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PATIENT AND HEALTHCARE DELAYS IN HEAD AND NECK CANCER

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ACADEMIC DISSERTATION

To be presented for public discussion with the permission of the Medical Faculty of the University of Helsinki, in the Richard Faltin lecture hall of the Surgical Hospital, Kasarmikatu 11-13, on December 15th, 2023, at 1300, in the afternoon.

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1. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I. Nieminen M, Aro K, Jouhi L, Bäck L, Mäkitie A, Atula T. Causes for delay before specialist consultation in head and neck cancer. Acta Oncol. 2018;57(12):1677-1686.

II. Nieminen M, Atula T, Bäck L, Mäkitie A, Jouhi L, Aro K. Factors influencing patient and health care delays in oropharyngeal cancer. J Otolaryngol Head Neck Surg. 2020;49(1):22.

III. Atula M*, Aro K, Irjala H, Halme E, Jouppila-Mättö A, Koivunen P, Wilkman T, Blomster H, Mäkitie A, Atula T. Patient and health care delays in large (class T3-T4) oral, oropharyngeal, and laryngeal carcinomas. Head Neck. 2023;45(5):1215-1225.

IV. Atula M*, Atula T, Aro K, Irjala H, Halme E, Jouppila-Mättö A, Koivunen P, Wilkman T, Mäkitie A, Elovainio M, Pulkki-Råback L. Psychosocial factors and patient and healthcare delays in large (class T3-T4) oral, oropharyngeal, and laryngeal carcinomas. A manuscript.

V. Nieminen M, Aro K, Mäkitie A, Harlin V, Kainulainen S, Jouhi L, Atula T. Challenges in diagnosing head and neck cancer in primary health care. Ann Med. 2021;53(1):26-33.

*né Nieminen

The publications are referred in the text to their roman numerals.

2. ABBREVIATIONS

BDI	Beck's Depression Inventory
CCI	Charlson Comorbidity Index
CPP	Standardized cancer patient pathway
CI	Confidence interval
CNB	Core-needle biopsy
CT	Computed tomography
CDS	Cynical Distrust Scale
(C)RT	(Chemo)radiotherapy
DSS	Disease-specific survival
ER	Emergency room
FNAC	Fine-needle aspiration cytology
GP	General practitioner
HCP	Healthcare provider
HED	Heavy episodic drinking
HNC	Head and neck cancer
HPV	Human papillomavirus
HR	Hazard ratio
HR-HPV	High-risk human papillomavirus
MRI	Magnetic resonance imaging
MSC	Make Sense campaign
NCDB	National Cancer Database
OP	Oropharynx
OPSCC	Oropharyngeal squamous cell carcinoma
OR	Odds ratio
ORL	Otorhinolaryngology
OS	Overall survival
RR	Relative risk
RS	Relative survival
RT	Radiotherapy
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PHC	Primary healthcare
QoL	Quality of life
SC	Specialist care
SCC	Squamous cell carcinoma
SES	Socioeconomic status
SSQ	Social Support Questionnaire
TDI	Total diagnostic interval

UK	The United Kingdom
US	The United States

3. ABSTRACT

Head and neck cancers (HNCs) are the seventh most common malignancy globally, accounting for nearly 900,000 new cases each year. HNCs are often diagnosed at an advanced stage. Patients with advanced stage disease usually need multimodality treatment leading to higher treatment costs, poorer prognosis, poorer functional result and quality of life (QoL), compared to patients with early-stage disease.

Delay before the initiation of curative treatment can lead to tumor growth, disease advancement, and worse prognosis. Delay can be patient derived, if the patient prolongs his/her attempt to seek medical attention, or can occur in primary healthcare (PHC), or specialist care (SC). Multiple patient-related factors (socioeconomic status, living arrangements, alcohol use), certain symptoms, and tumor-related factors (tumor site, disease advancement) have been associated with patient delay. When the patient has arrived to PHC, the decisions made by the general practitioner (GP) at the initial appointment (whether a referral to SC is made or a follow-up appointment is scheduled) affect PHC delay. Misdiagnosis also plays a part. In SC, tumor site and the chosen treatment modality: surgery vs. (chemo)radiotherapy ([C]RT), influence SC and treatment delays.

This thesis consists of 5 studies done between 2014 and 2023. Studies I-IV were prospective cohort studies where we investigated the lengths and different factors associated with patient, PHC, and SC delays among all HNC patients (Study I), oropharyngeal (OP) squamous cell carcinoma (SCC) patients (Study II), among patients with a large (T3-T4) oral, OP, or laryngeal SCC (Studies III and IV). In Study IV, we also compared our patient cohort to the age- and sex-matched Finnish general population using the FinTerveys 2017 report. In Studies I-IV, the data were prospectively obtained from patients using semi-constructed, multiple choice, questionnaires, and from the patients' hospital medical records. Because the delays were not normally distributed, the data were analyzed using nonparametric Mann-Whitney *U* test and the Kruskal-Wallis test applying the Dunn-Bonferroni correction for pairwise comparisons (Studies I-IV). For multivariable analysis (Studies I-III), factors significantly associated with delays identified through univariate analysis were included. Study V was a retrospective register study, where we collected data on different HNC related ICD-10 diagnosis codes used at outpatient visits at PHC centers in the city of Helsinki in 2016 and compared

the data on all new HNCs diagnosed in the city of Helsinki at the same time period. We also studied the physician-related PHC delay more closely.

