Follow-up after the curative treatment of oral squamous cell carcinoma in the Netherlands

Transition to a personalized approach

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Follow-up after the curative treatment of oral squamous cell carcinoma in the Netherlands

Transition to a personalized approach

Doctoral Thesis

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from Radboud University Nijmegen
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Chapter 1

General introduction

Oral cancer in the Netherlands

In 2017, 3117 patients in the Netherlands were diagnosed with head and neck cancer. The most important subsites of head and neck cancer are the oral cavity, the oropharynx, hypopharynx and the larynx. These subsites have a heterogeneous etiology and treatment.[1] This thesis will focus on oral cavity cancer, of which the incidence is rising. In 2017 902 patients were diagnosed with oral cancer in the Netherlands, which accounts for almost one third of all head and neck cancer cases (Fig. 1).[2] The peak incidence is observed at age 60-70 years. A small majority of patients is male (53%).[2] The most common histological subtype of oral cancer is squamous cell carcinoma (OSCC).[1] The main treatment modality for these patients is surgery, with or without adjuvant radiotherapy or chemotherapy.[1]

In the Netherlands, diagnostics, treatment and follow-up of oral cancer is addressed in the national guideline 'head and neck tumours'.[3] Care for OSCC patients is centralized in the eight University Medical Centres and six affiliated centres, which use the same treatment protocols.[4] Even though care has been centralized, delivering optimal care for patients with oral cancer remains complex due to the high impact treatment has on eating, speaking, swallowing and other aspects of oral function. Therefore, many specialties are involved in care and an integrated approach is essential.[5]

After curative treatment, patients with oral cancer frequently present with new disease. It is common practice to enroll patients treated for OSCC in a follow-up programme. The Dutch guideline recommends a follow-up period of 5 years after treatment.[3] The follow-up is usually done in one of the primary or affiliated medical centres.

The incidence of oral cancer has almost tripled since 1989 and is the subsite within the head and neck area with the highest incidence (Fig. 1).[2] This will have consequences for follow-up as all of these patients will be enrolled in a follow-up programme. In 2017, approximately 3000 patients received care or follow-up for OSCC, and this number is increasing (Fig. 2).[6] Given the potential impact on resources, it is important that follow-up is evidence based.

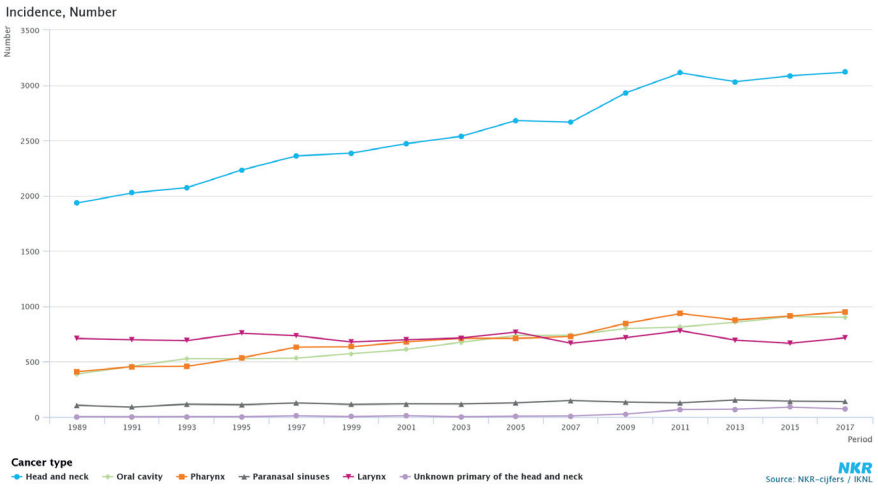

Figure 1. Incidence of oral- and head and neck cancer in the Netherlands in the period 1989-2017.

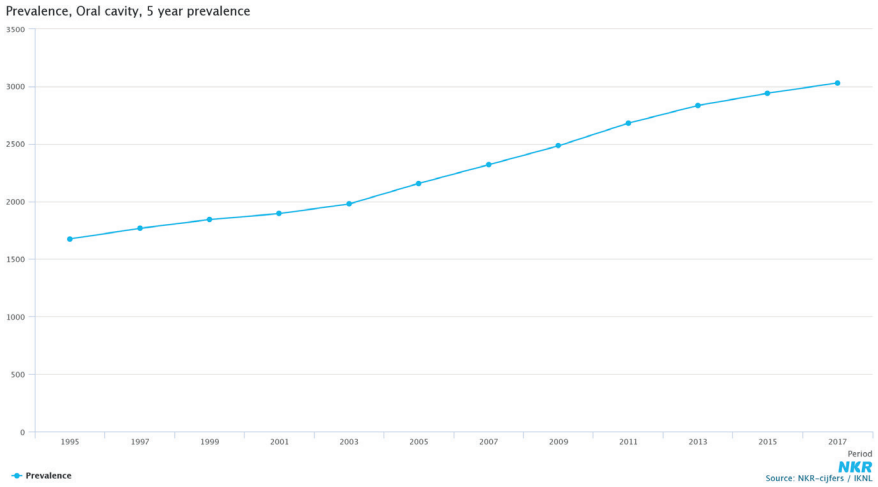

Figure 2. Five-year prevalence of oral cavity cancer in the Netherlands in 1995-2017.

The objectives of routine follow-up after cancer

The Health Council of the Netherlands defines the primary goal of routine follow-up after cancer as limiting the burden of disease for the patient in terms of longevity and quality of life.[7] This is done by regular monitoring of treatment response, early- and late treatment morbidity, and by giving the patient psychological and emotional support.
Another goal is the early detection of new disease. New disease can be a local or regional recurrence of the primary tumour, a second primary tumour or distant metastasis. Second primary tumours can occur at the same site or at a site which is prone to similar risk factors. For example, as head and neck cancer is often caused by smoking with or without excessive alcohol use, patients are also at risk of a second primary cancer in the lungs as the main etiological factor for this is smoking. Patients can also be at risk of a second primary cancer that is caused by their treatment, such as a radiation induced tumour. Routine testing for new disease can be seen as a form of screening. It is essential that follow-up leads to a better outcome for the patient when compared to no follow-up.[7]
The last goal is to evaluate medical treatment and quality of care with the aim to improve treatment for future patients and for training.[7]

The emphasis on the various goals might change over follow-up time. Soon after primary treatment, monitoring early side effects of the treatment will be more important, while later on the detection of second primary tumours may have higher significance.

In the literature on follow-up, the emphasis is most often on the detection of new disease. Crawford et al describe the following requirements for follow-up after cancer.[8] Firstly, the follow-up duration and the interval between the consultations should be determined according to the maximum risk of new disease. Early discovery of new disease should benefit the patients in terms of cure, survival and quality of life. Additional investigations should be done on the basis of the most likely locations of new disease, i.e. should aim at the detection of a second primary tumour or recurrence. In order to avoid false positive results, tests should have high positive and negative predictive values.[8]

Follow-up after oral cancer

The current follow-up guideline for patients curatively treated for oral cancer in the Netherlands includes follow-up examinations every 2-3 months in the first year, every 3 months in the second, every 4-6 months in the third, and biannually in the fourth and fifth year post-treatment.[3] After a disease-free interval of five years, patients can be discharged. At the follow-up visits, history taking and clinical examination, with or without flexible nasoendoscopy are used to detect new disease. In the Netherlands, a routine chest x-ray during follow-up is not performed.[3] Other investigations such as ultrasound and PET-CT are also not routinely used but only on specific indication.[3]

The Dutch guideline is largely based on expert opinion and consensus, and is not site specific for oral cancer.[3] In the guideline it is noted that the value of follow-up for the early detection of new disease depends on a number of parameters including the incidence of new disease; the availability of a cost-effective and accurate diagnostic test with a minimum burden to the patient; the availability of an effective treatment when new disease is diagnosed and if early detection leads to a better prognosis. Finally, the patient should be willing and able to undergo further treatment upon the diagnosis of new disease.[3]

Routine follow-up also has important disadvantages. Hospital visits can be a (psychological) burden to the patient. With an increased number of visits, there is an increased risk of the suspicion of new disease and also an increased risk of false positive tests or incidental findings. Newly found asymptomatic disease can also be incurable, by which patients are burdened with this knowledge prematurely.[8]

Thesis study objectives

In this thesis we aim to provide evidence-based knowledge on follow-up of OSCC and focus on the evaluation of the follow-up programme aiming at the asymptomatic detection of new disease. The other goals of routine follow-up will not be addressed. New disease is defined as local recurrence, regional recurrence, distant metastasis and second primary disease after the treatment of OSCC. The objective of this thesis is to assess who to screen, when to screen and what to screen for during routine follow-up after curative treatment for oral cancer, in order to aid the development of an evidence based follow-up programme after curative treatment for oral cancer. The question on which investigations such as imaging should be used to screen for new disease will not be addressed in this thesis.

To address these objectives, this study will answer the following questions.

1. What is the current evidence base for follow-up after treatment for oral cancer with curative intent?
2. To what extent is the epidemiology of oral cancer in the Netherlands changing and what consequences will this have for the follow-up policy in the Netherlands?
3. What are the time patterns of occurrence of new disease?
4. In what locations does new disease occur?
5. Is it possible to formulate high-risk groups with an increased risk of new disease?

Thesis outline

Chapter two aims to answer the first question by presenting a review of the literature on follow-up guidelines after treatment for OSCC. Insight will be provided on the current evidence base for the duration of follow-up, adherence to follow-up protocols and effectiveness of routine follow-up.
The *third chapter* provides an overview of the incidence, mortality and survival of oral cancer in the Netherlands of patients diagnosed from 1991 to 2010.
The next part of the thesis will address the timing of new disease. The (time) patterns of new disease are essential for the determination of the timing, duration of a follow-up schedule and the tests that are chosen. *Chapter four* investigates the time patterns of recurrences, distant metastasis and second primary tumours in patients curatively treated for OSCC at the Head and Neck Cancer Unit of the Radboud University Medical Centre in Nijmegen, the Netherlands, in 2000-2012. As time progresses, the emphasis of follow-up will be on the early detection of second primary tumours. *Chapter five* assesses the incidence, timing and location of second primary tumours after OSCC in patients treated for OSCC in the Netherlands from 1991-2015.
In the final part of this thesis, we will discuss the consequences to follow-up (*chapter six)* and give suggestions for an evidence-based follow-up programme and for further research on this subject matter (*chapter seven*).

References

1. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet. 2008;371: 1695-1709.
2. Available from www.cijfersoverkanker.nl [accessed 19/8/2019].
3. Dutch Society for Otorhinolaryngology, Head and Neck Surgery. Guideline Head and Neck Tumors. Utrecht: Nederlandse Vereniging voor KNO, 2014.
4. Stichting Oncologische Samenwerking. Multidisciplinaire normering oncologische zorg in Nederland. SONCOS normeringsrapport 7 2019.
5. Licitra L, Keilholz U, Tahara M, et al. Evaluation of the benefit and use of multidisciplinary teams in the treatment of head and neck cancer. Oral Oncol. 2016;59: 73-79.
6. Cancer surveillance comitee of the Dutch Cancer Society. Cancer in the Netherlands up to 2020. Trends and prognosis. Oisterwijk: VDB Almeodeon BV, 2011.
7. Health Council of the Netherlands. Follow-up in oncology. Identify objectives, substantiate actions. The Hague: Health Council of the Netherlands, 2007.
8. Crawford B, Greenberg DD. Introduction to Cancer Surveillance Strategies. In: Johnson FE, editor. Patient surveillance after cancer treatment. New York, Heidelberg, Dordrecht, London: Humana/ Springer, 2013:9-14.

Chapter 2

Follow-up after curative treatment for oral squamous cell carcinoma. A critical appraisal of the guidelines and a review of the literature

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Abstract

The oral cavity is the commonest subsite of head and neck squamous cell carcinoma (HNSCC). Because of the rising incidence and increasing survival, more patients will be enrolled in a routine follow-up program. This review gives an overview of the evidence and guideline recommendations concerning follow-up after oral squamous cell carcinoma (OSCC).

There is limited evidence concerning the effectiveness of follow-up after OSCC. This lack of evidence is reflected in a variation in guideline recommendations with respect to test interval and duration (i.e. for 3-5 years or lifelong).

Most studies on the value of routine follow-up after curative treatment include all HNSCC subsites. The available literature shows, that these subsites have a different timing of recurrence and a different risk of second primary tumours at different locations. This leaves no rationale for applying the same follow-up program to each of the HNSCC subsites. There is agreement in the literature that OSCC follow-up can either be discontinued after two or three years or should be lifelong based on the risk of second primary tumours. Many authors advocate a personalized follow-up regimen that is based on the risk of new disease rather than a one-size-fits-all surveillance program. The literature is conflicting about the survival benefits of asymptomatic detection of new disease for HNSCC.

To aid the development of evidence-based follow-up advise after OSCC, future research should focus on risk stratification, the value of symptom-free detection of recurrences and the active role that patients might play in determining their own follow-up regimen.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the world.[1] The most common subsite in HNSCC is the oral cavity.[1] Worldwide and in the Netherlands, the incidence and survival of oral squamous cell carcinoma (OSCC) has risen in the last years.[1, 2] With a rising incidence and increasing survival, there will be more cancer survivors.[2]

It is common practice to enroll patients treated for OSCC in a routine follow-up program. Routine follow-up after OSCC has several goals: early detection of recurrence or second primary tumours (SPT), monitoring functional rehabilitation, psychological support and quality control. One of the assumptions is that routine follow-up leads to a decreased cancer-specific morbidity, an improved survival or a better functional outcome. However, it has not been proven that clinical- or even more specifically survival benefits exist. Many questions remain unanswered about the optimal duration of the follow-up program and the frequency of follow-up. As a result, follow-up programs differ. In the Netherlands follow-up is addressed in the guideline 'oral cavity- and oropharyngeal carcinoma' which is used nationwide and advises a routine follow-up until 5 years after treatment.[3] Other guidelines advocate lifelong follow-up.[4] As a result of these intensive programs, routine follow-up places a considerable burden on healthcare.[5]

Over the past decade, several reviews have addressed this topic, covering the subject of routine follow-up from the viewpoint of the entire head and neck area.[6-11] These place a great emphasis on imaging during follow-up consultations[6, 7, 10, 12] by extensively discussing the accuracy and value of available tests (e.g. imaging) for routine follow-up. We therefore did not include this subject in our review. As over 90% of OSCC's are squamous cell carcinomas, this review will focus on this histological subtype. This review gives an overview of the current guidelines and their development process and critically reviews the literature on the value of routine follow-up after OSCC from the perspective of early detection of new disease (i.e. recurrences or SPTs).

Materials and methods

Guidelines including recommendations for the follow-up after treatment for OSCC were identified by a Pubmed search using the search terms guideline, follow-up and head and neck cancer. In addition, the Standards and Guidelines Evidence database[13] was searched manually. Eligible for inclusion were guidelines describing

the follow-up of OSCC or HNSCC as a whole. Only guidelines of professional societies or governmental organizations were included. If the search revealed multiple versions of one guideline, only the most recent was included. Five guidelines were identified. The quality of every guideline was assessed independently by two authors (MB and SG) using the AGREE II instrument.[14]

A Pubmed search for English and Dutch language publications concerning follow-up of OSCC published in 1990 to December 2016 was conducted. Case reports, reviews and studies including a histology different from squamous cell carcinoma were excluded. Search terms used were follow-up, surveillance and oral cancer. This rendered 3262 papers. After a selection based on title (43 selected), abstract (23 selected) and full text, 19 articles were considered eligible for review. As this were very few, the search was expanded to include studies that comprised the entire head and neck area, including patients with OSCC. In this search, papers on specific subsites of the head and neck area other than the oral cavity (i.e. larynx, oropharynx, nasopharynx, hypopharynx) were excluded. Search terms used were follow-up, surveillance and head and neck cancer. This search rendered 1872 papers. After a selection based on title (68 selected), abstract (49 selected) and full text, 35 articles were eligible for review. Of these, 5 articles were already identified in the first search. The combined searches led to the inclusion of 49 articles. These articles will be discussed according to the following themes: the duration of follow-up, adherence to follow-up protocols, the value of asymptomatic detection and costs of routine follow-up.

Results

Guidelines

The follow-up recommendations of the five included guidelines are presented in Table 1. The advised length of follow-up varied from 3 years after treatment to lifelong. The AGREE II scores are presented in Table 2. All guidelines were deemed good enough to use, albeit some with modifications. Most guidelines scored high in stating a clear scope and purpose of the guidelines and a clear presentation of the recommendations. The stakeholder involvement, rigor of development, applicability of the recommendations and the editorial independence as assessed by the AGREE II instrument, varied greatly between the guidelines.

Follow-up duration

To determine the duration of routine follow-up, the timing of the occurrence of recurrences or SPTs is pivotal.

Table 1. Guidelines for the follow-up of oral cancer and monthly follow-up interval per year

Guideline	Year	Scope	Year after treatment					
			1	2	3	4	5	>5
Scottish Intercollegiate Guidelines Network (SIGN)	2006 (reviewed in 2012)	Head and neck cancer	"frequently"	"frequently"	"frequently"	-	-	-
National Comprehensive Cancer Network (NCCN)	2016	Head and neck cancer	1-3	2-6	4-8	4-8	4-8	12
Cancer Care Ontario	2009	Head and neck cancer	3	4	6	-	-	-
Dutch Head and Neck Society	2003	Oral oropharyngeal cancer	2-3	3	4-6	6	6	-
Multidisciplinary Guideline of the British Association of Otorhinolaryngology, Head and Neck Surgery (ENT-UK)	2011	Head and neck	2	2	3-6	3-6	3-6	For high risk patients, frequency undetermined

Table 2. Agree scores for the guidelines for the follow-up of oral cancer.

Guideline		Domain						Overall quality (out of 7)
	Appraiser	1	2	3	4	5	6	
Scottish Intercollegiate Guidelines Network (SIGN)	MB	14	21	45	18	27	6	6
	SG	13	19	42	18	25	12	6
	Total domain score	72%	94%	74%	83%	92%	58%	
National Comprehensive Cancer Network (NCCN)	MB	11	10	27	20	6	8	6
	SG	9	13	26	20	6	8	5
	Total domain score	39%	23%	38%	94%	12%	50%	
Cancer Care Ontario	MB	16	13	40	12	10	11	5
	SG	21	10	43	20	5	14	4
	Total domain score	89%	50%	70%	72%	33%	88%	
Dutch Head and Neck Working Group (NHHWG)	MB	21	20	41	15	18	3	6
	SG	21	20	42	19	27	11	6
	Total domain score	100%	94%	60%	77%	77%	33%	
Multidisciplinary Guideline of the British Association of Otorhinolaryngology, Head and Neck Surgery (ENT-UK)	MB	11	16	14	16	21	2	5
	SG	13	12	14	16	5	2	3
	Total domain score	50%	61%	28%	72%	38%	0%	

Domains: 1: Scope and purpose, 2: Stakeholder involvement, 3: Rigour of development, 4: Clarity of presentation, 5: Applicability, 6: Editorial independence. Appraisers: MB: M.T. Brands, SG: S.M.E. Geurts.

Patterns of new disease - recurrences

Sasaki et al found that all recurrences after OSCC were detected within three years after treatment and most (86%) within the first year after treatment.[15] Merkx et al found that 90% of locoregional OSCC recurrences occurred within two years after treatment and found a wider range for the time to the occurrence of SPTs in a cohort of $T_{1\text{-}2}N_0M_0$ oral tongue cancers than more advanced tumours.[16] Wensing et al reported that 83% of OSCC recurrences after a clinically negative neck occurred within two years.[17] Kumar et al found that 82% of the recurrences in the oral cavity occurred within three years, but did not provide recurrence curves with information on the first three years.[18]

Haas et al showed that about 60% of the new tumour manifestations in the head and neck area occurred in the first two years, 30% in years three to five and 10% after five years after initial treatment.[19] Dhooge confirmed that over 90% of recurrences of HNSCCs occurred within the first two years after treatment for the primary tumour.[20] Jung at al did not find a difference in occurrence of new disease between the subsites of the head and neck area.[21] Jung et al observed that 41% of HNSCC patients had a second event in year one, 27% in year two, 14% in year three, 12 in year four, 7% in year five and 1% after five years.[21]

Most studies therefore conclude that follow-up for OSCC can be stopped after the first three years of follow-up.[7, 10, 18, 22, 23] Some authors advocate longer follow-up because of the lifelong risk of SPTs.[24] These differences are also reflected in the follow-up regimens presented in Table 1.

It is tempting to conclude that follow-up after curative treatment for oral cancer to detect recurrences should be terminated after three years. The exact year is difficult to define based on the available literature as the above mentioned studies did not present recurrence curves nor risk of recurrence data for all individual years post-treatment.

Patterns of new disease – second primary tumours

Multiple authors have confirmed that patients with HNSCC have a lifelong risk of a SPT, both within the head and neck area as well as at other locations.[25-27] They reported a cumulative incidence of SPTs varying between 5.3% and 36.0%. The reported annual risks ranged between 1.5% and 3.8%.[28-31] The variation observed might be explained by the differences in definition of SPT and in follow-up time.[25-31]

The incidence of SPT differed between the subsites of the head and neck. Patients with primary OSCC have a relatively low risk of a SPT, while patients with an index tumour of the hypopharynx have the highest risk.[26, 27] Lee at al reported a 5- and 10-year SPT occurrence of 36% and 42% for hypopharyngeal cancer, respectively, 17% and 23% for laryngeal cancer, 15% and 17% in OSCC and 12 and 19% in oropharyngeal cancer.[26] These patterns have been confirmed by Jung et al.[32]

Patients with an index OSCC have, when compared with other HNSCC subsites, the highest risk of a SPT that is located in the head and neck area, a relatively high risk of a SPT that is located in the esophagus and one of the lowest risks of a SPT that is located in the lungs or bronchus.[33-36] These results are confirmed by Jung et al, except for the fact that they found a relatively low risk of a SPT of the

esophagus.[32] Patients with an oropharynx tumour had a significantly lower risk for the development of SPT, probably because of the HPV-related etiology of the tumour.[32, 37] These patients also had a higher chance of developing a tumour at sites that were not related to smoking (i.e. not lung/head and neck).[37] This has been confirmed by other authors.[33]

In conclusion, patients with a HNSCC in general and an OSCC in specific remain lifelong at risk for a SPT. This risk differs according to the index tumour. It is the question whether routine follow-up will benefit these patients. This is a balance between expected gain in survival and quality of life of the patients who will experience new disease versus the unnecessary anxiety and tests patients without new disease will have.

Adherence to follow-up protocols

In order for a guideline to have value, it needs to have good adherence.
The literature reports a difference between the number of visits that the guideline prescribes and the actual number of visits in HNSCC populations.[22, 38, 39] Non-adherence increased after the first year of follow-up in a HNSCC population in the United Kingdom advised to be seen every two months in year one, every four months in year two and every six months in year three-five.[22] Paniello et al observed a good guideline adherence in follow-up years 1-3, where HNSCC patients in the USA are advised to attend 4-12 visits in the first year, 3-6 in the second, 2-4 in the third, 2-3 in the fourth and fifth and once a year after five years of treatment.[40] A small underuse was observed in follow-up years 4-5.[40] Gellrich et al reported that only 50% of patients treated for OSCC in a German hospital regularly received follow-up consultations. The prescribed frequency was 12 visits in the first year, six in the second year, four in the third year, twice in the fourth year and after four years once a year.[41] Agrawal et al found no survival benefit from being compliant to post-treatment surveillance.[42]

A number of researchers have studied which patient-, tumour- and clinician-related factors are associated with non-adherence. An underuse of follow-up visits was observed in patients with low T stage,[22, 38, 40] patients who lived far from the hospital[38] and in patients who continued to smoke.[38] The literature is conflicted about the role of age and treatment modality on guideline compliance.[22, 38] Kerawala et al found that clinicians determined follow-up interval according to tumour stage, site, lymph node status and age of the patient.[43]
Compliance could be improved by a more patient-centered follow-up protocol. In the study of de Zoysa et al this resulted in a higher compliance to follow-up consultations (0 missed vs. 42% missed in the clinician led group).[44]

Clinician related factors may also play a role. Johnson et al concluded that there was a significant variation in follow-up policies in the US.[45] Clark at al found that surgeon age did not significantly influence follow-up policy and explained this by postgraduate education.[46] In the UK, maxillofacial surgeons seemed more inclined to follow their patient lifelong, when compared to ENT surgeons, oncologists or plastic surgeons.[47]

In conclusion, the guidelines for follow-up after HNSCC are not always strictly followed, this is partially caused by clinicians who apply risk stratification in some form in their follow-up consults and partially because of non-compliance by patients.

Effectiveness of routine follow-up

Pick-up rates

A parameter to assess the efficacy of follow-up is the pick-up rate, i.e. the number of consultations it takes to discover one patient with new disease.

Gellrich et al reported that the pick-up rates during OSCC follow-up declined with time after treatment and identified new disease in 1 in 69 consultation in the first year, 1 in 118 consultations in the second year and only 1 in 215 consultations in the third year after treatment.[41] Boysen et al found a pick-up rate of recurrences and SPTs of respectively 1 in 34 and 1 in 110 in patients with OSCC.[48]

The same study reported a pick-up rate of 1 in 36 consults and 1 cure in 113 consults for HNSCC patients.[48] Jung et al found evidence of new disease in one in 79 consultations in HNSCC patients.[21] Other authors found 30 recurrences and 4 SPTs in 1408 visits in a HNSCC population, this results in a pick-up rate of recurrences of about 1 in 47 and 1 in 352 of a SPT. [39] Morris et al found in an analysis of SPTs after HNSCC in the SEER database, that it was necessary for one year to observe 145 patients with an index tumour of the oral cavity to identify one additional lung or bronchus SPT, 86 to identify a new HNSCC, 95 to identify a SPT in the oral cavity or pharynx, 3663 in the oropharynx, 796 in the larynx and 1145 of the hypopharynx.[34] These numbers varied per subsite of the first primary tumour.[34] Pagh et al reported a pick-up rate of one asymptomatic recurrence after HNSCC in 99 consults.[49]

Asymptomatic detection rates

For the OSCC population, no studies were found who determined if the detection of a recurrence or SPT before a patient experiences symptoms also means a better survival, function or quality of life than when detected by the patient.

There are no studies that specifically report the asymptomatic detection rates for an OSCC population. The number of symptom free discoveries in HNSCC patients varies. Kothari et al found that 10% of all HNSCC patients routinely seen were

suspected of having a recurrence.[50] This rose to 68% if a patient requested an extra visit because of new symptoms.
Schwartz et al investigated follow-up in 100 HNSCC patients, their follow-up frequency was highly variable and they found that 86% of the salvageable recurrences were discovered by patient-reported symptoms rather than by test results.[51] Haas et al found that 60% of new tumour manifestations of HNSCC patients were detected at scheduled routine follow-up examinations, of those 40% were symptomatic.[19] Pagh et al found in a population that comprised the entire head and neck area, that the risk of suspicion of recurrence is higher in a patient initiated visit.[39]
Pain was a significant risk factor for both suspicion of recurrence and an actual recurrence.[39] 17% (of 30 in total) patients were asymptomatic.[39] In another study by the same authors, 25% of patients with recurrent disease after HNSCC treatment were asymptomatic.[49] 86% of the symptomatic recurrences were detected at a regular follow-up visit.[49] These rates are similar to those reported by others reporting on HNSCC patients.[20, 42, 52] Smit et al found that 30% of their HNSCC patient cohort suffered an asymptomatic recurrence. 70% of patients with a new disease suffered from pain while only 2% of the matched control group did.[53] The study reported an interval of 4 months from the onset of complaints to the diagnosis of the recurrence.[53] The positive predictive value of patient reported symptoms was 56.3%, the negative predictive value of a patient without symptoms was 99.6%.[50] The absence of pain in HNSCC patients without a recurrence has also been reported by other authors.[52]

Survival benefit of asymptomatic detection

Merkx et al found no significant difference in overall survival between OSCC recurrences detected at a routine follow-up visit versus those detected at a self-initiated visit.[16]
De Visscher et al reported in a cohort of HNSCC patients (treated from 1979 to 1983) that the mean survival after detection of these events was significantly better with routine follow-up than with self-referral ($p<0.05$).[54] These findings are not supported by all studies. In a cohort of stage III/IV HNSCC patients, no significant difference in disease free or overall survival between the symptom-based routine follow-up and physician detected recurrence groups.[55] Agrawal et al found no difference in survival according to mode of detection.[42]

In conclusion, reported pick-up rates vary greatly. It is plausible that the pick-up rates are higher in the first years after treatment. The survival benefit for OSCC does not seem to exist, the literature on HNSCC remains conflicted. This is an argument in favor of limiting the duration of follow-up after OSCC.

Cost-effectiveness of follow-up

We found no studies that addressed the cost-effectiveness of OSCC or HNSCC follow-up. However, two studies were found who determined its costs. Virgo et al investigated the reimbursement charges for 5-year follow-up for HNSCC or its subsites for the US situation in 1992 for 31 different follow-up strategies reported in the literature.[56] The charges of OSCC-specific follow-up schedules varied between $2,396 and $3,630 per patient, under the assumption of complete follow-up. The costs of generic HNSCC follow-up schedules varied between $1,198 and $7,526 per patient. Translating these generic figures to the annual patient cohort and adjusting for survival figures led to 5-year HNSCC follow-up charges varying from $68 to $429 million. The estimated costs of detecting one recurrence varied from $2,587-$49,242.[56] Based on a retrospective study in the Netherlands, van Agthoven et al estimated the average hospital costs of diagnosis, treatment and 2-year follow-up of OSCC and HNSCC in 1996 at 25,096€ and 21,581€ per new patient, respectively.[57] Furthermore, they estimated the average costs of 3- to 10-year follow-up for OSCC and HNSCC both at 423€ per new patient, this estimate consisted mainly of specialist costs and did not include the costs of unnecessary diagnostic procedures.[57]

In conclusion, the economic burden and cost-effectiveness of OSCC follow-up has been poorly studied. It is not possible to make a statement about the cost-effectiveness of follow-up due to lack of data.

Discussion

This review gives an overview of the current literature on follow-up after OSCC treatment. There is limited evidence base for follow-up after the curative treatment of HNSCC in general and OSCC in specific. The studies available are mostly about the entire head and neck area and have a low level of evidence. No randomized clinical trials on the survival benefits of follow-up were found. The literature shows distinctly different outcomes for effectiveness indicators, the most important being the survival benefit of follow-up and treatment outcome after salvage therapy. The literature is ambiguous with respect to effects on survival benefits and is difficult to interpret because it comprises the entire, very heterogeneous, head and neck area.[12, 16] Positive and negative effects were found in low-level evidence, this points in the direction that follow-up has no effect on survival. The observed benefit might be biased by study design and length time bias.
The lack of evidence is reflected in current guidelines. Guidelines, especially those of poor quality, have to be treated very carefully because they might create

liabilities. The poor quality of the guidelines may also be caused by a poor quality of the development process, reflected by the low AGREE scores.

In response to our findings we would like to advice several directions for future research to answer the question how long and how frequent patients should be followed after the end of treatment and which patient groups might or might not benefit from follow-up.

Ideally, the timing and duration of routine follow-up depends on the timing and risks of recurrences and SPTs. This can be extracted from recurrence curves, providing risks for all possible follow-up periods. Unfortunately, most studies did not report recurrence curves, but rather reported a time span within which the recurrences occurred. Because the reported time-spans differed between studies, a comparison between studies was difficult. However, all published studies showed that most recurrences after OSCC occurred in 2-3 years post-treatment.
A methodological difficulty in comparing studies is that almost all studies use different definitions of SPT. We found five different interpretations of the Warren and Gates criteria.[58] Another problem with interpreting the cumulative incidence rates and site distribution patterns of SPTs is that some studies only take SPTs in the head and neck area into account while others also describe SPTs in other sites such as the lung.
All studies confirmed that the head and neck is a heterogeneous area with a variation in the time of recurrence and survival after recurrence that seems to be influenced by location. This is partially caused by different anatomical barriers and lymphatic drainage patterns that make salvage surgery impossible.[59] This incidence and subsite of SPTs also differs greatly between the sites of the first primary tumour.[34] Lester et al reported that 95% of recurrences of larynx carcinomas occurred in 4.7 years.[60] They also found that late stage oropharyngeal cancer had a wider range of recurrence (0.2-4.7 years) than early stage oropharyngeal cancer (0.2-1.7 years).[60] This difference in patterns of new disease makes a guideline for follow-up that covers the entire head and neck area simply impossible.

