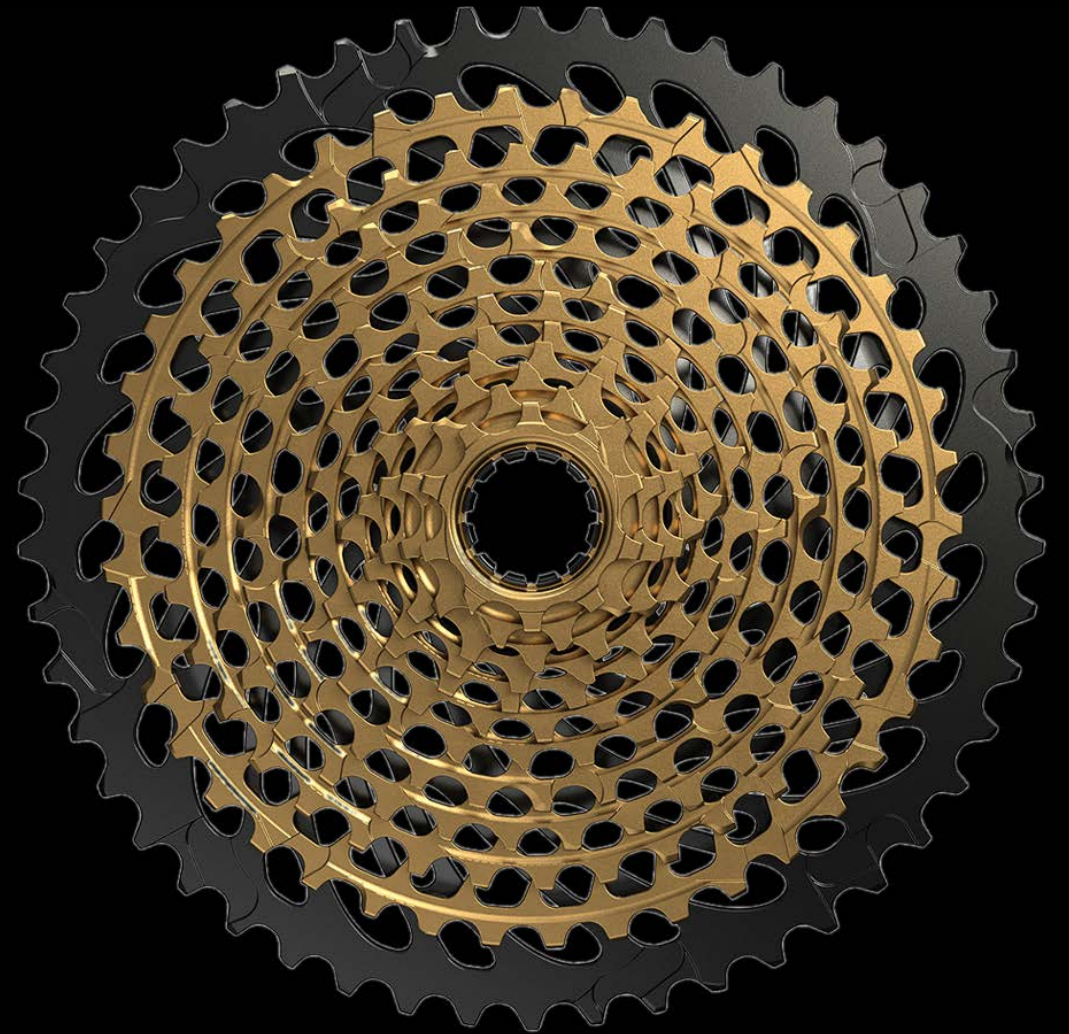
General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

QUALITY INDICATORS IN HEAD AND NECK ONCOLOGY



Mischa de Ridder

QUALITY INDICATORS IN HEAD AND NECK ONCOLOGY

M. de Ridder



2017

QUALITY INDICATORS IN HEAD AND NECK ONCOLOGY

MISCHA DE RIDDER

COLOFON

Cover photo: SRAM™ Eagle MTB cassette

Printed by: Nauka Amsterdam
ISBN: 978-94-91688-08-9
Online: <http://dare.uva.nl>

Printing of this thesis was kindly supported by:
ACTA - KWF

The research described in this thesis was performed at the Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, the Netherlands. This research was partly funded by the Dutch Cancer Foundation. All rights reserved. No part of this book may be reproduced in any form, by print, photocopy, electronic data transfer or any other means, without prior permission of the author.

Copyright © by M. de Ridder 2017

QUALITY INDICATORS IN HEAD AND NECK ONCOLOGY

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel

op dinsdag 12 september 2017, te 12.00 uur

door

Martinus de Ridder
geboren te Woudenberg

PROMOTIECOMMISSIE

Promotores: Prof. dr. A.J.M. Balm, Universiteit van Amsterdam
Prof. dr. L.E. Smeele, Universiteit van Amsterdam

Co-promoteres: Dr. B.A.C. van Dijk, Rijksuniversiteit Groningen
Dr. M.W.J.M. Wouters, Antoni van Leeuwenhoek, Amsterdam

Overige leden: Prof. dr. M.W.M. van den Brekel, Universiteit van Amsterdam
Prof. dr. J. de Lange, Universiteit van Amsterdam
Prof. dr. C. Lucas, Universiteit van Amsterdam
Prof. dr. M.A.W. Merkx, Radboud Universiteit, Nijmegen
Prof. dr. C.H.J. Terhaard, Universiteit van Utrecht
Prof. dr. M.J. van de Vijver, Universiteit van Amsterdam

Faculteit der Tandheelkunde

Aan Denise

CONTENTS

CHAPTER 1.	General introduction and outline of thesis	9
------------	--	---

STRUCTURE INDICATORS

CHAPTER 2.	Volume criteria for the treatment of head and neck cancer: are they evidence based? <i>Head and neck. 2014; 36: 760-762</i>	31
------------	--	----

CHAPTER 3.	Variation in head and neck cancer care in the Netherlands. A retrospective cohort evaluation of incidence, treatment and outcome. <i>European Journal of Surgical Oncology 2017 in press</i>	41
------------	---	----

PROCESS INDICATORS

CHAPTER 4.	The association of treatment delay and prognosis in head and neck squamous cell carcinoma patients in a Dutch comprehensive cancer center. <i>Oral oncology. 2014; 50: 282-290</i>	59
------------	---	----

CHAPTER 5.	The influence of nodal yield in neck dissections on lymph node ratio in head and neck cancer. <i>Oral oncology. 2014; 50: 59-64</i>	79
------------	--	----

CHAPTER 6.	A critical evaluation of lymph node ratio in head and neck cancer. <i>Virchows Archiv. 2016; 469: 635-641</i>	93
------------	--	----

OUTCOME INDICATORS

CHAPTER 7.	An epidemiological evaluation of salivary gland cancer in the Netherlands (1989-2010). <i>Cancer epidemiology. 2015; 39: 14-20</i>	111
CHAPTER 8.	Salivary gland pleomorphic adenoma in the Netherlands: an observational nationwide study on primary tumor incidence and recurrence rate. <i>Oral oncology. 2017; 66: 93-99</i>	129
CHAPTER 9.	Summary, discussion and conclusions Samenvatting (NL) Authors and affiliations List of publications Curriculum vitae auctoris Dankwoord	151

CHAPTER 1

General introduction
and outline of thesis

GENERAL INTRODUCTION

HEAD AND NECK CANCER

Head and Neck cancer represents a heterogeneous group of tumors. The majority of these lesions arises from the mucosa of the upper aerodigestive tract and is classified as squamous cell carcinomas. Other, rarer entities are adenocarcinomas or sarcomas. Classical risk factors for the development of mucosal head and neck squamous cell cancer are smoking, alcohol consumption or the combination of both¹. The last decades the HPV-16 was added as an important etiologic factor mostly affecting younger patients². Nasopharyngeal carcinoma, except for squamous cell carcinoma, forms an exception to the above-mentioned etiologies and is strongly related to Epstein Barr virus, but genetic factors and environmental influences are also of importance in the pathogenesis of this disease. Much less is known about the etiology of salivary gland cancer. Exposure to radiation in the past is suggested as risk factor, based upon studies of atomic bomb survivors from Japan³ and patients irradiated in their childhood for any cause^{4,5}.

For initial treatment, surgery was long considered the only curative treatment option for most head and neck carcinomas. Since this treatment modality causes serious functional deficits in locally advanced cases, the combination of chemotherapy and radiotherapy gained terrain rapidly as organ sparing therapy during the last decades⁶. Next to chemoradiotherapy, radio-sensitizing drugs (like the monoclonal antibody cetuximab) were introduced in order to improve outcome⁷. The radiation component of these multimodality treatments has improved over the last decade. The introduction of intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) have led to an improvement of efficacy and also decreased toxicity (i.e. xerostomia) of radiotherapy, compared to the previously used 3D conformal technique^{8,9}. Surgical techniques also evolved during the last decades, with the introduction of minimal invasive techniques, such as CO2 laser¹⁰ and transoral robotic surgery¹¹ for small, localized cancers in the oral cavity, larynx and pharynx. The anatomically complex head and neck area makes treatment of head and neck cancer challenging, particularly since there is a delicate balance between functional and oncologic outcome. The influence of inter-patient variety and treatment choices on this balance makes that the field of head and neck cancer can be classified as “high-risk” cancer care.

CONCEPT OF QUALITY

In general, quality of an ordinary product is defined by the phrase: “It does what you expect of it to do”. This might be a realistic expectation for simple products, but defining “quality” in healthcare is much more complex for multiple reasons. The Institute of Medicine¹², a division of the National Academies of Science, Engineering and Medicine in the USA, issued the following definition for quality of care: “Quality of care is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge”¹². It helps government and patients by providing information to make proper health decisions and by providing robust evidence with help of experts in the field. Another, more detailed definition, also issued by the same institute is: “Getting the right care, to the right patient, in the right setting, in the right way, by the right (team of) doctors, at the right time, every time!”

Within quality of care several quality domains can be defined¹³:

<i>Safety</i>	Health care is intended to help patients, so adverse events must be avoided at any time.
<i>Effectiveness</i>	Use the available health care wisely, according to up to date scientific data. In short: avoid over- and underuse of the available health care facilities.
<i>Patient-centered</i>	Health care should be provided in a tailored fashion to individual patients with respect to all patients’ with their preferences, needs and values.
<i>Timeliness</i>	Finding the optimal balance between available health care facilities and reducing (harmful) delay.
<i>Efficiency</i>	In this era of increased interest in durability, also health care providers must minimize waste of products, but also minimize waste of time, ideas and energy.
<i>Equity</i>	It must be unthinkable that quality of provided care is based on ethnicity, gender, geographic location and socio-economic status.

In order to critically evaluate quality of care, the perspective needs to be clear. Each time one has to question whether it concerns the health care system as a whole, a single health care institution, a single health care professional or a specific intervention^{14,15}. After assuring the domain focus and the approach, the next step concerns the evaluation of the actual quality. In this thesis our focus is on the domains: safety and effectiveness.

In 1988, Donabedian et al.¹⁵ suggested the implementation of an indicator model, based upon three types: structure, process and outcome indicators. All three are separately involved in assessment of quality, but are also causally cross-linked. Nevertheless, by exploring these three separately, it is possible to gain better insight in the complexity of health care quality assessment. The following issues have to be addressed before assessing quality: Who is being assessed? What are the activities being assessed? How are these activities supposed to be conducted? What are they meant to accomplish?

After analyzing these issues, the context of the system being assessed might become more evident.

I. STRUCTURE INDICATORS

Structure indicators describe the health care environment, the setting in which care is provided. Examples in this group are the number of qualified personnel and the equipment of the assessed facility. Structure indicators are meaningful for explanation of results of exceptional surgeries like pancreaticoduodenectomies¹⁶, esophagectomies¹⁷, cystectomies¹⁸ and other high risk surgeries like open cardiac surgery¹⁹. The use of structural indicators often has the advantage of easy and inexpensive access to data, mostly administrative of origin. The biggest disadvantage of using these indicators is that they are only proxies for quality of care and no guarantee for it. Moreover, structural indicators lack the opportunity to learn from differences in care processes. The consequence of using structural indicators is that clinical improvements are obtained more slowly or even impossible: low volume hospitals cannot turn into high volume hospitals at once.

II. PROCESS INDICATORS

Process indicators describe the process of health care using organizational parameters involved in the primary care process. This involves the whole diagnostic and, medical decision-making process as well as the treatment trajectory. Often-discussed examples of process indicators are waiting times, discussion in a multidisciplinary team (MDT) and pre-operative antibiotics. Process indicators are mostly based on evidence-based guidelines or consensus-based quality standards, and measure the adherence to these guidelines or standards on a patient level. An often-used example of a process indicator is waiting time. The shorter-the better is the adagio for waiting times, but is it gut feeling or evidence based?

Another example of a process indicator is the routing of surgical specimen after resection, i.e. the way histopathology is acquired and reported.

As mentioned above, evidence based guidelines are often the foundation for process indicators, which measure the implementation of these guidelines in real clinical practice (locally or nationally). Examples of these are diagnostic trajectory guidelines and definition of optimal treatment regimes. For instance, magnetic resonance imaging (MRI) has superior soft tissue contrast that is crucial for delineating tumor extension in the head and neck area. However, MRI has its limitations in moving target volumes, i.e. the larynx during swallowing reflexes, thus for imaging of the laryngeal area a more rapid imaging technique, computer tomography (CT), is preferred. This illustrates the basis of a process indicator evaluating the use of the right diagnostic modality for the right tumor extension.

Many process indicators are based on what is considered strongly evidence based, i.e. based on results from randomized trials or meta-analyses. New scientific evidence can change 'state of the art' care processes within short time periods. Striking examples of randomized trials in the head and neck cancer treatment leading to paradigm shifts are: the Veterans Affairs Administration²⁰ and RTOG²¹ organ preservation trials in laryngeal cancer with platinum-based chemo-radiotherapy. The RADPLAT trial²², showing the non-inferiority of intravenous administration of Cisplatin compared with intra-arterial delivery of Cisplatin and the Bonner trial⁷ combining Cetuximab and radiation for organ preservation with less toxicity. These studies have led to alterations in guidelines.

Although working according to guidelines can be seen as useful process indicator, there remain some pitfalls. For instance: trial populations may differ substantially from the population of patients seen in daily practice, which may hamper the one-on-one transfer of (positive) trial results. Or what used to be state of the art care can change over time, causing the process indicator outdated, especially if a guideline is not changed quickly enough. For example: the above-mentioned RTOG91-11²¹ became the standard for larynx preserving therapy in a very short time frame, although the pendulum now seems to swing back in favor for surgical treatment²³.

Process indicators have proven to be of general importance since the 20th century. However, they also carry possible disadvantages like the easy influences of population mismatches. A currently discussed topic in head and neck cancer societies, in line with population mismatch, is whether all data on oropharyngeal cancer also count for HPV positive tumors²⁴, because over the years they have constituted a distinct entity²⁵. General process indicators developed for oropharyngeal cancer might fall short in the current practice where there is a dichotomy in oropharynx cancer based on HPV status. Reason for this shortcoming is that increasing evidence appears about differences in, for instance chemo- and radiotherapy sensitivity between HPV positive and HPV negative oropharyngeal cancers²⁶.

Currently a multicenter prospective randomized trial (NCT01687413) is accruing patients to determine whether treatment de-intensification is safe in HPV positive oropharyngeal cancer patients. This data can be used to define HPV positive/negative specific process indicators.

Moreover, despite the availability of a validated guideline, in the era of shared decision-making, sometimes patients choose for personal reasons to be treated differently than the guideline prescribes. Therefore, process indicators should not pursue 100 percent guideline adherence, because real world clinical practice differs from the trials the guidelines were based on. These two examples show clearly the difficulty in defining evidence based process indicators. This stresses the need for choosing carefully relevant indicators and to update them regularly.

III. OUTCOME INDICATORS

The third component of Donabedian's paradigm consists of outcome indicators, which denote the actual outcome of health care, provided, tailored to the health of individual patients or populations. The final outcome is what counts most for individual patients and doctors. From an economical point of view, health insurance companies are interested in outcome as well, because this helps them to decide which hospital to contract for a specific care product. The involved parameters cover a broad spectrum ranging from very objective (death) to more subjective [questionnaires, like patient reported outcome (PROM) and experience (PREM) measures]. This spectrum contains on the one hand pearls, for example the opportunity to inform patients on outcome for their specific disease, but on the other hand also pitfalls when an outcome measure does not match with the clinical significance. For example, overall survival is not always a meaningful outcome parameter in palliative care, while it is meaningful in curative care. So when interpreting outcome parameters one needs to know the context in which they were measured and investigated. Another aspect of outcome indicators is that outcome is often determined by a combination of factors instead of by one specific factor. This makes it difficult to design effective measures to improve outcome. Interpreting differences in indicators and thus assessment of quality of care is only possible by knowing the cross-linked connection between the three types of indicators. An example to illustrate the complexity of assessment of quality of care delivered by individual providers can be illustrated for laryngectomies performed in different institutes:

STRUCTURE:

- o Are these laryngectomies performed in a certified head and neck cancer center?
- o What is the procedural volume of laryngectomies in this specific center?

PROCESS:

- o Are all pharyngeal defects primary closed?
- o How is the closure procedure conducted?
- o Is oral intake resumed immediately post-surgery²⁷?
- o Are patients discussed in a MDT meeting?

OUTCOME:

- o What is the complete resection rate?
- o How many patients have had complications postoperatively and how many die due to these complications (failure to rescue)?
- o How is the quality of life?

To make valid comparisons in quality of care between centers performing laryngectomies, risk-adjustment of outcome indicators must be appropriate and could be focused on the unraveling of differences between centers with attention for:

- o Percentage of patients with multiple comorbidities
- o Percentage of smokers
- o Percentage of locally advanced tumors
- o Percentage of primary tumors vs. recurrences
- o Percentage of patients with prior treatment with radiotherapy

The connection between the different indicators can be illustrated by the following hypothetical example: a certain hospital has the opportunity to appoint an additional, certified head and neck specialist (structure indicator – number of certified specialists). Due to this extra physician the outpatient clinic capacity increases and waiting times for patients shorten (process indicator – time between first visit and treatment). Also, the volume of the hospital can be increased (in case the number of patients is unlimited). Previously, the organization of a MDT meeting was not possible due to an under-staffed department, but now regular MDT meetings can be organized (process indicator – number of patients discussed in a MDT). This might lead to improved treatment strategies reflected in higher complete resection rates, better survival and quality of life (outcome parameters).

However, it remains still unclear which parameter is crucial for the improved outcome of the individual patient: it could be the experience of the surgeon, the MDT discussion, or the shorter waiting time or a combination of these factors.

The quality of care concept of Donabedian et al¹⁵ is a tool to clearly describe and organize quality of care. The two components (structure, process) are complementary to each other and all components are necessary to describe quality as complete as possible [figure 1].

QUALITY IMPROVEMENT

Randomized controlled trials

Striving for the best result for the individual patient is an inherent trait of health care professionals. One of the tools to achieve better clinical results is by conducting Randomized Controlled Trials (RCT). Pubmed generates almost 400,000 hits for RCTs from 1970 to 2015. Half of these RCTs are published during the last ten years, indicating the increased interest in health care improvement. Whether this flood of data leads to optimal quality of care for every patient remains questionable. Quality or impact of a single RCT (as can be assessed by the critical appraisal tool for RCT (Oxford university 2005 ©) can be too limited to initiate changes in nationwide guidelines (strict inclusion criteria or inappropriate primary outcome). However, it can provide useful information for the treatment of specific subgroups of patients. Moreover, limited impact RCTs can be included in meta-analyses contributing to highly powered evidence. Not all clinical questions regarding clinical problems in individual cases can be solved by RCTs. To search for epidemiological trends or to investigate outcome from one institute, population-based or cohort studies can be more suitable and can provide 'real world' clinical evidence for smaller patient groups.

Quality standards

Next to all research efforts, several other strategies are internationally used to improve quality of care, for instance: regulation of care, marketplace competition, payment incentives, or the introduction of a program for continuous improvement of quality (which is encouraged by organizations like The Joint Commission on Accreditation of Healthcare Organization, the National Committee for Quality Assurance)²⁸ or in the Netherlands "Quality institute" as part of "The national health care institute".

The most relevant factor for the Dutch situation is regulation of care and can be determined by setting minimal volume standards. The Dutch Federation of Oncologic Societies (SONCOS) was founded in 2009 with the objective to improve collaboration between three oncology-oriented specialisms (surgical oncology, medical oncology and radiation oncology). One of the achievements of SONCOS is a structured document with multidisciplinary quality standards for oncologic care in general and for each tumor type.

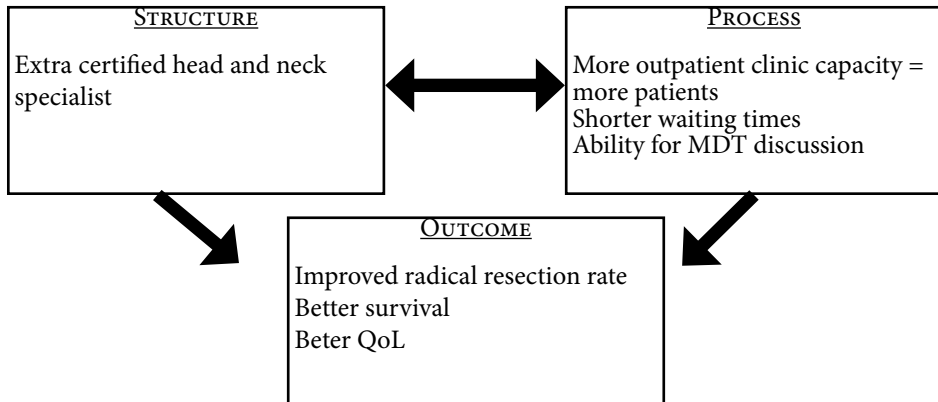


Figure 1 Example of the relation between quality indicators. This example starts with an extra certified head and neck specialist. Due to extra capacity, shorter waiting times and increased patient volume could be reached. This creates higher efficiency and leads to improved oncologic outcome and patient quality of life (or another patient reported outcome) with two components (structure and, process) acting in a complementary fashion.

Today, more than 20 professional societies contribute to this document and most stakeholders, like the Health Care Inspectorate (IGZ), health care Insurance companies, hospitals and policy makers have adopted the SONCOS quality standards. Cancer or procedure specific volume standards are an important part of the document and are the only standards that can be actively enforced by insurers and inspectorate.

Volume

Luft et al.²⁹ were the first to publish on volume-outcome relationship as quality indicator in surgery. In their paper they questioned whether higher hospital volume leads to lower mortality²⁹. In total 1498 hospitals were included and 12 procedures of varying complexity were examined. In a multiple regression model, including hospital size, teaching status, geographical location and cost improvement, volume was one of the most important factors determining mortality. The authors concluded that experience and health care infrastructure were the main explanations for this finding in high-risk surgery.

Many studies^{16,17,30-34} have shown beneficial outcome for high volume hospitals, using mortality and/or survival as outcome. Soon it became clear that this relationship was most clear in high-risk procedures like pancreaticoduodenectomies (i.e. Whipple procedure), esophagectomies, gastrectomies, cystectomies and radical prostatectomies (table 1)^{16,17,30-32}.

Author	Year	N=	Procedure	Outcome	Volume effect
Van Heek ¹⁷	2005	19688*	Pancreaticoduodenectomy	Mortality	Hospital volume: inverse relation
Wouters ¹⁸	2012	80202*	Esophagectomy	Mortality	Hospital volume: inverse relation
Wilt ²¹	2008	206141*	Radical prostatectomy	Mortality	Hospital volume: inverse relation
Van Gijn ²⁵	2010	80481*	Colorectal	Mortality	Hospital volume: inverse relation
Dikken ³⁰	2013	n.r.*	Gastrectomy	Mortality	Hospital volume: inverse relation
Hollenbeck ³²	2007	4465*	Cystectomy	Mortality	Hospital volume: inverse relation

Abbreviations: n.r. not reported. * Systematic reviews

In conclusion, although volume as quality indicator is determined by multiple parameters, currently available data repeatedly show that higher hospital volume leads to better outcome in different types of high-risk surgery^{16,18,34,36,37}. Therefore, centralization of services for high-risk or complex cancer treatment could lead to quality improvement and better outcomes. Pieper et al.³⁴ evaluated 5 systematic reviews on the volume-outcome relationship for clinical outcome (postoperative mortality, complications and survival) in surgery. Fourteen types of surgery, including benign as well as malignant diseases, were included. Besides the positive volume- outcome relationship, the authors defined some methodological pitfalls. The first is the definition of high volume hospitals: numerically high volume hospitals in the Netherlands for example could be defined as low volume in the United States, indicating that the definition of high volume hospitals is partly geographically determined. For a proper judgment of volume effects, correction for case-mix is indisputable, although it remains impossible to correct for every single variable of case-mix. This renders volume to be a surrogate indicator for several unknown factors. For example, a high volume hospital with a well-functioning tumor board, might lead to excellent patients' outcomes, while the actual interaction of the tumor board remains an undetectable factor.

Clinical Audit

Next to regulation of care by setting volume standards, programs for continuous improvement of quality are important. Registration programs play a pivotal role in this respect. In the Netherlands, registries like: "The nationwide network and registry of histo- and cytopathology in the Netherlands" [PALGA] and the Netherlands Cancer Registry (NCR) were founded in the eighties. This NCR covers all newly diagnosed cancers by registering all pathology reports and hospital discharge diagnoses.

Specifically trained data managers gather several patient, tumor and treatment parameters in the individual hospitals. Vital status is annually assessed by linkage to Municipal Personal Records (in Dutch: “Basisregistratie Personen or BRP”). Over the years, the nation-wide coverage reached at least 95%³⁸. This registry is a unique base for epidemiological studies and due to its high coverage it is also suitable for quality control studies.

Individual hospitals have been scoring complications for decades, but since 2000 better-organized registries started evaluating the whole process of hospital care and its outcome, adjusting for differences in case-mix between participating hospitals. An example are the 23 quality registries of the Dutch Institute for Clinical Auditing (DICA)³⁹, which was founded in 2010 after the successful initiation of the Dutch Surgical Colorectal Audit in the Netherlands. Initially, the DSCA was a surgery-based registry, which started with the registration of primary colorectal cancer patients’ characteristics, treatment and outcome. Feedback is given continuously through a web-based system in which hospitals find their own results in perspective to the other hospitals in the country (benchmarking). This is called the audit-feedback principle and leads to an awareness of each hospital’s performance in comparison to the rest of the hospitals. In case hospitals persistently perform below the national average, this system will give a notice. A team of specialists appointed by the Association of Surgeons in the Netherlands will visit such a hospital to try to identify points for improvement, resulting in a thorough problem analysis and quality improvement program. Subsequently the continuous audit monitors the effect of the initiated quality improvement programs, which completes the “audit-cycle”.

HEAD AND NECK CANCER AND QUALITY

The head and neck departments in the Netherlands have been pioneers in centralizing multidisciplinary care in order to improve quality. Already in 1984 the Dutch Head and Neck collaborative group was founded⁴⁰. Goals were initially to share knowledge and collaborate in research, but soon after foundation quality improvement was added by stating that every single malignant head and neck tumor should be treated in one of the eight head and neck cancer centers or one of the preferred partners. This resulted in a centralization rate of above 95% in the mid 90’s⁴¹. The remaining 5% possibly were small T1 laryngeal tumors that were easily removed by the oto-rhinolaryngologist or salivary gland carcinomas that were thought to be benign on preoperative workup. Nowadays, six preferred partner hospitals are participating in the Netherlands head and neck oncology center network, resulting into 14 certified head and neck centers in the country.

Head and neck cancer patients often deal with swallowing problems and impaired speech either induced by tumor growth or by treatment, with serious consequences for their quality of life.

Since both function and esthetics are easily affected, treatment of head and neck cancer is typically dependent on a multidisciplinary approach, in which the surgeon (oncologic and reconstructive), radiation oncologist, medical oncologist and paramedics play their individual roles.

An integrated multidisciplinary care program, containing all disciplines, has led to increased patients satisfaction and higher quality of life⁴². Such a quality improvement program is made up by different indicators, which cover all three fields of quality (structure, process and outcome). Ouwens et al.⁴³ developed a set of clinical quality indicators consisting of eight specific integrated care indicators (for instance, availability of a clinical pathway, case managers and the number of patients that feel well informed) and 23 specific head and neck indicators (for instance, availability of head and neck radiologists, number of patients with swallowing problems and the availability of a multidisciplinary stop-smoking program)⁴³. With this set of indicators, they studied head and neck cancer care quality in one certified Head and Neck Center. They found that especially assessment of nutrition, waiting times; swallowing and speech rehabilitation and emotional support leave room for improvement. All of these were patient-oriented items, showing the gap in focus between doctors and patients in relation to quality of care improvement. An implementation study of the program published by Ouwens et al.⁴⁴ also showed the positive effect of such integrated care program on quality of care in head and neck cancer patients, especially on patient information by introducing an information folder, waiting times by optimizing the process and improved nutrition guidance by strict dietician control (improvement from 44% to 88% in dietician visits). The multidisciplinary rehabilitation program after treatment for head and neck cancer is another example of an evidence based quality improvement program. This program contains a dedicated multidisciplinary (para-) medical team of specialists in rehabilitation aiming for a personalized rehabilitation program, which leads to improvement in health related quality of life and also in less distress⁴⁵.

The aforementioned audit-feedback principle, like the DICA system, has also been assessed for head and neck surgeons in MD Anderson, Houston Texas⁴⁶. Investigators evaluated a patient cohort containing 2618 procedures (2004 – 2008). After evaluation several (quality) indicators they confronted the surgeons/departments with their individual performance. Thereafter, they evaluated a post feedback series of procedures (n=1389) from 2009-2010, to check the influence of feedback on performance. They found a significant decrease in the mean length of stay as well as the number of negative performance measures (mortality, readmission, reoperation, surgical site infection, blood transfusion).

This thesis deals with an exploration of potential indicators in a well-centralized head and neck cancer setting and is outlined as follows.

OUTLINE OF THE THESIS

Quality of health care is a very large and unbounded concept. In order to streamline this research project, the concept of quality assessment of Donabedian et al¹⁵ was used. This thesis describes quality of head and neck cancer care in the Netherlands. It is divided into the three components of quality indicators, which are structure, process and outcome.

STRUCTURE INDICATORS

Because head and neck cancer is centralized the Netherlands, the question arose whether increasing volume of hospitals improves outcome. In [CHAPTER 2](#) a literature search was performed to find evidence whether higher (centralized) volume in head and neck is associated with better outcome.

In [CHAPTER 3](#) variation of care was evaluated in seven head and neck cancer centers and three preferred partner hospitals to assess whether centralization leads to uniformity in diagnostic and treatment processes

PROCESS INDICATORS

In [CHAPTER 4](#) we analyzed the influence of waiting times in the Netherlands Cancer Institute on survival as process indicator. Processing of pathological specimens is another important process indicator, which is almost unknown among clinicians. All of the steps involved in the pathology process are quality sensitive steps, meaning that small disturbances can lead to misinterpretation or even wrong diagnosis. To uniform these steps all pathology laboratories in the Netherlands work with quality assured protocols.

The influence of a pathology protocol change has been investigated in [CHAPTER 5](#) with focus on lymph node yield in neck dissection specimens, comparing two examination protocols.

[CHAPTER 6](#) focuses on the outcome variation evolving from the pathology protocol of lymph node dissections. In this chapter we studied the variation in prognostic value of Lymph Node Ratio (LNR) in relation to changes in pathology protocols.

OUTCOME INDICATORS

Outcome in cancer care is mostly defined as overall survival or disease specific survival. Besides the variation of care, [CHAPTER 3](#) also describes different outcome indicators (survival and recurrence rate) for head and neck squamous cell carcinomas in the Netherlands.

This chapter specifically describes variables (including hospital volume) influencing the outcome of head and neck cancer patient cohort from 2008.

Despite the fact that salivary gland carcinoma treatment should be centralized in head and neck cancer centers; the centralization rate remains lower for salivary gland tumors compared to most other head and neck carcinomas. Salivary gland tumors are unique since this group consists of both benign and malignant neoplasms. To achieve better knowledge of the epidemiology of salivary gland carcinoma we performed nationwide studies on outcome of salivary gland carcinomas over the past 21 years (CHAPTER 7) and pleomorphic adenoma over the same period (CHAPTER 8).

REFERENCES

1. Talamini R, Bosetti C, La Vecchia C, et al. Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. *Cancer causes & control* : CCC 2002;13:957-64.
2. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2005;14:467-75.
3. Saku T, Hayashi Y, Takahara O, et al. Salivary gland tumors among atomic bomb survivors, 1950-1987. *Cancer* 1997;79:1465-75.
4. Boukheris H, Ron E, Dores GM, Stovall M, Smith SA, Curtis RE. Risk of radiation-related salivary gland carcinomas among survivors of Hodgkin lymphoma: a population-based analysis. *Cancer* 2008;113:3153-9.
5. Schneider AB, Lubin J, Ron E, et al. Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose-response relationships. *Radiat Res* 1998;149:625-30.
6. Pignon JP, le Maitre A, Maillard E, Bourhis J, Group M-NC. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2009;92:4-14.
7. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* 2010;11:21-8.
8. Gupta T, Agarwal J, Jain S, et al. Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: a randomized controlled trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2012;104:343-8.
9. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011;12:127-36.
10. Grant DG, Repanos C, Malpas G, Salassa JR, Hinni ML. Transoral laser microsurgery for early laryngeal cancer. *Expert Rev Anticancer Ther* 2010;10:331-8.
11. van Loon JW, Smeele LE, Hilgers FJ, van den Brekel MW. Outcome of transoral robotic surgery for stage I-II oropharyngeal cancer. *Eur Arch Otorhinolaryngol* 2015;272:175-83.
12. Institute of Medicine. 2001.
13. Institute_of_Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. 2001.
14. Evans DB, Edejer TT, Lauer J, Frenk J, Murray CJ. Measuring quality: from the system to the provider. *International journal for quality in health care : journal of the International Society for Quality in Health Care / ISQua* 2001;13:439-46.
15. Donabedian A. The quality of care. How can it be assessed? *JAMA* 1988;260:1743-8.
16. van Heek NT, Kuhlmann KF, Scholten RJ, et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. *Ann Surg* 2005;242:781-8, discussion 8-90.
17. Wouters MW, Gooiker GA, van Sandick JW, Tollenaar RA. The volume-outcome relation in the surgical treatment of esophageal cancer: a systematic review and meta-analysis. *Cancer* 2012;118:1754-63.
18. Goossens-Laan CA, Gooiker GA, van Gijn W, et al. A systematic review and meta-analysis of the relationship between hospital/surgeon volume and outcome for radical cystectomy: an update for the ongoing debate. *European urology* 2011;59:775-83.

19. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med* 2011;364:2128-37.
20. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med* 1991;324:1685-90.
21. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol* 2013;31:845-52.
22. Rasch CR, Hauptmann M, Schornagel J, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial. *Cancer* 2010;116:2159-65.
23. Timmermans AJ, de Gooijer CJ, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. T3-T4 laryngeal cancer in The Netherlands Cancer Institute; 10-year results of the consistent application of an organ-preserving/-sacrificing protocol. *Head Neck* 2015;37:1495-503.
24. Dahlstrom KR, Garden AS, William WN, Jr, Lim MY, Sturgis EM. Proposed Staging System for Patients With HPV-Related Oropharyngeal Cancer Based on Nasopharyngeal Cancer N Categories. *J Clin Oncol* 2016;34:1848-54.
25. Lewis A, Kang R, Levine A, Maghami E. The New Face of Head and Neck Cancer: The HPV Epidemic. *Oncology (Williston Park)* 2015;29:616-26.
26. Kelly JR, Husain ZA, Burtness B. Treatment de-intensification strategies for head and neck cancer. *Eur J Cancer* 2016;68:125-33.
27. Timmermans AJ, Lansaat L, Kroon GV, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Early oral intake after total laryngectomy does not increase pharyngocutaneous fistulization. *Eur Arch Otorhinolaryngol* 2014;271:353-8.
28. Chassin MR, Galvin RW. The urgent need to improve health care quality. Institute of Medicine National Roundtable on Health Care Quality. *JAMA* 1998;280:1000-5.
29. Luft HS. The relation between surgical volume and mortality: an exploration of causal factors and alternative models. *Med Care* 1980;18:940-59.
30. Dikken JL, Stiekema J, van de Velde CJ, et al. Quality of care indicators for the surgical treatment of gastric cancer: a systematic review. *Ann Surg Oncol* 2013;20:381-98.
31. Wilt TJ, Shamlivyan TA, Taylor BC, MacDonald R, Kane RL. Association between hospital and surgeon radical prostatectomy volume and patient outcomes: a systematic review. *J Urol* 2008;180:820-8; discussion 8-9.
32. Hollenbeck BK, Wei Y, Birkmeyer JD. Volume, process of care, and operative mortality for cystectomy for bladder cancer. *Urology* 2007;69:871-5.
33. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128-37.
34. Pieper D, Mathes T, Neugebauer E, Eikermann M. State of evidence on the relationship between high-volume hospitals and outcomes in surgery: a systematic review of systematic reviews. *J Am Coll Surg* 2013;216:1015-25 e18.
35. van Gijn W, Gooiker GA, Wouters MW, Post PN, Tollenaar RA, van de Velde CJ. Volume and outcome in colorectal cancer surgery. *Eur J Surg Oncol* 2010;36 Suppl 1:S55-63.
36. Aquina CT, Probst CP, Becerra AZ, et al. High volume improves outcomes: The argument for centralization of rectal cancer surgery. *Surgery* 2015.
37. Cheung MC, Koniaris LG, Perez EA, Molina MA, Goodwin WJ, Salloum RM. Impact of hospital volume on surgical outcome for head and neck cancer. *Ann Surg Oncol* 2009;16:1001-9.
38. van der Sanden GA, Coebergh JW, Schouten LJ, Visser O, van Leeuwen FE. Cancer incidence in The Netherlands in 1989 and 1990: first results of the nationwide Netherlands cancer registry. Coordinating Committee for Regional Cancer Registries. *Eur J Cancer* 1995;31A:1822-9.

39. <http://www.dica.nl> (accessed March 2017).
40. <http://www.nwhht.nl> (accessed March 2017)..
41. Nederlandse Werkgroep HoofdHals Tumoren (NWHHT) journal. 2010;43.
42. Ouwens M, Wollersheim H, Hermens R, Hulscher M, Grol R. Integrated care programmes for chronically ill patients: a review of systematic reviews. *International journal for quality in health care : journal of the International Society for Quality in Health Care / ISQua* 2005;17:141-6.
43. Ouwens MM, Marres HA, Hermens RR, et al. Quality of integrated care for patients with head and neck cancer: Development and measurement of clinical indicators. *Head Neck* 2007;29:378-86.
44. Ouwens MM, Hermens RR, Hulscher MM, et al. Impact of an integrated care program for patients with head and neck cancer on the quality of care. *Head Neck* 2009;31:902-10.
45. Passchier E, Stuiver MM, van der Molen L, Kerkhof SI, van den Brekel MW, Hilgers FJ. Feasibility and impact of a dedicated multidisciplinary rehabilitation program on health-related quality of life in advanced head and neck cancer patients. *Eur Arch Otorhinolaryngol* 2016;273:1577-87.
46. Lewis CM, Monroe MM, Roberts DB, Hessel AC, Lai SY, Weber RS. An audit and feedback system for effective quality improvement in head and neck surgery: Can we become better surgeons? *Cancer* 2015;121:1581-7.

