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A nationwide study on cancer recurrences, second primary tumours, distant metastases and survival after treatment for primary head and neck cancer in the Netherlands

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ABSTRACT

Introduction: There is no consensus on the optimal duration of post-treatment follow-up after head and neck cancer (HNC). To generate site-specific input for follow-up guidelines, this study describes the incidence and timing of manifestations of disease during five years of follow-up.
Methods: All patients diagnosed with HNC in the Netherlands in 2015 were selected from the Netherlands Cancer Registry. The follow-up events local recurrence (LR), regional recurrence (RR), second primary tumour (SPT), distant metastasis (DM) and death were studied per follow-up-year. The cumulative incidence of these events was calculated using competing risk analyses, with LR, RR and SPT of the head and neck (SPHNC) as events and SPT outside the head-neck (SPOHN), DM and death as competing events. Analyses were performed for oral cavity-, oropharynx-, larynx- and hypopharynx squamous cell carcinoma (SCC), and all HNC patients.
Results: The 1-, 1.5-, and 2-year cumulative incidence of an event (LR, RR, SPHNC) were 10% (95%CI 8–13), 12% (95%CI 10–15), and 13% (95%CI 10–16) for oral cavity SCC; 6% (95%CI 4–9), 10% (95%CI 7–14), and 11% (95%CI 8–15) for oropharynx SCC; 7% (95%CI 5–10), 11% (95%CI 9–15), and 13% (95%CI 10–16) for larynx SCC and 11% (95%CI 6–19), 19% (95%CI 12–27), and 19% (95%CI 12–27) for hypopharynx SCC.
Conclusions: One year of follow-up for oral cavity SCC, and 1.5 years for oropharynx-, larynx-, and hypopharynx SCC suffices for the goal of detecting disease manifestations after treatment. More research into other aspects of follow-up care should be performed to determine the optimal follow-up regimen.

1. Introduction

The Global Burden of Disease study estimated a worldwide incidence of 890,000 Head and Neck Cancers (HNC) in 2017 [1]. In the Netherlands, HNC was diagnosed 3130 times in 2019 [2]. The four main sites are the oral cavity (28%), larynx (22%), oropharynx (22%), and hypopharynx (7%) [2]. Since the 1990s, the age-standardized incidence for HNC has been rising. Meanwhile, the relative survival rate has improved [2]. As a result, the number of people enrolled in routine follow-up after HNC treatment has increased, and is likely to increase further in the upcoming years as survival rates continue to improve and the population ages.

Abbreviations: HNC, head and neck cancer; LR, local recurrence; RR, regional recurrence; SPT, second primary tumour; SPHNC, second primary tumour of the head and neck; SPOHN, second primary tumour outside the head and neck; DM, distant metastasis; MOD, manifestation of disease; NCR, Netherlands Cancer Registry; N, absolute number; SD, standard deviation.

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An important goal of HNC follow-up is detecting new disease ahead of clinical symptoms. Other aims of follow-up are to monitor treatment response, and provide psychosocial counselling and post-treatment rehabilitation [3]. HNC protocols recommend a post-treatment follow-up duration of three years to lifelong with varying intensity [4,5]. The Dutch guideline advises five years of follow-up.

Several aspects of current HNC follow-up protocols are in need of improvement. First, these protocols are not based on evidence but on expert opinion and consensus [4–6]. The effectiveness of routine follow-up in improving prognosis has not been proven [7–10]. Second, most protocols consider HNC as one entity, while it comprises a heterogenous group in terms of treatment, and patterns of developing new disease such as second primary tumours [11,12]. Finally, HNC patients' needs and preferences for follow-up care vary widely and are not addressed in the "one-size-fits-all" protocols [13].

HNC recurrence patterns have only been studied in relatively small, retrospective studies, making them subject to bias [8–10,14–16]. Some studies, like most follow-up protocols, consider HNC one entity and do not analyse different sites separately regarding recurrence rates. Also, the results do not always show risk of recurrence by post-treatment year [9,10,16].

It is essential to comprehend HNC recurrence patterns per site to develop a guideline for the goal of detecting disease manifestations after treatment. To evaluate the current follow-up length of five years and generate evidence-based input for site-specific follow-up guidelines, we aimed to describe local recurrences (LR), regional recurrences (RR), second primary tumours (SPT), distant metastases (DM) and deaths over five years of HNC follow-up.