There are indications that it is possible to identify groups that, regardless of being detected early, will not have any survival benefit from routine follow-up after curative treatment for OSCC. This is partially caused by the fact that in case of recurrence, there is no curative treatment available.[51, 61-63] This is confirmed by Cooney and Poulson who found that in stage III or IV HNSCC, fewer than 50% patients with recurrence were given salvage treatment, with a success rate lower than 5%.[63] Another study found that in patients with stage III/IV HNSCC treated

with multiple treatment modalities, routine follow-up had no significant influence in improving survival after recurrence.[55] The authors concluded that in this patient group routine follow-up did not improve disease free or overall survival.[55] This is in line with the findings of Ritoe et al who concluded that a routine follow-up program did not lead to survival benefits in patients with an asymptomatic recurrence of a laryngeal carcinoma.[64]
Goodwin performed a meta-analysis of 32 studies in order to estimate the effect of salvage surgery in patients with HNSCC.[65] He concluded that the average 5-year survival was 39% and that the success of salvage surgery was limited in stage III and IV recurrences.[65] Boysen et al reported that initial earlier stage HNSCCs are more likely to be successfully salvaged.[48] This has been confirmed by other authors.[42]
Another important factor for unsuccessful treatment of a recurrence is the disease free interval.[65] Kowalski et al reported a marked difference between patients who had their recurrence within and beyond the first six months after treatment (5Y OS was 0% vs. 22.5%). This observation was confirmed by other authors.[51, 66] Gleich et al however reported that the disease free interval was not significant in a group of HNSCC patients who initially had T3-4 tumours.[62] Prior early stage disease proved beneficial to survival in another study.[42] Patient related factors such as performance status, comorbidities and quality of life also influence the success of salvage surgery.[59] Previous treatment is also of importance. Patients who have had a previous neck dissection have a worse overall survival after a neck recurrence.[67, 68] HNSCC patients who have had previous surgery and radiotherapy have a very small chance of successful salvage.[62, 69] Surgery as treatment of the recurrence is linked to a better prognosis.[70]

The variation in the literature in follow-up schedules and protocols, make it difficult to calculate the economic burden of follow-up. Virgo et al noted in this context that there is no support in the literature for a higher efficacy of protocols with and without frequent additional tests. They therefore recommend a “minimalist approach” where test are only done based on clinical indicators of recurrence.[56]
It is important to remark that most studies that are conducted on the economic burden of follow-up are based on US data. As the economic burden of follow-up is determined by factors that vary from country to country it is important that more research is done on this subject in Europe.[71]

The optimal follow-up regimen should be based on the length of the preclinical detectable phase, the timing and risk of new disease and the burden of routine testing, aspects for which there is hardly any data available. Furthermore it has to be realistic for patients to be compliant to. If the schedule is too demanding and

patients will not visit, no disease will be detected.[41] Trinidade conducted a survey on HNSCC patients' opinions concerning follow-up in a non-validated patient questionnaire and found that 84% of patients found their follow-up visits too frequent. They suggest a more personalized approach in determining the follow-up schedule, without going into specifics.[72] A majority of patients would prefer a symptom driven follow-up system where the clinical nurse specialist would be the first to contact.[72]

As the evidence is limited, it is not possible to give definitive advice for follow-up after curative treatment for OSCC. One could either wait for more evidence to come available before changing the guidelines, or change the follow-up policy based on the sparse information there is. Follow-up for recurrences could for example be limited to 2 years after treatment and one could refrain from life-long follow-up to detect SPTs until enough evidence on its (cost-)effectiveness is available. The latter approach is in line with population screening. It is up to the local- and national guideline committees to weigh the expected benefits, harms and costs of routine follow-up in their institution or country.
If a shorter follow-up program is chosen, it is advisable to include education of patients about the symptoms of new disease. Patients that are no longer in follow-up should have easy access to the clinic if they have symptoms. Education on symptoms of new disease has already been proven successful in improving patient compliance with follow-up.[44] Longer follow-up may be indicated according to the patients' physical and psychosocial needs.

Another important reason for follow-up is the monitoring of treatment related functional and psychological morbidity. We found no studies that related quality of life or functional outcome to follow-up. The longer a patient is in follow-up, the more the focus shifts to functional problems instead of the detection of new disease.[73] Pagh et al found that no new treatment-related morbidity was discovered after 3.5 years.[39] This shift emphasizes the importance of the other members of the multidisciplinary team such as dentists and speech and language therapists.[73] Needs of HNSCC patients during a follow-up consult differ between subsites and cancer stage.[73] For example the main concern that early stage patients would like to discuss during a follow-up consult is the fear of recurrence, while this was only one of the many problems that late-stage head and neck cancer patients wanted to discuss.[73] This also holds true for site-specific functional problems. A patient who has had a total laryngectomy will, for example, have other needs than a patient who has had a partial maxillectomy. Therefore, site specific recommendations are essential.

We envisage a follow-up program where, if the chances of finding new disease are small, the patient is no longer necessarily seen by the surgeon, but according to the individual patients needs only by a clinical nurse specialist or a dentist. Trials with nurse-led follow-up have led to better patient satisfaction when compared to physician-led follow-up.[74, 75]

Conclusion

This review highlights the lack of high quality evidence on OSCC follow-up. The available evidence is insufficient to design the optimal follow-up schedule. There is no evidence to continue follow-up beyond two years from a survival point of view. Further research should focus on stratification of the risk of new disease for the specific subsites of the head and neck area, the relevance of symptom free discovery for survival and the active role that patients might play in determining their own follow-up regimen. This will aid the development of an evidence based and patient-tailored follow-up regimen specifically for the oral cavity.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66: 7-30.
2. van Dijk BA, Brands MT, Geurts SM, Merkx MA, Roodenburg JL. Trends in oral cavity cancer incidence, mortality, survival and treatment in the Netherlands. Int J Cancer. 2016;139: 574-583.
3. Nederlandse Werkgroep Hoofd/halstumoren Richtlijn Mondholte- en Orofarynxcarcinoom Alphen aan den Rijn: Van Zuiden communications B.V., 2004.
4. NCCN. NCCN Clinical Practice Guidelines in Oncology. Version 2.2016 — October 11, 20162016.
5. De Paepe A, Vandeneede N, Strens D, Specenier P. Medical Cost Associated with Treatment and Follow-Up of Pantients with Head and Neck Cancer. Value Health. 2015;18: A449.
6. Denaro N, Merlano MC, Russi EG. Follow-up in Head and Neck Cancer: Do More Does It Mean Do Better? A Systematic Review and Our Proposal Based on Our Experience. Clin Exp Otorhinolaryngol. 2016;9: 287-297.
7. Digonnet A, Hamoir M, Andry G, et al. Post-therapeutic surveillance strategies in head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol. 2013;270: 1569-1580.
8. Kawecki A, Krajewski R. Follow-up in patients treated for head and neck cancer. Memo. 2014;7: 87-91.
9. Kazi R, Manikanthan K, Pathak KA, Dwivedi RC. Head and neck squamous cell cancers: need for an organised time-bound surveillance plan. Eur Arch Otorhinolaryngol. 2010;267: 1969-1971.
10. Manikantan K, Khode S, Dwivedi RC, et al. Making sense of post-treatment surveillance in head and neck cancer: when and what of follow-up. Cancer Treat Rev. 2009;35: 744-753.
11. Morton RP, Hay KD, Macann A. On completion of curative treatment of head and neck cancer: why follow up? Curr Opin Otolaryngol Head Neck Surg. 2004;12: 142-146.
12. Liu G, Dierks EJ, Bell RB, Bui TG, Potter BE. Post-therapeutic surveillance schedule for oral cancer: is there agreement? Oral Maxillofac Surg. 2012;16: 327-340.
13. http://www.cancerview.ca/TreatmentAndSupport/GRCMain/GRCSAGE/GRCSAGESearch/.
14. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182: E839-842.
15. Sasaki M, Aoki T, Karakida K, et al. Postoperative follow-up strategy in patients with oral squamous cell carcinoma. J Oral Maxillofac Surg. 2011;69: e105-111.
16. Merkx MA, van Gulick JJ, Marres HA, et al. Effectiveness of routine follow-up of patients treated for T1-2N0 oral squamous cell carcinomas of the floor of mouth and tongue. Head Neck. 2006;28: 1-7.
17. Wensing BM, Merkx MA, Krabbe PF, Marres HA, Van den Hoogen FJ. Oral squamous cell carcinoma and a clinically negative neck: the value of follow-up. Head Neck. 2011;33: 1400-1405.
18. Kumar R, Putnam G, Dyson P, Robson AK. Can head and neck cancer patients be discharged after three years? J Laryngol Otol. 2013;127: 991-996.
19. Haas I, Hauser U, Ganzer U. The dilemma of follow-up in head and neck cancer patients. Eur Arch Otorhinolaryngol. 2001;258: 177-183.
20. Dhooge IJ, De Vos M, Van Cauwenberge PB. Multiple primary malignant tumors in patients with head and neck cancer: results of a prospective study and future perspectives. Laryngoscope. 1998;108: 250-256.
21. Jung YH, Song CM, Park JH, et al. Efficacy of current regular follow-up policy after treatment for head and neck cancer: Need for individualized and obligatory follow-up strategy. Head Neck. 2014;36: 715-721.
22. Kanatas A, Bala N, Lowe D, Rogers SN. Outpatient follow-up appointments for patients having curative treatment for cancer of the head and neck: are the current arrangements in need of change? Br J Oral Maxillofac Surg. 2014;52: 681-687.
23. O'Meara WP, Thiringer JK, Johnstone PA. Follow-up of head and neck cancer patients post-radiotherapy. Radiother Oncol. 2003;66: 323-326.
24. Boysen M, Natvig K, Winther FO, Tausjo J. Value of routine follow-up in patients treated for squamous cell carcinoma of the head and neck. J Otolaryngol. 1985;14: 211-214.

25. van der Haring IS, Schaapveld MS, Roodenburg JL, de Bock GH. Second primary tumours after a squamous cell carcinoma of the oral cavity or oropharynx using the cumulative incidence method. Int J Oral Maxillofac Surg. 2009;38: 332-338.
26. Lee DH, Roh JL, Baek S, et al. Second cancer incidence, risk factor, and specific mortality in head and neck squamous cell carcinoma. Otolaryngol Head Neck Surg. 2013;149: 579-586.
27. Chuang SC, Scelo G, Tonita JM, et al. Risk of second primary cancer among patients with head and neck cancers: A pooled analysis of 13 cancer registries. Int J Cancer. 2008;123: 2390-2396.
28. Leon X, Martinez V, Lopez M, Garcia J, Quer M. Risk of third and fourth tumors in patients with head and neck cancer. Head Neck. 2010;32: 1467-1472.
29. Day GL, Blot WJ, Shore RE, et al. Second cancers following oral and pharyngeal cancer: patients' characteristics and survival patterns. Eur J Cancer B Oral Oncol. 1994;30B: 381-386.
30. Day GL, Blot WJ. Second primary tumors in patients with oral cancer. Cancer. 1992;70: 14-19.
31. Cianfriglia F, Di Gregorio DA, Manieri A. Multiple primary tumours in patients with oral squamous cell carcinoma. Oral Oncol. 1999;35: 157-163.
32. Jung YS, Lim J, Jung KW, Ryu J, Won YJ. Metachronous Second Primary Malignancies after Head and Neck Cancer in a Korean Cohort (1993-2010). PLoS One. 2015;10: e0134160.
33. Jegu J, Binder-Foucard F, Borel C, Velten M. Trends over three decades of the risk of second primary cancer among patients with head and neck cancer. Oral Oncol. 2013;49: 9-14.
34. Morris LG, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol. 2011;29: 739-746.
35. Chen MC, Chen PT, Chan CH, et al. Second primary esophageal or lung cancer in patients with head and neck carcinoma in Taiwan: incidence and risk in relation to primary index tumor site. J Cancer Res Clin Oncol. 2011;137: 115-123.
36. Haughey BH, Gates GA, Arfken CL, Harvey J. Meta-analysis of second malignant tumors in head and neck cancer: the case for an endoscopic screening protocol. Ann Otol Rhinol Laryngol. 1992;101: 105-112.
37. Gan SJ, Dahlstrom KR, Peck BW, et al. Incidence and pattern of second primary malignancies in patients with index oropharyngeal cancers versus index nonoropharyngeal head and neck cancers. Cancer. 2013;119: 2593-2601.
38. Deutschmann MW, Sykes KJ, Harbison J, Cabrera-Muffly C, Shnayder Y. The impact of compliance in posttreatment surveillance in head and neck squamous cell carcinoma. JAMA Otolaryngol Head Neck Surg. 2015;141: 519-525.
39. Pagh A, Grau C, Overgaard J. A longitudinal study of follow-up activities after curative treatment for head and neck cancer. Acta Oncol. 2015;54: 813-819.
40. Paniello RC, Virgo KS, Johnson MH, Clemente MF, Johnson FE. Practice patterns and clinical guidelines for posttreatment follow-up of head and neck cancers: a comparison of 2 professional societies. Arch Otolaryngol Head Neck Surg. 1999;125: 309-313.
41. Gellrich NC, Schramm A, Bockmann R, Kugler J. Follow-up in patients with oral cancer. J Oral Maxillofac Surg. 2002;60: 380-386; discussion 387-388.
42. Agrawal A, Hammond TH, Young GS, Avon AL, Ozer E, Schuller DE. Factors affecting long-term survival in patients with recurrent head and neck cancer may help define the role of post-treatment surveillance. Laryngoscope. 2009;119: 2135-2140.
43. Kerawala CJ, Newlands C, Coombes D. Follow-up after treatment of squamous cell carcinoma of the oral cavity: current maxillofacial practice in the United Kingdom. Br J Oral Maxillofac Surg. 2007;45: 361-363.
44. De Zoysa N, Lee A, Joshi A, et al. Developing a follow-up surveillance protocol in head and neck oncological surgery: enhanced 'traffic light' surveillance - a prospective feasibility study. Clin Otolaryngol. 2017;42: 446-450.
45. Johnson FE, Johnson MH, Clemente MF, Paniello RC, Virgo KS. Geographical variation in surveillance strategies after curative-intent surgery for upper aerodigestive tract cancer. Ann Surg Oncol. 2006;13: 1063-1071.

46. Clark JG, Virgo KS, Clemente MF, Johnson MH, Paniello RC, Johnson FE. How surgeon age affects posttreatment surveillance strategies for upper aerodigestive tract cancer patients. Am J Otolaryngol. 1999;20: 217-222.
47. Joshi A, Calman F, O'Connell M, Jeannon JP, Pracy P, Simo R. Current trends in the follow-up of head and neck cancer patients in the UK. Clin Oncol (R Coll Radiol). 2010;22: 114-118.
48. Boysen M, Lovdal O, Tausjo J, Winther F. The value of follow-up in patients treated for squamous cell carcinoma of the head and neck. Eur J Cancer. 1992;28: 426-430.
49. Pagh A, Vedtofte T, Lynggaard CD, et al. The value of routine follow-up after treatment for head and neck cancer. A national survey from DAHANCA. Acta Oncol. 2013;52: 277-284.
50. Kothari P, Trinidade A, Hewitt RJD, Singh A, O'Flynn P. The follow-up of patients with head and neck cancer: an analysis of 1,039 patients. Eur Arch Otorhinolaryngol. 2011;268: 1191-1200.
51. Schwartz DL, Barker J, Jr., Chansky K, et al. Postradiotherapy surveillance practice for head and neck squamous cell carcinoma--too much for too little? Head Neck. 2003;25: 990-999.
52. Agrawal A, deSilva BW, Buckley BM, Schuller DE. Role of the physician versus the patient in the detection of recurrent disease following treatment for head and neck cancer. Laryngoscope. 2004;114: 232-235.
53. Smit M, Balm AJ, Hilgers FJ, Tan IB. Pain as sign of recurrent disease in head and neck squamous cell carcinoma. Head Neck. 2001;23: 372-375.
54. de Visscher AV, Manni JJ. Routine long-term follow-up in patients treated with curative intent for squamous cell carcinoma of the larynx, pharynx, and oral cavity. Does it make sense? Arch Otolaryngol Head Neck Surg. 1994;120: 934-939.
55. Flynn CJ, Khaouam N, Gardner S, et al. The value of periodic follow-up in the detection of recurrences after radical treatment in locally advanced head and neck cancer. Clin Oncol (R Coll Radiol). 2010;22: 868-873.
56. Virgo KS, Paniello RC, Johnson FE. Costs of posttreatment surveillance for patients with upper aerodigestive tract cancer. Arch Otolaryngol Head Neck Surg. 1998;124: 564-572.
57. van Agthoven M, van Ineveld BM, de Boer MF, et al. The costs of head and neck oncology: primary tumours, recurrent tumours and long-term follow-up. Eur J Cancer. 2001;37: 2204-2211.
58. Warren S, Gates L. Multiple malignant tumors, a survey of the literature and statistical study. Am J Cancer. 1932;16: 1358-1414.
59. Ho AS, Kraus DH, Ganly I, Lee NY, Shah JP, Morris LG. Decision making in the management of recurrent head and neck cancer. Head Neck. 2014;36: 144-151.
60. Lester SE, Wight RG. 'When will I see you again?' Using local recurrence data to develop a regimen for routine surveillance in post-treatment head and neck cancer patients. Clin Otolaryngol. 2009;34: 546-551.
61. Agra IM, Filho JG, Martins EP, Kowalski LP. Second salvage surgery for re-recurrent oral cavity and oropharynx carcinoma. Head Neck. 2010;32: 997-1002.
62. Gleich LL, Ryzenman J, Gluckman JL, Wilson KM, Barrett WL, Redmond KP. Recurrent advanced (T3 or T4) head and neck squamous cell carcinoma: is salvage possible? Arch Otolaryngol Head Neck Surg. 2004;130: 35-38.
63. Cooney TR, Poulsen MG. Is routine follow-up useful after combined-modality therapy for advanced head and neck cancer? Arch Otolaryngol Head Neck Surg. 1999;125: 379-382.
64. Ritoe SC, Krabbe PF, Kaanders JH, van den Hoogen FJ, Verbeek AL, Marres HA. Value of routine follow-up for patients cured of laryngeal carcinoma. Cancer. 2004;101: 1382-1389.
65. Goodwin WJ, Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope. 2000;110: 1-18.
66. Agra IM, Carvalho AL, Ulbrich FS, et al. Prognostic factors in salvage surgery for recurrent oral and oropharyngeal cancer. Head Neck. 2006;28: 107-113.
67. Kowalski LP. Results of salvage treatment of the neck in patients with oral cancer. Arch Otolaryngol Head Neck Surg. 2002;128: 58-62.
68. Wong LY, Wei WI, Lam LK, Yuen AP. Salvage of recurrent head and neck squamous cell carcinoma after primary curative surgery. Head Neck. 2003;25: 953-959.

69. Argiris A, Li Y, Forastiere A. Prognostic factors and long-term survivorship in patients with recurrent or metastatic carcinoma of the head and neck. Cancer. 2004;101: 2222-2229.
70. Lim JY, Lim YC, Kim SH, Byeon HK, Choi EC. Factors predictive of successful outcome following salvage treatment of isolated neck recurrences. Otolaryngol Head Neck Surg. 2010;142: 832-837.
71. Wissinger E, Griebsch I, Lungershausen J, Foster T, Pashos CL. The economic burden of head and neck cancer: a systematic literature review. Pharmacoeconomics. 2014;32: 865-882.
72. Trinidade A, Kothari P, Andreou Z, Hewitt RJ, O'Flynn P. Follow-up in head and neck cancer: patients' perspective. Int J Health Care Qual Assur. 2012;25: 145-149.
73. Kanatas A, Ghazali N, Lowe D, et al. Issues patients would like to discuss at their review consultation: variation by early and late stage oral, oropharyngeal and laryngeal subsites. Eur Arch Otorhinolaryngol. 2013;270: 1067-1074.
74. de Leeuw J, Prins JB, Teerenstra S, Merkx MA, Marres HA, van Achterberg T. Nurse-led follow-up care for head and neck cancer patients: a quasi-experimental prospective trial. Support Care Cancer. 2013;21: 537-547.
75. Wells M, Semple CJ, Lane C. A national survey of healthcare professionals' views on models of follow-up, holistic needs assessment and survivorship care for patients with head and neck cancer. Eur J Cancer Care (Engl). 2015;24: 873-883.

Chapter 3

Trends in oral cavity cancer incidence, mortality, survival and treatment in the Netherlands

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Abstract

Information on epidemiology is essential to evaluate care for the growing group of oral cancer patients. We investigated trends in incidence, mortality and relative survival rates for oral cavity cancer (OCC) and its subsites in the Netherlands from 1991–2010, and relate these to changes in stage and treatment.

Patient (age, sex), tumour (subsite, stage) and treatment characteristics of patients diagnosed with OCC (ICD-O-3: C02-C06) in 1991–2010 were extracted from the Netherlands Cancer Registry. Incidence, mortality and 5-year relative survival rates over time are presented, as well as trends in type of treatment.

The incidence of OCC increased with +1.2% (95%CI: +0.9%;+1.6%) per year: more strongly in women, stage I and IV disease, and in cancers of the tongue and gum. The mortality rate slightly rose (+0.8%, 95%CI: +0.3%;+1.3% per year), but differed by subsite. The 5-year relative survival improved from 57% in 1991-1995 to 62% in 2006-2010. The 5-year relative survival was better for women compared with men (64% and 55%, respectively), decreased with increasing stage, was the best for tongue cancer (63%) and the worst for cancer of the gum (56%) and floor of mouth cancer (55%). The relative excess risk of dying was higher for non-surgery-based treatments. Surgery was the main treatment option and the proportion of “surgery only” rose in stage I and III disease.

The incidence and, to a lesser extent, mortality of OCC are increasing and therefore, even with slightly improving survival rates, OCC is an increasingly important health problem.

Introduction

The incidence of oral cavity cancer (OCC) is increasing and has replaced laryngeal cancer as the most frequently occurring cancer in the head and neck area in the Netherlands.[1, 2] Between 1989 and 2011, the absolute number of OCCs has doubled, whereas the overall occurrence of cancer of the head and neck has risen less fast. In 2011, roughly one in three head and neck cancer cases was OCC compared with one in four in 1989.[2] These changes are also observed in other European countries and the world.[3, 4] Fortunately, mortality rates did not rise at the same pace.[1]

Changes in incidence, mortality and survival may reflect changes in risk factors, diagnostics, staging and treatment.[5] Several of these factors have changed for OCC over the past decades. The main risk factors for OCC are smoking and alcohol consumption, with a combined multiplicative effect.[6] Therefore, the increase in OCC in women was explained by the increase of smoking among women.[4] Even though staging of OCC has not fundamentally changed, the introduction of fine needle aspiration (FNA) and improvement of imaging such as MRI and CT[7] may have led to increased detection and more detailed staging of cancers. Examples of changes in treatment include the abandoning the elective neck dissection of the clinically negative neck for small tumours in favour of ultrasound guided follow-up of the neck.[2, 8, 9] Also, postoperative chemoradiation was introduced for patients with positive resection margins and extranodal growth.[7, 10, 11]

Monitoring the trends in OCC is essential for policy decisions towards optimized prevention, treatment and surveillance care for the growing group of patients.[12] Most studies report on head and neck cancer or oral and oropharyngeal cancer combined, but this is a heterogeneous group with regards to aetiology, treatment and prognosis. Furthermore, few studies presented specific analyses for subsites[1] or on treatment changes.

In this study we report trends in incidence, mortality and relative survival rates for OCC and its subsites in the Netherlands from 1991-2010 and relate these to changes in stage and treatment.

Materials and methods

Patients

All primary epithelial (excluding melanoma, sarcoma, haematological malignancies) OCC diagnosed between 1991 and 2010 were extracted from the Netherlands Cancer Registry (NCR). The Netherlands Cancer Registry covers all residents of the Netherlands. The registry receives lists of all newly diagnosed cancers from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) and receives cancer-related hospital discharge records from Dutch Hospital Data. Following notification, trained tumour registration clerks extract patient, tumour and treatment characteristics from the hospital records. The completeness of the Netherlands Cancer Registry was estimated to be at least 95%.[13] Vital status and date of death were obtained by linkage to the municipal records on December 31st, 2013.

Definitions

Topography was coded according to the international classification of diseases for oncology (ICD-O-3).[14] The following subsites were included: tongue (C02), gum (C03), floor of mouth (FOM) (C04), palate (C05) and mouth, not otherwise specified (C06). Histology was coded according to the ICD-O-3 morphology coding and subdivided into squamous cell carcinoma (M8050–M8084) or other.

Tumour stage was recorded using the International Union against Cancer (UICC) TNM classification according to the 4th, fully revised edition from 1989–1992, the 4th edition 2nd revision from 1993–1998, the 5th edition from 1999–2002, the 6th edition from 2003–2009 and the 7th edition in 2010. Stage IV was additionally subdivided according to the presence of distant metastasis at diagnosis. There were no relevant changes in stage classification over this time period.

To evaluate changes over time, four 5-year periods were defined: 1991–1995, 1996–2000, 2001–2005 and 2006–2010. Patients were classified into age groups; 45 years and younger, 46–60 years, 61–75 years and older than 75 years at diagnosis.

Statistical analysis

European standardised rates (ESR) for incidence and mortality were calculated for 1989–2012 (years with information available), using reference data from Statistics Netherlands.

Using the Joinpoint Regression Program, (Version 3.5.3. May 2012; Statistical Research and Applications Branch, National Cancer Institute), the estimated annual percentage change (EAPC) over the standardised incidence and mortality rates (ESR) was calculated using the log-linear model, allowing for a maximum of four joinpoints.[15]

Table 1. Patient (N=13,108) and tumour (N=13,399) characteristics for oral cavity cancer patients diagnosed in the Netherlands in 1991-2010.

		Total		1991-1995		1996-2000		2001-2005		2006-2010	
		N	column%	N	column%	N	column%	N	column%	N	column%
Total	Tumours	13,399		2,697		3,069		3,570		4,063	
	Patients	13,108		2,665		3,007		3,489		3,947	
Sex	Male	7,588	57.9	1,604	60.2	1,714	57.0	2,002	57.4	2,268	57.5
	Female	5,520	42.1	1,061	39.8	1,293	43.0	1,487	42.6	1,679	42.5
Age	<=45 years	1,140	8.7	293	11.0	252	8.4	302	8.7	293	7.4
	46-60 years of age	4,808	36.7	945	35.5	1,154	38.4	1,369	39.2	1,340	34.0
	61-75 years of age	4,854	37.0	968	63.3	1,087	36.2	1,223	35.1	1,576	39.9
	>75 years of age	2,306	17.6	459	17.2	514	17.1	595	17.1	738	18.7
Morphology	Squamous cell carcinoma	12,517	93.4	2,525	93.6	2,857	93.1	3,323	93.1	3,812	93.8
	Other	882	6.6	172	6.4	212	6.9	247	6.9	251	6.2
Stage	I	4,514	33.7	841	31.2	981	32.0	1,220	34.1	1,472	36.2
	II	2,239	16.7	522	19.4	511	16.7	558	15.6	648	16.0
	III	1,612	12.0	327	12.1	377	12.3	466	13.1	442	10.9
	IV M0	4,550	34.0	877	32.5	1,081	35.2	1,202	33.7	1,390	34.2
	IV M1	158	1.2	27	1.0	31	1.0	50	1.4	50	1.2
	Unknown	326	2.4	103	3.8	88	2.9	74	2.1	61	1.5
Subsite	Tongue	4,411	32.9	846	31.4	925	30.1	1,220	34.2	1,420	35.0
	Gum	1,600	11.9	299	11.1	363	11.8	420	11.8	518	12.8
	FOM*	3,710	27.7	827	30.7	898	29.3	936	26.2	1,049	25.8
	Palate	1,611	12.0	296	11.0	406	13.2	457	12.8	452	11.1
	Mouth, NOS*	2,067	15.4	429	15.9	477	15.5	537	15.0	624	15.4
Treatment†	Surgery only	6,179	46.1	1,205	44.7	1,404	45.8	1,601	44.9	1,969	48.5
	Radiotherapy only	1,592	11.9	307	11.4	338	11.0	455	12.8	492	12.1
	Surgery + radiotherapy	3,971	29.6	833	30.9	914	29.8	1,100	30.8	1,124	27.7
	Radiotherapy + chemotherapy	445	3.3	43	1.6	108	3.5	151	4.2	143	3.5
	Surgery + radiotherapy + chemotherapy	150	1.1	43	1.6	29	1.0	13	0.4	65	1.6
	Other	297	2.2	108	4.0	101	3.3	55	1.5	33	0.8
	No treatment	765	5.7	158	5.9	175	5.7	195	5.5	237	5.8

*FOM: Floor of Mouth; NOS: Not Otherwise Specified.

†10382 (77.5%) patients were treated surgically (surgery only + "surgery + radiotherapy" + "surgery + chemotherapy" + "surgery + radiotherapy + chemotherapy"; lymph node dissection only or metastasectomy are not included in surgery.

To evaluate changes in treatment proportion over time, we calculated a chi- square statistic for the trend over the time periods using ptrend in STATA[16], and reported this as statistically significant if a) the p-value was below 0.05 and b) the deviation from the trend line was not statistically significant.
Relative survival rates were calculated using Paul Dickman's STATA model for relative survival (Ederer II method).[17] In relative survival analyses the ratio of observed survival to the expected survival was calculated by sex, age and year obtained from Statistics Netherlands. Survival time was defined as date of diagnosis to date of death or date of censoring (date of emigration or December 31st 2013, i.e. date of record linkage to the municipal records). Patients who died on the day of diagnosis were excluded (N=2). Poisson regression modelling was used to calculate the adjusted relative excessive risk (RER) of dying.[18] Time period was included in this model and tested for linearity using a *post hoc* trend test on the RER estimates for period fitted as a continuous term. In the multivariable model, sex, age, stage, site, treatment and period were included.
Statistical analyses were performed using STATA data analysis and statistical software (version 10.0, StataCorp LP, Texas, 1996).

Results

Study population

In 1991–2010, 13,399 OCCs were diagnosed in 13,108 patients. The total number of OCCs increased from 2,697 in 1991–1995 to 4,063 in 2006–2010 (Table 1).
Seventy percent of patients was aged 46-75 years. Slightly more males (58%) than females were affected by OCC, but there were differences by subsite: the proportion of males ranged from 48% for the gum to 67% for FOM. The most common subsites were tongue (33%) and FOM (28%). Tumours were mainly stage I (34%) or stage IV without distant metastasis (34%) (Table 1).
46% was treated by surgery only, 12% with radiotherapy only and 30% by surgery + radiotherapy. Only 6% did not receive any treatment. Untreated patients were on average older (71 compared with 62) and more often diagnosed with stage IV (57% compared with 34%) or unknown stage (16% compared with 2%) tumours.

Incidence

The incidence rate of OCC increased from 2.70 per 100,000 in 1989 to 4.09 per 100,000 in 2012 (+1.2%; 95%CI: +0.9;+1.6% per year) (Fig. 1a) and increased more strongly in women (+1.8% per year) than in men (+0.8% per year). The increase in incidence was furthermore stronger in patients over 60 years of age (Fig. 1b). The increasing trend for 46–60-year olds became a decline after 2005 (Fig. 1b),

while the trend for patients aged 45 years or younger was stable over time (Fig. 1b).

The most pronounced increases in incidence rates were observed in cancer of the tongue (+1.9%; 95%CI: +1.2;+2.4% per year) and gum (+2.0%; 95%CI: +1.3;+2.6% per year) (Fig. 1c). FOM and palate cancer both showed significantly increasing incidence rates followed by stable incidence rates from the early/late nineties (Fig. 1c).

The incidence increased statistically significant in stage I and stage IV M_0 tumours, which was most pronounced for stage I tumours (+2.5%; 95%CI: +2.0;+3.0% per year) (Fig. 1d). Rates for other stages were stable, except for a decline in unknown stage.

The numbers for tongue and FOM cancer were sufficiently large to evaluate stage within these subsites (data not shown). For tongue cancer, an increasing incidence was observed in all evaluable stages, with the most pronounced increases in stage I ($T_1N_0M_0$) (+2.9%; 95%CI: +2.3;+3.6% per year) and stage III ($T_3N_0M_0$ or $T_{1-3}N_1M_0$) tumours (+1.8%; 95%CI: +0.5;+3.1% per year). For FOM, the incidence of stage I tumours increased (+2.0%; 95%CI: +1.2;+2.9% per year), while the incidence for stage II through stage IV M_0 decreased from the mid-nineties onwards.

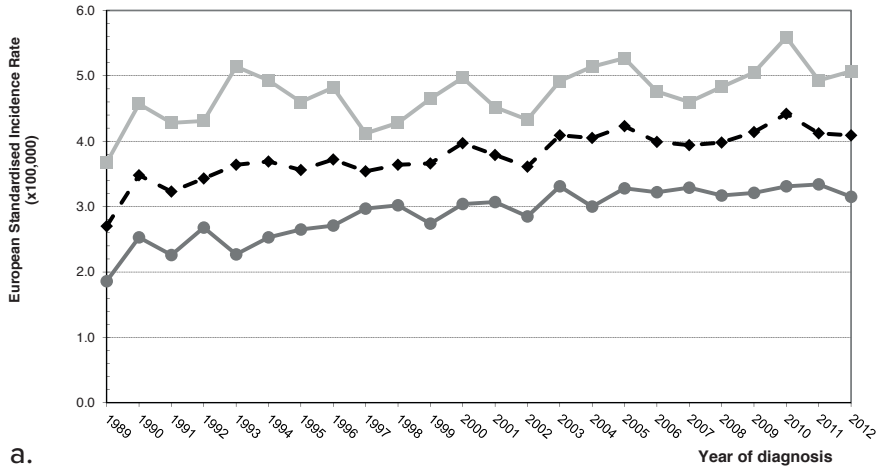
Mortality

The mortality rate of OCC increased from 0.82 per 100,000 in 1989 to 0.97 per 100,000 in 2012 (+0.8%; 95%CI: +0.3;+1.3% per year). Sex-specific rates were stable over the total period (Fig. 2a). Increasing mortality rates were observed for FOM tumours until 2003, for “mouth, NOS”, and was borderline significant for tongue tumours. A decreasing rate was observed for gum tumours (-5.5% per year; 95%CI: -10;-0.61%) (Fig. 2b).

Survival

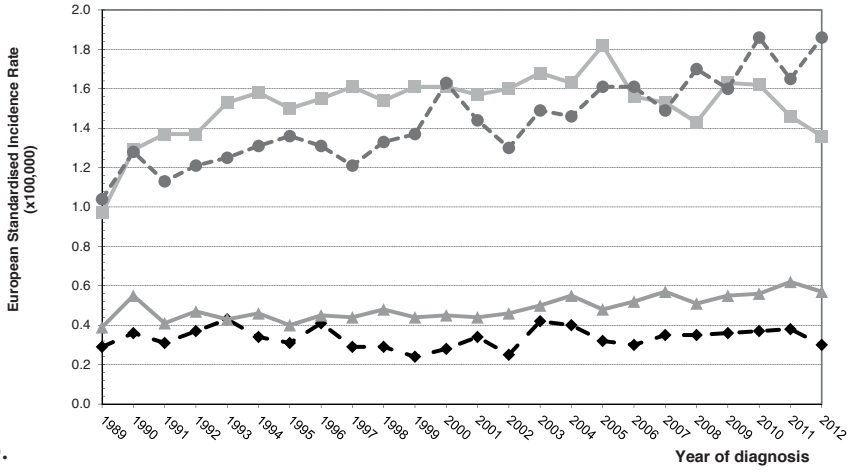
Overall 5-year survival was 52% and relative survival 59%. Five-year relative survival was better for women compared with men (65% vs. 55%), decreased with increasing age and stage, was the best for tongue cancer (63%) and worse for gum cancer (56%) and FOM (55%) (Table 2). Survival increased over time, most pronounced in younger patients, stage III tumours and patients treated with radiotherapy only (Table 2).