STRUCTURE INDICATORS

CHAPTER 2

2

Volume criteria for the treatment of head and neck cancer: Are they evidence based?

Mischa de Ridder
Ludi E. Smeele
Michiel W. M. van den Brekel
Michel C. van Harten
Michel W. J. M. Wouters
Alfons J. M. Balm

Rising health care costs and increasing incidence of cancer prioritize the improvement of the effectiveness of cancer care¹. This induces a progressing interest in quality indicators measuring the quality and effectiveness of health care in a standardized way. These indicators comprise 3 categories focused on structural, process, and outcome aspects². They are developed to measure health care performance and compare health care providers, for example, on postoperative complication rates, reinterventions, blood transfusions, length of hospital stay, and mortality. In colorectal cancer, measuring the hospitals' performance on these indicators have played decisive roles at several levels of health care management and economics³.

PROCEDURAL VOLUME

One of the quality indicators frequently mentioned in literature is procedural volume, hospital, or surgeon based⁴. The rationale lying behind this indicator is the notion that the experience of a surgeon with a certain, often complex surgical procedure is related to the outcome⁵. However, experienced surgeons do not treat patients on their own, a multi-disciplinary team of medical specialists and nurses is involved in the care for individual patients. Therefore, hospital volume can act as a surrogate for surgeon volume, although it also adds additional information on the quality of care provided.

Generally, high-volume hospitals have more specialized (diagnostic) facilities, well-organized multidisciplinary meetings, and shorter diagnosis–treatment interval. Thereby, high-volume centers tend to adhere more to national guidelines; the volume effect may also partly represent the institutional organization.

PROCEDURAL VOLUME AND OUTCOME FOR OTHER CANCER PROCEDURES

Over the past decade, a strong relation between hospital volume and survival has been reported, suggesting that procedural volume is an important determinant of outcome in surgery and patient care^{4–13}. Birkmeyer et al⁷ studied the impact of volume of surgical cancer treatment in general and reported a statistically significant inverse relation (adjusted mortality decreased in high-volume centers ranging from 20.3% to 8.4% after esophagectomy and from 2.6% to 2.1% after nephrectomy). This publication was followed by many confirmatory reports, next to esophagectomy, also focusing on other specific high-risk low-volume procedures, like radical prostatectomy and pancreatectomy^{8–10}. Wouters et al⁸ performed a systematic review of 43 studies (>70,000 patients), studying the relation between volume and outcome in esophagectomies.

They concluded that outcome of esophageal cancer surgery is significantly better when performed at a high-volume hospital. Next to esophagectomies, this correlation has also been established in a systematic review for pancreatectomy by van Heek et al⁹. They included 12 studies with >19,000 patients and found that pancreatic resections performed at high-volume hospitals had lower mortality rates than low-volume hospitals (0% to 3.5% vs 13.8% to 16.5%; $p < .001$). In a recently published systematic review covering >30 (n532) systematic reviews for different surgical procedures (oncology and non-oncology), it was concluded that, especially for cancer procedures, there is a tendency to support a hospital-volume-outcome relationship¹⁴. Although they were able to summarize evidence, they did not attempt to calculate the minimum volumes (cutoff values) required to provide high-quality cancer care.

HEAD AND NECK CANCER

For head and neck cancer, surgery is still the mainstay of primary treatment and its role as salvage treatment after (chemo-)radiation is increasing. As stated before, in general, head and neck surgical procedures are of a high-risk nature and are often performed in a low-volume setting. The risk of functional sequelae is high by the impact of surgery on swallowing, speech, self-image, and shoulder function with a major influence on the patient's quality of life. The essence of high-risk surgical care in this patient group is always balancing between complete resection and preservation of function¹⁵. In contrast to the plethora of studies on the volume aspects of other high-risk cancer surgeries, a literature search of volume aspects in head and neck surgery did reveal only 8 suitable articles published in the English language¹⁶⁻²³. An overview of these studies is available in Table 1. These studies did not exceed a total number of 19,000 patients. It remains disappointing that head and neck cancer, which can be characterized as a relatively rare disease with a typical low-volume high-risk profile, contrasts so significantly with the analysis of volume aspects of other surgical procedures. The main reason could be that in contrast to esophagectomies, for example, the studies performed in head and neck cancer evaluate a group of various disease entities, whereas other volume-outcome studies assess single procedures. Therefore, more focused studies on the volume-outcome relationship for specific head and neck procedures, such as neck dissection, laryngectomy, parotidectomy, and transoral resection, are required.

TABLE 1. Studies about the relation between volume and outcome of head and neck cancer surgery

Study	Country	Tumor site	Patients	Hospitals	Surgeons	Case mix adjustment
Gourin 2011 ¹⁷	US	Larynx	1,981	37	284	C, D, U
Cheung 2009 ¹⁸	US	Oral cavity, larynx, pharynx/salivary glands	4,160	333	N.R.	C, D, S, T
Gourin 2011 ¹⁹	US	Oropharynx	1,534	36	233	C, D, U
Morton 2009 ²⁰	NZ	Neck	289	1	10	N.R.
Lin 2008 ²¹	Taiwan	Oral cavity	6,666	89	427	C, D, V
Lee 2010 ²²	Taiwan	Oral cavity	1,256	N.R.	215	C, D, V
Chen 2009 ²³	US	Larynx	11,000	1,427	N.R.	C, D, E, V, S

	Hospital volume			Surgeon volume				
	Volume categories	Morbidity	Mortality	Survival	Volume categories	Morbidity	Mortality	Survival
Gourin 2011 ¹⁷	18	NS	NS	-	7	NS	NS	-
Cheung 2009 ¹⁸	Tertiles	-	-	Sig	-	-	-	-
Gourin 2011 ¹⁹	30	NS	NS	-	6	NS	NS	-
Morton 2009 ²⁰	-	-	-	-	1, 2, 3, 4, 7, 35, 98, 182	-	-	-
Lin 2008 ²¹	1-342; 343-531; >531	-	-	NS	1-51; 52-141; >141	-	-	Sig
Lee 2010 ²²	Categorical	-	-	NS	<8; -21; >22	-	-	Sig
Chen 2009 ²³	Median	-	-	Sig	-	-	-	-

Abbreviations: US, United States; C, adjusted for comorbidities; D, adjusted for demographic data (eg, patient age, sex, race, income); U, adjusted for urgency of the operation; N.R., not reported; S, adjusted for tumor characteristics (eg, stage, grade, location); T, adjusted for treatment differences; NZ, New Zealand; V, adjusted for other hospital characteristics (eg, teaching or academic status); E, socio-economic area; NS, statistically not significant; Sig, statistically significant.

CAUSES FOR LATE CENTRALIZATION: METHODOLOGICAL PROBLEMS IN VOLUME–OUTCOME STUDIES

Causes why head and neck surgeons respond late to the trend of evidence-based centralization are philosophical. In most countries, large databases with detailed clinical information, including outcomes of head and neck cancer procedures, are lacking. Most volume–outcome studies evaluate mortality as their main outcome measure, whereas the a priori mortality rate after major head and neck surgery is relatively low. Furthermore, treatment-related effects are multidimensional, complex to investigate, and often lacking administrative and clinical databases. Another methodological problem of “procedural volume studies” is weighing differences in case mix factors between volume-groups. Most positive head and neck volume-outcome relations were found in studies with poor or even without case mix adjustments. Head and neck cancer cohorts are, by definition, heterogeneous, because they consist of many different diseases, with different etiologies, disease stages, and different intrinsic prognoses. For example, half of the studies we found were not corrected for disease stage or treatment (concurrent chemoradiation, primary radiotherapy, or adjuvant radiotherapy after surgery, etc.)^{18,20,22,23}. The difficulty in case-mix adjustment is that you do not know whether all possible influencing variables are investigated. Only large detailed clinical databases provide enough variables; although the more variables you include, the more patients are needed to obtain statistically significant results. Another methodological pitfall is the definition of “high” and “low” volume head and neck cancer centers. This remains vague, without any clear evidence-based volume cutoff values. In our systematic literature search, the cutoff points for “high volume” range widely from 22 to 182 procedures annually. Because of differences in subsites and treatment modalities, a firm conclusion on cutoff points based upon the current available literature can therefore not be made. These results are in contrast with volume cutoffs for esophageal cancer, aiming at a minimum of 20 resections annually for high-volume hospitals⁸. Nonetheless, in esophageal cancer, there is also no international consensus reached on the definition of a high-volume hospital.

For head and neck cancer, there is not (yet) an evidence-based volume standard, but the Dutch Head and Neck Society recommends a minimum of 200 new patients with head and neck cancer per year. Another difficulty is the wide variety in biological behavior of all different types of head and neck tumors. For instance, the biological nature of nasopharyngeal carcinomas is completely different from that of hypopharyngeal carcinomas.

Also, surgeries differ significantly from each other; petrosectomy differs in risk and complexity from a transoral excision. It is conceivable that the true effect of hospital volume in head and neck cancer is overshadowed by the above-mentioned case mix differences. Therefore, to represent the true effect of procedural volume in a study, thorough case mix adjustments based on detailed clinical data are crucial²⁴. Most volume studies are cross-sectional studies, without exploring changes in volume and performances over time. All of our selected studies belong to this category. Last, volume should be modeled as a continuous variable; by using logistic regression analysis to examine how a set of variables predicts outcome measurements²⁵. None of the referenced studies met this criterion

CONCLUSION

This all makes it problematic to generalize and meta-analyze data regarding volume versus outcome and compare it with well organized studies, like in esophageal surgery⁸ and pancreatic surgery⁹. Despite these limitations, volume-criteria studies investigating the relation between volume and outcome are of great importance, because they can move the head and neck field forward. The proposed benefit of high-volume care advocates the foundation of a limited number of comprehensive head and neck cancer centers. Following the example of major head and neck cancers in the world, with annual new patient visits surpassing 4000,²⁶⁻²⁹ it should be possible to unravel the process contributing to better head and neck cancer care. With larger patient cohorts and standardized treatment protocols, it might be possible to compare the effect of volume on treatment results. Our comparative survey on volume effects in pancreatic, esophagus, and head and neck surgery makes it definitely clear that more research needs to be done to define the volume–outcome relationship in head and neck cancer. In our opinion, the best study setup would be to start a study comparing international “real” high-volume centers and low-volume centers with thorough case-mix adjustments (stage, treatment, histology, etc.) in specific head and neck procedures (laryngectomy, parotidectomy, and neck dissection). After that, it might be possible to draw evidence-based conclusions and define clear cutoff points for hospital volume in head and neck procedures, as has been done for other types of surgery.

REFERENCES

1. Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;12:933–980.
2. Birkmeyer JD, Dimick JB, Birkmeyer NJ. Measuring the quality of surgical care: structure, process, or outcomes? *J Am Coll Surg* 2004;198:626–632.
3. Kolfshoten NE, Gooiker GA, Bastiaannet E, et al. Combining process indicators to evaluate quality of care for surgical patients with colorectal cancer: are scores consistent with short-term outcome? *BMJ Qual Saf* 2012;21:481–489.
4. Livingston EH, Cao J. Procedure volume as a predictor of surgical outcomes. *JAMA* 2010;304:95–97.
5. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003;349:2117–2127.
6. Killeen SD, O’Sullivan MJ, Coffey JC, Kirwan WO, Redmond HP. Provider volume and outcomes for oncological procedures. *Br J Surg* 2005;92: 389–402.
7. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128–1137.
8. Wouters MW, Gooiker GA, van Sandick JW, Tollenaar RA. The volumeoutcome relation in the surgical treatment of esophageal cancer: a systematic review and meta-analysis. *Cancer* 2012;118:1754–1763.
9. van Heek NT, Kuhlmann KF, Scholten RJ, et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. *Ann Surg* 2005;242:781–788; discussion 788–790.
10. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. *N Engl J Med* 2002;346:1138–1144.
11. Wen HC, Tang CH, Lin HC, Tsai CS, Chen CS, Li CY. Association between surgeon and hospital volume in coronary artery bypass graft surgery outcomes: a population-based study. *Ann Thorac Surg* 2006;81:835–842.
12. Vassileva CM, Boley T, Markwell S, Hazelrigg S. Impact of hospital annual mitral procedural volume on mitral valve repair rates and mortality. *J Heart Valve Dis* 2012;21:41–47.
13. Holt PJ, Karthikesalingam A, Hofman D, et al. Provider volume and longterm outcome after elective abdominal aortic aneurysm repair. *Br J Surg* 2012;99:666–672.
14. Pieper D, Mathes T, Neugebauer E, Eikermann M. State of evidence on the relationship between high-volume hospitals and outcomes in surgery: a systematic review of systematic reviews. *J Am Coll Surg* 2013;216:1015–1025.
15. Kreeft A, Tan IB, van den Brekel MW, Hilgers FJ, Balm AJ. The surgical dilemma of ‘functional inoperability’ in oral and oropharyngeal cancer: current consensus on operability with regard to functional results. *Clin Otolaryngol* 2009;34:140–146.
16. Chen AY, Fedewa S, Pavluck A, Ward EM. Improved survival is associated with treatment at high-volume teaching facilities for patients with advanced stage laryngeal cancer. *Cancer* 2010;116:4744–4752.
17. Gourin CG, Forastiere AA, Sanguineti G, Koch WM, Marur S, Bristow RE. Impact of surgeon and hospital volume on short-term outcomes and cost of laryngeal cancer surgical care. *Laryngoscope* 2011;121:85–90.
18. Cheung MC, Koniaris LG, Perez EA, Molina MA, Goodwin WJ, Salloum RM. Impact of hospital volume on surgical outcome for head and neck cancer. *Ann Surg Oncol* 2009;16:1001–1009.
19. Gourin CG, Forastiere AA, Sanguineti G, Marur S, Koch WM, Bristow RE. Impact of surgeon and hospital volume on short-term outcomes and cost of oropharyngeal cancer surgical care. *Laryngoscope* 2011;121:746–752.

20. Morton RP, Gray L, Tandon DA, Izzard M, McIvor NP. Efficacy of neck dissection: are surgical volumes important? *Laryngoscope* 2009;119:1147–1152.
21. Lin CC, Lin HC. Effects of surgeon and hospital volume on 5-year survival rates following oral cancer resections: the experience of an Asian country. *Surgery* 2008;143:343–351.
22. Lee CC, Ho HC, Chou P. Multivariate analyses to assess the effect of surgeon volume on survival rate in oral cancer: a nationwide population-based study in Taiwan. *Oral Oncol* 2010;46:271–275.
23. Chen AY, Pavluck A, Halpern M, Ward E. Impact of treating facilities' volume on survival for early-stage laryngeal cancer. *Head Neck* 2009;31: 1137–1143.
24. Wouters MW, Karim–Kos HE, le Cessie S, et al. Centralization of esophageal cancer surgery: does it improve clinical outcome? *Ann Surg Oncol* 2009;16:1789–1798.
25. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med* 2002;137:511–520.
26. Memorial Sloan–Kettering Cancer Center for adult patients with head and neck cancer. Available at: <http://www.mskcc.org/cancer-care/adult/headneck>. Accessed June 2013.
27. MD Anderson Cancer Center patient and cancer information. Available at: <http://www.mdanderson.org/patient-and-cancer-information/care-centers-andclinics/care-centers/head-neck/index>. Accessed June 2013.
28. University of Toronto, Faculty of Medicine, Otolaryngology – Department of Head and Neck Surgery. Available at: <http://www.otolaryngology.utoronto.ca/site3.aspx>. Accessed June 2013.
29. Tata Memorial Hospital, Service, Research, and Education, Department of Surgical Oncology. Available at: <https://tmc.gov.in/medical/departments/surgery.htm>. Accessed June 2013.

CHAPTER 3

Variation in head and neck cancer care in the Netherlands. A retrospective cohort evaluation of incidence, treatment and outcome

Eur J Surg Oncol. 2017 in press

M. de Ridder
A.J.M. Balm
S.M. Willems
M.W.J.M. Wouters
R.J. Baatenburg de Jong
C.H.J. Terhaard
R.J. Takes
M. Slingerland
H. Bouman
R.J.E. Sedee
J.G.A.M. de Visscher
L.E. Smeele
B.A.C. van Dijk

*On behalf of the Dutch Head and Neck
Research Group*

ABSTRACT

BACKGROUND

To explore variation in numbers and treatment between hospitals that treat head and neck cancer (HNC) in the Netherlands.

MATERIAL AND METHODS

Patient, tumor and treatment characteristics were collected from the Netherlands Cancer Registry, while histopathological features were obtained by linkage to the national pathology record register PALGA. Inter-hospital variation in volume, stage, treatment, pathologically confirmed loco-regional recurrence and overall survival rate was evaluated by tumor site.

RESULTS

In total, 2094 newly diagnosed patients were included, ranging from 65 to 417 patients in participating hospitals treating HNC in 2008. Oral cavity cancer was mainly treated by surgery only, ranging from 46-82% per hospital, while the proportion of surgery with (chemo) radiotherapy ranged from 18-40%. Increasing age, male sex, and high stage were associated with a higher hazard of dying. In oropharynx cancer, the use of (chemo)radiotherapy varied from 31-82% between hospitals. We found an indication that higher volume was associated with a lower overall hazard of dying for the total group, but not by subsite. Low numbers, e.g. for salivary gland, nasopharynx, nasal cavity and paranasal sinus, did not permit all desired analyses.

CONCLUSION

This study revealed significant interhospital variation in numbers and treatment of especially oropharyngeal and oral cavity cancer. This study is limited because we had to rely on data recorded in the past for a different purpose. To understand whether this variation is unwanted, future research should be based on prospectively collected data, including detailed information on recurrences, additional case-mix information and cause of death.

KEY WORDS:

Head and neck cancer, outcome, survival, epidemiology, treatment, quality of care

INTRODUCTION

Head and neck cancer (HNC) consists of a heterogeneous group of cancers. The individual types are characterized by their low incidences, but as group they take the 7th and 9th place in men and women, respectively, in the Netherlands¹.

Because of the many vital functions in the head and neck, the delicate balance between optimal oncological and functional outcome characterizes treatment choices for of HNC. Centralization of care was shown to improve outcome in HNC and other high-complex types of cancer treatment²⁻⁹.

Since the foundation of the Dutch Head and Neck Society (DHNS) in 1984, over 90 % of HNC patients are treated in specialized head and neck cancer centers (HNCC) in the Netherlands¹⁰. Several HNCCs collaborate with regional hospitals (Preferred Partner clinics (PPC)). In the Netherlands, possibly related to this centralization, survival rates are good for HNC compared to other European countries^{11, 12}.

Despite the presence of national guidelines, differences in treatment patterns have been described for the American¹³ and British¹⁴ setting. To discover the extent of variation between hospitals treating HNC in the Netherlands, we studied variation in patient and tumor characteristics, type of treatment, volume, recurrences and overall survival for HNC patients within the participating hospitals.

PATIENTS AND METHODS

DATA SOURCES

All patients diagnosed with primary invasive HNC in 2008 identified in the Netherlands Cancer Registry (NCR) and known in one of the participating hospitals were included. Patients with carcinoma in situ, skin cancer, sarcomas or hematological malignancies of the head and neck area were excluded.

The NCR is population-based and cancer cases are identified from pathology records received from the nationwide pathology network PALGA, as well as from the hospital discharge registry. The completeness of the NCR was estimated to equal at least 95%¹⁵. Following notification, trained tumor registration clerks abstract a minimum data set, including patient, tumor and treatment characteristics from hospital records.

To evaluate recurrences within 5 year from diagnosis, the dataset of the NCR was linked to PALGA data by a trusted third party. PALGA data included all conclusions from pathology reports, containing information on tissue site, procedure for tissue retrieval, histopathological diagnosis and date of specimen retrieval.

Participating hospitals (HNCC N=7 and PPC N=3) consented to anonymous analyses of their data; an independent employee at the NCR performed anonymization.

DEFINITIONS

Patients were classified based on ICD-O-3¹⁶ code: oral cavity cancer (C02, C03, C04, C05.0, C05.8, C05.9, C06), oropharyngeal cancer (C01.9, C05.1, C05.2, C09, C10 (except C10.1)), laryngeal cancer (C10.1, C32), hypopharyngeal cancer (C12, C13) and cancer at other subsites [salivary gland, nasopharynx, para-nasal sinus or nasal cavity] (C07, C08, C11, C30, C31, C14).

In case patients were known in more than one HNCC, the center in which patients were treated was chosen as coding center. Second opinions without treatment were not included in the numbers per center. Volume was included in accordance with the previous report by Halm et al¹⁷.

Pathological TNM (6th edition¹⁸) was used and complemented with the clinical classification if pathological stage was unavailable.

Treatment was classified into 4 groups: surgery only, surgery plus (chemo-)radiotherapy (C) RT), (C)RT or other/palliative therapy. Patients with distant metastases at diagnosis (M+) or untreated patients were excluded from analyses on treatment and survival.

All recurrences reported are pathologically verified recurrences, since the pathology databank was our only source with information on recurrences; thus clinical recurrences could not be included.

STATISTICAL ANALYSIS

Univariate testing was done by Chi-square, Kruskal-Wallis or Fisher's Exact test. Recurrence and survival analyses using the Kaplan-Meier method. Multivariate survival analyses including sex, age, stage and hospital volume was performed using the Cox regression analysis. P-values <0.05 were considered statistically significant.

Statistical programs used were SPSS (version 22.0, IBM Chicago, IL) and STATA data analysis and statistical software (version 10.0, StataCorp LP, TX, 1996).

RESULTS

In total 2094 patients, were included in this study. The number of newly diagnosed patients in 2008 ranged from 129-417 in HNCC and from 65-86 in PPC. There was variation in site distribution and in sex between hospitals (table 1). In all subsites, men were more affected than women.

Table 1. Patient and tumor characteristics by hospital

	HNCC1	HNCC2	HNCC3	HNCC4	HNCC5	HNCC6	HNCC7	PPC1	PPC1	PPC1	Total	P-value
Age [median (min/max)]	62 (19-94)	63 (14-94)	62 (13-93)	63 (10-92)	63 (10-97)	64 (15-91)	63 (36-93)	62 (29-88)	60 (31-91)	64 (15-87)	63 (10-97)	P=0.893 (Kruskal Wallis)
Sex [N (%)]												
Male	162 (65)	220 (68)	177 (67)	204 (64)	310 (74)	136 (78)	96 (74)	58 (67)	46 (70)	41 (63)	1450 (69)	0.010 (χ^2)
Female	88 (35)	102 (32)	86 (33)	117 (36)	107 (26)	39 (22)	33 (26)	28 (33)	20 (30)	24 (37)	644 (31)	
Stage [N (%)]												
I	76 (30)	79 (25)	64 (24)	82 (26)	99 (24)	38 (22)	37 (29)	28 (33)	25 (38)	23 (35)	551 (26)	0.065 (χ^2)
II	42 (17)	71 (22)	43 (16)	79 (25)	75 (18)	21 (12)	25 (19)	19 (22)	9 (14)	15 (23)	399 (19)	
III	33 (13)	44 (14)	41 (16)	44 (14)	69 (17)	30 (17)	24 (19)	10 (12)	10 (15)	4 (6)	309 (15)	
IV M0	85 (34)	101 (31)	92 (35)	100 (31)	130 (31)	76 (43)	38 (29)	24 (28)	20 (30)	18 (27)	684 (33)	
IV M1	9 (4)	9 (3)	14 (5)	12 (4)	35 (8)	8 (5)	3 (2)	2 (2)	2 (3)	4 (6)	98 (5)	
Missing	5 (2)	18 (6)	9 (3)	4 (1)	9 (2)	2 (1)	2 (2)	3 (4)	0 (0)	1 (2)	53 (3)	
Site [N (%)]												
Oral cavity	80 (32)	94 (29)	61 (23)	119 (37)	100 (24)	40 (23)	29 (22)	23 (27)	20 (30)	36 (55)	602 (29)	<0.001 (χ^2)
Oropharynx	45 (18)	64 (20)	83 (32)	57 (18)	91 (22)	33 (13)	33 (26)	19 (22)	13 (20)	15 (23)	453 (22)	
Larynx	72 (29)	92 (29)	55 (21)	83 (26)	133 (32)	63 (36)	40 (31)	19 (22)	18 (27)	10 (15)	585 (28)	
Hypopharynx	15 (6)	25 (8)	25 (10)	21 (7)	43 (10)	19 (11)	12 (9)	6 (7)	8 (12)	1 (2)	175 (7)	
Other	38 (15)	47 (15)	39 (15)	41 (13)	50 (12)	20 (11)	15 (12)	19 (22)	7 (11)	3 (5)	279 (13)	
Total [N]	250	322	263	321	417	175	129	86	66	65		

Abbreviations: HNCC – head neck cancer center, PPC – preferred partner clinic

ORAL CAVITY CANCER

There were 602 patients with oral cavity squamous cell cancer. Hospital volume ranged from 23-119. Most patients had stage I disease (36%), followed by stage IVM0 (27%), stage II (18%), stage III (12%) and stage IVM1 (6%). The stage distribution was not different between hospitals ($p=0.639$). After exclusion of M+/untreated patients 565 patients were analyzed. Surgery only was treatment of first choice, ranging from 46%-80% between hospitals ($P<0.001$) (table 2). The proportion of surgery with adjuvant (C)RT, which was almost exclusively postoperative radiotherapy (PORT), ranged from 18%-40%. The use of PORT differed significantly between the hospitals ($p<0.001$), but appeared independent from hospital volume ($p=0.162$).

The pathology proven loco-regional recurrence rate after 5 years was 29% (162 recurrences).

There was no significant difference in recurrence rates between the hospitals ($p=0.779$).

The overall 5-year survival was 60% (227 events) and was significantly associated with stage ($p<0.001$): stage I 78% (45 events), stage II 71% (30 events), stage III 52% (32 events) and stage IVM0 36% (113 events) [figure 1a].

In multivariate cox regression analysis: higher age, male sex and higher stage were negatively associated with overall survival (table 3).

OROPHARYNGEAL CANCER

In total 453 patients were diagnosed with oropharyngeal cancer. The number of newly diagnosed patients ranged from 13-91 in participating hospitals. Most patients were diagnosed with stage IV (55%). The stage distribution did not differ between hospitals ($p=0.647$). For patients without distant metastases and undergoing treatment ($n=406$; 90%) organ-sparing treatment was performed in most cases (73%), ranging from 31-85% ($p=0.002$). Primary surgery was given in up to 36% (range 15-36%) of the patients in HNCCs (table 2). Use of primary radiotherapy varied from 7%-58% between HNCCs and the use of primary chemoradiation ranged from 20%-55%.

The 5-year pathology proven loco-regional recurrence rate was 26% (107 recurrences).

There was no statistically significant difference in recurrence rate between the hospitals ($p=0.901$).

Five-year overall survival was 52% (196 events) and did not statistically differ by stage (I: 59% (21 events), II: 56% (28 events), III 53%, (36 events) and IVM0 47% (110 events); $p=0.310$) [figure 1b].

In multivariate Cox regressions analysis stage IV (HR 1.60 (95%CI 1.02-2.49) and higher age (HR 1.04 for each year (95%CI 1.02-1.05) were associated with a lower overall survival (table 3).

Table 2. Treatment variation by tumor site and hospital

	HNCCI	HNCC2	HNCC3	HNCC4	HNCC5	HNCC6	HNCC7	PPCI	PPCI	PPCI	Total	P-value
Oral cavity cancer patients [N (%)]												
Surgery	35 (46.1%)	52 (58.4%)	34 (60.7%)	69 (62.2%)	43 (48.3%)	21 (53.8%)	15 (53.6%)	18 (81.8%)	12 (60.0%)	23 (65.7%)	322 (57.0%)	<0.001 (Fisher's Exact)
Surgery with (C)RT	25 (32.9%)	29 (32.6%)	12 (21.5%)	38 (34.2%)	36 (40.4%)	7 (17.9%)	7 (25.0%)	4 (18.2%)	6 (30.0%)	12 (34.3%)	176 (31.2%)	
(C)RT	15 (19.5%)	8 (8.9%)	10 (17.9%)	4 (3.6%)	10 (11.2%)	10 (25.7%)	6 (21.4%)	0	2 (10.0%)	0	65 (11.5%)	
Other therapy	1 (1.3%)	0	0	0	0	1 (2.6%)	0	0	0	0	2 (0.4%)	
Total	76	89	56	111	89	39	28	22	20	35	565	
Oropharynx cancer patients [N (%)]												
Surgery (with or without adjuvant therapy)	13 (31.7%)	12 (20.3%)	27 (35.5%)	8 (14.8%)	16 (21.1%)	6 (20.0%)	11 (35.5%)	9 (69.2%)	2 (18.2%)	4 (30.8%)	108 (26.7%)	0.004 (Fisher's Exact)
(C)RT	28 (68.3%)	47 (79.7%)	49 (64.5%)	46 (85.2%)	60 (78.9%)	24 (80.0%)	20 (64.5%)	4 (30.8%)	9 (81.8%)	9 (69.2%)	296 (73.3%)	
GRT	10 (24.4%)	12 (20.0%)	29 (38.2%)	19 (35.2%)	19 (35.2%)	9 (30.0%)	7 (22.6%)	3 (21.4%)	6 (54.5%)	6 (46.2%)	120 (29.6%)	
RT	18 (43.9%)	35 (58.3%)	20 (26.3%)	27 (50.0%)	41 (53.9%)	15 (50.0%)	13 (41.9%)	1 (7.1%)	3 (27.3%)	3 (23.1%)	176 (43.3%)	
Total	41	59	76	54	76	30	31	13	11	13	404	
Larynx cancer patients [N (%)]												
Surgery (with or without adjuvant therapy)	28 (40.1%)	19 (20.9%)	15 (28.8%)	26 (32.6%)	29 (22.8%)	16 (27.2%)	17 (42.5%)	4 (21.1%)	1 (5.6%)	1 (10.0%)	156 (27.6%)	0.004 (Fisher's Exact)
(C)RT	42 (60.0%)	71 (78.0%)	37 (71.1%)	54 (67.6%)	98 (77.1%)	43 (72.9%)	22 (55.0%)	15 (79.0%)	17 (94.4%)	9 (90.0%)	408 (72.1%)	
Other therapy	0	1 (1.1%)	0	0	0	0	1 (2.5%)	0	0	0	2 (0.3%)	
Total	70	91	52	80	127	59	40	19	18	10	566	
Hypopharynx cancer patients [N (%)]												
Surgery (with or without adjuvant therapy)	1 (8.3%)	2 (9.5%)	4 (20.0%)	6 (31.6%)	10 (29.4%)	1 (6.3%)	5 (41.7%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	30 (20.1%)	0.149 (Fisher's Exact)
(C)RT	11 (91.7%)	19 (90.5%)	16 (80.0%)	13 (68.4%)	24 (70.6%)	15 (93.8%)	7 (58.3%)	6 (100.0%)	7 (87.5%)	1 (100.0%)	119 (79.9%)	
Total	12	21	20	19	34	16	12	6	8	1	149	

Abbreviations: HNCC - head neck cancer center, PPC - preferred partner clinic, (C)RT - (chemo)radiotherapy, RT - radiotherapy

LARYNGEAL CANCER

In total 585 patients were identified with laryngeal cancer. Hospital volume ranged from 10-133 newly diagnosed patients per year.

Stage distribution varied significantly between the hospitals; stage I ranged from 30-41% and stage IV from 18%-33% ($p=0.012$).

The proportion of stage I patients was higher in PPCs compared to HNCCs (36% vs. 26%, $p=0.003$). Stage II, III and IV did not significantly vary between PPCs and HNCCs ($p=0.804$, 0.096 and 0.084 respectively).

After exclusion of M+/untreated patients, 566 patients were left for additional analyses.

Most patients with laryngeal cancer were treated by an organ preserving treatment (55%-94%, $p=0.004$) (table 2)

After 5 years, pathology proven loco-regional recurrences were found in 20% of the patients (114 events). The recurrence rate did not vary between hospitals ($p=0.779$). The 5-year overall survival of laryngeal cancer equaled 66% (194 events) (stage I: 80% (39 events), stage II 74% (39 events), stage III 58% (38 events), stage IVM0 40% (74 events) ($p<0.001$) [figure 1c].

Multivariate Cox regression analysis showed significantly increased hazard rates of dying for higher stage (stage III: HR 3.20 (95%CI 2.12-4.85) & stage IV disease: HR 5.74 (95%CI 3.96-8.33), increasing age (HR 1.07 95% CI 1.05-1.08) and (borderline significant) female gender (HR 1.42 95%CI 1.00 -2.01). Hospital volume was not associated with overall survival (table 3).

HYPOPHARYNGEAL AND OTHER TYPES OF HNC

Hypopharyngeal cancer ($n=175$, hospital range 1-43) was mostly diagnosed staged IV disease (>70%). The stage distribution did not differ between hospitals.

After exclusion of primary metastasized or untreated patients 149 patients were included in the treatment and survival analyses.

The majority of the patients were treated with organ preserving treatment regimens [mean 80%, hospital range 58%-100% ($p=0.149$)] (table 2).

The pathology proven recurrence rate was 25%. This did not statistically differ between the hospitals ($p=0.257$).

Five-year overall survival was 39% with the worst survival (32%) for stage IV patients ($p=0.08$). Due to low number of events, multivariate analysis could not be performed.

Hundred patients (hospital range 1-18) with salivary gland cancer were represented in this study cohort. For nasal cavity and para-nasal sinus cancer, the number of patients was 114 (hospital range 1-25). For nasopharyngeal cancer, there were 63 patients ranging from 0-14 per hospital. These low numbers did not allow further analysis.

Table 3. Multivariate analyses for overall survival

	Oral cavity			Oropharynx			Larynx			Total		
	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
Male	Ref.			Ref.			Ref.			Ref.		
Female	0.71	0.55 – 0.92	0.009	0.84	0.62 – 1.13	0.245	1.42	1.00 – 2.01	0.049	0.89	0.77 – 1.03	0.108
Age (per year)	1.04	1.03 – 1.06	<0.001	1.04	1.02 – 1.05	<0.001	1.07	1.05 – 1.08	<0.001	1.04	1.04 – 1.05	<0.001
Stage I	Ref.			Ref.			Ref.			Ref.		
Stage II	1.18	0.79 – 1.77	0.409	1.20	0.71 – 2.02	0.501	1.50	1.01 – 2.23	0.046	1.37	1.10 – 1.72	<0.001
Stage III	2.40	1.59 – 3.63	<0.001	1.40	0.84 – 2.32	0.205	3.20	2.12 – 4.85	<0.001	2.33	1.87 – 2.92	<0.001
Stage IV	3.69	2.70 – 5.02	<0.001	1.60	1.02 – 2.49	0.042	5.74	3.96 – 8.33	<0.001	3.56	2.97 – 4.28	<0.001
Hospital volume per 25	0.96	0.92 – 1.00	0.075	0.97	0.93 – 1.02	0.193	0.98	0.94 – 1.03	0.461	0.98	0.95 – 1.00	0.034
HNCC	Ref.			Ref.			Ref.			Ref.		
PPC	0.99	0.60 – 1.64	0.970	1.11	0.63 – 1.98	0.714	1.20	0.68 – 2.13	0.538	0.99	0.75 – 1.31	0.950

HR – hazard ratio, Ref. – reference, HNCC – head and neck cancer center, PPC – preferred partner clinic

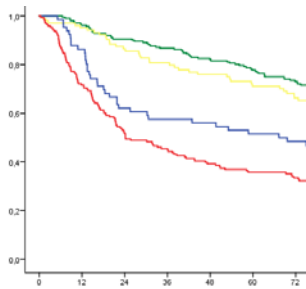


Figure 1a. Kaplan Meier curve of overall survival of oral cavity cancer patients by stage. [green: stage I; yellow: stage II; blue: stage III; red: stage IV M0]

Months	0	12	24	36	48	60	72
Numbers at risk	564	491	416	388	340	336	312

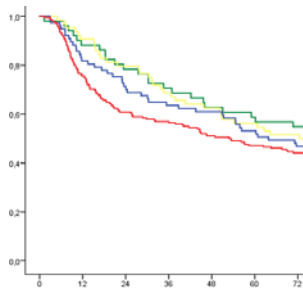


Figure 1b. Kaplan Meier curve of overall survival of oropharynx cancer patients by stage. [green: stage I; yellow: stage II; blue: stage III; red: stage IV M0]

Months	0	12	24	36	48	60	72
Numbers at risk	405	328	277	252	228	208	191

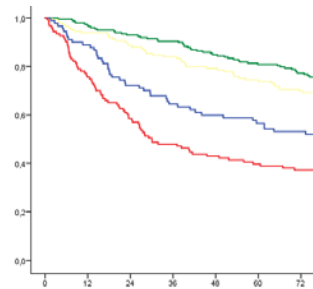


Figure 1c. Kaplan Meier curve of overall survival of larynx cancer patients by stage. [green: stage I; yellow: stage II; blue: stage III; red: stage IV M0]

Months	0	12	24	36	48	60	72
Numbers at risk	565	511	458	423	392	370	350

DISCUSSION

This study describes HNC patients' characteristics and outcome from 7 HNCCs and 3 PPCs in 2008 in the Netherlands. The number of HNC patients equaled 2094 and ranged from 65-417 per center.

Variation in treatment is one of the primary findings in this study and has been described in the literature before. In previous American¹³ and British¹⁴ studies, differences in treatment regimens were described, despite the presence of national guidelines, mainly due to health care organization. However, these studies are not representative for the Dutch setting because there are fundamental differences in health care organization between these countries and the Netherlands (e.g. insurance for every inhabitant and only cancer care in non-private hospitals). Our study is the first to show significant variation in treatment in a country with centralized head and neck cancer care.

In oral cavity cancer, the use of PORT differed. This difference could probably be explained by unmeasured pathological characteristics, such as the presence of close or involved resection margins, extracapsular lymph node extension, or perineural growth: all indicating adjuvant treatment according to the guideline^{13,19}. Therefore, we cannot draw further conclusions about the source of this difference.

In oropharynx cancer patients there was a wide variation in the primary use of (C)RT. Because the updated version of the national guideline, with chemoradiation as standard treatment for advanced stages instead of radiotherapy alone, was published in 2010, early adoption of the guideline in 2008 by some centers could be an explanation for this observed variation. For national uniformity in treatment, continuously updated guidelines and rapid adherence are essential.

For laryngeal cancer, the differences in treatment between hospitals were less clear, probably because the treatment guidelines can be applied more straightforward in an organ setting with more clearly defined anatomical boundaries as compared with other head and neck sites. An ongoing debate on treatment of laryngeal cancer is how to treat T4 laryngeal carcinomas. Unfortunately, our series contained insufficient number of T4 laryngeal cancer patients per center to evaluate differences.

However, there is a recent publication of Timmermans et al²⁰ that showed there is a declining tendency in primary laryngectomy for laryngeal cancer in the Netherlands over the past 20 years. However, this analysis was not split for different centers, so whether there is hospital based variation in treatment of T4 laryngeal cancer remain a topic of future research.

Another interesting observation in the laryngeal cancer group was the higher hazard of death for female patients (HR: 1.42 (95% CI: 1.00-2.01), while for most cancer types, the survival is better for women compared to for men²¹. This can be explained by the fact that women more often have supraglottic cancer, associated with higher stage, as shown in another study from the Netherlands²².

