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Is locally advanced head and neck cancer 'increasing' in the Netherlands? The paradox of absolute numbers, standardized incidence rates and proportional share☆

M.A. van Beers [a,*], W.H. Schreuder [a,b], A.J.M. Balm [a,b], B.A.C. van Dijk [c,d]

[a] Department of Head and Neck Oncology & Surgery, Antoni van Leeuwenhoek/Netherlands Cancer Institute, Amsterdam, The Netherlands
[b] Department of Oral and Maxillofacial Surgery, AmsterdamUMC, University of Amsterdam, Amsterdam, The Netherlands
[c] Netherlands Comprehensive Cancer Organization (IKNL), Department of Research and Development, Utrecht, The Netherlands
[d] University of Groningen, University Medical Centre Groningen, Department of Epidemiology, Groningen, The Netherlands

A R T I C L E I N F O

Keywords:
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ESR
Trends
Incidence

A B S T R A C T

Background: Several reports have indicated that locally advanced head and neck cancer (LAHNC) has increased in the past decade. However, incidence trends cannot be easily compared because slightly different definitions of LAHNC were used.
Aim: To investigate if the incidence of locally advanced disease (LAD) in the oral cavity, oropharynx, hypopharynx and larynx is indeed increasing over time, considering the growing and ageing population in the Netherlands.
Patients and methods: Data were obtained from the Netherlands Cancer Registry (NCR). Primary head and neck squamous cell carcinomas of the oral cavity, oropharynx, hypopharynx and larynx diagnosed between 1989 and 2017 were included. Yearly numbers and European standardized incidence rates (ESRs) were reported by extent of disease. The annual percentage change (APC) over time in ESRs was calculated to assess trends.
Results: Absolute numbers and ESRs of LAD increased over time for oral cavity and most prominently for oropharynx carcinomas (before 1996, APC: 0.4, 95%CI: 0.1; 0.8 and APC: 5.7 (95%CI: 3.1; 8.4) after 1996: 1.5 (1.0; 2.0) respectively. For hypopharynx cancer the absolute number and ESR of LAD increased until 1997 and declined with 0.8% per year since 1997. Absolute numbers of patients with larynx cancer stayed stable over time, while ESR decreased (APC: −0.8 (95%CI: −1.1; −0.6)).
Conclusion: The perception of an increasing trend in LAD in the Netherlands can be attributed to the increasing incidence of oral cavity and oropharynx carcinomas. For LAD of the hypopharynx a decreasing trend was observed. In larynx cancer, the proportional share of LAD of the larynx increased, even though incidence rates declined.

Introduction

Amongst the most common cancers worldwide head and neck cancer (HNC) comprises the sixth place with 890,000 new cases and 450,000 deaths in 2018 [1]. Head and neck squamous cell carcinoma (HNSCC) is the most prevalent type.

Patients diagnosed with HNSCC present mainly with locally advanced disease (LAD) [2]. Over 40% of patients are classified as stage IVA or B at first presentation and 10% of cases are even classified as stage IVC [3,4]. Though reports on incidence time trends for LAD are sparse [5], most evidence points to an increasing trend of LAD over time.

This increasing trend of LAD is worrisome. First, the oncological outcome is worse. Secondly, more complex and multimodality treatments are required, negatively influencing treatment related adverse effects and quality of life. Thirdly, it will increase healthcare costs and strain on resources. Considering this overall negative impact of LAD, it is important that the assumption of an increasing incidence trend is assessed on information retrieved from population-based databases.

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* Corresponding author.
E-mail address: maartjevanbeers@hotmail.com (M.A. van Beers).

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Most studies define LAD as UICC TNM stage III, IVA and IVB [6–8], while others deviate from this definition [9] or add slight modifications. In addition, some studies base conclusions on trends on absolute numbers, while other use proportional share of LAD. These dyscongruencies complicate the discussion, meanwhile stressing the need for a uniform definition and the use of all different measures (absolute numbers, proportional share and standardized incidence rates) in comprehensive population-based assessments of trends in LAD.

The aim of this study is to investigate the population-based trend in LAD of the oral cavity, oropharynx, hypopharynx and larynx in the Netherlands using all necessary measures. Furthermore, we attempt to reformulate the definition of LAD for standard use to enhance comparability of future studies.

Patients & methods

Patients

Data were retrieved from the Netherlands Cancer Registry (NCR), which is mainly build on pathology reports retrieved from the nationwide network and Dutch registry of histo- and cytopathology (PALGA). The registry is completed by annual cancer-related hospital discharge records from Dutch Hospital Data. Trained data managers extract patient, tumor and treatment characteristics from the hospital records.