We found patient delay to be the most important factor affecting the total delay before the initiation of treatment. Regarding patient-related factors, in Study II, unemployed or retired patients had a longer patient delay compared to employed or studying patients. Lower levels of education, and heavy use of alcohol were associated with a longer patient delay in Study III. Certain symptoms were associated with patient delay; a lump in the neck lead to a shorter delay, while hoarseness and difficulties breathing were associated with a longer delay (Studies I and III). Patients with longer patient delays generally had a higher number of different symptoms (Study II). Tumor site and the presence of regional metastases were also associated with patient delay (Study I), while p16 status did not affect patient delay (Study II).

Our studies revealed that certain healthcare-related factors are associated with PHC delay. Patients who had initially visited otorhinolaryngologists (ORL), had shorter PHC delay (Study I). The number of visits, and whether a follow-up appointment was scheduled, had an association with PHC delay (Studies I and II). If the patient's symptoms were treated as an infection by the general practitioner (GP) PHC delay was longer (Study III). Treatment modality affected SC delay: patients treated with surgery had significantly shorter SC and treatment delays compared to patients treated with (C)RT (Studies I-III). Patients who eventually received palliative treatment had had long patient, but short PHC delays (Study III).

In Study IV, we found that depression was common among HNC patients. A comparison to the Finnish general population revealed that HNC patients had lower educational levels, and were more often unemployed, tobacco smokers, and heavy users of alcohol. However, we found no association between psychosocial factors and patient delay.

In Study V, we found that for each HNC patient, a GP working in PHC center sees around 6000 other patients, of whom a hundred have sought medical attention because of a sign/symptom that might be caused by HNC. Still, the median physician related PHC delay was only 5 days, and half of patients with HNC were referred to SC at the initial visit.

By investigating the lengths of, and reasons behind different delay intervals among HNC patients, we can better find solutions to shorten these delays leading to better overall care and prognosis of HNC patients.

4. SUMMARY IN FINNISH

Vuosittain maailmassa diagnosoidaan 900 000 uutta pään ja kaulan alueen syöpää ja ne ovat seitsemänneksi yleisin syöpätyyppi. Pään ja kaulan syövät diagnosoidaan yleensä myöhäisessä vaiheessa pitkälle edenneinä. Pitkälle edennyt pään ja kaulan syöpä vaatii usein yhdistelmähoitoja, mikä on kalliimpaa, johtaa huonompaan toiminnalliseen lopputulokseen, huonompaan elämänlaatuun, ja näillä potilailla on yleensä huonompi ennuste.

Viive ennen kuratiivisen hoidon aloitusta voi johtaa kasvaimen kasvuun, taudin etenemiseen ja huonompaan ennusteeseen. Viive voi johtua potilaasta itsestään, mikäli hän viivyttelee hoitoon hakeutumista, tai se voi tapahtua perusterveydenhuollossa (PTH) tai erikoissairaanhoidossa (ESH). Useilla eri potilaisiin liittyvillä tekijöillä (sosioekonominen status, asumisjärjestelyt, alkoholinkäyttö), sekä eräillä kasvaimeen liittyvillä tekijöillä (kasvaimen sijainti ja Stage) on havaittu yhteyttä potilasviiveeseen. PTH:ssa yleislääkärin ensikäynnillä tekemät hoitopäätökset (tehdäänkö lähete ESH:n, sovitaanko kontrollikäynti) vaikuttavat PTH viiveeseen. Virheellisellä diagnoosilla on myös vaikutusta. ESH:ssa kasvaimen sijainti ja valittu hoitomodaliteetti: kirurgia tai (kemo)sädehoito, vaikuttavat ESH- ja hoitoviiveisiin.

Tämä väitöskirja koostuu viidestä osatyöstä. Osatyöt I-IV olivat prospektiivisia kohorttitutkimuksia, joissa tutkimme eri tekijöiden vaikutusta potilasviiveeseen, PTH viiveeseen ja ESH viiveeseen valikoimattomassa aineistossa kaikkia pään ja kaulan syöpiä (Osatyö I), suunielusyöpäpotilailla (Osatyö II), ja potilailla, joilla todettiin kookas (T3-T4) suuontelon, suunielun tai kurkunpään levyepiteelikarsinooma (Osatyöt III ja IV). Osatyössä IV lisäksi vertasimme potilaskohorttiamme iän ja sukupuolen osalta samankaltaistettuun suomalaiseen verrokkiväestöön käyttämällä FinTerveys 2017 raporttia. Tiedot kerättiin prospektiivisesti monivalintakysymyksiä sisältävillä kyselylomakkeilla (Osatyöt I-IV), sekä potilastietojärjestelmistä. Koska viiveiden pituudet eivät olleet normaalisti jakautuneita, käytimme yksimuuttuja-analyyseissä nonparametrisia Mann-Whitney *U* testiä, sekä Kruskal-Wallis testiä Dunn-Bonferroni korjauksella (Osatyöt I-IV). Osatyö V oli retrospektiivinen rekisteritutkimus, jossa selvitimme erilaisten pään ja kaulan syöpiin liittyvien ICD-10 diagnoosikoodien yleisyyttä Helsingin terveyskeskusten yleislääkärien vastaanotoilla vuonna 2016 ja vertasimme sitä

samana vuonna Helsingin alueelta diagnosoituihin uusiin pään ja kaulan syöpiin. Lisäksi tutkimme tarkemmin yleislääkäriin liittyvää PTH viivettä.