The exclusion of untreated or metastasized patients from treatment analyses may introduce bias because differences in techniques used to evaluate distant metastasis may differ between hospitals, as well as the decision to treat or not to treat curatively. However, a fairly good consensus on when to treat curatively was shown in the Netherlands²³.

A second important finding of our study is the variation in site distribution per hospital. Quite a large difference in site distribution is found, which might be explained by historically defined referral patterns. Another explanation could be the variation in composition of the population in the adherence area of the HNCC. A clear example of that is the distribution of Asian immigrants across the Netherlands and the clustering of nasopharyngeal cancer in accordance with that distribution.

Our survey revealed low numbers of salivary gland, nasopharynx, nasal cavity and paranasal sinus cancer, rarely exceeding twenty cases per center. These low numbers did not permit any robust data analysis, and will never be sufficient to evaluate variation. To obtain sufficient numbers, centralization may be advocated. However, other considerations should be taken into account: salivary gland cancers are part of a larger cohort of benign salivary gland tumors also providing surgical expertise. Another example is chemoradiation for nasopharynx, which demands experience and specific expertise from the radiation oncologist, as well as experience and specific expertise of the supporting personnel with toxicity and complications related to the treatment. More or less similar considerations play a role for paranasal sinus cancer with the need of functional endoscopic and neuro-surgical expertise. Assuming that increasing volume contributes to improved quality of care, further centralization of these rare HNC might contribute to better outcomes.

We found a significantly lower hazard rate of dying with increasing hospital volume, after correction for age, gender and stage (HR 0.98 per 25 patients, $p=0.034$). However, volume was no longer statistically significant in analyses restricted by subsite. This is probably the result of the lower number of patients by subsite in combination with the low effect for volume.

We found a significantly lower hazard rate of dying with increasing hospital volume, after correction for age, gender and stage (HR 0.98 per 25 patients, $p=0.034$). However, volume was no longer statistically significant in analyses restricted by subsite. This is probably the result of the lower number of patients by subsite in combination with the low effect for volume.

Our findings are in line with a report on head and neck surgery²⁴ showing, that the hazard of dying was lower in high-volume hospitals (HR per 25 patients 0.976 (95% CI 0.955-0.997) in multivariate analysis). A recent meta-analysis, including five large ($n= 805-19,326$) studies showed a similar volume-survival relationship in 49,403 HNC patients (HR 0.886 (95% CI, 0.820-0.956)²⁵. However, volume cutoffs of the original studies were used, causing heterogeneity in numbers classified as high or low volume. It was argued that differences in definitions of volume only change the amplitude and not the relationship of the effect²⁶. This study was mainly limited by the fact that data were recorded in the past, and not specifically for this goal. Specific characteristics necessary for case-mix adjustments, like performance status, comorbidity, smoking, alcohol drinking and HPV status, are lacking. Another limitation of this study was the missing pathology data; available information was mainly free unstandardized text, complicating complete and uniform extraction of data.

Despite insufficient information to score perineural growth, extracapsular spread or resection margins, pathologically proven recurrences could be scored. Several studies showed that the use of standardized pathology reports improves the quality of the reports^{27, 28}. Furthermore, the list of important pathology items for HNC grows rapidly PALGA is currently working on a national protocol for synoptic reporting in HNC. The use of only pathology proven recurrences definitely leads to an underestimation of the recurrence rate, and may contribute to differences in tumor recurrence rates between hospitals, since centers may utilize different techniques to prove a recurrence. Therefore recurrence-free survival should be interpreted with caution. Some precaution should also be made in the interpretation of survival, since only overall survival data was available for this cohort. Ideally disease specific survival is the outcome parameter of choice. The Dutch national prospective audit will provide additional detailed information on case-mix, recurrences (both clinical and pathological) and cause of death in the future.

Summarizing, our study revealed significant variation in treatment of head and neck carcinomas and low numbers of salivary gland, nasopharyngeal and paranasal cancer per hospital. To understand whether this variation is unwanted or not, we need more detailed information on large number of cases to accommodate robust analysis. Even though HNC care is already at a high level of centralization in the Netherlands, there may still be opportunities for improvement.

REFERENCES

1. Netherlands Cancer Registry. Incidence of head and neck cancer 2016 [09-12-2016]. Available from: <http://www.cijfersoverkanker.nl>.
2. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med*. 2002 Apr 11;346(15):1128-37.
3. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med*. 2003 Nov 27;349(22):2117-27.
4. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. *Ann Surg*. 2007 May;245(5):777-83.
5. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med*. 2011 Jun 2;364(22):2128-37.
6. Wouters MW, Gooiker GA, van Sandick JW, Tollenaar RA. The volume-outcome relation in the surgical treatment of esophageal cancer: a systematic review and meta-analysis. *Cancer*. 2012 Apr 1;118(7):1754-63.
7. van Heek NT, Kuhlmann KF, Scholten RJ, de Castro SM, Busch OR, van Gulik TM, et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. *Ann Surg*. 2005 Dec;242(6):781-8, discussion 8-90.
8. Birkmeyer JD, Finlayson SR, Tosteson AN, Sharp SM, Warshaw AL, Fisher ES. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. *Surgery*. 1999 Mar;125(3):250-6.
9. Wuthrick EJ, Zhang Q, Machtay M, Rosenthal DI, Nguyen-Tan PF, Fortin A, et al. Institutional clinical trial accrual volume and survival of patients with head and neck cancer. *J Clin Oncol*. 2015 Jan 10;33(2):156-64.
10. Dutch Head and Neck Oncology Collaboration Group. 2016 [09-12-2016]. Available from: <http://www.nwhht.nl>.
11. Gatta G, Botta L, Sanchez MJ, Anderson LA, Pierannunzio D, Licitra L, et al. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. *Eur J Cancer*. 2015 Sep 6.
12. Zigon G, Berrino F, Gatta G, Sanchez MJ, van Dijk B, Van Eycken E, et al. Prognoses for head and neck cancers in Europe diagnosed in 1995-1999: a population-based study. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2011 Jan;22(1):165-74.
13. Chen MM, Roman SA, Yarbrough WG, Burtness BA, Sosa JA, Judson BL. Trends and variations in the use of adjuvant therapy for patients with head and neck cancer. *Cancer*. 2014 Nov 1;120(21):3353-60.
14. Nouraei SA, Middleton SE, Hudovsky A, Darzi A, Stewart S, Kaddour H, et al. A national analysis of the outcome of major head and neck cancer surgery: implications for surgeon-level data publication. *Clin Otolaryngol*. 2013 Dec;38(6):502-11
15. van der Sanden GA, Coebergh JW, Schouten LJ, Visser O, van Leeuwen FE. Cancer incidence in The Netherlands in 1989 and 1990: first results of the nationwide Netherlands cancer registry. Coordinating Committee for Regional Cancer Registries. *Eur J Cancer*. 1995 Oct;31A(11):1822-9.
16. Fritz A. International classification of disease for oncology. Geneva: World Health Organization. 2000.
17. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med*. 2002 Sep 17;137(6):511-20.

18. Sobin L, Wittekind C. TNM classification of malignant tumours 6th ed. Wiley-Liss. 2002.
19. NVKNO. Head and neck cancer guideline 2014 [09-02-2016]. Available from: www.richtlijndatabase.nl/richtlijn/hoofd-halstumoren.
20. Timmermans AJ, van Dijk BA, Overbeek LI, van Velthuysen ME, van Tinteren H, Hilgers FJ, et al. Trends in treatment and survival for advanced laryngeal cancer: A 20-year population-based study in The Netherlands. *Head Neck*. 2015 Aug 28.
21. Baili P, Di Salvo F, Marcos-Gragera R, Siesling S, Mallone S, Santaquilani M, et al. Age and case mix-standardised survival for all cancer patients in Europe 1999-2007: Results of EURO-CARE-5, a population-based study. *Eur J Cancer*. 2015 Sep 6.
22. van Dijk BA, Karim-Kos HE, Coebergh JW, Marres HA, de Vries E. Progress against laryngeal cancer in The Netherlands between 1989 and 2010. *Int J Cancer*. 2014 Feb 1;134(3):674-81.
23. Kreeft A, Tan IB, van den Brekel MW, Hilgers FJ, Balm AJ. The surgical dilemma of 'functional inoperability' in oral and oropharyngeal cancer: current consensus on operability with regard to functional results. *Clin Otolaryngol*. 2009 Apr;34(2):140-6.
24. Eskander A, Irish J, Groome PA, Freeman J, Gullane P, Gilbert R, et al. Volume-outcome relationships for head and neck cancer surgery in a universal health care system. *Laryngoscope*. 2014 Sep;124(9):2081-8.
25. Eskander A, Merdad M, Irish JC, Hall SF, Groome PA, Freeman JL, et al. Volume-outcome associations in head and neck cancer treatment: a systematic review and meta-analysis. *Head Neck*. 2014 Dec;36(12):1820-34.
26. Kulkarni GS, Laupacis A, Urbach DR, Fleshner NE, Austin PC. Varied definitions of hospital volume did not alter the conclusions of volume-outcome analyses. *Journal of clinical epidemiology*. 2009 Apr;62(4):400-7.
27. King PM, Blazeby JM, Gupta J, Alderson D, Moorghen M. Upper gastrointestinal cancer pathology reporting: a regional audit to compare standards with minimum datasets. *Journal of clinical pathology*. 2004 Jul;57(7):702-5.
28. Lankshear S, Strigley J, McGowan T, Yurcan M, Sawka C. Standardized synoptic cancer pathology reports - so what and who cares? A population-based satisfaction survey of 970 pathologists, surgeons, and oncologists. *Arch Pathol Lab Med*. 2013 Nov;137(11):1599-602.

PROCESS INDICATORS

CHAPTER 4

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

Michel C. van Harten
Mischa de Ridder
Olga Hamming-Vrieze
Ludi E. Smeele
Alfons J.M. Balm
Michiel W.M. van den Brekel

4

Oral oncology. 2014; 50: 282-290

ABSTRACT

OBJECTIVE

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

METHODS

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

RESULTS

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

CONCLUSION

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

KEY WORDS

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

INTRODUCTION

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

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

PATIENTS AND METHODS

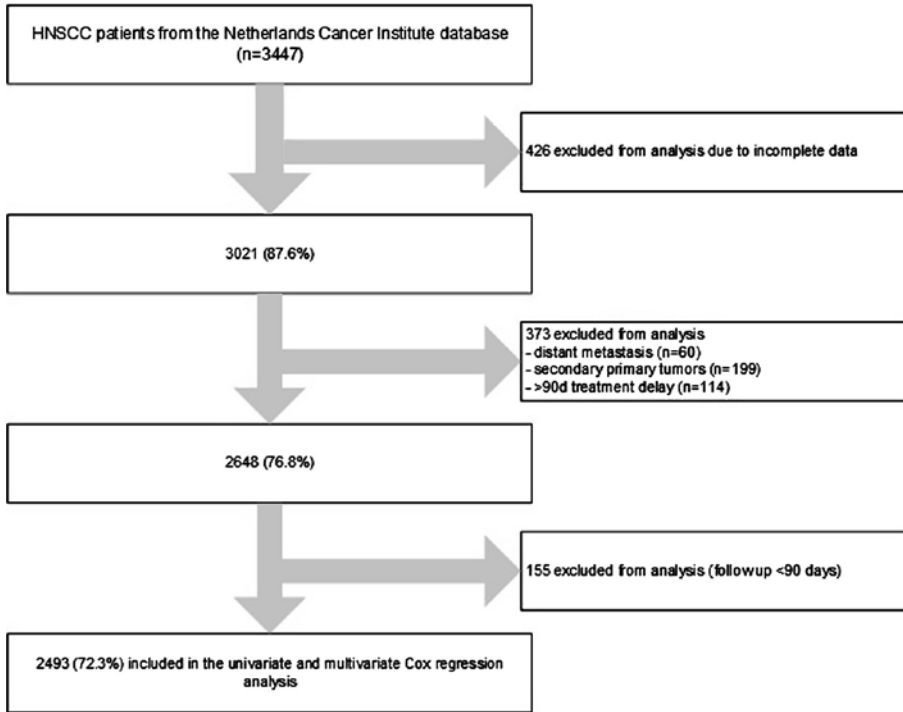
STUDY POPULATION

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

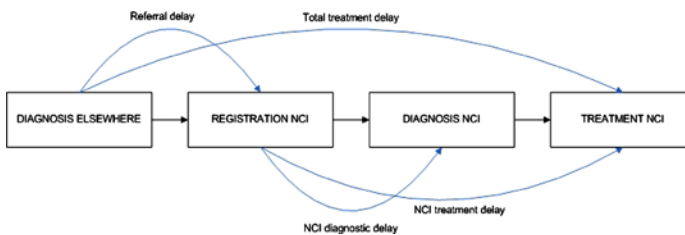
Patient and tumor characteristics such as sex, age, date of registration, date of pathological diagnosis, anatomical site of tumor, TNM classification, treatment modality and date, date of recurrence, survival and cause of death were extracted from the tumor register and were complete in 3021 patients.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

DEFINITION OF PROFESSIONAL DELAY

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



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



STATISTICAL ANALYSIS

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

RESULTS

STUDY POPULATION

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

PROFESSIONAL DELAY

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

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

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

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

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

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

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

Characteristic	Total number (%) by characteristic, divided in subgroups based on referral delay to the NCI			Referral delay (days) in relation to characteristic			Total number (%) by characteristic, divided in subgroups based on NCI treatment delay			NCI Treatment delay (days) in relation to characteristic		
	All	0-14 days	>14 days	Median (25-75% IQR)	Mean ± SEM	p Value ^a	0-30 days	>30 days	p value ^a	Median (25-75% IQR)	Mean ± SEM	p Value ^b
All	763	472 (62)	291 (38)	10 (1-22)	13.55 ± 3.44		259 (34)	504 (66)		36 (2.6-48)	38.32 ± 687	
Sex												
Male	553	341 (62)	212 (38)	10 (1-22)	13.49 ± 6.41	.949	188 (34)	365 (66)	.961	35 (2.6-48)	37.68 ± 782	.285
Female	210	131 (62)	79 (38)	10 (1-22)	13.72 ± 10.32		71 (34)	139 (66)		38 (2.7-48)	40.02 ± 1.406	
Age												
< 40	11	9 (82)	2 (18)	10 (0-14)	12.73 ± 5.328	.858	4 (36)	7 (64)	.757	31 (17-52)	35.82 ± 6.060	.424
40-49	75	46 (61)	29 (39)	12 (3-19)	14.33 ± 2.249		27 (36)	48 (64)		36 (2.5-45)	37.52 ± 2.470	
50-59	249	162 (65)	87 (35)	8 (1-21)	12.56 ± 8.72		86 (34)	163 (76)		36 (2.6-48)	38.04 ± 1.168	
60-69	229	135 (59)	94 (41)	10 (1-21)	14.05 ± 1.001		65 (28)	164 (72)		36 (2.8-48)	40.26 ± 1.223	
>70	199	120 (60)	79 (40)	11 (1-24)	13.97 ± 10.21		77 (39)	122 (61)		35 (2.3-48)	36.99 ± 1.359	
Year of diagnosis												
1990-1994	101	73 (73)	28 (28)	9 (3-16)	12.08 ± 1.361	.000	50 (49)	51 (51)	.023	31 (21-45)	34.24 ± 1.975	.000
1995-1999	123	70 (57)	53 (43)	13 (7-20)	15.01 ± 1.229		47 (38)	76 (62)		36 (2.2-47)	37.09 ± 1.900	
2000-2004	216	112 (52)	104 (48)	13 (1-26.5)	15.68 ± 9.94		47 (22)	169 (78)		41 (31-55)	42.98 ± 1.205	
2005-2010	323	217 (67)	106 (33)	6 (0-20)	12.03 ± 8.91		115 (36)	208 (64)		34 (2.6-46)	36.96 ± 1.011	
Tumor site												
Oral cavity	180	142 (79)	38 (21)	1 (0-13)	8.97 ± 1.119	.000	83 (46)	97 (54)	.063	31 (2.2-45)	34.95 ± 1.371	.004
Oropharynx	216	152 (70)	64 (30)	8 (0-19)	11.61 ± 10.388		57 (26)	159 (77)		38 (2.8.5-51)	40.85 ± 1.294	
Hypopharynx	121	76 (63)	45 (37)	11 (4-21)	14.42 ± 1.293		41 (34)	80 (66)		38 (2.6-48)	38.43 ± 1.720	
Larynx	246	102 (41)	144 (59)	17 (6-27)	18.18 ± 8.87		78 (32)	168 (68)		36.5 (27-48)	38.52 ± 1.220	
Stage												
Stage I-II	303	145 (48)	158 (52)	15 (1-29)	17.56 ± 9.22	.000	93 (31)	210 (69)	.124	39 (2.7-53)	41.53 ± 1.138	.000
Stage III-IV	460	327 (71)	133 (29)	7 (1-17)	10.91 ± 6.39		166 (36)	294 (64)		34 (2.6-45)	36.21 ± 8.45	
Treatment												
Surgery ± adjuvant radiotherapy	388	269 (69)	119 (31)	6 (0-19)	12.49 ± 8.78	.000	195 (50)	193 (50)	.000	30 (2.0-44)	33.57 ± 1.039	.000
Radiotherapy/chemoradiation	375	203 (54)	172 (46)	13 (4-23)	14.65 ± 6.28		64 (17)	311 (83)		40 (3.2-52)	45.25 ± 8.21	

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



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

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

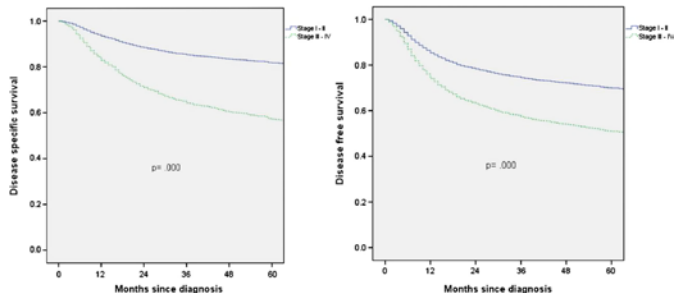


Figure 3. Adjusted Kaplan-Meier curves for stage. Disease Specific Survival (DSS) left, Disease Free Survival (DFS) right.

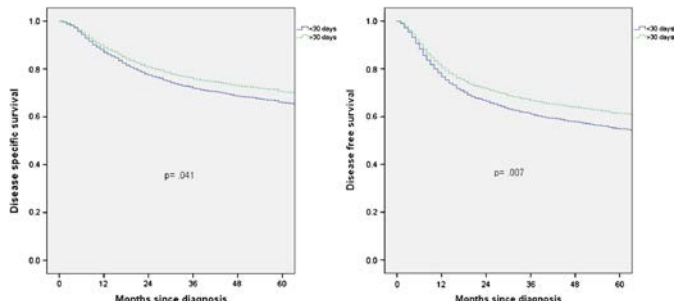


Figure 4. Adjusted Kaplan-Meier curves for total treatment delay. Disease Specific Survival (DSS) left, Disease Free Survival (DFS) right.

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

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

SURVIVAL

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

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

DISCUSSION

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

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

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

CONCLUSION

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

REFERENCES

1. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer (Oxford, England: 1990)* 2010;46(4):765–81.
2. Gourin CG, Frick KD. National trends in oropharyngeal cancer surgery and the effect of surgeon and hospital volume on short-term outcomes and cost of care. *Laryngoscope* 2012;122(3):543–51.
3. Chien CR, Lin HW, Yang CH, et al. High case volume of radiation oncologists is associated with better survival of nasopharyngeal carcinoma patients treated with radiotherapy: a multifactorial cohort analysis. *Clin Otolaryngol: Off J ENTUK; Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg* 2011;36(6):558–65.
4. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *New Engl J Med* 2002;346(15):1128–37.
5. Bilimoria KY, Ko CY, Tomlinson JS, et al. Wait times for cancer surgery in the United States: trends and predictors of delays. *Ann Surg* 2011;253(4):779–85.
6. Primdahl H, Nielsen AL, Larsen S, et al. Changes from 1992 to 2002 in the pretreatment \ delay for patients with squamous cell carcinoma of larynx or pharynx: a Danish nationwide survey from DAHANCA. *Acta Oncol (Stockholm, Sweden)* 2006;45(2):156–61.
7. Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. *Semin Oncol* 1996;23(Suppl. 2):89–97.
8. Brazda A, Estroff J, Euhus D, et al. Delays in time to treatment and survival impact in breast cancer. *Ann Surg Oncol* 2010;17(Suppl. 3):291–6.
9. Myrdal G, Lambe M, Hillerdal G, Lamberg K, Agustsson T, Stahle E. Effect of delays on prognosis in patients with non-small cell lung cancer. *Thorax* 2004;59(1):45–9.
10. Simunovic M, Rempel E, Theriault ME, et al. Influence of delays to nonemergent colon cancer surgery on operative mortality, disease-specific survival and overall survival. *Can J Surg [Journal article]* 2009;52(4):E79–86.
11. Raptis DA, Fessas C, Belasyse-Smith P, Kurzawinski TR. Clinical presentation and waiting time targets do not affect prognosis in patients with pancreatic cancer. *Surgeon: J Royal Colleges Surgeons Edinburgh Ireland* 2010;8(5):239–46.
12. Yun YH, Kim YA, Min YH, et al. The influence of hospital volume and surgical treatment delay on long-term survival after cancer surgery. *Ann Oncol: ESMO* 2012(May 2).
13. Kulkarni GS, Urbach DR, Austin PC, Fleshner NE, Laupacis A. Longer wait times increase overall mortality in patients with bladder cancer. *J Urol* 2009;182(4):1318–24.
14. Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral Oncol* 2008 Jan;44(1):10–22.
15. van der Waal I, de Bree R, Brakenhoff R, Coebergh JW. Early diagnosis in primary oral cancer: is it possible? *Medicina Oral Patologia Oral y Cirugia Bucal* 2011;16(3):e300–5.
16. Wildeman MA, Fles R, Adham M, et al. Short-term effect of different teaching methods on nasopharyngeal carcinoma for general practitioners in Jakarta, Indonesia. *PLoS ONE* 2012;7(3):e32756.
17. Brouha XD, Tromp DM, Koole R, Hordijk GJ, Winnubst JA, de Leeuw JR. Professional delay in head and neck cancer patients: analysis of the diagnostic pathway. *Oral Oncol* 2007;43(6):551–6.
18. Waaijer A, Terhaard CH, Dehnad H, et al. Waiting times for radiotherapy: consequences of volume increase for the TCP in oropharyngeal carcinoma. *Radiother Oncol: J Eur Soc Therap Radiol Oncol* 2003;66(3):271–6.

19. Begg AC, Haustermans K, Hart AA, et al. The value of pretreatment cell kinetic parameters as predictors for radiotherapy outcome in head and neck cancer: a multicenter analysis. *Radiother Oncol: J Eur Soc Therap Radiol Oncol* 1999;50(1):13–23.
20. Jensen AR, Nellesmann HM, Overgaard J. Tumor progression in waiting time for radiotherapy in head and neck cancer. *Radiother Oncol: J Eur Soc Therap Radiol Oncol* 2007;84(1):5–10.
21. Tromp DM, Brouha XD, De Leeuw JR, Hordijk GJ, Winnubst JA. Psychological factors and patient delay in patients with head and neck cancer. *Eur J Cancer (Oxford, England: 1990)* 2004;40(10):1509–16.
22. Johnson NW, Jayasekara P, Amarasinghe AA. Squamous cell carcinoma and precursor lesions of the oral cavity: epidemiology and aetiology. *Periodontology* 2000 2011;57(1):19–37.
23. Sciubba JJ. Oral cancer. The importance of early diagnosis and treatment. *Am J Clin Dermatol* 2001;2(4):239–51.
24. Thompson L. World Health Organization classification of tumours: pathology and genetics of head and neck tumours. *Ear Nose Throat J.* 2006;85(2):74.
25. Nederlandse Werkgroep Hoofd-Hals Tumoren (NWHHT). Hoofd-Hals J 43, 2010; www.nwhht.nl.
26. Goldstein D, Jeremic G, Werger J, Irish J. Wait times in the diagnosis and treatment of head and neck cancer: comparison between wait times in 1995 and 2005 – a prospective study. *J Otolaryngol* 2007 Dec;36(6):336–43.
27. Lyhne NM, Christensen A, Alanin MC, et al. Waiting times for diagnosis and treatment of head and neck cancer in Denmark in 2010 compared to 1992 and 2002. *Eur J Cancer (Oxford, England: 1990)* 2013;49(7):1627–33.
28. Chen Z, King W, Pearcey R, Kerba M, Mackillop WJ. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. *Radiother Oncol: J Eur Soc Therap Radiol Oncol* 2008;87(1):3–16.
29. Leon X, de Vega M, Orus C, Moran J, Verges J, Quer M. The effect of waiting time on local control and survival in head and neck carcinoma patients treated with radiotherapy. *Radiother Oncol: J Eur Soc Therap Radiol Oncol* 2003;66(3):277–81.
30. Seoane J, Takkouche B, Varela-Centelles P, Tomas I, Seoane-Romero JM. Impact of delay in diagnosis on survival to head and neck carcinomas: a systematic review with meta-analysis. *Clinical otolaryngology: official journal of ENT-UK; official journal of Netherlands Society for to-Rhino-Laryngology & Cervico- Facial Surgery* 2012 Apr; 37(2):99–106.
31. Datema FR, Ferrier MB, van der Schroeff MP, Baatenburg de Jong RJ. Impact of comorbidity on short-term mortality and overall survival of head and neck cancer patients. *Head Neck* 2010;32(6):728–36.
32. Derks W, de Leeuw RJ, Hordijk GJ. Elderly patients with head and neck cancer: the influence of comorbidity on choice of therapy, complication rate, and survival. *Curr Opin Otolaryngol Head Neck Surg* 2005;13(2):92–6.
33. Scott SE, Grunfeld EA, Main J, McGurk M. Patient delay in oral cancer: a qualitative study of patients' experiences. *Psycho-oncology* 2006;15(6):474–85.
34. Fedewa SA, Edge SB, Stewart AK, Halpern MT, Marlow NM, Ward EM. Race and ethnicity are associated with delays in breast cancer treatment (2003–2006). *J. Health Care Poor Underserved* 2011;22(1):128–41.
35. Gorin SS, Heck JE, Cheng B, Smith SJ. Delays in breast cancer diagnosis and treatment by racial/ethnic group. *Arch Intern Med* 2006;166(20):2244–52.
36. Gorey KM, Luginaah IN, Holowaty EJ, Fung KY, Hamm C. Wait times for surgical and adjuvant radiation treatment of breast cancer in Canada and the United States: greater socioeconomic inequity in America. *Clin Invest Med* 2009;32(3):E239–49.

37. Munck K, Ali MJ, Murr AH, Goldberg AN. Impact of socioeconomic status on the diagnosis to treatment interval in Waldeyer's ring carcinoma. *Laryngoscope* 2005;115(7):1283–7.
38. Flory N, Lang EV. Distress in the radiology waiting room. *Radiology* 2011;260(1):166–73.
39. Eskander A, Devins GM, Freeman J, et al. Waiting for thyroid surgery: a study of psychological morbidity and determinants of health associated with long wait times for thyroid surgery. *Laryngoscope* 2012(2).
40. Seklehner S, Hladschik-Kermer B, Lusuardi L, Schabauer C, Riedl C, Engelhardt PF. Psychological stress assessment of patients suffering from prostate cancer. *Scand J Urol Nephrol* 2012(12).
41. Greer JA, Pirl WF, Park ER, Lynch TJ, Temel JS. Behavioral and psychological predictors of chemotherapy adherence in patients with advanced non-small cell lung cancer. *J Psychosom Res* 2008;65(6):549–52.

CHAPTER 5

The influence of nodal yield in neck dissections on lymph node ratio in head and neck cancer

5

C.C.M. Marres
M. de Ridder
I. Hegger
M.L.F. van Velthuisen
M. Hauptmann
A. Navran
A.J.M. Balm

Oral oncology. 2014; 50: 59-64

ABSTRACT

OBJECTIVES

Recent studies suggest that lymph node ratio (LNR) is a strong prognostic factor in head and neck cancer. This study aims to determine if the yield of harvested lymph nodes (LNs) influences the LNR.

METHODS

The study included 522 head and neck cancer patients, undergoing 638 primary and salvage (selective) neck dissections between 2002 and 2012. Before 2007 the neck dissection specimens were macroscopically and microscopically examined by pathologists and after 2007 the macroscopic examination was performed by pathology technicians. For comparison of mean LN yields, univariate and multivariate analyses were performed.

RESULTS

The mean number of LNs among 374 specimens examined by pathologists was 24 (range 0–89) vs. 32 (range 2–89) among 264 specimens examined by pathology technicians ($P < .001$). This caused the mean LNR in the non pre-treated patient group to drop from 11.4% to 8.7%. The counts of LNs per type of neck dissection were significantly different and increased with the number of levels involved. However, there was no linear relationship and the higher yields could be mostly ascribed to LNs in level V. The LNR varied from 8.1% to 18.4% among the different types of neck dissections.

CONCLUSIONS

A significant increase in the number of harvested LNs, but a decrease in LNR was observed after introducing pathology technicians for macroscopic examination. A clear association between the extent of the dissection and the number of harvested LNs was observed. LNR appears to be strongly dependent on the harvesting protocol and the extent of the dissection.

INTRODUCTION

Head and neck cancer tends to metastasize to cervical lymph nodes (LNs) and the presence of lymph node metastases is an important prognostic indicator¹. The probability of distant metastases is dependent on the extent of lymph node disease in the neck and determines overall survival. Although the TNM classification – where N status is based on the diameter, bilateral occurrence and number of positive nodes – has developed into an important instrument for determining the prognostic impact, other ‘lymph node associated factors’, such as the exact number of positive nodes, the total number of harvested nodes and the presence of extra-capsular growth^{2,3} also play an important role and are not included in the current TNM classification. The lymph node ratio (LNR), a possible alternative for prognosis, represents the fraction of metastatic nodes among all harvested nodes. This ratio determines the extent of cancer spread and extent of clearance. In stomach-, bladder- and esophageal cancer, the LNR has been proven to be a reliable prognostic factor and has been used as an indicator for adjuvant treatment⁴⁻⁶. Evidence has emerged showing that the LNR also seems to be a strong prognostic factor in head and neck cancer, outweighing the TNM classification in multivariate analysis⁷⁻¹². Nevertheless, before introducing the LNR as a reliable prognostic index, standardization of harvesting the LNs from the neck dissection specimen and accurate classification of the extent of neck dissection is of utmost importance. In the literature on this subject, uniformity of analysis is lacking.

In order to lower the workload of pathologists in our institution, pathology technicians were introduced for taking over certain routine activities, including harvesting LNs. Since October 2007 pathology technicians assess neck dissection specimens in accordance with a standardized protocol. The aim of this study is to determine if the yield of harvested lymph nodes (LNs) influences the lymph node ratio, by determining the nodal yield after introducing pathology technicians for examining the specimen and by investigating the influence of the extensiveness of the neck dissection on nodal yield.

MATERIAL AND METHODS

PATIENTS

All patients who underwent primary and salvage (modified) radical neck dissections [(M) RND] and selective neck dissections (SND) for primary tumors of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and lip, between 2002 and 2012 in our institute, were selected. We excluded patients who received a super selective neck dissection (SSND) (two levels or less, or three levels separately) or those with a previous ipsilateral neck dissection. In total, 638 (selective) neck dissections were performed in 522 patients, of which 104 bilateral procedures, as well as fourteen patients who underwent a subsequent operation at the contralateral side were considered as separate cases. Patients, who underwent previous (chemo) radiation targeted at the neck, were excluded from calculating the LNR analyses. (Selective) neck dissection specimen processing All neck dissections, either SND or (M) RND were performed in a standardized manner by experienced Head and Neck Surgeons. Operation specimens were fixated in neutral buffered formaldehyde. From 2002 to 2007, neck dissection specimens were both macroscopically and microscopically examined by a pathologist and from 2007 to 2012 the macroscopic examination was done by a pathology technician. Over the whole period three technicians did the macroscopic lymph node counting according to a strict protocol (see below). Microscopic examination was still done by a pathologist. The macroscopic examination was done in accordance with a standardized protocol, based on the international level classification of the neck¹³. The protocol started with orientation of the specimen based on beads, indicating the separate neck node levels, applied by the surgeon, and the identification of the sternocleidomastoid muscle, salivary glands and the internal jugular vein. Subsequently, a macro photo was made and the levels were designated in the photograph; submandicular–submental (I), high jugular (II), mid jugular (III) low jugular (IV) posterior triangle V and sometimes the anterior triangle/paratracheal (VI). Thereafter, the specimens were accurately manually palpated for LNs and all identified LNs were counted, embedded in paraffin and stained with hematoxylin–eosin.

STATISTICAL ANALYSIS

Univariate analysis was based on Mann–Whitney U-tests, Kruskal–Wallis tests and Jonckheere–Terpstra tests. Multivariate analysis was based on linear regression. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 20.0 software (SPSS Inc, Chicago, IL). As stated in the previous section, 118 of the 522 patients (23%) contributed two neck dissections, which could have introduced dependence among our observations. However, we believe that for the outcomes studied here, i.e. the number of LNs and the LNR, little or no correlation remains among neck dissections from the same patient, given the factors included in the multivariate linear regression. We therefore did not perform clustered analysis.

RESULTS

PATIENT DEMOGRAPHICS

The study population of 522 head and neck squamous cell carcinoma patients consisted of 449 men and 189 women with a mean age of 62 (range 28–89). Relevant patient demographics are summarized in Table 1.

NECK DISSECTIONS

The type of neck dissection included 337 (53%) (modified) radical neck dissection (M)RND (level I to V), 119 (19%) selective neck dissection (SND) including level I to III, 65 (10%) SND level II to V, 103 (16%) SND level II to IV and 14 (2%) SND level I to IV. Sixty-four percent of patients received no treatment before surgery. Twelve percent received chemoradiotherapy prior to surgery and 24% radiotherapy.

Table 2 shows the mean number of LNs found, before and after October 2007, by type of neck dissection. Overall, the (M)RND (level I–V) produced the largest number of LNs (range: 1–89; mean 34), followed by SND level II–V (range: 2–60; mean 23), SND level I–III and SND II–IV, (respectively range: 3–52; mean 18 and range: 2–47; mean 17). We included both salvage patients as well as non treated patients. In the group of previously untreated patients there were 17 specimens containing <10 lymph nodes. Fifteen of those specimens were processed before 2007, i.e. according to the old protocol. The remaining specimens (both SND) were processed after 2007, yielding 4 and 7 lymph nodes. [Fig. 1] The mean number of LNs differed significantly by type of dissection. ($P < .001$). Node counts increased significantly by number of neck levels involved. ($P < .001$).

Table 1 Patient demographics.				
Variables	Before Oct '07 N (%)*	After Oct '07 N (%)*	Total N (%)*	P Value
Age				
Average (SD)	61.16	62.60	61.75	0.073**
Range	35–88	28–89	28–89	
Sex				
Female	99 (26.5)	92 (34.8)	191 (29.9)	.028***
Male	275 (73.5)	172 (65.2)	447 (70.1)	
Site of carcinoma				
Lip	7 (1.9)	9 (3.4)	16 (2.5)	.011***
Oral cavity	137 (36.5)	130 (49.4)	267 (41.8)	
Oropharynx	87 (23.2)	47 (17.9)	134 (21.0)	
Nasopharynx	5 (1.3)	1 (0.4)	6 (0.9)	
Hypopharynx	40 (10.7)	19 (7.2)	59 (9.2)	
Larynx	98 (26.1)	58 (22.0)	156 (24.4)	
Type of neck dissection				
Level I-V	197 (52.7)	140 (53.0)	337 (52.8)	.112***
Level II-V	41 (11.0)	24 (9.1)	65 (10.2)	
Level I-IV	5 (1.3)	9 (3.4)	14 (2.2)	
Level I-III	63 (16.8)	56 (21.2)	119 (18.7)	
Level II-IV	68 (18.2)	35 (13.3)	103 (16.1)	
Preoperative treatment				
No treatment	245 (65.5)	168 (63.6)	413 (64.7)	.778***
Chemoradiotherapy	46 (12.3)	31 (11.7)	77 (12.1)	
Radiotherapy	83 (22.2)	65 (24.6)	148 (23.2)	
Total	374 (100)	264 (100)	638 (100)	
* Unless otherwise stated in the first column.				
** Mann–Whitney U-test.				
*** Exact Chi-square test.				

	Before Oct '07*		After Oct '07*		Total		p Value (Mann-Whitney)	
	LN Mean (SD)	Positive LNs (SD)**	LN Mean (SD)	Positive LNs (SD)**	LN Mean (SD)	Positive LNs (SD)**	LN Mean (SD)	Positive LNs (SD)**
Level I-V	29 (13.8)	2.7 (5.1)	41 (16.4)	2.8 (6.3)	34 (17.1)	2.8 (5.6)	<.001	<0.701
Level II-V	21 (12.1)	2.8 (2.9)	29 (15.3)	1.3 (1.9)	24 (14.6)	2.3 (2.7)	.027	<0.467
Level I-IV	22 (12.2)	1.0 (1.7)	27 (9.7)	1.0 (1.8)	25 (10.4)	1.0 (1.1)	.257	<0.720
Level I-III	17 (9.8)	.88 (1.9)	19 (9.6)	.81 (1.8)	18 (9.3)	.60 (1.4)	.173	<0.085
Level II-IV	17 (9.4)	.57 (0.9)	17 (11.4)	1.0 (1.3)	17 (10.1)	.7 (1.0)	.738	<0.313
Total	24 (14.5)	1.9 (4.1)	32 (17.7)	2.1 (6.1)	27 (16.4)	2.0 (4.5)	<.001	<0.519

All LN means are completed on whole LNs.
 * Before October 2007, nodal yield was determined by a pathologist compared with a pathology technician thereafter.
 ** All salvage patients were excluded in calculating the mean number of positive LNs.

A clear dichotomy could be discriminated between the number of lymph nodes harvested from specimens before 2007 and thereafter (Table 2). The 374 (M) RND and SND specimens before 2007 had a mean of 24 and a median of 20 LNs (range 0–89). The 243 (M) RND and SND specimens after October 2007 had a mean of 32 and a median of 29 LNs (range 2–89) ($P < .001$). Between the SND I–III and SND II–IV no differences were found in lymph node counts after introducing pathology technicians (2002–2007 vs. 2007–2012). However, in specimens of (modified) RND, as well as the SND II–V significantly more lymph nodes were found after October 2007, respectively 29 vs. 41 and 20 vs. 29 ($P < .001$), indicating that this difference was determined by the extra number of nodes found in level V (Fig. 2). The LNR is calculated as the ratio of positive lymph nodes to the total number of lymph nodes removed (Table 2) multiplied by 100. The LNR dropped from a mean of 11.4% to a mean of 8.7% after introducing pathology technicians ($p = .016$) (Table 3).

	LNR (SD)			P Value (Mann-Whitney)
	Before Oct '07	After Oct '07	Total	
Level I-V	10.8 (14.6)	8.8 (13.3)	10.0 (14.1)	.075
Level II-V	21.3 (16.0)	5.5 (5.3)	18.4 (15.1)	.076
Level I-IV	21.4*	5.8 (2.9)	8.4 (6.9)	.143
Level I-III	10.7 (6.1)	10.1 (10.3)	10.3 (8.6)	.174
Level II-IV	8.7 (4.8)	6.7 (1.8)	8.1 (4.3)	.792
Total	11.3 (15.6)	8.7 (11.8)	10.2 (13.2)	.015

All salvage patients were excluded in calculating the lymph node ratio.
 * With exclusion of salvage patients this group consisted of only one patient.