All newly diagnosed first and consecutive primary HNSCCs from the most common subsites (oral cavity, oropharynx, hypopharynx and larynx) between 1989 and 2017 were included.

Definitions.

Topography was coded according to the international classification of diseases for oncology (ICD-0-3) [10]. Included subsites are shown in Table 1.

Tumor staging was performed according to the International Union against Cancer (UICC) TNM classification with the fourth edition (1989–1992), the second revision of the fourth edition (1993–1998), the fifth edition (1999–2002), the sixth edition (2003–2009) and the seventh edition (2010–2017).

Locally advanced disease (LAD) was defined as tumors clinically staged as stage III, IVA or IVB. Local disease (LD) was defined as tumors clinically staged as stage I or II.

Outcome measures and statistical analysis

The primary outcome measures were incidence numbers, the proportional distribution of stage groups and incidence rates standardized to the European Standardized population (ESR) per stage group to evaluate LAD changes over time. Standardized incidence rates were calculated using the standardized rate to the European standard population (1976 ESP) and population data were retrieved from the Central Bureau of Statistics (CBS). Using the ESR ensures trends were calculated over comparable numbers as changes in population size and age distribution are abolished. Joinpoint software (version 4.1.1) was used to calculate the annual percentage change (APC) over the years with a linear regression over log-transformed ESR [11]. Permutation test was used for trend breaks.

Table 1
Included subsites and their ICD-O code.

Subsite	ICD-O code
Oral Cavity	C00.3–5, C00.8–9, C02-C04, C05.0, C5.8–9, C06
Oropharynx	C01, C05.1–2, C09, C10.0, C10.2–4, C10.8–9
Hypopharynx	C12-C13
Larynx	C10.1, C32

Ethical considerations

This study does not fall under the scope of the Medical Research Involving Human Subjects Act. Therefore, formal approval by an accredited Multicenter Medical Research and Ethics Committee (MREC) was not mandatory.

Results

Stage per tumor type

Of all subsites, the highest numbers of HNSCC patients were observed in the larynx followed by the oral cavity, oropharynx and hypopharynx respectively (Fig 1). The proportion of LAD was lowest for SCC of the larynx (LSCC) at 34%, followed by SCC of the oral cavity (OSCC) at 42%. For SCC of the oropharynx (OPSCC) and SCC of the hypopharynx (HPSCC) the proportion of LAD was much higher at 74% and 80%, respectively.

Oral cavity

The absolute numbers (N) of both LD and LAD of the oral cavity increased over time (Fig. 2a). Overall, OSCC showed an increasing trend in both absolute numbers and standardized incidence rates (ESR) over the years (APC: 0.9, 95%CI: 0.7;1.2) (Fig 2a). ESR of LD increased rapidly in the earlier years with 11.3 % per year until 1991. From 1991 until 2014 this trend leveled off to an increase of 1.7 % per year (95%CI: 1.2; 2.2). Whereas, from 2014 onwards, the incidence rate decreased with 3.2 % per year (95%CI: −12.7; 7.3). The ESR of LAD in the oral cavity increased slowly with 0.4 % per year (95%CI 0.1; 0.8).

Oropharynx

The absolute number of patients with OPSCC increased over the last decade (Fig 2b). The absolute number of patients with LD of the OPSCC showed a slight increase, whereas the increasing number of patients suffering from LAD particularly contributed to the overall growing number. Also, ESR increased, with 5.3% per year (95%CI: 3.5;7.2) till 1997 and 1.2% per year afterwards (95%CI: 0.7;1.6). ESR of both LD as LAD increased over time (APC 1.4, 95%CI:0.8; 2.1 resp. APC 2.2, 96%CI: 1.8; 2.6), with the strongest increase in both LD and LAD before 1997 (APC 7.2, 95%CI 4.1; 10.4 and APC 5.7, 95 %CI 3.1; 8.4, respectively). After 1997, an increasing trend could only be detected for LAD with an APC of 1.5% from 1996 (95%CI;1.1; 1.2), while LD stayed stable over the last 10 years (APC 0.0; 95%CI −0.8; 0.7).

Hypopharynx

Absolute numbers of hypopharynx cancer were increasing over time, which can be explained by the rising numbers of LAD as can be seen in Fig. 2c. The overall ESR also showed an increasing trend until 1997 and a tendency to a slowly decreasing trend afterwards. (APC: 3.4 95 %CI: 1.0; 5.8, after 1997: APC −0.4 95%CI −1.0; 0.2). This pattern was also seen in the trend of LAD (before 1997: APC:3.6 95%CI: 0.7; 6.7, after 1997: APC −0.8 95%CI: −1.5; −0.1). The APC in LD was 0.6% (95%CI: −0.4; 1.5) indicating stable rates over time (Fig. 2c).