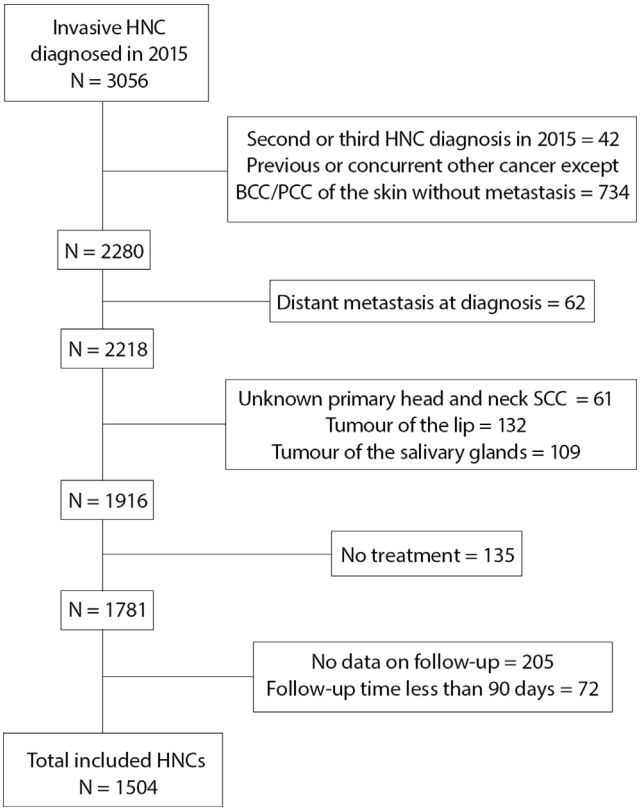


Fig. 1. Flow chart of the exclusion criteria.

2. Materials and methods

2.1. Patients and data collection

Patients were extracted from the Netherlands Cancer Registry (NCR) using codes C00–C14, C30–C32 following the International Classification of Diseases for Oncology, third edition (ICD-*O*-3) [17]. Hematologic malignancies, neuroendocrine tumours, sarcomas and melanomas were excluded, resulting in 3065 patients diagnosed with an invasive HNC in 2015, the first year of follow-up data collection. Hereby, analysis of five years follow-up time could be achieved. Exclusion criteria were: a previous or concurrent cancer; distant metastasis at diagnosis; unknown primary tumour; cancer of the lip or salivary glands (Fig. 1). Also excluded were patients who received no treatment, whose follow-up data were unavailable (two hospitals, n = 205), or whose follow-up time was under 90 days (Fig. 1). Ultimately, 1,504 patients with a primary HNC were included. The 7th edition of the UICC TNM classification was used. Pathological staging was used, if unavailable clinical staging was used [18]. Development of LR, RR, SPT, DM, and last date of follow-up were recorded. Vital status was obtained by linkage to the municipal registries. This study was exempt from review by a medical ethics board due to the retrospective design and use of anonymised data.

2.2. Definitions

Manifestations of disease (MOD) included LR, RR, SPT, and DM. SPTs were categorized as second primary HNC (SPHNC), located at C00–C14, C30–C32, or SPT outside the head and neck (SPOHN). SPTs were distinguished from recurrences based on three-digit ICD-*O*-3 topography code. If multiple MODs were detected at the same time, the most extensive localisation was selected for further analyses, e.g., in the event of a simultaneous LR and RR, the RR was used for analyses. The recurrent cancer was included for further analyses. Follow-up time started at 90 days after diagnosis since most treatments would have been completed by then. Follow-up ended at the date of MOD; death; or last consultation if the patient was lost to follow-up, and was counted to a maximum of five years, the follow-up time recommended in the Dutch guideline [6]. Routine follow-up, according to the Dutch guideline, consists of a control visit every two months in the first, three months in the second, four months in the third and every six months in the fourth and fifth year after treatment [6]. A visit includes history taking and physical examination of the head and neck area. Imaging is not routinely performed unless on specific indications [6].

2.3. Statistical analysis

The first occurring follow-up event after treatment, LR, RR, SPT, DM or death, was included for analyses. All analyses were performed for squamous cell carcinoma (SCC) of the oral cavity, oropharynx, larynx and hypopharynx, as well as for all HNC patients. Descriptive statistics (absolute number (N), percentages, mean, standard deviation (SD)) were used to describe patient, disease and treatment characteristics. Survival was estimated using Kaplan-Meier survival-analyses. Competing risk methods [19] were used to calculate the cumulative incidence of LR, RR or SPHNC, as they can be found in the area examined at regular HNC check-ups. Competing events were SPOHN, DM, and death. Statistical analyses were performed using Stata Statistical Software: Release 17.0.

Table 1
Patient characteristics and follow-up events during five years of follow-up for squamous cell carcinoma of the oral cavity, oropharynx, larynx and hypopharynx.