In the multivariable analysis, including sex, age, stage, subsite, treatment and period, the RER of dying was lower for women and increased with increasing age and stage (Table 3). All treatment strategies, with the exception of surgery + radiotherapy, were associated with a significantly higher RER of dying than surgery only. The RER of dying decreased over time (univariable p-value: 0.04; multivariable p-value: 0.0004) (Table 3).



a.

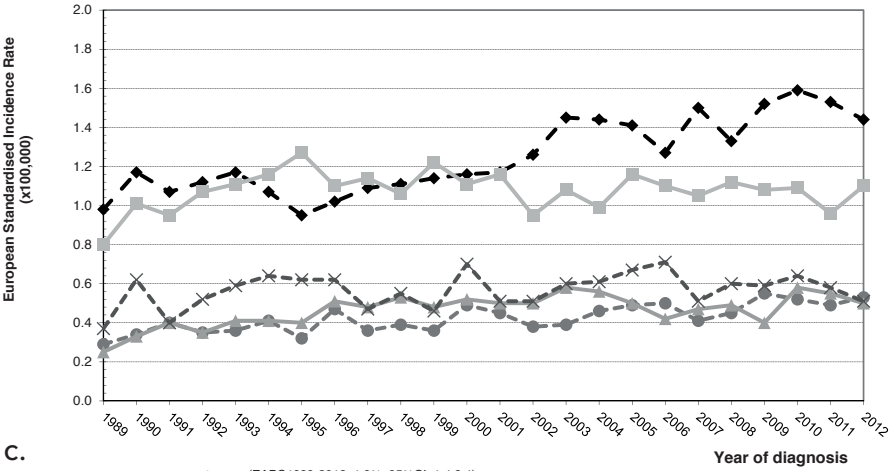
total (EAPC1989-2012: 1.2%; 95%CI: 0.9;1.6)
male (EAPC1989-2012: 0.8%; 95%CI: 0.3;1.3)
female (EAPC1989-2012: 1.8%; 95%CI: 1.3;2.3)



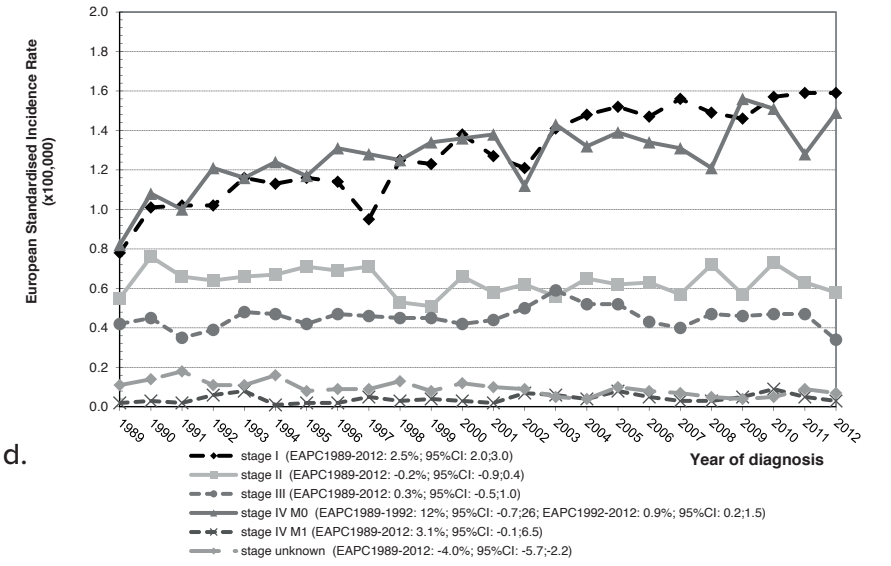
b.

<=45 years (EAPC1989-2012: 0.2%; 95%CI: -0.8;1.2)
46-60 years (EAPC1989-1991: 20%; 95%CI: 4.6;38; EAPC1991-2005: 1.1%; 95%CI: 0.3;1.8; EAPC2005-2012: -2.4%; 95%CI: -4.2;-0.6)
61-75 years (EAPC1989-2012: 2.0%; 95%CI: 1.5;2.4)
>75 years (EAPC1989-2012: 1.3%; 95%CI: 0.8;1.9)

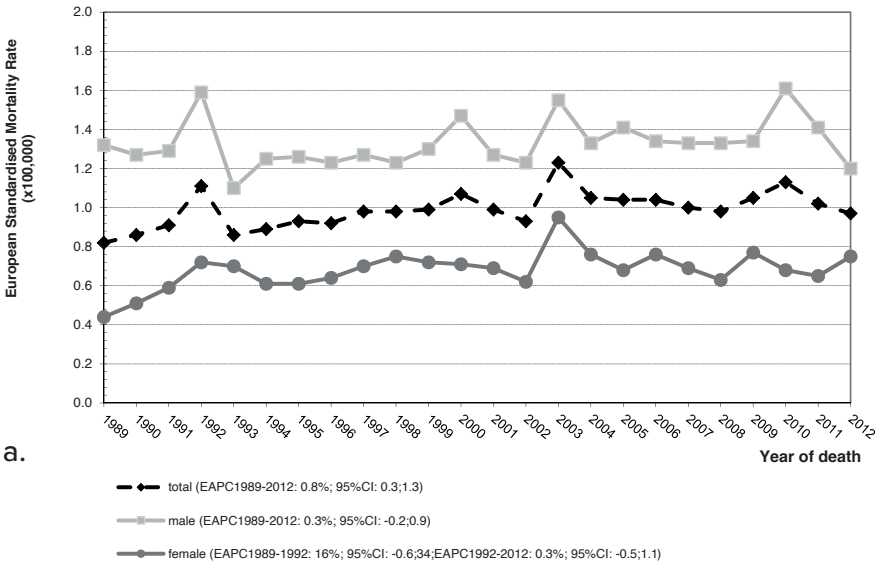
Figure 1. Incidence rate for the period 1989-2012 for oral cavity cancer; **a.** total and by sex, **b.** age, **c.** subsite, and **d.** stage.


European Standardised Incidence Rate (x100,000)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012
Year of diagnosis
tongue (EAPC1989-2012: 1.9%; 95%CI: 1.4;2.4)
fom (EAPC1989-1993: 8.1%; 95%CI: 1.4;15; EAPC1993-2012: -0.5%; 95%CI: -1.1;0.1)
gum (EAPC1989-2012: 2.0%; 95%CI: 1.3;2.6)
palate (EAPC1989-1997: 7.2%; 95%CI: 3.4;11; EAPC1997-2012: -0.2%; 95%CI: -1.6;1,2)
mouth,NOS (EAPC1989-2012: 0.8%; 95%CI: -0.1;1.8)

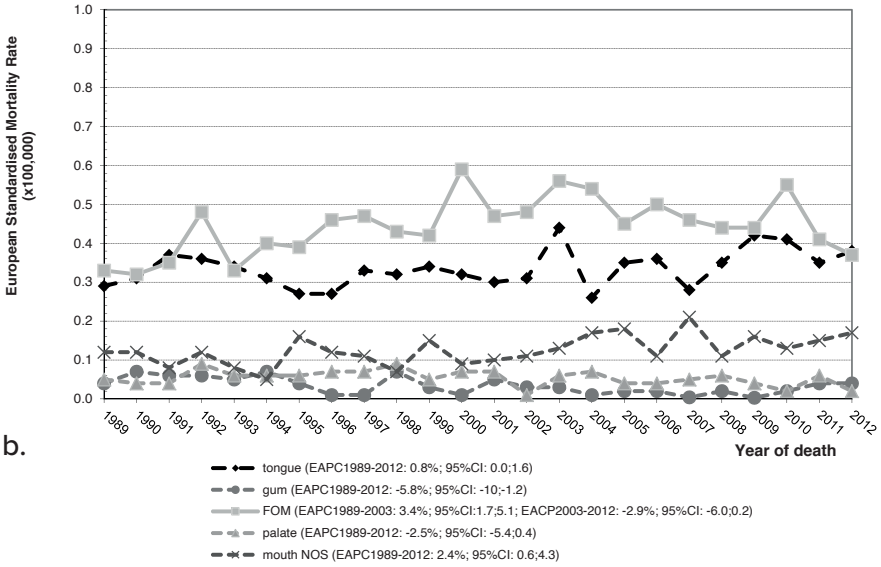
c.


European Standardised Incidence Rate (x100,000)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012
Year of diagnosis
stage I (EAPC1989-2012: 2.5%; 95%CI: 2.0;3.0)
stage II (EAPC1989-2012: -0.2%; 95%CI: -0.9;0.4)
stage III (EAPC1989-2012: 0.3%; 95%CI: -0.5;1.0)
stage IV M0 (EAPC1989-1992: 12%; 95%CI: -0.7;26; EAPC1992-2012: 0.9%; 95%CI: 0.2;1.5)
stage IV M1 (EAPC1989-2012: 3.1%; 95%CI: -0.1;6.5)
stage unknown (EAPC1989-2012: -4.0%; 95%CI: -5.7;-2.2)

d.



a.



b.

Figure 2. Mortality rate for the period 1989-2012 for oral cavity cancer; **a.** total and by sex, and **b.** subsite.

Treatment

Surgery only was the most common treatment over the entire period and increased from 45% in 1991-1995 to 49% in 2006–2010 (p=0.004) (Table 1).

Fig. 3a shows that stage I and II tumours were mostly surgically treated and that surgical treatment for stage I increased over time (p<0.001). For stage III tumours, the proportion of surgery only increased (p=0.006), whereas the proportion of surgery + radiotherapy decreased non-significantly over time. The proportion of patients untreated in case of unknown stage at diagnosis was higher in the later periods (p=0.006), while the proportion for surgery only was lower (p=0.02) (Fig. 3a).

Between 1991-1995 and 2006-2010 an increase in surgery only (p<0.001) for tongue tumours (overall 42% of tongue tumours were stage I at diagnosis, data not shown). For palate tumours an increase for radiotherapy only (p=0.001) and a decline in surgery + radiotherapy was observed (p=0.001; Fig. 3b). Treatment hardly changed over time for the other subsites.

Treatment over time by age shows that younger patients were more often treated by surgery only (p<0.001) instead of surgery + radiotherapy (p=0.001), while treatment remained constant over time for the other age groups (Fig. 3c).

Table 2. 5-year relative survival estimates (95%CI) for oral cavity cancer patients, total and patient subgroups, by 5-year time period

		N	5-year Relative Survival (%) (95%CI)				
			Total	1991-1995	1996-2000	2001-2005	2006-2010
Total		13,106	59 (58;60)	57 (55;59)	58 (56;60)	59 (57;61)	62 (60;63)
Sex	Men	7,586	55 (54;57)	53 (51;56)	54 (52;57)	55 (53;58)	58 (55;60)
	Women	5,520	65 (63;66)	63 (59;66)	63 (60;66)	65 (62;67)	67 (64;70)
Agegroup	≤45	1,140	74 (71;76)	70 (65;75)	72 (66;77)	75 (70;80)	78 (73;83)
	46-60	4,807	61 (59;62)	57 (54;60)	61 (58;64)	60 (57;63)	64 (61;67)
	61-75	4,854	58 (56;59)	56 (52;60)	54 (51;58)	58 (55;61)	61 (58;64)
	75+	2,305	51 (48;54)	52 (44;59)	50 (43;57)	52 (46;58)	51 (45;57)
Stage	I	4,343	82 (81;84)	79 (75;83)	82 (79;85)	83 (80;85)	83 (80;86)
	II	2,185	69 (67;71)	66 (61;71)	69 (64;74)	67 (63;72)	73 (68;77)
	III	1,595	54 (51;57)	49 (43;55)	49 (43;55)	57 (51;62)	59 (53;64)
	IV M0	4,517	36 (35;38)	35 (32;39)	36 (32;39)	36 (33;39)	38 (36;41)
	IV M1	156	7 (3;12)	8 (1;24)	8 (1;23)	7 (2;17)	5 (1;15)
	Unknown	310	53 (46;59)	59 (47;71)	58 (45;71)	50 (37;63)	35 (21;50)
Subsite	Tongue	4,260	63 (62;65)	61 (57;65)	64 (60;67)	63 (60;66)	65 (62;68)
	Gum	1,571	56 (53;59)	56 (49;63)	59 (52;65)	55 (49;61)	53 (48;59)
	FOM*	3,644	55 (53;57)	57 (53;60)	53 (50;57)	52 (49;56)	57 (53;60)
	Palate	1,588	60 (57;63)	53 (46;59)	57 (51;62)	63 (58;68)	65 (60;70)
	Mouth, NOS*	2,043	61 (58;63)	55 (50;61)	57 (51;62)	63 (58;68)	67 (62;71)
Treatment	Surgery only	5,988	78 (76;79)	74 (71;78)	78 (75;81)	78 (75;80)	79 (77;82)
	Radiotherapy only	1,566	31 (29;34)	25 (20;30)	28 (23;33)	32 (28;37)	37 (32;42)
	Surgery + radiotherapy	3,928	57 (56;59)	58 (54;61)	55 (51;59)	58 (54;61)	60 (56;63)
	Radiotherapy + chemotherapy	439	27 (23;32)	5 (1;16)	22 (14;31)	35 (27;43)	30 (22;38)
	Surgery + radiotherapy + chemotherapy	149	43 (34;51)	49 (32;64)	27 (12;45)	50 (21;76)	38 (20;56)
	Other	292	43 (36;49)	44 (33;54)	48 (37;59)	34 (21;49)	35 (17;54)
	No treatment	744	6 (5;9)	9 (4;15)	6 (3;11)	8 (5;13)	3 (1;7)

*FOM: Floor of Mouth; NOS: Not Otherwise Specified.

Table 3. Relative Excess Risk (RER) of dying for oral cavity cancer, univariable and multivariable model results

Variable		Unadjusted	All variables included in the model
		RER of dying (95%CI)	RER of dying (95%CI)
Sex	Men	1	1
	Women	0.74 (0.69;0.79)	0.78 (0.73;0.83)
Agegroup	≤45	1	1
	46-60	1.67 (1.48;1.89)	1.42 (1.25;1.61)
	61-75	1.91 (1.69;2.17)	1.67 (1.47;1.89)
	75+	2.76 (2.41;3.18)	2.31 (2.01;2.66)
Stage	I	1	1
	II	1.97 (1.73;2.24)	1.55 (1.37;1.76)
	III	3.45 (3.06;3.90)	2.53 (2.24;2.86)
	IV M0	6.29 (5.69;6.95)	4.48 (4.02;5.00)
	IV M1	28.1 (23.3;34.0)	10.4 (8.58;12.7)
	Unknown	4.09 (3.33;5.03)	1.58 (1.29;1.95)
Subsite	Tongue	1	1
	Gum	1.32 (1.19;1.46)	0.77 (0.70;0.86)
	FOM	1.29 (1.19;1.39)	0.95 (0.88;1.03)
	Palate	1.08 (0.98;1.20)	0.59 (0.53;0.65)
	Mouth, NOS	1.08 (0.98;1.19)	0.72 (0.66;0.79)
Treatment	Surgery only	1	1
	Radiotherapy only	5.36 (4.88;5.88)	3.22 (2.90;3.56)
	Surgery + radiotherapy	2.21 (2.03;2.41)	1.03 (0.93;1.13)
	Radiotherapy + chemotherapy	6.01 (5.27;6.86)	2.44 (2.12;2.82)
	Surgery + radiotherapy + chemotherapy	3.55 (2.80;4.49)	1.52 (1.19:1.94)
	Other	4.04 (3.38;4.83)	2.79 (2.34;3.32)
	No treatment	22.3 (20.1;24.7)	10.9 (9.72;12.2)
Period	1991-1995	1	1
	1996-2000	0.97 (0.89;1.07)	0.92 (0.84;1.00)
	2001-2005	0.93 (0.85;1.01)	0.86 (0.79;0.94)
	2006-2010	0.89 (0.82;0.97)	0.84 (0.77;0.91)

*FOM: Floor of Mouth; NOS: Not Otherwise Specified.

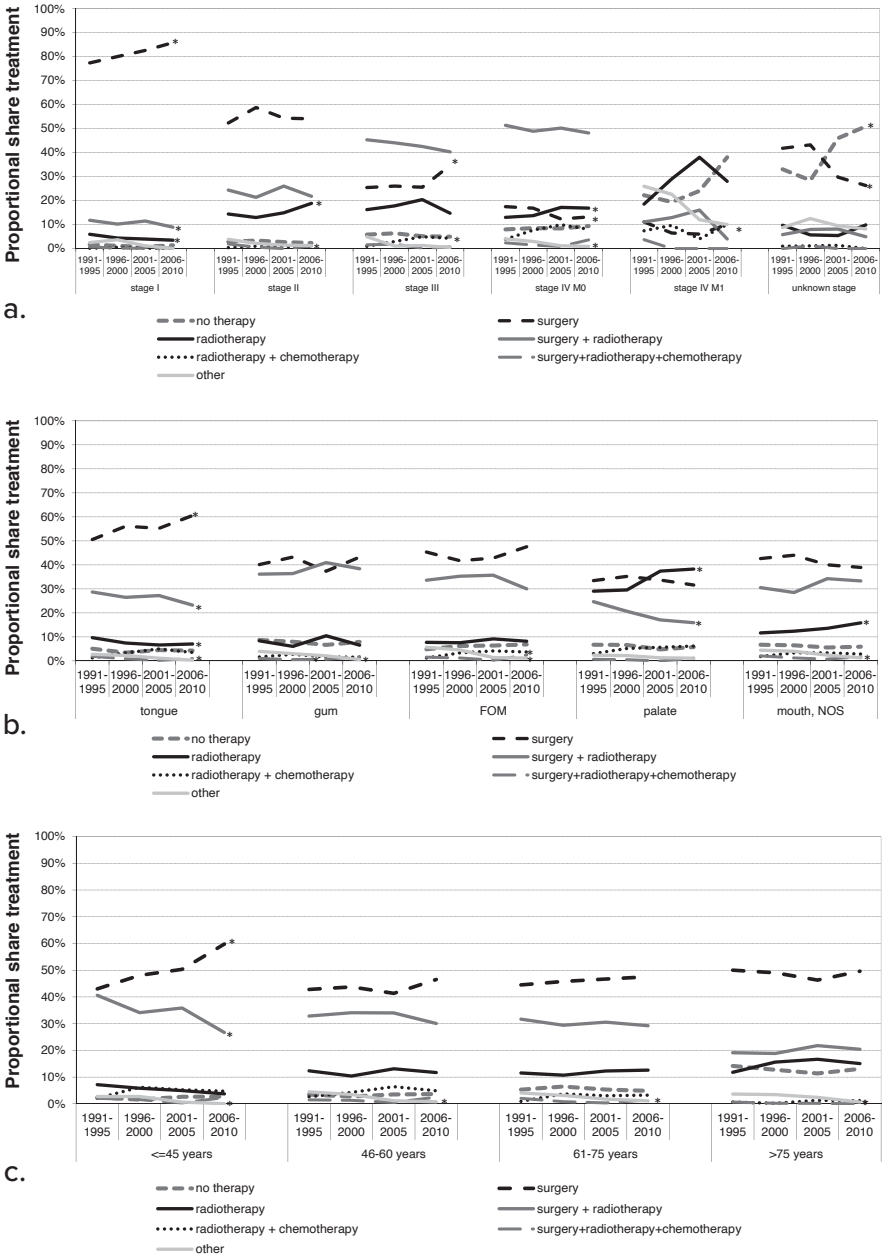


Figure 3. Treatment of oral cavity cancer by 5-year time periods and **a.** stage, **b.** subsite and **c.** age.

Discussion

Incidence

We observed an increasing incidence rate over the years, stronger for women than for men. Alcohol consumption and an increase of chewing tobacco have been mentioned as an explanation for a rise in OCC incidence[4, 19], but this does not explain the rise in OCC incidence in our population. In the Netherlands, alcohol consumption has been stable since 1990.[20] Chewing tobacco is hardly consumed: the majority of tobacco is consumed by smoking, less than one percent by pipe or chewing tobacco.[21] Tobacco consumption in the Netherlands has been declining for men since the 1960's and for women since the 1970's.[22]
Other authors see the rise in incidence as a reflection of changing smoking habits.[5] However, we did not see a decreasing trend in incidence rates for males as was observed in other smoking related cancers such as lung and laryngeal cancer in the Netherlands.[23, 24] The stronger increase in incidence in women than in men has also been reported by others[4, 19] and is frequently explained by the fact that women started smoking later than men.[25] However, Chaturvedi et al. concluded that under these circumstances an increase in lung cancer is also expected, which was not the case.[4, 25] The discrepancy between the trends in lung and head and neck cancer incidence was also reported in other countries such as Brazil, Denmark and the United Kingdom.[4]

HPV has been reported as an etiological factor in certain subsets of head and neck cancer.[26] However, most studies indicated that HPV did not play a role in the pathogenesis, not even in non-smoking non-drinking or young oral cavity SCCs.[27] Furthermore, a recent Dutch population based study concluded that even in the subset of oropharyngeal cancer, the rising incidence was not clearly attributable to HPV and that etiological factors such as smoking and drinking remain to have an important etiological role.[28] On the other hand, a continuous increase in the incidence of HPV-related oropharyngeal squamous cell carcinomas in multiple developed countries was also shown.[29]
In conclusion, we cannot fully explain the trend of the rising incidence of oral cancer in general by changes in the most common etiological factors.

The increased incidence in OCC was most pronounced for stage I ($T_1N_0M_0$) and tongue cancers. An increase in tongue cancer is also reported by other authors,[30] as well as an increase in lower stage head and neck cancer in general.[30, 31] Women were more frequently diagnosed with stage I tumours, which may be related to the greater cancer awareness in women.[32, 33] Another contribution may have come from a greater awareness among general practitioners and dentists.[31]

Additionally, a rise in stage IV tumours was observed. In our population, gum cancer was relatively frequently diagnosed as stage IV disease. In gum cancer, bone invasion also occurs with small tumours because gum is defined as attached gingiva where there is no subcutaneous tissue between mucosa and bone. Of note, gum cancer has a relative good prognosis and less chance of regional or distant metastasis when compared to other sites.[34] Another cause for the increase of stage IV cancer is the improvement of imaging techniques, which enables the distinction between bone invasion and erosion.[35]

Mortality

We noticed a slight, yet significant, rise in mortality, which was mainly based on an increase in the early nineties. Still, mortality rates were at best stable. This is worrisome, given the fact that the cancer specific mortality in the Netherlands declined between 1989 and 2012 for all cancers from 234 to 185 per 100.000 (ESR) and for head and neck cancer from 4.7 to 3.9 per 100,000 (ESR).[2] This corresponds with the global trend that the mortality of OCC increases or declines much slower than the overall cancer mortality.[36] A possible cause of this increase may be that the majority of OCC patients have relatively many comorbidities because of common aetiology, which negatively impacts mortality.[37, 38] It is also known that the presence of comorbidities is a competing mortality risk in oral cancer patients.[39] Exact data on the changes in prevalence of comorbidities in the Netherlands is unavailable. A population based study on Dutch colon cancer patients, a group with overlapping risk factors, showed that the prevalence of comorbidities rose from 47% to 62% between 1995 and 2010.[40] In the current study, the OCC-specific mortality was based on death certificate information as collected by Statistics Netherlands, which means it also depends on co-existing diseases reported as an underlying cause of death. The size of this possible bias is unknown.

Survival

The 5-year relative survival rate was highest in the period 2006–2010. This development is in line with other countries.[36] Van Dijk et al. reported a 5-year relative survival rate for OCC in 2000-2002 in Europe of 48%.[41] For 2000-2007, this estimate was 45% in Europe and 56% for The Netherlands (however, tongue cancer was excluded compared with the earlier report).[42] Our 5-year relative survival estimate of 59% was higher compared with EUROCARE-5[42] estimates because tongue cancer was included and compared with RARECARE[41] estimates because Eastern European countries were included in the European estimate. The higher overall relative survival rates can be explained on the one hand by a rise in stage I diagnoses, which have a higher survival and a rise in survival rates

in all stage categories. A higher survival might also be a reflection of improved treatment strategies, which we will discuss in the next paragraph.

Treatment

Surgery only remained the main treatment in stage I and II OCC. The proportion of surgery only rose for stage III cancer. This can partially be explained by better surgical and reconstructive techniques for T3 tumours, which enables the surgeon to perform more radical resections without the need for adjuvant treatment.[43] This is also reflected in the improved 5-year relative survival for stage III tumours.

Our results did not show the expected rise in adjuvant chemoradiation after publication of the studies by Cooper[10] and Bernier[44] in 2004 and the subsequent adaptation of local guidelines. This may be explained because adjuvant chemo-radiation was not yet included in the national guideline[11] or the fact that the indication for adjuvant chemoradiation is very specific and that it is usually not given to patient over 70 years of age.

Strengths and limitations of this study

This study is based on data registered by the Netherlands Cancer Registry. A strength of this cohort is the national coverage, >95% completeness and lack of selection bias. Stage and treatment information were available, but more detailed treatment information and information on comorbidities could have aided our interpretation of results on treatment and relative survival.

Another limitation of our study is the selection of subsites based on the two-digit ICD-O-3 codes, since this was the highest level of detail available for mortality rates. This means that soft palate was included in the oral cavity, while soft palate is usually considered to be an oropharyngeal site. However, only 2.5% of records in this report were soft palate tumours.

Implications for OCC surveillance

The rising incidence and survival rates lead to an increasing OCC prevalence, which poses challenges for surveillance care. Patients treated with curative intent receive an intensive follow-up regimen, comprising at least 17 check-up visits within 5 years to detect recurrence and second primary head and neck cancers early.[45,46] Furthermore, because of the negative impact of treatment on oral function, patients will not only rely on their medical specialist, but also on an array of supportive specialties, such as dentists, dieticians and physical therapists. This will increase the use of health care resources and budgets and may lead to capacity problems.

In conclusion, OCC incidence is increasing, especially in women and stage I and IV tumours. Surgery remains the most important (curative) treatment modality in

OCC. In line with the incidence, OCC mortality is also increasing, despite the better relative survival rate in the latest period. The increasing OCC incidence and mortality rates show that OCC is an increasingly important health problem.

Acknowledgement

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References

1. Braakhuis BJ, Visser O, Leemans CR. Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: Increasing incidence, but not in young adults. Oral Oncol. 2009;45: e85-89.
2. Nederlandse Kankerregistratie. Cijfers over kanker in Nederland. Available from URL: http://www.cijfersoverkanker.nl/?language=en [last accessed: 25-01-2016]
3. Braakhuis BJ, Leemans CR, Visser O. Incidence and survival trends of head and neck squamous cell carcinoma in the Netherlands between 1989 and 2011. Oral Oncol. 2014;50: 670-675.
4. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol. 2013;31: 4550-4559.
5. 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 1990s. Eur J Cancer. 2008;44: 1345-1389.
6. Hashibe M, Brennan P, Chuang SC, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2009;18: 541-550.
7. Wensing BM, Deserno WM, de Bondt RB, et al. Diagnostic value of magnetic resonance lymphography in preoperative staging of clinically negative necks in squamous cell carcinoma of the oral cavity: a pilot study. Oral Oncol. 2011;47: 1079-1084.
8. Kelner N, Vartanian JG, Pinto CA, Coutinho-Camillo CM, Kowalski LP. Does elective neck dissection in T1/T2 carcinoma of the oral tongue and floor of the mouth influence recurrence and survival rates? Br J Oral Maxillofac Surg. 2014;52: 590-597.
9. Fasunla AJ, Greene BH, Timmesfeld N, Wiegand S, Werner JA, Sesterhenn AM. A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. Oral Oncol. 2011;47: 320-324.
10. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350: 1937-1944.
11. Nederlandse Werkgroep Hoofd-halstumoren. Richtlijn Mondholte- en Orofarynxcarcinoom Alphen aan den Rijn: Van Zuiden communications B.V., 2004.
12. Kiemeney LA, Meulenpas JM. Kanker in Nederland tot 2020. Trends en prognoses. Oisterwijk: KWF kankerbestrijding, 2011.
13. 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: 1822-1829.
14. International Classification of Diseases for Oncology. 3rd ed. Geneva: World Health Organization 2000.
15. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med. 2000;19: 335-351.
16. Royston P. Stata module for trend analysis for proportions. Available from URL: https://ideas.repec.org/c/boc/bocode/s426101.html [accessed 25/1/2016].
17. Dickman PW, Coviello E, Hills M. Estimating and modelling relative survival. The Stata Journal. 2013: 1-25.
18. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Stat Med. 2004;23: 51-64.
19. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45: 309-316.
20. van Laar MW, Cruts AAN, Verdurmen JEE, van Ooyen MMJ, Meijer RF. Nationale Drug Monitor Jaarbericht 2007. Houten: Ladenius Communicatie BV, 2007.
21. van Laar MW, van Ooyen MMJ, Cruts AAN, Meijer RF, Croes EA, Ketelaars APM, van der Pol, P.M. Nationale Drug Monitor Jaarbericht 2013/2014. Utrecht/Den Haag: Trimbos instituut/WODC, 2014.
22. Janssen F, van Poppel F. The Adoption of Smoking and Its Effect on the Mortality Gender Gap in Netherlands: A Historical Perspective. Biomed Res Int. 2015;2015: 370274.

23. Karim-Kos HE, Kiemeney LA, Louwman MW, Coebergh JW, de Vries E. Progress against cancer in the Netherlands since the late 1980s: an epidemiological evaluation. Int J Cancer. 2012;130: 2981-2989.
24. 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;134: 674-681.
25. Karim-Kos HE, Janssen-Heijnen ML, van Iersel CA, van der Meer RM, de Vries E, Coebergh JW. The beginning of the end of the lung cancer epidemic in Dutch women? Int J Cancer. 2008;123: 1472-1475.
26. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2015;33: 3235-3242.
27. Mirghani H, Amen F, Moreau F, Lacau St Guily J. Do high-risk human papillomaviruses cause oral cavity squamous cell carcinoma? Oral Oncol. 2015;51: 229-236.
28. van Monsjou HS, Schaapveld M, van den Brekel MW, Balm AJ. The epidemiology of head and neck squamous cell carcinoma in The Netherlands during the era of HPV-related oropharyngeal squamous cell carcinoma. Is there really evidence for a change? Oral Oncol. 2015;51: 901-907.
29. Gooi Z, Chan JY, Fakhry C. The epidemiology of the human papillomavirus related to oropharyngeal head and neck cancer. Laryngoscope. 2016;126: 894-900.
30. Doobaree IU, Landis SH, Linklater KM, El-Hariry I, Moller H, Tyczynski J. Head and neck cancer in South East England between 1995-1999 and 2000-2004: An estimation of incidence and distribution by site, stage and histological type. Oral Oncol. 2009;45: 809-814.
31. Rafiq R, Brocklehurst P, Rogers SN. Effect of Mouth Cancer Awareness Week on urgent suspected head and neck cancer referrals. Br J Oral Maxillofac Surg. 2013;51: e183-185.
32. Luryi AL, Yarbrough WG, Niccolai LM, et al. Public awareness of head and neck cancers: a cross-sectional survey. JAMA Otolaryngol Head Neck Surg. 2014;140: 639-646.
33. Hvidberg L, Pedersen AF, Wulff CN, Vedsted P. Cancer awareness and socio-economic position: results from a population-based study in Denmark. BMC Cancer. 2014;14: 581.
34. Montero PH, Yu C, Palmer FL, et al. Nomograms for preoperative prediction of prognosis in patients with oral cavity squamous cell carcinoma. Cancer. 2014;120: 214-221.
35. Arya S, Rane P, Deshmukh A. Oral cavity squamous cell carcinoma: role of pretreatment imaging and its influence on management. Clin Radiol. 2014;69: 916-930.
36. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65: 5-29.
37. Boje CR. Impact of comorbidity on treatment outcome in head and neck squamous cell carcinoma - a systematic review. Radiother Oncol. 2014;110: 81-90.
38. Boje CR, Dalton SO, Primdahl H, et al. Evaluation of comorbidity in 9388 head and neck cancer patients: a national cohort study from the DAHANCA database. Radiother Oncol. 2014;110: 91-97.
39. Rose BS, Jeong JH, Nath SK, Lu SM, Mell LK. Population-based study of competing mortality in head and neck cancer. J Clin Oncol. 2011;29: 3503-3509.
40. van Leersum NJ, Janssen-Heijnen ML, Wouters MW, et al. Increasing prevalence of comorbidity in patients with colorectal cancer in the South of the Netherlands 1995-2010. Int J Cancer. 2013;132: 2157-2163.
41. Van Dijk BA, Gatta G, Capocaccia R, et al. Rare cancers of the head and neck area in Europe. Eur J Cancer. 2012;48: 783-796.
42. Gatta G, Botta L, Sanchez MJ, 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;51: 2130-2143.
43. Cannady SB, Rosenthal EL, Knott PD, Fritz M, Wax MK. Free tissue transfer for head and neck reconstruction: a contemporary review. JAMA Facial Plast Surg. 2014;16: 367-373.
44. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350: 1945-1952.
45. Gonzalez-Garcia R, Naval-Gias L, Roman-Romero L, Sastre-Perez J, Rodriguez-Campo FJ. Local recurrences and second primary tumors from squamous cell carcinoma of the oral cavity: a retrospective analytic study of 500 patients. Head Neck. 2009;31: 1168-1180.
46. Liu CH, Chen HJ, Wang PC, Chen HS, Chang YL. Patterns of recurrence and second primary tumors in oral squamous cell carcinoma treated with surgery alone. Kaohsiung J Med Sci. 2013;29: 554-559.

Chapter 4

Time patterns of recurrence and second primary tumours in a large cohort of patients treated for oral cavity cancer

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Abstract

Introduction: Routine follow-up after curative treatment of patients with oral squamous cell carcinoma (OSCC) is common practice considering the high risk of second primaries and recurrences (i.e. second events). Current guidelines advocate a follow-up period of at least five years. The recommendations are not evidence-based and benefits are unclear. This is even more so for follow-up after a second event. To facilitate the development of an evidence- and personalized follow-up program for OSCC, we investigated the course of time until the second and subsequent events and studied the risk factors related to these events.