Larynx

The total number of patients with larynx cancer (LSCC) was stable over time (Fig. 2d). On the contrary to earlier described tumor sites, the ESR of LSCC for both LD and LAD decreased over time (overall APC −1.9, 95%CI: −2.1; −1.8). Interestingly, the APC in ESR was greater for LD (APC: −2.5, 95%CI: −2.8; −2.3), especially after 2008 (before 2008: APC −2.1 95%CI: −2.5; −1.8, after 2008: APC −3.8, 95%CI: −4.9; −2.6)) than for LAD (-0.8%, 95%CI: −1.1; −0.6) leading to a larger

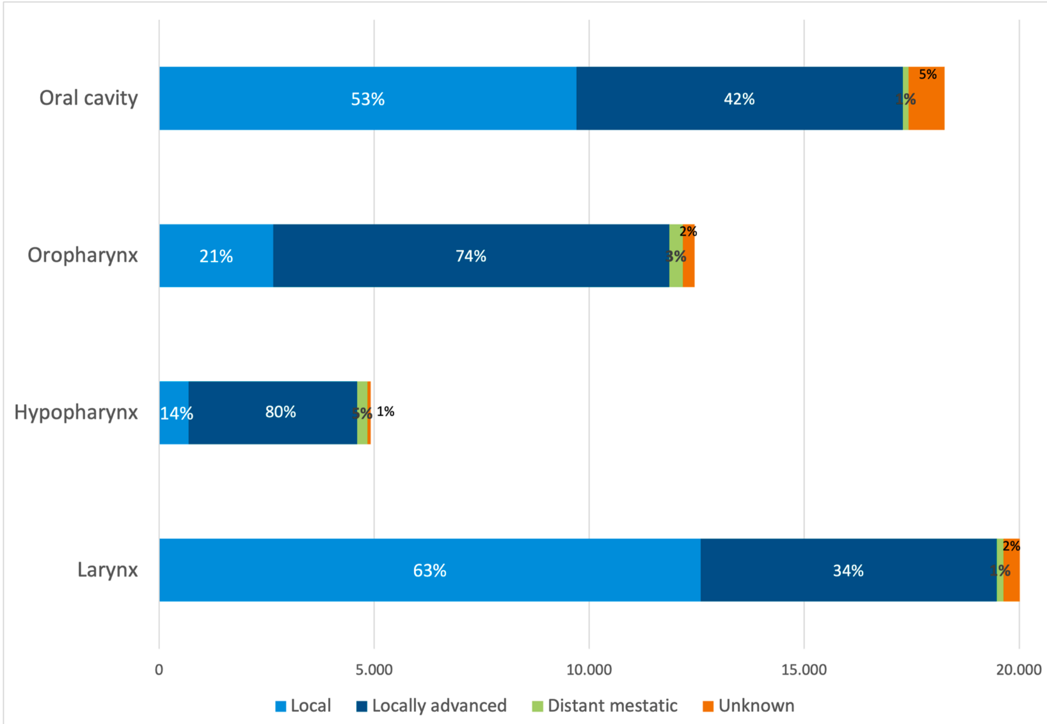

Figure 1. Proportional distribution of stage groups by tumor site over the period of 1989–2017.