RADIOTHERAPY OR CHEMORADIOTHERAPY

In the salvage (selective) neck dissections, both preoperative radiotherapy (RT) and chemoradiotherapy (CRT) had a significant influence on the number of harvested LNs compared to the untreated neck dissections (Table 4). In total, 76 neck dissection specimens, from patients who underwent preoperative CRT had a mean of 18 LNs (range 2–83). 146 specimens from patients who received only RT had a mean of 20 LNs (range 1–78). The 413 neck dissections from patients receiving no treatment had a mean of 31 LNs (range 4–89). The differences between pre-treated and untreated neck dissection specimens were statistically significant ($P < .001$).

MULTIVARIATE ANALYSIS

In the multivariate analysis we included all above-mentioned variables; before or after 2007, type of neck dissection and preoperative treatment. The variables age and sex, which might influence the LN yield, were also added. In multivariate linear regression none of the patient characteristics influenced the lymph node counting, whereas all the above mentioned factors showed a significant relationship with the number of LNs ($P < .003$, Table 5).

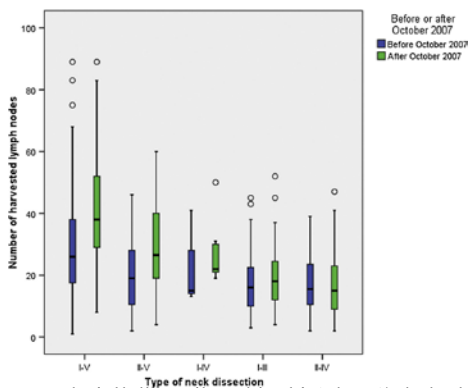


Figure 1. Box plots of nodal yield per type of dissection, before and after October 2007. These box plots indicate the smallest observation, the lower quartile, the median, the upper quartile, and largest observation.

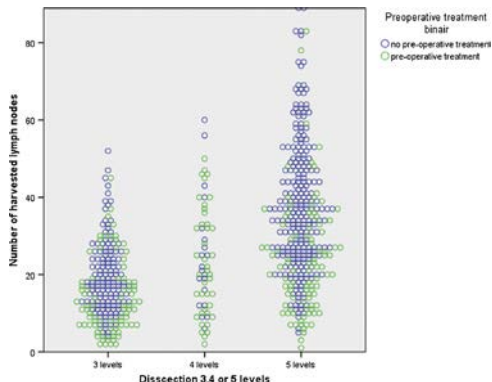


Figure 2. Difference in lymph node yield between previously untreated and treated patients, subcategorized in dissected levels.

	LN mean (SD)	P Value
No treatment	31 (16.6)	<.001 (Mann-Whitney)
Radiotherapy	20 (13.5)	
Only radiotherapy	21 (14.0)	.099 (Kruskal-Wallis)
Chemoradiotherapy	18 (12.4)	
All LN means are completed on whole LNs.		

Variable	Coefficient B	95% CI	P value
Constant	39.1	32.8 to 45.5	
Sex, man vs. woman	-9.4	-1.9 to 2.7	.743
Age at diagnosis (per year)	-0.1	-.2 to .0	.060
After vs. before October 2007	8.5	6.1 to 10.3	<.001
Preoperative treatment vs. no treatment			
Chemoradiotherapy	-12.0	-15.3 to -8.7	<.001
Radiotherapy	-9.4	-12.1 to -6.8	<.001
Neck dissection vs. I-V			
II-V	-5.6	-9.4 to -1.9	.003
I-IV	-10.8	-17.9 to -3.7	.003
I-III	-17.2	-20.0 to -14.5	<.001
II-IV	-13.4	-16.4 to -10.4	<.001

DISCUSSION

This is the first report comparing LN harvesting from neck dissection specimens by pathologists and pathology technicians. Our study showed a significant increase of LN harvesting after the introduction of the pathology technician with the use of a standard protocol. In colorectal resection specimens it has already been demonstrated that the introduction of the pathology technician results in a significantly improved retrieval of LNs¹⁴.

Kuijpers et al

showed that a pathology technician recovers more and, in particular, smaller LNs from colorectal resection specimens than the pathologist; 83% of the pathology technicians vs. 61% of the pathologists sampled more than 10 LNs per specimen.

This is most probably caused by the increased amount of time they can spend on harvesting lymph nodes, due to the nature of their job. In that study, after the introduction of pathology technicians for harvesting lymph nodes in colon specimens, the number of patients eligible for adjuvant chemotherapy reduced from 17% to 1% and diminished thereby the costs and morbidity. However, increased nodal yield will not only subject the LNR to shifting, it will also lower the risk of missing micro-metastases¹⁵. Ebrahimi et al⁹ even suggest that nodal yield may be a surrogate quality control measure, with more thorough pathological analysis of the specimen leading to higher nodal yields and reducing the likelihood of under staging. Regarding the utility of the LNR in head and neck carcinomas, previous studies on LNR describe cutoff values for therapeutic decision making. These values vary between 2.5% and 20.0% (median: 6%) among the different studies⁷⁻¹². In our study the LNR dropped from a mean of 11.4% to a mean of 8.7% after introducing pathology technicians ($p = .016$) (Table 3). It is obvious that such a change might have consequences for patients in determining the necessity of adjuvant treatment.

In contrast to other studies on LNR^{7-9,11,12}, we made a clear distinction between the extensiveness of neck dissections. As opposed to Friedman et al¹⁶, we found a clear correlation between the number of harvested LNs and the extent of the dissection. Surprisingly, in SND I–III and II–IV there is no significant difference in LNs count before and after introducing pathology technicians, as opposed to the (M)RND and SND II–V, indicating that this difference was determined by the number of nodes harvested from level V. This could imply that level V entails a larger amount and more difficult to identify LNs compared to LNs in other levels. From our analysis it became apparent that the number of levels involved in the neck dissection and number of LNs are not directly linearly related. Recent studies show a very low prevalence of metastasis in level V^{17,18}; nonetheless lymph node counts in level V significantly influence the LNR, with LNR ranging from 8.1% to 18.4% in the different type of neck dissections. It should therefore be emphasized that cutoff points for LNR are inextricably linked to the extensiveness of the neck dissection, demonstrated by the different mean LNR per type of dissection (Table 3). The prognostic impact of LNR could perhaps be more substantial if the type of neck dissection was taken into account^{8,9,11,12}.

The higher number of primary neck dissections before 2007 in our series may be due to the introduction of organ preserving chemo-irradiation, which led to an increase of salvage super selective neck dissections¹⁹. All recent studies on LNR exclude patients treated with radiotherapy prior to surgery.

The known literature regarding preoperative RT or CRT and cervical LNs counts is conflicting with regards to the decrease of lymph node number in the specimen^{20,21} as found by us (mean 31 vs. 20). This effect was even more pronounced in the group which received concurrent CRT (mean 18). In a small amount of cases it remains unclear if the radiation field included all the dissected levels, or if the radiation field was limited to fewer neck node levels, but even after we excluded these cases the outcome remained similar in both univariate and multivariate analyses. The negative influence of radiotherapy has also been described in patients who have been treated for rectal cancer^{22,23}. Whether we are dealing with an actual decrease in number of lymph nodes or with a more difficult detection of lymph nodes by radiotherapy induced fibrosis remains to be elucidated²⁴. If the LNR could have prognostic impact in patients, undergoing salvage neck surgery after (C)RT should be further investigated.

CONCLUSIONS

The results of this study show a significant increase in the number of harvested LNs, but a decrease in LNR after introducing pathology technicians for examination of the neck dissection specimen. We also found a clear correlation between the number of harvested LNs and the extent of the dissection. Based on our findings, it appears that in order for the LNR to become a reliable index, a standardized protocol in harvesting LNs and different cutoff points of LNR per type of neck dissection should be applied.

REFERENCES

1. Tankere F, Camproux A, Barry B, Guedon C, Depondt J, Gehanno P. Prognostic value of lymph node involvement in oral cancers: a study of 137 cases. *Laryngoscope* 2000;110(12):2061–5.
2. Ebrahimi A, Zhang WJ, Gao K, Clark JR. Nodal yield and survival in oral squamous cancer: defining the standard of care. *Cancer* 2011;117:2917–25.
3. Shingaki S, Takada M, Sasai K, et al. Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas. *Am J Surg* 2003;185:278–84.
4. Medina-Franco H, Cabrera-Mendoza F, Almaguer-Rosales S, Guillén F, Suárez-Bobadilla YL, Sánchez-Ramón A. Lymph node ratio as a predictor of survival in gastric carcinoma. *Am Surg* 2013;79:284–9.
5. Kassouf W, Agarwal PK, Herr HW, et al. Lymph node density is superior to TNM nodal status in predicting disease-specific survival after radical cystectomy for bladder cancer: analysis of pooled data from MDACC and MSKCC. *J Clin Oncol* 2008;26:121–6.
6. Ooki A, Yamashita K, Kobayashi N, et al. Lymph node metastasis density and growth pattern as independent prognostic factors in advanced esophageal squamous cell carcinoma. *World J Surg* 2007;31:2184–91.
7. Shrime MG, Bachar G, Lea J, Volling C, et al. Nodal ratio as an independent predictor of survival in squamous cell carcinoma of the oral cavity. *Head Neck* 2009;31:1482–8.
8. Kim SY, Nam SY, Choi SH, Cho KJ, Roh JL. Prognostic value of lymph node density in node-positive patients with oral squamous cell carcinoma. *Ann Surg Oncol* 2011;18:2310–7.
9. Ebrahimi A, Clark JR, Zhang WJ, et al. Lymph node ratio as an independent prognostic factor in oral squamous cell carcinoma. *Head Neck* 2011;33:1245–51.
10. Liao CT, Hsueh C, Lee LY, et al. Neck dissection field and lymph node density predict prognosis in patients with oral cavity cancer and pathological node metastases treated with adjuvant therapy. *Oral Oncol* 2012;48:329–36.
11. Gil Z, Carlson DL, Boyle JO, et al. Lymph node density is a significant predictor of outcome in patients with oral cancer. *Cancer* 2009;115:5700–10.
12. Süslü N, Hosal AS, Sözeri B. Prognostic value of metastatic lymph node ratio in node-positive head and neck carcinomas. *Am J Otolaryngol* 2010;31:315–9.
13. Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the American head and neck society and the American academy of otolaryngology-head and neck surgery. *Arch Otolaryngol Head Neck Surg* 2002;128:751–8.
14. Kuijpers CC, van Slooten HJ, Schreurs WH, et al. Better retrieval of lymph nodes in colorectal resection specimens by pathologists' assistants. *J Clin Pathol* 2013;66:18–23.
15. van den Brekel MW, van der Waal I, Meijer CJ, Freeman JL, Castelijn JA, Snow GB. The incidence of micrometastases in neck dissection specimens obtained from elective neck dissections. *Laryngoscope* 1996;106:987–91.
16. Friedman M, Lim JW, Dickey W, et al. Quantification of lymph nodes in selective neck dissection. *Laryngoscope* 1999;109:368–70.
17. Kainuma K, Yano T, Kitoh R, Naito T, Usami SI. Prevalence of level V metastasis in head and neck squamous cell carcinoma. *Acta Otolaryngol* 2013;133:218–24.
18. Naibog'lu B, Karapinar U, Agrawal A, Schuller DE, Ozer E. When to manage level V in head and neck carcinoma? *Laryngoscope* 2011;121:545–7.
19. Mazon R, Tao Y, Lusinchi A, Bourhis J. Current concepts of management in radiotherapy for head and neck squamous-cell cancer. *Oral Oncol* 2009;45:402–8.

20. Johnstone PA, Miller ED, Moore MG. Preoperative radiotherapy decreases lymph node yield of neck dissections for head and neck cancer. *Otolaryngol Head Neck Surg* 2012;147:278–80.
21. Moore MG, Bhattacharyya N. Effectiveness of chemotherapy and radiotherapy in sterilizing cervical nodal disease in squamous cell carcinoma of the head and neck. *Laryngoscope* 2005;115:570–3.
22. Mekenkamp LJ, van Krieken JH, Marijnen CA, van de Velde CJ, Nagtegaal ID. Lymph node retrieval in rectal cancer is dependent on many factors—the role of the tumor, the patient, the surgeon, the radiotherapist, and the pathologist. *Am J Surg Pathol* 2009;33:1547–53.
23. Damin DC, Rosito MA, Contu PC, et al. Lymph node retrieval after preoperative chemoradiotherapy for rectal cancer. *J Gastrointest Surg* 2012;16:1573–80.
24. Shvero J, Koren R, Marshak G, et al. Histological changes in the cervical lymph nodes after radiotherapy. *Oncol Rep* 2001;8:909–11.

CHAPTER 6

A critical evaluation of lymph node ratio in Head and Neck cancer

6

M. de Ridder
C.C.M. Marres
L.E. Smeele
M.W.M. van den Brekel
M. Hauptmann
A.J.M. Balm
M.L.F. van Velthuisen

Virchows Archiv. 2016; 469: 635-641

ABSTRACT

In head and neck squamous cell carcinoma (HNSCC), the search for better prognostic factors beyond TNM-stage is ongoing. Lymph node ratio (LNR) (positive lymph nodes/total lymph nodes) is gaining interest in view of its potential prognostic significance.

All HNSCC patients at the Netherlands Cancer Institute undergoing neck dissection for lymph node metastases in the neck region between 2002 and 2012 ($n = 176$) were included. Based on a protocol change in specimen processing, the cohort was subdivided in two distinct consecutive periods (pre and post 2007). The prognostic value of LNR, N-stage, and number of positive lymph nodes for overall survival was assessed.

The mean number of examined lymph nodes after 2007 was significantly higher (42.3) than before (35.8) ($p = 0.024$). The higher number concerned mostly lymph nodes in level V. The mean number of positive lymph nodes before 2007 was 3.3 vs. 3.6 after 2007 ($p = 0.745$). By multivariate analysis of both pre- and post-2007 cohort data, two factors remained associated with an increased hazard of dying: N2 [HR 2.1 (1.1–4.1) and 2.4 (1.0–5.8)] and >3 positive lymph nodes [HR 2.0 (1.1–3.5) and 3.1 (1.4–6.9)]. Hazard ratio for LNR >7 % was not significantly different: pre 2007 at 2.2 (1.3–3.8) and post 2007 at 2.1 (1.0–4.8, $p = 0.053$).

In this study, changes in specimen processing influenced LNR values, but not the total number of tumor positive nodes found. Therefore, in HNSCC, the number of positive nodes seems a more reliable parameter than LNR, provided a minimum number of lymph nodes are examined.

Keywords Prognosis .Lymph nodemetastases . Lymph node ratio . Staging . Head and neck cancer

INTRODUCTION

Lymph node metastases are among the most important independent prognostic factors in head and neck carcinoma^{3, 17, 21} and, as a consequence, N-stage has a significant influence on treatment choice. In addition, the number of metastatic lymph nodes, contra-lateral lymph node status, level (s) involved, and extracapsular extension (ECE) are independent prognostic parameters and contribute to further tailoring of treatment^{3, 21}. However, the value of N-stage as prognostic indicator is under discussion, in particular for patients after postoperative radiotherapy^{2, 22, 28}. Bernier et al compared the results of two trials (EORTC #22931 and RTOG #9501) which studied postoperative chemo-radiotherapy of locally advanced head and neck squamous cell carcinoma². They found as a prognostic factor, for both loco-regional recurrence and survival, involvement of resection margins and ECE is more significant than N-stage. Others reported similar findings in patients who had undergone complete surgical excision and postoperative radiotherapy^{7, 22, 28}. In a recent study, however, ECE lost its prognostic significance in patients who had undergone postoperative radiotherapy¹⁰. For malignancies other than head and neck cancer, the lymph node ratio (LNR), the proportion of lymph nodes with metastases relative to the total number of examined lymph nodes, has emerged as an important prognostic parameter in surgically treated patients^{1, 11, 18, 19, 38}. In colorectal cancer, LNR is a significant prognostic factor for a 5-year overall survival (OS) and disease-specific survival (DSS)¹. For gastric cancer, by multivariate analysis, LNR but not N-category emerged as an independent prognostic factor for overall survival¹⁸. Data on the prognostic influence of LNR in head and neck cancer predominantly focus on surgically treated oral cavity carcinomas (Table 1), and show poor prognosis in patients with higher LNR values^{6, 8, 12–16, 23–25, 29–32, 34, 36, 37}. In a recent multi-institutional study on oral cavity carcinoma, reliability and applicability of the LNR were assessed in predicting outcome²³. An LNR above 7 % was associated with a significantly increased risk of death from oral cancer [multivariate HR 1.62 (p = 0.004)]. In a multivariate model, TNM with LNR (TLNRM) stage was superior to TNM stage. However, LNR is a derivative of two variables which are both related to the lymph nodes “harvested” from surgical specimens. To investigate the effect of these two variables, we compared in two consecutive time frames, which differed in the method of processing of neck dissection specimens, the prognostic impact of LNR, traditional N-stage, and the number of positive lymph nodes found.

PATIENTS AND METHODS

PATIENTS

Medical records of all 522 head and neck cancer patients, undergoing a (modified) radical [(M) RND] or selective neck dissection (SND) for squamous cell cancer of the larynx, hypopharynx, oropharynx, and oral cavity between 2002 and 2012, were retrieved. We did not include patients with a stage pN0 or pN3 (the latter often representing clusters of metastatic lymph nodes) and patients with a prior neck dissection or prior radiotherapy, as the number of lymph nodes in these specimens is influenced by previous treatment (s) or cannot be reliably counted²⁰. In total, 176 patients were included in the study.

SPECIMEN PROCESSING

All neck dissections were performed in the same institute by experienced head and neck surgeons. Levels of dissection were classified according to the guidelines of the American Head and Neck Society²⁶. Between 2002 and 2007, pathologists performed macroscopic examination of the specimen.

From 2007 to 2012, pathology technicians processed the specimens according to a standard protocol, which included a more thorough examination of the neck dissection specimen and yielded a higher number of examined lymph nodes [20]. Cutoff value for high and low LNR was set at 7 %, based upon a large international series of >4000 patients²³.

STATISTICAL ANALYSIS

Median overall survival (OS) was calculated using the Kaplan-Meier method. OS was defined as time between surgery and death. We evaluated the prognostic effect of T-stage, N-stage, ECE, LNR and number of positive nodes, sex, age, adjuvant therapy, and number of evaluated nodes. Univariate significant factors were retained in the final multivariate Cox regression model. Analyses were done separately for the time periods before and after 2007. Outcome analyses were done for individual patients. Categorical data were analyzed using chi-square test or Fisher's exact, normally distributed continuous data using t test. Trend tests were based on the p value of the coefficient for the continuous variable. Significance levels were set at <0.05. All analyses were done by PASW statistics 20.0 (SPSS Inc. Chicago).

Table 1. Literature overview: lymph node ratio as survival predictor in head and neck cancer							
Author	Year	Site	n	N+	Ntot	LNR cut off	OS / DSS
Shrime[14]	2009	Oral cavity	2955	3	26 (N1) 32 (N2)	0% - 6%, 6% - 12.5%, >12.5%	OS
Gil[18]	2009	Oral cavity	386	3	35	6%	OS/DSS
Suslu[23]	2010	Larynx, hypopharynx, oral cavity, oropharynx, skin	142	2	n.a.	4%	OS / DSS
Ebrahimi[17]	2010	Oral cavity	313	3	27	2.5% - 7.5%, 7.5% - 20%, >20%	OS / DSS
Kim[19]	2011	Oral cavity	211	2	25	6%	DSS
Liao[20]	2011	Oral cavity	148	I-III 3, I-V 5	I-III 40, I-V 57	4.8%	OS/DSS
Rudra[21]	2013	Oropharynx, Oral cavity, CUP, Larynx Hypo-pharynx	38	n.a.	n.a.	2%	OS/DFS
Künzel[26]	2013	Oropharynx	384	4	4	10%	DSS
Sayed[22]	2013	Oral cavity	1408	3	3	8.8%	OS / DSS
Patel[16]	2013	Oral cavity	4254	3	3	7%	OS/DSS
Wang[24]	2014	Hypopharynx	916	2	2	R0 - 0, R1 - <5%, R2 - 5-30%, R3 - >30%	CSS/OS
Künzel[25]	2014	Oral cavity	374	3	3	5% - 7%	DSS
Wang[29]	2014	Larynx	1963	2	2	R1 - <9%, R2 - 9-20%, R3 - >20%	OS
Prabhu[27]	2014	Larynx, oral cavity	350	n.a.	n.a.	20%	LRR
Reinisch[28]	2014	HNSCC	291	n.a.	n.a.	6%	OS, LRR
Künzel[30]	2015	Larynx	202	3	3	5%, 7%, 9%	DSS

Abbreviations: OS - overall survival, DSS - disease specific survival, DFS - disease free survival, LNR - lymph node ratio, CSS - cause specific survival, LRR - locoregionall recurrence. N+ - mean number of positive LN found, Ntot - mean total number of LN examined, n.a. - not available, HNSCC - head and neck squamous cell carcinoma, CUP - carcinoma of unknown primary

RESULTS

PATIENT CHARACTERISTICS (TABLE 2)

Of the 176 patients who met the inclusion criteria, 118 (67 %) were male and 58 (33 %) were female. Of the patients, 13 % had laryngeal, 3 % hypopharyngeal, 19 % oropharyngeal, and 64 % oral cavity cancer. Of the 33 oropharyngeal tumors, 17 (52 %) were HPV positive. The pre-2007 period contained 30 oropharynx carcinoma patients, of whom 15 were HPV positive. The majority of patients (135; 77 %) underwent a (Modified) Radical Neck Dissection [(M)RND] and 41 (33 %) a selective neck dissection. Details about the different types of neck dissection are listed in Table 3. The majority of patients (61 %) underwent postoperative radiotherapy and 21 % were treated with postoperative concurrent cisplatin-based chemo-radiotherapy. Less than half of the patients (40 %) suffered from recurrent disease. Of those, 20 % had a loco-regional recurrence without distant metastases and 20 % had distant metastases (some in addition to locoregional recurrent disease). Patient characteristics did not significantly differ between the periods before and after October 2007, except for tumor site, as after 2007, there were significantly less oropharyngeal carcinomas (27 vs. 5 %, $p = 0.004$). Patient, tumor, and treatment characteristics were equally distributed between both groups.

LYMPH NODE PARAMETERS

The mean number of examined lymph nodes was 38.1 (range 7–100; median 36). Mean LNR was 8 % (range 1–77 %; median 5 %) (Table 2). There was no difference in LNR between SND and (M) RND ($p = 0.757$). The mean number of examined lymph nodes in the period after the change in protocol was significantly higher (35.8 before and 42.3 after October 2007; $p = 0.024$) (Table 2). The increased number was notably on account of more lymph nodes in level V (Table 3). The mean number of detected lymph node metastases was not significantly different between the two periods (3.6 vs. 3.3 nodes; $p = 0.745$) (Table 2). Also, N-stage distribution was similar ($p = 0.740$).

	Total		Pre 2007		Post 2007		p-value
	n	%	n	%	n	%	
Age							
<65	116	66	73	65	43	68	0.624
≥65	60	34	40	35	20	32	
Sex							
Male	118	67	79	70	39	62	0.279
Female	58	33	34	30	24	38	
Tumor site							
Larynx	24	14	17	15	7	11	0.004
Hypopharynx	6	3	5	4	1	2	
Oral cavity	113	64	61	54	52	83	
Oropharynx	33	19	30	27	3	5	
HPV+	17	52	15	50	2	67	
HPV-	11	33	10	33	1	33	
HPV doubtful	3	9	3	10	-	-	
HPV n.a.	2	6	2	7	-	-	
T-stage							
T1-2	90	51	58	51	32	51	0.867
T3-4	71	40	40	35	31	49	
Tx	15	9	15	13	-	-	
N-stage							
N1	64	36	37	33	27	43	0.740
N2a	12	7	11	10	1	2	
N2b	78	44	48	43	30	48	
N2c	22	13	17	15	5	8	
ECE							
Absent	90	51	49	43	41	65	0.554
Present	82	47	61	54	21	33	
Unknown	4	2	3	3	1	2	
Additional therapy							
None	24	14	8	7	16	25	0.070
Radiotherapy	108	61	75	66	33	52	
Concurrent chemo-radiation	37	21	25	22	12	19	
Other	7	4	5	4	2	3	
Type of dissection							
MRND	135	77	90	80	45	71	0.151
SND	41	24	23	20	18	29	
Level II-V	9	22	7	6	2	3	
Level I-IV	6	15	1	1	5	8	
Level I-III	14	34	6	5	8	13	
Level II-IV	12	29	9	8	3	5	
Vital status							
Alive	93	53	57	50	36	57	
Death	83	47	56	50	27	43	
LNR (Mean (range))	10.2 (1.2-90.9)		10.8 (1.5-90.9)		9.0 (1.2-66.7)		0.382
Number of positive nodes (Mean (range))	3.5 (1-45)		3.6 (1-45)		3.3 (1-22)		0.745
Lymph node yield (Mean (range))	38.1 (7-100)		35.8 (9-100)		42.3 (7-83)		0.024

Abbreviations: HPV – human papilloma virus, n.a. – not available - ECE – extracapsular extension, MRND – modified radical neck dissection, SND – selective neck dissection, LNR – lymph node ratio

OVERALL SURVIVAL (TABLE 4)

Median overall survival of the cohort was 71 months (95%CI 45–97 months), in which 83 events occurred. There was no significant difference in overall survival between the two time periods ($p = 0.270$). Cox regression analysis of the period before October 2007 yielded as significant prognostic factors for overall survival LNR $>7\%$ HR 2.2 (95 % CI 1.3–3.8), T3–4 HR 2.0 (95 % CI 1.1–3.6), N2 HR 2.1(95 % CI 1.1–4.1), and the number of positive lymph nodes >3 HR 2.0 (95 % CI 1.1–3.5). For the period after October 2007, these were N2 HR 2.4 (95 % CI 1.0–5.8), ECE HR 2.5 (95 % CI 1.1–5.3), and number of positive nodes >3 HR 3.1 (95 % CI 1.4–6.9). After exclusion of patients with HPV-positive oropharyngeal carcinoma, HRs were similar except for T-stage which was no longer significant. Adding individual lymph node parameters in a multivariate model did not change the outcome of the analysis. Since LNR and number of positive lymph nodes are continuous variables, a similar multivariate model introducing step-wise LNR and number of positive nodes as continuous variables was performed, indicating trend p values of positive lymph nodes and LNR as listed in Table 4.

Table 3. Number of examined and positive nodes by level and year				
	Mean examined nodes		Mean positive nodes	
	Pre 2007	Post 2007	Pre 2007	Post 2007
MRND				
Level I-V	36.0	47.2	3.5	3.4
SND	34.1	51.5	5.0	2.5
Level II-V	14.0	25.6	3.0	1.4
Level I-III	34.0	24.8	3.5	4.3
Level II-IV	38.9	37.3	3.0	3.7
Total	35.8	42.3	3.6	3.3
Abbreviations: MRND: Modified radical neck dissection, SND: selective neck dissection				

Table 4. Multivariate Cox regression analysis for overall survival

	Before October 2007				After October 2007			
	HPV + included		HPV + excluded		HPV + included		HPV + excluded	
	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value
T-classification								
T3-4 vs. T1-2	2.0 (1.1-3.6)	0.023	1.7 (0.9-3.2)	0.09	1.6 (0.8-3.5)	0.216	1.7 (0.8-3.6)	0.18
Extra capsular extension								
ECE + vs. ECE -	1.4 (0.8-2.4)	0.253	1.3 (0.7-2.4)	0.35	2.5 (1.1-5.3)	0.024	2.5 (1.1-5.3)	0.02
LNR								
>7% vs. <=7%	2.2 (1.3-3.8)	<0.001*	1.9 (1.1-3.2)	0.03	2.1 (1.0-4.8)	0.086*	2.0 (0.9-4.4)	0.07
Positive nodes								
>3 vs. <=3	2.0 (1.1-3.5)	<0.001*	1.6 (0.9-3.0)	0.12	3.1 (1.4-6.9)	0.037*	3.2 (1.5-7.1)	0.004
N-classification								
N2 vs. N1	2.1(1.1-4.1)	0.026	2.1 (1.1-4.1)	0.03	2.4 (1.0-5.8)	0.044	2.4 (1.0-5.6)	0.05

Abbreviations: HR, hazard ratio; LNR, lymph node ratio; ECE, extra capsular extension; HPV, human papilloma virus; CI, confidence interval
* P-values were based on the p-value of the coefficient for the continuous variable

DISCUSSION

LNR is a ratio, based upon the number of tumor-positive lymph nodes in a neck dissection specimen as numerator and the total number of lymph nodes as denominator. The potential advantage of LNR relative to the number of metastatic nodes only is that LNR takes into account both parameters. Studies on the prognostic value of LNR are part of an international search for accurate and objective staging methods. The prognostic value of LNR has been demonstrated in a variety of cancer types^{1, 11, 18, 19, 38}, including head and neck cancer (see Table 1)^{6, 8, 12-16, 23-25, 29-32, 34, 36, 37}. Several authors^{15, 23, 36} have suggested that LNR might be added to the current TNM staging. Based upon a series of more than 4000 oral cancer patients, Patel et al. reported that LNR is superior to the current N-stage²³ and suggested to include LNR as a rule in TNM staging.

In a recent paper, however, Roberts et al²⁷ questioned the role of LNR as a prognostic factor for HNSCC on a multivariate analysis of 12,437 patients. They did not confirm prognostic significance of LNR, whereas the prognostic value of pN and AJCC stage was confirmed. Gleisner et al⁹ also questioned the value of the total number of examined lymph nodes in a SEER database study on a series of 154, 208 colorectal cancer patients and found that outcome for patients with the same LNR could be completely different. As an example, a patient with one metastasis in a single examined lymph node (LNR = 1) had a better prognosis than a patient with 12 metastases in 12 lymph nodes (LNR = 1). Examination of a single lymph node probably represented serious under-sampling. Their conclusion was that the number of positive lymph nodes is a better indicator of survival than the LNR. We have previously shown that the total number of examined nodes varies significantly between different methods of neck dissection specimen processing²⁰.

The present study documents that a more detailed protocol applied by pathology technicians resulted in a significantly higher number of harvested lymph nodes, while the lower mean LNR (from 10.8 to 9.0 %) and range (from 1.5–90.9 % to 1.2–66.7%) were not statistically significant. The latter may be due to the low number of cases collected since 2007. Many of the additional lymph nodes were found in level V, where lymph nodes as a rule are rather small. It is unlikely that the higher number of lymph nodes can be attributed to a change in surgical technique as this has not changed being performed by a stable group of surgeons in our institution. It is more likely that the difference in the number is due to the introduction of a stricter protocol executed by pathology technicians. The observation that the mean number of positive lymph nodes did not change significantly lends credibility to this assumption. Our data show that the prognostic value of three lymph node status-associated prognostic factors, total number, number of nodes with metastases, and LNR, is influenced by variations in pathology specimen processing. We document intra-institutional variation but contend that this can be extrapolated to interinstitutional variations in specimen processing. Why LNR does not emerge uniformly as valuable prognostic factor is clarified by the results of our study in that different lymph node procurement protocols result in different yield with an effect on LNR. The finding that prognostic significance of LNR was not different between the two time frames while that of the number of positive lymph nodes appeared stronger after 2007 merits some comments. A higher yield of lymph nodes not accompanied by more lymph node metastases only dilutes LNR importance. The importance of LNR is that it provides insight into the quality of lymph node dissection/sampling. For other cancer types, this problem has been addressed by requiring examination of a minimum number of lymph nodes, resulting in a quality indicator of at least 10–12 evaluated lymph nodes in colon cancer [4]. A recent paper on lymph node sampling in colon cancer showed that a higher yield of lymph nodes does not necessarily increase the number of nodes with metastases or of lymph node-positive cases³⁵. The UICC guideline states that selective neck dissection ordinarily includes 6, and (modified) radical neck dissection ordinarily includes 10 lymph nodes[^] and Bif lymph nodes are negative, but the number ordinarily examined is not met, they have to classify as pN0[^] [33]. This statement does not clarify what the minimum number of lymph nodes is to qualify sampling of a neck dissection specimen as sufficient. The numbers stated in the UICC guideline seem to be very low, as in the literature reviewed; for our study, we found 23 as the lowest number of sampled lymph nodes (Table 1).

We argue that a minimum number of lymph node samples from a MRND should be 20 rather than the 10 required by the UICC. A limitation of our study is that several important elements differ from previously published studies on the subject. The majority of our patients underwent a modified radical neck dissection. This is important, since MRND includes level V lymph nodes but SND does not, which dilutes LNR significantly. Furthermore, changes in the treatment protocol, such as inclusion in 2010 of postoperative chemo-radiotherapy in cases with positive tumor resection margins and ECE, might have influenced impact of lymph node-related prognostic factors. A final issue is that we included all head and neck squamous cell carcinomas and not only oral cavity cancer as most other studies^{6, 8, 12, 14, 16, 23, 29, 31}, which we consider justified because lymph node staging and its prognostic value are not different between head and neck subsites. However, for HPV-positive tumors, TNM stage is less predictive⁵, and therefore, we performed the multivariate analyses twice, including HPV-positive tumors and excluding HPV-positive tumors.

In conclusion, we show that LNR is prognostic in head and neck cancer. However, as LNR varies according to the protocols applied for processing of neck dissection specimens which may vary between institutions and in time, it is subject to important variability. We find that the number of positive lymph nodes is as least as good as LNR but less susceptible to variation, provided that lymph node sampling is adequate. The requirement for the minimum number of lymph nodes to be examined in an MRND specimen should be increased from the presently UICC required number of 10 to 20.

REFERENCES

1. Berger AC, Sigurdson ER, LeVoyer T, Hanlon A, Mayer RJ, Macdonald JS, Catalano PJ, Haller DG (2005) Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. *J Clin Oncol* 23:8706–8712. doi:10.1200/JCO.2005.02.8852
2. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, Ozsahin EM, Jacobs JR, Jassem J, Ang KK, Lefebvre JL (2005) Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck* 27:843–850. doi:10.1002/hed.20279
3. Bernier J, Domette C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A, van Glabbeke M (2004) Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 350:1945–1952. doi:10.1056/NEJMoa032641
4. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA (2007) Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst* 99:433–441. doi:10.1093/jnci/djk092
5. Dahlstrom KR, Garden AS, WNWJr, LimMY, Sturgis EM (2016) Proposed staging system for patients with HPV-related oropharyngeal cancer based on nasopharyngeal cancer N categories. *J Clin Oncol* 34:1848–1854. doi:10.1200/JCO.2015.64.6448
6. Ebrahimi A, Clark JR, ZhangWJ, Elliott MS, Gao K, Milross CG, Shannon KF (2011) Lymph node ratio as an independent prognostic factor in oral squamous cell carcinoma. *Head Neck* 33:1245–1251. doi:10.1002/hed.21600
7. Freeman DE, Mendenhall WM, Parsons JT, Million RR (1992) Does neck stage influence local control in squamous cell carcinomas of the head and neck? *Int J Radiat Oncol Biol Phys* 23:733–736
8. Gil Z, CarlsonDL, Boyle JO, Kraus DH, Shah JP, Shaha AR, Singh B, Wong RJ, Patel SG (2009) Lymph node density is a significant predictor of outcome in patients with oral cancer. *Cancer* 115:5700–5710. doi:10.1002/cncr.24631
9. Gleisner AL, Mogal H, Dodson R, Efron J, Gearhart S, Wick E, Lidor A, Herman JM, Pawlik TM (2013) Nodal status, number of lymph nodes examined, and lymph node ratio: what defines prognosis after resection of colon adenocarcinoma? *JAmColl Surg* 217: 1090–1100. doi:10.1016/j.jamcollsurg.2013.07.404
10. Herman MP, Dagan R, Amdur RJ, Morris CG, Werning JW, Vaysberg M, Mendenhall WM (2015) Postoperative radiotherapy for patients at high risk of recurrence of oral cavity squamous cell carcinoma. *Laryngoscope* 125:630–635. doi:10.1002/lary.24938
11. Herr HW (2003) Superiority of ratio based lymph node staging for bladder cancer. *J Urol* 169:943–945. doi:10.1097/01.ju.0000032474.22093.06
12. Kim SY, Nam SY, Choi SH, Cho KJ, Roh JL (2011) Prognostic value of lymph node density in node-positive patients with oral squamous cell carcinoma. *Ann Surg Oncol* 18:2310–2317. doi:10.1245/s10434-011-1614-6
13. Kunzel J, Mantsopoulos K, Psychogios G, Agaimy A, Grundtner P, Koch M, Iro H (2015) Lymph node ratio is of limited value for the decision-making process in the treatment of patients with laryngeal cancer *European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies* 272:453–461. doi:10.1007/s00405-014-2997-3
14. Kunzel J, Mantsopoulos K, Psychogios G, Grundtner P, Koch M, Iro H (2014) Lymph node ratio as a valuable additional predictor of outcome in selected patients with oral cavity cancer. *Oral surgery, oral medicine, oral pathology and oral radiology* 117:677–684. doi:10.1016/j.oooo.2014.02.032

15. Kunzel J, Psychogios G, Mantsopoulos K, Grundtner P, Waldfahrer F, Iro H (2014) Lymph node ratio as a predictor of outcome in patients with oropharyngeal cancer *European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies* 271:1171–1180.
16. Liao CT, Hsueh C, Lee LY, Lin CY, Fan KH, Wang HM, Huang SF, Chen IH, Kang CJ, Ng SH, Tsao CK, Huang YC, Yen TC (2012) Neck dissection field and lymph node density predict prognosis in patients with oral cavity cancer and pathological node metastases treated with adjuvant therapy. *Oral Oncol* 48:329–336.
17. Mamelle G, Pampurik J, Luboinski B, Lancar R, Lusinchi A, Bosq J (1994) Lymph node prognostic factors in head and neck squamous cell carcinomas. *Am J Surg* 168:494–498
18. Marchet A, Mocellin S, Ambrosi A, Morgagni P, Garcea D, Marrelli D, Roviello F, de Manzoni G, Minicozzi A, Natalini G, De Santis F, Baiocchi L, Coniglio A, Nitti D (2007) The ratio between metastatic and examined lymph nodes (N ratio) is an independent prognostic factor in gastric cancer regardless of the type of lymphadenectomy: results from an Italian multicentric study in 1853 patients. *Ann Surg* 245:543–552.
19. Mariette C, Piessen G, Briez N, Triboulet JP (2008) The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. *Ann Surg* 247:365–371.
20. Marres CC, de Ridder M, Hegger I, van Velthuysen ML, Hauptmann M, Navran A, Balm AJ (2014) The influence of nodal yield in neck dissections on lymph node ratio in head and neck cancer. *Oral Oncol* 50:59 – 64 .
21. Olsen KD, Caruso M, Foote RL, Stanley RJ, Lewis JE, Buskirk SJ, Frassica DA, DeSanto LW, O'Fallon WM, Hoverman VR (1994) Primary head and neck cancer. Histopathologic predictors of recurrence after neck dissection in patients with lymph node involvement. *Arch Otolaryngol Head Neck Surg* 120:1370–1374
22. Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR (1997) An analysis of factors influencing the outcome of postoperative irradiation for squamous cell carcinoma of the oral cavity. *Int J Radiat Oncol Biol Phys* 39:137–148
23. Patel SG, Amit M, Yen TC, Liao CT, Chaturvedi P, Agarwal JP, Kowalski LP, Ebrahimi A, Clark JR, Cernea CR, Brandao SJ, Kreppel M, Zoller J, Fliss D, Fridman E, Bachar G, Shpitzer T, Bolzoni VA, Patel PR, Jonnalagadda S, Robbins KT, Shah JP, Gil Z (2013) Lymph node density in oral cavity cancer: results of the international consortium for outcomes research. *Br J Cancer*.
24. Prabhu RS, Hanasoge S, Magliocca KR, Hall WA, Chen SA, Higgins KA, Saba NF, El-Deiry M, Grist W, Wadsworth JT, Chen AY, Beitler JJ (2014) Lymph node ratio influence on risk of head and neck cancer locoregional recurrence after initial surgical resection: implications for adjuvant therapy. *Head Neck*.
25. Reinisch S, Kruse A, Bredell M, Lubbers HT, Gander T, Lanzer M (2014) Is lymph-node ratio a superior predictor than lymph node status for recurrence-free and overall survival in patients with head and neck squamous cell carcinoma? *Ann Surg Oncol* 21:1912– 1918.
26. Robbins KT, Shaha AR, Medina JE, Califano JA, Wolf GT, Ferlito A, Som PM, Day TA (2008) Consensus statement on the classification and terminology of neck dissection. *Arch Otolaryngol Head Neck Surg* 134:536–538.
27. Roberts TJ, Colevas AD, Hara W, Holsinger FC, Oakley-Girvan I, Divi V (2016) Number of positive nodes is superior to the lymph node ratio and American Joint Committee on Cancer N staging for the prognosis of surgically treated head and neck squamous cell carcinomas. *Cancer* 122:1388–1397.
28. Rudoltz MS, Benammar A, Mohiuddin M (1995) Does pathologic node status affect local control in patients with carcinoma of the head and neck treated with radical surgery and postoperative radiotherapy? *Int J Radiat Oncol Biol Phys* 31:503–508.