	Total		Local recurrence		Regional recurrence		SPT head and neck		SPT outside head and neck		Distant metastasis		Death	
	N	Column%	N	Row%	N	Row%	N	Row%	N	Row%	N	Row%	N	Row%
Oral cavity	519	100	31	6	44	8	15	3	44	8	40	8	47	9
Age at diagnosis														
Mean* (sd)	65*	(12)	67*	(13)	64*	(13)	64*	(12)	71*	(9)	63*	(12)	77*	(12)
Sex														
Male	268	52	19	7	20	7	8	3	28	11	26	10	21	8
Female	251	48	12	5	24	10	7	3	16	6	14	6	26	10
TNM-stage														
I	207	40	10	5	15	7	7	3	16	7	0	0	10	5
II	76	15	3	4	6	8	2	3	5	7	3	4	7	9
III	57	11	4	7	6	11	1	2	6	11	1	2	2	4
IVA	171	33	12	7	17	10	5	3	17	10	34	20	26	15
IVB	7	1	2	29	0	0	0	0	0	0	2	29	2	29
Unknown	1	0	0	0	0	0	0	0	0	0	0	0	1	100
Treatment														
Surgery only	290	56	13	4	22	8	9	3	25	9	2	1	19	7
Surgery + radiotherapy	127	24	13	10	13	10	2	2	13	10	18	14	12	9
Surgery + radiotherapy + systemic therapy	37	7	0	0	1	3	1	3	0	0	11	30	3	8
Radiotherapy only	40	8	3	8	5	13	2	5	4	10	4	10	11	28
Radiotherapy + systemic therapy	23	4	1	4	3	13	1	4	2	9	5	22	1	4
Other/unknown	2	0	1	50	0	0	0	0	0	0	0	0	1	50
Oropharynx	307	100	20	7	17	6	4	1	32	10	29	10	27	9
Age at diagnosis														
Mean* (sd)	62*	(9)	65*	(9)	65*	(8)	60*	(8)	65*	(9)	61*	(10)	65*	(13)
Sex														
Male	209	68	13	6	13	6	3	1	18	9	21	10	20	10
Female	98	32	7	7	4	4	1	1	14	14	8	8	7	7
TNM-stage														
I	11	4	1	9	3	27	1	9	1	9	0	0	0	0
II	47	15	3	6	0	0	0	0	11	23	1	2	5	11
III	53	17	1	2	1	2	0	0	5	9	4	8	3	6
IVA	179	58	15	8	11	6	3	2	14	8	22	12	15	8
IVB	17	6	0	0	2	12	0	0	1	6	2	12	4	24
Treatment														
Surgery only	4	1	0	0	1	25	0	0	1	25	0	0	0	0
Surgery + radiotherapy	39	13	3	8	1	3	1	3	2	5	3	8	3	8
Surgery + radiotherapy + systemic therapy	16	5	1	6	0	0	0	0	2	13	1	6	0	0
Radiotherapy only	113	37	7	6	7	6	1	1	20	18	8	7	13	12
Radiotherapy + systemic therapy	133	43	8	6	8	6	2	2	7	5	17	13	11	8
Other/unknown	2	1	1	50	0	0	0	0	0	0	0	0	0	0
Larynx	414	100	53	13	11	3	5	1	48	12	20	5	42	10
Age at diagnosis														
Mean* (sd)	66*	(10)	67*	(11)	61*	(4)	65*	(9)	66*	(10)	65*	(10)	72*	(11)
Sex														
Male	342	83	49	14	7	2	3	1	36	11	19	6	38	11
Female	72	17	4	6	4	6	2	3	12	17	1	1	4	6
TNM-stage														
I	180	43	27	15	0	0	1	1	20	11	1	1	12	7
II	73	18	7	10	4	5	2	3	7	10	1	1	8	11
III	95	23	12	13	3	3	1	1	15	16	8	8	12	13
IVA	64	15	7	11	4	6	1	2	5	8	10	16	9	14
IVB	2	0	0	0	0	0	0	0	1	50	0	0	1	50
Treatment														
Surgery only	104	25	23	22	0	0	0	0	13	13	0	0	5	5
Surgery + radiotherapy	31	7	1	3	1	3	0	0	3	10	4	13	2	6
Surgery + radiotherapy + systemic therapy	6	1	0	0	0	0	0	0	0	0	2	33	1	17
Radiotherapy only	224	54	26	12	7	3	4	2	22	10	8	4	28	13
Radiotherapy + systemic therapy	49	12	3	6	3	6	1	2	10	20	6	12	6	12
Hypopharynx	98	100	9	9	10	10	2	2	16	16	15	15	14	14
Age at diagnosis														
Mean* (sd)	64*	(9)	62*	(6)	69*	(9)	65*	(8)	63*	(9)	61*	(10)	71*	(9)
Sex														
Male	81	83	8	10	8	10	1	1	13	16	14	17	10	12
Female	17	17	1	6	2	12	1	6	3	18	1	6	4	24
TNM-stage														
I	1	1	0	0	0	0	0	0	1	100	0	0	0	0
II	6	6	1	17	0	0	1	17	1	17	0	0	2	33
III	17	17	0	0	2	12	1	6	2	12	3	18	3	18
IVA	61	62	8	13	4	7	0	0	12	20	11	18	4	7
IVB	13	13	0	0	4	31	0	0	0	0	1	8		38

Table 1 (*continued*)