Potilasviive oli suurin viivettä aiheuttava tekijä ennen hoidon aloitusta. Osatyössä II eläkeläisillä ja työttömillä oli pidemmät potilasviiveet verrattuna työssä käyviin tai opiskeleviin potilaisiin. Alhaisempi koulutustaso ja runsas alkoholinkäyttö olivat yhteydessä pidempään potilasviiveeseen Osatyössä III. Eräillä oireilla havaittiin yhteys potilasviiveeseen: kaulakyhmy oli yhteydessä lyhyeen potilasviiveeseen, kun taas äänen käheys ja hengitysvaikeus olivat yhteydessä pitkään potilasviiveeseen (Osatyöt I ja III). Potilailla, joilla oli pitkä potilasviive, oli myös useampia oireita (Osatyö II). Kasvaimen sijainti ja paikalliset etäpesäkkeet olivat yhteydessä potilasviiveeseen (Tutkimus I), kun taas p16 status ei vaikuttanut viiveeseen (Osatyö II).

Tutkimuksemme osoittivat eräiden terveydenhuoltoon liittyvien tekijöiden vaikuttavan PTH viiveeseen. Mikäli potilas hakeutui yksityiselle korva-, nenä- ja kurkkutautien erikoislääkärille, johti se lyhyeen PTH viiveeseen (Osatyö I). Lääkärikäyntien lukumäärällä ja sillä, sovittiinko ensikäynnillä kontrollia, oli yhteys PTH viiveeseen (Osatyöt I ja II), ja mikäli potilaan oireita hoidettiin infektiona, johti se pidempään PTH viiveeseen (Osatyö III). Hoitomodaliteetti vaikutti ESH viiveeseen: kirurgisesti hoidetuilla potilailla oli huomattavasti lyhyempi ESH viive verrattuna (kemo)sädehoidettuihin potilaisiin (Osatyöt I-III). Potilailla, jotka loppujen lopuksi joutuivat palliatiiviseen hoitoon, oli ollut pitkä potilasviive, mutta lyhyt PTH viive (Osatyö III).

Masennusoireet olivat yleisiä pään ja kaulan syöpäpotilailla (Osatyö IV). Vertailu suomalaiseen väestöön paljasti, että pään ja kaulan syöpäpotilailla oli alhaisempi koulutustaso, he olivat useammin työttömiä, tupakoivia, ja useammin alkoholin liikakäyttäjiä. Emme kuitenkaan löytäneet psykososiaalisilla tekijöillä yhteyttä potilasviiveeseen.

Viidennessä osatyössä selvitimme terveyskeskuksessa työskentelevän yleislääkärin haasteita pään ja kaulan syövän löytämisessä muusta potilasmateriaalista. Jokaista pään ja kaulan syöpäpotilasta kohti yleislääkäri tapaa 6000 muuta potilasta, joista noin sata on hakeutunut vastaanotolle pään ja kaulan syöpään sopivan oireen vuoksi. Tästä huolimatta PTH:n lääkäriin liittyvän viiveen mediaani oli vain 5 päivää ja puolet potilaista lähetettiin ESH:n ensikäynnillä.

Viiveitä tutkimalla voimme löytää keinoja viiveiden lyhentämiseen, mikä parantaa pään ja kaulan syöpäpotilaan hoitoa ja ennustetta.

5. INTRODUCTION

Head and neck cancers (HNCs) are the seventh most common malignancy in the world accounting for nearly 900,000 new cases annually [1]. Over 90% are squamous cell carcinomas (SCCs), with tobacco smoking and alcohol consumption being the two most important etiological risk factors [2]. In recent years the incidence of human papillomavirus (HPV) related oropharyngeal (OP) SCC has been rising especially in the Western countries [3-5]. The size of the primary tumor (T Class), its regional metastases (N Class), and distant metastases (M Class) are the most important factors that affect survival in HNC [6, 7]. The survival of advanced stage HNC remains low [6, 7]. Patients with a small primary tumor and low stage disease can usually be treated with single modality treatment, resulting in better survival, fewer recurrences, and better functional outcome [8].

Delay before the initiation of curative treatment leads to growth of the primary tumor, disease advancement, and worse prognosis [9-12]. Usually, delays are divided into patient delay (from the first symptom/sign to the initial contact to a healthcare-provider [HCP]), PHC delay (from the patient's initial contact to the referral to SC), and SC delay (from the referral to the initiation of curative treatment) [13].

Multiple factors have been shown to be associated with longer patient delay: living alone [14, 15], lower socioeconomic status (SES) [16, 17], heavy use of alcohol [18, 19], certain HNC symptoms as well as the patient's knowledge of cancer symptoms [14, 20, 21], tumor site [14, 22], and disease advancement [14, 23]. There is large variation between studies in the median patient delay among patients with HNC: a study from the US reported a median patient delay of 21 days for patients with OPSCC [24], while a Brazilian study reported a median of 10 months for all HNC patients [25].