29. Rudra S, Spiotto MT, Witt ME, Blair EA, Stenson K, Haraf DJ (2013) Lymph node density—prognostic value in head and neck cancer. *Head Neck*.
30. Sayed SI, Sharma S, Rane P, Vaishampayan S, Talole S, Chaturvedi P, Chaukar D, Deshmukh A, Agarwal JP, D'Cruz AK (2013) Can metastatic lymph node ratio (LNR) predict survival in oral cavity cancer patients? *J Surg Oncol* 108:256–263.
31. Shingaki S, Takada M, Sasai K, Bibi R, Kobayashi T, Nomura T, Saito C (2003) Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas. *Am J Surg* 185:278–284
32. Shrime MG, Ma C, Gullane PJ, Gilbert RW, Irish JC, Brown DH, Goldstein DP (2009) Impact of nodal ratio on survival in squamous cell carcinoma of the oral cavity. *Head Neck* 31:1129–1136.
33. Sobin LHGMKWC (2009) *The classification of malignant tumours 7th edition*.
34. Suslu N, Hosal AS, Sozeri B (2010) Prognostic value of metastatic lymph node ratio in node-positive head and neck carcinomas. *Am J Otolaryngol* 31:315–319.
35. van Erning FN, Crolla RM, Rutten HJ, Beerepoot LV, van Krieken JH, VE L (2014) No change in lymph node positivity rate despite increased lymph node yield and improved survival in colon cancer. *Eur J Cancer* 50:3221–3229.
36. Wang YL, Feng SH, Zhu J, Zhu GP, Li S, Wang Y, Zhu YX, Sun GH, Ji QH (2013) Impact of lymph node ratio on the survival of patients with hypopharyngeal squamous cell carcinoma: a population-based analysis. *PLoS One* 8:e56613.
37. Wang YL, Li DS, Wang Y, Wang ZY, Ji QH (2014) Lymph node ratio for postoperative staging of laryngeal squamous cell carcinoma with lymph node metastasis. *PLoS One* 9:e87037.
38. Woodward WA, Vinh-Hung V, Ueno NT, Cheng YC, Royce M, Tai P, Vlastos G, Wallace AM, Hortobagyi GN, Nieto Y (2006) Prognostic value of nodal ratios in node-positive breast cancer. *J Clin Oncol* 24:2910–2916.

SUPPLEMENTAL MATERIAL

Supplement table 1.						
	Model 1		Model 2		Model 3	
	<okt2007	>okt2007	<okt2007	>okt2007	<okt2007	>okt2007
Sex	0.836 (0.622)	1.109 (0.797)	0.817 (0.576)	1.016 (0.968)	0.890 (0.746)	0.886 (0.765)
T_group	1.752 (0.076)	1.374 (0.424)	1.970 (0.025)	1.644 (0.205)	1.880 (0.038)	1.688 (0.180)
ECE	1.345 (0.289)	1.712 (0.242)	1.190 (0.540)	2.259 (0.042)	1.261 (0.407)	1.971 (0.111)
Pos LN	1.832 (0.089)	2.973 (0.008)	*	*	*	*
LNR	*	*	2.184 (0.011)	2.150 (0.050)	*	*
N_group	*	*	*	*	1.957 (0.074)	2.538 (0.037)

Abbreviations: ECE: extra capsular extension, LN: lymph node, LNR: lymph node ratio

Supplement table 2. Univariate analysis						
	<2007			>2007		
	HR	95% CI	P	HR	95% CI	P
Sex	1.025	0.574-1.831	0.925	1.059	0.486-2.305	0.854
T_group	1.993	1.100-3.613	0.018	1.622	0.754-3.489	0.204
ECE	1.375	0.797-2.373	0.274	2.453	1.126-5.344	0.031
Pos LN	1.985	1.119-3.520	0.010	3.134	1.421-6.911	0.002
Pos LN_cont	1.113	1.065-1.162	<0.001	1.072	1.005-1.143	0.021
LNR	2.165	1.250-3.751	0.006	1.978	0.921-4.249	0.080
LNR_cont	1.044	1.026-1.062	<0.001	1.029	1.006-1.052	0.011
N_group	2.121	1.096-4.107	0.018	2.436	1.026-5.782	0.031
Nodal yield	0.992	0.977-1.008	0.280	1.003	0.982-1.024	0.650

Abbreviations: HR: hazard ratio, ECE: extra capsular extension, LN: lymph node, LNR: lymph node ratio

OUTCOME INDICATORS

CHAPTER 7

An epidemiological evaluation of salivary gland cancer in het Netherlands (1989-2010)

7

Mischa de Ridder
Alfons J.M. Balm
Ludi E. Smeele
Michel W.J.M. Wouters
Boukje A.C. van Dijk

Cancer epidemiology. 2015; 39: 14-20

ABSTRACT

BACKGROUND

The relative 5-year survival rate of salivary gland cancer is moderate at best. This study was set up to evaluate whether the improvements in diagnosis and treatment in the last decades impacted the incidence, mortality and survival of salivary gland cancer.

METHODS

Data on patients with salivary gland cancer from 1989 through 2010 were extracted from the Netherlands Cancer Registry (NCR); we examined incidence, mortality and relative survival. Furthermore, information on sex, age, tumor stage, histology, and treatment was taken into account.

RESULTS

A total of 2737 patients were included. Fifty-three percent (53%) were males and 47% were females with a significant higher proportion of early stages in women. In 2010, the incidence rate (European Standardized Rate (ESR)) of salivary gland cancer was 0.9 per 100,000 per year. The estimated annual percentage change in incidence rate since 1989 equaled 0.6% (95%CI: 0.2–1.4). Mortality rates (ESR) decreased in men until 1997 and increased thereafter. Mortality in women remained stable at 1.5 per 100,000.

Over time more patients were treated by surgery and radiotherapy ($p < .001$). The relative five-year survival rate equaled 69% and did not change in time.

CONCLUSION

We observed no relevant changes in incidence or mortality rates in the last two decades. Despite the increased combined treatment by surgery and radiotherapy, survival did not improve. This implies an urgent need for the development of new effective treatment modalities

INTRODUCTION

‘What progress has been made against cancer?’ is one of the most frequently asked questions in Western medicine. With this question in mind, several large cancer survival studies have been published over the past years, generally showing that incidence, as well as survival rates are rising¹⁻⁵. Increasing incidence has mainly been explained by population aging and better cancer detection. Improvements in early detection and treatment may explain better survival rates. However, the war against cancer is still far from over^{3,4}. Incidence trends of head and neck cancer differ by localization; the calculated incidence of oral cavity and pharyngeal cancer according to estimated annual percentage change EAPC increased with 1% per year for males and 2% for females since 1989, while the incidence in laryngeal cancer decreased with 2% per year for males and remained stable for females⁴. The most likely explanation for decreasing laryngeal cancer incidence in males is the decline in smoking prevalence^{6,7}. Salivary gland carcinomas are a special group among head and neck carcinomas, because of its relatively rare occurrence at 150 new diagnoses per year in the Netherlands, and a greater variation in the histological subtypes. Also, malignancy rates differ by localization. About 80% of salivary glands tumors originate from parotid glands (25% malignant), 10% from the submandibular gland (50% malignant), 1% from the sublingual gland (95% malignant) and 9% from small submucous glands (60% malignant)⁸. Furthermore, the most important risk factors for head and neck cancer tobacco and alcohol use⁹, are less clearly associated to salivary gland tumors. Some reports suggest that exposure to ionizing irradiation¹⁰ or Epstein Barr virus (EBV) infection¹¹ could be risk factors. Radiation was suspected based on the observation of high incidence rates among atomic bomb survivors in Japan¹² and patients who received radiation in childhood for indications like Hodgkin lymphoma^{10,13}. The current knowledge suggests that only lymphoepithelial carcinoma, constituting 0.4% of all malignant salivary gland tumors, might be strongly associated with EBV¹¹. This study was initiated to assess whether progress has been made regarding salivary gland cancer. Therefore, we calculated the changes in burden, indicated by incidence, mortality and survival rates over a 22-year period in the Netherlands.

2. PATIENTS AND METHODS

2.1. PATIENTS

For this study, all primary cancers of the salivary glands diagnosed between 1989 and 2010 were extracted from the Netherlands Cancer Registry (NCR), leading to 2764 tumors in 2760 patients. We excluded 4 second primary salivary gland tumors, and 23 other non-carcinomas (sarcomas) resulting in data for 2737 patients. The NCR covers the total population of the Netherlands (16,574,989 inhabitants in 2010). The registry receives lists of all newly diagnosed cancers on a regular basis from the nationwide pathology network PALGA (all pathology laboratories in the Netherlands participate in PALGA). In addition, the NCR receives also diagnoses from the hospital discharge registries. The completeness of incidence of the NCR was estimated to equal at least 95%¹⁴. Following notification, trained tumor registration clerks abstract a minimum data set, including patient characteristics (sex, age at diagnosis), tumor information (date of diagnosis, topography, histology, stage at diagnosis) and treatment information from hospital records.

2.2. TUMORS

Topography was coded according to the international classification of diseases for oncology (ICD-O-3)¹⁵; codes C07 (parotid gland)–C08 (other salivary glands) were included. The histology was coded according to the ICD-O-3 morphology coding and categorized into 7 groups as described in Table 1. Tumor stage was recorded according to the International Union against Cancer (UICC) TNM classification according to the UICC 4th edition from 1989 through 1996 (1st and 2nd revision)^{16,17}, the UICC 5th edition from 1999 until 2002¹⁸, the UICC 6th edition from 2003 to 2009¹⁹ and the UICC 7th edition in 2010²⁰. Major changes in classification were: from 5th to 6th edition all tumors >4 cm were considered T3 tumors (previous editions limited T3 tumors to tumors 4–6 cm in size) and T4 tumors were divided into T4a (tumor invasion of skin, mandible, ear canal and/or facial nerve) and T4b (tumor invasion of skull base, pterygoid plates and/or encasement of carotid artery). Scoring all T4, T4a and T4b as T4 tumor obviated the latter change. To evaluate changes over time, five equal time periods were defined: 1989–1993, 1994–1998, 1999–2002, 2003–2006 and 2007–2010.

Table 1 ICD-O-3 histology code grouping of salivary gland tumors.

Group	ICD-O code
Adenoid cystic carcinoma	8200
Muco-epidermoid carcinoma	8430
Acinic cell carcinoma	8550, 8551
Squamous cell carcinoma	8070, 8071, 8072, 8074, 8075, 8078, 8083
Adenocarcinoma NOS	8140, 8190, 8201, 8230, 8240, 8440, 8450, 8471, 8480, 8481, 8490, 8501, 8525, 8574
Carcinoma ex pleomorphic adenoma	8022, 8940, 8941
Myo-epithelial carcinoma	8562, 8982
Salivary duct carcinoma	8500
Other salivary gland carcinomas	See below
Neoplasm NOS	8000
Malignant tumor cells NOS	8001
Carcinoma NOS	8010
Large cell carcinoma NOS	8012
Neuro-endocrine carcinoma NOS	8013
Undifferentiated carcinoma	8020
Anaplastic carcinoma	8021
Large cell carcinoma	8031
Spindle cell carcinoma	8032
Sarcomatoid carcinoma	8033
Small cell carcinoma	8041
Lympho-epithelial carcinoma	8082
Basosquamous carcinoma	8094
Basiloideno carcinoma	8147
Neuro-endocrine carcinoma	8246
Merckel cell carcinoma	8247
Oropharyngeal adenocarcinoma	8290
Clear cell adenocarcinoma	8310
Comedocarcinoma	8501
Medullary adenocarcinoma	8510
Adenosquamous carcinoma	8560
Metaplastic carcinoma	8575
Sarblastoma	8974
Carcinoma sarcoma NOS	8980

Table 2 Patient, tumor and treatment characteristics in time.

	1989–1993	1994–1998	1999–2002	2003–2006	2007–2010	p-value
Sex						
Women	276 (51.1%)	310 (55.5%)	288 (54.7%)	246 (48.3%)	353 (56.1%)	0.057b
Men	260 (48.5)	249 (44.5%)	239 (54.3%)	263 (51.7%)	276 (43.9%)	
Age						
Median (p25–p75)	64 (50 – 74)	64 (50-74)	62 (48-74)	64 (52-75)	64 (52-75)	0.623a
Localisation						
Parotid gland	416 (77.7%)	418 (74.9%)	436 (82.7%)	388 (76.2%)	505 (80.3%)	0.012b
Minor salivary glands	120 (22.3%)	141 (25.1%)	91 (17.3%)	121 (23.8%)	124 (19.7%)	
Histology						
Adenoid cystic carcinoma	86 (16.0%)	116 (20.7%)	81 (15.4%)	88 (17.3%)	84 (13.4%)	0.001b
Muco-epidermoid carcinoma	87 (16.4%)	61 (10.9%)	80 (15.2%)	65 (12.8%)	80 (12.7%)	
Acinic cell carcinoma	65 (12.1%)	79 (14.3%)	78 (14.8%)	75 (14.7%)	109 (17.3%)	
Carcinoma ex pleiomorphic adenoma	43 (8.0%)	35 (6.2%)	39 (7.4%)	52 (10.2%)	38 (6.0%)	
Adenocarcinoma, NOS	99 (18.4%)	102 (18.2%)	73 (13.8%)	84 (16.5%)	93 (14.8%)	
Squamous Cell Carcinoma	55 (10.2%)	62 (11.1%)	59 (11.2%)	42 (8.3%)	59 (9.4%)	
Other salivary gland ca	101 (19.0%)	104 (18.7%)	117 (20.2%)	103 (20.2%)	166 (26.4%)	
Stage						
1 & 2	260 (48.5%)	286 (51.2%)	277 (52.6%)	250 (49.1%)	297 (47.2%)	0.001b
3 & 4	198 (36.9%)	207 (37.0%)	201 (38.1%)	221 (43.4%)	282 (44.8%)	
X	78 (14.6%)	66 (11.8%)	49 (9.3%)	38 (7.5%)	53 (8.0%)	
Therapy						
No therapy	26 (4.9%)	27 (4.8%)	26 (4.9%)	27 (5.3%)	38 (6.0%)	<0.001b
Surgery	158 (29.5%)	144 (25.8%)	132 (25.1%)	106 (20.8%)	118 (18.8%)	
Radiotherapy	29 (5.4%)	34 (6.1%)	53 (10.1%)	34 (6.7%)	65 (10.3%)	
Surgery & radiotherapy	316 (59.0%)	349 (62.4%)	309 (58.6%)	334 (65.6%)	393 (62.5%)	
Other treatment	7 (1.3%)	5 (0.9%)	7 (1.3%)	8 (1.6%)	15 (2.4%)	
Total	536 (19.4%)	559 (20.3%)	527 (19.1%)	509 (18.4%)	629 (22.8%)	

a Fisher's exact, b Chi-square.

2.3. STATISTICAL ANALYSIS

Differences between groups were assessed using Fischer's exact test or chi-square test (whichever was appropriate). Trends in incidence and mortality were evaluated using Joinpoint Regression Program, Version 3.5.3. May 2012; Statistical Research and Applications Branch, National Cancer Institute²¹, calculating the estimated annual percentage change (EAPC) over the European Standardized rates. Overall survival was analyzed using Kaplan–Meier estimations. Relative survival rates were calculated using Paul Dickman's STATA model for relative survival (Ederer II method)²². In relative survival analyses the ratio of observed survival to the expected survival was calculated. Survival time was defined as date of diagnosis to date of death or date of censoring (date of emigration or date of record linkage to the municipal records to assess the vital status). The administrative censoring date was December 31, 2010. Patients with a survival time of 0 days were excluded (N = 1). Poisson regression modeling was used to calculate the multivariable relative excessive risk of dying (RER)²². All statistical analyses were performed using STATA data analysis and statistical software (version 10.0, StataCorp LP, TX, 1996).

3. RESULTS

3.1. PATIENTS, TUMOR AND TREATMENT CHARACTERISTICS

A total of 2737 patients were included in the study. This cohort consists of 1464 (53.5%) male patients and 1273 (46.5%) female patients (Tables 2 and 3). The median age of male salivary gland cancer patients was 64 years, while female patients had a median age of 62 years ($p = 0.03$). In this cohort 78.3% of the tumors were from the parotid gland. The other 21.7% were found in submandibular, sublingual or minor salivary glands (Tables 2 and 3). Most patients were treated with a combined scheme of surgery and postoperative radiotherapy (61.8%), sometimes combined with chemotherapy. Other treatment modalities included only surgery (23.8%) and only primary radiotherapy (7.8%). A total of 5.1% of the patients did not undergo any form of treatment (only best supportive care) (Tables 2 and 3). The distribution of all different histological types of salivary gland cancer over the years is shown in Table 2.

Table 3 Patient, tumor and treatment characteristics by sex			
	Male	Female	p-value
Age			
Median, years	64	62	0.032a
Year of diagnosis			
1989 – 1993	276 (18.9%)	260 (20.2%)	0.064b
1994 – 1998	310 (21.0%)	249 (19.5%)	
1999 - 2002	288 (19.5%)	239 (18.5%)	
2003 – 2006	246 (16.7%)	263 (20.4%)	
2007 - 2010	353 (23.9%)	276 (21.4%)	
Histology			
Adenoid cystic carcinoma	184 (12.5%)	271 (21.0%)	<0.001b
Muco-epidermoid carcinoma	184 (12.5%)	189 (14.6%)	
Acinic cell carcinoma	189 (12.8%)	217 (16.9%)	
Carcinoma ex pleiomorphic adenoma	114 (7.7%)	93 (7.2%)	
Adenocarcinoma NNO	279 (18.9%)	172 (13.3%)	
Squamous cell carcinoma	199 (13.5%)	78 (6%)	
Other salivary glandcarcinoma	324 (22.0%)	267 (20.8%)	
Localisation			
Parotid gland	1167 (79.3%)	996 (77.4%)	0.244b
Minor salivary gland	306 (20.8%)	291 (22.6%)	
Stage			
1 & 2	623 (42.3%)	747 (58.0%)	<0.001b
3 & 4	697 (47.3%)	412 (32.0%)	
X	152 (10.3%)	128 (10.0%)	
Therapy			
No therapy	79 (5.4%)	65 (5.1%)	0.013b
Surgery	322 (21.9%)	336 (26.1%)	
Radiotherapy	130 (8.8%)	85 (6.6%)	
Surgery + radiotherapy	914 (62.1%)	787 (61.2%)	
Other therapy	28 (1.9%)	14 (1.1%)	
Total	1473 (53.4%)	1287 (46.6%)	
a) Fisher exact, b) Chi square			

Over the total study period there was a significant change in stage. The proportion of patients with unknown stage, due to missing data, declined over time from 8.4% to 5.4%. The proportion of patients treated by surgery only declined over time and most likely shifted toward surgery with radiotherapy (Table 2). There were striking differences between male and female patients (Table 3). While adenoid cystic carcinoma is most common in female patients (21%), adenocarcinoma NOS was most common in male patients (19%, $p < 0.001$). Also, male patients had a significant higher disease stage than female patients at first diagnosis (stages III and IV disease, respectively 47.5% and 31.6%) ($p < 0.001$). More primary radiotherapy was reported in men (8.7% vs. 6.7% in women), while surgery only was more frequent in women (26.1% vs. 21.7% in men, $p = 0.012$).

3.2. TRENDS IN INCIDENCE AND MORTALITY RATES

The incidence (ESR) of salivary gland cancer changed from 0.63 per 100,000 per year in 1989 to 0.74 per 100,000 per year in 2010 with an estimated average annual percentage change (EAPC) of 0.6% (95%CI: 0.2; 1.4) (Fig. 1). This trend was similar in males and females. Mortality rates declined statistically significantly between 1989 and 1997 with an EAPC of 6.3% (95%CI: 10.7; 1.6), while from 1997 onwards the EAPC was positive, indicating stable/increasing mortality rates (the EAPC equaled 2.0% (95%CI: 0.3; 4.4)) (Fig. 2). The changes in mortality rates showed a similar pattern in males, whereas female mortality rates remained stable over the entire period.

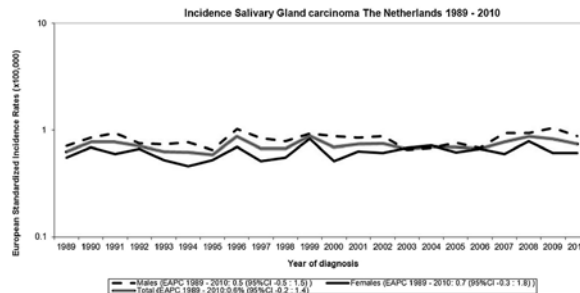


Fig. 1. Incidence of salivary gland cancer in the Netherlands 1989–2010

3.3. SURVIVAL

The overall 5-year survival was 59.6% (95%CI: 57.7–61.5); 10-year survival equaled 46.1% (95%CI: 44.0–48.2). The 5- and 10-year relative survival rate equaled 69.1% (95%CI: 66.8–71.3%) and 61.7% (95%CI: 58.8–64.5%), respectively. Relative survival stratified by sex and time period is visualized in Fig. 3. Males had a significant lower relative survival than female patients. Five-year relative survival in male patients was 63%, compared to 76% for females ($p < 0.001$). Relative survival did not change over the years as shown in Fig. 3. The relative survival differed by histology: the best 5-year relative survival rate was observed for acinic cell carcinoma 97% (95%CI: 93–99%), while intermediate rates were found for adenoid cystic carcinoma 79% (95%CI: 75–84%) muco-epidermoid carcinoma 76% (95%CI: 70–81%), and carcinoma ex pleomorphic carcinoma 72% (95%CI: 63–80%).



Fig. 2. Mortality of salivary gland cancer in the Netherlands 1989–2010.

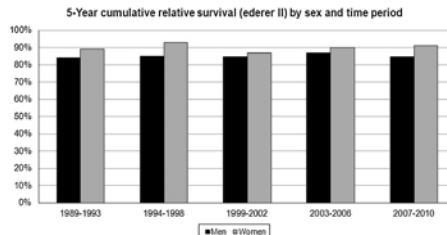


Fig. 3. Five-year relative survival estimates by sex and time period.



Worse 5-year relative survival rates were observed for other salivary gland carcinomas 59% (95%CI: 54–64%), adenocarcinoma NOS 54% (95%CI: 48–60%), and especially squamous cell carcinoma 44% (95%CI: 36–51%). Table 4 shows the multivariate relative excess risk of dying for malignant salivary gland tumors in the Netherlands. Patients with adenocarcinoma NOS and primary SCC were twice as likely to die compared to patients with adenoid cystic carcinoma. Patients with acinic cell carcinoma had the least relative excess risk of dying (0.44 (95%CI: 0.25–0.79). Females had a RER of 0.88 (95%CI: 0.74– 1.04), which was not statistically significant.

Table 4. Multivariate RER of dying from salivary gland cancer in the Netherlands			
Variable		RER multivariate	95% confidence interval
Sex	Male	1	reference
	Female	0.91	0.77 – 1.06
Stage	I	1	reference
	II	2.79	1.77 – 4.40
	III	5.59	3.58 – 8.72
	IV	9.77	6.50 – 14.67
Histology	Adenoid cystic carcinoma	1	reference
	Muco-epidermoid carcinoma	1.51	1.07 – 2.13
	Acinic cell carcinoma	0.46	0.25 – 0.80
	Ca ex pleiomorphic adenoma	1.50	1.01 – 2.23
	Adenocarcinoma NOS	1.92	1.42 – 2.59
	Squamous cell carcinoma	2.47	1.79 – 3.39
	Other salivary gland carcinoma	2.18	1.63 – 2.93
Treatment	No therapy	1	reference
	Surgery	0.20	0.15 – 0.28
	Radiotherapy	0.50	0.37 – 0.67
	Surgery + radiotherapy	0.18	0.14 – 0.24
	Other	0.65	0.42 – 1.02
Year of diagnosis grouped	1989 – 1993	1	reference
	1994 – 1998	0.96	0.75 – 1.23
	1999 – 2002	1.04	0.81 – 1.33
	2003 – 2006	0.98	0.76 – 1.26
	2007 – 2010	0.77	0.60 – 1.01

4. DISCUSSION

4.1. MAIN FINDINGS

Over the past 22 year, the standardized incidence rate of salivary gland carcinomas in the Netherlands was stable, but hospitals still see a greater number of patients due to population growth and aging. The most remarkable findings are related to sex differences in mortality (stable in women; significantly decreasing until 1997 in men and stable, but tending toward increasing afterwards) and relative survival (63% for men and 76% for women). These differences could be explained by the finding that male patients more often presented with higher stage disease than female patients and with different histological subtypes (male more often adenocarcinoma NOS and women adenoid cystic carcinoma).

4.2. COMPARISON INCIDENCE TO LITERATURE AND POSSIBLE EXPLANATIONS OF CHANGES/TRENDS

Crude incidence of salivary gland carcinoma in the Netherlands is 0.9 per 100,000 in 2010, and equals other international studies reporting crude incidences from 0.7 per 100,000 per year to 1.3 per 100,000 per year²³⁻²⁹. Age standardized (ESR) incidence rate in this cohort is approximately 0.8 per 100,000 per year in the Netherlands. The male: female ratio of 1:0.87 is in agreement with the international literature, which ranges from 0.67 to 1.04^{23,24,30-32}.

Furthermore, the mean and median age of patients found in this study corresponds well to the ages reported in the literature^{23,24,28,32,33}. Over the years, we found a stable incidence rate, although a tendency toward an increase could not be neglected. Changes in incidence rate may sometimes reflect the improvement of the diagnosis or reclassification of benign salivary gland tumors to malignant salivary gland tumors²³.

The diagnosis is clearly a challenge for epithelial salivary gland carcinoma since they are uncommon and very heterogeneous appearance (anatomy as well as histology). The current World Health Organization (WHO) categories no less than 24 different malignant salivary gland lesions. It is the general opinion of experts in the field that from the moment pathologists in the Netherlands started to centralize the pathological review of parotid tumors, often consulting their experts in case of difficult classification, a higher percentage of malignancies have been diagnosed. Because this trend started slowly a clear starting year cannot be given. Interestingly, there was an absolute increase observed of T1-T2 tumors. This could be due to the widespread use of ultrasound-guided fine-needle-aspiration cytology (FNAC)³⁴ and magnetic resonance imaging (MRI)³⁵ in the Netherlands. In this cohort, the most common histological type was adenoid cystic carcinoma, followed by adenocarcinoma NOS, acinic cell carcinoma, and muco-epidermoid carcinoma (respectively 16.56%, 16.5%, 14.78% and 13.6%).

Adenocarcinoma NOS, was the number one diagnosis in male patients, whereas adenoid cystic carcinoma was most common in females. Internationally, muco-epidermoid carcinoma represents the major subtype, followed by adenoid cystic carcinoma and adenocarcinoma NOS^{23,24,26,30-32,36-40}. Two studies described the same pattern of sex difference in histology^{23,24}. This phenomenon is not well understood. The significantly higher tumor stage at diagnosis in male patients compared to female patients (stage IV: 36.2% vs. 21.3%, respectively $p < 0.001$), may be related to the greater attention of women to their appearance and to disease, as has been suggested by Micheli et al⁴¹.

4.3. COMPARISON MORTALITY TO LITERATURE AND POSSIBLE EXPLANATIONS OF CHANGES/TRENDS

Mortality showed an interesting difference between men and women. We have no explanation for the trend break in 1997 for men. As far as we know, such a trend break has not been described before.

4.4. COMPARISON RELATIVE SURVIVAL TO LITERATURE AND POSSIBLE EXPLANATIONS OF CHANGES/TRENDS

The relative survival curve was significantly lower for male patients compared to female patients for all time periods. This can partly be explained by an early stage at diagnosis and more favorable histological subtypes in women.

A prognostic benefit in women for adenoid cystic carcinoma of the head and neck has been described previously⁴², while sex differences for other types of salivary gland carcinomas have never been described before. However, in the multivariate RER analysis the sex difference, in favor of females, disappeared. Differences in the trend analysis were thus mainly determined by stage and histology.

4.5. TREATMENT IN RELATION TO INTERNATIONAL TRENDS AND RELATION TO PROGNOSIS

Since 1989 treatment regimens consist of primary surgery, with or without adjuvant irradiation. More recent literature demonstrates that chemo-radiotherapy as part of the treatment leads to better survival^{43,44}. Pederson et al showed better 5-year locoregional progression free survival (96% vs. 86%) for adjuvant chemo-radiotherapy compared to surgery with radiotherapy for loco-regionally advanced and high-risk salivary gland cancer in a series of 24 consecutive patients⁴³. Another study found a 92% 3-year overall loco-regional control rate in the post surgery chemo-radiotherapy group, even though more high-risk patients (high-risk included: T3-T4 disease, nodal positivity and positive resection margins) were included in the chemo-radiotherapy group⁴⁴. In our cohort, only 22 patients were treated by chemoradiotherapy for advanced disease.

This treatment modality did not increase over the years. It is doubtful whether chemoradiotherapy contributes to outcome of our study, but future analysis of adjuvant chemo-radiation should certainly be performed in a prospective randomized fashion. This initiative should be taken up by the International Head and Neck Oncological societies to combine efforts for improving the survival rates for patients with head and neck cancer.

4.6. CHANCES FOR IMPROVEMENT

For several tumors (e.g. esophagus, pancreas and bladder), a positive relationship between higher surgical volume and better outcome has been shown⁴⁵⁻⁴⁸. Since salivary gland cancer, and in fact all head and neck cancers, can be qualified as rare disease, the volume-outcome relationship is likely to be positive, although a recent editorial showed the lack of good studies confirming this relationship⁴⁹. A fact is that rare tumors require experienced decision-making, so the Dutch head and neck cancer co-operative group started centralizing head and neck cancer in 1984⁵⁰. However, due to the low incidence rate the mean number of salivary gland carcinomas per head and neck cancer center does not exceed 15 new patients per year. Compared to other major clinics in the world, this remains a very low number. It may be expected that further centralization of this rare disease will improve patient outcomes.

4.7. LIMITATIONS AND ASSETS

Compared to other salivary gland carcinoma epidemiological studies in the literature, we describe one of the largest populationbased cohorts from the Western world. In this study, information over a total of 22 years was available, which made it possible to evaluate time trends. However, the numbers still did not permit extensive subgroup analyses. And since it was retrospective, some data was missing.

5. CONCLUSION

Summarizing, incidence, mortality and relative survival did not improve. Progress may be possible by further centralizing the treatment of salivary gland carcinomas by exploring multimodality therapies and by increasing the public awareness to prevent high stage cancers in male patients.

REFERENCES

1. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer. *JAMA* 2000;283:2975–8.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
3. Karim-Kos HE, Kiemeney LA, Louwman MW, Coebergh JW, de Vries E. Progress against cancer in the Netherlands since the late 1980: an epidemiological evaluation. *Int J Cancer* 2012;130:2981–9.
4. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990. *Eur J Cancer* 2008;44:1345–89.
5. Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer* 2005;114:806–16.
6. Lee YC, Boffetta P, Sturgis EM, Wei Q, Zhang ZF, Muscat J, et al. Involuntary smoking and head and neck cancer risk: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomark Prev* 2008;17:1974–81.
7. Laar MWvan. Nationale drug monitor jaarbericht 2007. Utrecht: Trimbosinstituut, 2008.
8. Guzzo M, Locati LD, Prott FJ, Gatta G, McGurk M, Licitra L. Major and minor salivary gland tumors. *Crit Rev Oncol Hematol* 2010;74:134–48.
9. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348:1625–38.
10. Boukheris H, Ron E, Dores GM, Stovall M, Smith SA, Curtis RE. Risk of radiation-related salivary gland carcinomas among survivors of Hodgkin lymphoma: a population-based analysis. *Cancer* 2008;113:3153–9.
11. Tsang W, Kuo T, Chan J. Lymphoepithelial carcinoma. In: Barnes EL, Eveson JWP, Sidransky R, eds. *World Health Organization classification of tumours pathology and genetics of head and neck tumours*. Lyon: IARC Press, 2005: 251–2.
12. Saku T, Hayashi Y, Takahara O, Matsuura H, Tokunaga M, Tokuoka S, et al. Salivary gland tumors among atomic bomb survivors, 1950–1987. *Cancer* 1997;79:1465–75.
13. Schneider AB, Lubin J, Ron E, Abrahams C, Stovall M, Goel A, et al. Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose–response relationships. *Radiat Res* 1998;149:625–30.
14. van der Sanden GA, Coebergh JW, Schouten LJ, Visser O, van Leeuwen FE. Cancer incidence in the Netherlands in 1989 and 1990: first results of the nationwide Netherlands cancer registry. Coordinating Committee for Regional Cancer Registries. *Eur J Cancer* 1995;31A:1822–9.
15. Fritz A. *International classification of disease for oncology*. Geneva: World Health Organization, 2000.
16. Hermanek P, Sobin LH. *TNM classification of malignant tumours*. 4th ed. Springer Verlag; 1987.
17. Hermanek P. *TNM classification of malignant tumours*. 4th ed. Berlin: Springer Verlag, 1992 [2nd revision].
18. Sobin LH, Fleming ID. *TNM classification of malignant tumors*. 5th ed. *Cancer*, vol. 80, 5th ed. Union Internationale Contre le Cancer and the American Joint Committee on Cancer; 1997: 1803–4.
19. Sobin L, Wittekind C. *TNM classification of malignant tumours*. 6th ed. Wiley- Liss; 2002.
20. Sobin LH. *TNM classification of malignant tumours*. 7th ed. New York: Blackwell Publishing Ltd., 2010.

21. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19:335–51.
22. Dickman PW, Sloggett A, Hills M, Hakulien T. Regression models for relative survival. *Stat Med* 2004;23:51–64.
23. Bjorndal K, Krogdahl A, Therkildsen MH, Overgaard J, Johansen J, Kristensen CA, et al. Salivary gland carcinoma in Denmark 1990–2005: a national study of incidence, site and histology. Results of the Danish Head and Neck Cancer Group (DAHANCA). *Oral Oncol* 2011;47:677–82.
24. Boukheris H, Curtis RE, Land CE, Dores GM. Incidence of carcinoma of the major salivary glands according to the WHO classification, 1992 to 2006: a population-based study in the United States. *Cancer Epidemiol Biomark Prev* 2009;18:2899–906.
25. Guntinas-Lichius O, Wendt T, Buentzel J, Esser D, Lochner P, Mueller A, et al. Head and neck cancer in Germany: a site-specific analysis of survival of the Thuringian cancer registration database. *J Cancer Res Clin Oncol* 2010;136: 55–63.
26. Ostman J, Anneroth G, Gustafsson H, Tavelin B. Malignant salivary gland tumours in Sweden 1960–1989 – an epidemiological study. *Oral Oncol* 1997;33:169–76.
27. Pinkston JA, Cole P. Incidence rates of salivary gland tumors: results from a population-based study. *Otolaryngol Head Neck Surg* 1999;120:834–40.
28. Sun EC, Curtis R, Melbye M, Goedert JJ. Salivary gland cancer in the United States. *Cancer Epidemiol Biomark Prev* 1999;8:1095–100.
29. Vargas PA, Gerhard R, Araujo Filho VJ, de Castro IV. Salivary gland tumors in a Brazilian population: a retrospective study of 124 cases. *Rev Hosp Clin Fac Med Sao Paulo* 2002;57:271–6.
30. Terhaard CH, Lubsen H, Van der Tweel I, Hilgers FJ, Eijkenboom WM, Marres HA, et al. Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. *Head Neck* 2004;26:681–92. discussion 92–3.
31. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2807 patients. *Head Neck Surg* 1986;8:177–84.
32. Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. *J Pathol* 1985;146:51–8.
33. Etit D, Ekinci N, Tan A, Altinel D, Dag F. An analysis of salivary gland neoplasms: a 12-year, single-institution experience in Turkey. *Ear Nose Throat J* 2012;91:125–9.
34. Schmidt RL, Hall BJ, Wilson AR, Layfield LJ. A systematic review and metaanalysis of the diagnostic accuracy of fine-needle aspiration cytology for parotid gland lesions. *Am J Clin Pathol* 2011;136:45–59.
35. Eida S, Sumi M, Nakamura T. Multiparametric magnetic resonance imaging for the differentiation between benign and malignant salivary gland tumors. *J Magn Reson Imaging* 2010;31:673–9.
36. Therkildsen MH, Christensen M, Andersen LJ, Schiodt T, Hansen HS. Salivary gland carcinomas – prognostic factors. *Acta Oncol* 1998;37:701–13.
37. Kakarala K, Bhattacharyya N. Survival in oral cavity minor salivary gland carcinoma. *Otolaryngol Head Neck Surg* 2010;143:122–6.
38. Renehan AG, Gleave EN, Slevin NJ, McGurk M. Clinico-pathological and treatment-related factors influencing survival in parotid cancer. *Br J Cancer* 1999;80:1296–300.
39. Sultan I, Rodriguez-Galindo C, Al-Sharabati S, Guzzo M, Casanova M, Ferrari A. Salivary gland carcinomas in children and adolescents: a population-based study, with comparison to adult cases. *Head Neck* 2011;33:1476–81.