	Total		Local recurrence		Regional recurrence		SPT head and neck		SPT outside head and neck		Distant metastasis		Death	
	N	Column%	N	Row%	N	Row%	N	Row%	N	Row%	N	Row%	N	Row%
Treatment														
Surgery only	1	1	0	0	0	0	0	0	0	0	1	100	0	0
Surgery + radiotherapy	11	11	0	0	0	0	0	0	2	18	3	27	1	9
Surgery + radiotherapy + systemic therapy	7	7	1	14	0	0	0	0	1	14	3	43	0	0
Radiotherapy only	37	38	3	8	6	16	2	5	6	16	3	8	9	24
Radiotherapy + systemic therapy	42	43	5	12	4	10	0	0	7	17	5	12	4	10

3. Results

3.1. Patients and follow-up events

In total, 1504 primary HNCs were included, of which 1424 (95%) were SCCs (Appendix, Table A.1). Of all included HNCs, 1338 (94%) were located in the oral cavity (N = 519), oropharynx (N = 307), larynx (N = 414), or hypopharynx (N = 98). Patient-, tumour-, and treatment characteristics, and the follow-up events according to site are summarized in Table 1.

In the entire HNC group, 595 (44%) events occurred, of which 113 (9%) LR, 82 (6%) RR, 26 (2%) SPHNC, 140 (11%) SPOHN, 104 (8%) DM, and 130 (10%) deaths (Fig. 2; Appendix, Table A.2).

The most common events for patients with oral cavity SCC (N = 519) were RR (8%), SPOHN (8%), and death (9%) (Table 1). SPOHN occurred most in men, 11% compared to 6% in women. Death was registered most for women, 10% versus 8% in men. RR (7%) and SPOHN (7%) happened most in patients with stage I disease (N = 207). DM (20%) and death (15%) were recorded most often for patients with stage IVA disease (N = 171).

Patients with oropharynx SCC (N = 307) were mainly diagnosed with a SPOHN (10%) and DM (10%) as first event. SPOHN (23%) was recorded the most for patients with stage II disease (N = 47). DM (12%) was registered most for patients with stage IVA disease (N = 179).

Most patients with larynx SCC (N = 414) developed LR (13%) as first event, followed by SPOHN (12%). LR was recorded the most for men, 14% versus 6% in women. SPOHN was registered mainly for women, 17% versus 11% in men. LR (15%) was mainly registered for patients with stage I disease (N = 180). SPOHN neck was registered predominantly (16%) for patients with stage III disease (N = 95).

For patients with hypopharynx SCC (N = 98), SPOHN (16%) and DM (15%) were registered most as first event, followed by death (14%). DM was the most common event for men, 17% versus 6% in women. Death was registered most often in women, 24% versus 12% in men, followed by SPOHN (18%) (Table 1).

3.2. Competing risk analyses – LR, RR or SPHNC

The cumulative incidence of LR, RR and SPHNC increased the most in the first year for oral cavity SCC and the first 1.5 years for oropharynx, larynx and hypopharynx SCC. The cumulative incidence of competing events increased evenly throughout five years of follow-up (Fig. 3). The 1-, 1.5-, and 5-year cumulative incidence of LR, RR, and SPHNC was 10% (95%CI 8–13), 12% (95%CI 10–15), and 17% (95%CI 14–21) for oral cavity SCC; 6% (95%CI 4–9), 10% (95%CI 7–14) and 13% (95%CI 9–18) for oropharynx SCC; 7% (95%CI 5–10), 11% (95%CI 9–15) and 17% (95%CI 13–20) for larynx SCC; and 11% (95%CI 6–19), 19% (95%CI 12–27) and 22% (95%CI 14–30) for hypopharynx SCC (Appendix, Table A.4).

4. Discussion

This is the first study using a population-based cancer registry to analyse the cumulative incidence of manifestations of disease after HNC treatment [20]. The cumulative incidence of LR, RR, and SPHNC increased the most in the first follow-up year for oral cavity SCC, and in the first 1.5 years for oropharynx-, larynx- and hypopharynx SCC. The increase was negligible afterwards for all groups.

For patients with oral cavity SCC, the most common events after treatment were RR and SPOHN. The incidence of LR, RR, and SPHNC increased the most in follow-up year one, and less in years two and three. It remained stable thereafter. The incidence of RRs increased the most in follow-up year one, consistent with findings from other studies. Sasaki et al. described that most follow-up events (86%) were detected within one year after treatment, of which 68% were RRs [21]. Brands et al. reported that the majority of RRs occurred in the first year after treatment [15]. Our results showed that the incidence of SPOHN did not decrease over five years of follow-up, which is in agreement with other literature [22,23].