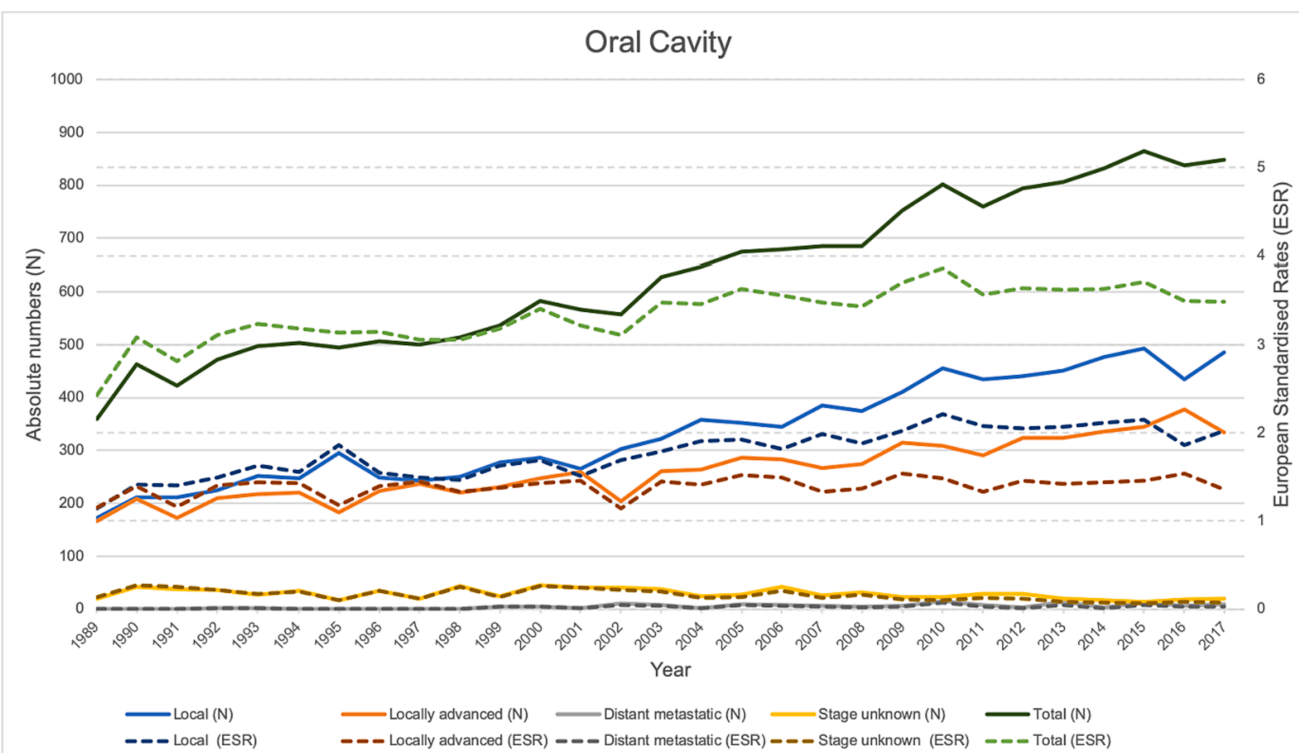

Figure 2a. Absolute incidence numbers and incidence rates standardized to the European Standardized population (ESR) in cancer of the oral cavity over time.

proportional share comparing to LD.

Annual percentage changes for all included sites are summarized in Table 2.

Discussion

In this population-based analysis we evaluated incidence trends of HNSCC in the Netherlands with the emphasis on LAD over time. The highest proportion of 80% LAD was observed in the hypopharynx followed by the oropharynx (74%), oral cavity (42%) and larynx (34%).