Materials and methods: We retrospectively studied 594 OSCC patients treated with curative intent at the Head and Neck Cancer Unit of the Radboud University Medical Centre from 2000-2012. Risk of recurrence was calculated addressing death from intercurrent diseases as competing event.

Results: One-, five- and ten-year cumulative risks of a second event were 17% (95% CI: 14%;20%), 30% (95% CI: 26%;33%) and 37% (95% CI: 32%; 41%). Almost all locoregional recurrences occurred in the first 2 years after treatment. The incidence of second primary tumours was relatively stable over the years. The time pattern of presentation of third events was similar.

Discussion: Our findings support a follow-up time of 2 years after curative treatment for OSCC. Based on the risk of recurrence there is no indication for a different follow-up protocol after first and second events. After 2 years, follow-up should be tailored to the individual needs of patients for supportive care, and monitoring of late side-effects of treatment.

Introduction

Oral squamous cell carcinoma (OSCC) continues to be an important burden on health care, with an increasing incidence and only moderately improving survival.[1-4] 25-45% of OSCC patients will develop local- or regional recurrence (LRR), a second primary tumour (SPT) or distant metastasis (DM) (further called second events) after primary curative-intent treatment.[4, 5] Current guideline-recommendations advocate follow-up after curative treatment for all patients of at least 5 years.[6] The main reason for follow-up is the early detection of second events; other goals are functional rehabilitation and psychosocial support.

Follow-up guidelines are not evidence- but consensus-based. Empirical studies on follow-up after treatment for OSCC are scarce and usually combine the data of all head and neck cancers (HNCs), which have a different etiology, treatment, prognosis and timing of second events.[7-9] The available studies on OSCC are small and do not address the question whether specific patient groups are in need of more or less intensive follow-up.[10-13]
The current 'one-size-fits-all' follow-up programs can be criticized on several points.[14, 15] Firstly, it is questionable if such a program is beneficial to all patients as some may be at higher risk of a second event than others.[16, 17] The time frame of five years is debatable as most tumours seem to recur in the first few years.[7, 12] Furthermore, it has never been investigated whether patients should receive a different follow-up schedule after curative-intent treatment of a second event.

It is of utmost importance to optimize and personalize OSCC follow-up to avoid unnecessary testing and anxiety in patients, optimize the use of health care resources and minimize the time clinicians spend on ineffective follow-up consultations. Therefore, this study investigates the time patterns, risks and treatment intent of second and subsequent events after curative-intent treatment of OSCC.

Materials and methods

Patients

Between 2000 and 2012, 756 patients were diagnosed with primary OSCC (ICD O codes C.00-06 excluding C.01, C.05.1 and C.05.2) and treated at the Head and Neck Cancer Unit of the Radboud University Medical Centre. Of these patients, 57 were excluded from analysis for the following reasons: not a first primary OSCC (n=23), a previous or synchronous tumour in other subsites of the head and neck

area (n=32) and other reasons (n=2). Of the remaining 699 patients, 594 (85%) were treated with curative intent and eligible for analysis.
Patients were staged according to the seventh UICC TNM classification. Treatment intent and therapy choices were based on the Dutch national guideline. Decisions concerning therapy and treatment intent were taken after discussion in a multi-disciplinary team meeting.[15]
Patients received follow-up examinations every 2 and 3 months during the first and second year post-treatment, respectively, every 4 months in the third year and every 6 months during the fourth and fifth year. Survival was updated in November 2014 using the municipal registration of deaths.
The difference between a LRR and a SPT was based on p53 mutation analysis. If unavailable, the modified Warren and Gates criteria as described by Re et al were used.[18, 19]

Statistical analysis

Overall survival (OS) from the date of last primary treatment was calculated with the Kaplan-Meier method. Median follow-up time was determined by the inverse Kaplan-Meier method (censored data as events).
Risk of recurrence was calculated using competing risk methods with death from intercurrent disease as competing event.[20] Conditional risk of recurrence per follow-up year was defined as the probability of experiencing a recurrence in that year (y), given that the patient had been recurrence-free up to the previous follow-up year (x). Annual conditional risk of event is calculated by dividing the cumulative risk of event-free survival at 'x+y' years after primary treatment by the cumulative risk at 'x' years after treatment.[21] Risk estimates are given with 95% confidence intervals (CI).
Independent prognostic factors were selected through forward stepwise regression with $p<0.10$ as a cutoff. The Fine and Gray modified Cox proportional hazards model was used to determine prognostic factors for risk of recurrence. The hazard rate ratio's (sHR) for the final model including the selected prognostic factors were presented. The observed 5-year risks of recurrence for all combination of the selected prognostic variables were determined, categorized and presented in a flow chart. Logistic regression was performed to identify prognostic factors for the probability of curative-intent treatment. For the final model including the selected factors, the odds ratios (OR) were presented, and the observed proportion of second events treated with curative intent categorized. The potential prognostic factors studied are presented in the supplementary data (Appendix Table 1).

Results

First event

The patient, tumour and treatment characteristics of 594 patients treated with curative intent for primary OSCC (first event) are displayed in Table 1.

Risk stratification

Risk of a second event

The one-, five-, and ten-year cumulative risks of a second event (i.e. recurrence, new primary tumour or DM) were 17% (95% CI: 14%;20%), 30% (95% CI:26%;33%) and 37% (95% CI:32%;41%). The majority of LRR occurred within the first year after treatment, and all the DMs within three years. The incidence rate of SPTs was stable over the entire follow-up period (Fig. 1a).

Annual *conditional* risk of a second event was highest in the first year of follow-up. i.e. 17% and decreasing in the following years (Fig. 1c). Annual conditional risks of a second event were higher for the non-surgically treated group compared with the surgically treated group (Appendix Fig. 1).

Surgical primary treatment was a statistically significant prognostic factor for risk of a second event (p-value Gray test: <0.01). The five-year cumulative risk was 28% (95% CI:25%;32%) after surgical treatment and 50% (95% CI:31;67%) after non-surgical treatment. In patients treated surgically, vasoinvasive growth, cervical lymph node dissection, buccal mucosa, and extranodal growth were important independent prognostic factors for risk of second event (Table 2). Based on these factors, a flowchart was built with corresponding 5-year cumulative risks of a second event (Fig. 2). Nine risk groups, with an observed five-year risk of second event varying between <10% for patients who received surgical treatment and had a previous malignancy and 50%, for patients without surgical treatment were identified. The group size of the non-surgically treated group did not permit further risk stratification, but were considered as separate risk group.

Treatment intent

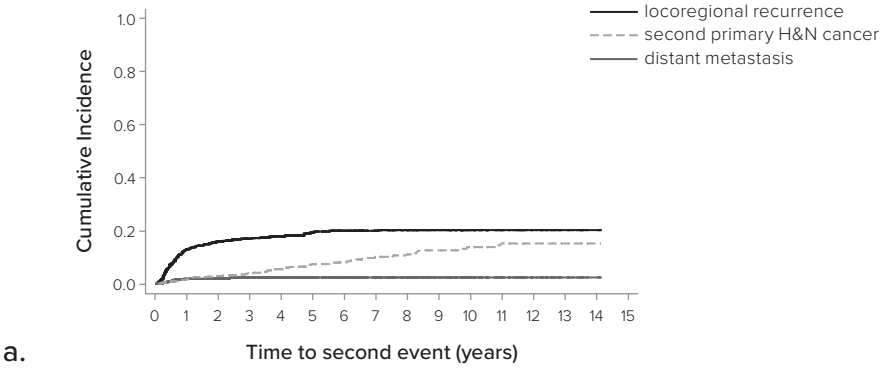
The proportion of the 193 second events that could be treated with curative intent increased with follow-up time from 32 (95% CI:20%;45%) for early recurrences (0-6 months after treatment) to 71% (95% CI:57%;69%) for patients who had a second event 24-60 months after treatment. The annual conditional risk of a second event that could not be treated curatively was highest in the first year after treatment (Fig. 1e). The proportion of patients with a LRR that could be treated curatively decreased, while the proportion of patients with a SPT that could be treated curatively was stable over time.

Table 1. Patient, tumor and treatment characteristics, and survival and recurrence rates of patients treated for primary (N=594) and recurrent (N=106) OSCC with curative intent.

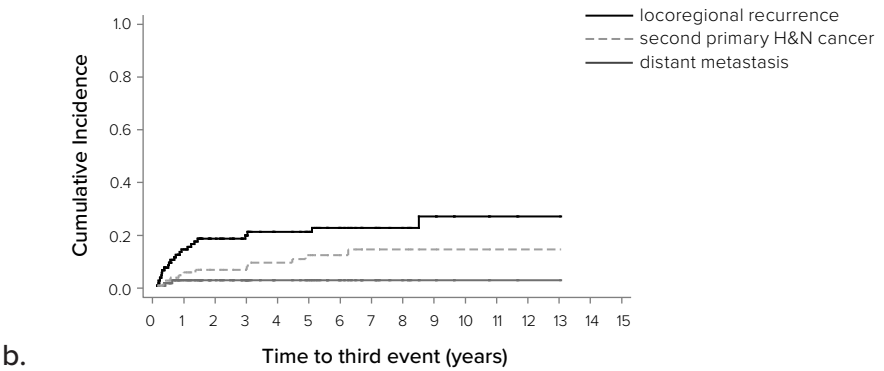
		First event (N=594)		Second event (N=106)	
		No	%	No	%
Overall		594		106	
Patient characteristics					
Gender	Male Female	359 235	60% 40%	62 44	58% 42%
Age at diagnosis	<40years 40-60years ≥60years	24 237 333	4% 40% 56%	6 32 68	6% 30% 64%
ASA score at primary diagnosis	I II III IV Unknown	145 323 96 2 28	24% 54% 16% 1% 5%	29 59 13 - 5	27% 56% 12% - 5%
Malignancies in the past (primary diagnosis)	Yes No	35 559	6% 94%	2 104	2% 98%
Oral pre-malignancies in the past (primary diagnosis)	Yes No Unknown	27 564 3	4% 95% 1%	12 94 -	11% 89% -
Karnofsky Performance Score at primary diagnosis	<60 60 70 80 90 100 Unknown	3 13 18 32 79 55 394	1% 2% 3% 6% 13% 9% 66%	- - 2 7 12 16 69	- - 2% 7% 11% 15% 65%
Smoking and alcohol at primary diagnosis	Never smoker, none-moderate alcohol use Never smoker, problematic alcohol use (ex) smoker, none-moderate alcohol use (ex) smoker, problematic alcohol use Unknown	96 3 217 206 72	16% 1% 36% 35% 12%	25 0 38 31 12	24% - 36% 29% 11%
Tumor characteristics					
Tumor stage	1 2 3 4 (a+b) Unknown	222 214 45 113 -	37 % 36 % 8 % 19% -	36 10 5 5 50	34% 9% 5% 5% 47%

Table 1. Continued.

		First event (N=594)		Second event (N=106)	
		No	%	No	%
Tumor characteristics					
Nodal stage	0 1 2 Unknown	368 68 127 31	62% 12% 21% 5%	55 17 10 24	52% 16% 9% 23%
Stage	1 2 3 4 Unknown	177 129 68 189 31	30% 22% 11% 32% 5%	33 8 9 6 50	31% 8% 8% 6% 47%
Location	Tongue Buccal mucosa Floor of the mouth Retromolar trigone Alveolar process Other	216 48 208 52 66 4	36% 8% 35% 9% 11% 1%	20 9 16 4 14 43	19% 8% 15% 4% 13% 41%
Treatment characteristics					
Therapy	Surgery only Radiotherapy only Surgery and radiotherapy Surgery and chemoradiation Chemoradiation Chemotherapy only Surgery and chemotherapy	260 11 276 27 20 - -	44% 2% 46% 5% 3%	53 8 28 8 6 2 1	50% 8% 26% 8% 5% 2% 1%
Surgery	Yes No	563 31	95% 5%	89 17	84% 16%
Optimal treatment as advised by the tumor board	Yes No Unknown	509 78 7	86% 13% 1%	82 22 2	77% 21% 2%
Follow-up characteristics					
Follow-up time	Median (range) years	7.8 (0.1-14.5)		6.0 (0.1-13.0)	
5-year overall survival	(95% CI)	65% (61%;69%)		64% (52%;74%)	
5-year CIF recurrence	(95% CI) recurrence	30% (26%;33%)		36% (26%;46%)	
5-year CIF competing event	(95% CI) intercurrent death	17% (14%;20%)		21% (13%;31%)	



a.



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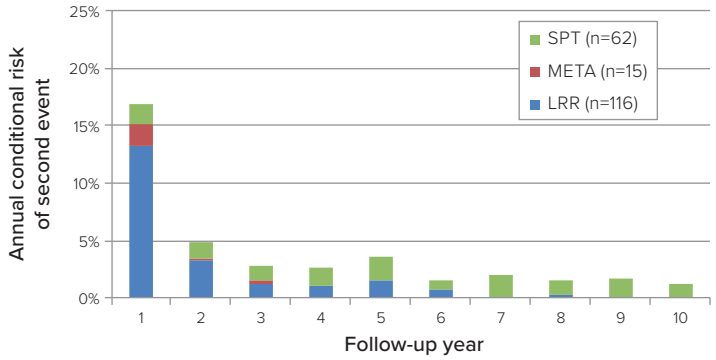
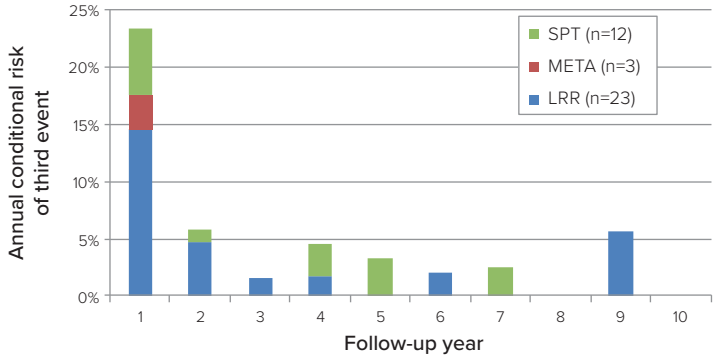


c.

Figure 1. Cumulative risk of second event (**a,b**), annual conditional risk of second event by event type (**c,d**) and treatment intent (**e,f**).

a. Cumulative risk of a second event, by event type.
b. Cumulative risk of a third event, by event type.
c. Annual conditional risk of a second event, by event type.

d.



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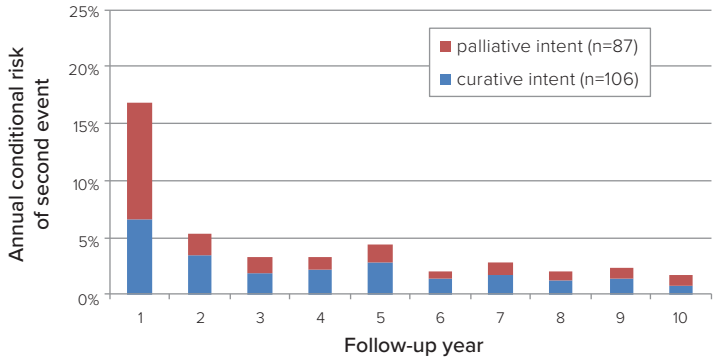

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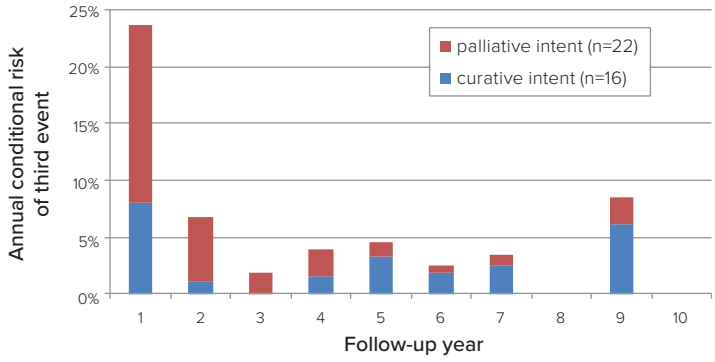


Figure 1. Continued.

d. Annual conditional risk of a third event, by event type.
e. Annual conditional risk of a second event, by treatment intent.
f. Annual conditional risk of a third event, by treatment intent.

Table 2. Independent prognostic factors for the **risk of recurrence** after curative-intent **surgical** treatment for primary OSCC: results from the forward selection procedure

Prognostic factor	sHR (95% CI)
Vasoinvasive growth (yes vs. no)	1.6 (1.1; 2.2)
Cervical node dissection (yes vs. no)	0.6 (0.4; 0.8)
Buccal mucosa (vs. all other locations)	2.1 (1.3; 3.3)
Extranodal growth (yes vs. no)	1.6 (1.0; 2.5)

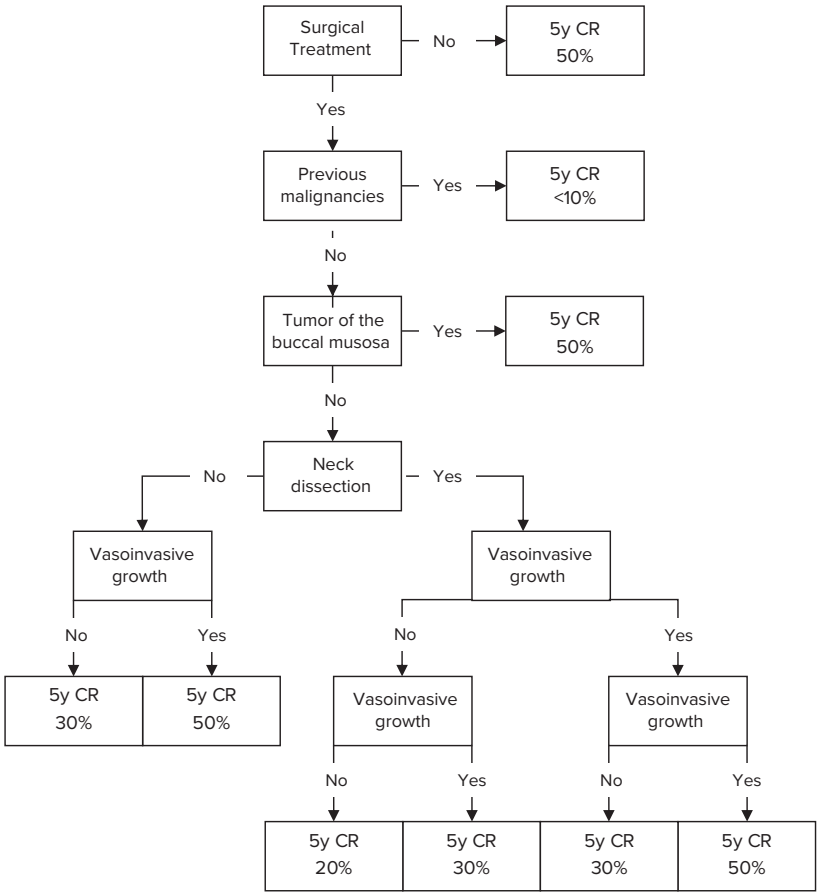


Figure 2. Flow chart for the observed 5-year cumulative risk of a second event after curative-intent treatment for OSCC.

Table 3. Independent prognostic factors for the **treatment intent** of second events after curative-intent **surgical** treatment for primary OSCC: results from the forward selection procedure

Prognostic factor	OR (95% CI)
Radiotherapy (yes vs. no)	0.1 (0.0; 0.4)
Nodal stage 2 (vs. stage 0 or 1)	0.2 (0.1; 0.5)
Tumor stage 4 (vs. stage 1-3)	0.1 (0.0; 0.5)
ASA III or IV (vs. ASA I or II)	0.1 (0.0; 0.4)
Invasion dept ≥4mm (vs. <4mm)	0.3 (0.1; 1.3)

Patients having their recurrence detected after primary surgical treatment had a higher chance of curative treatment of the second event when compared with recurrences detected after non-surgical treatment: 58% (95% CI:50%;65%) vs. 25% (95% CI:10%;50%). In patients treated surgically, postoperative radiotherapy for the first event, tumour size, nodal status, ASA-score and invasion depth were important independent prognostic factors for curative-intent treatment of a second event (Table 3). Based on the number of risk factors, the chance of curative intent treatment varied between 0% (four risk factors) and 96% (no risk factors) (Table 4).

Second event

The characteristics of the 106 patients curatively treated for a second event are summarized in Table 1. The five-year OS rate after completion of the treatment of the second event was 49% (95% CI: 38%;59%).

Risk stratification

Risk of a third event

One-, five-, and ten-year cumulative risks of a third event were 23% (95% CI:16%;32%), 37% (95% CI: 27%;47%), and 45% (95% CI:32%;57%). Almost all local and/or regional recurrences occurred within two years after treatment (Fig. 1b). The risk of a new primary tumour as third event was constant over time.

The annual *conditional* risk of a third event was 24% in the first year after treatment, 7% in the second year and decreased to 4% in the fifth year after treatment (Fig. 1d).

The risk for a third event did not significantly differ between patients treated with (n=88) and without (n=17) surgery for their second event (p-value Gray test: 0.42). The number of third events was too small (n=38) for a reliable search for independent prognostic factors. However, univariable analyses for prognostic

Table 4. The observed proportion of patients with their second event treated with curative intent related to the number of risk factors, relating to the first primary OSCC (radiotherapy, pN_2, pT_4, ASA3/4, invasion depth >4mm)

Number of risk factors	Number of patients	Observed % curative intent	(95% CI)
0	27	96%	81%-100%
1	30	97%	83%-100%
2	39	62%	45%-77%
3	38	26%	13%-43%
4	12	0%	0%-26%[a]
Missing information on one or more risk factors	31	42%	25%-61%

[a]one-sided, 97.5% confidence interval

factors for the risk of a third event showed similar trends when compared with univariable analyses for the risk of a second event (Appendix Table 1).

Treatment intent

Of the 38 third events, 16 (42%) could be treated with curative intent (Fig. 1f). SPTs were more often treated with curative intent (58%) than LRRs (39%). None of the three DMs were treated with curative intent. Patient numbers were too small to draw conclusions about the trends in time or to reliably compare prognostic factors for treatment intent for second versus third events. Patient- and tumour-related factors for second and third events and their relationship to treatment intent are presented in the appendix (Appendix Table 2).

Discussion

This study is the first comprehensive analysis of patterns of occurrence of new disease that focuses specifically on OSCC. First and second events which include both recurrences and SPTs in a large cohort with a long follow-up time are described. The cumulative risk of recurrence for both surgically and non-surgically treated patients was highest in the first year after treatment. Almost all LRRs occurred in the first two years after treatment. The incidence of SPTs was stable over the years. The time patterns of presentation of third events did not differ from that of second events. Our results are clinically highly relevant, because these patterns are not adequately reflected in the current guidelines for routine follow-up after OSCC treatment which advocate five year or lifelong follow-up after the

treatment for OSCC.[15, 22] Determining the optimal follow-up schedule is very important from a patient's perspective, because unnecessary follow-up will create unnecessary anxiety and false expectations.
Our results are consistent with the results from other authors who reported that 86-94% of new disease after curatively treated OSCC occurred within two years.[11, 12, 23, 24] Consistent with Vaamonde et al. we confirm that the risk for a SPT is stable over time.[25]

Arguments for lifelong follow-up are based on the assumption that early, asymptomatic, detection of new primary tumours leads to improved survival. The literature, which comprises all HNSCCs rather than the oral cavity alone, remains equivocal on this subject.[26] Site-specific studies on laryngeal carcinomas and early-stage OSCC did not show survival benefits.[27] The proportion of patients treated with curative intent in our study did not differ between SPTs detected within 5 years (i.e. during the follow-up period) and those detected after five years, suggesting that it is safe to shorten the follow-up period. When shortening the follow-up program, it is important to educate patients about the symptoms of new disease and provide them easy access to the clinic in case of symptoms.[28]

If follow-up is proven to be beneficial to patients, customization of follow-up schedules based on risk of recurrence can be beneficial. Using six independent prognostic factors, namely surgical treatment, previous malignancy, presence of vasoinvasive growth, neck dissection, localization of the tumour and the presence of extranodal growth, we were able to identify patient groups with five-year risks of a second event varying between <10% and 50%. The prognostic value of these factors has been confirmed by several other authors.[29, 30] In our patient group the risk of recurrence between the different locations differed significantly ($p<0.01$). The literature concerning the effect of location on the risk of recurrence is not unequivocal, with some authors reporting a significant effect on the risk of recurrence[31, 32] and others not. [33, 34] This reflects the complex multifactorial nature of oral cancer, which goes beyond purely anatomical factors.

Of interest is also that patients with a previous malignancy have a statistically significant lower risk of second events. This is likely to be caused by the fact that they have a higher risk of intercurrent death from other causes (data not shown). Another important prognostic factor for a second event was if the patient underwent an elective neck dissection for the treatment of their first primary tumour. This can partially be explained by the fact that patients with a clinically negative neck, a small tumour and an invasion depth <4mm did not undergo an elective neck dissection. Montero et al. built a nomogram predicting the probability

of LRR-free survival comprising nodal status, the subsites, bone invasion and primary tumour size.[35] These parameters largely overlap ours. If routine follow-up is considered effective, the nomograms for the risk of a second event might aid the development of a personalized follow-up program, but should undergo further detailed evaluation and validation.

Another way to personalize follow-up is by considering the chance of curative intent treatment of a second event. This strategy has been advocated by Kanatas et al, who suggested that patients with early disease who were treated with a single modality, might benefit from earlier discharge.[36] Patients who develop DM will have no chance to be cured. The likelihood of curative intent treatment of the second event could be predicted using five factors, i.e. previous radiotherapy, nodal status of the first primary tumour, tumour size, invasion depth, and ASA-score resulting in observed probabilities ranging between 0% and 96%. The factors associated with a treatment with curative intent are all related to the possibilities a patient has left to receive therapy. Many patients will have undergone treatment for the neck consisting of neck dissection and/or (chemo)radiotherapy.[4] Several authors confirmed that patients with previous neck dissections had a markedly smaller chance of successful salvage surgery.[24, 37, 38] Likewise, in most patients who had previous radiotherapy another course of radiotherapy will not be possible.[39]

Other authors mentioned performance status, ASA-score and previous quality of life as important factors for a successful salvage.[9] Our results confirm that time to recurrence yields important prognostic information for the success of salvage.[24, 40, 41] This is the first attempt to determine subgroups of patients for whom curative treatment of second events may be available. Patients who are unlikely to be treated curatively for their next event might benefit from a follow-up program that focuses more on quality of life than on the early detection of new disease.

A limitation of this study is that changes in patient-related factors such as smoking, alcohol use and ASA-score could not be taken into account as these data were only available at the time of the first diagnosis.[42] As the Karnofsky score was only available in 44% of the patients, we could not include this parameter in our prediction models.
Strengths of this study are the large, site-specific patient cohort that was followed by a strict protocol with very high compliance rates and the description both first and second events. By the use of competing-risk analysis, a more accurate estimation of absolute risks is given than the Kaplan-Meyer method which usually over-estimates the cumulative risk of events when competing risks, like mortality, occur.

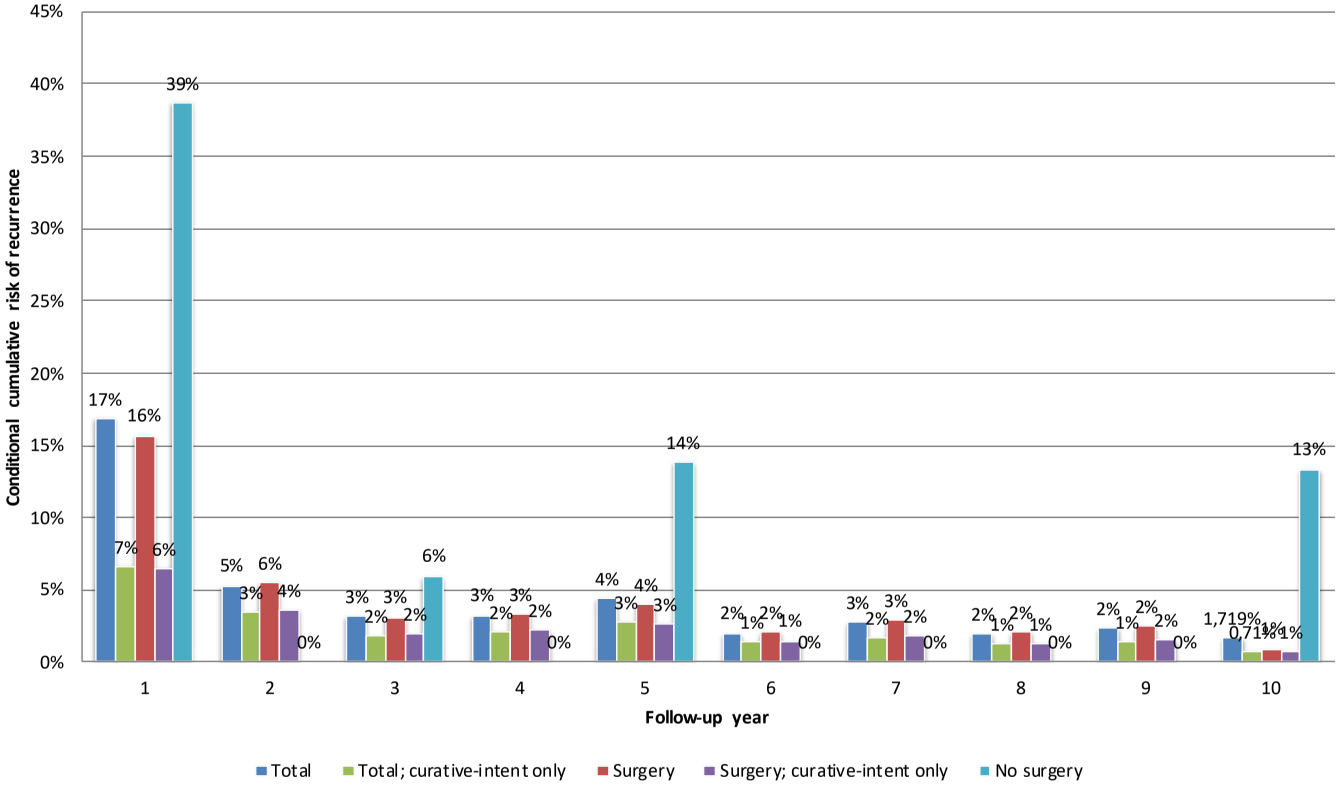
Our study shows that a two-year follow-up period is sufficient for the detection of LRRs. Longer follow-up may be indicated on an individual basis for treatment-related morbidities and dental rehabilitation.[43, 44] We therefore advocate a personalized follow-up schedule with a "core follow-up" for 2 years after which frequency, type of clinician and duration are tailored to the patient's needs. In order to timely diagnose new disease after discharge, patients should be educated to recognize symptoms of new disease.[36]

Our findings support a follow-up time of 2 years after curative-intent treatment for OSCC. Longer follow-up may be needed for some individual patients due to treatment-related morbidities and psychological needs. Based on the patterns of occurrence of third events, a separate follow-up protocol after curative treatment of a second event is not needed. The two prediction models developed in this study might, after validation, be a good starting point when personalizing OSCC follow-up. In order to further optimize the guidelines for follow-up and determine the optimal duration of follow-up future research should focus on elucidating the benefits and risks of risk-stratified follow-up and its influence on survival or quality of life.

References

1. 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 1990s. Eur J Cancer. 2008;44: 1345-1389.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66: 7-30.
3. van Dijk BA, Brands MT, Geurts SM, Merkx MA, Roodenburg JL. Trends in oral cavity cancer incidence, mortality, survival and treatment in the Netherlands. Int J Cancer. 2016;139: 574-583.
4. Rogers SN, Brown JS, Woolgar JA, et al. Survival following primary surgery for oral cancer. Oral Oncol. 2009;45: 201-211.
5. Mucke T, Wagenpfeil S, Kesting MR, Holzle F, Wolff KD. Recurrence interval affects survival after local relapse of oral cancer. Oral Oncol. 2009;45: 687-691.
6. Brands MT, Brennan PA, Verbeek ALM, Merkx MAW, Geurts SME. Follow-up after curative treatment for oral squamous cell carcinoma. A critical appraisal of the guidelines and a review of the literature. Eur J Surg Oncol. 2018;44: 559-565.
7. Boysen M, Lovdal O, Tausjo J, Winther F. The value of follow-up in patients treated for squamous cell carcinoma of the head and neck. Eur J Cancer. 1992;28: 426-430.
8. Kothari P, Trinidade A, Hewitt RJD, Singh A, O'Flynn P. The follow-up of patients with head and neck cancer: an analysis of 1,039 patients. Eur Arch Otorhinolaryngol. 2011;268: 1191-1200.
9. Ho AS, Kraus DH, Ganly I, Lee NY, Shah JP, Morris LG. Decision making in the management of recurrent head and neck cancer. Head Neck. 2014;36: 144-151.
10. Liu CH, Chen HJ, Wang PC, Chen HS, Chang YL. Patterns of recurrence and second primary tumors in oral squamous cell carcinoma treated with surgery alone. Kaohsiung J Med Sci. 2013;29: 554-559.
11. Merkx MA, van Gulick JJ, Marres HA, et al. Effectiveness of routine follow-up of patients treated for T1-2N0 oral squamous cell carcinomas of the floor of mouth and tongue. Head Neck. 2006;28: 1-7.
12. Sasaki M, Aoki T, Karakida K, et al. Postoperative follow-up strategy in patients with oral squamous cell carcinoma. J Oral Maxillofac Surg. 2011;69: e105-111.
13. Taslim SJ, Leemans CR, van der Waal I, Karagozoglu KH. Follow-up of oral cancer patients: three uneventful years may be enough. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122: 434-439.
14. Crawford B, Greenberg DD. patient surveillance after cancer treatment. New York: Springer, 2013.
15. Nederlandse Werkgroep Hoofd-halstumoren. Richtlijn Mondholte- en Orofarynxcarcinoom Alphen aan den Rijn: Van Zuiden communications B.V. , 2004.
16. Flynn CJ, Khaouam N, Gardner S, et al. The value of periodic follow-up in the detection of recurrences after radical treatment in locally advanced head and neck cancer. Clin Oncol (R Coll Radiol). 2010;22: 868-873.
17. Cooney TR, Poulsen MG. Is routine follow-up useful after combined-modality therapy for advanced head and neck cancer? Arch Otolaryngol Head Neck Surg. 1999;125: 379-382.
18. Warren S, Gates L. Multiple malignant tumors, a survey of the literature and statistical study. Am J Cancer. 1932;16: 1358-1414.
19. Curtis R, Ries L. New malignancies among cancer survivors: SEER Cancer Registries 1973-2000. Bethesda: National Cancer Institute, 2006:9-14.
20. Coviello V, Boggess M. Cumulative incidence estimation in the presence of competing risks. Stata Journal. 2004;4: 103-112.
21. Skuladottir H, Olsen JH. Conditional survival of patients with the four major histologic subgroups of lung cancer in Denmark. J Clin Oncol. 2003;21: 3035-3040.
22. NCCN. NCCN Clinical Practice Guidelines in Oncology. Version 2.2016 — October 11, 20162016.
23. Kissun D, Magennis P, Lowe D, Brown JS, Vaughan ED, Rogers SN. Timing and presentation of recurrent oral and oropharyngeal squamous cell carcinoma and awareness in the outpatient clinic. Br J Oral Maxillofac Surg. 2006;44: 371-376.
24. Kowalski LP. Results of salvage treatment of the neck in patients with oral cancer. Arch Otolaryngol Head Neck Surg. 2002;128: 58-62.