The number of visits, and whether referral or a follow-up visit was scheduled during the initial visit, have been associated with PHC delay in a Dutch and a Finnish study [26, 27]. Misdiagnosis can also play a part in PHC delay [28]. The mean PHC delay varies greatly between different countries: a systematic review on oral cancer reported a mean PHC delay of 16 days [29], while a study from Canada on multiple HNC sites reported a mean PHC delay of nearly 11 months [15].

Tumor site and treatment modality significantly affect the SC, and treatment delays (from histopathological diagnosis to initiation of curative treatment) in HNC; patients treated with surgery have a significantly shorter median treatment delay (17 days) compared to 31 days for patients treated with radiotherapy (RT) and 34 days for patients treated with chemoradiotherapy [30].

Much effort has been placed on shortening PHC and SC delays: for example, in Denmark, a fast-track system was implemented to shorten these delays, which resulted in a 12 day reduction in median PHC delay (from 21 days to 9 days), and an 11 day reduction in SC delay (from 26 days to 15 days) [31]. There have also been community and individual level interventions to reduce patient delay. One such is the Make Sense campaign (MSC), which aims to raise public awareness of HNC symptoms [32]. However, the effectiveness of these campaigns remains limited [20].

Our aim was to study different factors associated with patient, PHC, and SC delays to better understand the underlying reasons and possibly find ways to shorten these delays.

6. REVIEW OF THE LITERATURE

6.1 HEAD AND NECK CANCER

Head and neck cancers (HNC) are malignant neoplasms arising from the mucosa of the oral cavity, nasal cavity, pharynx (divided into nasopharynx, oropharynx, and hypopharynx), larynx (divided into supraglottic, glottic and subglottic tumors) and salivary glands. Over 90 % of HNCs are squamous cell carcinomas (SCCs) [2]. Malignant neoplasms of the skin, thyroid and lymphomas are not regarded as HNCs.

In Finland, around 900 new HNCs are diagnosed annually [33] and nearly 900,000 new cases globally [1]. The incidence of HNCs is increasing in the Western Countries, including Finland, and is related to the increasing incidence of human papillomavirus (HPV)-related oropharyngeal (OP) SCC (OPSCC) [3-5].

6.1.1 RISK FACTORS AND OTHER FACTORS ASSOCIATED WITH HNC

6.1.1.1 Smoking and alcohol consumption

Tobacco smoking and excessive alcohol consumption have been shown to play a causal role in the development of certain cancers, including cancers of the head and neck [34, 35]. Evidence suggests a dose-dependent synergistic relationship between smoking and alcohol consumption, with the greatest risk for HNC being among people who are both heavy smokers and heavy alcohol users [34].

Tobacco smoking accounts for 21% of all cancer deaths worldwide, followed by an unhealthy diet (8%), alcohol consumption (7%) and excess body weight (5%), according to the International Agency for Research in Cancer (IARC) [36]. A study by Carter et al. analyzed the relative risk (RR) of death for different malignancies among current smokers compared to never smokers, from a population of 954,029 aged 55 or over, followed from 2000 to 2011

[37]. The cancer sites associated with tobacco smoking, in order of RR magnitude, included lung (23.9), larynx (17.4), oral cavity and pharynx (5.7), esophagus (4.3), and other cancers to a lesser extent [37]. Smoking prevalence among adults is decreasing globally (23.6% in 2018 compared to 33.3% in 2000)[38] and in Finland (12% in 2020 compared to 23% in 1997) [39].

Alcohol consumption is estimated to cause 337,000 cancer deaths per year worldwide [40]. A meta-analysis by Bagnardi et al. assessed the RR between alcohol consumption and developing a specific cancer, using a total of 572 studies including 486,538 cancer cases of various sites [41]. They found a dose-dependent association (from light [<12.5g of 100% alcohol per day] to heavy drinking [>50g per day]) for certain sites including cancer of the oral cavity and pharynx: RR 1.13 for light, RR 1.83 for moderate and RR 5.13 for heavy drinking (n = 52 studies) [41]. Moderate and heavy drinking (but not light) were also associated with laryngeal cancer (RR 1.44 for moderate and RR 2.65 for heavy drinking, n = 41 studies). In Finland, total alcohol consumption (100% alcohol per individual aged 15 or over per year) has increased from 3.7 liters in 1960 to 10.3 liters in 2016, but started to decrease steadily since then, being 9.1 liters in 2021 [42].

6.1.1.2 Human papillomavirus (HPV)

Uncleared oral infections of oncogenic high-risk human papillomavirus (HR-HPV) have been shown to be responsible for the increasing incidence of HR-HPV-related OPSCC [43-45]. According to a study from the US, the prevalence of HR-HPV infection in oral mucosa is 6.0% among men and 1.1% among women [46]. A high number of oral sexual partners increases the odds of getting a HR-HPV infection [46, 47], and tobacco smoking delays the healing of the acquired infection [48]. HR-HPV infection isn't exclusively sexually transmitted disease, it can be acquired already during the fetal period, which can predispose to a chronic HPV infection [49, 50]. The vast majority of HPV infections are cleared within a year without ever resulting in HPV-related cancer [51].

Compared to HPV-unassociated OPSCC, individuals with HR-HPV-related OPSCC are more likely to be younger non-smoking males and have a higher number of sexual partners [52, 53]. They typically present with a smaller primary tumor but more advanced regional lymph node spread, resulting in a more advanced stage [53-55], but have better overall survival (OS) [56]. Protein p16 overexpression can be used as a surrogate marker for HR-HPV status in OPSCC with good sensitivity, but limited specificity [57]. The latest

TNM Classification uses p16 overexpression as an indicator to reflect HPV status when dividing OPSCC into HR-HPV-related and HPV-unassociated disease [58].