After oropharynx SCC treatment, SPOHN and DM were registered the most. The incidence of LRs was highest in the first year of follow-up. RRs were detected at equal rates in year one and two. Both LRs and RRs were registered in only three cases during follow-up years three to five. This pattern of LR and RR detection is similar to that reported in other studies [24,25]. The incidence of SPTs remained stable through the entire follow-up period of five years, which is, again, consistent with other data on HNC [22,23]. Unfortunately, the presence of human papillomavirus (HPV) in oropharyngeal cancers was not routinely reported in the electronic patient records of Dutch HNC care centres in 2015. Therefore, this information was often missing. We do not know whether testing for HPV was not performed or whether reporting was an issue. Ultimately, we were unable to analyse oropharynx SCC by HPV-status. This would have been interesting, given that the aetiology of oropharynx SCC has shifted from tobacco- and alcohol-related to predominantly oncogenic HPV-related since the early 1990s and the oropharynx now has the lowest risk of second primary malignancies of all HNC sites [26].

In the group with larynx SCC, LRs were registered most often. The majority (81%) occurred within two years. The incidence of RRs and SPHNC was highest in years one and two and remained stable thereafter. Ritoe et al. also found that laryngeal cancer recurrences mainly developed at the primary tumour location (45%), and 78% were detected within three years after treatment [8]. More than 90% of recurrences were detected within two years of follow-up after total laryngectomy with curative intent [27]. It should be noted that Ritoe et al. did not distinguish LR, RR, and SPHNC from SPOHN and DM in their analyses, which could explain their three-year timeframe for the detection of recurrences.

For hypopharynx SCC, almost no LR, RR, or SPHNC were observed after two years. Hall et al. also reported that most follow-up events occurred within one year after treatment, and that 95%