25. Vaamonde P, Martin C, del Rio M, LaBella T. Second primary malignancies in patients with cancer of the head and neck. Otolaryngol Head Neck Surg. 2003;129: 65-70.
26. Liu G, Dierks EJ, Bell RB, Bui TG, Potter BE. Post-therapeutic surveillance schedule for oral cancer: is there agreement? Oral Maxillofac Surg. 2012;16: 327-340.
27. Ritoe SC, Krabbe PF, Kaanders JH, van den Hoogen FJ, Verbeek AL, Marres HA. Value of routine follow-up for patients cured of laryngeal carcinoma. Cancer. 2004;101: 1382-1389.
28. De Zoysa N, Lee A, Joshi A, et al. Developing a follow-up surveillance protocol in head and neck oncological surgery: enhanced 'traffic light' surveillance - a prospective feasibility study. Clin Otolaryngol. 2017;42: 446-450.
29. Jung YH, Song CM, Park JH, et al. Efficacy of current regular follow-up policy after treatment for head and neck cancer: Need for individualized and obligatory follow-up strategy. Head Neck. 2014;36: 715-721.
30. Agrawal A, Hammond TH, Young GS, Avon AL, Ozer E, Schuller DE. Factors affecting long-term survival in patients with recurrent head and neck cancer may help define the role of post-treatment surveillance. Laryngoscope. 2009;119: 2135-2140.
31. Fan KH, Wang HM, Kang CJ, et al. Treatment results of postoperative radiotherapy on squamous cell carcinoma of the oral cavity: coexistence of multiple minor risk factors results in higher recurrence rates. Int J Radiat Oncol Biol Phys. 2010;77: 1024-1029.
32. Brandwein-Gensler M, Teixeira MS, Lewis CM, et al. Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. Am J Surg Pathol. 2005;29: 167-178.
33. Huang TY, Hsu LP, Wen YH, et al. Predictors of locoregional recurrence in early stage oral cavity cancer with free surgical margins. Oral Oncol. 2010;46: 49-55.
34. Ghantous Y, Bahouth Z, Abu El-Naaj I. Clinical and genetic signatures of local recurrence in oral squamous cell carcinoma. Arch Oral Biol. 2018;95: 141-148.
35. Montero PH, Yu C, Palmer FL, et al. Nomograms for preoperative prediction of prognosis in patients with oral cavity squamous cell carcinoma. Cancer. 2014;120: 214-221.
36. Kanatas A, Bala N, Lowe D, Rogers SN. Outpatient follow-up appointments for patients having curative treatment for cancer of the head and neck: are the current arrangements in need of change? Br J Oral Maxillofac Surg. 2014;52: 681-687.
37. Wong LY, Wei WI, Lam LK, Yuen AP. Salvage of recurrent head and neck squamous cell carcinoma after primary curative surgery. Head Neck. 2003;25: 953-959.
38. Lim JY, Lim YC, Kim SH, Byeon HK, Choi EC. Factors predictive of successful outcome following salvage treatment of isolated neck recurrences. Otolaryngol Head Neck Surg. 2010;142: 832-837.
39. Argiris A, Li Y, Forastiere A. Prognostic factors and long-term survivorship in patients with recurrent or metastatic carcinoma of the head and neck. Cancer. 2004;101: 2222-2229.
40. Goodwin WJ, Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope. 2000;110: 1-18.
41. Kernohan MD, Clark JR, Gao K, Ebrahimi A, Milross CG. Predicting the prognosis of oral squamous cell carcinoma after first recurrence. Arch Otolaryngol Head Neck Surg. 2010;136: 1235-1239.
42. Bosetti C, Gallus S, Peto R, et al. Tobacco smoking, smoking cessation, and cumulative risk of upper aerodigestive tract cancers. Am J Epidemiol. 2008;167: 468-473.
43. Pagh A, Grau C, Overgaard J. A longitudinal study of follow-up activities after curative treatment for head and neck cancer. Acta Oncol. 2015;54: 813-819.
44. Wetzels JW, Koole R, Meijer GJ, de Haan AF, Merkx MA, Speksnijder CM. Functional benefits of implants placed during ablative surgery: A 5-year prospective study on the prosthodontic rehabilitation of 56 edentulous oral cancer patients. Head Neck. 2016;38 Suppl 1: E2103-2111.



Appendix Fig 1. Annual conditional risk of recurrence (all, and only for recurrences treated with curative-intent), total (n=594), those surgically treated (n=563), and non-surgically treated (n=31).

Appendix Table 1. Prognostic factors for the occurrence of recurrent disease after curative-intent surgical treatment of an OSCC: univariable competing risk regression analyses after event 1 (n=563) and event 2 (n=105), respectively.

		First event (N=563)					Second event (N=105)				
		No	%	sHRR (95% CI)	Gray's p-value	5-yr risk of recurrence	No	%	sHRR (95% CI)	Gray's p-value	5-yr risk of recurrence
Patient characteristics											
Gender	Male	336	60%	Ref.	0.51	28%	62	59%	Ref.	0.32	29%
	Female	227	40%	1.1 (0.8; 1.5)		29%	43	41%	1.6 (0.9; 3.1)		48%
Age	<40 years	24	4%	1.7 (0.8; 3.5)	<0.01		7	6%	0.7 (0.2; 3.2)	0.83	
	40-59 years	225	40%	Ref.		40-59: 23%	45	43%	Ref.		40-59: 36%
	≥60 years	314	56%	1.4 (1.1;2.0)		<40|≥60: 32%	53	51%	1.0 (0.5; 1.8)		<40|≥60: 36%
ASA score	I	137	24%	Ref.	0.25	25%	29	28%	Ref.	0.25	30%
	II	310	55%	1.2 (0.8; 1.8)		28%	58	55%	1.5 (0.7; 3.3)		38%
	III or IV	92	16%	1.2 (0.7; 2.0)		30%	13	12%	1.6 (0.5; 5.4)		38%
	Unknown	24	4%				5	5%			
Malignancies in the past	No	530	94%	Ref.	0.03	30%	103	98%	Ref.	0.59	50%
	Yes	33	6%	**0.2 (0.1;0.8)***		9%	2	2%	1.4 (0.2; 7.9)		36%
Smoking and alcohol	Never smoker, none-moderate alcohol use	95	17%	Ref.	0.16	34%	25	24%	Ref.	0.54	43%
	(Ex) smoker, none-moderate alcohol use	204	36%	0.8 (0.5; 1.2)		28%	37	35%	1.1 (0.5; 2.7)		40%
	Problematic alcohol use	195	35%	**0.6 (0.4; 1.0)***		25%	31	30%	0.6 (0.2; 1.6)		25%
	Unknown	69	12%				12	11%			
Tumor characteristics											
Location	Tongue	212	38%	Ref.	<0.01	BM: 48%	20	19%	Ref.	0.15	BM: 88%
	Buccal mucosa (BM)	45	8%	**2.3 (1.4;3.7)***		Other: 27%	8	8%	**3.0 (1.1; 8.4)***		Other: 32%
	Floor of the mouth	195	35%	1.0 (0.7; 1.5)			16	15%	0.8 (0.2; 2.9)		
	Retromolar trigone	43	8%	0.9 (0.5; 1.7)			4	4%	1.1 (0.4; 2.7)		
	Alveolar process	64	11%	1.7 (1.1; 2.6)			14	13%	1.5 (0.5; 4.4)		
	Other	4	1%	0.9 (0.1; 7.4)			43	41%	N.A.		

Appendix Table 1. Continued.

		First event (N=563)					Second event (N=105)				
		No	%	sHRR (95% CI)	Gray's p-value	5-yr risk of recurrence	No	%	sHRR (95% CI)	Gray's p-value	5-yr risk of recurrence
Tumor characteristics											
Pathological T-stage	1 2 3 4 (a+b) Unknown	221 210 37 95 -	39% 37% 7% 17%	Ref. 1.0 (0.7; 1.5) 0.9 (0.5; 1.9) 1.4 (0.9; 2.1)	0.21	27% 27% 22% 36%	36 9 5 5 50	34% 9% 5% 5% 48%	Ref. **3.6 (1.4; 9.4)*** 1.3 (0.3; 6.1) 2.1 (0.5; 9.7)	0.05	32% 80% 40% 50%
Pathological N-stage	0 1 2 Unknown	368 68 127	65% 12% 23%	Ref. 1.0 (0.6; 1.7) **1.6 (1.1; 2.3)***	<0.01	26% 27% 37%	54 17 10 24	51% 16% 10% 23%	Ref. 0.5 (0.2; 1.3) 1.2 (0.4; 4.0)	0.40	46% 27% 40%
Optimal treatment	Yes No Unknown	504 54 5	90% 10% 1%	Ref. **2.0 (1.3; 3.1)***	<0.01	27% 51%	81 22 2	77% 21% 2%	Ref. **1.8 (0.9; 3.5)***	0.02	32% 73%
Surgery	Yes No	N.A.					88 17	84% 16%	Ref. 0.4 (0.1; 1.5)	0.42	40% 19%
Histological characteristics											
Differentiation tumor	Well Moderate Poor Unknown	85 369 78 31	15% 66% 14% 6%	Ref. 0.8 (0.6; 1.2) 1.1 (0.6; 1.8)	0.45	33% 26% 34%	14 37 16 38	13% 35% 15% 36%	Ref. 2.1 (0.7; 6.7) 1.9 (0.5; 7.2)	0.37	31% 51% 44%
Resection margins	Negative margins Positive margins Unknown	460 87 16	83% 15% 3%	Ref 1.6(1.1;2.4)	0.44	26% 38%	47 14 44	45% 13% 42%	Ref 5.4 (2.5;11.6)	<0.001	26% 86%
Perineural growth	No Yes No surgery Unknown	338 181 N.A. 44	60% 32% 8%	Ref. 1.3 (0.9; 1.7)	0.09	26% 32%	38 9 41 17	36% 9% 39% 16%	Ref. **3.0 (1.2; 7.6)*** 0.8 (0.4; 1.8)	0.05	38% 56% 27%

Vasoinvasive growth	No Yes No surgery Unknown	351 164 N.A. 48	62% 29% 9%	Ref. **1.5 (1.1; 2.1)***	<0.01	25% 35%	36 8 41 20	34% 8% 39% 19%	Ref. **3.4 (1.3; 8.9)*** 0.8 (0.4; 1.8)	0.02	39% 63% 27%
Spidery growth	No Yes No surgery Unknown	339 166 N.A. 58	60% 29% 11%	Ref. 1.0 (0.7; 1.4)	0.85	27% 27%	29 13 41 22	28% 12% 39% 21%	Ref. **2.3 (0.9; 5.6)*** 1.0 (0.4; 2.2)	0.11	36% 54% 27%
Bone invasion	No Yes No surgery Unknown	476 85 N.A. 2	85% 15% 0%	Ref. 1.3 (0.9; 1.9)	0.11	27% 33%	57 4 40 4	54% 4% 38% 4%	Ref. **3.2 (1.2; 8.9)*** 0.7 (0.3; 1.4)	0.09	41% 67% 25%
Extranodal growth	No Yes No cervical node dissection Unknown	379 81 100 3	68% 14% 18% 0%	Ref. **1.7 (1.1; 2.5)*** **1.6 (1.1; 2.3)***	<0.01	25% 37% 35%	31 21 47 6	30% 50% 45% 5%	Ref. 0.7 (0.3; 1.9) 0.7 (0.4; 1.5)	0.64	40% 34% 37%
Invasion depth in mm	<4mm ≥4mm Unknown	117 388 58	21% 69% 10%	Ref. 0.8 (0.5; 1.1)	0.24	32% 26%	17 25 63	16% 24% 60%	Ref. **2.4 (0.9; 6.7)***	0.08	25% 58%

*p<0.10
N.A. not applicable

Appendix Table 2. Univariable logistic regression for treatment intent at time of recurrence of an OSCC (curative 1, palliative 0), in initially surgically treated patients with a second event and all relapsed patients with a third event.

		Treatment intent second event (N=177)				Treatment intent third event (N=38)			
			N	(%) curative	Univariable OR (95% CI)		N	(%) curative	Univariable OR (95% CI)
Total		177	102	58%		38	16	41%	
Patient characteristics									
Gender	Male	102	58	57%	Ref.	18	6	33%	Ref.
	Female	75	44	59%	1.1 (0.6; 2.0)	20	10	50%	2.0 (0.5; 7.4)
Age	<40years	9	7	78%	1.5 (0.3; 7.7)	2	1	50%	1.7 (0.1; 31.9)
	40-60years	61	43	70%	Ref.	16	6	38%	Ref.
	≥60years	107	52	49%	**0.4 (0.2; 0.8)***	20	9	45%	1.4 (0.4; 5.2)
ASA score	I	38	28	74%	Ref.	9	5	56%	Ref.
	II	98	59	60%	0.5 (0.2; 1.2)	21	10	48%	0.7 (0.2; 3.5)
	III or IV	28	11	39%	**0.2 (0.1; 0.7)***	5	1	20%	0.2 (0.0; 2.6)
	Unknown	13	4	31%		3	0	0%	
Malignancies in the past	No	173	101	58%	Ref.	37	16	43%	N.A.
	Yes	4	1	25%	0.2 (0.0; 2.3)	1	0	0%	
Smoking and alcohol	Never smoker, none-moderate alcohol use	36	25	69%	Ref.	10	4	40%	Ref.
	(Ex) smoker, none-moderate alcohol use	64	36	56%	0.6 (0.2; 1.3)	15	7	47%	1.3 (0.3; 6.6)
	Problematic alcohol use	53	29	55%	0.5 (0.2; 1.3)	7	3	43%	1.1 (0.2; 8.0)
	Unknown	24	12	50%		5	2	40%	
Tumor characteristics									
LocatioN	Tongue	58	37	64%	Ref.	6	3	50%	Ref.
	Buccal mucosa	23	10	43%	**0.4 (0.2; 1.2)***	7	3	43%	0.8 (0.1; 6.7)
	Floor of the mouth	55	36	65%	1.1 (0.5; 2.3)	4	0	0%	-
	Alveolar process	27	13	48%	0.5 (0.2; 1.3)	6	4	67%	2.0 (0.2; 20.6)
	Retromolar trigone or other	14	6	43%	0.4 (0.1; 1.4)	15	6	40%	0.7 (0.1; 4.5)
Pathological T-stage	1	67	57	85%	Ref.	13	10	77%	Ref.
	2	64	36	56%	**0.2 (0.1; 0.5)***	6	0	0%	-
	3	10	3	30%	**0.1 (0.2; 0.3)***	2	1	50%	0.3 (0.0; 6.4)
	4 (a+b)	36	6	17%	**0.04 (0.01; 0.1)***	2	0	0%	-
	Unknown					15	5	33%	

Pathological N-stage	0 1 2 Unknown	107 19 51	78 13 11	73% 68% 22%	Ref. 0.8 (0.3; 2.3) **0.1 (0.1; 0.2)***	25 5 4 4	12 3 1 0	48% 60% 25% 0%	Ref. 2.8 (0.3; 30.4) 4.5 (0.3; 80.6)
Optimal treatment	Yes No Unknown	152 24 1	91 10 1	60% 42% 100%	Ref. **0.5 (0.2; 1.1)***	27 11	13 3	48% 27%	Ref. 2.5 (0.5; 11.4)
Surgery	Yes No	N.A.	N.A.	N.A.		35 3	15 1	43% 33%	Ref. 0.7 (0.1; 8.1)
Histological characteristics									
Differentiation tumor	Well Moderate Poor Unknown	30 110 28 9	19 67 12 4	63% 61% 43% 44%	Ref. 0.9 (0.4; 2.0) 0.4 (0.2; 1.2)	4 20 7 7	2 8 2 4	50% 40% 29% 57%	Ref. 0.7 (0.1; 5.7) 0.4 (0.0; 5.2)
Resection margins	Negative margins Positive margins Unknown	138 34 5	90 10 2	65% 29% 40%	Ref. **0.2 (0.1;0.5)***	17 11 10	9 3 4	53% 27% 40%	Ref. 0.3 (0.1;1.7)
Perineural growth	No Yes No surgery Unknown	100 61 N.A. 16	74 21 7	74% 34% 44%	Ref. **0.2 (0.1; 0.4)***	15 5 11	7 0 5	47% 0% 45%	Ref. - 1.0 (0.2; 4.5)
Vasoinvasive growth	No Yes No surgery Unknown	95 65 N.A. 17	63 31 8	66% 48% 47%	Ref. **0.5 (0.2; 0.9)***	15 5 11	6 2 5	40% 40% 45%	Ref. 1.0 (0.1; 7.9) 1.3 (0.3; 6.0)
Spidery growth	No Yes No surgery Unknown	10547 N.A.25	73 20 9	70% 42% 36%	Ref. **0.3 (0.2; 0.7)***	10 8 11	5 2 5	50% 25% 45%	Ref. 0.3 (0.0; 2.5) 0.8 (0.1; 4.6)
Bone invasion	No Yes No surgery Unknown	144 32 N.A.1	96 6 0	67% 19% 0%	Ref. **0.1 (0.0; 0.3)***	24 2 10	10 0 4	42% 0% 40%	Ref. - 0.9 (0.2; 4.2)

Appendix Table 2. Continued.

		Treatment intent second event (N=177)				Treatment intent third event (N=38)			
			N	(%) curative	Univariable OR (95% CI)		N	(%) curative	Univariable OR (95% CI)
Histological characteristics									
Extranodal growth	No	105	64	61%	Ref.	15	7	47%	Ref.
	Yes	32	11	35%	**0.4 (0.2; 0.8)***	6	2	33%	0.6 (0.1; 4.1)
	No cervical node dissection	40	27	68%	1.3 (0.6; 2.9)	15	7	47%	1.0 (0.2; 4.2)
	Unknown								
Invasion depth in mm	<4mm	43	35	81%	Ref.	6	4	67%	Ref.
	≥4mm	10925	56	51%	**0.2 (0.1; 0.6)***	14	4	29%	0.2 (0.0; 1.6)
	Unknown		11	44%					

*p<0.10

Chapter 5

Second primary tumours after squamous cell carcinoma of the oral cavity

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Abstract

Background: The aim of this study was to determine the incidence, location and timing of second primary tumours (SPT) after diagnosis of oral squamous cell carcinoma (OSCC) and after head and neck squamous cell carcinoma (HNSCC) and relate the risk of SPT to the general population in order to provide empirical evidence to develop evidence-based and individualized follow-up programs.

Materials and methods: All patients diagnosed with OSCC or HNSCC in the Netherlands in 1991-2015 were selected from the Netherlands Cancer Registry. Cumulative incidence rates and Standardized Incidence Ratios (SIR) were calculated. Analysis were stratified by incidence period and age at primary diagnosis of the index tumour, follow-up time, and site of the SPT.

Results: We included 11263 patients with OSCC from a population of 34244 patients with HNSCC, of which the median follow-up time was 4.0 years. The 5-year risk of SPT and SIR (95% confidence intervals) were respectively 0.13 (0.13-0.14) and 3.0 (2.9-3.1) for OSCC, and 0.13 (0.13-0.14) and 2.6 (2.5-2.7) for all HNSCC sites combined. The risk of a SPT was continuous over follow-up time and calendar period but decreased with an increasing age at diagnosis of the index tumour up to the age of 75 and there were differences in sites of SPT.

Conclusions: OSCC SPT develop in different patterns and at different locations than after HNSCC. This warrants a separate follow-up protocol for each subsite and can form the basis of the development of a more individualized follow-up protocol after OSCC.

Introduction

The incidence and survival of patients with oral squamous cell carcinoma (OSCC) is increasing,[1] but the risk of new disease such as locoregional recurrences and second primary tumours (SPT) is still high.[2] After treatment with curative intent of the primary tumour (further called index tumour), patients enroll in a follow-up program of five years or even lifelong mainly aiming at early detection of new disease.[3] The follow-up schedule for OSCC is often based on guidelines that are uniform for the entire group of head and neck cancer patients. Head and neck squamous cell carcinoma (HNSCC) is a disease that can develop at several subsites, which have a heterogeneous etiology, different treatment and different pattern of developing new disease.[3, 4]

As most locoregional recurrences after OSCC occur in the first two years after treatment, the emphasis from a survival point of view after two years will be on the diagnosis of SPT.[3, 5]

The incidence and location of SPT after HNSCC differs per index tumour site and is also influenced by individual factors such as smoking cessation after diagnosis.[4, 6, 7] Empirical data on the risks of SPT are needed in order to determine whom to screen and with which tests and frequency. The goal of this study is to determine the incidence, location and timing of SPT in patients diagnosed with OSCC in particular and investigate the differences with patients diagnosed with an index HNSCC and furthermore with the general population in the Netherlands in 1991-2015.

Materials and methods

Patients

Patients diagnosed with HNSCC (ICD-O-3 morphology M8050–M8089, topography; C00.3-5, C01, C02-6, C09, C10, C12, C13 and C32) in the Netherlands from 1991-2015 were selected from the Netherlands Cancer Registry (NCR), leading to 47914 included patients.[8] Patients with unknown tumour stage (n=599), distant metastasis (n=917), and patients with a previous or synchronous (up to 6 months after diagnosis) malignancy other than non-melanoma skin cancer without regional and distant metastasis (n=8301) were excluded. Patients with a follow-up period of less than 6 months (n=3873; of which 814 were diagnosed from July 1st until December 31st in 2015; 3038 patients died and 21 were lost to follow-up) were also excluded from the analysis, leaving 34224 records.

Vital status and date of death were obtained by linkage to the municipal records. Vital status and occurrence of SPT was complete until December 31st, 2015.

Definitions

Tumour stage was recorded using the International Union against Cancer (UICC) TNM classification according to the 4th, fully revised edition from 1991–1992, the 4th edition 2nd revision from 1993–1998, the 5th edition from 1999–2002, the 6th edition from 2003–2009 and the 7th edition from 2010-2015. There were no relevant changes in stage classification for HNSCC in this time period.
A SPT was defined as a tumour arising in a different localization according to the 3-digit ICD-O-3 topography code or if the 3-digit ICD-O-3 code was the same, but the histological subtype was different.

Statistical analysis

All analyses were performed for the total group of HNSCC patients and more specifically for OSCC. HNSCC consisted of 4 subsites: oral cavity, oropharynx, hypopharynx and larynx.
Follow-up ended at date of diagnosis of the first SPT (if there were 2 SPT within 90 days, these were both considered synchronous), date of death, or data-censoring date (December 31st, 2015 or date of lost to follow-up, e.g., in case of emigration). Cumulative incidence of SPT over follow-up time was calculated using the competing risk method, and adjusted for the competing event "death", as well as for competing event "other SPT". (stcompet in Stata/SE14.1 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.)[9]
We estimated the standardized incidence ratio (SIR) to assess the potential excess occurrence of a SPT after having an index OSCC or HNSCC when compared with the general population. The SIR was calculated by dividing the number of SPT observed by the expected number calculated from the cancer incidence rates in the Dutch general population of similar age, sex and calendar year.

Results

Study population

Of the 34224 patients with HNSCC, 11263 (38%) were patients with OSCC. 58% of OSCC patients and 72% of HNSCC patients were male (Table 1). Median age was 62 years for both OSCC and HNSCC patients. Patient and treatment characteristics are summarized in Table 1.

Cumulative incidence (risk)

The median follow-up time was 3.8 year for OSCC and 4.0 year for HNSCC, 22% of the patients developed an SPT after both an index HNSCC and OSCC.

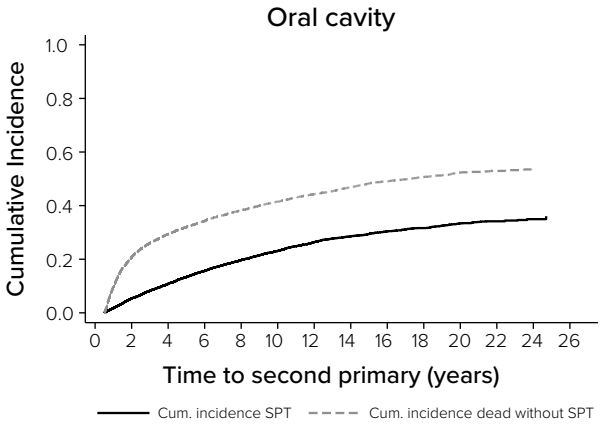
Table 1. Patient and tumour characteristics by subsite of the index tumour

		Head and neck all sites		Oral cavity	
		n	%	n	%
	Total	34224	100%	11263	100%
Sex	Male	24556	72%	6492	58%
	Female	9668	28%	4771	42%
Age at time of diagnosis (years)	<46	2177	6%	1003	9%
	46-60	13068	38%	4104	36%
	61-75	14369	42%	4286	38%
	>75	4610	13%	1870	17%
Incidence period	1991-1995	5989	18%	1803	16%
	1996-2000	6495	19%	1970	17%
	2001-2005	6980	20%	2266	20%
	2006-2010	7549	22%	2666	24%
	2011-2015	7211	21%	2558	23%
Stage	I	10529	31%	4190	37%
	II	6460	19%	1906	17%
	III	5072	15%	1419	13%
	IVm0	12163	36%	3748	33%
Treatment	Surgery only	8206	24%	5737	51%
	Radiotherapy alone	13563	40%	725	6%
	Surgery + radiotherapy	7103	21%	3670	33%
	Radiotherapy + chemotherapy	4022	12%	440	4%
	Surgery + chemotherapy + radiotherapy	586	2%	348	3%
	Other	299	1%	150	1%
	No treatment	445	1%	193	2%
SPT*	Yes	7679	22%	2465	22%
	No	26545	78%	8798	78%

* Second primary tumour; follow-up until January 2016

The different subsites of the head and neck showed a differential distribution in at which sites SPTs developed (Appendix Table 1). The 5-year risks (95% confidence intervals) of SPT for OSCC and HNSCC was 0.13 (0.13-0.14) (Fig. 1a and b). The risks of SPT were stable across the follow-up period for both OSCC and HNSCC (Fig. 2a and b).

a.



b.

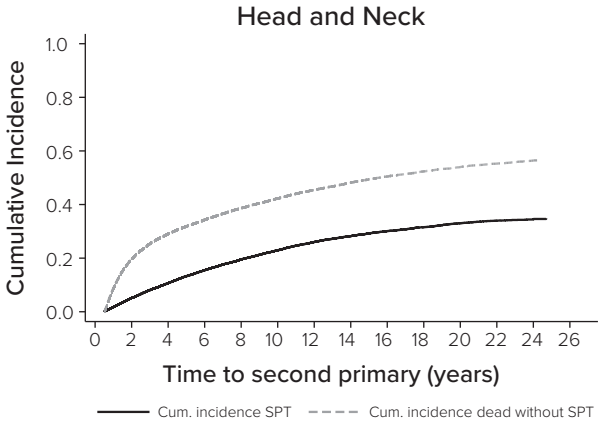
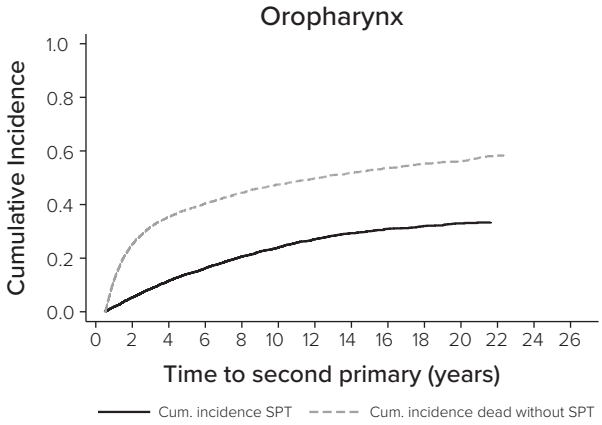


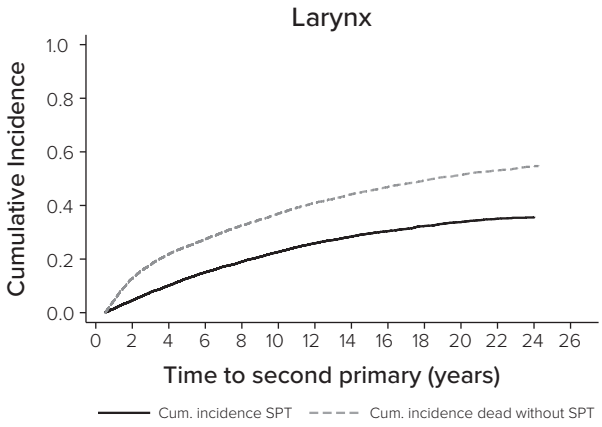
Figure 1. Cumulative incidence of a SPTs after OSCC, HNSCC and other HNSCC subsites.

a. Cumulative incidence of SPTs over time for an index OSCC
b. Cumulative incidence of SPTs over time for an index HNSCC
c. Cumulative incidence of SPTs over time for an index tumour of the oropharynx
d. Cumulative incidence of SPTs over time for an index tumour of the larynx
e. Cumulative incidence of SPTs over time for an index tumour of the hypopharynx

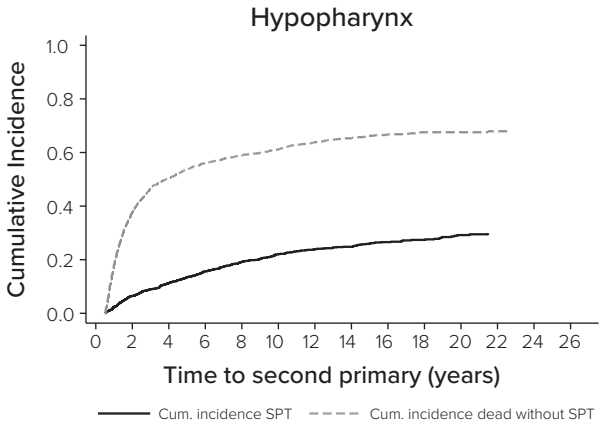
c.


Oropharynx
Cumulative Incidence
1.0
0.8
0.6
0.4
0.2
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Time to second primary (years)
Cum. incidence SPT
Cum. incidence dead without SPT

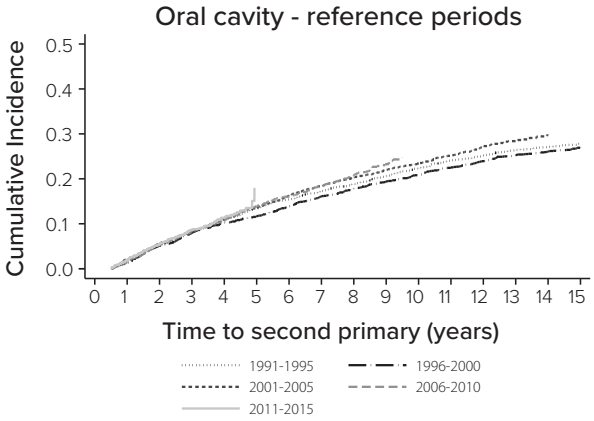
d.


Larynx
Cumulative Incidence
1.0
0.8
0.6
0.4
0.2
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Time to second primary (years)
Cum. incidence SPT
Cum. incidence dead without SPT

e.


Hypopharynx
Cumulative Incidence
1.0
0.8
0.6
0.4
0.2
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Time to second primary (years)
Cum. incidence SPT
Cum. incidence dead without SPT

a.



b.