40. Tian Z, Li L, Wang L, Hu Y, Li J. Salivary gland neoplasms in oral and maxillofacial regions: a 23-year retrospective study of 6982 cases in an eastern Chinese population. *Int J Oral Maxillofac Surg* 2010;39:235–42.
41. Micheli A, Mariotto A, Giorgi Rossi A, Gatta G, Muti P. The prognostic role of gender in survival of adult cancer patients. EURO CARE Working Group. *Eur J Cancer* 1998;34:2271–8.
42. Ellington CL, Goodman M, Kono SA, Grist W, Wadsworth T, Chen AY, et al. Adenoid cystic carcinoma of the head and neck: incidence and survival trends based on 1973–2007 surveillance, epidemiology, and end results data. *Cancer* 2012;118:4444–51.
43. Pederson AW, Salama JK, Haraf DJ, Witt ME, Stenson KM, Portugal L, et al. Adjuvant chemoradiotherapy for locoregionally advanced and high-risk salivary gland malignancies. *Head Neck Oncol* 2011;3:31.
44. Schoenfeld JD, Sher DJ, Norris Jr CM, Haddad RI, Posner MR, Balboni TA, et al. Salivary gland tumors treated with adjuvant intensity-modulated radiotherapy with or without concurrent chemotherapy. *Int J Radiat Oncol Biol Phys* 2012;82:308–14.
45. Livingston EH, Cao J. Procedure volume as a predictor of surgical outcomes. *JAMA* 2010;304:95–7.
46. van Heek NT, Kuhlmann KF, Scholten RJ, de Castro SM, Busch OR, van Gulik TM, et al. Centralisation of pancreatic resection: a systematic review and evaluation in the Netherlands. *Ned Tijdschr Geneesk* 2006;150:791–8.
47. Wouters MW, Gooiker GA, van Sandick JW, Tollenaar RA. The volume-outcome relation in the surgical treatment of esophageal cancer: a systematic review and meta-analysis. *Cancer* 2012;118:1754–63.
48. Killeen SD, O’Sullivan MJ, Coffey JC, Kirwan WO, Redmond HP. Provider volume and outcomes for oncological procedures. *Br J Surg* 2005;92:389–402.
49. de Ridder M, Smeele LE, van den Brekel MW, van Harten MC, Wouters MW, Balm AJ. Letter to the editor: volume criteria for the treatment of head and neck cancer: are they evidence based. *Head Neck* 2014;36(5):760–2.
50. Centralization of head and neck cancer. *NWHHT J* 2010;1.

CHAPTER 8

Salivary gland pleomorphic adenoma in The Netherlands: an observational nationwide study on primary tumor incidence and recurrence rate.

8

M.H. Valstar*
M. de Ridder*
E.C. van den Broek
M.M. Stuiver
B.A.C. van Dijk
M..L.F. van Velthuysen
A.J.M. Balm
L.E. Smeele

* Both authors contributed equally

Oral oncology. 2017; 66: 93-99

ABSTRACT

INTRODUCTION

Whereas salivary gland pleomorphic adenoma (SGPA) is the most common type of salivary gland tumor, little is known about its epidemiology, as national cancer registries do not register this disease.

OBJECTIVES

Our aim was to look at SGPA incidence trends, and to establish recurrence rates and associated factors, as well as rates of secondary malignant transformation in the Netherlands.

MATERIALS AND METHODS

After retrieving SGPA data from the Dutch pathology registry PALGA for the years 1992, 1997, 2002, 2007, and 2012, we calculated figures for incidence, epidemiology, recurrence, and secondary malignant transformation, and performed multivariate analysis to discover the risk factors for recurrence.

RESULTS

We counted 3 506 cases of SGPA, and calculated an overall European standardized rate of 4.2-4.9 per 100 000 person-years. Our figures showed a female preponderance (1:1.43) with an annual 1% rise in female incidence (95% confidence interval [CI]: 0.2-1.8) and a bimodal age distribution in women ($p < 0.0001$). The overall 20-year recurrence rate was 6.7%, and median time to first recurrence was 7 years. Positive and uncertain resection margins and younger age at diagnosis were risk factors for recurrence, with odds ratios (ORs) of 4.62 (95%CI 2.84-7.51), 4.08 (95%CI 2.24-7.43), and 0.42 (95%CI 0.29- 0.63), respectively. Tumor locations in minor salivary glands had lower odds of recurrence than tumor sites in the parotids (OR 0.24; 95% CI: 0.07-0.77; $p < 0.016$). Malignant transformation occurred in 0.15% of SGPAs (3.2% of recurrences).

CONCLUSION

This first nationwide study clearly showed sex differences in SGPA epidemiology, possibly suggesting some underlying hormonal mechanism. Long-term recurrence risks were low, and secondary malignant transformation risks were very low.

INTRODUCTION

Most salivary gland tumors are benign, with only 14% malignant lesions^{1,2}. The most common type is salivary gland pleomorphic adenoma (SGPA), which accounts for no less than 70% of benign epithelial tumors. These well-circumscribed tumors with ductal and myoepithelial elements affect both major and minor salivary glands, though most occur in the parotids. They seem to develop more often in women and diagnosis is mostly at middle age (40-59)^{2,3}. The standard of treatment is nerve-conserving, superficial parotidectomy (or extracapsular dissection in well-trained hands), which shows a 5% recurrence rate, whereas enucleation shows recurrence rates of up to 45%^{4,5}. Favorable results in retrospective series suggest that postoperative radiotherapy may be helpful after incomplete resection or tumor spill, or in multiple or multinodular recurrences^{4,6,7}.

In 1.8-6.2% of cases, SGPA transforms into carcinoma ex pleomorphic adenoma^{8,9}. These cases make up 7.7-11.6% of all malignant salivary gland tumors^{8,10}. In recurrent SGPA, de novo malignant transformation is reported in 0-23%⁴. As common a tumor as SGPA may be, its epidemiology has long remained uncertain for lack of national registration practices^{9,11,12}. Some research focused on benign salivary gland tumors in general or subgroups of SGPA^{2,13-16}. Others looked at regional incidence of SGPA or national incidence of parotid SGPA^{1,9}, but national incidence of all-location SGPA and trends over time were not investigated. Of course, without any national data, no rates can be calculated for all-location SGPA incidence, recurrence, and secondary malignant transformation while ruling out referral bias. We, therefore, decided to turn to PALGA, the Dutch nationwide registry of pathology reports. This registry is not restricted to any specific type of finding or disease, thus making a suitable database for studying SGPA epidemiology features, including trends over time.

OBJECTIVES

Our primary aim was to accurately establish SGPA incidence rates and trends over time, as well as any age and sex differences. We further aimed to establish recurrence rates and risks of secondary malignant transformation and to explore risk factors. This knowledge will help physicians to measure treatment results and express population-based prognoses.

MATERIALS AND METHODS

DATABASE

Set up in 1991, the PALGA registry automatically receives anonymized pathology reports from all Dutch laboratories, which include age, sex, date, and diagnosis. Excerpts are available for research purposes.

PATIENT SELECTION

We searched the PALGA registry for codes of pleomorphic adenoma or mixed tumor and manually checked all excerpts thus created for SGPA. Then, we included all patients who had a first histology diagnosis in 1992, 1997, 2002, 2007, or 2012. We excluded 442 patients (11%) for reasons mentioned in Additional Table A. Likewise, we analyzed histology and cytology data about recurrences up to September 1, 2013, defining recurrence as a secondary tumor occurring in the same tumor site at a minimum of six months post surgery.

INCIDENCE

We calculated SGPA incidence in the Netherlands from mid-year population size figures provided by Statistics Netherlands (CBS)¹⁷, and worked out the male to female incidence ratio by looking at average male and female incidence data. To cancel out changes in age structure of the Dutch population over time, we computed European standardized incidence rates (ESRs), basing our calculations on the “2013 reference population”^{18,19}.

PATIENT, TUMOR, AND TREATMENT CHARACTERISTICS

To further analyze our primary tumor data, we scored for sex, age at diagnosis, salivary gland of origin, side of the body, surgical procedure, and margin status. In case of ambiguity, we checked with the author pathologists to decide on interpretation. Recurrence rates and malignant transformation: Focusing on patients with at least five years of follow-up, we calculated first-recurrence rates at 5, 10, and 15 years, as well as median time to first and subsequent recurrences. We excluded primary carcinomas ex pleomorphic adenoma from our database, and counted secondary carcinomas ex pleomorphic adenoma (SGPAs that recurred as malignant tumors) both as malignant transformations and as recurrences. Carcinomas in situ ex pleomorphic adenoma were not considered malignant transformations.

RISK FACTORS FOR RECURRENCE

In determining risk factors, we looked at sex, age, tumor site, and margin status. As the type of surgery was not always specified, and reporting practices varied, we decided to exclude this factor from our observations.

STATISTICAL ANALYSIS

We analyzed our data with SPSS (version 21.0; SPSS Inc., Chicago, III) and R^{20,21}, taking a p-value of <0.05 to be statistically significant for all purposes. Using linear regression and the natural log rhythm of ESR, we computed annual percent changes (APCs) by sex and overall, and we applied finite mixture models to investigate distribution patterns for age at diagnosis²². With the Kaplan-Meier method, we calculated times to recurrence, and we identified potential predictors of recurrence using multivariate logistic regression analysis. In addition to our analysis of complete cases, we performed missing data analysis and multiple-imputation analysis, imputing missing data by letting the R MICE package generate five imputed datasets and comparing the pooled results to our analysis of complete cases.

RESULTS

INCIDENCE

After data cleaning, 3 504 unique patients remained of a total of 3 948 diagnosed with pleomorphic adenoma (Table 1). Two developed a second primary SGPA at a different anatomical site. Overall crude incidence varied from 3.9 to 4.7 per 100 000 person-years (Tables 2a and 2b). ESR ranged between 4.2 and 4.9 per 100 000 person-years. After stratifying for sex, we found a statistically significant annual rise of ESR in women (APC= 1.0% per year; 95% CI: 0.2-1.8), but not in men (APC= 0% per year; 95% CI:-1.0 to 0.9) (Figure 1).

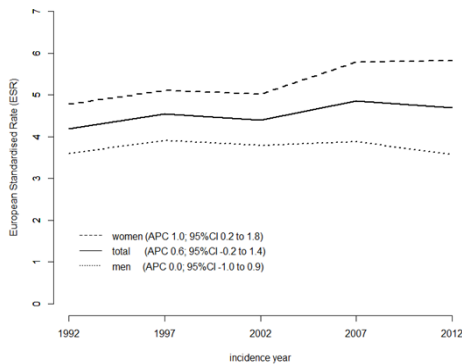


Figure 1. European Standardized Rate (ESR) in the five investigated years, with interpolation in the periods in between. The annual percent change (APC), calculated from the five years, shows an increase in female SGPA incidence.

Table 1. Population characteristics primary SGPA and 1st recurrence

		Primary [n (%)]			1st Recurrence [n(%)]
		Overall (n=3 506)	Male (n=1 421)	Female (n=2 085)	Overall (n=125)
Patients					
Age	Mean (range)	49 (8-94)	48 (9-92)	50 (8-94)	39 (8-89)
Age group	0-19	112 (3)	54 (4)	58 (3)	12 (10)
	20-39	959 (27)	393 (28)	566 (27)	60 (48)
	40-59	1417 (40)	600 (42)	817 (39)	33 (26)
	60-79	919 (26)	343 (24)	576 (28)	18 (14)
	≥ 80	99 (3)	31 (2)	68 (3)	2 (2)
Location	Parotid gland	2733 (78)	1112 (78)	1621 (78)	110 (88)
	Superficial lobe	2603 (74)	1066 (75)	1537 (74)	102 (82)
	Deep lobe	130 (4)	46 (3)	84 (4)	8 (6)
	Submandibular gland	310 (9)	93 (7)	217 (10)	9 (7)
	Sublingual gland	6 (<1)	4 (<1)	2 (<1)	0
	Minor salivary glands	377 (11)	187 (13)	190 (9)	6 (5)
	Unknown	38 (1)	13 (<1)	25 (1)	6 (5)
	Missing	42 (1)	12 (<1)	30 (1)	0
Side	Left	1 423 (41)	571 (40)	852 (41)	64 (51)
	Right	1 399 (40)	560 (39)	839 (40)	53 (42)
	Unknown	684 (19)	290 (20)	394 (19)	8 (6)
Treatment					
Procedure	Local excision	297 (8)			
	Partial parotidectomy	1 214 (35)			
	Total parotidectomy / Submandib. gl.resection	227 (6)			
	Subtotal parotidectomy	67 (2)			
	Excision deep lobe parotid	103 (3)			
	Biopsy	114 (3)			
	Unknown type of excision	1 449 (41)			
	Missing	35 (1)			
	Negative	2 028 (58)			
	Resection margins	Positive	491 (14)		
Uncertain		261 (7)			
Unknown		726 (21)			

PATIENT, TUMOR, AND TREATMENT CHARACTERISTICS

Primary SGPAs occurred more often in women (59.5%) than in men (40.5%) (Table 1), showing a female to male ratio of 1.43:1. The mean age at primary diagnosis was 48.0 in men, and 49.6 in women. Seventy-eight patients (2%) were under 18 when diagnosed. Around 40% of cases occurred in the age group of 40-59. In women, a bimodal age distribution was found, with peaks around the ages of 38 and 64 ($p < 0.0001$). Age in men showed a normal distribution (Figure 2). The most common tumor site by far was the parotid gland (78%), followed by the minor salivary glands (11%) and the submandibular glands (9%). Only six SGPAs occurred in sublingual glands (<1%). Submandibular SGPA was more common in women than in men, whereas for minor-gland SGPA, this was the other way around (Table 1). In patients under 18, the minor and submandibular glands were affected more often than in adults (Additional Table B). Surgery had comprised partial parotidectomy in 35% of cases, local excision in 8%, and complete gland removal in 6%. In 41%, the excerpts did not specify the type of excision performed, and in 1%, there was no mention of type of procedure at all. Margin status was negative in 58%, positive in 14%, uncertain in 7%, and unknown in 21%.

RECURRENCE RATES, CHARACTERISTICS, AND MALIGNANT TRANSFORMATION

The disease recurred in 125 (4.6%) of the 2 719 patients who had at least five years of follow-up. Twenty (16%) also had a second recurrence, and two (10%) had a third. In 4 patients (0.15%), the disease recurred as carcinoma ex pleomorphic adenoma, which means that 3.2% of all recurrences (4/125) showed malignant transformation. First-recurrence rates were 2.3% at five years, 4.0% at 10 years, 5.6% at 15 years, and 6.7% at 20 years of follow-up, with a 7 years' median time to first recurrence (range 0.6-20.7, 95% CI 5.9-8.1) (Figure 3). Second-recurrence rates were 12% at five years and 14% at ten years of follow-up. The median time to second recurrence was 2 years (95% CI: 0.9-3.1). Sex distribution patterns were similar in both recurrences and primary tumors (58% females versus 42% males). The mean age at primary diagnosis was 40 in patients who later developed recurrent disease and 49.3 in patients who did not develop recurrent disease. This 10-year age difference appeared in both sexes.

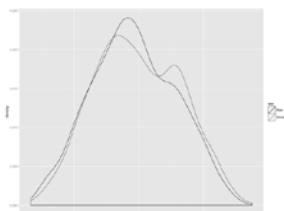


Figure 2: Age distribution, showing a bimodal curve in women.

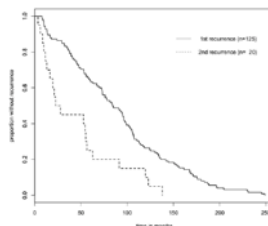


Figure 3: Recurrence-free survival in patients who develop a recurrence, reflecting a decrease in median time to recurrence: 7 years to 1st recurrence and 2 years between 1st and 2nd.

Table 2a. Number of SGPAs in the cohort in relation to the Dutch population

	SGPAs (n)			Dutch population (n)		
	M	F	Total	M	F	Total
1992	253	343	596	7 480 422	7 648 728	15 129 150
1997	280	384	664	7 696 803	7 870 304	15 567 107
2002	288	401	689	7 971 967	8 133 318	16 105 285
2007	304	466	770	8 088 514	8 269 478	16 357 992
2012	296	491	787	8 282 871	8 447 477	16 730 348
Total	1 421	2 085	3 506			

Abbreviations: SGPA salivary gland pleomorphic adenoma; M male; F female

RISK FACTORS FOR RECURRENCE

Margin status, age at diagnosis, and tumor location all turned out to be associated with risk of recurrence (Table 3). As to margin status, the odds ratios in complete cases (n=1 663) were 4.62 for positive resection margins (95% CI 2.84-7.51), and 4.08 for uncertain margins (95% CI 2.24-7.43), when compared to clear margins. For young age at diagnosis, the odds ratio was 0.42% (per IQR [25y]; 95% CI 0.29-0.63). Primary tumor location showed an odds ratio of 0.24 for minor salivary gland disease when compared to parotid disease (95% CI 0.07-0.77). Risk factors for malignant transformation of recurrent SGPA could not be determined, due to the low event rate (0.15%).

Table 2b. Incidence of SGPAs in the Dutch population

	Crude incidence (per 100 000 per year)			ESR (per 100 000 per year)		
	M	F	Total	M	F	Total
1992	3.38	4.48	3.94	3.60	4.78	4.19
1997	3.64	4.88	4.27	3.91	5.11	4.54
2002	3.61	4.93	4.28	3.78	5.02	4.39
2007	3.76	5.64	4.71	3.88	5.79	4.85
2012	3.57	5.81	4.70	3.57	5.81	4.69

Abbreviations: ESR European Standardized Rate; SGPA Salivary Gland Pleomorphic Adenoma; M Male; F Female

MISSING DATA AND IMPUTATION

Type of surgery performed and margin status were not mentioned in 42% and 21% of excerpts, respectively. There were 1 663 complete cases. Missing data on resection margins showed a significant association with recurrence (OR 1.5; 95% CI 1.00-2.23; $p = 0.04$). Taking this association into account, our analysis of imputed data with multiple-imputation models revealed the same risk factors as our analysis of complete data (Table 3).

Table 3. Multivariate analysis of factors possibly associated with recurrence

Complete-case analysis				
	β -Coefficient	SE (of β)	OR (95% CI)	p-value
Resection margins				
Negative	Reference			
Positive	1.53	0.25	4.62 (2.84 to 7.51)	<0.001
Uncertain	1.41	0.31	4.08 (2.24 to 7.43)	<0.001
Female	-0.15	0.23	1.16 (0.75 to 1.81)	0.501
Age *	-0.86	0.18	0.42 (0.29 to 0.63)	<0.001
Location				
Parotid gland	Reference			
Submandibular gland	-1.02	0.60	0.36 (0.11 to 1.16)	0.087
Minor gland	-1.44	0.60	0.24 (0.07 to 0.77)	0.016
Deep lobe of parotid gland	0.13	0.45	1.13 (0.47 to 2.73)	0.778
Imputed analysis				
	β -Estimate	SE	OR (95% CI)	p-value
Resection margins				
Negative	Reference			
Positive	1.47	0.24	4.35 (2.75 to 6.96)	<0.001
Uncertain	1.38	0.29	3.98 (2.23 to 7.10)	<0.001
Female	-0.07	0.19	0.93 (0.63 to 1.35)	0.711
Age	-0.04	0.01	0.96 (0.95 to 0.97)	<0.001
Location				
Parotid gland	Reference			
Submandibular gland	-0.34	0.38	0.71 (0.34 to 1.51)	0.374
Minor gland	-0.86	0.38	0.42 (0.20 to 0.89)	0.024
Deep lobe of parotid gland	0.24	0.39	1.28 (0.59 to 2.75)	0.535

Abbreviations: OR, odds ratio; SE, standard error; CI, confidence interval; a, b and OR for 1 interquartile range (25 years) of change.

DISCUSSION

Our investigations of a large cohort of 3 506 patients with extended periods of follow-up have shed new light on SGPA incidence, recurrence, and secondary malignant transformation. Novel findings were a rising female incidence, a bimodal age distribution in women, and an overall 20-year recurrence risk of 6.7%. Positive or uncertain margins and younger age at diagnosis showed an increased overall risk of recurrence, whereas primary tumor locations in minor salivary glands showed lower recurrence.

INCIDENCE

Direct comparisons with previous research on SGPA incidence are hard to make. In the past 50 years, crude incidence figures between 1.5 and 7.2 per 100 000 person-years^{1,2,9,13-16} (Additional Table C) have been reported. However, most authors had not categorized tumors by anatomical site, and only one paper discussed national figures, which related solely to parotid SGPAs and did not standardize for age⁹. Interestingly, SGPA ESR in 2012 was 4.7 per 100 000 person-years, whereas salivary-gland cancer ESR in 2010 was 0.74²³. These figures indicate that any salivary gland lump is 6.5 times more likely to be SGPA than carcinoma. The 1% annual increase of SGPA ESR in women was a remarkable finding, as was the female preponderance of SGPA. Possibly, women are more aware of their appearance than men and more willing to seek medical attention for any lumps they find²⁴⁻²⁶. On the other hand, there may also be an influence of gonadal hormones, as in breast cancer, since SGPA is known to express estrogen and progesterone receptors^{27,28}. Salivary gland neoplasms have been associated with breast cancer before²⁹. One risk factor for breast cancer is advanced maternal age at first childbirth³⁰⁻³². In the Netherlands, this age rose from 28.0 to 29.4 in the period we investigated¹⁷. A link with the increase we found in female SGPA incidence is not inconceivable.

PATIENT, TUMOR, AND TREATMENT CHARACTERISTICS

The bimodal age distribution in female SGPA incidence remains unexplained. Further research is needed to explore any hormone influences. According to literature, salivary gland tumors affect the parotid, submandibular, and minor glands in a ratio of 10:1:1^{1,33}. The ratio we found was 12:1:2, possibly because of an absence of selection bias in our data. In our cohort, submandibular SGPAs were more common in women than in men, whereas minor salivary gland SGPAs were more common in men than in women. Since we found no previous mention of any sex differences in SGPA location, further research is needed to confirm and explain this finding. As the PALGA database focuses on pathology, information on the type of surgery performed was often missing (42%). Recently, new insights about the benefits of standardized structured pathology reporting³⁴ have led to improved reporting practices for high-incidence cancers in Dutch laboratories. Hopefully, this systematic approach will be adopted for other diseases, too, including for SGPA. Resection margins had not been recorded in 21% of cases. In a posthoc analysis, these cases turned out to have a 1.5-fold higher likelihood of recurrence, even after adjustment for gender, age, topography, and type of treatment. There may be several reasons why margin data are often missing. First, SGPAs are usually removed without complete margins of normal salivary gland tissue, for instance when they are close to the facial nerve.

Second, covering (pseudo) capsules may be very thin, and multinodular growth patterns make it hard to determine whether any nodules have been left behind. Third, SGPAs are benign, so there is little priority in describing their margins, unless the pathology order holds a specific request to do so, along with sufficient clinical information.

RECURRENCE RATES AND MALIGNANT TRANSFORMATION

Whereas the 4.6% first-recurrence rate we found in patients with at least five years of follow-up (2,719) replicates previous findings⁴, our 12% second recurrence rate at five years is lower than the 14% stated in most papers (Additional Table D). However, some caution is needed here, as populations and follow-up periods vary between cohorts, and none of the figures have taken any clinical or mortality data into account. For this present research project, we excluded malignant transformations of primary SGPA. In earlier research, however, we found 34 cases of salivary gland carcinoma ex pleomorphic adenoma in the same period of investigation²³. Four occurred in recurrent SGPA and were added to our database, leaving 30 cases to account for a 1.1% risk of de novo malignant transformation of primary SGPA (30 in 2,749). This is a similar percentage as the 1.8% that was reported in parotid pleomorphic adenoma in Denmark⁹.

This is a similar percentage as the 1.8% that was reported in parotid pleomorphic adenoma in Denmark⁹. Earlier publications reported a mean 6.2% risk, but their figures relate to single-center data and may reflect a referral bias^{8,35}. The 0.15% secondary malignant transformation rate we found (carcinoma ex pleomorphic adenoma in recurrent SGPA in our SGPA cohort; 3.2% of all recurrences) is in the low range of earlier findings⁴. These numbers are also lower than the Danish 0.35% and 12.6% respectively. To some extent, the differences may be explained by different inclusion criteria, but more importantly, we ruled out referral bias by compiling a nationwide cohort, rather than using single-center data. Our results confirm that on a population level, complete surgical removal of SGPA can be difficult, leading to a 4.6% first-recurrence rate and a 16% second-recurrence rate (median times to recurrence 7 and 2 years, respectively). Recurrences are often multinodular (around 50), with a mean number of 25 nodules found in the primary resection bed³⁶. These figures provide a strong argument for MRI follow-up after all first recurrences, to avoid a need for more extensive surgery at some later point in time.

RISK FACTORS FOR RECURRENCE

We found margin status to be the primary risk factor for recurrence. However, our margin data were based on microscopy, whereas in practice, margin status is often determined macroscopically by the surgeon. In many resections, sufficient margins cannot be taken because of adjacent facial nerve branches, and the pathologist will only have a very thin capsule to examine.

This problem may raise doubt as to the reliability of microscopy data for multivariate analysis. Still, if margins are positive or uncertain, it is highly plausible to expect higher recurrence, since positive microscopic margins are accepted as a primary cause for tumors to recur, as are rupture and spillage^{4,37}.

A second recurrence risk factor we found was age. Mean age at primary SGPA diagnosis was 49 in patients who did not develop a recurrence later on, and 40 in patients who did. Although there may be an age bias here (higher age suggesting shorter survival, with death as a competing event), our findings are in line with literature^{33,38–40}. Some researchers have explained the age difference by suggesting that surgeons tend to take a less radical approach and make smaller incisions in younger patients, for esthetic reasons³⁶. Our multivariate analysis, however, did not show any correlation between age and margin status. Wittekindt et al. observed a further age difference.

In their study population, mean age at primary diagnosis turned out to be lower in single-recurrence patients than in multiple-recurrence patients (30.2 versus 40.3)³⁶. Possibly, tumor biology is somehow different in younger patients, because of hormonal aspects, genetic background, or some other factor as yet unknown.

A third risk factor for recurrence in our cohort was tumor location, which to our knowledge is a novel finding. SGPA in minor salivary glands was found to recur less frequently than SGPA in larger glands. Lumps in the minor glands are possibly more likely to be noted at an earlier stage. Moreover, complete excision of these lumps is easier to achieve, although margin status may be hard to assess for lack of capsule formation⁴¹. Female gender was not found to be a recurrence risk factor, which is in line with Maran et al⁴² in smaller series, but in contrast to other publications^{36,43,44}.

LIMITATIONS

There are some limitations to our study. First, there is a slight information bias. Given the suboptimal diagnostic accuracy of cytology (84%–99%)⁴⁵, we included histology-confirmed SGPA, only. With only 98 cytology diagnoses, however, and no data on nonpathology-proven recurrences, the 4.6% recurrence rate we found may be something of an underestimate, although hardly a gross one. A second limitation is the lack of radiotherapy data. Literature suggests there is a (small) role for radiotherapy in the adjuvant treatment of recurrent SGPA^{6,46,47}. Third, since we retrieved all our information from nonstandardized pathology reports, there may be an interpretation bias concerning the description of margins by pathologists and the information supplied by surgeons.

CONCLUSION

Nationwide pathology data regarding SGPA in the Netherlands in the period 1992-2012 reflect some remarkable incidence trends: female incidence was on the rise, there was a bimodal age distribution in women, and women were affected more often than men. These findings may suggest some underlying hormonal mechanism. Overall figures for this period showed an ESR ranging between 4.2 and 4.9 per 100,000 person-years, a 4.6% first-recurrence rate after at least five years of follow-up, and a 6.7% recurrence rate at 20 years of follow-up. Malignant transformation had occurred in 1.1% of primary, and 0.15% of secondary SGPAs at 5 years of follow-up (3.2% of all recurrences). Risk factors for recurrence were positive or uncertain surgical margins, younger age at primary diagnosis, and primary tumor location, with lower odds for minor-gland primaries to recur, when compared to parotid SGPAs. Where margin data were missing, the odds of recurrence were higher, which emphasizes the need for improved, possibly standardized reporting in a joint effort by both surgeons and pathologists alike.

REFERENCES

1. Bradley PJ, McGurk M. Incidence of salivary gland neoplasms in a defined UK population. *Br J Oral Maxillofac Surg* 2013;51:399–403. doi:10.1016/j.bjoms.2012.10.002.
2. Przewoźny T, Stankiewicz C. Neoplasms of the parotid gland in northern Poland, 1991-2000: an epidemiologic study. *Eur Arch Otorhinolaryngol* 2004;261:369–75. doi:10.1007/s00405-003-0698-4.
3. Spiro R. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. *Head NeckSurg* 1986;8:177–84.
4. Witt RL, Eisele DW, Morton RP, Nicolai P, Poorten V Vander, Zbären P. Etiology and management of recurrent parotid pleomorphic adenoma. *Laryngoscope* 2014:1–6. doi:10.1002/lary.24964.
5. Albergotti WG1, Nguyen SA, Zenk J GM. Extracapsular dissection for benign parotid tumors: a meta-analysis. *Laryngoscope* 2012;122:1954–60.
6. Buchman C, Stringer SP, Mendenhall WM, Parsons JT, Jordan JR CN. Pleomorphic adenoma: effect of tumor spill and inadequate resection on tumor recurrence. *Laryngoscope* 1994;104:1231–4.
7. Natvig K SR. Relationship of intraoperative rupture of pleomorphic adenomas to recurrence: an 11-25 year follow-up study. *Head Neck* 1994;16:213–7.
8. Gnepp D. Malignant mixed tumors of the salivary glands: a review. *Pathol Annu* 1993;28:279–328.
9. Andreasen S, Therkildsen MH, Bjørndal K, Homøe P. Pleomorphic adenoma of the parotid gland 1985-2010: A Danish nationwide study of incidence, recurrence rate, and malignant transformation. *Head Neck* 2016;38:E1364–9. doi:10.1002/hed.24228.
10. de Ridder M, Balm AJM, Smele LE, Wouters MWJM, van Dijk B a. C. An epidemiological evaluation of salivary gland cancer in the Netherlands (1989–2010). *Cancer Epidemiol* 2015;39:14–20. doi:10.1016/j.canep.2014.10.007.
11. M.H. Valstar, M. de Ridder, M.L.F. van Velthuysen, L.I.H. Overbeek, B.A.C. van Dijk, A.J.M. Balm LES. Salivary gland pleomorphic adenoma: a 20-year incidence study. In: Ramsay-Baggs P, editor. XXII Congr. Eur. Assoc. Cranio-Maxillo-Facial Surgery; B. Abstr., Prague: ProvidedServices s.r.o; 2014, p. 310.
12. PJ. Bradley OG-L. Salivary gland disorders and diseases: diagnosis and management. 1st ed. Stuttgart and New York: Thieme; 2011.
13. Gunn P. Parotid Tumors Northern Regional Health Authority of the United Kingdom 1978-1982. *Br J Surg* 1988;75:1144–6.
14. Pinkston J a, Cole P. Incidence rates of salivary gland tumors: results from a population-based study. *Otolaryngol Head Neck Surg* 1999;120:834–40. doi:S0194599899002442 [pii].
15. Moeller K, Esser D, Boeger D, Buentzel J, Hoffmann K, Jecker P, et al. Parotidectomy and submandibulectomy for benign diseases in Thuringia, Germany: a population-based study on epidemiology and outcome. *Eur Arch Otorhinolaryngol* 2013;270:1149–55. doi:10.1007/s00405-012-2225-y.
16. Mortensen KS1, Hjortlund J, Bjørndal K, Krogdal A GC. Salivary gland tumors in the County of Funen, 1984-2003. *Ugeskr Laeger* 2008;170:545–8.
17. Statistics Netherlands, Central Bureau of Statistics (CBS). n.d. <http://statline.cbs.nl/statweb> (accessed December 15, 2015).
18. Pace M, Lanzieri G GM et al. Revision of the European Standardized Population. Report of Eurostat’s task force. Eurostat’s Methodologies and working papers. 2013.

19. Waterhouse JAH, Muir CS CP et al. Cancer incidence in five continents. n.d.;3:456.
20. R Core Team. R Foundation Statistical Computing, Vienna A. R: A language and environment for statistical computing. 2015. <http://www.r-project.org/>.
21. Van Buuren S G-OK. Mice: Multivariate Imputation by Chained Equations. R J Stat Software, 45(3), 1-67 2011.
22. Benaglia, T., Chauveau, D., Hunter, D. R., and Young D. Mixtools: An R package for analyzing finite mixture models. J Stat Softw 2009;32:1–29.
23. de Ridder M, Balm AJM, Smeele LE, Wouters MWJM, van Dijk BAC. An epidemiological evaluation of salivary gland cancer in the Netherlands (1989-2010). Cancer Epidemiol 2015;39:14–20. doi:10.1016/j.canep.2014.10.007.
24. Micheli A, Mariotto A, Giorgi Rossi A, Gatta G, Muti P. The prognostic role of gender in survival of adult cancer patients. Eur J Cancer 1998;34:2271–8. doi:10.1016/S0959-8049(98)00324-4.
25. Gove WR, Hughes M. Possible causes of the apparent sex differences in physical health: an empirical investigation. Am Sociol Rev 1979;44:126–46.
26. Cleary PD, Mechanic D, Greenley JR. Sex differences in medical care utilization: an empirical investigation. J Health Soc Behav 1982;23:106–19.
27. Pietras RJ, Márquez-Garbán DC. Membrane-associated estrogen receptor signaling pathways in human cancers. Clin Cancer Res 2007;13:4672–6. doi:10.1158/1078-0432.CCR-07-1373.
28. Glas AS, Hollema H, Nap RE, Plukker JT. Expression of estrogen receptor, progesterone receptor, and insulin-like growth factor receptor-1 and of MIB-1 in patients with recurrent pleomorphic adenoma of the parotid gland. Cancer 2002;94:2211–6. doi:10.1002/cncr.10445.
29. In der Maur CD, Klokman WJ, van Leeuwen FE, Tan IB, Rutgers EJT, Balm AJM. Increased risk of breast cancer development after diagnosis of salivary gland tumour. Eur J Cancer 2005;41:1311–5. doi:10.1016/j.ejca.2005.02.023.
30. Kelsey JL BL. Epidemiology and prevention of breast cancer. Annu Rev Public Heal 1996 1996;17:47–67.
31. Reeves GK, Pirie K, Green J, Bull D BVMWSC. Reproductive factors and specific histological types of breast cancer: prospective study and meta-analysis. Br J Cancer 2009;100:538–44.
32. Ewertz M, Duffy SW, Adami HO, Kvåle G, Lund E, Meirik O, Møller A, Soini I TH. Age at first birth, parity and risk of breast cancer: a meta-analysis of 8 studies from the Nordic countries. Int J Cancer 1990;46:597–603.
33. Phillips PP OK. Recurrent pleomorphic adenoma of the parotid gland: report of 126 cases and a review of the literature. Ann Otol Rhinol Laryngol 1995;104:100–4.
34. Ellis DW, Srigley J. Does standardised structured reporting contribute to quality in diagnostic pathology? The importance of evidence-based datasets. Virchows Arch 2015;1–9. doi:10.1007/s00428-015-1834-4.
35. Antony J, Gopalan V, Smith R a., Lam AKY. Carcinoma ex Pleomorphic Adenoma: A Comprehensive Review of Clinical, Pathological and Molecular Data. Head Neck Pathol 2012;6:1–9. doi:10.1007/s12105-011-0281-z.
36. Wittekindt C1, Streubel K, Arnold G, Stennert E G-LO. Recurrent pleomorphic adenoma of the parotid gland: analysis of 108 consecutive patients. Head Neck 2007 Sep;29(9)822–8 2007;29:822–8.
37. Zbären P, Vander Poorten V, Witt RL, Woolgar J a., Shaha AR, Triantafyllou A, et al. Pleomorphic adenoma of the parotid: Formal parotidectomy or limited surgery? Am J Surg 2013;205:109–18. doi:10.1016/j.amjsurg.2012.05.026.

38. Zbären P1, Tschumi I, Nuyens M SE. Recurrent pleomorphic adenoma of the parotid gland. *Am J Surg* 2005;189:203–7.
39. McGregor a D, Burgoyne M, Tan KC. Recurrent pleomorphic salivary adenoma--the relevance of age at first presentation. *Br J Plast Surg* 1988;41:177–81. doi:10.1016/0007-1226(88)90048- 3.
40. Renehan, Gleave EN MM. An analysis of the treatment of 114 patients with recurrent pleomorphic adenomas of the parotid gland.e. *Am J Surg* 1996;172:710–4.
41. Turk AT WB. Ovid: Pitfalls in the Biopsy Diagnosis of Intraoral Minor Salivary Gland Neoplasms: Diagnostic Considerations and Recommended Approach. *Adv Anat Pathol* 2014 Jan;21(1)1-11 2014;21:1–11.
42. Maran AG, Mackenzie IJ SR. Recurrent pleomorphic adenomas of the parotid gland. *Arch Otolaryngol* 1984;110:167–71.
43. Myssiorek D, Ruah CB HR. Recurrent pleomorphic adenomas of the parotid gland. *Head Neck* 1990;12:332–6.
44. Maxwell EL, Hall FT FJ. Recurrent pleomorphic adenoma of the parotid gland. *J Otolaryngol* 2004;33:181–4.
45. Postema RJ, van Velthuysen ML, van den Brekel MW, Balm AJ PJ. Accuracy of fine-needle aspiration cytology of salivary gland lesions in the netherlands cancer institute. *Head Neck* 2004;26:418–24.
46. Patel S, Mourad WF, Wang C, Dhanireddy B, Concert C, Ryniak M, Khorsandi AS, Shourbaji RA, Li Z, Culliney B, Patel R, Bakst RL, Tran T, Shasha D, Schantz S, Persky MS, Hu KS HL. Postoperative radiation therapy for parotid pleomorphic adenoma with close or positive margins: treatment outcomes and toxicities. *Anticancer Res* 2014 Aug;34(8)4247-51 2014;34:4247–51.
47. Wallace AS, Morris CG, Kirwan JM, Werning JW, Mendenhall WM. Radiotherapy for pleomorphic adenoma. *Am J Otolaryngol* 2013;34:36–40. doi:10.1016/j.amjoto.2012.08.002.