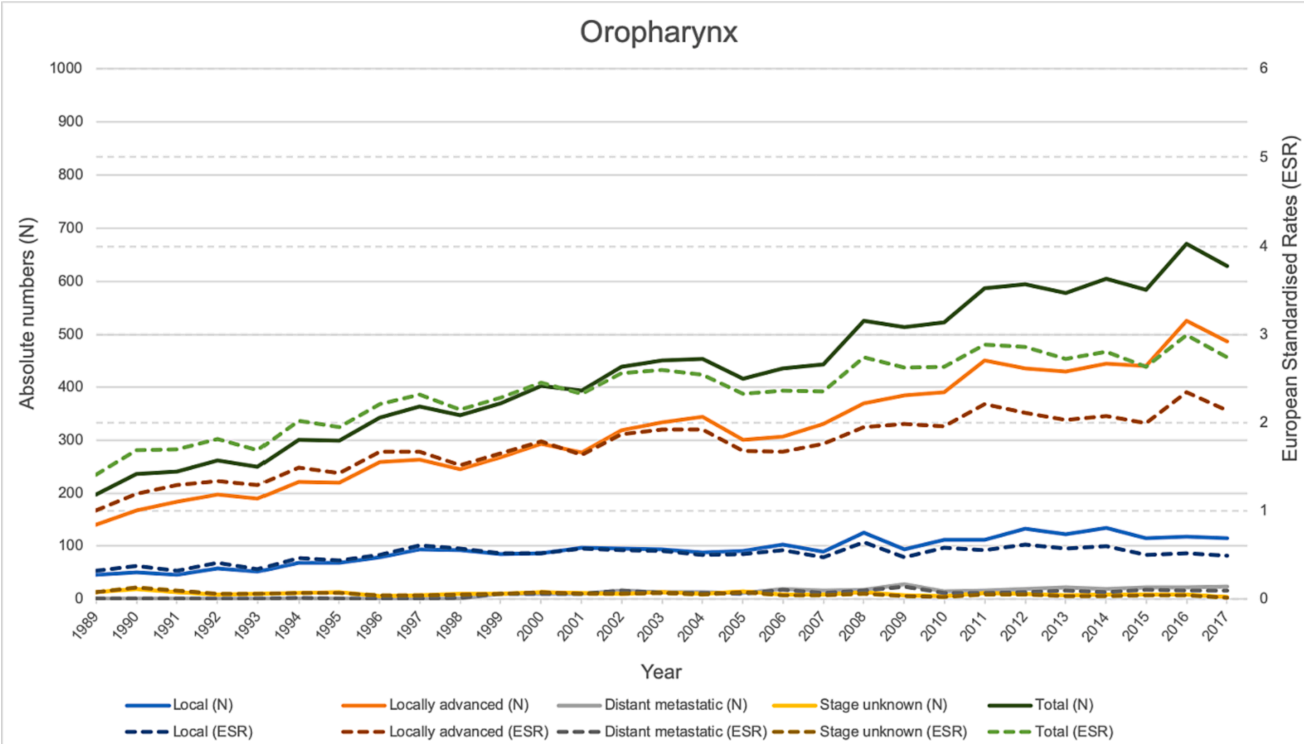

Figure 2b. Absolute incidence numbers and incidence rates standardized to the European Standardized population (ESR) in cancer of the oropharynx over time.

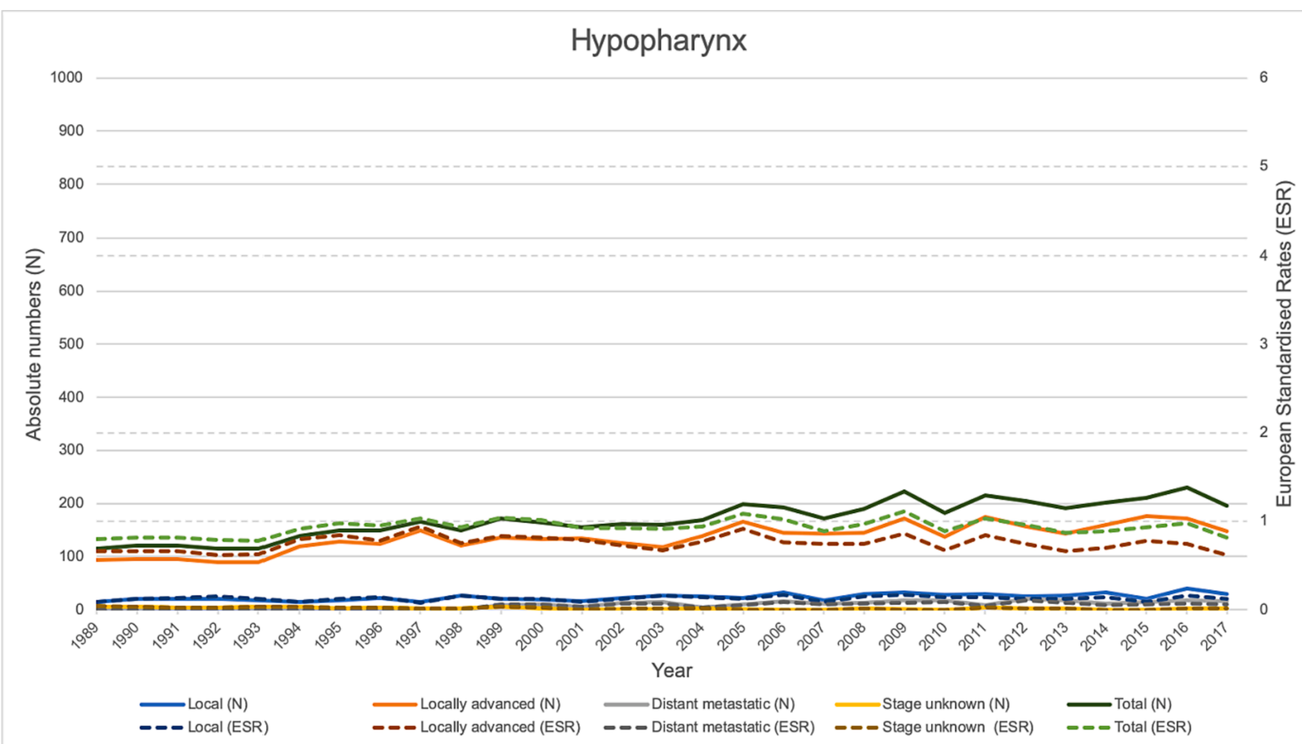

Figure 2c. absolute incidence numbers and incidence rates standardized to the European Standardized population (ESR) in cancer of the hypopharynx over time.