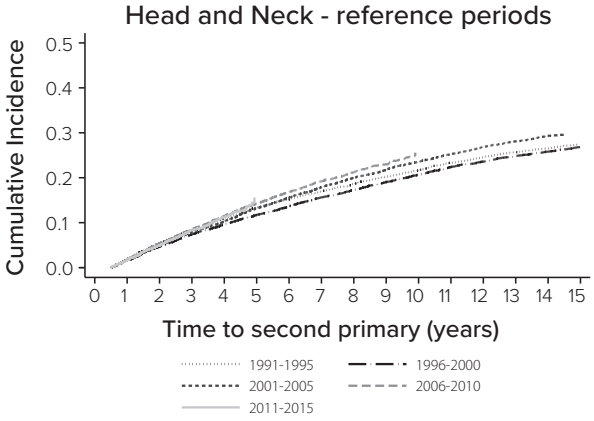
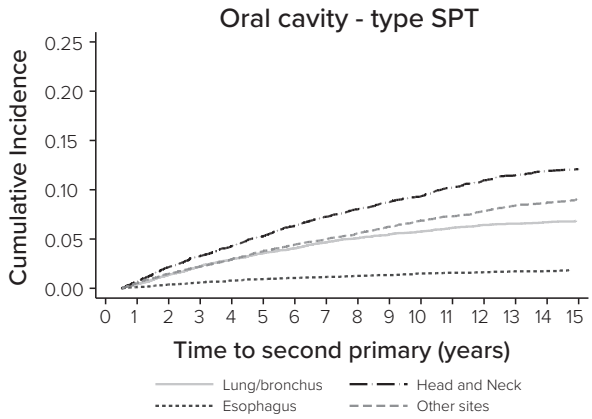


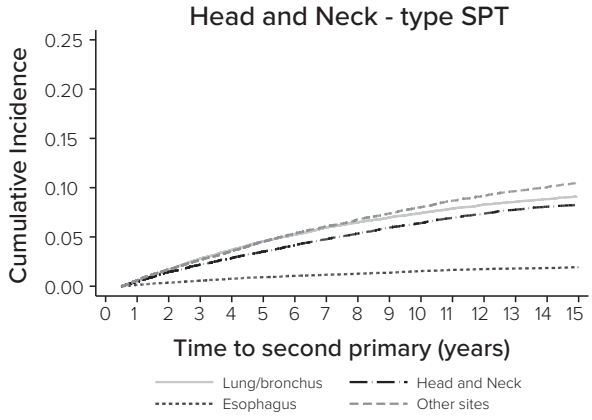
Figure 2. Cumulative incidence of STPs after an index OSCC and HNSCC by reference period, SPT-type and patient age.

a. Cumulative incidence of SPTs over time for an index OSCC by reference period
b. Cumulative incidence of SPTs over time for an index HNSCC by reference period
c. Cumulative incidence of SPTs over time for an index OSCC by type of SPT
d. Cumulative incidence of SPTs over time for an index HNSCC by type of SPT
e. Cumulative incidence of SPTs over time for an index OSCC by age at index tumour diagnosis
f. Cumulative incidence of SPTs over time for an index HNSCC by age at index tumour diagnosis

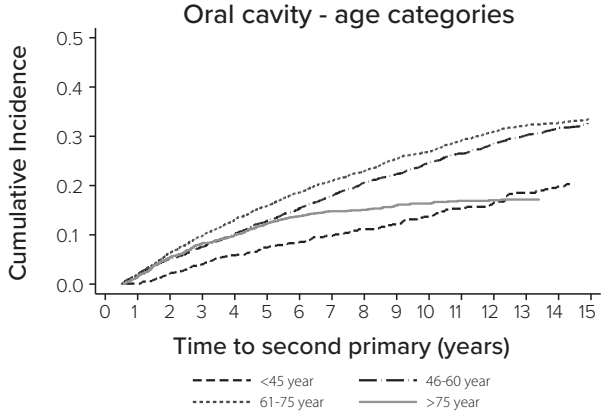
c.


Oral cavity - type SPT
Cumulative Incidence
0.25
0.20
0.15
0.10
0.05
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time to second primary (years)
Lung/bronchus
Head and Neck
Esophagus
Other sites

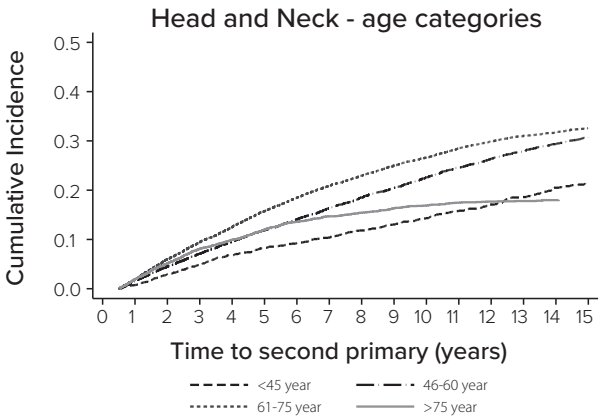
d.


Head and Neck - type SPT
Cumulative Incidence
0.25
0.20
0.15
0.10
0.05
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time to second primary (years)
Lung/bronchus
Head and Neck
Esophagus
Other sites

e.


Oral cavity - age categories
Cumulative Incidence
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time to second primary (years)
<45 year
46-60 year
61-75 year
>75 year

f.



With OSCC as index tumour, the highest 5-year risk was observed for HNSCC as SPT (0.05 (0.04-0.05)), followed by 'other sites' (0.04 (0.04-0.05)) (Fig. 2c). For HNSCC as index tumour, the highest 5-year cumulative incidence was found for 'other sites' (0.05 (0.04-0.05)), followed by lung/bronchus (0.05 (0.04-0.05)) (Fig. 2d). For OSCC, the cumulative incidence curve for lung cancer and esophageal cancer appeared to become less steep over the reported 15 years, while the SPT lines for HNSCC appeared to keep on increasing.

The risk of SPT by age-group showed similar patterns for patients primarily diagnosed with an index OSCC and HNSCC (Fig. 2e and f). Patients aged 61-75 years had the highest risk, followed by patients aged 46-60 year; patients aged <45 years had the lowest risk of SPT. In the first six years of follow-up, the risk of SPT in patients aged >75 years was similar to patients 46-60 years of age, and then leveled off.

Standardized incidence ratio

Compared with the general population, patients with OSCC index tumour have a 3 times higher risk of SPT, which is higher than for an index HNSCC (Fig. 3a and b, Appendix Table 2). The SIR of developing a SPT after both OSCC and HNSCC is continuous over follow-up years 1-5, and remains high thereafter (Fig. 3a and b, Appendix Table 2). The SIR of developing a SPT is highest for patients under the age of 46 for both OSCC and HNSCC index tumours and decreased with age (Fig. 3e and f, Appendix Table 2).

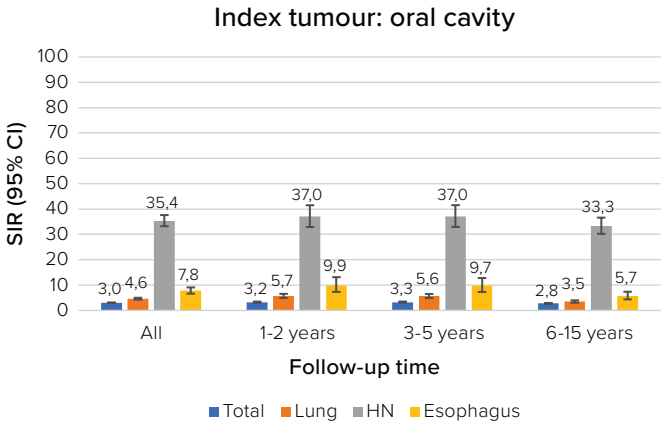
The SIR of a lung SPT decreased after five years of follow-up after an index OSCC and HNSCC and was highest in the age cohorts <46 years for both OSCC and HNSCC (Fig. 3a and b, Appendix Table 2).

The patients who had an index OSCC are at a much higher risk for a HNSCC SPT than the whole group of patients with a HNSCC index tumour. In OSCC and HNSCC, the risk is highest in those that had their index tumour <46 years which (Fig 3e and f, Appendix Table 2).

The SIRs for the different sublocations of SPT were similar over the incidence periods for both index OSCC and HNSCC (Fig. 3c and d, Appendix Table 2).

SPT of the esophagus were more common than in the general population in both OSCC and HNSCC, especially in the first two years after the index tumour (Fig 3a and b, Appendix Table 2). A higher SIR was observed in younger patients (<46 years) for both OSCC and HNSCC index cancers compared to older patients >75 years. Patients >75 years appear to be at a less increased risk of SPT of the esophagus after an index OSCC (Fig. 3e and f, Appendix Table 2).

a.



b.

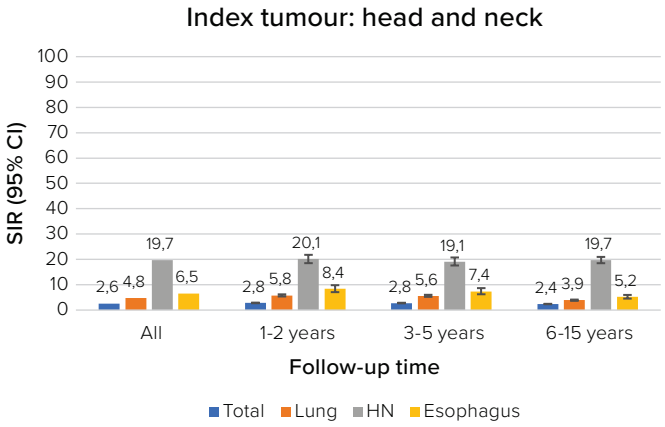
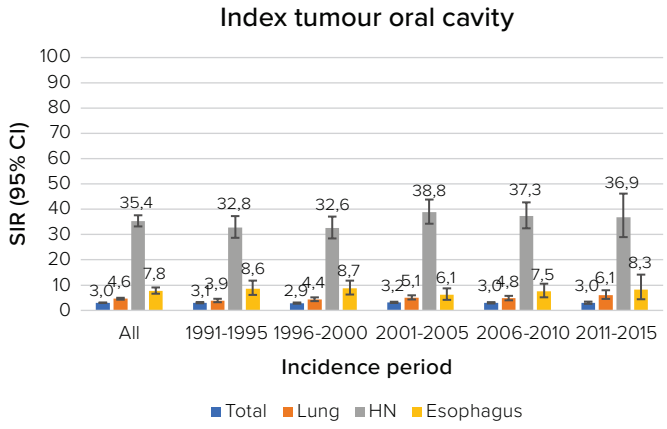


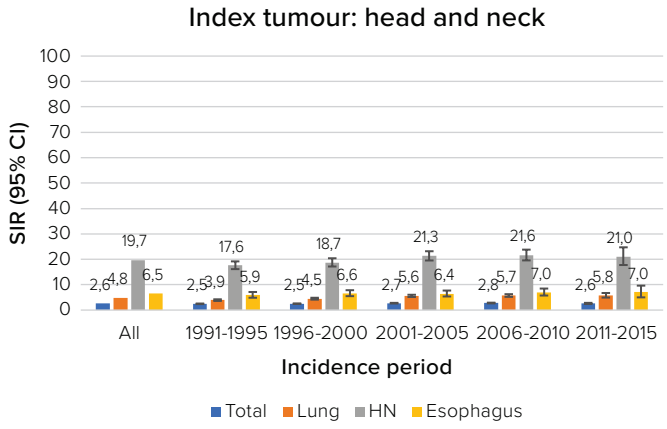
Figure 3. Standardised incidence ratio (SIR) of SPTs according to type of SPT, follow-up period (**a**,**b**), incidence period (**c**,**d**) and age category (**e**,**f**).

a. SIR of SPTs according to follow-up time for index OSCC
b. SIR of SPTs according to follow-up time for index HNSCC
c. SIR of SPTs according to incidence period for index OSCC
d. SIR of SPTs according to incidence period for index HNSCC
e. SIR of SPTs according to age classification for index OSCC
f. SIR of SPTs according to age classification for index HNSCC

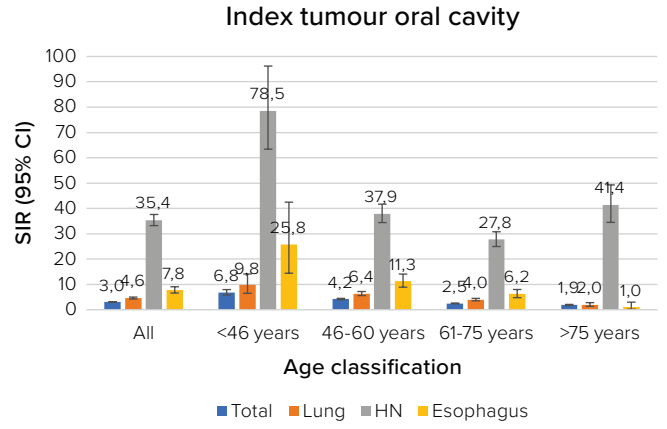
c.

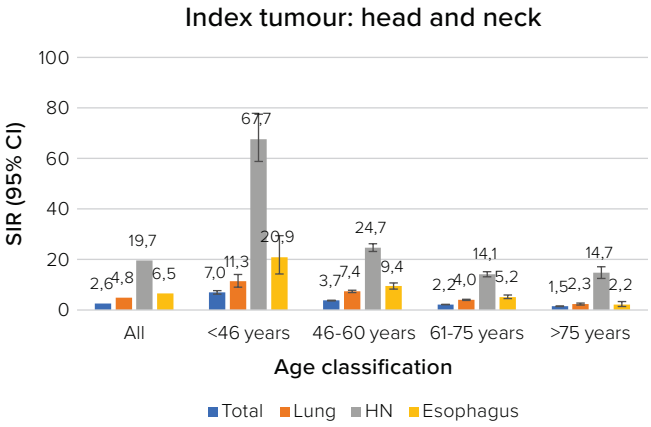

Index tumour oral cavity
SIR (95% CI)
100
90
80
70
60
50
40
30
20
10
0
3,0
4,6
35,4
7,8
3,1
3,9
32,8
8,6
2,9
4,4
32,6
8,7
3,2
5,1
38,8
6,1
3,0
4,8
37,3
7,5
3,0
6,1
36,9
8,3
All
1991-1995
1996-2000
2001-2005
2006-2010
2011-2015
Incidence period
Total
Lung
HN
Esophagus

d.


Index tumour: head and neck
SIR (95% CI)
100
90
80
70
60
50
40
30
20
10
0
2,6
4,8
19,7
6,5
2,5
3,9
17,6
5,9
2,5
4,5
18,7
6,6
2,7
5,6
21,3
6,4
2,8
5,7
21,6
7,0
2,6
5,8
21,0
7,0
All
1991-1995
1996-2000
2001-2005
2006-2010
2011-2015
Incidence period
Total
Lung
HN
Esophagus

e.


Index tumour oral cavity
SIR (95% CI)
100
90
80
70
60
50
40
30
20
10
0
3,0
4,6
35,4
7,8
6,8
9,8
78,5
25,8
4,2
6,4
37,9
11,3
2,5
4,0
27,8
6,2
1,9
2,0
41,4
1,0
All
<46 years
46-60 years
61-75 years
>75 years
Age classification
Total
Lung
HN
Esophagus



f.

Discussion

In this population-based study including 34224 HNSCC patients and 11263 patients primarily diagnosed with OSCC in the Netherlands in 1991-2015, we showed a different pattern of SPT locations after an index OSCC when compared with the entire HNSCC and the general population. The cumulative incidence rate increased continuous over follow-up time, except for patients aged 75^{+} years, where the risk leveled off after 6 years of follow-up. The cumulative incidence and SIRs were continuous over (calendar)years. The absolute risk of SPT after OSCC and HNSCC was highest in patients aged 61-75 years, whereas the SIR compared with the general population was highest for patients aged <46 years.

The dissimilarity between incidence of SPT and different locations of SPTs after an index tumour in one of the HNSCC subsites was also reported in the USA in 1975-2006 and in France in 1975-2006.[4, 10] In our study, the SIR for all SPT after an index OSCC (3.0(2.9-3.1)) was higher than observed in the USA (2.8 (2.7-2.9)) and lower than found in France (5.4 (5.0-5.9)). SIRs for the total group of SPT's after index OSCC are higher than after HNSCC in our population. Site-specific SIRs were also different; for example patients with an index OSCC have a high SIR of OSCC as SPT when compared with index HNSCC in general which is in agreement with literature. [4] Age and risk factor differences between the countries and study populations could explain the different findings between the three studies.[1, 4, 11] Age, which is strongly related to the risk of a SPT, and the starting point of observation varied between the study populations. Furthermore, the prevalence of smoking and alcohol consumption differ between the Netherlands, France and the USA.[12, 13]

Finally, comparing incidences between studies is difficult given the many different definitions of SPT that are used in literature.[3, 14] In addition, in clinical practice the difference between a SPT in the lung and a metastasis is sometimes hard to make.

Routine testing as part of the follow-up after cancer treatment should be considered as screening. If a risk of a SPT at a certain location is not elevated compared to the general population and if there is no population screening in place, it is difficult to justify screening for that tumor during follow-up. Risks of a SPT in the head and neck, lung and esophagus are high and elevated in patients with an index OSCC compared to the general population. Currently, HNSCC patients do not receive routine lung cancer screening in the Netherlands.[15] A previous study showed that biannual plain chest x-ray had no survival benefit.[16] Lung cancer screening with CT reduces mortality in certain high risk groups, with similar risk factors (smoking) as OSCC patients.[17, 18] It is expected that a large percentage of OSCC patients would meet the inclusion criteria of this study.[18] Implementing screening requires an extensive organization that is in our opinion better done by an appropriate specialty, possibly within the context of a population-based screening program.

The literature on follow-up after OSCC and HNSCC is scarce and conflicted when it comes to the survival benefits of early detection of new disease in general and SPT in specific.[3] To the best of our knowledge, there is no literature on the effects of early discovery of SPT in relation to quality of life or function. Notwithstanding the limited evidence, routine testing can only be beneficial if there is a curative treatment option available or if this leads to an increased survival or quality of life in the palliative setting when compared to no testing. Some patients may have exhausted all of their treatment options or are unable to undergo further treatment due to their comorbidities or personal preferences. The necessity and expected benefits of routine follow-up should be discussed with these patients after primary treatment.

If a follow-up consult is considered a test, the benefits for the patients depend on the accuracy of the examination, i.e. the sensitivity and specificity, and on the lead-time. This is dependent on the actual follow-up protocol that is used and the underlying incidence of the disease that is screened for.[19, 20] The Dutch guideline recommends history taking and physical examination at a follow-up consult, but does not recommend routine imaging except on strict indication.[15] The prevalence of the SPT that is screened for has to be high enough to prevent harm being brought to patients by diagnostic tests.[21] Stalpers et al. developed a calculator to determine the prevalence-based indication area to do a test (in this context

follow-up examination) or not.[22] Even though the SIR is higher, the actual incidence of SPTs is low, implying a high number needed to screen. Over a third of SPT emerge outside of the head and neck area, and would require invasive investigations for early discovery. This indicates that follow-up specifically aimed at the discovery at SPTs is not warranted and could discontinue once the risk of locoregional recurrences has minimized.[5]

There are also other ways to identify subgroups of patients who might or might not benefit from screening for SPTs.
Firstly, on the basis of etiological factors. The risk and incidence of the different SPT as well as the aetiology and risk factor profile differ per country.[4, 10] This will have consequences for what tumour to screen for, the optimal follow-up program may therefore vary between countries.
Age is another potential factor for the selection of high or low-risk groups. Our study shows that patients aged 46-75 years have the highest risk of a SPT, especially for HNSCC and oesophageal SPT. Furthermore, the risk of a SPT after an index OSCC in patients aged 75^{+} years after 6 years of follow-up is nihil, and therefore follow-up for a longer period may not be indicated.

To our knowledge, this is the first study that addresses the subject of SPT after OSCC from the follow-up perspective and focuses on the changing incidence rates throughout the timeline of survivorship. In order to definitively answer the question if follow-up after OSCC is needed several factors need to be elucidated, the most important one being the effect of routine follow-up on survival and quality of life. As the SPT incidence and prevalence of etiological factors differs, the answer to the question what to screen for, whom, and how to screen will not be the same in every population.

Due to the different distribution of SPT sites and different timing of occurrence, there is no place for a 'one size fits all' HNSCC follow-up protocol. Given the continuous risk of SPT over follow-up time after the diagnosis on the index OSCC, the five-year cut-off point for follow-up is arbitrary. This study shows that routine follow-up should either stop after two years of follow-up or continue lifelong if effectiveness is proven. Screening for a specific type of SPT might benefit certain high-risk patient populations, but certainly not all. The individual follow-up examination and the choice of additional investigations should be based on a patient's individual risk profile and discussion between the patient and their named consultant.

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References

1. van Dijk BA, Brands MT, Geurts SM, Merkx MA, Roodenburg JL. Trends in oral cavity cancer incidence, mortality, survival and treatment in the Netherlands. Int J Cancer. 2016;139: 574-583.
2. Goodwin WJ, Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope. 2000;110: 1-18.
3. Brands MT, Brennan PA, Verbeek ALM, Merkx MAW, Geurts SME. Follow-up after curative treatment for oral squamous cell carcinoma. A critical appraisal of the guidelines and a review of the literature. Eur J Surg Oncol. 2018;44: 559-565.
4. Morris LG, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol. 2011;29: 739-746.
5. Brands MT, Smeekens EAJ, Takes RP, et al. Time patterns of recurrence and second primary tumors in a large cohort of patients treated for oral cavity cancer. Cancer Med. 2019;8: 5810-5819.
6. Chuang SC, Scelo G, Tonita JM, et al. Risk of second primary cancer among patients with head and neck cancers: A pooled analysis of 13 cancer registries. Int J Cancer. 2008;123: 2390-2396.
7. Marron M, Boffetta P, Zhang ZF, et al. Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. Int J Epidemiol. 2010;39: 182-196.
8. 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: 1822-1829.
9. Coviello V, Boggess M. Cumulative incidence estimation in the presence of competing risks. Stata Journal. 2004;4: 103-112.
10. Jegu J, Binder-Foucard F, Borel C, Velten M. Trends over three decades of the risk of second primary cancer among patients with head and neck cancer. Oral Oncol. 2013;49: 9-14.
11. 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: 806-816.
12. World Health Organization. WHO report on the global tobacco epidemic 2009: implementing smoke-free environments. Geneva, Switzerland, 2009.
13. World Health Organization. Global status report on alcohol and health. Geneva, Switzerland, 2011.
14. Coyte A, Morrison DS, McLoone P. Second primary cancer risk - the impact of applying different definitions of multiple primaries: results from a retrospective population-based cancer registry study. BMC Cancer. 2014;14: 272.
15. Dutch Society for Otorinolaryngology and head and neck surgery. Guideline Head and Neck Tumors. Utrecht: Nederlandse Vereniging voor KNO, 2014.
16. Merkx MA, Boustahji AH, Kaanders JH, et al. A half-yearly chest radiograph for early detection of lung cancer following oral cancer. Int J Oral Maxillofac Surg. 2002;31: 378-382.
17. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365: 395-409.
18. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020;382: 503-513.
19. Digonnet A, Hamoir M, Andry G, et al. Post-therapeutic surveillance strategies in head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol. 2013;270: 1569-1580.
20. Liu G, Dierks EJ, Bell RB, Bui TG, Potter BE. Post-therapeutic surveillance schedule for oral cancer: is there agreement? Oral Maxillofac Surg. 2012;16: 327-340.
21. Siontis KC, Siontis GC, Contopoulos-Ioannidis DG, Ioannidis JP. Diagnostic tests often fail to lead to changes in patient outcomes. J Clin Epidemiol. 2014;67: 612-621.
22. Stalpers LJ, Nelemans PJ, Geurts SM, Jansen E, de Boer P, Verbeek AL. The indication area of a diagnostic test. Part I--discounting gain and loss in diagnostic certainty. J Clin Epidemiol. 2015;68: 1120-1128.

Appendix Table 1 Characteristics of second primary tumours (SPT) by subsite of index tumours diagnosed in 1991-2015.

	Oral cavity		Oropharynx		Larynx		Hypopharynx		All sites	
SPT type	n	%	n	%	N	%	n	%	n	%
Total SPT	2504	100%	1465	100%	3352	100%	516	100%	7837	100%
Lung/ bronchus	592	24%	422	29%	1239	38%	173	35%	2426	32%
Head and neck	1006	41%	493	34%	508	15%	139	28%	2146	28%
Oral cavity	618	25%	190	13%	120	4%	40	8%	968	13%
Oropharynx	219	9%	172	12%	145	4%	53	11%	589	8%
Larynx	63	3%	38	3%	94	3%	4	1%	199	3%
Hypopharynx	82	3%	71	5%	104	3%	33	7%	290	4%
Esophagus	158	6%	122	9%	165	5%	59	12%	504	7%
Other sites	748	30%	428	30%	1440	44%	145	29%	2761	36%

Appendix Table 2 Standardised incidence ratio (SIR) of second primary tumours (SPT) compared with the general population, according to type of SPT, follow-up period, incidence period and age classification.

		Index tumour of the oral cavity			Index tumour of the head and neck		
		Observed	Expected	SIR	Observed	Expected	SIR
SPT=any		2465	814.5	3.0 (2.9-3.1)	7679	2950.7	2.6 (2.5-2.7)
Follow-up time (years)	1-2	718	221.1	3.2 (3.0-3.5)	2153	763.3	2.7 (2.6-2.9)
	3-5	729	224.3	3.3 (3.0-3.5)	2219	801.5	2.8 (2.7-2.9)
	5-15	1018	369.1	2.8 (2.6-2.9)	3307	1385.9	2.5 (2.3-2.5)
Period of diagnosis of index tumour	1991-1995	585	191.6	3.1 (2.8-3.3)	1905	771.8	2.5 (2.4-2.6)
	1996-2000	561	194.8	2.9 (2.6-3.1)	1865	743.5	2.5 (2.4-2.6)
	2001-2005	616	194.3	3.2 (2.9-3.4)	1886	694.4	2.7 (2.6-2.8)
	2006-2010	514	171.1	3.0 (2.7-3.3)	1496	539.2	2.8 (2.6-2.9)
	2011-2015	189	62.7	3.0 (2.6-3.5)	527	201.9	2.6 (2.4 -2.8)
Age category at diagnosis of index tumour	<46 year	164	24	6.8 (5.8-8.0)	397	57.1	7.0 (6.3-7.7)
	46-60 year	1015	240.4	4.2 (4.0-4.5)	3095	827.2	3.7 (3.6-3.9)
	61-75 year	1028	411.8	2.5 (2.3-2.7)	3519	1614.7	2.2 (2.1-2.3)
	>75 year	258	138.3	1.9 (1.6-2.1)	668	451.7	1.5 (1.4-1.6)
SPT=Lung		592	128.5	4.6 (4.2-5.0)	2426	502.7	4.8 (4.6-5.0)
Follow-up time (years)	1-2	185	32.7	5.7 (4.9-6.5)	731	126.6	5.8 (5.4-6.2)
	3-5	195	34.6	5.6 (4.9-6.5)	758	135.1	5.6 (5.2-6.0)
	5-15	212	61.2	3.5 (3.0-4.0)	937	241	3.9 (3.6-4.1)
Period of diagnosis of index tumour	1991-1995	131	33.8	3.9 (3.2-4.6)	587	150	3.9 (3.6-4.2)
	1996-2000	137	31.4	4.4 (3.7-5.2)	583	130.4	4.5 (4.1-4.8)
	2001-2005	152	29.8	5.1 (4.3-6.0)	625	112.1	5.6 (5.1-6.0)
	2006-2010	120	24.9	4.8 (4.0-5.8)	467	81.7	5.7 (5.2-6.3)
	2011-2015	52	8.5	6.1 (4.5-8.0)	164	28.4	5.8 (4.9-6.7)
Age category at diagnosis of index tumour	<46 year	28	2.9	9.8 (6.5-14.1)	83	7.3	11.3 (9.0-14.1)
	46-60 year	252	39.6	6.4 (5.6-7.2)	1012	137.5	7.4 (6.9-7.8)
	61-75 year	281	70.4	4.0 (3.5-4.5)	1184	295	4.0 (3.8-4.2)
	>75 year	31	15.7	2.0 (1.3-2.8)	147	62.9	2.3 (2.0-2.7)

Appendix Table 2 Continued.

		Index tumour of the oral cavity			Index tumour of the head and neck		
		Observed	Expected	SIR	Observed	Expected	SIR
SPT=Head & Neck all sites		1006	28.4	35.4 (33.2-37.6)	2146	109.2	19.7 (8.8-20.5)
Follow-up time (years)	1-2	291	7.9	37.0 (32.9-41.5)	588	29.2	20.1 (18.5-21.8)
	3-5	292	7.9	37.0 (32.9-41.5)	576	30.1	19.1 (17.6-20.8)
	5-15	423	12.7	33.3 (30.2-36.6)	982	49.8	19.7 (18.5-21.0)
Period of diagnosis of index tumour	1991-1995	232	7.1	32.8 (28.7-37.3)	526	29.9	17.6 (16.1-19.2)
	1996-2000	226	6.9	32.6 (28.5-37.1)	525	28	18.7 (17.2-20.4)
	2001-2005	262	6.7	38.8 (34.3-43.8)	539	25.3	21.3 (19.5-23.2)
	2006-2010	211	5.7	37.3 (32.5-42.7)	410	19	21.6 (19.6-23.8)
	2011-2015	75	2	36.9 (29.0-46.2)	146	6.9	21.0 (17.7-24.7)
Age category at diagnosis of index tumour	<46 year	93	1.2	78.5 (63.4-96.2)	209	3.1	67.7 (58.8-77.5)
	46-60 year	428	11.3	37.9 (34.4-41.7)	1011	41	24.7 (23.2-26.2)
	61-75 year	359	12.9	27.8 (25.0-30.8)	765	54.1	14.1 (13.1-15.2)
	>75 year	126	3	41.4 (34.5-49.3)	161	11	14.7 (12.5-17.1)
SPT=Oral Cavity		618	7.4	83.3 (79.6-90.1)	968	25.2	38.3 (36.0-40.8)
Follow-up time (years)	1-2	197	2.1	94.2 (81.5-108.3)	299	6.7	45.0 (40.0-50.4)
	3-5	183	2	91.8 (79.0-106.1)	291	6.8	42.5 (40.0-50.4)
	5-15	238	3.3	71.4 (62.6-81.0)	378	11.8	32.2 (29.0-35.6)
Period of diagnosis of index tumor	1991-1995	128	1.7	75.3 (62.8-89.5)	194	6.3	30.9 (26.7-35.6)
	1996-2000	146	1.8	83.0 (70.0-97.6)	235	6.3	37.3 (32.7-42.4)
	2001-2005	160	1.8	88.7 (75.5-103.6)	252	6.1	41.4 (36.4-46.8)
	2006-2010	137	1.6	87.6 (73.5-103.5)	210	4.8	43.9 (38.2-50.2)
	2011-2015	47	0.6	79.5 (58.4-105.8)	77	1.8	42.8 (33.8-53.5)
Age category at diagnosis of index tumor	<46 year	46	0.3	134.5 (98.4-179.4)	70	0.9	80.6 (62.8-101.8)
	46-60 year	221	3	74.2 (64.8-84.7)	427	10.2	41.8 (37.9-45.9)
	61-75 year	240	3.1	76.3 (66.9-86.5)	352	11.7	30.2 (27.1-33.5)
	>75 year	111	1	116.3 (95.9-140.4)	119	2.5	47.5 (39.3-56.8)

SPT=Oropharynx		219	5.2	42.4 (37.0-48.5)	589	18.5	31.9 (29.3-34.5)
Follow-up time (years)	1-2	48	1,4	35.4 (26.1-46.9)	137	4.9	27.9 (23.4-33.0)
	3-5	67	1.4	47.0 (36.5-59.7)	150	5.1	29.6 (24.9-34.5)
	5-15	104	2.4	43.7 (35.7-53.0)	302	8.5	35.8 (31.7-39.9)
Period of diagnosis of index tumor	1991-1995	58	1,1	52.6 (39.9-68.0)	171	4.2	40.5 (34.7-47.0)
	1996-2000	44	1.2	35.5 (25.8-47.7)	151	4.6	32.9 (27.9-38.6)
	2001-2005	61	1.,3	47.8 (36.6-61.4)	142	4.5	31.3 (26.3-36.9)
	2006-2010	44	1.1	39.3 (28.6-52.8)	95	3.7	25.8 (20.9-31.6)
	2011-2015	12	0.4	28.4 (14.7-49.6)	30	1.5	20.6 (13.9-29.4)
Age category at diagnosis of index tumor	<46 year	26	0.3	85.6 (55.9-125.4)	75	0.8	99.4 (73.1-132.2)
	46-60 year	122	2.6	46.8 (38.8-55.8)	313	9	33.2 (29.0-37.8)
	61-75 year	64	2	32.7 (25.2-41.8)	189	7.7	21.9 (18.5-25.7)
	>75 year	7	0.3	24.0 (9.6-49.4)	12	1	8.5 (3.7-16.7)
SPT=Larynx		63	8.9	7.1 (5.4-9.1)	199	37.0	5.4 (4.7-6.2)
Follow-up time (years)	1-2	11	2.4	4.6 (2.3-8.3)	58	9.9	5.8 (4.4-7.6)
	3-5	16	2.5	6.5 (3.7-10.5)	46	10.2	4.5 (3.3-6.0)
	5-15	36	4	8.9 (6.2-12.3)	95	16.9	5.6 (4.6-6.9)
Period of diagnosis of index tumor	1991-1995	15	2.5	6.0 (3.3-9.9)	56	11.3	4.9 (3.7-6.4)
	1996-2000	18	2.2	8.1 (4.8-12.7)	57	9.7	5.8 (4.4-7.6)
	2001-2005	14	2.1	6.8 (3.7-11.4)	43	8.3	5.2 (3.8-7.0)
	2006-2010	10	1.6	6.3 (3.0-11.6)	29	5.7	5.1 (3.4-7.3)
	2011-2015	6	0.5	11.6 (4.3-25.3)	14	1.9	7.2 (3.9-12.1)
Age category at diagnosis of index tumor	<46 year	6	0.3	20.9 (7.7-45.5)	30	0.8	39.1 (26.4-55.8)
	46-60 year	30	3.4	8.9 (6.0-12.7)	78	12.7	6.2 (4.9-7.7)
	61-75 year	24	4.4	5.4 (3.5-8.1)	79	19.8	4.0 (3.2-5.0)
	>75 year	3	0.8	3.6 (0.7-10.6)	12	3.7	3.2 (1.7-5.7)
SPT=hypopharynx		82	2.2	37.1 (29.5-46.0)	290	8.5	34.1 (30.3-38.2)
Follow-up time (years)	1-2	19	0.6	32.8 (19.7-51.2)	55	2.2	26.6 (18.5-32.0)
	3-5	26	0.6	42.8 (27.9-62.6)	67	2.3	28.6 (22.2-36.3)
	5-15	37	1	36.2 (25.5-49.8)	168	3.9	42.8 (36.6-49.8)

Appendix Table 2 Continued.