SUPPLEMENTAL MATERIAL

Additional Table A. Excluded patients	
Exclusion criterion	n
Cytological diagnosis	98
Malignancy	62
Revision of earlier diagnosis	21
Non salivary gland	178
Recurrence/residual disease	63
Expertise for foreign patient	8
Missing data on diagnosis	6
Primary not in inclusion period	6
Total	442

Additional Table A. Excluded patients					
	Age groups [n (%)]				
Localisation	0-19	20-39	40-59	60-79	≥ 80
Parotid gland	67 (60)	759 (80)	1,139 (80)	694 (76)	74 (75)
Superficial lobe	63 (56)	735 (77)	1,075 (76)	662 (72)	68 (69)
Deep lobe	4 (4)	24 (3)	64 (5)	32 (3)	6 (6)
Submandibular gland	21 (19)	78 (8)	113 (8)	92 (10)	6 (6)
Sublingual gland	1 (1)	1 (<1)	3 (0)	1 (0)	0
Minor glands	19 (17)	100(10)	130 (9)	190 (12)	19 (19)
Unknown salivary gland	1 (1)	12 (1)	13 (1)	12 (1)	0
Unknown localization	3 (3)	9 (1)	19 (1)	11 (1)	0
Total	112	959	1,417	919	99

Author, year (country)	Period	Tumor	n	Parotid	SM	Minor	SL	Incidence	SR
Gunn (U.K.) ¹	1978-1982	SGPA	232	232	0	0	0	1.5	NR
Pinkston (U.S.A.) ²	1968-1989	Benign SG	209	181	28	NR	0	3.05	NR
Przewozny (Poland) ³	1991-2000	Benign SG	354	354	0	0	0	1.35	1.6
Mortensen (Denmark) ⁴	1984-2003	Benign SG	621	571	73	NR	0	6.6	NR
Bradley (U.K.) ⁵	1988-2007	SGPA	651	538	67	46	0	6.3-7.3	NR
Moeller (Germany) ⁶	2005	Surg. SGPA	81	71	10	0	0	3.05	NR
Andreasen (Denmark) ⁷	1985-2010	SGPA	5497	5497	0	0	0	4.29	NR

Abbreviations: SG salivary gland; SGPA salivary gland pleomorphic adenoma; SM submandibular gland; SL sublingual gland; SR standardized ratio; NR not reported

Author	n	Follow up (year)	Re-recurrence rate
Phillips, 1995 ⁸	126	Mean 14,5	32.5%
Glas, 2001 ⁹	52	Median 9	15%
Zbären, 2005 ¹⁰	33	Mean 9	18%
Wittekindt, 2007 ¹¹	108	Total 22	16, 42, 75% (1, 5, 15 year)
Redaelli de Zinis, 2008 ¹²	33	Median 10.5	14, 31, 43, 57% (5, 10, 15, 20 year)
Makeieff, 2010 ¹³	62	Median 9	9.7%
Riad, 2011 ¹⁴	18	Mean 5	11%

REFERENCES

- Gunn P. Parotid Tumors Northern Regional Health Authority of the United Kingdom 1978-1982. *Br J Surg.* 1988;75:1144-1146.
- Pinkston J a, Cole P. Incidence rates of salivary gland tumors: results from a population-based study. *Otolaryngol Head Neck Surg.* 1999;120(6):834-840. doi:S0194599899002442 [pii].
- Przewozny T, Stankiewicz C. Neoplasms of the parotid gland in northern Poland, 1991-2000: an epidemiologic study. *Eur Arch Otorhinolaryngol.* 2004;261(7):369-375. doi:10.1007/s00405-003-0698-4.
- Mortensen KS1, Hjortlund J, Bjørndal K, Krogdal A GC. Salivary gland tumors in the County of Funen, 1984-2003. *Ugeskr Laeger.* 2008;170(7):545-548.
- Bradley PJ, McGurk M. Incidence of salivary gland neoplasms in a defined UK population. *Br J Oral Maxillofac Surg.* 2013;51(5):399-403. doi:10.1016/j.bjoms.2012.10.002.
- Moeller K1, Esser D, Boeger D, Buentzel J, Hoffmann K, Jecker P, Mueller A, Radtke G, Piesold JU, Schultze-Mosgau S, Finkensieper M, Bitter T G-LO. Parotidectomy and submandibulectomy for benign diseases in Thuringia, Germany: a population-based study on epidemiology and outcome. *Eur Arch Otorhinolaryngol.* 2013;270(3):1149-1155. doi:10.1007/s00405-012-2225-y.
- Andreasen S, Therkildsen MH, Bjørndal K, Homøe P. Pleomorphic adenoma of the parotid gland 1985-2010: A Danish nationwide study of incidence, recurrence rate, and malignant transformation. *Head Neck.* 2016;38(S1):E1364-E1369. doi:10.1002/hed.24228.
- PP Phillips KO. Recurrent pleomorphic adenoma of the parotid gland: report of 126 cases and a review of the literature. *Ann Otol Rhinol Laryngol.* 1995;104(2):100-104.
- Glas AS, Vermey A, Hollema H, et al. Surgical treatment of recurrent pleomorphic adenoma of the parotid gland: a clinical analysis of 52 patients. *Head Neck.* 2001;23(4):311-316.
- Zbären P1, Tschumi I, Nuyens M SE. Recurrent pleomorphic adenoma of the parotid gland. *Am J Surg.* 2005;189(2):203-207.
- Wittekindt C1, Streubel K, Arnold G, Stennert E G-LO. Recurrent pleomorphic adenoma of the parotid gland: analysis of 108 consecutive patients. *Head Neck.* 2007 Sep;29(9):822-8. 2007;29(9):822-828.
- Redaelli De Zinis LO, Piccioni M, Antonelli AR, Nicolai P. Management and prognostic factors of recurrent pleomorphic adenoma of the parotid gland: Personal experience and review of the literature. *Eur Arch Oto-Rhino-Laryngology.* 2008;265(4):447-452. doi:10.1007/s00405-007-0502-y.
- Makeieff M1, Pelliccia P, Letois F, Mercier G, Arnaud S, César C, Garrel R, Crampette L GB. Recurrent pleomorphic adenoma: results of surgical treatment. *Ann Surg Oncol.* 2010;17(12):3308-3313. doi:10.1245/s10434-010-1173-2.
- Riad MA, Abdel-Rahman H, Ezzat WF, Adly A, Dessouky O, Shehata M. Variables related to recurrence of pleomorphic adenomas: outcome of parotid surgery in 182 cases. *Laryngoscope.* 2011;121(7):1467-1472. doi:10.1002/lary.21830.

SUMMARY, DISCUSSION AND CONCLUSIONS
SAMENVATTING (NL)
AUTHORS AND AFFILIATIONS
LIST OF PUBLICATIONS
CURRICULUM VITAE
DANKWOORD

CHAPTER 9

Summary, discussion and
conclusions

9

SUMMARY

CHAPTER 1.

GENERAL INTRODUCTION OF THE THESIS

This thesis describes the search for quality indicators in head and neck oncology. The National Healthcare Institute of the Netherlands states that aging of the population will lead to an increased pressure on the Dutch healthcare system in 2030¹. Taken into account the costs of all healthcare innovations, especially in the field of oncology, a challenge lies ahead to still treat every patient according to the highest standard in decades from now. Obviously, current high standards should not be compromised and quality of care must be clearly defined. The first step to define current quality is to develop a set of indicators for the assessment of quality.

In order to structure the assessment of quality of care, Donabedian et al.² subdivided quality of care into three indicator pillars: structure, process and outcome. All three components are not only separately involved in assessment of quality, but also related to each other. Structure indicators describe the health care setting in which care is provided (hospital type, numbers of qualified personnel and hospital volume). Process indicators measure the process of diagnosis and treatment on a patient level and are based on evidence from literature or consensus between experts. Outcome indicators denote the actual outcome of treatment. This can be evaluated by a broad spectrum of measurements ranging from undesired events during treatment (complications, incomplete resections) to survival of patients and quality of life scores using validated questionnaires.

The main objective of this thesis is to explore currently available information on variation in care and possible quality indicators in head and neck cancer care and derive lessons for future studies and quality evaluations.

CHAPTER 2.

VOLUME CRITERIA FOR THE TREATMENT OF HEAD AND NECK CANCER: ARE THEY EVIDENCE BASED?

It is already known from other low-volume high-risk fields of oncology (for instance esophageal and pancreatic cancer treatment) that provider or procedural volume relates to outcome. The purpose of this literature review is to evaluate the volume-outcome relationship in head and neck cancer care.

Our literature search led to the inclusion of eight published papers on the volume-outcome relationship in head and neck cancer. All eight studies describe a positive relationship; increased provider or procedural volume leads to improved survival.

Several comments can be made in relation to the volume-outcome literature:

1. Outcome measures should be clinically relevant. Sometimes 30-days mortality is chosen as outcome parameter for high-risk surgical procedures, whereas 30-days mortality of head and neck cancer procedures is typically low.
2. Volume is often presented as a categorical variable, where volume actually needs to be analyzed as a continuous variable. There is also much heterogeneity of cut-off points presented in literature.
3. Case mix is an important factor when analysing results of different hospitals. Many studies lack adequate adjustment for differences in case-mix between providers.
4. Head and neck cancer is a group of distinct cancer types with all (subtle) different treatment options and outcome. To consider head and neck cancer as one group in volume-outcome studies can cause under-/overestimation of the effect on individual head and neck cancer subsites.

Despite all limitations, all reviewed papers point towards a positive volume-outcome relationship. Definitely more research needs to be done to further characterize this relationship with emphasis on case mix adjustment and tumor specific volume effects.

CHAPTER 3.

VARIATION IN HEAD AND NECK CANCER CARE IN THE NETHERLANDS - A RETROSPECTIVE COHORT EVALUATION OF INCIDENCE, TREATMENT AND OUTCOME.

Head and neck cancer consists of a heterogeneous group of cancers. As a group it is the 9th most common cancer type. However, all subtypes can be viewed as low incidence tumors. Since the foundation of the Dutch Head and Neck Oncology Collaborative Group in 1984, head and neck cancer is treated predominantly in eight specialized head and neck centers or one of the six preferred partner hospitals across the country. The aim of this study was to evaluate variation of care in the Netherlands.

A large (n=2094) retrospective (2008) nationwide cohort of patients with head and neck squamous cell carcinoma was identified in the Netherlands Cancer Registry. The variation in numbers, treatments and treatment results between 7 tertiary head and neck cancer centers and 3 preferred partner clinics across the Netherlands was studied. The number of new head and neck cancer patients varied from 129 to 417 between the head and neck cancer centers. The numbers per center of the more rare cancer types (nasopharynx, nasal cavity, salivary gland) were less than 10 patients per year in nearly all centers. Types of treatment and outcome varied between the centers especially in oral cavity and oropharyngeal cancer. In oral cavity cancer there was for instance diversity in the use of postoperative radiotherapy (18% to 40%) and survival varied significantly. In oropharyngeal cancer there was variation in the amount of patients treated with organ preserving therapy [i.e. (chemo-) radiotherapy] with a range of 65 to 85% per center and survival differed significantly between the hospitals. For laryngeal cancer there were no statistically significant differences between the hospitals regarding treatment and outcome.

In the total cohort of head and neck cancer patients a significant volume-overall survival relation was found, stratified for age, sex and stage, since the hazard of dying was 0.98 (95% CI) for every increase with 25 patients per year.

From this study, we concluded that there was interhospital variation in 2008 in treatment for oropharynx, oral cavity, hypopharynx cancer, but not for larynx cancer. The numbers of the more rare cancer types (nasopharynx, salivary gland and paranasal sinus) were too low per hospital for meaningful analyses.

CHAPTER 4.

THE ASSOCIATION OF TREATMENT DELAY AND PROGNOSIS IN HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC) PATIENTS IN A DUTCH COMPREHENSIVE CANCER CENTER

Waiting time is one of the most psychologically distressing parts of the whole process from symptoms to diagnosis and treatment. In this study we evaluated the association between treatment delay and long-term outcome for head and neck squamous cell carcinoma in a Dutch tertiary head and neck cancer center.

We retrospectively studied a cohort of 2,493 HNSCC patients of the Netherlands Cancer Institute (NCI), diagnosed between 1990-2011. Professional delay was categorized into three categories: referral, diagnostic and total treatment delay.

The median time from diagnosis to treatment was 39 days (25-75% inter quartile range: 26.5 – 51), and it was found that year of diagnosis (early period), tumor site (oral cavity) and type of therapy (surgery) were all statistically significant of influence on the delay. We also found that referral time (time from biopsy elsewhere to first visit at NCI) significantly increased over time (from 10 – 13 days).

In the multivariate Cox proportional regression analyses performed, we found that patients with a treatment delay of less than 30 days had a higher risk of dying from the head and neck tumor [HR 0.82 (95% CI: 0.70–0.95)].

In sub-analyses this effect was independent from tumor (stage) or patient (age, sex) characteristics. An explanation could be that the early treated (<14 days) patients were selected by the physician to start early because of a biologically more aggressive tumor (history of tumor growth or more complaints of pain). In this study population prolonged waiting did not negatively influence survival.

CHAPTER 5.

THE INFLUENCE OF NODAL YIELD IN NECK DISSECTIONS ON LYMPH NODE RATIO IN HEAD AND NECK CANCER

The occurrence of cervical lymph node metastases is one of the most important prognostic factors in head and neck cancer. In the currently used TNM-staging, lymph node metastases classification is based on diameter, bilateral occurrence and number of positive nodes. In order to optimize prognostication, the concept of lymph node ratio was introduced. The lymph node ratio is calculated by dividing the number of positive nodes by the total number of harvested lymph nodes at a neck dissection. This ratio determines the extent of cancer spread, but also the extent of clearance.

The purpose of this study was to investigate the influence of nodal yield in neck dissections on the lymph node ratio.

The focus was on the influence of change in specimen processing at the pathology department on lymph node yield and lymph node ratio. The protocol of specimen processing encompassed a change in 2007: pathologists harvested the lymph nodes themselves before 2007, thereafter pathology technicians were involved.

This change in protocol resulted in a significantly higher yield of lymph nodes after 2007 (24 vs. 32, $p < 0.001$), with a stable number of positive lymph nodes (1.9 vs. 2.1, $p = 0.519$), leading to a decline in LNR. This increased number of lymph nodes was partly explained by an increased number of lymph nodes found in level V. Literature, as well as this study, confirmed that level V contains many (small) lymph nodes. The total number of lymph nodes decreased significantly after pre-operative (chemo-) radiotherapy, from a mean of 31 in patients without pre-operative treatment to 20 after radiotherapy or even 18 after (chemo-) radiotherapy ($p < 0.001$).

This study showed that standardization of pathology processing is an important quality indicator before interpretation of the prognostic value of LNR.

CHAPTER 6

A CRITICAL EVALUATION OF LYMPH NODE RATIO IN HEAD AND NECK CANCER

The previous study (chapter 5) showed that lymph node ratio is strongly dependent on the protocol of specimen processing. The aim of this study was to investigate the influence of this protocol change on the prognostic value of lymph node ratio.

Only patients with cervical lymph node metastases were included. Those with a conglomerate of lymph nodes (N3 disease) were excluded because lymph node ratio is less reliable in those patients. Also patients who have been previously treated with radiotherapy on the neck were excluded, because total lymph node harvest in previously irradiated patients is significantly lower³.

In total 176 patients with positive nodal HNSCC were studied. We performed survival estimate analyses on two time periods, based upon a switch in pathology processing protocol. This switch caused an increased yield of lymph nodes and a stable amount of positive lymph nodes found in neck dissection specimens. The lymph node ratio was calculated for both periods and the prognostic value was evaluated.

In the multivariate analyses it was found that pN-stage was an equally potent or even better prognosticator than the LNR. This can be explained by the earlier finding of the denominator variation of the ratio (total number of harvested lymph nodes) and a stable numerator (total number of positive nodes). To set a quality standard and to be able to reliably compare hospitals regarding lymph node dissections a minimum of lymph nodes need to be examined, like for instance in colon carcinoma.

It can be concluded from this study that without standardization of specimen processing LNR is unreliable as prognosticator. Total number of harvested lymph nodes should be used as quality indicator instead.

CHAPTER 7

AN EPIDEMIOLOGICAL EVALUATION OF SALIVARY GLAND CANCER IN THE NETHERLANDS (1989-2010) - TRENDS IN SALIVARY GLAND CANCER

Salivary gland carcinomas are a special group among head and neck carcinomas, because of the very low incidence, a great variation in histopathological subtypes and the lack of “classical head and neck” risk factors.

The aim of this study was to evaluate the progress made in salivary gland cancer over the past 22 years. Data was extracted from the Netherlands Cancer Registry, resulting in 2737 patients with a primary salivary gland carcinoma.

Trends over time in incidence and mortality were evaluated by calculating estimated annual percentage changes over the European Standardized Rates (ESR).

Incidence remained stable around 0.7 per 100,000. Most of the tumors (78%) originated from the parotid glands. Surgery (with or without radiotherapy) was treatment of choice in 84% of the cases. Over time the use of adjuvant radiotherapy increased (~6%).

Adenocarcinoma was the most common histological type, followed by squamous cell carcinomas, acinic cell carcinomas, adenoid cystic carcinomas and muco-epidermoid carcinomas. Striking differences were found between sexes. Mortality tended to increase in men over the years, whereas in women it remained stable. Also the 5-year relative survival was lower for men (63%) compared to women (76%). This effect could be partly explained by the higher initial tumor stage and/or by the higher proportion of poorly differentiated adenocarcinomas (with worse prognosis) in men.

We concluded that there has been barely any progress made in treatment of salivary gland cancer over the past 22 years.

CHAPTER 8

SALIVARY GLAND PLEOMORPHIC ADENOMA IN THE NETHERLANDS: AN OBSERVATIONAL NATIONWIDE STUDY OF PRIMARY TUMOR INCIDENCE AND RECURRENCE RATE.

The majority of the salivary gland tumors is benign of origin. Of the benign salivary gland tumors, pleomorphic adenomas are the most frequent. Pleomorphic adenomas are known for their ability to transform from benign to malignant, so-called carcinoma ex pleomorphic adenoma. Literature on the occurrence of pleomorphic adenoma, recurrence rate after surgery and primary or secondary malignant transformation is only available from single institution series. National data is hard to retrieve in the Netherlands, since its Cancer Registry only registers malignant tumors. So for this study, we used the nationwide pathology database PALGA.

From PALGA, excerpts of all patients that have had a pleomorphic adenoma since 1992 (16,437 patients) were retrieved. Data from this database is not coded and consists of free text, which had to be hand-coded to be able to perform analyses. For that reason we depicted 5 incidence years (1992, 1997, 2002, 2007 and 2012, representing in total 3506 patients) as a representative sample of possible pleomorphic adenomas and performed trend analyses on this data.

We found that the European standardized incidence rate of pleomorphic adenoma in 2012 in the Netherlands was 4.7 per 100,000 (total number of patients: a little less than 800 per year). The incidence of pleomorphic adenomas in women rose over the years with 1% per year, whereas it remained stable in men.

The long-term risk of (histology proven) recurrence was 4.6% for first recurrence. This percentage increased steeply for second, third etc. recurrence. Malignant transformation was very rare (1%) and transformed recurrences were not seen in our cohort. To define risk factors for recurrence we performed a multivariable analysis: lower age at diagnosis and positive or uncertain resection margins were associated with risk of recurrence.

This study is the first to give an accurate overview of nationwide incidence and recurrence of pleomorphic adenoma. Statistically significant risk factors for recurrence were identified, like positive or uncertain surgical margins, younger age at primary diagnosis or primary pleomorphic adenoma in the parotid gland.

DISCUSSION

Driven by the public's attention and demand for transparency, quality assessment in medicine has become increasingly important during the last decades. The vast expansion of health care innovations forces administrations to make deliberate choices on organization and evaluation of care to secure optimal quality and cost effectiveness of treatments. This makes quality of care currently a key factor in all healthcare policies in the Western world. One of the challenges is to deal with the dilemma how to keep quality high for all patients in light of increasing demands that stem from demographic and societal developments. In several fields of medicine like surgical oncology and cardiovascular surgery major progress has been made using quality assessment as a tool for increasing quality of services. For instance, the New England cardiovascular project reduced the mortality rate (minus 24%) of coronary artery bypass surgery by a structured program of visits, data sharing and training⁴. Also in cancer care, several quality improvement programs or initiatives started up in the last decade. In the Netherlands, the Dutch Pancreatic Cancer Group was formed in 2010, aiming at multidisciplinary collaboration in research, guideline development and they also introduced a nation-wide prospective audit (Dutch Pancreatic Cancer Audit; DPCA)⁵. In the audit detailed clinical data are collected of all patients with pancreatic cancer in whom surgery is performed in the Netherlands, to provide clinicians with timely, actable and benchmarked feedback information to improve the quality of their care process and outcomes. In addition, this collaboration resulted in several multicenter trials and further improvement in pancreatic cancer care. For upper gastro-intestinal tract cancer an identical group was formed, the Dutch Upper GI cancer group (DUCG)⁶. Their mission is to improve quality of care in upper GI cancer patients by supporting multidisciplinary clinical and translational research and support in patient registries. In contrast, the head and neck cancer counterpart, the Dutch Head and Neck Audit (DHNA), is relatively new and does not have published results yet.

FACTORS THAT DETERMINE QUALITY

As mentioned in the introduction of this thesis, quality is hard to capture. The multi-dimensional and, in case of head and neck cancer, multidisciplinary character, makes it hard to define it in concrete terms. Many medical specialists, each of them with specific super-specialized expertise, are responsible for a (small) part of the process (i.e. head and neck surgeon, radiation oncologist, medical oncologist, radiologist, pathologist, nuclear physician). Added thereto the involved paramedics (i.e. nursing staff, speech pathologist, dietician and physical therapist) make it even harder to define the process of quality assessment. To create more clarity in the field of quality, Donabedian et al. in 1988² developed a model of quality indicators categorized in three components: structure, process and outcome.

STRUCTURE INDICATORS

Procedural volume – on a hospital or surgeon level - is one of the most frequently studied, though also one of the most controversial structure indicators. “Practice makes perfect” may be a strong argument, especially in surgical disciplines, but is it sufficiently strong to explain the volume-outcome relation? As mentioned in the introduction, almost all literature regarding the volume-outcome relations in high-risk and or low-volume care shows a positive association⁷⁻¹¹. A supplementary explanation for this could be that several (infrastructural) factors (like the function of a tumor board, efficiency of the infrastructure between different services or training of paramedics for instance) are better organized in high volume hospitals than in low volume hospitals. This volume effect will probably be more outspoken in countries with non-centralized head and neck cancer care.

Although many studies pointed to a logical correlation between volume and outcome for high risk – low volume care, it is still necessary to define a minimum number of procedures. Compared to the North American counterparts like Memorial Sloan Kettering Cancer Center, MD Anderson, UCSF, Princes Margaret Toronto and Johns Hopkins, all Dutch head and neck cancer centers are low volume centers with mean volumes of ± 250 new patients per year¹²). Taking into account the differences between the Dutch centers and American Cancer Centers, it is remarkable that each of these US head and neck cancer centers surpasses the number of 4000 new patients per year¹³⁻¹⁶, compared to the total of 3000 new patients per year in the Netherlands, who are treated in eight different head and neck centers [or one of the six preferred partners]. This indicates a high level of efficiency and cost effectiveness in these US centers. This high standard of head and neck cancer care attracts many second opinions from all over the world, which can be seen as a quality indicator by itself. Although there are very few standardized outcome measures to compare head and neck cancer centers internationally. Moreover, it should be realized that these large cancer centers are also exceptional in the US and that a large proportion of head and neck cancer patients are treated in general hospitals, with larger differences in hospital volumes in the US than in the Netherlands.

Measured by European standards the level of head and neck cancer care in the Netherlands is high and according to the survival analyses in the EUROCARE-5 studies one of the best in Europe¹⁷. Despite the variation in care as described in chapter 3, this leading position in Europe can be attributed to the well-organized care in tertiary head and neck cancer centers, national treatment guidelines and standardized multidisciplinary approach in each of these centers.

VARIATION OF CARE AND GUIDELINE ADHERENCE

Evidence-based guidelines are tools meant to guarantee the same basic knowledge regarding the best treatment options available for medical teams in all hospitals. Adherence to guidelines is often used as process indicator with the assumption that overall a more evidence-based care process leads to better patient outcomes. Guidelines standardize treatment and set standards of care. Variation of care should not be confused with variation in quality of care. Guidelines leave room for variation to optimize treatment in individual cases in certain circumstances. A striking example in this respect is the treatment of T1 laryngeal cancer. The Dutch guideline states that endoscopic treatment is comparable to radiation in oncologic outcome as well as functional outcome. In such a case, specific expertise of the head and neck team and patient preferences will cause variation in care that is according to the guideline.

Adherence to guidelines can serve as surrogate marker for differences in quality of care and few studies evaluated adherence to guidelines and its effect on outcomes for the head and neck cancer setting^{5,6,18,19}. A study evaluating the protocol compliance of radiotherapy plans for advanced head and neck cancer patients, showed that 25% of the plans were non-compliant^[6]. For patients planned to receive over 60 Gy (curative dose) with major deficits in the treatment plan, it was found that survival significantly declined (5-y survival 50% vs. 70%). Of note, major deficiencies in the treatment plan were highly correlated to low volume hospitals ($p < 0.001$)⁶.

The volume-guideline adherence relationship was reproduced by Eskander et al.¹⁹ in a cohort of 5720 surgical head and neck patients. They observed a guideline adherence of around 75%. Several recommendations of the guideline were evaluated, like head and neck imaging, chest imaging, multidisciplinary meetings and follow up. Higher hospital volume and even higher surgeon volume were significantly associated with better guideline adherence ($p < 0.001$). The influence of guideline adherence on outcome was also demonstrated in a Dutch retrospective study¹⁸ evaluating over 800 head and neck cancer patients eligible for curative treatment. It was found that 17% of the patients did not receive guideline compliant therapy. Ten percent was due to non-compliant advice by the tumor board and the other 7% due to patients' preferences. Patients receiving non-standard treatment due to non-compliant advice had significantly lower overall survival after 3y (HR 2.1 – 95% CI 1.49-3.03). Since guidelines encompass the best evidence based treatment for specific patients the outcome of the study might not be surprising, however, if we combine the aforementioned study results, it is striking that most probably 10-15% of the head and neck cancer patients had a two times higher risk of dying within three years due to guideline non-compliance.

PROCESS INDICATORS

The counter effect of increased volume can be prolonged waiting times for diagnostics or treatment. Waiting time (or treatment delay) makes patients feel insecure and nervous²⁰. And due to possibly rapid tumor growth in head and neck cancer, there is a rationale for research on waiting times as quality indicator. A clear definition and method to measure treatment delay (day of first visit – first day of treatment) make it a potentially strong indicator. In other sites (uterine²¹ and breast²² for instance) the effect of treatment delay on outcome was already shown. In head and neck cancer, however, the literature was not clear on this point. Our study of 2400 patients²³ showed that patients treated with the shortest treatment delay had the worst survival. This effect, called the waiting time paradox, is explained by confounding by indication (patients with rapid progression or extreme symptoms are treated first). The larger population-based study by van Harten et al.²⁴ (over 13,000 patients), however, showed the negative impact on survival of prolonged treatment delay. They found a curve describing hazard ratio of dying that rapidly ascends from 0-25 days of delay, followed by a plateau until two months and after two months another rapid ascend. The cutoff point formulated by the Dutch head and neck collaborative group (NWHHT) of 30 days was not found to be significant in this study.

One of the options to shorten waiting times is to implement short-track programs, like all diagnostics and tumor board meeting on one day. Currently several head and neck cancer centers are implementing or have implemented such a program. One of the conditions necessary for short track programs combined with higher volume care is optimal logistics without increasing the costs extraordinarily.

Optimizing logistics is also at stake in the chain of surgery and specimen processing. First is the issue of the extent of the lymph node dissection. The more (fatty) tissue is removed, the more lymph nodes will be found. Therefore neck dissections should be performed in a standardized fashion²⁵ and taking into account the anatomical boundaries of the neck levels. When surgery is performed according to these guidelines, variance in the extent of surgery will be limited. Training institutions should focus on the adherence to surgical guidelines, supervised by independent audit committees composed of professionals. This brings us to the last part: the specimen processing at the pathology department. Should the pathologist try to find, evaluate and describe every node present in the specimen? There is growing literature about the (prognostic) value of the lymph node ratio (LNR) in various surgical fields^{26, 27}. LNR represents the ratio between total number of positive lymph nodes and total number of harvested lymph nodes. This last mentioned part of the lymph node ratio is critical. The total number of removed lymph nodes roughly depends on three factors. The first is the variable number of neck nodes; it is known that total number of lymph nodes varies considerably between humans²⁸.

However, this variation is indefinable since surgery is not standardized and specimen processing is not standardized.

We found that the introduction of a different specimen processing protocol changed the results in the number of lymph nodes found in dissection specimens^{29,30}. If calibration scales differ between two centers, results cannot reliably be compared anymore.

Another critical step in the diagnostic (and/or treatment) trajectory is the pathology report. Synoptic pathology reporting can be part of an improvement strategy, incorporating only important and crucial information in a standardized fashion. This can act as a sort of scale calibration, provided that a uniform acquisition of input is guaranteed (in our study for instance, the protocol of specimen processing).

Standardized (synoptic) pathology reports result in more complete reports on pathology, more consistency of the reports and also in quicker available and unambiguous information³¹. This will make it easier for clinicians to adhere to guidelines and possibly lead to a minimization of treatment delay, increase the efficiency of multidisciplinary tumor boards and also increase the quality of (retrospective) research. Another possible solution to improve the process is to combine efforts of maxillo-facial surgeons and otorhinolaryngologists working in the field of head and neck cancer to set up uniform training schedules and head and neck oncology departments, solely dedicated to the diagnosis and treatment of this disease. Apart from the logistic benefits this will also contribute to savings of costs, time and energy.

These are just examples, and nearby future research needs to focus on how to develop an efficient workflow.

OUTCOME INDICATORS

Especially in case of “orphan” head and neck cancers like salivary gland, nasopharynx and paranasal sinus cancer, the field demands a major step forward. For nasopharyngeal³² and paranasal sinus carcinomas³³ the lack of improvement in survival is shown in literature. As we have demonstrated in this thesis, the current centralization rate for salivary gland carcinomas does not lead to volumes with enough power for research on quality or improvement of outcome (some centers only saw 3 new patients in 2008). We demonstrated a lack of improvement in outcome over the past 22 years for salivary carcinomas, most probably due to the absence of effective (neo-adjuvant) systemic therapy³⁴. A reason could be that randomized clinical trials are almost impossible to initiate, if there are no international collaborations to create enough statistical power. Centralization or redistribution of patients with salivary gland cancer, currently not surpassing 10 patients/year per center and representing more than 20 histological subtypes, seems almost inevitable and might contribute to a less fragmented participation in international collaborations in search for new treatment regimens.

A nice example of such international collaboration for rare tumors is seen in Ewing sarcomas within the framework of EURAMOS³⁵. Ewing sarcomas are very rare soft tissue tumors (20-25 patients per year in the Netherlands, which are centralized treated in four specialized centers), where it was possible to perform a randomized trial comparing several treatment regimens³⁶ due to sufficient patient accrual across borders.

Such international collaborative initiatives may be the key for improvements in salivary gland cancer treatment. Of note, salivary gland cancer exist of much more different entities compared to Ewing sarcomas, thus it will remain hard to design and initiate randomized trials. Existing and proven effective, international collaborations, like the European Head and Neck Society (EHNS), International Federation of Head and Neck Societies (IFHNOS) or EORTC need to get together and initiate international (randomized) studies for these rare tumors.

FUTURE IMPROVEMENT PROGRAMS

A part of the above-mentioned indicators are currently included in a prospective audit of the Dutch Head and Neck cooperative group (NWHHT) that is being rolled out nationwide¹⁸. A full set of multidisciplinary quality indicators has been developed by the Scientific Institute for Quality of Healthcare³⁷. This audit will prospectively gather information on patient, tumor, treatment and hospital characteristics in all head and neck cancer centers in the Netherlands. The Dutch Head and Neck Audit (DHNA) is collaboration between the Dutch head and neck collaborative group (NWHHT), the Scientific Institute for Quality of Healthcare and the Dutch Federation for University Medical Centers.

The strength of clinical auditing lies in the total package it covers. It combines guideline adherence, case-mix differences and different outcome measures to give an overview of the current quality of care at specific hospitals. Benchmarking hospital-specific results catalyzes quality improvement³⁸. Hospitals scoring well on certain indicators are challenged to keep their reputation on level and hospitals scoring worse on certain indicators are challenged to score as well as their bench marked partners. Conceptually beautiful, but hospitals need to be willing to be completely transparent. Our retrospective study on variation already showed that lack of transparency of hospitals could limit quality of care research; see chapter 3.

TRANSPARENCY

Transparency is the key factor for quality improvement programs. Hospitals need to open up and show their results. As a hospital organization you can learn from others or others can learn from you on certain indicators, but you need to know the performance from each other. According to Wouters³⁹, transparency can be seen as a 7 level process (figure 1).

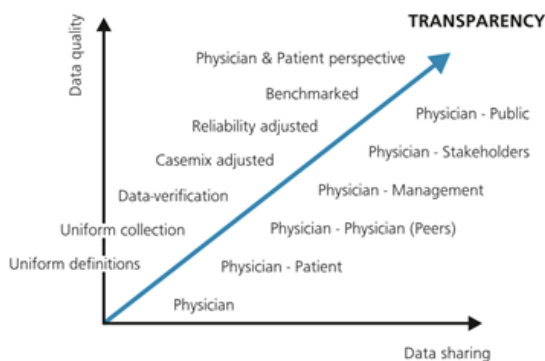


Figure 1. The seven level process of transparency

The spectrum of transparency starts with availability of trivial hospital specific outcome information and it ends with full publicly availability of hospital or physician specific outcome data. The goal of transparency is dual: for patients, so they are able to choose the best hospital for their treatment and for hospitals to create a transparent benchmarked situation so less performing hospitals know where to target their improvement efforts. The Dutch Institute for Clinical Auditing (DICA) has delivered the proof of concept³⁸ for comparing hospital-specific risk-adjusted indicator results, primarily to provide doctors with benchmarked feedback information, though also to make (differences in) quality of care transparent for all stakeholders.

The benefit of transparency disappears if the reporting of results is not correct. A hospital can publish superior results on their website, but if they are selective, manipulated or incorrectly gathered the benefit of transparency turns 180 degrees.

Austin et al.[40] described how to avoid pitfalls in five steps of quality measurement and reporting.

1. Measures must be developed and specified for the performance measured. If not, you are extrapolating or assuming, which decreases the quality of your data tremendously.
2. Data must be identified and collected to populate the measures. So you need to have a measurement specific quality assurance, in order to guarantee quality of the data.
3. Collected data must be applied to the measured specifications. An example in this respect is blood loss during surgery in ml. One surgeon measures it accurately, whereas the other surgeon makes estimates based on impression. This leads to variability and uncertainty in the collected data.

4. Public reports must be reliable regarding classification. Any predefined category must be reported concordantly. So “hospital A”, must be “hospital A” in your dataset and “physician B”, must be “physician B”. This to prevent misclassification and thereby misinterpretation of the data.
5. Communicate results in such a way that there is no room for misinterpretation. Make sure your report for the press is written according to the knowledge level of the reader.

These five steps are visible in the approach of DICA and were taken into account at the foundation of the DHNA²⁹.

VALUE-BASED HEALTH CARE

Internationally there are several initiatives to transform health care from a volume-driven to an outcome-driven industry. According to Michael Porter, a healthcare economist from the Harvard Business School, providers should make patient value the overarching goal to keep high quality health care sustainable, especially in Western countries. Maximizing value for patients, means achieving the best outcomes at the lowest costs. This adds another dimension to the perception of (high) quality care described in this thesis. With the initiation of the DHNA the Dutch Institute for Clinical Auditing will provide the Head and neck cancer centers in the Netherlands with benchmarked feedback on their outcomes; clinical as well as patient reported outcomes. Head and neck cancer centers should use this information to learn from each other and start fine-tuning and individualizing their multi-disciplinary care processes. If also the costs of these care processes are measured and stay on the same level or show a relatively low increase, patient value will improve. In addition, better care processes may not only lead to better outcomes on the short term, though also long-term functional outcomes of patients may improve leading to less disabilities and better societal participation. The International Consortium of Health Outcomes Measurement (ICHOM) organizes global teams of physician leaders, outcomes researchers and patient advocates to define Standard Sets of outcomes per medical condition, and then drives adoption to enable health care providers globally to compare, learn, and improve their care [www.ichom.org]. By bringing health outcome measurement from a national to an international level, insight in variation in care processes and the resulting outcomes between providers in different countries could lead to even more improvement in patient value. An international standard set for measuring outcomes of Head and neck cancer patients is not available yet, though will certainly be developed in the near future.

CONCLUSION

This thesis shows the complexity and multidimensional concept of quality of care in head and neck cancer. The selected topics represent examples of quality assessment using structure [centralization ([CHAPTER 2](#)) and variation of care ([CHAPTER 3](#))], process [waiting time ([CHAPTER 4](#)) and pathologic specimen handling ([CHAPTER 5, 6](#))] and outcome indicators [influence of volume and variation of care on outcome ([CHAPTER 3](#)) and specific outcome of rare head and neck tumors arising in the salivary gland ([CHAPTER 7, 8](#))].

Head and neck cancer care in the Netherlands is centralized in specific head and neck cancer centers, but nonetheless the care given varied per head and neck center. We showed that volume may play a role in this variation, but several other quality related aspects of head and neck cancer care are of influence as well. For instance: waiting time differences, as we showed that waiting time has significant influence on outcome. What we also showed is that pathology specimen handling is another key factor, and that non-standardized workflow leads to differences and non-uniformity.

For the more rare types of head and neck cancer, like salivary gland tumors, the low volume in the Netherlands makes quality assurance almost impossible. For proper quality assessment and thereby quality assurance, based upon this thesis, redistribution of rare head and neck cancers appears inevitable. The variation in numbers and treatment we found could have been biased by case-mix factors we did not include. The relatively small sample size of our study population limited us regarding some statistics. With data currently being gathered in the DHNA, more insights in the variation of care can be given. Especially on detailed, stage corrected treatment variation. Hopefully the prospective audit database (DHNA) will serve as a unique source of answers to quality of care questions and will give direction to further improvement of the (already) high quality head and neck cancer care in the Netherlands.

REFERENCES

1. <https://www.zorginstituutnederland.nl/publicaties/rapport/2014/08/17/indicatie-van-de-zorgvraag-in-2030---prognoses-van-functioneren-en-chronische-aandoeningen-rotterdam-rapport-tno> (accessed March 2017)..
2. Donabedian A. The quality of care. How can it be assessed? *JAMA*. 1988;260:1743-8.
3. Johnstone PA, Miller ED, Moore MG. Preoperative radiotherapy decreases lymph node yield of neck dissections for head and neck cancer. *Otolaryngol Head Neck Surg*. 2012;147:278-80.
4. O'Connor GT, Plume SK, Olmstead EM, Morton JR, Maloney CT, Nugent WC, et al. A regional intervention to improve the hospital mortality associated with coronary artery bypass graft surgery. The Northern New England Cardiovascular Disease Study Group. *JAMA*. 1996;275:841-6.
5. Lewis CM, Hessel AC, Roberts DB, Guo YZ, Holsinger FC, Ginsberg LE, et al. Prereferral head and neck cancer treatment: compliance with national comprehensive cancer network treatment guidelines. *Arch Otolaryngol Head Neck Surg*. 2010;136:1205-11.
6. Peters LJ, O'Sullivan B, Giralt J, Fitzgerald TJ, Trotti A, Bernier J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. *J Clin Oncol*. 2010;28:2996-3001.
7. van Heek NT, Kuhlmann KE, Scholten RJ, de Castro SM, Busch OR, van Gulik TM, et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. *Ann Surg*. 2005;242:781-8, discussion 8-90.
8. Goossens-Laan CA, Gooiker GA, van Gijn W, Post PN, Bosch JL, Kil PJ, et al. A systematic review and meta-analysis of the relationship between hospital/surgeon volume and outcome for radical cystectomy: an update for the ongoing debate. *European urology*. 2011;59:775-83.
9. Pieper D, Mathes T, Neugebauer E, Eikermann M. State of evidence on the relationship between high-volume hospitals and outcomes in surgery: a systematic review of systematic reviews. *J Am Coll Surg*. 2013;216:1015-25 e18.
10. Aquina CT, Probst CP, Becerra AZ, Iannuzzi JC, Kelly KN, Hensley BJ, et al. High volume improves outcomes: The argument for centralization of rectal cancer surgery. *Surgery*. 2015.
11. Cheung MC, Koniari LG, Perez EA, Molina MA, Goodwin WJ, Salloum RM. Impact of hospital volume on surgical outcome for head and neck cancer. *Ann Surg Oncol*. 2009;16:1001-9.
12. Dutch Head and Neck Oncology Collaboration Group. 2016 - <http://www.nwhht.nl> (accessed March 2017).
13. <http://www.mskcc.org/cancer-care/adult/head-neck> (accessed March 2017).
14. <http://www.mdanderson.org/patient-and-cancer-information/care-centers-and-clinics/care-centers/head-neck/index> (accessed March 2017)..
15. <http://www.otolaryngology/utoronto.ca/site3.aspx> (accessed March 2017).
16. <http://tmc.gov.in/medical/departements/surgery.htm> (accessed March 2017)..
17. Gatta G, Botta L, Sanchez MJ, Anderson LA, Pierannunzio D, Licitra L, et al. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EURO CARE-5 population-based study. *Eur J Cancer*. 2015.
18. Dronkers EA, Mes SW, Wieringa MH, van der Schroeff MP, Baatenburg de Jong RJ. Non compliance to guidelines in head and neck cancer treatment; associated factors for both patient and physician. *BMC Cancer*. 2015;15:515.
19. Eskander A, Monteiro E, Irish J, Gullane P, Gilbert R, de Almeida J, et al. Adherence to guideline-recommended process measures for squamous cell carcinoma of the head and neck in Ontario: Impact of surgeon and hospital volume. *Head Neck*. 2016;38 Suppl 1:E1987-92.
20. Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. *Seminars in oncology*. 1996;23:89-97.
21. Elit LM, O'Leary EM, Pond GR, Seow HY. Impact of wait times on survival for women with uterine cancer. *J Clin Oncol*. 2014;32:27-33.
22. McLaughlin JM, Anderson RT, Ferketich AK, Seiber EE, Balkrishnan R, Paskett ED. Effect on survival of longer intervals between confirmed diagnosis and treatment initiation among low-income women with breast cancer. *J Clin Oncol*. 2012;30:4493-500.