Both absolute numbers and ESR of LAD of the oral cavity and oropharynx have been rising over the past decade, while ESR of locally advanced hypopharyngeal and laryngeal cancer both have been decreasing. Interestingly, ESR of LD in the larynx declined faster than LAD, resulting in an increase in the proportionate share of LAD.

Oral cavity

Our analysis showed a rising overall trend in incidence of OSCC over the past years, similarly as has been observed in other European regions like Finland, Germany and the UK [12].

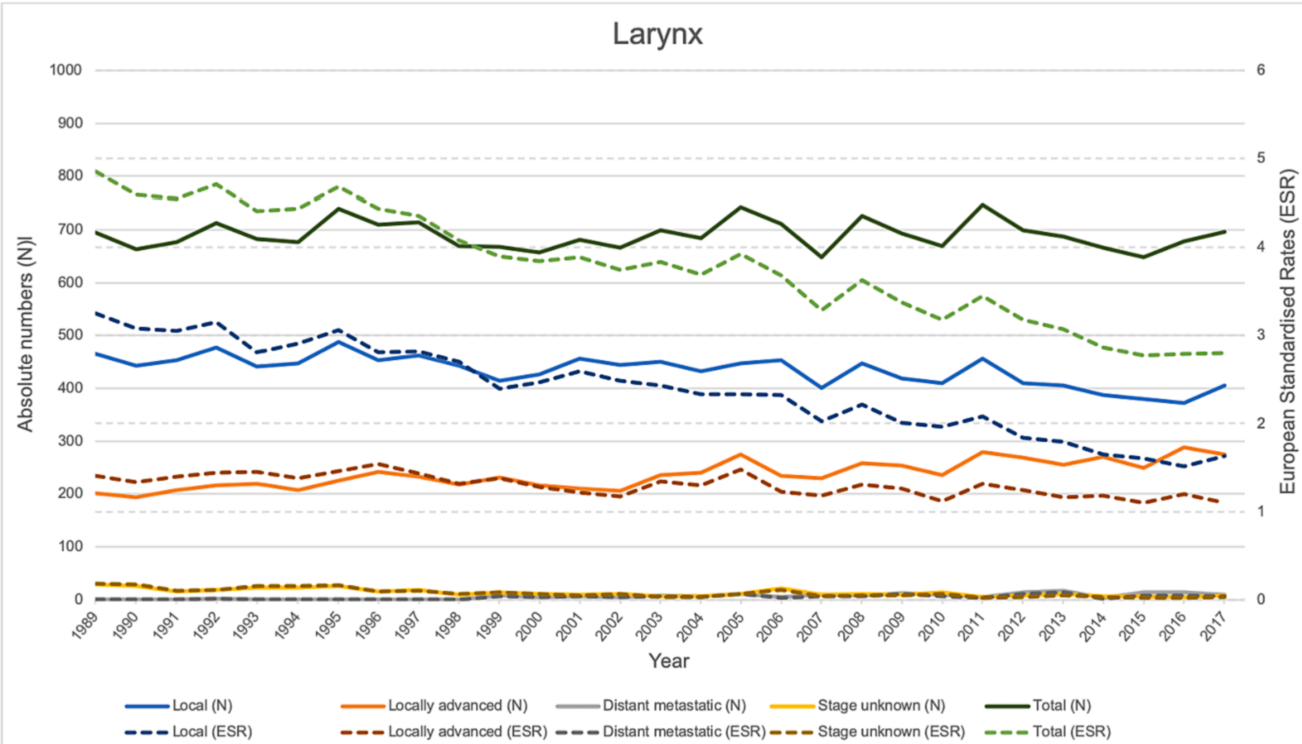

Figure 2d. absolute incidence numbers and incidence rates standardized to the European Standardized population (ESR) in cancer of the larynx over time.

Table 2
Annual percentage change (APC) (95%CI) in standardized incidence rates (ESR) over incidence years.