		Index tumour of the oral cavity			Index tumour of the head and neck		
		Observed	Expected	SIR	Observed	Expected	SIR
Period of diagnosis of index tumor	1991-1995	24	0.5	45.4 (29.1-67.5)	70	2.2	32.3 (25.2-40.8)
	1996-2000	16	0.5	29.6 (16.9-48.0)	68	2.2	31.4 (24.4-39.8)
	2001-2005	19	0.5	35.1 (21.2-54.9)	82	2	40.0 (31.8-49.7)
	2006-2010	19	0.4	42.7 (25.7-66.7)	61	1.6	39.1 (29.9-50.2)
	2011-2015	4	0.2	25.8 (7.0-66.0)	9	0.6	15.9 (7.3-30.2)
Age category at diagnosis of index tumor	<46 year	11	0.1	104.4 (52.1-186.8)	29	0.3	101.6 (68.0-145.9)
	46-60 year	53	1	50.7 (37.9-66.3)	161	3.8	42.5 (36.2 -49.6)
	61-75 year	17	0.9	18.6 (10.8-29.8)	94	3.9	24.3 (19.6-29.7)
	>75 year	1	0.1	6.8 (0.2-38.0)	6	0.6	10.6 (3.9-23.1)
SPT= Esophagus		158	20.3	7.8 (6.6-9.1)	504	77.5	6.5 (5.9-7.1)
Follow-up time (years)	1-2	48	4.9	9.9 (7.3-13.1)	149	17.8	8.4 (7.1-9.8)
	3-5	52	5.3	9.7 (7.3-12.8)	148	20.1	7.4 (6.2-8.7)
	>5	58	10.2	5.7 (4.3-7.4)	207	39.7	5.2 (4.5-6.0)
Period of diagnosis of index tumor	1991-1995	39	4.5	8.6 (6.1-11.8)	110	18.6	5.9 (4.9-7.1)
	1996-2000	42	4.8	8.7 (6.3-11.8)	127	19.3	6.6 (5.5-7.8)
	2001-2005	31	5	6.1 (4.2-8.7)	123	19.1	6.4 (5.4-7.7)
	2006-2010	33	4.4	7.5 (5.2-10.6)	105	15	7.0 (5.7-8.5)
	2011-2015	13	1.6	8.3 (4.4-14.2)	39	5.5	7.0 (5.0-9.6)
Age category at diagnosis of index tumor	<46 year	15	0.6	25.8 (14.4-42.5)	32	1.5	20.9 (14.3-29.4)
	46-60 year	78	6.9	11.3 (8.9-14.1)	237	25.1	9.4 (8.3-10.7)
	61-75 year	62	9.9	6.2 (4.8-8.0)	213	41	5.2 (4.5-5.9)
	>75 year	3	2.9	1.0 (0.2-3.0)	22	9.9	2.2 (1.4-3.3)

Chapter 6

Should we be rethinking follow-up for oral cancer patients?

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EDITORIAL

After curative treatment, oral cancer patients will enter a routine follow-up program, with the aim of early detection of second primary disease, recurrences and distant metastasis. Most of the currently available follow-up guidelines are for the generic head and neck area rather than a specific subsite such as the oral cavity. Several criteria have been suggested to create a successful surveillance program.[1] Firstly, the length of the follow-up period and the intervals between appointments and investigations should match the timing and risk of recurrence. Appropriate follow-up should benefit the patient in terms of improved chance of cure, survival or quality of life. Routine investigations should be able to detect new disease significantly earlier than detection based on patient-reported symptoms. Furthermore, these investigations should be non-invasive and have a low false-positive rate. The risk and location of possible second primary tumours should also be taken into account when considering additional investigations as part of the patient's care.[1]

At present, the current guidelines for patient follow-up after curative treatment for oral squamous cell carcinoma (OSCC) cancer do not seem to fulfill these criteria.

Most guidelines currently recommend following patients for 5 years or even for life. This cutoff point seems artificial, because most recurrences tend to occur in the first 1-2 years after treatment and patients have a lifelong risk for developing a second primary tumour.

Practices differ for routine investigations during follow-up consultations around the world. Some colleagues only perform a physical examination, including the oral cavity and neck nodes, while others routinely use imaging modalities including ultrasound and cross sectional scans (CT and/or MRI). Neither regimen has been proven to be better than the other or cost effective. The chances of a false positive diagnosis and the psychological distress that investigations cause for patients should be carefully considered. This is important where the chance of finding new disease in an asymptomatic patient is low, for example after two years after primary treatment.

Follow-up is based on the assumption that asymptomatic detection leads to improved survival or a higher chance of cure, but there is at best limited evidence to support these claims with very few studies on follow-up regimens published. Most currently available literature includes the entire head and neck area. As the aetiology, treatment and patterns of recurrence differ between the various head and neck anatomical sites, an evidence based follow-up program specifically for

OSCC needs to be based around this tumour site only rather than all head and neck tumours. Furthermore, the few methodologically sound studies lack large patient numbers.

As psychological support is another important goal of follow-up, improved survival or a better chance of cure is not the only indicator of follow-up success.[2] Whether follow-up actually improves quality of life or not for patients has not been investigated to date. The potential psychological effects of follow-up such as anxiety in some patients also needs be addressed.

Each primary subsite of the head and neck cancer has a different risk of developing second primary tumours at different locations. For example, the risk of a second primary tumour in primary HPV positive oropharyngeal carcinoma is much lower than in patients with a primary hypopharynx carcinoma, having implications for the routine investigations that are requested during follow-up.[3] A site-specific follow-up regimen is therefore indicated.

Should we be rethinking follow-up?

Do we need a change in thinking for following up our OSCC patients? Given all of the above, is it time to be considering follow-up guidelines that are tailored to specific patient, tumour and site characteristics? When other risk factors such as age and nodal status are taken into account a more personalized follow-up protocol could be created in future, leading to closer follow-up for high-risk patients while low-risk patients can be discharged earlier. Active involvement by the patient in their follow-up regimen is very important as they become more familiar with symptoms of new disease. Many OSCC patients present in our clinics at their own request between routine follow-up appointments, having noticed a change in their oral mucosa, and seek reassurance or diagnosis. Patient education about what to look for is also valuable for earlier presentation of recurrence, and seems to improve follow-up visit compliance.[4]

It is important to review which team member is appropriate to conduct routine follow-up. For example, a patients' anxiety may be reduced using a specialized nurse in the clinic who has received appropriate training and is supported by the clinical team.

This editorial aims to highlight that current follow-up protocols are in need of improvement. In order to create an evidence-based follow-up protocol, we need to know which patients we should follow-up, when and for how long, and who is

the best professional to do this. Future studies should investigate the effects of routine follow-up on survival, treatment intent and on quality of life of the patient and we would welcome those at JOPM.

References

1. Crawford B, Greenberg DD. patient surveillance after cancer treatment. New York: Springer, 2013.
2. Aaronson NK, Mattioli V, Minton O, et al. Beyond treatment - Psychosocial and behavioural issues in cancer survivorship research and practice. EJC Suppl. 2014;12: 54-64.
3. Morris LG, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol. 2011;29: 739-746.
4. De Zoysa N, Lee A, Joshi A, et al. Developing a follow-up surveillance protocol in head and neck oncological surgery: enhanced 'traffic light' surveillance - a prospective feasibility study. Clin Otolaryngol. 2017;42: 446-450.

Chapter 7

Summary and general discussion

Incidence and survival of oral cancer increases in the Netherlands.[1] The great majority of oral cancers are squamous cell carcinomas (OSCC). After treatment of the first primary tumour, or index tumour, patients are enrolled in a follow-up programme. The increase in incidence has sparked an interest in routine follow-up after OSCC treatment because more patients will be in follow-up. This is supported by the 2007 report on routine follow-up by the Health Council of the Netherlands.[2] The need for more capacity for follow-up will not only have consequences for surgeons, medical- and radiation oncologists, but also for supporting specialties such as dentists, specialist nurses, speech and language therapists and dieticians.

According to the Health Council a follow-up programme must be a systematic, and if possible evidence-based, programme with clear objectives.[2] Objectives concern first of all the early detection of new disease. New disease can be a local or regional recurrence, a distant metastasis or second primary tumour (SPT). Screening should only be done if there is sufficient evidence that asymptomatic detection leads to a better prognosis. The Council's view on active surveillance for late side-effects is similar. Another objective of follow-up is quality control and/or scientific research, but this should be made explicit, and requires a patient's informed consent. It is encouraged that the way follow-up is carried out and necessity of follow-up is evaluated one year after it has been started.[2]

An important, integrated part of follow-up is psychological aftercare and information on survivorship including post-treatment sequelae. Follow-up has to be coordinated and performed by a care-provider that is qualified and competent to do so. When treatment is completed, a survivorship care plan needs to be put in place, which should include an indication when follow-up can be discontinued.[2]

A follow-up guideline should be supported by professional organizations and be evaluated regularly. The report on routine follow-up by the Health Council of the Netherlands emphasizes that, should the programme be based on expert opinions, more research needs to be done in order to create a programme that is supported by evidence.[2] The current Dutch guideline for follow-up after OSCC is not evidence- based but consensus based. It is not site-specific, but the head and neck and its subsites are seen as one entity.[3]

Apart from the great pressure on resources, there are also other reasons why follow-up should be given careful consideration. Follow-up might give patients a false sense of security and could delay presentation of new disease as they might wait until their next follow-up appointment to present with symptoms. With scheduled follow-up appointments, the risk of unnecessary tests increases and

therefore the risk of false positive results. Patients experience anxiety in the time around follow-up appointments, and unnecessary anxiety should be avoided.[4, 5]

The main goal of follow-up that is addressed in this thesis is the detection of new disease during routine follow-up, its appropriateness and clues for improvement. In this chapter the results of the studies that were conducted to assess this aim and their consequences for an evidence-based routine follow-up programme will be discussed.

Epidemiology

In *chapter three*, the trends in incidence, mortality and relative survival for oral cancer in the Netherlands are presented. 93% of oral cancers in the Netherlands were squamous cell carcinomas. From 1991-2010, the incidence of oral cancer rose with 1.2% annually (95% CI: 0.9-1.6%), this increase was more pronounced in women (+1.8% vs +0.8% per year). The increase in incidence in women during this period was also observed in other countries such as Denmark and Ireland.[6, 7] These authors hypothesized that despite a decrease in alcohol- and tobacco consumption, the proportion of heavy smokers and heavy drinkers (the people with a high risk of OSCC) remained the same.[6] The increase in OSCC incidence is contrary to the decline in incidence that has been reported in the USA from 2004-2012, except for patients aged 30-39 years.[8, 9]

The mortality rate in the Netherlands increased slightly from 0.82 per 100,000 person-years in 1989 to 0.97 in 2012 (+0.8% (95% CI: +0.3-+1.3%), *chapter three*). In the study period, the five-year survival rate increased from 57% in 1991–1995 to 62% in 2006–2010. Improved survival for OSCC was also seen in the USA.[8, 9] In Denmark, the five-year survival increased in the period 1980-2014, and is lower (44% for patients diagnosed from 2005-2009) than the one reported in our study.[6] The increased survival in Denmark was attributed to increased surgical possibilities which led to an increased proportion of patients being treated surgically, which improved patients' prognosis.[6] Other factors mentioned in Denmark and the USA are decreased waiting times, centralization, the introduction of sentinel lymph node biopsies and the introduction of concurrent chemoradiation in specific indications.[6, 9] The relationship between time to treatment and prognosis has been established in the Dutch population.[10] There are indications that hospital- and surgeon- volume are associated with increased survival for head and neck cancer, so increased centralization could possibly account for some of the increased survival after oral cancer in the Netherlands.[11] A sub-analysis of patients

treated in Dutch head and neck cancer centres in 2008 did not show a relationship between hospital volume and survival for oral cancer, however these data are from after head and neck cancer care was centralized in the Netherlands.[12]

When does new disease occur

To determine the optimal duration of the follow-up programme it is important to know when new disease occurs.

As demonstrated in *chapter two*, the majority of guidelines for follow-up after OSCC are not site-specific and target cancers of the entire head and neck area. Most guidelines have a cut-off point for follow-up of five year, but others such as the National Comprehensive Cancer Network and the ENT-UK guideline advocate lifelong follow-up.

In *chapter four* we analysed the occurrence of new disease in a population of 756 patients with a primary OSCC, treated at the Head and Neck Cancer Unit of the Radboud University Medical Centre. The one-, five-, and ten-year cumulative risks of a second event (i.e. recurrence, second primary tumour or distant metastasis) were 17% (95% CI: 14%-20%), 30% (95% CI: 26%-33%) and 37% (95% CI: 32%-41%), respectively.

In our study, the majority of locoregional recurrences occurred within the first year after treatment, when the risk of a second event was highest, i.e. 17% (*chapter four*). These results are in line with the studies on local- and regional recurrences reviewed in *chapter two*, where the majority of recurrences occurred within the first two to three years after treatment.[13-16] A German study observed that 88.2% of second events occurred within the first two years after OSCC diagnosis.[17] It is difficult to draw firm conclusions on the basis of the literature as very few studies present recurrence curves or risk of recurrence data on individual post-treatment years. Also, studies frequently do not assess SPTs, recurrences and distant metastases as separate entities, but just as new disease.

More recently, the sentinel lymph node biopsy has been added to the diagnostic armamentarium to assess the status of the neck.[18] The SENT trial showed that sentinel lymph node biopsies are an oncologically safe alternative to elective neck dissection in early stage OSCC.[19] The Radboudumc population that was studied in *chapter four* did not include patients that had a sentinel lymph node biopsy as part of their procedure.

In our population, the incidence rate of SPT was stable over the entire follow-up period (median follow-up 7.8 years, *chapter four*). We could confirm this in an analysis of the OSCC population in the Netherlands from 1991-2005 (*chapter five*). Patients are at a life-long risk for SPTs, with a very wide range of incidence rates reported in the literature from 5.3% to 36.0% (*chapter two*).[20-23] Comparing the risk of a SPT between studies is difficult as many different definitions of SPT are used. In some studies SPTs are limited to the head and neck, while in other studies it includes SPTs in other sites as well. Another problem is the different follow-up time per study that accounts for different cumulative percentages of SPTs.

Our reported five-year risk of a SPT (all sites) after OSCC is 0.13 (95% CI: 0.13-0.14), the highest risk was observed for a SPT in the head and neck area with a 5-year risk of 0.05 (95% CI: 0.04-0.05). An analysis of 347 patients from Liverpool (United Kingdom) found that the cumulative incidence curve flattened after 10-15 years; the five year cumulative incidence of second primary cancer in the head and neck area was 0.05 (95% CI: 0.03-0.08) and the 10 year incidence was 0.08 (95% CI: 0.05-0.11), comparable to our results.[24]

In *chapter five*, it is also shown that there is a differential distribution of type of SPT after an index OSCC when compared to the entire group of HNSCC patients and the individual subsites. Examples of this is are that after an index OSCC 25% of SPTs occurred in the oral cavity, while this was only the case for 13% of SPTs after all HNSCCs, 8% of the SPTs after hypopharyngeal cancer, 4% after laryngeal cancer and 13% after oropharyngeal cancer. Also, after an index HNSCC 32% of SPTs develop in the lung or bronchus, while this is the case for 38% of SPTs after an index tumour of the larynx, while after an index OSCC only 24% of SPTs develop in the lung or bronchus. This differential distribution was also seen by Morris et al.[25] This is an argument in favor of developing separate follow-up protocols for the different subsites of the head and neck area.

Analyzed per subsite, *chapter five* demonstrates that the cumulative incidence curve for lung cancer and esophageal cancer appeared to become less steep over the reported 15 years, while the curves for HNSCC as SPT appeared to keep on increasing.

If viewed as a whole, the risk of developing a SPT after OSCC remains elevated when compared to the general population, also after five years of follow-up. If the separate subsites are analyzed, it is seen that the standardized incidence ratio (SIR) of a lung SPT decreases five years after an index OSCC. The highest SIR for esophageal SPTs is seen in the first two years after diagnosis of the index OSCC (*chapter five*). To our knowledge this was the first study to demonstrate these timelines for OSCC index tumours specifically.

We further observed in *chapter four* that all the distant metastases after an index OSCC occurred within three years after primary treatment. The great majority of distant metastasis after OSCC occur in the lung. Other sites less frequently affected are the bones and liver.[26] In the Netherlands, patients are not routinely screened for distant metastasis after oral cancer, because no health benefit can be expected.[3] A short interval between diagnosis of the primary tumour and presentation of the distant metastasis is predictive of a worse prognosis.[27, 28]

Where does new disease occur

For follow-up to be effective, it is important to investigate the places where new disease occurs. The current follow-up programme is based on history taking and physical examination and does not include routine investigations such as imaging for every patient during every routine follow-up appointment. In many cases even flexible naso-endoscopy will only be done if symptoms are present. This means that recurrences emerging in the oral cavity may be detected asymptomatically, but that distant metastases and SPTs apart from those in the oral cavity will not be found during routine follow-up. In *chapter five* it was shown that 2459 SPTs were found in a cohort of 11153 patients with primary OSCC diagnosed in the Netherlands from 1991-2015. In these 25 years of follow-up of all OSCC patients in the Netherlands, only 577 of the SPT's (23%) were found in the oral cavity. It is unlikely that all of those were discovered asymptomatically within the five years of the follow-up programme. Morris et al report an incidence of 16.8% OSCC SPT after an index OSCC in a population 36107 OSCC patients in the USA.[25]
In our study (*chapter five*) 59% of SPTs after an index OSCC were diagnosed outside of the head and neck area in places such as the lung (five-year risk 0.04 (95% CI: 0.03-0.04)), the esophagus (five-year risk 0.01 (95% CI: 0.01-0.01)) and in sites other than head and neck, lung and esophagus (five-year risk 0.04 (95% CI: 0.04-0.05)).

If compared to the general population *(chapter five)*, patients with an index OSCC have a highly elevated risk of developing a SPT in the head and neck area (SIR: 35.4 (95% CI: 33.2-37.6)), which was also reported by Morris et al, albeit less elevated (26.2 (95% CI: 24.9-27.4)).[25] The SIR of developing a SPT in the lung was 4.6 (95% CI: 4.2-5.0), again slightly higher than if compared to the findings of Morris et al who reported a SIR of 4.0 (95% CI: 3.7-4.2). Morris et al report a SIR of an esophagus SPT of 15.05 (95% CI: 13.4-16.8), which is almost twice as high as the risk in our population (7.8 (95% CI: 6.6-9.1)).

Effectiveness of early detection

Follow-up is based on the assumption that a diagnosis in the detectable preclinical phase leads to a better prognosis in terms of survival and treatment intent than if diagnosed symptomatically. The literature on this subject consists of observational cohort studies and has therefore to be interpreted with some caution as the outcome measures might be influenced by lead time and length time bias. Lead time bias is entering the scene if survival time is calculated from the time that the relapse is diagnosed. Asymptomatically diagnosed patients will have a longer survival as their tumour is diagnosed before they had symptoms. Length time bias may occur if slow-growing tumours, those with a likely favorable prognosis, are relatively more frequently detected asymptomatically.

Asymptomatic detection rates have not been investigated specifically for OSCC. In a HNSCC population, only 17- 30% of new disease is reported to be asymptomatically detected (*chapter two*).[29-31] The detection of new disease in both OSCC and HNSCC patients is largely dependent on symptoms such as pain.[30]
As demonstrated in *chapter five*, the majority of SPTs occur in sites that are not routinely screened for and would require invasive investigations. A recent Italian study found no difference in curability of new disease that was clinically and radiologically diagnosed versus disease that was symptomatically diagnosed in a HNSCC population treated with chemo-radiation and who received yearly or twice yearly routine imaging as part of their follow-up.[32] An American study in patients with HNSCC treated with primary radiotherapy found no survival difference between patients with recurrences that were found on clinical examination versus those detected by routine imaging.[33]

As described in our review (*chapter two*), the only study that was conducted on asymptomatic detection of OSCC was a study of a cohort of 102 patients treated for OSCC of the tongue and floor of the mouth, which showed no survival benefit for recurrences that were detected at a routine visit versus those that were found at a patient-initiated visit.[13] The literature on survival benefits of routine follow-up after HNSCC showed no unequivocal benefit.[34, 35] A dated study by de Visscher et al showed that patients who had their new disease detected at a routine visit had a better mean survival.[36] Also, Pagh et al showed that in a cohort of 2062 curatively treated HNSCC patients, of whom 556 (27%) OSCC, patients with asymptomatically detected recurrences had a significantly lower risk of disease-specific death compared to patients with symptomatic new disease.[37] No significant difference was noticed between symptomatic patients and patients who had their recurrence detected on a self-initiated or routine visit.[37]

We did not study the survival effect in our population yet, but we observed (*chapter four*) no difference in treatment intent between SPTs detected during the five-year follow-up programme and outside the schedule, which suggests a limited benefit from routine follow-up at the most.

Effectiveness of early detection can also be measured in other ways, for example as improvement in quality of life. The effectiveness of routine follow-up should be studied from the perspective of cost-effectivity and cost-utility in order to justify the use of public funds.

Generalization of the findings

The current thesis is mostly based on Dutch data, and can only be translated to other countries with caution as differences in incidence, mortality and relative survival between countries may be explained by differences in risk factors and healthcare systems.

Differences in risk factors

The most important risk factors for HNSCC, including OSCC, are alcohol and smoking, which combined have a synergistic effect on the risk of a tumour.[38] The presence of these risk factors are not the same in every country: the percentage of smokers and the amount of alcohol consumed in the USA is for example lower than in the Netherlands.[39, 40] This will likely have an influence on the risk of and incidence of SPTs, and may explain the difference in SPTs observed by Morris et al[25] in the USA and by us (*chapter five*) in the Netherlands. The difference of risk and incidence of SPT at specific locations will influence which additional investigations will be chosen during routine follow-up.

Differences in access to healthcare

It has been noted that a relatively high proportion of HNSCC patients live in areas of high deprivation, where the prevalence of smoking and alcohol use are higher than in less deprived communities.[41, 42] Even after correction for these risk factors, the risk of developing HNSCC in general and OSCC specifically is higher in deprived communities.[41, 43, 44] A Scottish study showed, that the incidence rates of OSCC in areas with the highest deprivation score (Scottish Index of Multiple Deprivation) was more than double that of the least deprived areas (9.55 vs 3.94 per 100,000 person-years).[44] A French study showed that patients with a lower socioeconomic status (SES) had a longer time from diagnosis to start of treatment than patients from a more privileged background.[45] Since a delay in treatment is

known to have a negative impact on prognosis,[10] this may explain the lower overall survival observed in patients with a low SES. In patients with primary HNSCC, restricted access to healthcare is a known risk factor for late disease presentation.[46] An explanation for the relationship between deprivation and restricted health care access could be that patients have a lower health awareness and that it might be more difficult to obtain a doctor's appointment for referral without private health care insurance. For some patients a short distance to the hospital can already be too far because the price of a bus ticket is too high. Another study found that travel distance to the hospital was an independent factor for advanced T-stage on presentation in low-income patients.[47]

As this might be difficult to capture in a formal guideline, physicians might choose to keep patients from deprived and low socioeconomic backgrounds longer in follow-up to give them an easy access to healthcare. This problem will likely differ from country to country.

In addition, insurance status has implications for stage of disease at diagnosis and survival after cancer.[48, 49] The way healthcare is financed can also have implications for follow-up. In the Netherlands, the basic health insurance is compulsory for all residents and will cover the cost of hospital visits and additional investigations that are needed during follow-up. On top of their insurance fees, patients will have to pay a contribution (385 euros in 2020) if they use healthcare services. In other countries, such as the USA, healthcare is private and not everyone has health insurance. The costs of follow-up consultations and additional investigations might hold patients back in regularly attending. This aspect needs further investigating especially in countries without universal health care coverage.

Differences in histology

More than 95% of the malignancies in the oral cavity is squamous cell carcinoma.[38] Other malignancies in the oral cavity such as sarcoma and salivary gland malignancies have a different treatment and a different pattern of recurrence. An example is adenoid cystic carcinoma, which is characterized by late recurrences and a high distant failure rate. Expert opinion is to keep this group under surveillance for over 15 years.[50] To the best of our knowledge there is no specific data available on the pattern and distribution of SPTs after non-squamous cell cancers in the oral cavity. The different pattern of recurrence and the lack of information on the characteristics of SPT mean that the data from our study cannot be applied to other types of tumours than squamous cell carcinomas.

Effective additional investigations

Given the time patterns of new disease, the focus of follow-up is likely to change from detecting locoregional recurrences in the first years to SPTs in the later years. Even if follow-up might have beneficial effects in terms of survival or quality of life, follow-up can still have a detrimental effect on the patients who do not develop SPTs due to, amongst others, false positive test results.

If it is decided to screen for SPTs, it is important that the right additional investigations are chosen. The Stalpers calculator, discussed in *chapter five*, can apply to additional investigations done at follow-up.[51] Knowing the sensitivity and specificity of a test, and the clinical consequences of the true/false positive and true/false test results, the calculator provides for probabilities when to meaningfully doing the test.[51]

The incidence of a SPT in our population is low, i.e. 1% per year (*chapter five*). Not all elements of the Stalpers calculator are known for our population and will have to be investigated in order to help to choose the right investigations and assemble an evidence-based follow-up schedule. If approached from this perspective, we should refrain from actively screening for second primary disease in places that are currently not routinely screened for until more information becomes available. This is also the way this issue is approached by the Health Council of the Netherlands.[2] In some countries, routine screening for SPTs will have some overlap with national cancer screening programmes such as lung cancer, where screening with CT reduces mortality in certain high-risk groups with similar risk factors (smoking) as to OSCC patients.[52, 53] The American Society for Head and Neck Cancer refers to the American Cancer Society early detection guidelines and does not create a specific screening for second primary lung cancers or esophageal cancers.[54] Implementing screening requires an extensive logistic framework and is in our opinion better done by an appropriate specialty with sufficient experience in further treatment of the particular type of cancer.

Currently there are two trials ongoing that assess intensified imaging-based follow-up regimens for HNSCC patients. The first study is registered as SURVEILL'ORL (NCT03519048), where its first arm consists of conventional clinical follow-up and a yearly low dose CT-chest for patients who smoked >20 pack years, and other imaging only on clinical indication. The effect of this regimen on overall survival is compared to a regimen wherein all patients receive a yearly whole body PET-CT, yearly CT head/neck/chest and a yearly upper gastrointestinal endoscopy with Lugols iodine for three years in addition to the conventional follow-up regimen. The other study is HETeCo, (NCT 02262221) and compares a regimen of follow-up visits without scheduled imaging to one where patients undergo two yearly CT or

MRI scans in the two years and yearly in the third and fourth year. In addition to that, patients who are >50 years old and have a smoking history of >20 pack-years will receive yearly PET-CT scans in the first three years after treatment.
The development of new techniques to detect new disease, such as liquid biopsies for HNSCC, will hopefully contribute to a more effective way of diagnosing new disease early and selecting patients for additional investigations.[55]

Personalizing follow-up

There is a need for specified follow-up protocols for the sublocations of the head and neck due to the variation in time and risk of recurrence and difference in areas where SPTs occur. Currently, follow-up protocols are not strictly followed, some clinicians apply a form of risk stratification.[56-59] Furthermore, compliance to routine follow-up is expected to differ between patients. A more patient-centered follow-up protocol can improve adherence.[60]
There are several ways to personalize follow-up, one of them is selecting patients with high or low risk of new disease. Patients with a high risk of new disease might benefit from an intensified follow-up regimen, whilst patients with a low risk of new disease, a low chance of cure or limited life expectancy could benefit from a de-intensified follow-up regimen. The latter could include a shorter follow-up programme or follow-up conducted by health professionals other than the treating physicians and focus on goals other than early detection of new disease.

High vs low risk of new disease

In *chapter four*, a flowchart is presented, which aims to predict the five year cumulative risk of a second event after surgical treatment of OSCC. Based on treatment type, previous malignancy, tumour location, whether the patient underwent a neck dissection, the presence of extracapsular spread and the presence of vaso-invasive growth, risk groups were identified with a higher or lower risk of a second event. This flowchart is a first step towards personalized follow-up but needs further validation.
In *chapter five* the risk of SPTs were studied in specific, demonstrating that the risk of a SPT decreases with increasing age at diagnosis of the index tumor, with the exception of patients aged 70^{+} years in whom the risk levels off after six years of follow-up. Risk patterns also differed for different sites of SPTs.

High vs low chance of curative-intent treatment for new disease

In *chapter four* an instrument is presented which helps in predicting the treatment intent for patients on the basis of tumor size, nodal status, previous treatment, invasion depth and ASA score. If a patient possesses four risk factors or more, the chance of curative intent treatment was 0%, and if the patient had none of the risk factors, the chance of curative intent treatment was 96%. After further validation in other patient populations, this can be another way of personalizing follow-up by selecting patients who will not have any curative treatment options left. Patients with low curative prospects could benefit from a de-intensified follow-up programme, because follow-up is considered ineffective in this group. These parameters are similar to the model that was developed by Shen et al to predict HNSCC-specific death.[61] Their model consisted of age, size of the tumor, nodal status, T-stage, subsite in the head and neck area, grade, race and marital status.[61]

Generally, patients with distant metastasis after OSCC are consistently found to have a bad prognosis and are therefore not routinely screened in the Netherlands as it is assumed this will not lead to health benefits.[28, 62]
There is, however, evidence in HNSCC populations that, metastasis-directed therapy (surgery, chemotherapy or radiotherapy) decreases the risk of death, especially in patients with a single metastasis, a higher performance score at diagnosis of the metastasis and a longer metastatic-free interval.[62] Patients who have undergone resection of pulmonary metastasis have a reported five-year survival ranging from 20-59%.[28, 63, 64] Patients with primary OSCC do have a worse prognosis.[28, 63, 64] The number of metastasis has a negative influence on survival.[28, 63, 64] This evidence indicates that there might be a possibility to improve survival if these cases are discovered early.
In the past decade, a lot of progress has been made when it comes to systemic therapies for metastatic HNSCC with the introduction of targeted agents and immunotherapy having positive results on survival for OSCC patients.[65] It remains unknown whether early detection of metastatic disease after OSCC has a positive influence on the effect of systemic therapies.

The fact that there are therapies available that are life-prolonging in selected patient groups of HNSCC patients is not enough to say that it is necessary and effective to screen the whole group of OSCC patients for distant metastasis. More needs to be elucidated on metastatic directed therapy, selection of appropriate patient groups and the influence of early detection of metastasis on its effectiveness before a decision on screening for distant metastasis can be taken.

Influence of other patient-related factors

Some patients may have a limited life-expectancy due to high age and comorbidities related to their smoking- and alcohol habits and therefore have a high risk of non-OSCC related death. Those patient may qualify for a de-intensified follow-up schedule. A study of 23494 HNSCC patients diagnosed between 2000-2010 in the USA showed a 0.13 (95% CI: 0.12-0.13) five-year incidence and a 0.23 (95% CI: 0.21-0.24) ten-year cumulative incidence of death from other causes.[61] Their model for predicting other causes of death consisted of age, sex, marital status, race, radiation and subsite in the head and neck area.[61] Patients with OSCC had a higher cancer-related mortality compared to other subsites of the head and neck area (HR 3.38 (95% CI:2.67-4.28)).[61] In a Finnish study, HNSCC patients at risk of death of other causes were generally older and had a high comorbidity score.[66]

Survivorship and patient-centered follow-up

Follow-up cannot be seen outside the context of survivorship. Survivorship is defined by the National Cancer Institute as follows: "Survivorship focuses on the health and life of a person with cancer post treatment until the end of life. It covers the physical, psychosocial, and economic issues of cancer, beyond the diagnosis and treatment phases. Survivorship includes issues related to the ability to get health care and follow-up treatment, late effects of treatment, second cancers, and quality of life. Family members, friends, and caregivers are also considered part of the survivorship experience."[67] Since the 2006 report of the American Institute of Medicine From Cancer Patient to Cancer Survivor: Lost in Transition, this subject has received more attention.[68] In its 2007 report The Health Council of the Netherlands recommends that for every patient a detailed aftercare plan is written, which is in accordance to the Cancer Survivorship Care Plan from the American Institute of Medicine.[2, 68] This will not only benefit the patient, but also the general practitioner and the general dental practitioner.

Cancer survivors have different preferences when it comes to follow-up care.[69] This is dependent on gender, education level and age.[69] A survivorship care plan should therefore be an individualized document. More research needs to be done on patient preferences.

A Canadian study reported that 61% of HNSCC patients have unmet needs as measured with the CaSUN scale, a measurement of patient-reported supportive care needs for cancer survivors.[70] The most common domain where patients reported unmet needs was comprehensive cancer care, as patients were frequently worried if their doctors were communicating to one another.[70] Another Canadian

study using the Supportive Care Needs Survey found that 68% of HNSCC patients had unmet needs, mostly in the psychological domain.[71] It is unlikely that these needs will be adequately met by the surgeon. We should therefore consider alternatives for the current follow-up programme.

Alternative approaches to the current follow-up programme

With the effectiveness of follow-up in early detection of new disease being put into question, the focus of follow-up programmes might shift to other aspects of survivorship care. This creates new opportunities to shape follow-up in a way that truly meets the needs of the patients and get other health professionals involved (*chapter six*).

Patient education

The Health Council of the Netherlands has emphasized the need for patient education on the consequences of disease and symptoms of new disease as part of a survivorship care plan. Currently, there is little specific literature on survivorship after the treatment of OSCC. Future research is advised to focus on two aspects. Firstly the education of patients on new symptoms of their disease. This is especially important after follow-up is discontinued and should also focus on the symptoms of SPT with a high incidence after OSCC. De Zoysa et al gave all of their patients a follow-up card with alarm symptoms that warranted an urgent outpatient appointment.[60] Effects on survival were not evaluated.[60] Web-based interventions have reported improved outcomes in lung cancer.[72] A French randomized study, compared survival in patients with advanced lung cancer between a group with regular interval visits and imaging, and a group with a weekly symptoms monitoring via a web-based patient-reported outcome instrument.[72] The latter group showed a significantly improved outcome.[72]

The second aspect is patient education on the health consequences of their disease and treatment, including among other aspects psychosocial concerns and treatment-related side-effects. An example of this is 'Oncokompas', a Dutch web-based patient self-management system for survivorship where on the basis of socio-demographic and clinical factors and health-related quality of life questionnaires the patient is offered specific interventions.[73] Not only education on malignant disease is relevant. Patients who have undergone radiotherapy are at a risk of developing caries and osteoradionecrosis.[74] It is beneficial to have a timely involvement of an oral- and maxillofacial surgeon when patients develop osteoradionecrosis.[74] Patients therefore need to be educated on this, but also stimulated

to attend their dentist regularly to diagnose this condition at an early stage and ensure early referral.