6.1.1.3 Age and sex

Age is a well-established risk factor for all SCCs as it takes time to develop all the necessary pro-oncogenic mutations. The most important oncogenic risk factors, tobacco smoking and alcohol consumption, are cumulative and dose-dependent in nature. Furthermore, aging leads to a decline in the function of multiple biomolecular mechanisms, including our immune system, which is involved in tumor suppression.

Three-quarters of patients with HNC are male. This difference is most likely due to the difference in tobacco and alcohol consumption habits between sexes. HPV-related OPSCC is also more prevalent among males, even though there are more non-drinkers and non-smokers among this patient group [59].

6.1.1.4 Socioeconomic status (SES)

Socioeconomic status (SES) is a theoretical construct used to measure and analyze social determinants of health [60]. Individual-based factors include income, education, occupation/employment, wealth, housing conditions and social capital. Income is strongly correlated with education and occupation/employment, as education usually determines the available occupations, and occupation usually determines the attainable income [36]. Social environments may impact individuals through exogenous exposures (air pollution, viral exposure, occupational exposure) or behavioral exposures (tobacco smoking, alcohol use).

Low SES early in life and in adulthood has been associated with chronically elevated inflammatory scores [61], and elevated CRP levels along the life course [62]. Chronic inflammation plays a crucial role in cancer pathogenesis [63]. Additionally, pathogens acquired early in life can affect the maturation of the immune system, which might eventually have an effect on the development of different malignancies [64]. These effects are partially socially driven: a study by Gares et al. noted that infection of Epstein-Barr virus early in life was associated with low SES [65]. Furthermore, epigenetic changes in gene expression vary across the lifespan and affect physiological aging in

individuals [66]. The most studied epigenetic change, DNA methylation, is many times used as a biomarker for physiological aging [67, 68]. Maternal and paternal SES can affect an individual's DNA methylation at birth [69], and low SES is associated with advanced epigenetic aging across the lifespan [70].

Low SES can affect individual's health through a difference in health-related lifestyle choices. There is a strong association between a low SES and tobacco smoking. A meta-analysis by Casetta et al. including 93 studies assessing the link between income and smoking prevalence, found that lower income was associated with higher smoking prevalence (odds ratio [OR] 1.45; 95% confidence interval [CI] 1.35 – 1.56). The association remained significant in all geographical subgroup analyses and for both sexes [71]. Furthermore, this difference has been increasing. A recent German study investigating relative and absolute socioeconomic differences in smoking prevalence between 1995 and 2013 among a German population aged between 25 and 64 (n = 857,264), concluded that relative and absolute inequalities between smokers and non-smokers have increased regarding income, education and occupation/employment favoring non-smokers, especially among women [72], a finding similar to another recent study from South Korea [73]. Multiple aspects have been suggested as factors behind this change, including differences in risk awareness and access to counselling and treatment for nicotine dependence, and effective targeted marketing of tobacco products for disadvantaged populations [36, 71, 74, 75].

According to an international systematic review article synthesizing data from three reviews and four meta-analyses, contrarily to tobacco smoking, alcohol consumption is more prevalent among high SES groups compared to low SES groups [76], and the prevalence of heavy episodic drinking (HED) is more common in high SES groups [76, 77]. However, in Finland this difference was not observed among men, and among women, HED was conversely more prevalent among low SES groups [42]. The adverse health effects of alcohol fall to the low SES groups [76, 78, 79], including HNC [80]. Even though HED is globally (but not in Finland) more prevalent among high SES groups, the frequency of HED and the number of drinks per drinking episode were higher among low SES people who participated in HED [77]. This has been proposed as one of the reasons behind the unequally distributed health differences [76, 77, 81].

Low SES is associated with an increased incidence of certain cancers, especially cancers associated with tobacco smoking and alcohol consumption. A large Danish study with a population of 3.22 million Danish residents aged

30 or over, and 147,973 cancers, followed up trends in cancer incidence between 1994 and 2003. This study found that the incidence of cancers, especially cancers associated with tobacco smoking or other lifestyle choices, increased in people with low SES between 1994 and 2003, while the incidence of cancers of prostate, breast and malignant melanoma, decreased [82]. The relative risk for developing oral or pharyngeal cancer between people with low and high SES was 1.43 for men and 1.21 for women, and for laryngeal cancer 1.67 and 3.23 for men and women, respectively [82].

A large meta-analysis by Conway et al., consisting of 31 studies from 27 different countries including 23,964 HNCs and 31,954 controls, found that low SES was associated with an increased risk for developing HNC (OR 2.50; 95% CI 2.02 – 3.09). Furthermore, approximately a third of this increased risk was not explained by the differences in smoking and alcohol use, and the risk remained elevated even among never smokers and nondrinkers (OR 1.61; 95% CI 1.13-2.31) [83]. Another meta-analysis by Conway et al. on oral cancer, consisting of 41 studies with 15,344 oral cancer cases and 33,852 controls, reported that people at increased risk for developing oral cancer were those with a low educational level (OR 1.85; 95% CI 1.60 – 2.15; n = 37 studies), low occupational class (OR 1.84; 95% CI 1.47 – 2.31; n = 14 studies) and low income (OR 2.41; 95% CI 1.59 – 3.65; n = 5 studies) [84]. The association between low SES and increased risk for developing oral cancer remained significant in low and high income countries, across the world, even after adjusting for behavioral confounders [84].