	Overall (all subsites included)	Oral cavity	Oropharynx	Hypopharynx	Larynx
Overall (all stages included)	**APC 1989–1995:** 1.7 (0.3; 3.2) **APC 1995–2017:** −0.2 (−0.4; 0.0)	**APC 1989–2017:** 0.9 (0.7; 1.2)	**APC 1989–1997:** 5.3 (3.5; 7.2) **APC 1997–2017:** 1.2 (0.7; 1.6)	**APC 1989–1997:** 3.4 (1.0; 5.8) **APC 1997–2017:** −0.4 (- 1.0; 0.2)	**APC 1989–2017:** −1.9 (−2.1; −1.8)
Local disease (LD)	**APC 1989–2011:** −0.3 (−0.5; −0.0) **APC 2011–2017:** −2.3 (−3.9; −0.7)	**APC 1989–1991:** 11.3 (−9.4; 36.8) **APC 1991–2014:** 1.7 (1.2; 2.2) **APC 2014–2017:** −3.2 (−12.7; 7.3)	**APC 1989–1997:** 7.2 (4.1; 10.4) **APC 1997–2017:** −0.0 (−0.8; 0.7)	**APC 1989–2017:** 0.6 (−0.4; 1.5)	**APC 1989–2008:** −2.1 (−2.5; −1.8) **APC 2008–2017:** −3.8 (-4.9; −2.6)
Locally advanced disease (LAD)		**APC over the years:** 0.4 (0.1; 0.8)			
	APC 1989–1996: 2.6 (1.0; 4.3) **APC 1996–2017:** 0.2 (- 0.1; 0.5)	**APC 1989–2017:** 0.4 (0.1; 0.8)	**APC 1989–1996:** 5.7 (3.1; 8.4) **APC 1996–2017:** 1.5 (1.0; 2.0)	**APC 1989–1997:** 3.6 (0.7; 6.7) **APC 1997–2017:** −0.8 (-1.5; −0.1)	**APC 1989–2017:** −0.8 (-1.1; −0.6)
Metastatic	*NA*	*NA*	*NA*	*NA*	*NA*
Stage unknown	APC 1989–2017: −4.7 (-5.5; −3.9)	**APC 1989–2002:** 0.7 (-3.4; 5.0) **APC 2002–2017.** −7.1 (-10.2; −3.9)	**APC over the years:** −4.0 (-5.6;-2.4)	*NA*	**APC over the years.** −6.6 (-8.1;-5.0)

Chaturvedi et al [13] and Braakhuis et al [14] performed respectively a worldwide and nationwide population-based study on the incidence rates of HNSCC, including gender-specific rates. In both studies, a growing incidence trend in overall OSCC (restricted to males in Chaturvedi's study) could be detected [13,14]. The authors suggested that excessive alcohol intake and the use of (chewing) tobacco could be possible causative factors. Since the percentage of people with excessive alcohol and especially tobacco use has been declining over the past years in the Netherlands [15] and chewing tobacco use is not very prevalent, this does not seem the most likely explanation for our study results. Migration of populations from countries with high overall incidence rates of HNC was also suggested by Chaturvedi et al [13,16,17]. However, the recent annual migration balance of about 80,000 people in the Netherlands seems too small to be a possible explanation for this rising trend [18]. Oral hygiene habits are also being explored as possible oncogenic factors for the development of OSCC, as indicated by Zeng et al. [19]. Although the overall percentage of people who went to visit oral health caretakers stayed quite stable over the years in the Netherlands [20], oral hygiene remains hard to be disentangled from other oncogenic factors like smoking, chewing tobacco and alcohol [21]. Human papilloma virus (HPV) infection does not seem a relevant risk factor for OSCC [22]. Apparently, the search for a yet unknown oncogenic factor to explain the increasing incidence in oral cancer is needed.

Oropharynx

A rise of both LAD and LD of OPSCC was observed in our study. This is in line with literature and primarily driven by the increased incidence of HPV-related oropharyngeal cancer [12,23]. It has been shown that HPV-related OPSCCs are more likely to present with more advanced stages, meaning low primary tumor size (T) and high nodal metastases rate (N) [24], which immediately leads to a higher stage in staging classifications prior to introduction of the 8th edition. As such, Würdemann et al. found 93% (140/150) high staged OPSCCs, defined as stage III and IV, following TNM7 staging and 27% (40/150) following TNM8 staging [25]. Therefore, it seems likely that the increasing incidence of LAD, both in our study and other reports, reflect the increase in proportion of HPV-associated OPSCC [26,27]. It should be kept in mind that the TNM 8th edition is used for prognostic stratification, and the lower stage does not mean that localization and volume/size of tumor has changed.

Hypopharynx

Hypopharyngeal cancer (HPSCC) is mostly diagnosed relatively late as tumors at this site often do not present with specific symptoms. Our observation that the overall incidence and the incidence of locally advanced HPSCC is slightly decreasing or stable from 1997 onwards, seems to be in agreement with other reports [23,28,29]. However, a population-based study performed in Denmark found a significant increase in the incidence of HPSCC, without discussing the possible cause of this trend [30]. A decreasing incidence seems most plausible given that the combination of smoking and heavy alcohol consumption, which is the main risk factor, is decreasing [15].