Nurse-led follow-up

Follow-up should not necessarily be conducted by physicians. In a single-centre Dutch study, nurse-led consultations had a positive influence on health-related quality of life in a population of 180 HNSCC patients (of whom 66 with OSCC).[75] Psychosocial nurse-led counseling reduces depressive symptoms one year post treatment in HNSCC patients.[76] The patient group also showed a significant improvement in pain, swallowing and mouth opening.[77] Further research should be done on the cost-effectiveness of nurse-led follow-up and whether it is possible to replace standard follow-up by physicians by specialist nurses.

Conclusion

With the increasing OSCC incidence and improving survival, more patients will be enrolled in a post-treatment follow-up programme. The data reported in this thesis provides part of the evidence base for developing more evidence-based follow-up after treatment of OSCC. On the basis of current evidence, a cutoff point after five year does not make sense from a detection of new disease point of view. Follow-up should stop after two years from a locoregional recurrence point of view. After that, the life-long risk of a second primary cancer is not high enough to support life-long follow-up in its current form as second primary disease more often than not occurs in sites that are not routinely examined during follow-up. It is possible to identify risk groups who are at higher risk for new disease and who might benefit from follow-up for more than two years. Examples of this are patients with a high risk of a specific SPTs and patients with difficult access to healthcare. If patients have exhausted all of their therapeutic options, or are unfit to undergo treatment of their SPT, a de-intensified follow-up schedule could be preferable. Follow-up should be individualized after careful discussion with the patient and comprises much more than screening for new disease. Other forms of follow-up such as follow-up by physician assistants, other allied health professionals or web-based applications should be explored. From current available evidence it is not clear if follow-up leads to improved survival or quality of life. The (cost-) effectiveness of current- and alternative follow-up needs further investigation.

References

1. van Dijk BA, Brands MT, Geurts SM, Merkx MA, Roodenburg JL. Trends in oral cavity cancer incidence, mortality, survival and treatment in the Netherlands. Int J Cancer. 2016;139: 574-583.
2. Health Council of the Netherlands. Follow-up in oncology. Identify objectives, substantiate actions. The Hague: Health Council of the Netherlands, 2007.
3. Dutch Society for Otorhinolaryngology, Head and Neck Surgery. Guideline Head and Neck Tumors. Utrecht: Nederlandse Vereniging voor KNO, 2014.
4. Lampic C, Wennberg A, Schill JE, Brodin O, Glimelius B, Sjoden PO. Anxiety and cancer-related worry of cancer patients at routine follow-up visits. Acta Oncol. 1994;33: 119-125.
5. Glynne-Jones R, Chait I, Thomas SF. When and how to discharge cancer survivors in long term remission from follow-up: the effectiveness of a contract. Clin Oncol (R Coll Radiol). 1997;9: 25-29.
6. Karnov KKS, Gronhoj C, Jensen DH, et al. Increasing incidence and survival in oral cancer: a nationwide Danish study from 1980 to 2014. Acta Oncol. 2017;56: 1204-1209.
7. Ali H, Sinnott SJ, Corcoran P, Deady S, Sharp L, Kabir Z. Oral cancer incidence and survival rates in the Republic of Ireland, 1994-2009. BMC Cancer. 2016;16: 950.
8. Patel MA, Blackford AL, Rettig EM, Richmon JD, Eisele DW, Fakhry C. Rising population of survivors of oral squamous cell cancer in the United States. Cancer. 2016;122: 1380-1387.
9. Cheraghlou S, Schettino A, Zogg CK, Judson BL. Changing prognosis of oral cancer: An analysis of survival and treatment between 1973 and 2014. Laryngoscope. 2018;128: 2762-2769.
10. van Harten MC, Hoebers FJP, Kross KW, van Werkhoven ED, van den Brekel MWM, van Dijk BAC. Determinants of treatment waiting times for head and neck cancer in the Netherlands and their relation to survival. Oral Oncol. 2015;51: 272-278.
11. Eskander A, Merdad M, Irish JC, et al. Volume-outcome associations in head and neck cancer treatment: A systematic review and meta-analysis. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck. 2014;36: 1820-1834.
12. de Ridder M, Balm AJM, Baatenburg de Jong RJ, et al. Variation in head and neck cancer care in the Netherlands: A retrospective cohort evaluation of incidence, treatment and outcome. Eur J Surg Oncol. 2017;43: 1494-1502.
13. Merkx MA, van Gulick JJ, Marres HA, et al. Effectiveness of routine follow-up of patients treated for T1-2N0 oral squamous cell carcinomas of the floor of mouth and tongue. Head Neck. 2006;28: 1-7.
14. Sasaki M, Aoki T, Karakida K, et al. Postoperative follow-up strategy in patients with oral squamous cell carcinoma. J Oral Maxillofac Surg. 2011;69: e105-111.
15. Wensing BM, Merkx MA, Krabbe PF, Marres HA, Van den Hoogen FJ. Oral squamous cell carcinoma and a clinically negative neck: the value of follow-up. Head Neck. 2011;33: 1400-1405.
16. Kumar R, Putnam G, Dyson P, Robson AK. Can head and neck cancer patients be discharged after three years? J Laryngol Otol. 2013;127: 991-996.
17. Peisker A, Raschke GF, Guentsch A, Luepke P, Roshanghias K, Schultze-Mosgau S. Evaluation of a post-treatment follow-up program in patients with oral squamous cell carcinoma. Clin Oral Investig. 2017;21: 135-141.
18. Govers TM, Hannink G, Merkx MA, Takes RP, Rovers MM. Sentinel node biopsy for squamous cell carcinoma of the oral cavity and oropharynx: a diagnostic meta-analysis. Oral Oncol. 2013;49: 726-732.
19. Schilling C, Stoeckli SJ, Haerle SK, et al. Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. Eur J Cancer. 2015;51: 2777-2784.
20. Leon X, Martinez V, Lopez M, Garcia J, Quer M. Risk of third and fourth tumors in patients with head and neck cancer. Head Neck. 2010;32: 1467-1472.
21. Day GL, Blot WJ. Second primary tumors in patients with oral cancer. Cancer. 1992;70: 14-19.
22. Day GL, Blot WJ, Shore RE, et al. Second cancers following oral and pharyngeal cancer: patients' characteristics and survival patterns. Eur J Cancer B Oral Oncol. 1994;30B: 381-386.
23. Cianfriglia F, Di Gregorio DA, Manieri A. Multiple primary tumours in patients with oral squamous cell carcinoma. Oral Oncol. 1999;35: 157-163.

24. Rogers SN, Swain A, Carroll C, Lowe D. Incidence, timing, presentation, treatment, and outcomes of second primary head and neck squamous cell carcinoma after oral cancer. Br J Oral Maxillofac Surg. 2019;57: 1074-1080.
25. Morris LG, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol. 2011;29: 739-746.
26. Sekikawa S, Kawachi H, Ogane S, et al. Which Factors Affect the Long-Term Survival of Patients With Oral Squamous Cell Carcinoma With Distant Metastasis? J Oral Maxillofac Surg. 2020;78: 469-478.
27. Leeman JE, Li JG, Pei X, et al. Patterns of Treatment Failure and Postrecurrence Outcomes Among Patients With Locally Advanced Head and Neck Squamous Cell Carcinoma After Chemoradiotherapy Using Modern Radiation Techniques. JAMA Oncol. 2017;3: 1487-1494.
28. Sun XS, Michel C, Babin E, et al. Approach to oligometastatic disease in head and neck cancer, on behalf of the GORTEC. Future Oncol. 2018;14: 877-889.
29. Haas I, Hauser U, Ganzer U. The dilemma of follow-up in head and neck cancer patients. Eur Arch Otorhinolaryngol. 2001;258: 177-183.
30. Smit M, Balm AJ, Hilgers FJ, Tan IB. Pain as sign of recurrent disease in head and neck squamous cell carcinoma. Head Neck. 2001;23: 372-375.
31. Pagh A, Grau C, Overgaard J. A longitudinal study of follow-up activities after curative treatment for head and neck cancer. Acta Oncol. 2015;54: 813-819.
32. Imbimbo M, Alfieri S, Botta L, et al. Surveillance of Patients with Head and Neck Cancer with an Intensive Clinical and Radiologic Follow-up. Otolaryngol Head Neck Surg. 2019;161: 635-642.
33. Ng SP, Pollard C, 3rd, Berends J, et al. Usefulness of surveillance imaging in patients with head and neck cancer who are treated with definitive radiotherapy. Cancer. 2019;125: 1823-1829.
34. Flynn CJ, Khaouam N, Gardner S, et al. The value of periodic follow-up in the detection of recurrences after radical treatment in locally advanced head and neck cancer. Clin Oncol (R Coll Radiol). 2010;22: 868-873.
35. Agrawal A, Hammond TH, Young GS, Avon AL, Ozer E, Schuller DE. Factors affecting long-term survival in patients with recurrent head and neck cancer may help define the role of post-treatment surveillance. Laryngoscope. 2009;119: 2135-2140.
36. de Visscher AV, Manni JJ. Routine long-term follow-up in patients treated with curative intent for squamous cell carcinoma of the larynx, pharynx, and oral cavity. Does it make sense? Arch Otolaryngol Head Neck Surg. 1994;120: 934-939.
37. Pagh A, Grau C, Overgaard J. Failure pattern and salvage treatment after radical treatment of head and neck cancer. Acta Oncol. 2016;55: 625-632.
38. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet. 2008;371: 1695-1709.
39. World Health Organization. WHO report on the global tobacco epidemic 2009: implementing smoke-free environments. Geneva, Switzerland, 2009.
40. World Health Organization. Global status report on alcohol and health. Geneva, Switzerland, 2011.
41. Mirza AH, Aylin P, Middleton S, King EV, Nouraei RAR, Repanos C. Impact of social deprivation on the outcome of major head and neck cancer surgery in England: A national analysis. Head Neck. 2019;41: 692-700.
42. Stanford-Moore G, Bradshaw P, Weissler MC, et al. Interaction between known risk factors for head and neck cancer and socioeconomic status: the Carolina Head and Neck Cancer Study. Cancer Causes & Control. 2018;29: 863-873.
43. Johnson S, McDonald JT, Corsten MJ. Socioeconomic factors in head and neck cancer. J Otolaryngol Head Neck Surg. 2008;37: 597-601.
44. Purkayastha M, McMahon AD, Gibson J, Conway DI. Trends of oral cavity, oropharyngeal and laryngeal cancer incidence in Scotland (1975-2012) - A socioeconomic perspective. Oral Oncol. 2016;61: 70-75.
45. Guizard AV, Dejardin O, Launay L, et al. What are the real waiting times for therapeutic management of head and neck cancer: a study in the general population in the north-west of France. Eur Arch Otorhinolaryngol. 2016;273: 3951-3958.

46. Adrien J, Bertolus C, Gambotti L, Mallet A, Baujat B. Why are head and neck squamous cell carcinoma diagnosed so late? Influence of health care disparities and socio-economic factors. Oral Oncol. 2014;50: 90-97.
47. Farquhar DR, Masood MM, Lenze NR, et al. Travel time to provider is associated with advanced stage at diagnosis among low income head and neck squamous cell carcinoma patients in North Carolina. Oral Oncol. 2019;89: 115-120.
48. Stubbs VC, Rajasekaran K, Chen J, Cannady SB, Brant JA, Newman JG. Impact of payer status on survival in parotid malignancy. Am J Otolaryngol. 2019;40: 555-559.
49. Halpern MT, Ward EM, Pavluck AL, Schrag NM, Bian J, Chen AY. Association of insurance status and ethnicity with cancer stage at diagnosis for 12 cancer sites: a retrospective analysis. Lancet Oncol. 2008;9: 222-231.
50. Coca-Pelaz A, Rodrigo JP, Bradley PJ, et al. Adenoid cystic carcinoma of the head and neck--An update. Oral Oncol. 2015;51: 652-661.
51. Stalpers LJ, Nelemans PJ, Geurts SM, Jansen E, de Boer P, Verbeek AL. The indication area of a diagnostic test. Part I--discounting gain and loss in diagnostic certainty. J Clin Epidemiol. 2015;68: 1120-1128.
52. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365: 395-409.
53. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020;382: 503-513.
54. Cohen EE, LaMonte SJ, Erb NL, et al. American Cancer Society Head and neck cancer survivorship care guideline. CA Cancer J Clin. 2016;66: 203-239.
55. van Ginkel JH, Huibers MMH, Noorlag R, de Bree R, van Es RJJ, Willems SM. Liquid Biopsy: A Future Tool for Posttreatment Surveillance in Head and Neck Cancer? Pathobiology. 2017;84: 115-120.
56. Kerawala CJ, Newlands C, Coombes D. Follow-up after treatment of squamous cell carcinoma of the oral cavity: current maxillofacial practice in the United Kingdom. Br J Oral Maxillofac Surg. 2007;45: 361-363.
57. Kanatas A, Bala N, Lowe D, Rogers SN. Outpatient follow-up appointments for patients having curative treatment for cancer of the head and neck: are the current arrangements in need of change? Br J Oral Maxillofac Surg. 2014;52: 681-687.
58. Deutschmann MW, Sykes KJ, Harbison J, Cabrera-Muffly C, Shnayder Y. The impact of compliance in posttreatment surveillance in head and neck squamous cell carcinoma. JAMA Otolaryngol Head Neck Surg. 2015;141: 519-525.
59. Paniello RC, Virgo KS, Johnson MH, Clemente MF, Johnson FE. Practice patterns and clinical guidelines for posttreatment follow-up of head and neck cancers: a comparison of 2 professional societies. Arch Otolaryngol Head Neck Surg. 1999;125: 309-313.
60. De Zoysa N, Lee A, Joshi A, et al. Developing a follow-up surveillance protocol in head and neck oncological surgery: enhanced 'traffic light' surveillance - a prospective feasibility study. Clin Otolaryngol. 2017;42: 446-450.
61. Shen W, Sakamoto N, Yang L. Cancer-specific mortality and competing mortality in patients with head and neck squamous cell carcinoma: a competing risk analysis. Ann Surg Oncol. 2015;22: 264-271.
62. Beckham TH, Leeman JE, Xie P, et al. Long-term survival in patients with metastatic head and neck squamous cell carcinoma treated with metastasis-directed therapy. Br J Cancer. 2019;121: 897-903.
63. Shiono S, Kawamura M, Sato T, et al. Pulmonary metastasectomy for pulmonary metastases of head and neck squamous cell carcinomas. Ann Thorac Surg. 2009;88: 856-860.
64. Liu D, Labow DM, Dang N, et al. Pulmonary metastasectomy for head and neck cancers. Ann Surg Oncol. 1999;6: 572-578.
65. Szturz P, Vermorken JB. Management of recurrent and metastatic oral cavity cancer: Raising the bar a step higher. Oral Oncol. 2019;101: 104492.
66. Vaisanen JA, Alho OP, Koivunen PT, Laara E. Cause-specific mortality in patients with head and neck cancer: Long-term follow-up of a population-based cohort from 1986 to 2012 accounting for competing risks. Oral Oncol. 2018;79: 20-26.

67. National Cancer Institute. Available from URL: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/survivorship [accessed 26/9/2019].
68. Committee on Cancer Survivorship: Improving Care and Quality of Life NCPB. From cancer patient to cancer survivor - lost in transition. In: Hewitt MG, S; Stovall E., editor. Washington, D.C., 2006.
69. Huibertse LJ, van Eenbergen M, de Rooij BH, et al. Cancer survivors' preference for follow-up care providers: a cross-sectional study from the population-based PROFILES-registry. Acta Oncol. 2017;56: 278-287.
70. Giuliani M, McQuestion M, Jones J, et al. Prevalence and nature of survivorship needs in patients with head and neck cancer. Head Neck. 2016;38: 1097-1103.
71. Henry M, Habib LA, Morrison M, et al. Head and neck cancer patients want us to support them psychologically in the posttreatment period: Survey results. Palliat Support Care. 2014;12: 481-493.
72. Denis F, Basch E, Septans AL, et al. Two-Year Survival Comparing Web-Based Symptom Monitoring vs Routine Surveillance Following Treatment for Lung Cancer. JAMA. 2019;321: 306-307.
73. Melissant HC, Verdonck-de Leeuw IM, Lissenberg-Witte BI, Konings IR, Cuijpers P, Van Uden-Kraan CF. 'Oncokompas', a web-based self-management application to support patient activation and optimal supportive care: a feasibility study among breast cancer survivors. Acta Oncol. 2018;57: 924-934.
74. Zhang Z, Xiao W, Jia J, et al. The effect of combined application of pentoxifylline and vitamin E for the treatment of osteoradionecrosis of the jaws: a meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020;129: 207-214.
75. de Leeuw J, Prins JB, Teerenstra S, Merkx MA, Marres HA, van Achterberg T. Nurse-led follow-up care for head and neck cancer patients: a quasi-experimental prospective trial. Support Care Cancer. 2013;21: 537-547.
76. van der Meulen IC, May AM, Ros WJ, et al. One-year effect of a nurse-led psychosocial intervention on depressive symptoms in patients with head and neck cancer: a randomized controlled trial. Oncologist. 2013;18: 336-344.
77. van der Meulen IC, May AM, de Leeuw JR, et al. Long-term effect of a nurse-led psychosocial intervention on health-related quality of life in patients with head and neck cancer: a randomised controlled trial. Br J Cancer. 2014;110: 593-601.

Appendices

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Samenvatting

Mondholtekanker komt steeds vaker voor in Nederland. Tussen 1991 en 2010 is het aantal patiënten met deze diagnose met 1,2% per jaar toegenomen (95% betrouwbaarheidsinterval: +0,9%; +1,6%) (*hoofdstuk 3*). De relatieve 5-jaarsoverleving van deze patiënten nam toe van 57% in 1991-1995 naar 62% in 2006-2010.
Patiënten die genezen zijn van mondholtekanker hebben een kans op een recidief of een tweede primaire tumor, samen ook wel een tweede 'event' genoemd. Om dit op tijd op te sporen worden patiënten na behandeling regelmatig gecontroleerd. Andere doelen van het nacontroleprogramma zijn het monitoren van de gevolgen en bijwerkingen van de behandeling en het bieden van psychologische ondersteuning aan de patiënt. Het nacontroleprogramma voor mondholtekanker wordt gebaseerd op de Nederlandse richtlijn hoofd/hals tumoren, waarin wordt geadviseerd om patiënten in principe vijf jaar te controleren.[1] Deze richtlijn is niet specifiek voor de mondholte, maar geldt ook voor de andere sublocaties in het hoofd/halsgebied. Er wordt aangenomen dat de patiënt een betere levensverwachting heeft als het recidief of de tweede primaire tumor wordt ontdekt wanneer een patiënt nog geen klachten heeft. De Gezondheidsraad besteedt in zijn rapport uit 2007 aandacht aan nacontrole in de oncologie en benadrukt het belang van een nacontrole programma dat is afgestemd op de individuele patiënt.[2]
Doordat er meer mensen mondholtekanker krijgen (een stijging van 2.665 patiënten in 1991-1995 naar 3.947 patiënten in 2006-2010) en overleving verbetert, zullen er meer patiënten in het nacontrole programma zijn opgenomen, dat zal leiden tot een toenemende druk op alle specialismen die de nacontrole uitvoeren en ondersteunen.

Doel

In dit onderzoek werd onderzocht hoe lang het nacontroleprogramma zou moeten duren, op welke locaties naar nieuwe kanker moet worden gezocht tijdens de nacontrole en welke patiënten het meeste baat bij nacontrole hebben.

Hoe lang moet de nacontrole duren?

De meeste internationale richtlijnen adviseren een nacontrole van vijf jaar of langer op basis van de mening van experts (*hoofdstuk twee*). Uit de literatuur blijkt dat de meeste recidieven in de eerste twee tot drie jaar na behandeling optreden en dat patiënten een levenslang risico hebben op een tweede primaire tumor (*hoofdstuk twee*). In *hoofdstuk vier* werd onderzocht hoe recidieven en tweede primaire tumoren over de tijd optreden in een groep van 756 patiënten die in de periode 2000-2012 in het Radboudumc in Nijmegen in opzet curatief voor mondholtekanker werden behandeld. Bijna alle recidieven traden op in de eerste twee

jaren na behandeling. Verder bleken patiënten een constant, levenslang risico op tweede primaire tumoren te hebben. Dit constante risico op tweede primaire tumoren werd ook gezien in de totale Nederlandse populatie (*hoofdstuk vijf*). Dit betekent dat, daar waar het doel van het nacontroleprogramma het opsporen van recidieven of tweede primaire tumoren betreft, de duur van het nacontroleprogramma op basis van deze resultaten ofwel twee jaar ofwel levenslang zou moeten zijn. Dit in tegenstelling tot de richtlijnen die een nacontroleprogramma van vijf jaar voorschrijven. Er bestaat een verhoogde kans op optreden van longkanker en slokdarmkanker bij patiënten die mondholtekanker hebben gehad, dit lijkt echter af te nemen 15 jaar na behandeling van de eerste primaire tumor (*hoofdstuk vijf*). Dit is niet het geval voor de kans op optreden van tweede primaire tumoren in het hoofd/halsgebied, die blijft constant. In vergelijking met de algemene bevolking is het risico op slokdarmkanker het sterkst verhoogd in de eerste twee jaar na behandeling van de eerste primaire tumor en neemt het verhoogde risico op longkanker af vijf jaar na behandeling.

Op welke tumorsoorten moet de nacontrole zich richten?

Om een recidief of tweede primaire tumor op een effectieve manier op te sporen moeten de plekken worden onderzocht waar patiënten het grootste risico lopen om een recidief of tweede primaire tumor te ontwikkelen. In Nederland bestaat een nacontrole uit anamnese en lichamelijk onderzoek van het hoofd/halsgebied. Aanvullend onderzoek wordt alleen gedaan als de klachten van de patiënt daar aanleiding toe geven.[1] Na twee jaar zal het accent van de nacontrole, doordat de kans op recidief erg klein is geworden, verschuiven naar het ontdekken van tweede primaire tumoren. Slechts 41% van de tweede primaire tumoren die in Nederland optraden bij patiënten die van 1991-2005 met een mondholtetumor werden gediagnosticeerd, bevond zich in het hoofd/halsgebied (*hoofdstuk vijf*). De andere 59% trad buiten het hoofd/halsgebied op, dus op plekken waar niet routinematig gecontroleerd wordt. Het risico werd ook vergeleken met het risico dat de algemene bevolking heeft op die tumorsoort (standardized incidence ratio, SIR). Er is immers minder reden om gericht te controleren op een bepaalde tumorsoort als het risico op een bepaalde tumor niet groter is dan dat van de algemene bevolking. Na een mondholtetumor hebben patiënten een 35 keer zo hoog risico op een tweede primaire tumor in het hoofd/halsgebied. De risico's op longkanker en slokdarmkanker zijn ook verhoogd ten opzichte van de algemene bevolking, maar minder sterk (respectievelijk vijf en acht keer zo hoog).

Patiënten met mondholtekanker kunnen ook metastasen op afstand ontwikkelen. Dat gebeurt meestal in de long maar soms ook in de botten of lever. Er wordt niet gescreend op afstandsmetastasen tijdens de nacontrole omdat op dit moment er vanuit wordt gegaan dat dit geen overlevingswinst oplevert.

Welke patiënten hebben het meeste baat bij nacontrole?

Niet alle patiënten hebben hetzelfde risico op een recidief of tweede primaire tumor. In *hoofdstuk vier* wordt een hulpmiddel besproken om op basis van tumor- en patiëntkenmerken patiënten te identificeren die een vergroot risico op een tweede event hebben. Patiënten die ouder zijn dan 70 jaar bij diagnose, hebben zes jaar na behandeling een lager risico op tweede primaire tumoren dan patiënten die jonger waren toen ze hun eerste primaire tumor kregen (*hoofdstuk vijf*).

Een andere groep die minder baat heeft bij nacontrole is de groep die niet in opzet curatief behandeld kunnen worden. In *hoofdstuk vier* wordt een hulpmiddel besproken waarbij op basis van tumorgrootte, uitzaaiingen in de lymfeklieren in de hals, eerdere behandelingen, invasiediepte van de primaire tumor en ASA-score kan worden bepaald wat de kans op curatieve behandeling van een volgende tumor is. Heeft een patiënt geen negatieve kenmerken dan is die kans 96%, maar als een patiënt vier of meer negatieve kenmerken heeft dan is de kans in de populatie van het Radboudumc 0%.

Een reden om nacontrole voor patiënten te beperken is, dat er geen behandelingsopties meer beschikbaar zijn, of dat de patiënten in een te slechte algemene conditie zijn om verdere behandeling te ondergaan.

Een gepersonaliseerd nacontroleprogramma

Dat patiënten een verhoogd risico op recidief of een tweede primaire tumor hebben, betekent niet dat nacontrole ook een positief effect heeft op de overleving, behandelingsintentie of kwaliteit van leven. De beperkte literatuur die over dit onderwerp beschikbaar is laat zien dat er slechts 17-30% van de recidieven en tweede primaire tumoren wordt ontdekt zonder dat de patiënt klachten heeft (*hoofdstuk twee*). Ook komt er geen overtuigend positief beeld naar voren over het effect op de overleving of behandelintentie in de patiëntengroep die behandeld is voor hoofd/halskanker (*hoofdstuk twee*). Er werd in onze patiëntenpopulatie geen verschil in behandelintentie gevonden tussen de groep patiënten die hun tweede event tijdens het vijfjarige nacontroleprogramma kregen en die hun tweede event kregen nadat het vijfjarige nacontroleprogramma was afgelopen kregen (*hoofdstuk vier*).

Tot er overtuigend bewijs wordt geleverd van de positieve effecten van nacontrole op overleving, behandelingsintentie of kwaliteit van leven wordt aanbevolen het nacontroleprogramma te beperken tot twee jaar. Follow-up moet worden afgestemd op het risicoprofiel en de behoeften van de individuele patiënt. Er moet onderzoek worden gedaan naar alternatieve vormen van nacontrole zoals follow-up door ander zorgverleners en patiënten moeten goed worden voorgelicht over het belang van zich vroegtijdig te melden bij klachten.

Referenties

1. Nederlandse vereniging voor KNO. Richtlijn Hoofd-halstumoren. Utrecht: Nederlandse vereniging voor KNO, 2014.
2. Gezondheidsraad. Nacontrole in de oncologie. Doelen onderscheiden, inhoud onderbouwen. Den Haag: Gezondheidsraad, 2007.

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Stafleden MKA-chirurgie in het Radboudumc en het Rijnstate ziekenhuis, ik heb mijn eerste stappen op chirurgisch vlak onder jullie leiding mogen zetten. Jullie inspirerende omgang met patiënten en de goed lopende hoofd/hals keten zijn dingen waar ik veel van heb geleerd.

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Curriculum Vitae

Marieke Brands werd op 11 september 1986 geboren te Apeldoorn. In 2013 behaalde zij haar VWO diploma aan het Greijdanus College te Zwolle. Van 2003-2008 studeerde zij tandheelkunde aan de Radboud Universiteit te Nijmegen (cum laude). Aan dezelfde universiteit studeerde zij van 2005-2011 Nederlands Recht (afstudeerrichting Staatsrecht) en van 2008-2013 Geneeskunde.

Tijdens haar perifere tandheelkunde stage MKA-chirurgie in het Rijnstate Ziekenhuis te Arnhem en haar afstudeerscriptie tandheelkunde bij prof. M.A.W. Merkx werd haar warme interesse voor de MKA-chirurgie in het algemeen en de hoofd/hals-oncologie in het bijzonder gewekt.
In 2012 startte zij met de opleiding tot Mond- Kaak en Aangezichtschirurg (opleider prof. S.J. Bergé) in het Radboudumc te Nijmegen. Het perifere deel van de opleiding werd gevolgd in het Rijnstate ziekenhuis in Arnhem (opleider dr. Th.J.M. Hoppenreijs). Tijdens haar opleiding startte zij met dit promotie-onderzoek onder leiding van prof. M.A.W. Merkx, prof. A.L.M. Verbeek en dr. ir. S.M.E. Geurts.

Na haar opleiding startte zij in 2017 met een fellowship hoofd/halsoncologie in het Queen Alexandra Hospital te Portsmouth. Van 2018-2019 was ze achtereenvolgens fellow aangezichtstraumatologie en fellow hoofd/hals oncologie inclusief micro-vasculaire reconstructieve chirurgie in het Queen Elizabeth University Hospital te Glasgow. In hetzelfde ziekenhuis was zij van 2019-2020 staflid. Zij is momenteel als staflid met als speciaal aandachtsgebied hoofd/hals oncologie en reconstructieve chirurgie werkzaam in Monklands University Hospital te Airdrie en Queen Elizabeth University Hospital te Glasgow.

List of publications

1. Brands MT, van den Bosch SC, Dieleman FJ, Berge SJ, Merkx MA. Prevention of thrombosis after microvascular tissue transfer in the head and neck. A review of the literature and the state of affairs in Dutch Head and Neck Cancer Centers. Int J Oral Maxillofac Surg. 2010;39: 101-106.
2. Brands W, Brands M, Brands-Bottema G. Limited rights of minors in the Dutch healthcare. J Forensic Odontostomatol. 2014;32 Suppl 1: 30-33.
3. van Dijk BA, Brands MT, Geurts SM, Merkx MA, Roodenburg JL. Trends in oral cavity cancer incidence, mortality, survival and treatment in the Netherlands. Int J Cancer. 2016;139: 574-583.
4. Brands MT, Hockey P, Sced A, Brennan PA. Fasting and surgical performance: potential source of harm? Br J Oral Maxillofac Surg. 2017;55: 755-756.
5. Brands MT, Merkx MAW, Geurts SME, Brennan PA. Should we be rethinking follow-up for oral cancer patients? J Oral Pathol Med. 2017;46: 665-666.
6. Brennan PA, Bradley KL, Brands M. Intensity-modulated radiotherapy in head and neck cancer - an update for oral and maxillofacial surgeons. Br J Oral Maxillofac Surg. 2017;55: 770-774.
7. Brands MT, Brennan PA, Verbeek ALM, Merkx MAW, Geurts SME. Follow-up after curative treatment for oral squamous cell carcinoma. A critical appraisal of the guidelines and a review of the literature. Eur J Surg Oncol. 2018;44: 559-565.
8. Brands MT AI, Brennan PA, Farah CS. Soft and Hard Tissue Operative Investigations in the Diagnosis and Treatment of Oral Disease. In: Farah C. BR, McCullough M., editor. Contemporary Oral Medicine: Springer, 2018.
9. Brennan PA, Brands MT, Caldwell L, et al. Surgical specimen handover from the operating theatre to laboratory-Can we improve patient safety by learning from aviation and other high-risk organisations? J Oral Pathol Med. 2018;47: 117-120.
10. Brennan PA, Brands MT, Gush R, Alam P. Laser-speckle imaging to measure tissue perfusion in free flaps in oral and maxillofacial surgery: a potentially exciting and easy to use monitoring method. Br J Oral Maxillofac Surg. 2018;56: 556-558.
11. Govers TM, Rovers MM, Brands MT, et al. Integrated prediction and decision models are valuable in informing personalized decision making. J Clin Epidemiol. 2018;104: 73-83.
12. Brands MT, Smeekens EAJ, Takes RP, et al. Time patterns of recurrence and second primary tumors in a large cohort of patients treated for oral cavity cancer. Cancer Med. 2019;8: 5810-5819.

13. Zubair F MJ, Afzali P, Cuschieri K, Schipani S, Brands MT, Ansell, MA. Staging and treatment outcomes in oropharynx squamous cell carcinoma – a single centre UK cohort. Accepted Br J Oral Maxillofac Surg.
14. Brands MT, Campschroer G, Merkx MAW, Verbeek ALM, van Dijk BAC, Geurts SME. Second primary tumors after squamous cell carcinoma of the oral cavity. Submitted to Eur J Cancer.

Portfolio

Conferences

2019 7th World congress of the International Academy for Oral Oncology, Rome, Italy
2016 Congress of the European Association for Craniomaxillofacial surgery, London, United Kingdom
2016 European congress for head and neck oncology, Budapest, Hungary
2015 European Head and Neck course, Birmingham, United Kingdom

Oral presentations

2016 *Patterns of recurrence in oral cancer*
Congress of the European Association for Craniomaxillofacial surgery, London, United Kingdom
2016 *The UICC staging system in surgically treated oral squamous cell carcinoma: a lack of prognostic value but are there alternatives?*
European congress for head and neck oncology, Budapest, Hungary
2015 *Trends in oral cavity cancer incidence, treatment survival and therapy in the Netherlands*
Annual congress of the Dutch association of Oral and Maxillofacial Surgeons, Amersfoort, the Netherlands

Courses and workshops

2018 Fundamentals of oncology
2017 Facial palsy – a hands on anatomical course
2017 Scientific integrity
2016 48th international course for flap raising and microsurgery
2015 Basic microsurgery course
2015 Around the Nose, course on reconstructive and aesthetic surgery of the nose and face
2014 Surgical Anatomy of the Head and Neck

Teaching and other activities

Lecturing

2016 Frequently occurring problems in the head and neck area for dental students
2016 Medication prescribing for dental students
2015 Oral cancer for biomedical science students (module clinical epidemiology)

Supervision of bachelor/master research students

2016 Vera Coenen: Development of a questionnaire concerning the cognitions of physicians concerning follow-up after oral cancer
2015 Therese Elkerbout: A Prognostic Model for Survival after Primary Oral Cancer treatment
2014 Lisette Smeekens: Disease-free survival after recurrence or second primary tumor in patients treated with curative intent for Oral Squamous Cell Carcinoma

Other activities

2014 Organization Young Investigators Day of the Dutch Head and Neck Society

Data management

The study in chapter three and five was conducted in cooperation with the Netherlands Cancer Registry (NCR). The data have been analyzed by researchers of the NCR and are stored there. The NCR registers and stores data of all individuals newly diagnosed with cancer in the Netherlands and works according to the FAIR principles.[1] A part of the data collected by the Netherlands Cancer Registration are available via www.cijfersoverkanker.nl, requests for more extensive or specific data can be made via the data application form of the NCR, available via www.iknl.nl. The specific published data generated or analyzed in these chapter are available from the authors on request.

The data on which chapter four is based are stored on the H: drive of the department of Oral- and Maxillofacial Surgery and for later use in the digital research environment of the Radboudumc and available on request. These data were since made available to other teams and used in their publications.

[1] Integraal Kankercentrum Nederland, Data laten leven, visiedocument over data in de oncologie, 2019.