6.1.1.5 Psychological factors and cancer

Social relationships, or the lack thereof, can have a negative impact on an individual's health [36]. There are multiple pathways that plausibly explain how lack of social relationships affects health [85]. First, psychosocial processes can affect malignancies by triggering stress responses in the autonomic nervous system and the hypothalamus-pituitary-adrenal axis [86], which induces downstream release of glucocorticoids such as cortisol from the adrenal cortex. This results in further activation of oncogenic viruses, including HR-HPV [87], and inhibition of anti-tumor and antiviral cellular immune responses [88]. In clinical studies, stressful life events have been associated with an increased risk of HPV infection and developing cervical cancer [89, 90].

Second, lack of social relationships is associated with behavioral factors (such as smoking and alcohol use) that are known risk factors for cancer [91]. Third,

socially isolated individuals may have more mental health problems, such as depression, which has been associated with increased overall cancer incidence [92], worse OS [93, 94] and quality of life (QoL) [95] in HNC.

A large meta-analysis, consisting of 51 studies and 2.6 million cancer patients with an average follow-up time of 10 years, found that depression and anxiety significantly increased cancer incidence (adjusted RR: 1.13, 90% CI: 1.06-1.19), cancer-specific mortality (RR 1.21, 90% CI: 1.16-1.26), and all-cause cancer mortality (RR 1.24, 90% CI: 1.13-1.35) [96].

Depression is common among cancer patients. A Swedish cohort study, including 304 118 cancer patients and 3,041,174 matched controls, found that the relative rate for all studied mental disorders (including depression) started to increase from 10 months before cancer diagnosis, peaking during the first week after diagnosis, and decreased quickly after but remained elevated for 10 years after diagnosis [97]. Similarly, according to a review studying depression among HNC patients (n = 52 studies), depression rates were particularly high at diagnosis (13% - 40%, n = 21 studies), during treatment (25% - 52%, n = 7 studies) and at the six month follow-up (11% - 45%, n = 11 studies) [98]. Three recent studies consisting of 71,541, 55,069 and 3466 patients with HNC found that the prevalence of major depressive disorder was 9.3%, 11.5% and 18.5%, respectively [93, 94, 99]. The highest prevalence was among patients with laryngeal cancer (28.5%) [99].

6.1.2 SIGNS AND SYMPTOMS

The signs and symptoms of a HNC depend on the site and size of the primary tumor and its potential for regional (and distant) metastases. In early stages, the disease causes only mild symptoms, such as throat ache, persistent hoarseness, or nasal obstruction, which can all be easily mistaken for a benign condition. For example, the prevalence of voice problems in Swedish general population was 16.9% (n = 114,538) [100] and in another cross-sectional population-based survey from the US (n = 10,336), 11.5% of participants reported symptoms for chronic rhinosinusitis (94-97% had nasal congestion and/or obstruction) [101]. Large tumors cause more easily noticeable symptoms like dysphagia or dyspnea.

The most common symptoms for oral cancer are a non-healing mucosal lesion (30% – 71%), followed by pain (25% – 65%) [9]. Cancer in the tonsil can cause

unilateral swelling and pain and is often initially treated as tonsillitis. The most common symptoms for pharyngeal cancer are sore throat (31% - 62%), neck mass (15% - 57%) and difficulty of painful swallowing (7% - 61%) [9]. Supraglottic cancers are often diagnosed at a late stage because they cause very little symptoms at first. Glottic cancer usually cause persistent hoarseness/voice change (90% - 99%)[9] and eventually difficulties breathing. Persistent, unilateral nasal obstruction and unilateral nosebleeds are the most common symptoms for sinonasal cancer and are often treated as a chronic sinusitis. Salivary gland cancers can cause a painless lump and may cause facial nerve palsy. The symptoms and signs for HNC are very diverse, requiring knowledge and attentiveness from both the patient and the clinical physician, and pose a challenge for general practitioners (GP).

The European Head and Neck Society launched the Make Sense campaign (MSC) in 2013 to spread knowledge about HNC to the general public and PHC personnel. The campaign website provides information about risk factors and symptoms of HNC while introducing a "1 for 3" rule regarding symptoms and their persistence. The symptoms are as follows: 1. sore tongue, non-healing mouth ulcers and/or red or white patches in the mouth, 2. pain in the throat, 3. persistent hoarseness, 4. painful and/or difficulty swallowing, 5. lump in the neck, 6. blocked nose on one side and/or bloody discharge from the nose. The rule states that if a patient has had one or more of the six most common HNC-related symptoms for more than three weeks, the GP should refer the patient to a head and neck specialist [32]. However, in Finland there haven't been any HNC symptom awareness campaigns aimed at the general population; cancer-related education is usually only directed towards healthcare personnel.