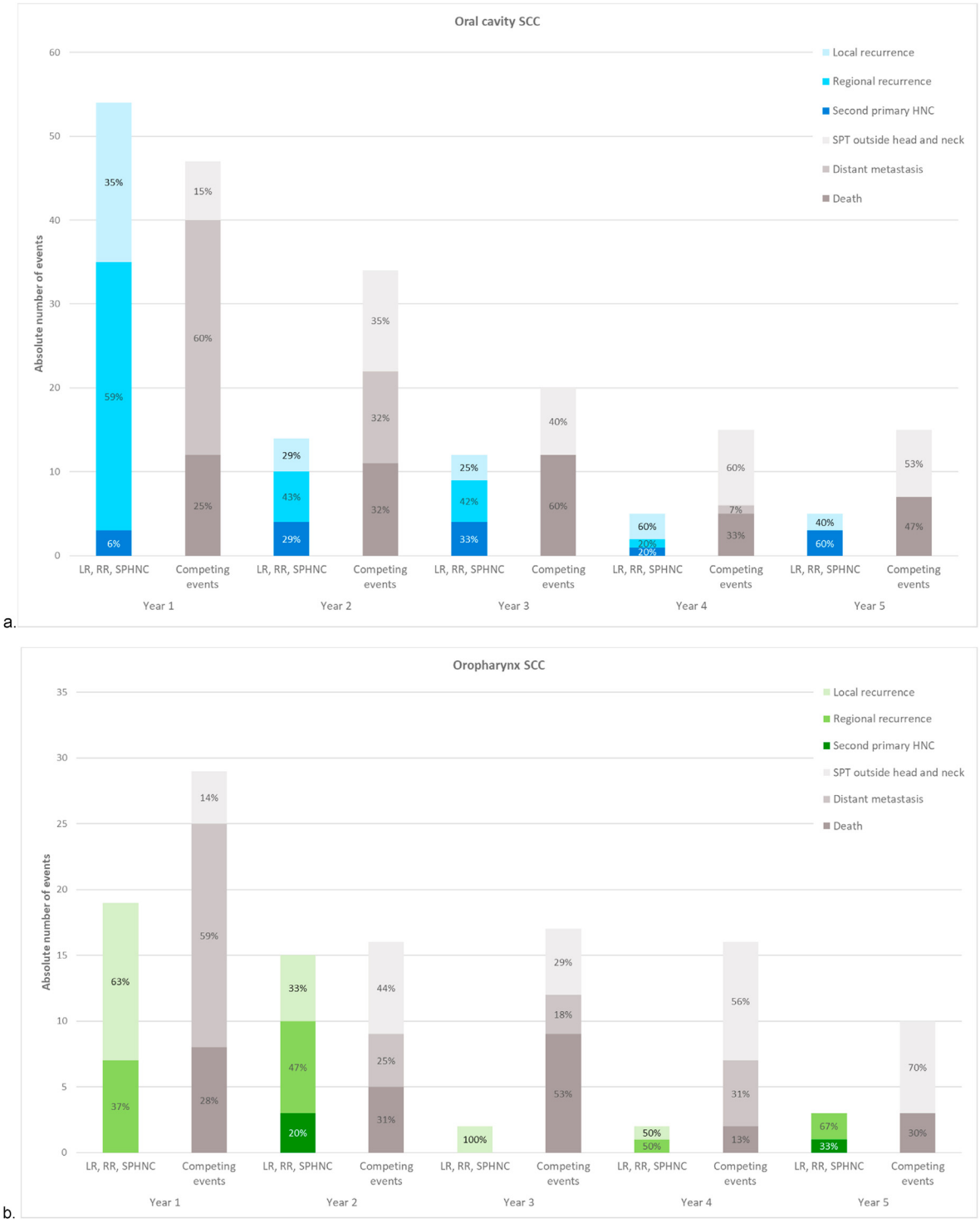


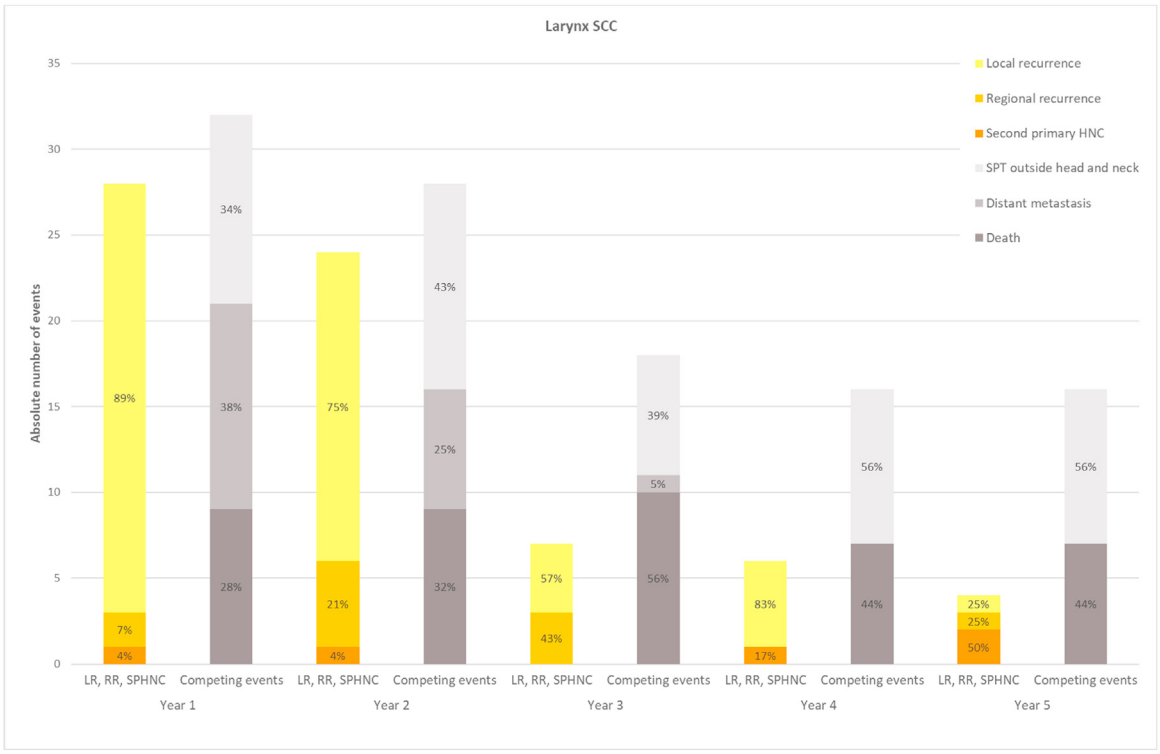
Fig. 2. Events per follow-up year for (a) oral cavity, (b) oropharynx, (c) larynx, (d) hypopharynx squamous cell carcinoma.

was discovered within 36 months [28]. Their events include SPOHN and DM, but they did not analyse the time to the event separately for LR, RR, and DM, which makes it difficult to compare our results. However, almost 50% of their follow-up events are DMs, similar to our findings.

Overall, we observed more distant metastases in patients with stage III-IV disease. However, our groups are small if we stratify by stage; therefore, we should be cautious interpreting these findings.

The majority of follow-up visits as they are currently performed are of no benefit in terms of early detection of new disease manifestations in follow-up years 2–5 for oral cavity- and 2.5–5 for oropharynx, larynx and hypopharynx SCC. For oral cavity SCC, we calculated a pick-up rate of one LR, RR, or SPHNC in 136 follow-up visits after follow-up year one. This was based on the number of LRs, RRs, and SPHNCs in years two through five (N = 36) related to the number of expected follow-up visits (N = 4897). The latter was

c.