Larynx

The overall ESR, ESR of local and of LAD have decreased over the years in the Netherlands. Together with the decreasing consumption of tobacco, this trend was expected, as predominantly smoking increases the risk of LSCC [32]. The faster decline in local disease than in LAD may explain the perception of a rising trend in LAD [33].

Possible non-disease related influences

The observed increasing incidence rates of LAD might not only be attributed to disease related factors. As such, the improved accuracy of diagnostic imaging might have had a significant influence on the (up) staging of HNC. Both the early radiological detection of bony and cartilage invasion [34] and more accurate detection of occult lymph node metastases by the sentinel lymph biopsy [35] has led to upward stage migration. To the same extent this applies to pretreatment diagnostic PET-CT use. VanderWalde et al. examined stage, patient and treatment characteristics in the pre-PET/CT era (2000–2004) and in PET/CT era (2005–2008) and found the increasing use of PET/CT in HNSCC patients to be associated with a greater number of LAD (defined as stage III, IVA and IVB) [36].

Limitations and strengths

Our study has some limitations. First, our analysis is based on a cancer registry in a period without information on smoking, drinking and HPV status. If these rates were recorded during the study period, statements on the prevalence could be made, although it is still not usable to elaborate on their role as risk factor since the time factor is missing.

As strong points, this is the first study to describe data on incidence trends of LAD from different HNSCC sites. This allows a better trend comparison of the various anatomical subsites and their relative contribution to LAD in general. Also, for all subsites TNM7 or earlier versions have been used for staging. Only slight changes, which did not affect the categorization into local disease and locally advanced disease for the reported sites, were present between the TNM classifications that were used in this report. In all these versions, tumor localization, size, and invasion of nearby structures is described to characterize the extent of the disease. Thereby, the recorded tumor stages reflect at best true disease extent and tumor burden for describing LAD. This aspect is partially lost with introduction of TNM8, since the HPV-related locally advanced oropharynx cancer is considered to be a lower stage than HPV-negative oropharynx cancer with a comparable tumor burden. The changes implemented in TNM8 are drafted for better prognostication and especially of value once future de-escalation treatment protocols based on specific prognostic tumor characteristics become standard of care [37]. Up till that moment, the true burden of disease as reflected in TNM7 is still the leading factor in treatment strategy as well as describing disease extent.

Future perspectives

The term LAD is frequently used but poorly defined in the international literature, confusingly ranging from inclusion of stages III, IVA and IVB [6–8] to solely T2–T4 lesions [18]. A statement on uniform definition and usage of the term LAD is therefore advocated for future research.

It is important to realize that the TNM is a classification system that not only describes the anatomic extent of head and neck cancer. It aims to predict prognosis and guides management. In addition, TNM classifications will keep adapting to various other tumor characteristics representative of tumor biology apart from tumor extent, especially, since increasingly distinct factors are shown to be important for prognostication. Meanwhile, LAD terminology is connected to a model based on tumor extension and is not so much a prognostic model. In our opinion, LAD should therefore exclusively be used to describe extent of disease and tumor load. It could be suggested to categorize HNC based on their radiological defined volumes as local disease, loco-regional advanced disease and distant disease [38]. Or LAD could be defined as a tumor with growth into structures nearby the specific site (for example in bone or muscle) with or without regional nodal metastases. LD is then defined as HNC without growth in nearby structures and without regional metastases. HNC with distant metastases could be classified as separate group. As future TNM classifications are expected to include more prognostic factors from successful discoveries on tumor biology and radio(geno)mics not strictly related to anatomical features, terminology exclusively based on extent of disease and tumor load will naturally claim its position and become more meaningful. However, the exact value and implication of terminology such as LAD can only be properly evaluated after a uniform implementation. Hence the first hurdle to take, is to reach unanimity on a common vocabulary and standard usage. With this paper, we sincerely hope to raise awareness on this current shortcoming and to ignite a discussion, for example on an international forum, to reach consensus across our field.

Conclusion

The incidence of HNSCC and of LAD is increasing for oral cavity and oropharynx cancer. Standardized rates of locally advanced hypopharyngeal and laryngeal cancer are decreasing over time. However, the proportionate share of LAD in larynx cancer increased, since the incidence of LD declined faster, explaining the paradoxical impression of increasing rates for locally advanced laryngeal squamous cell carcinoma. Definitions of LAD vary in the literature. There is an urgent need for standardization to enable a sound comparison of epidemiological studies at an international level. A classification that's mainly based on predictive abilities is not the most obvious to use in this case.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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