6.1.3 DIAGNOSIS

The diagnostic and treatment pathway, from suspicion of HNC to histopathological diagnosis and curative treatment, starts from patient contacting a HCP, usually in PHC, or occupational healthcare, the private sector, or the emergency room (ER), from which all professionals have similar opportunities to make a referral to a SC unit where HNCs are diagnosed and treated. If the suspicion of malignancy is apparent, in Finland the recommendation is to refer all patients directly to a tertiary care unit (University Hospital). In more uncertain cases, a fine-needle aspiration cytology (FNAC) might be taken beforehand, but it is not required for the referral.

After the referral is received by the hospital, it is handled urgently and the first visit to an otolaryngologist is scheduled within a week if there is a suspicion of malignancy. At the initial visit, a clinical examination is performed and if the tumor is visible, a biopsy is taken, and appropriate imagining is arranged (typically neck magnetic resonance imaging [MRI]/computer tomography [CT]). If the primary tumor isn't visible or is in a place, where performing a biopsy is not possible at the outpatient visit, imaging and endoscopy are performed to find or define the primary tumor and get the biopsy. If only a neck metastasis is found, an ultrasound and FNAC sample or core-needle biopsy (CNB) is performed, typically followed by positron emission tomography (PET) if the sample shows signs of SCC.

6.1.4 TREATMENT

In Finland, the management of HNC follows national guidelines and is centralized to the five University Hospitals. In some parts of the country, Central Hospitals are involved in the management of these patients to varying extents, but all HNC cases are discussed in collaboration with the University Hospital at their head and neck tumor board meetings.

After biopsies and imaging, a treatment strategy is discussed at a multidisciplinary tumor board meeting. Usually, preliminary planning for the most likely treatment, based on national treatment guidelines, has begun before the formal meeting. If the treatment modality is presumably going to be radiotherapy (RT), dental evaluation is ordered, and for surgically treated patients, planning for the operation starts from the first appointment. Dental care must be performed about two weeks before the start of RT. Furthermore, the patient's nutritional status must be evaluated before treatment and when necessary, a percutaneous endoscopic gastrostomy (PEG) tube must be placed to ensure sufficient nutrition before, during and after treatment. All these additional steps add to the treatment delay.

The treatment strategy for HNC is decided following national guidelines [102] according to the site and size of the primary tumor and its potential regional metastases (TNM and stage), considering the patient's general health condition, wishes, and resulting functional outcome. In Finland, treatment guidelines are updated yearly at a nationwide meeting [102], similarly to the US [103]. Small and localised HNCs are usually treated using single-modality treatments: for example, radical surgery in oral cavity cancer and definitive RT in supraglottic cancer, or in small glottic cancer (T1) either surgery or RT.

Large tumors often need multimodality treatment combining surgery with (chemo)RT ([C]RT), resulting in a poorer functional outcome and QoL [104]. p16-positive tumors are in most cases primarily treated with (C)RT, but surgery might be an option for small T1-T2 tumors, if clear margins can be achieved and there are maximum of two neck metastases both less than 3cm in diameter [102].

6.1.5 PROGNOSIS AND PROGNOSTIC FACTORS

The relative survival (RS; the relative survival rate of cancer patients compared to the general population) of HNC has increased from 55% in 1992-1996 to 66% in 2002-2006 [6]. In a recent international multicenter study of 4759 patients with HNC, the 5-year OS for all HNC was 52% and the primary tumor site affected survival: 50% for the oral cavity, 41% for the oropharynx, 35% for the hypopharynx and 64% for the larynx, while the disease-specific survival (DSS) for all HNCs was 57% [105]. In Finland, the 5-year OS and DSS for OPSCC were 60% and 71.5% for patients treated with curative intent [106].

6.1.5.1 TNM and stage

The extent of disease is defined through stage (I-IV), which is determined by the size of the primary tumor (T Class), its regional metastases (N Class), and distant metastases (M Class), according to the UICC TNM Classification of Malignant Tumors [58]. TNM and stage are the most important predictive factors for patient survival in HNC [6, 7]. According to a large register study of around 250,000 patients with HNC, the 5-year RS for local, regionally spread, and distantly metastasized disease were 68%, 33% and 8%, respectively [7]. In a Finnish study on laryngeal cancer (n = 366), the 5-year DSS rates for T1a, T1b, T2, T3, and T4 glottic SCC were 100%, 95%, 78%, 79%, and 53%, respectively [8].

6.1.5.2 Recurrence and second primary cancer

Locoregional recurrences usually occur during the first 2-3 years after definitive treatment. Furthermore, because HNC is strongly linked to tobacco smoking and alcohol consumption, patients with HNC have a high risk of developing a second primary cancer [107]. In a large multicenter study of 99,257 HNC patients, 11% of HNC patients developed a second primary [107]. In a recent multicenter study of 4005 HNC cases with a median follow-up time of 21 months, recurrence occurred in 29% of cases (31% of oral cancer, 31% of

OPSCC, 24% of laryngeal cancer patients) [108]. In a recent Finnish study on OPSCC (n = 495) with a follow-up period of 10 years, 14% of the patients were diagnosed with a recurrence, 86% of these occurred within the first three years [109].