23. van Harten MC, de Ridder M, Hamming-Vrieze O, Smeele LE, Balm AJ, van den Brekel MW. The association of treatment delay and prognosis in head and neck squamous cell carcinoma (HNSCC) patients in a Dutch comprehensive cancer center. *Oral Oncol.* 2014;50:282-90.
24. van Harten MC, Hoebbers FJ, Kross KW, van Werkhoven ED, van den Brekel MW, van Dijk BA. Determinants of treatment waiting times for head and neck cancer in the Netherlands and their relation to survival. *Oral Oncol.* 2015;51:272-8.
25. Balm AJ, Lohuis PJ, Copper MP. Surgical technique--unwrapping the neck node levels around a sternocleidomastoid muscle bar: a systematic way of performing (modified) radical neck dissection. *Eur J Surg Oncol.* 2005;31:1216-21.
26. Patel SG, Amit M, Yen TC, Liao CT, Chaturvedi P, Agarwal JP, et al. Lymph node density in oral cavity cancer: results of the International Consortium for Outcomes Research. *Br J Cancer.* 2013.
27. Liao CT, Hsueh C, Lee LY, Lin CY, Fan KH, Wang HM, et al. Neck dissection field and lymph node density predict prognosis in patients with oral cavity cancer and pathological node metastases treated with adjuvant therapy. *Oral Oncol.* 2012;48:329-36.
28. Friedman M, Lim JW, Dickey W, Tanyeri H, Kirshenbaum GL, Phadke DM, et al. Quantification of lymph nodes in selective neck dissection. *Laryngoscope.* 1999;109:368-70.
29. Marres CC, de Ridder M, Hegger I, van Velthuysen ML, Hauptmann M, Navran A, et al. The influence of nodal yield in neck dissections on lymph node ratio in head and neck cancer. *Oral Oncol.* 2014;50:59-64.
30. de Ridder M, Marres CC, Smeele LE, van den Brekel MW, Hauptmann M, Balm AJ, et al. A critical evaluation of lymph node ratio in head and neck cancer. *Virchows Arch.* 2016.
31. Sluijter CE, van Lonkhuijzen LR, van Slooten HJ, Nagtegaal ID, Overbeek LI. The effects of implementing synoptic pathology reporting in cancer diagnosis: a systematic review. *Virchows Arch.* 2016;468:639-49.
32. Arnold M, Wildeman MA, Visser O, Karim-Kos HE, Middeldorp JM, Fles R, et al. Lower mortality from nasopharyngeal cancer in The Netherlands since 1970 with differential incidence trends in histopathology. *Oral Oncol.* 2013;49:237-43.
33. Van Dijk BA, Gatta G, Capocaccia R, Pierannunzio D, Strojan P, Licitra L, et al. Rare cancers of the head and neck area in Europe. *Eur J Cancer.* 2012;48:783-96.
34. Goyal G, Mehdi SA, Ganti AK. *Salivary Gland Cancers: Biology and Systemic Therapy.* Oncology (Williston Park). 2015;29:773-80.
35. Marina N, Bielack S, Whelan J, Smeland S, Krailo M, Sydes MR, et al. International collaboration is feasible in trials for rare conditions: the EURAMOS experience. *Cancer Treat Res.* 2009;152:339-53.
36. Marina NM, Smeland S, Bielack SS, Bernstein M, Jovic G, Krailo MD, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. *Lancet Oncol.* 2016.
37. van Overveld LF, Braspenning JC, Hermens RP. Quality indicators of integrated care for patients with head and neck cancer. *Clin Otolaryngol.* 2016.
38. Van Leersum NJ, Snijders HS, Henneman D, Kolfshoten NE, Gooiker GA, ten Berge MG, et al. The Dutch surgical colorectal audit. *Eur J Surg Oncol.* 2013;39:1063-70.
39. Wouters MW. Measuring and improving quality of care in surgical oncology 2013.
40. Austin JM, McGlynn EA, Pronovost PJ. Fostering Transparency in Outcomes, Quality, Safety, and Costs. *JAMA.* 2016.

SAMENVATTING (NL)

HOOFDSTUK 1.

ALGEMENE INLEIDING

Dit proefschrift beschrijft de zoektocht naar kwaliteitsindicatoren in de hoofd-hals oncologie. Door vergrijzing van de populatie en toegenomen behandelingsmogelijkheden door de vooruitgang in de medische wetenschap is er een verhoogde druk ontstaan op de zorginstellingen om iedere patiënt volgens de hoogste standaard te behandelen (zeker binnen de oncologie). Het is essentieel dat kwaliteit van zorg te allen tijde bewaakt wordt. De eerste stap in dit proces is om de huidige kwaliteit - en de mogelijke variatie tussen zorgaanbieders - vast te stellen door het identificeren van belangrijke kwaliteitsaspecten en het ontwikkelen van kwaliteitsindicatoren.

Om onderzoek naar kwaliteit van zorg te structureren hebben Donabedian et al.¹ indicatoren in drie categorieën verdeeld: *structuur*, *proces* en *uitkomstindicatoren*. Deze worden niet alleen afzonderlijk, maar ook in relatie tot elkaar onderzocht.

Structuurindicatoren beschrijven de zorgomgeving waarbinnen zorg wordt geleverd (ziekenhuistype, patiënten aantallen en beschikbaarheid van gekwalificeerd personeel).

Procesindicatoren beschrijven het zorgproces: het diagnostisch traject, de medische besluitvorming, de behandeling en de nazorg.

Uitkomstindicatoren beschrijven de daadwerkelijke uitkomst van een behandeling binnen een breed spectrum variërend van overleving van een groep patiënten tot een door de individuele patiënt ingevulde vragenlijst over kwaliteit van leven.

De inhoud van dit proefschrift richt zich op onderzoek naar actuele variatie van hoofd-hals oncologische zorg en identificatie van mogelijke kwaliteitsindicatoren om toekomstig onderzoek naar kwaliteit van zorg te sturen.

HOOFDSTUK 2.

VOLUME CRITERIA VOOR DE BEHANDELING VAN HOOFDHALS KANKER: ZIJN DEZE “EVIDENCE BASED”?

Van andere ‘laag volume – hoog risico’ vormen van oncologische chirurgie, zoals slokdarm- en pancreaschirurgie is bekend dat volume per ziekenhuis of chirurg gerelateerd is aan uitkomst.

Wij onderzochten deze relatie aan de hand van acht gepubliceerde artikelen over de volume-uitkomst relatie bij hoofd-hals kanker. In alle gevallen werd een positieve correlatie aangetoond tussen een hoger volume en een langere overleving.

Bij dit literatuuronderzoek werden een aantal kritische kanttekeningen gemaakt

1. Uitkomst is klinisch niet altijd relevant gemeten: in sommige gevallen werd gekozen voor sterfte binnen 30 dagen na chirurgie als uitkomst; voor hoofd-hals kanker patiënten is deze sterftemaat erg laag en zijn verschillen daardoor minder relevant.
2. Volume werd vaak weergegeven als categorische variabele, echter volume is een continue variabele en dient ook als zodanig te worden onderzocht. Bovendien is er veel variatie in afkapwaarden gebruikt in de beschreven literatuur.
3. 'Case mix-correctie' is een belangrijk onderdeel van vergelijkingen van uitkomsten van ziekenhuizen en veel studies missen correctie voor deze verschillen in "case mix".
4. Hoofd-halskanker is een verzamelterm voor verschillende subtypen kanker met (subtiele) verschillen in behandeling en uitkomst. Door hoofd-halskanker als één groep te beschouwen in de volume-uitkomst studies bestaat er een kans op onder- of overschatting van het effect.

Ondanks alle beperkingen wijzen alle onderzochte artikelen in de richting van een positieve volume-uitkomst relatie. Met zekerheid kan gezegd worden dat er meer onderzoek nodig is om deze relatie verder te karakteriseren, waarbij de nadruk moet liggen op gedegen correctie voor 'case mix' en verschillen tussen tumortypen.

HOOFDSTUK 3.

VARIATIE VAN HOOFD-HALS ONCOLOGISCHE ZORG IN NEDERLAND – EEN RETROSPECTIEF COHORT ONDERZOEK NAAR INCIDENTIE, BEHANDELING EN UITKOMST.

Hoofd-halskanker bestaat uit een heterogene groep van aandoeningen. In Nederland is het de 9e meest voorkomende kankersoort. Individuele typen zijn ieder als zeldzame tumor te classificeren. Sinds de oprichting van de Nederlandse Werkgroep Hoofd-Hals Tumoren (NWHHT) in 1984 worden hoofd-halstumoren hoofdzakelijk behandeld in een van de acht hoofd-hals centra en zes zogenaamde 'preferred partners' verspreid over het land. Dit onderzoek richtte zich op variatie in hoofd-hals oncologische zorg tussen deze centra. Er werd een retrospectief landelijk cohortonderzoek verricht van 2094 hoofd-halskanker patiënten, die geregistreerd zijn door de Nederlandse Kanker Registratie. De variatie in patiënten aantallen, behandeling en uitkomsten werd vergeleken tussen 7 hoofd-halscentra en 3 preferred partners. Het aantal patiënten per jaar in 2008 varieerde van 129-417 tussen de hoofd-halscentra. Voor de meer zeldzamere typen, zoals speekselklier-, nasofarynx-, neus - en neusbijholten carcinoom, was het patiënten aantal minder dan 10 patiënten per jaar voor bijna alle deelnemende centra.

Behandeling en uitkomstmaten varieerden voornamelijk bij het mondholte- en orofarynxcarcinoom. Voor het mondholte carcinoom varieerde de toepassing van postoperatieve radiotherapie per centrum van 18% tot 40%. Tevens was er een significant verschil in overleving waar te nemen. Voor het orofarynxcarcinoom was er variatie in het percentage patiënten dat orgaansparend behandeld werd (65% - 85%). Eveneens varieerde de overleving significant binnen deze patiëntengroep. Voor larynxcarcinoom patiënten werd er geen verschil in behandeling of uitkomst gevonden tussen de verschillende centra. In het totale cohort werd er na multivariate analyse een significant volume-uitkomst effect vastgesteld na stratificatie voor leeftijd, geslacht en stadium. De hazard ratio (HR) voor overlijden was 0.98 per toename van 25 patiënten/jaar. Geconcludeerd wordt dat er was van een significante variatie tussen ziekenhuizen in 2008 voor wat betreft de behandeling van orofarynx-, mondholte- en hypofarynxcarcinoom. De patiënten aantallen voor de zeldzamere hoofd-halstumoren, nasofarynx-, speekselklier-, neus- en neusbijholtencarcinoom, waren te beperkt om in de overlevingsanalyse mee te nemen. Over het algemeen was er een tendens waarneembaar van een positieve relatie tussen ziekenhuisvolume en overleving voor de totale groep van hoofd-halstumoren.

HOOFDSTUK 4.

HET VERBAND TUSSEN WACHTTIJD TOT BEHANDELING EN PROGNOSE BIJ HOOFDHALSCARCINOOM PATIËNTEN UIT HET NEDERLANDS KANKER INSTITUUT/ANTONI VAN LEEUWENHOEK.

Een lange wachttijd is voor veel patiënten een stress verhogende factor gedurende het proces van diagnose en behandeling. In deze studie werd het verband tussen wachttijd en overleving onderzocht in een retrospectief cohort van 2493 hoofd-halscarcinoom patiënten (1990 – 2011) van het Antoni van Leeuwenhoek (AVL). Wachttijd werd onderverdeeld in drie groepen: wachttijd in het verwijzingsproces, gedurende de diagnostiek en in het geheel van de totale behandeling.

De mediane wachttijd tussen diagnose en behandeling was 39 dagen (25-75% met een spreiding van 26.5 – 51 dagen). Drie factoren waren significant gecorreleerd aan een langere wachttijd: een vroeger tijdvak van behandeling, behandeling voor een mondholtecarcinoom en primaire chirurgie behandeling. Tevens werd vastgesteld dat de tijd die verloopt tussen biopst in een ander ziekenhuis en het 1e bezoek in het AVL in de loop der jaren significant is toegenomen, van 10 naar 13 dagen. In het multivariate Cox regressie model bleek dat patiënten met de kortste wachttijd van minder dan 30 dagen een hoger risico hadden om te overlijden aan het hoofd-halscarcinoom [HR 0.82 (95% CI: 0.70–0.95)]. In een sub analyse bleek dit onverwachte resultaat onafhankelijk van tumor stadium, leeftijd of geslacht.

Een aannemelijke verklaring hiervoor zou kunnen zijn dat deze patiënten een klinisch snel progressieve tumor hadden met snelle toename van klachten, die het behandelend team ertoe deed besluiten deze patiënten met voorrang te behandelen.

In deze studie bleek een langere wachttijd de overleving niet negatief te beïnvloeden.

Toekomstig onderzoek zal zich richten op het onderzoeken van de relatie tussen wachttijd, psychologische stress en/of morbiditeit.

HOOFDSTUK 5.

DE INVLOED VAN LYMFEKLIER OPBRENGST NA HALSKLIERDISSECTIES OP DE LYMFEKLIERRATIO IN HOOFD-HALSKANKER.

De aanwezigheid van halskliermetastase(n) is een van de belangrijkste prognostische factoren voor overleving bij hoofd-halskanker. In de huidige TNM-classificatie worden lymfekliermetastasen geclassificeerd op basis van diameter, aantal en eenzijdig of dubbelzijdig voorkomen. In een poging het voorspellen van de prognose te verbeteren is het concept van de lymfeklierratio bedacht. Deze ratio wordt berekend door het aantal tumorpositieve lymfeklieren te delen door het totaal aantal verwijderde klieren. Hierdoor is niet alleen het aantal positieve klieren van belang, maar ook de uitgebreidheid van de chirurgische ingreep en het aantal lymfeklieren dat door de patholoog gevonden is in het verwijderde weefsel. Deze studie concentreerde zich op de invloed van de lymfeklieropbrengst na halsklierdissectie op de lymfeklierratio met focus op de invloed van een gewijzigd uitsnijprotocol van het operatiepreparaat. Het protocol hiervoor werd in 2007 gewijzigd, waardoor het niet meer de pathologen zelf waren die uitsneden, maar speciaal daartoe opgeleide laboranten. Dit resulteerde in een significant hogere opbrengst van totaal aantal lymfeklieren (24 vs. 32, $p < 0.001$), met een stabiel aantal positieve lymfeklieren (1.9 vs. 2.1, $p = 0.519$) met als gevolg een afnemende lymfeklierratio. Het toegenomen totaal aantal verwijderde lymfeklieren werd hoofdzakelijk verklaard door een toename van het aantal lymfeklieren in level V. Het totaal aantal lymfeklieren daalde significant wanneer patiënten preoperatieve (chemo-)radiatie hadden ondergaan. Deze studie laat zien dat standaardisatie van het pathologie protocol een belangrijke kwaliteitsindicator is alvorens lymfeklierratio betrouwbaar kan worden geïnterpreteerd als prognostische factor.

HOOFDSTUK 6.

EEN KRITISCHE EVALUATIE VAN LYMFEKLIERRATIO IN HOOFDHALSKANKER.

De studie voorafgaand aan deze studie (hoofdstuk 5) toonde dat lymfeklierratio sterk afhankelijk is van het protocol dat gebruikt wordt voor het uitsnijden van het preparaat. Deze studie richtte zich op de invloed van een uitsnijprotocolwijziging op de prognostische waarde van de lymfeklierratio. Hiervoor werden alleen patiënten met positieve hals lymfeklieren geïnccludeerd. Patiënten met N3 ziekte en voorafgaande (chemo)radiatie op de hals werden geëxcludeerd vanwege onbetrouwbaarheid van de lymfeklierratio bij deze patiënten. In totaal werden 176 patiënten met positieve halsklieren van een hoofd-halscarcinoom geïnccludeerd. Vervolgens werden er overlevingsanalyses gedaan voor de groep patiënten die voor en na de protocolwijziging zijn behandeld. Deze wijziging heeft tot een grotere opbrengst van lymfeklieren in het halsklierdissectiepreparaat geleid, zonder dat er extra metastasen werden gedetecteerd. In de multivariate analyse bleek pN-classificatie minstens even goed of zelfs beter voorspellend te zijn voor de prognose in vergelijking met de lymfeklier ratio. Dit kan verklaard worden door de eerder gevonden variatie in de noemer van de ratio (totaal aantal lymfeklieren) en een stabiele teller (aantal positieve lymfeklieren). Om een kwaliteitsstandaard neer te zetten en om tevens verantwoord te kunnen vergelijken tussen verschillende ziekenhuizen moet er een minimum gesteld worden aan het aantal onderzochte lymfeklieren, zoals dat ook gedaan is bij het coloncarcinoom. Uit deze studie kan geconcludeerd worden dat zonder standaardisatie van de wijze waarop een hals-lymfeklierdissectiepreparaat wordt uitgesneden de lymfeklierratio als onbetrouwbare prognostische factor kan worden aangemerkt. Als kwaliteitsindicator kan beter het totaal aantal onderzochte lymfeklieren gehanteerd worden.

HOOFDSTUK 7.

EEN EPIDEMIOLOGISCHE EVALUATIE VAN HET SPEEKSELKLIERCARCINOOM IN NEDERLAND(1989-2010).

Vanwege hun lage incidentie, grote variatie in histopathologie en het ontbreken van klassieke risicofactoren vormen speekselklier carcinoomen een speciale groep tumoren binnen het geheel van hoofd-halscarcinoomen. Het doel van deze studie was om te evalueren welke vooruitgang er geboekt is in de afgelopen 22 jaar bij de behandeling van het speekselklier carcinoom. Hiervoor werden er gegevens van 2737 patiënten met een primair speekselklier carcinoom opgevraagd bij de Nederlandse Kanker Registratie.

Trends in incidentie en mortaliteit werden geëvalueerd aan de hand van geschatte jaarlijkse procentuele veranderingen in Europees gestandaardiseerde cijfers voor incidentie en overleving.

Incidentie bleef stabiel, rond 0.7 per 100,000 patiënten per jaar. De meerderheid van de tumoren (78%) ontstond in de glandula parotis. De meeste patiënten (84%) werden chirurgisch behandeld, met of zonder adjuvante therapie. In de loop der jaren werd er een toename van ongeveer 6% gezien in toepassing van postoperatieve radiotherapie. Qua histologie kwamen achtereenvolgens adenocarcinomen het meest voor, gevolgd door plaveiselcelcarcinomen, acinic cell carcinomen, adenoïd cysteus carcinomen en muco-epidermoïd carcinomen. Opvallende verschillen werden gevonden tussen beide geslachten. De mortaliteit leek toe te nemen over de jaren bij mannen, waar deze bij de vrouwen stabiel bleef. Daarbij was ook de 5-jaars relatieve overleving lager voor mannen (63%) dan voor vrouwen (76%). Dit effect kan deels verklaard worden door het hogere tumor stadium en een groter aandeel van slecht gedifferentieerde adenocarcinomen (met een slechtere prognose) bij mannen. Concluderend is er weinig vooruitgang geboekt in de behandeling en prognose van speekselklieradenocarcinomen gedurende de laatste 22 jaar. Wij zijn ervan overtuigd dat verdere centralisering en toegenomen 'awareness' voor speekselklierzwellingen kunnen bijdragen aan betere uitkomsten.

HOOFDSTUK 8.

PLEIOMORF ADENOOM VAN DE SPEEKSELKLIEREN IN NEDERLAND: EEN OBSERVATIONELE LANDELIJKE COHORT STUDIE VAN INCIDENTIE EN RECIDIEF PERCENTAGE.

De meerderheid van de speekselkliertumoren zijn benigne van aard. Van deze benigne tumoren zijn pleiomorf adenomen de meeste voorkomende. Het pleiomorf adenoom staat erom bekend dat het maligne kan ontaarden tot een carcinoom ex pleiomorf adenoom. Over de incidentie van pleiomorf adenomen, recidief percentage na behandeling en secundaire maligne ontaarding is alleen literatuur beschikbaar van beperkte ziekenhuis series. Vanwege het feit dat de Nederlandse Kankerregistratie zich alleen richt op de registratie van maligne tumoren zijn landelijke gegevens moeilijk te verkrijgen. Om die reden is er voor gekozen om data te verzamelen uit het landelijke PALGA systeem (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief). Van alle patiënten die vanaf 1992 met een pleiomorf adenoom werden gediagnosticeerd (n=16437) werden gegevens opgevraagd uit PALGA. Omdat de onderzoeksgegevens in vrije tekst opgenomen waren moesten deze daaruit worden gedestilleerd en met de hand gecodeerd worden. Daarom is besloten om 5 incidentie jaren (1992, 1997, 2002, 2007 en 2012) te selecteren resulterend in 3506 representatieve patiënten .

De Europees gestandaardiseerde incidentie in Nederland van pleiomorf adenomen in 2012 werd door ons vastgesteld op 4.7 per 100,000 (totaal aantal patiënten ongeveer 800 per jaar). De incidentie van pleiomorf adenomen bij vrouwen steeg met 1% per jaar, waar deze bij mannen stabiel bleef.

De lange-termijnkans op een (histologisch bewezen) eerste recidief was 4.6%. Dit percentage liep snel op voor de kans op tweede, derde en volgende recidief. Maligne ontaarding was met ongeveer 1% zeer zeldzaam. Tumorrecidieven transformeerden in ons materiaal niet tot een maligniteit. Aan de hand van een multivariate analyse bleken een lage leeftijd bij het stellen van de diagnose en positieve of onzekere resectie marges bij pathologisch onderzoek risico factoren voor een recidief te zijn.

Concluderend gaf deze studie een vrij nauwkeurig overzicht van de incidentie en recidief kans van pleiomorf adenomen in Nederland.

CONCLUSIES

Dit proefschrift beschrijft de complexiteit van het kwaliteitsconcept rondom hoofd-hals oncologische zorg. Het is een complex onderwerp, omdat de hoofd-halskanker zorg per definitie multidisciplinair is en omdat de kwaliteit van zorg vanuit verschillende invalshoeken benaderd kan worden. In de drie domeinen van kwaliteit van zorg, *structuur*, *proces* en *uitkomst*, werden verschillende indicatoren onderzocht. Binnen het domein *structuur* werd de centralisatie en variatie van zorg bestudeerd. Hieruit bleek dat, ondanks de hoge centralisatie graad, de variatie in volume en behandeling tussen de hoofd-hals centra significant verschillend was. In de literatuur wordt een verminderde adherentie aan de richtlijnen genoemd om deze variatie te verklaren met een negatieve invloed op de overleving van patiënten. Binnen het domein *proces* werd de invloed van wachttijd op overleving onderzocht. In de studie zoals opgenomen in dit proefschrift vonden wij een contra-intuïtieve uitkomst, namelijk dat patiënten met de kortste wachttijd ook de slechtste overleving hadden. Deze paradox lijkt verklaard doordat patiënten met snel progressieve tumoren of snel levensbedreigende symptomen als eerste behandeld worden. Uit een daaropvolgende landelijke vervolgstudie² bleek de negatieve invloed van langere wachttijd op overleving aantoonbaar. Aangenomen wordt dat wachttijd een belangrijke kwaliteitsindicator is in de behandeling van hoofd-halskanker patiënten. Naast de wachttijd werd er in dit proefschrift ook aandacht besteed aan de rol van geprotocolleerd uitsnijden van een halsklierdissectiepreparaat. Hoewel wij ons realiseren dat het aantal lymfeklieren in de hals verschilt per patiënt, beperkt gestandaardiseerde chirurgie logischerwijs de variatie in aantallen. Door een wijziging in uitsnijprotocol van een halsklierdissectiepreparaat vond men significant meer lymfeklieren in het preparaat, terwijl het aantal tumor positieve lymfeklieren gelijk bleef.

In de literatuur beschrijven verschillende series de prognostische waarde van de ratio tussen tumor positieve lymfeklieren en het aantal verwijderde lymfeklieren in de hals. Dit wordt de lymfeklierratio genoemd. Door niet gestandaardiseerde chirurgie of pathologie wordt zo'n ratio volstrekt onbetrouwbaar en niet universeel toepasbaar als prognostische factor. Verdere concentratie van hoofd-halsoncologische zorg kan hier een positieve bijdrage aan leveren. Binnen het domein *uitkomst* focust dit proefschrift op een van de meer zeldzamere vormen van hoofd-halskanker, het speekselklier carcinoom. Uit ons onderzoek blijkt dat er in de afgelopen 22 jaar weinig tot geen verbetering in overleving wordt gezien. Bovendien is het aantal speekselklier carcinomen per hoofd-halscentrum dusdanig laag (soms 'slechts' 3 patiënten per jaar), dat er over kwaliteit van zorg geen statistisch valide uitspraken gedaan kunnen worden. Verdere centralisatie lijkt hiervoor een oplossing te kunnen bieden. Kanttekening daarbij is dat maligne speekselkliertumoren voorafgaand aan chirurgie niet altijd te onderscheiden zijn van benigne speekselkliertumoren.

De door de NWHHT geïnitieerde prospectieve landelijke registratie van alle hoofd-halstumoren in de 'Dutch Head and Neck Audit (DHNA)' zal ons meer gedetailleerde informatie verstrekken over de richtlijn adherentie, case-mix verschillen tussen de centra en eventuele verschillen in uitkomsten tussen de centra. Bovenal kan dit tot kritische introspectie leiden, waardoor potentiële verbeterpunten vroegtijdig gesignaleerd worden en als verbeterprojecten opgepakt kunnen worden. Essentiële voorwaarde voor het slagen van zo'n registratie is transparantie van de resultaten van de deelnemende centra.

REFERENTIES

1. Donabedian A. The quality of care. How can it be assessed? JAMA 1988;260:1743-8.
2. van Harten MC, Hoebers FJ, Kross KW, van Werkhoven ED, van den Brekel MW, van Dijk BA. Determinants of treatment waiting times for head and neck cancer in the Netherlands and their relation to survival. Oral Oncol. 2015;51:272-8.

AUTHORS AND AFFILIATIONS

R.J. BAATENBURG DE JONG, MD, PhD.

Department of Head and Neck Surgery and Otorhinolaryngology, Erasmus Medical Center, Rotterdam, The Netherlands

A.J.M. BALM, MD, PhD.

Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute -Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

Department of Oral and Maxillofacial Surgery, Academic Medical Centre, Amsterdam, The Netherlands.

M.W. M. VAN DEN BREKEL, MD, PhD.

Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute -Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

Department of Oral and Maxillofacial Surgery, Academic Medical Centre, Amsterdam, The Netherlands.

Institute of phonetic sciences, University of Amsterdam, Amsterdam, The Netherlands.

E.C. VAN DEN BROEK, MD, PhD.

The nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), Houten, The Netherlands.

H. BOUMAN, MD, PhD.

Department of Head and Neck Surgery and Otorhinolaryngology, Rijnstate hospital, Department of otorhinolaryngology, Arnhem, the Netherlands

B.A.C. VAN DIJK, MD, PhD.

Department of Research, Comprehensive Cancer Organisation (IKNL) The Netherlands, Utrecht, The Netherlands.

Department of Epidemiology, University of Groningen, University Medical Centre, Groningen, The Netherlands.

O. HAMMING-VRIEZE, MD.

Department of Radiation Oncology, The Netherlands Cancer Institute -Antoni van Leeuwenhoek, Amsterdam, The Netherlands

M.C. VAN HARTEN, MD.

Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute -Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

M. HAUPTMANN, MD, PhD.

Department of Epidemiology and Biostatistics, The Netherlands Cancer Institute -Antoni van Leeuwenhoek, Amsterdam, The Netherlands

I. HEGGER.

Department of Pathology, The Netherlands Cancer Institute -Antoni van Leeuwenhoek, Amsterdam, The Netherlands

C.C.M. MARRES, MD.

Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute -Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

A. NAVRAN, MD.

Department of Radiation Oncology, The Netherlands Cancer Institute -Antoni van Leeuwenhoek, Amsterdam, The Netherlands

R.J.E. SEDEE, MD.

Department of Head and Neck Surgery and Otorhinolaryngology, Medical Center Haaglanden, The Hague, The Netherlands

M. SLINGERLAND, MD, PHD.

Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands

L.E. SMEELE, MD, PHD.

Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

Department of Oral and Maxillofacial Surgery, Academic Medical Centre, Amsterdam, The Netherlands.

M.M. STUIVER, MD, PHD.

Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

R.J. TAKES, MD, PHD.

Department of Head and Neck Surgery and Otorhinolaryngology, Radboud University Medical Center, Nijmegen, The Netherlands

C.H.J. TERHAARD, MD, PHD.

Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

M.H. VALSTAR, MD.

Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

Department of Oral and Maxillofacial Surgery, Academic Medical Centre, Amsterdam, The Netherlands.

M..L.F. VAN VELTHUYSEN, MD, PHD.

Department of Pathology Erasmus Medical Centre, Rotterdam, The Netherlands.

J.G.A.M. DE VISSCHER, MD, PHD.

Department of Oral and Maxillofacial Surgery, Medical Center Leeuwarden, Leeuwarden, The Netherlands

S.M. WILLEMS, MD, PHD.

Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands

Department of Pathology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

The nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), Houten, The Netherlands.

M.W.J.M. WOUTERS, MD, PHD.

Department of Surgical Oncology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, The Netherlands.

LIST OF PUBLICATIONS

A Al-Mamgani, M de Ridder, A Navran, WMC Klop, MET Tesselaar, JP de Boer. The impact of cumulative dose of cisplatin on outcome of patients with head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol 2017 in press

MH Valstar*, M de Ridder*, EC van den Broek, MM Stuiver, BAC van Dijk, MLF van Velthuysen, AJM Balm, LE Smeele. Salivary gland pleomorphic adenoma in the Netherlands: A nationwide observational study of primary tumor incidence, malignant transformation, recurrence, and risk factors for recurrence.

Oral Oncology, 2017;66: 93-99

* Both authors contributed equally

M de Ridder, WMC Klop, O Hamming-Vrieze, JP de Boer, B Jasperse, L Smit, W Vogel, MWM van den Brekel, A Al-Mamgani. Unknown primary head and neck squamous cell carcinoma in the era of fluorodeoxyglucose-positron emission tomography/CT and intensity-modulated radiotherapy. Head and Neck 2017;39: 1382-1391

M de Ridder, ZAR Gouw, JJ Sonke, A Navran, B Jasperse, J Heukelom, MET Tesselaar, WMC Klop, MWM van den Brekel, A Al-Mamgani. Recurrent oropharyngeal cancer after organ preservation treatment: pattern of failure and survival. Eur Arch Otorhinolaryngol 2017;274: 1691-1700

M de Ridder, AJM Balm, SM Willems, MWJM Wouters, RJ Baatenburg-de Jong, CHJ Terhaard, RJ Takes, M Slingerland, H Bouman, RJE Sedee, JGAM de Visscher, LE Smeele, BAC van Dijk, on behalf of the Dutch Head and Neck research group. Variation in head and neck cancer care in the Netherlands. A retrospective cohort evaluation of incidence, treatment and outcome. Eur J Surg Oncol 2017 in press

M de Ridder, CCM Marres, LE Smeele, MWM van den Brekel, M Hauptmann, AJM Balm, MLF van Velthuysen. A critical evaluation of lymph node ratio in head and neck cancer. Virchows Arch 2016;469:635-641

M de Ridder, AJM Balm, LE Smeele, MWJM Wouters, BAC van Dijk. An epidemiological evaluation of salivary gland cancer in het Netherlands (1989-2010). Cancer Epidemiology 2015;39:14-20

M de Ridder, LE Smeele, MWM van den Brekel, MC van Harten, MWJM Wouters, AJM Balm. Volume criteria for the treatment of head and neck cancer: are they evidence based? *Head and Neck* 2014;36: 760-762

MC van Harten, M de Ridder, O Hamming-Vrieze, LE Smeele, AJM Balm, MWM van den Brekel. The association of treatment delay and prognosis in head and neck squamous cell carcinoma (HNSCC) patients in a Dutch comprehensive cancer center. *Oral Oncology* 2014;50:282-290

CCM Marres, M de Ridder, I Hegger, MLF van Velthuysen, M Hauptmann, A Navran, AJM Balm. The influence of nodal yield in neck dissections on lymph node ratio in head and neck cancer. *Oral Oncology* 2014;50:59-64

SHPP Roerink, M de Ridder, A Huibers, J Prins, ARMM Hermus, RT Netea-Maier. Screening for psychosocial distress in patients with differentiated thyroid carcinoma: high amounts of distress where everybody expected less. *Acta Oncologica* 2013;52:128-37

M de Ridder, LE Smeele, AJM Balm. Klinische les: Het pleiomorf adenoom van de glandula parotis; regels voor resectie. *Ned Tijdschrift Geneesk* 2012;156:A4662

CURRICULUM VITAE AUCTORIS

Mischa de Ridder is geboren op 26 februari 1986 te Woudenberg, waar hij ook opgroeide. Hij doorliep het Atheneum met de profielen natuur & gezondheid en natuur & techniek op het Ichthus college te Veenendaal. Daarna volgde hij de studie geneeskunde aan de Radboud Universiteit in Nijmegen. Tijdens de studie groeide de interesse voor de oncologische zorg wat er toe leidde dat hij een afsluitend coschap deed in het Antoni van Leeuwenhoek te Amsterdam op de afdeling hoofd-halsoncologie onder leiding van prof.dr. A.J.M. Balm. Direct na het behalen van zijn artsdiploma in december 2011 startte hij als arts-assistent voor de heelkundig oncologische disciplines in het Antoni van Leeuwenhoek onder leiding van dr. J.A van der Hage en dr. W.M.C. Klop. Dit combineerde hij met het promotie-onderzoek naar kwaliteitsindicatoren voor hoofd-halsoncologische zorg in Nederland onder leiding van prof.dr. A.J.M. Balm en prof.dr. L.E. Smeele. In 2014 startte hij met de opleiding tot radiotherapeut-oncoloog in het Academisch Medisch Centrum Amsterdam onder leiding van prof.dr. L.J.A. Stalpers en prof.dr. C.R.N. Rasch.

Hij is getrouwd met Denise de Ridder en heeft drie kinderen Amé (2012), Loudi (2014) en Olav (2016).

DANKWOORD

Graag wil ik iedereen bedanken die heeft bijgedragen aan dit proefschrift.

In het bijzonder,

Promotores,

Prof.dr. A.J.M. Balm, beste Fons, ik ken niemand met zo'n onuitputtelijke bron van energie, enthousiasme, motivatie en tempo. In plaats van terug te schakelen bij tegenslagen werd er na een korte peptalk weer altijd opgeschakeld om op een andere manier het doel te bereiken. Zowel binnen dit project als in de aanloop naar een opleidingsplek kon ik altijd rekenen op uw steun. Ontzettend veel dank daarvoor.

Prof.dr. L.E. Smeele, beste Ludi, de strakke lijnen en heldere boodschap komt grotendeels door jouw kritische commentaar op alle stukken. Ik kan me de afspraken op je kamer in het AMC nog goed herinneren waar je mij leerde om na te denken over wat ik wilde overbrengen om dat vervolgens op een wetenschappelijk verantwoorde manier te verwoorden. Veel dank voor alles.

Co-promotores,

Dr. B.A.C. van Dijk, beste Boukje, dankzij jou ben ik de wondere wereld van de epidemiologie leuk gaan vinden. De dagen in Groningen dat je me alles leerde over de kankerregistratie en epidemiologie zijn dingen die ik de rest van mijn carrière kan gebruiken. Ik hoop nog veel mooie dingen samen te kunnen doen in de toekomst.

Dr. M.W.J.M. Wouters, beste Michel, bedankt voor al je kennis aangaande kwaliteit van zorg. Gaandeweg het project leerde jij mij gelukkig steeds meer begrijpen over dit complexe onderwerp. Bedankt!

Leden van de promotiecommissie,

Prof. dr. M.W.M. van den Brekel, Prof. dr. J. de Lange, Prof. dr. C. Lucas, Prof. dr. M.A.W. Merckx, Prof. dr. C.H.J. Terhaard en Prof. dr. M.J. van de Vijver veel dank voor de tijd die u genomen hebt om het manuscript kritisch te beoordelen.

Alle medeauteurs, bedankt voor alle specifieke expertise en aanvullingen die noodzakelijk zijn geweest om dit proefschrift de vorm te geven die het thans heeft.

Collega's van de afdeling hoofd-halsoncologie van het Antoni van Leeuwenhoek, hoofd-halschirurgen, ANIOS, Marion en Henny bedankt voor alle ondersteuning die nodig was om dit proefschrift af te ronden. In het bijzonder dr. W.M.C. Klop, beste Martin, bedankt voor het zetten richting de radiotherapie, ik kan nu al zeggen dat dit één van de betere keuzes uit mijn carrière is geweest.

Prof. dr. L.J.A. Stalpers en prof.dr. C.R.N. Rasch, allereerst bedankt dat jullie mij willen opleiden in het mooiste medisch specialisme en eveneens bedankt voor de ruimte om dit proefschrift af te ronden tijdens mijn opleiding.

Ook veel dank voor de stafleden radiotherapie en arts-assistenten radiotherapie van het AMC

Als laatste natuurlijk mijn familie en vrienden, waarbij mijn gezin de hoogste plaats verdient.

Lieve Amé, Loudi en Olav, mijn drie plaatjes. Wat was het heerlijk om thuis te komen in een bad van kinderlijke vrolijkheid en de drukte van werken en promoveren (even) vergeten. Ik hou van jullie tot de maan en terug.

Lieve Denise, ik kan wel stellen dat zonder jou dit proefschrift er niet geweest was. Jouw onvoorwaardelijk steun in alles wat ik doe stuwt mij voort. Ik hou van je.