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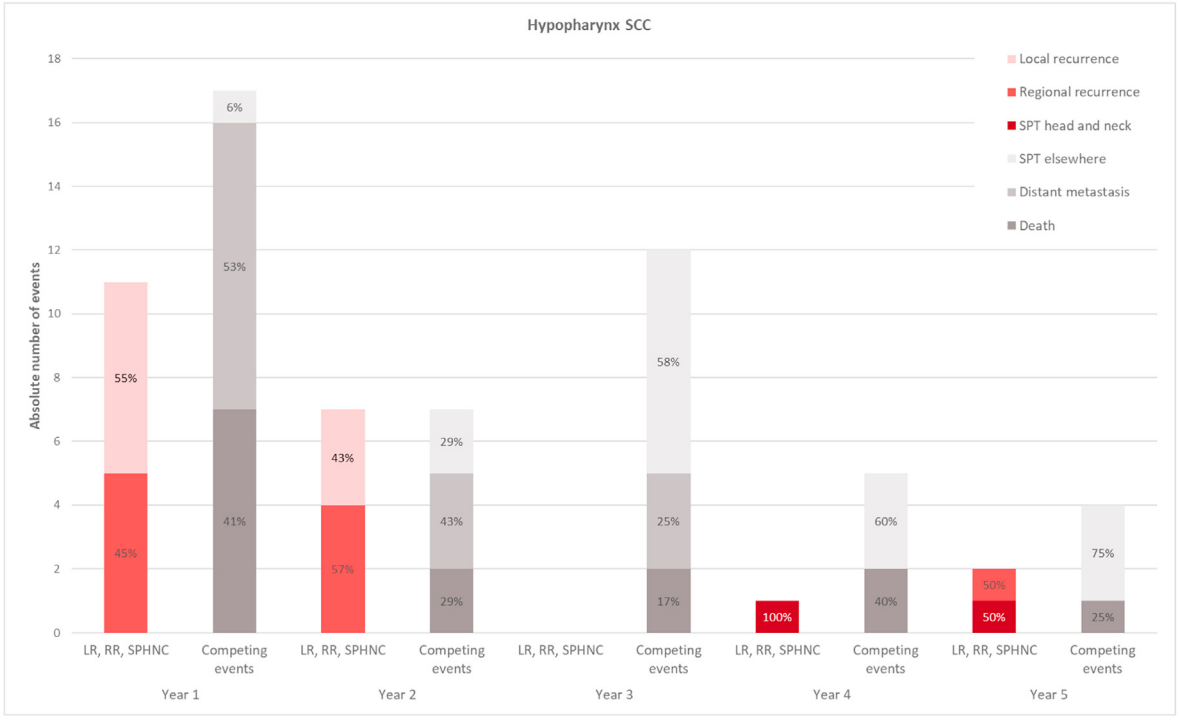

Fig. 2. (*continued*).

calculated by multiplying the number of remaining patients in oncological follow-up by the number of guideline-prescribed follow-up visits per year. In doing so, we considered 90% guideline adherence based on previous studies [8,29]. The same calculations for detecting LR, RR, and SPHNC in oropharynx-, larynx- and hypopharynx SCC after 1.5 follow-up years led to a pick-up rate of 1 in 235; 1 in 144; and 1 in 237 visits, respectively. These routine follow-up visits aim to detect asymptomatic cases.

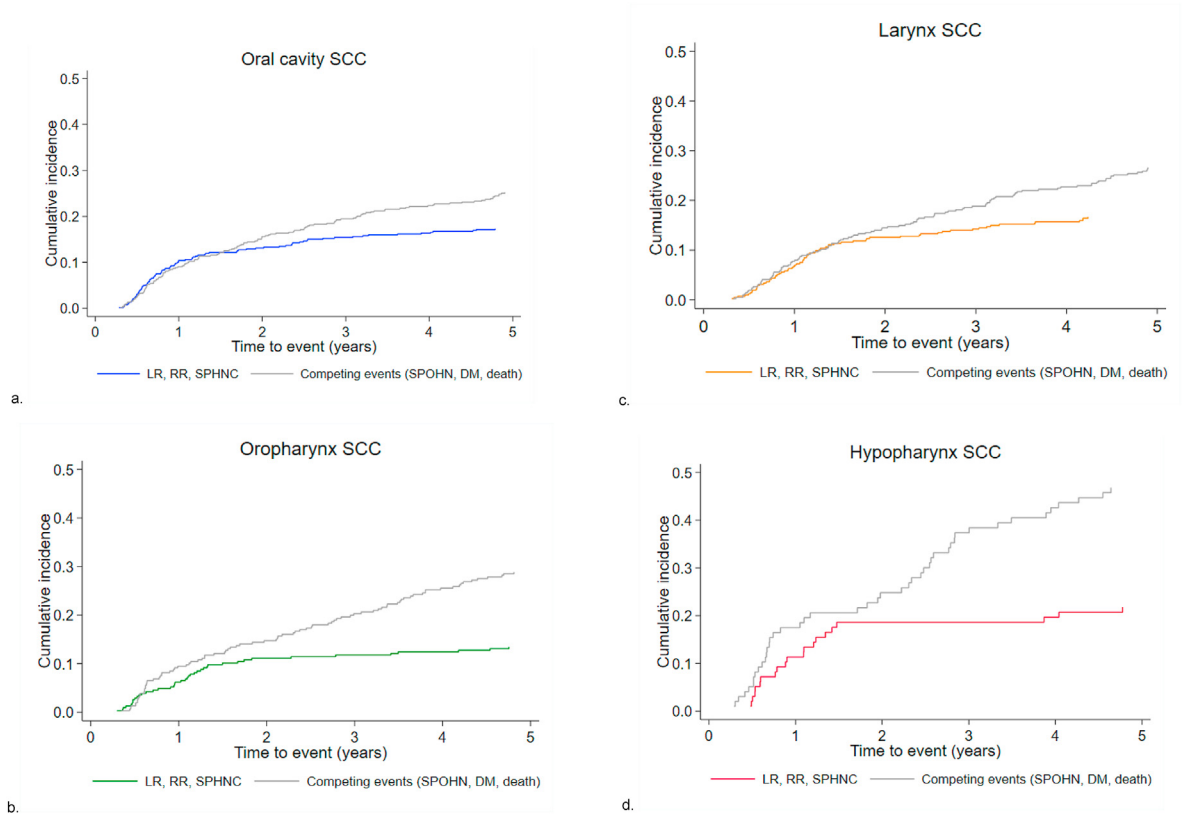

Fig. 3. Cumulative incidence of local recurrence, regional recurrence, or second primary head and neck cancer with second primary neck cancer outside the head and neck, distant metastasis and death as competing events, for (a) oral cavity, (b) oropharynx, (c) larynx, (d) hypopharynx squamous cell carcinoma.

However, it has already been established that most recurrences are accompanied by clinical symptoms and that a significant amount are discovered at patient-initiated visits [7–9]. Therefore, it is likely that the number of routine follow-up visits required to detect one case is even higher than our estimate. Also, the evidence for the effectiveness of asymptomatic discovery of new disease in terms of survival, treatment intent and quality of life is conflicting at best. Finally, very little research into the cost-effectiveness of follow-up has been conducted, and the available research is outdated [30–32]. Regardless of their follow-up schedule, we believe all HNC patients should be optimally educated about symptoms that may indicate recurrent or new disease and to contact their healthcare provider in case they experience those symptoms. This could reduce unnecessary routine check-ups, relieve pressure on healthcare resources, and lower healthcare costs.

Strengths of this study include the large population-based cohort which was followed for at least five years after treatment. Unfortunately, follow-up data from 12% of our patients was missing. This group included 24% oral cavity SCCs, compared to 36% in our analysed group. There were no significant differences in age, sex, and tumor stage between the missing and included patients in the total or SCC of the oral cavity group. Therefore, we do not expect this to affect our results. Other strengths are that the four most common HNC sites were addressed separately, and the distinction between events that can be detected by routine follow-up according to the Dutch guideline – LR, RR, SPHNC – and events that are not routinely investigated – SPOHN and DM. Finally, the use of competing risk analyses provided a more accurate estimate of the cumulative incidence of LR, RR, and SPHNC than Kaplan-Meier analyses because competing risk analyses take into account that experiencing a competing event modifies the chance of undergoing the event of interest [33].

The number of deaths in our population may seem low, but we only considered the first event. Deaths after another event are not shown. Our five-year survival for oropharynx SCC (68%; 95%CI 62–73) and hypopharynx SCC (44%; 95%CI 34–53) is similar to rates previously reported [34,35]. The five-year survival for oral cavity SCC (69%, 95%CI 64–72) and larynx SCC (71%; 95%CI 67–76) is higher in our population compared to other literature [36,37]. This could be explained by the more favourable stage in which oral cavity and laryngeal SCCs in our population were detected.

Routine follow-up also poses disadvantages for patients, such as anxiety, potentially unnecessary tests, and travel expenses. If patients are subjected to this, a proper evidence-base is needed. Therefore, our results should be adopted in Dutch HNC follow-up guidelines and extrapolated internationally, in particular to countries with similar patient populations and treatment and follow-up practices. However, the lack of effectiveness of follow-up in detecting (asymptomatic) recurrences, especially after 1–2 years of follow-up, is likely to be universal. Emphasis in HNC follow-up guidelines should be on other follow-up goals, such as post-treatment rehabilitation and psychosocial support.

5. Conclusions

This study supports a routine follow-up of one year for oral cavity SCC and 1.5 years for oropharynx, larynx and hypopharynx SCC for the purpose of detecting manifestations of disease.

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CRediT authorship contribution statement

Cecile van de Weerd: Conceptualization, Formal analysis, Data curation, Writing – original draft, Visualization, Project administration. **Boukje A.C. van Dijk:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Project administration. **Matthias A.W. Merkx:** Conceptualization, Investigation, Writing – review & editing, Supervision. **Robert P. Takes:** Conceptualization, Writing – review & editing, Supervision, Project administration. **Maria T. Brands:** Conceptualization, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.03.209.

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