6.1.5.3 Time before treatment initiation and survival

A delay before treatment initiation leads to tumor growth, disease advancement and may lead to worse prognosis. A study from the Netherlands reported that the mean growth of the primary tumor of OPSCC grew in volume by 70% in 56 days [110]. Similarly, a study from Denmark reported a median tumor volume doubling time of 99 days for all HNCs [111]. There was significant variation at the tumor growth rate: the fastest growing tumors doubled their volume in just 30 days [111]. A review article consisting of 27 studies reported that on average, HNC volume doubled in 86-97 days [9]. The positive association between delay and advanced stage at diagnosis is well established in the literature [11, 14, 23, 112-116]. A systematic review and meta-analysis (n = 11 studies) on oral cancer reported that longer referral delay was associated with increased disease stage at diagnosis and worse prognosis [12]. However, the large differences in tumor growth rates may affect the urgency of treatment, resulting in patients with the fastest growing aggressive tumors receiving treatment more quickly, but still resulting in worse survival. Crawford et al. has called this phenomenon as “the waiting time paradox” [117]. This paradoxical finding between longer total diagnostic interval (TDI) and better prognosis has been reported in a large Danish study (n = 1543) on breast, colorectal, lung, skin melanoma and prostate cancers [118]. Similarly, this might be the reason why in a study on HNC by Teppo et al., shorter patient delay was in some cancer groups associated with worse survival [119], and in a study by Van Harten et al., shorter treatment delay was associated with worse survival [120]. Although, in a later study by Van Harten et al. (n = 13,410), a significant association was found between longer treatment delay and worse prognosis [121].

The effect of treatment delay on OS has been widely investigated in multiple cancers. A systematic review and meta-analysis including 34 studies on 7 different cancers (head and neck, bladder, breast, cervix, colon, rectum, lung), with a total study population of nearly 1.3 million cancer patients, studying the effect of treatment delay on three different curative treatment modalities (surgery, RT, systemic treatment), reported an association between treatment delay exceeding four weeks and worse survival in 13 of the 17 studied cancer treatments [122]. For each four-week delay, the increased mortality hazard ratio (HR) for surgically treated HNC was 1.06 (95% CI 1.04 – 1.08) and for

RT 1.09 (95% CI, 1.05 – 1.14) [122]. Another large systematic review, consisting of 177 studies (including 41 studies on HNC) and 401,760 patients with cancer, investigating the relationship between increased time to diagnosis and treatment and survival, reported an association between shorter delays and better outcomes in most cancers [123]. Regarding HNC, a positive association was found in 20 out of 41 studies, and the remaining 21 studies reported no association [123]. A recent meta-analysis including 52 studies on HNC [112], reported that in 6 of the 9 studies that included multiple HNC sites, totaling 22,216 patients, increased treatment delay resulted in worse survival [30, 124-128], while 3 studies (n = 16,989) showed no association [129-131]. In studies focusing on a single HNC site, a negative association was observed between treatment delay and survival in 3 of 4 studies on oral cancer, only in 2 of 7 studies on OPSCC, in 2 of 2 studies on laryngeal cancer, and in one study on hypopharyngeal cancer, no association was found [112]. Furthermore, another recent systematic review consisting of 51 studies on HNC found that increased diagnostic and treatment delay seems to lead to worse survival [11].

6.1.5.4 Tobacco smoking and alcohol consumption and survival

Besides being the most important risk factors for developing HNC, tobacco smoking and alcohol consumption have been shown to affect OS in HNC [105, 132, 133]. The OS HR between excessive smokers (>20 cigarettes/day) vs. never smokers were 1.87 (95% CI 1.01–3.48) in OPSCC and 1.41 (95% CI 1.03–1.92) in oral cancer [105].

6.1.5.5 Socioeconomic status (SES) and survival

In many Western countries, absolute social inequalities in mortality are decreasing but relative inequalities are increasing [134-136]. This means that while the general health of all socioeconomic groups is increasing, it is increasing at different rates, benefiting people with high SES. Multiple different factors constitute to this difference, including differences in health-related behavior (tobacco, alcohol, physical exercise, diet), environmental and occupational exposures, knowledge of cancer symptoms, geographical and economical differences in access to healthcare and treatment, to name a few [36].

There is a clear difference in incidence and cancer mortality between people with high versus low SES, especially in cancers strongly associated with tobacco and alcohol use and chronic infections [137-139]. In these studies, they

noted that over the last decades cancer mortality has universally declined in high SES groups but stayed the same or even increased in low SES groups. People with a low educational level have 2-4 times higher cancer mortality for oral and pharyngeal cancers and 3-5 times higher for laryngeal cancers [36]. A retrospective study from the US, analyzing socioeconomic differences in cancer mortality, incidence and survival from all cancers combined between 1950 and 2014, reported that individuals living in deprived areas and people with lower education levels and income had higher cancer mortality and incidence rates compared to those in high SES groups [140]. According to two recent large studies by Weizman et al. and Bedir et al., consisting of 11,826 and 20,821 HNC patients, respectively, patients with a low SES had significantly lower OS compared to the most affluent ones [141, 142]. A similar result was reported by another study from the UK, but the inequalities in survival were fully explained by differences in age, sex, health, and behavioral factors between different SES groups [143]. A study from the US (n = 40,487) found that there was a significant association between disease stage at diagnosis and insurance status among patients with OPSCC. Uninsured and Medicaid patients presented with significantly higher stage disease compared to patients who had private insurance [144].

A large Belgian longitudinal study including 4.6 million people and 105,000 cancer deaths between 2001 and 2011, found that unemployment and certain employment classes (manual labor) had increased cancer mortality compared to employed and white-collar workers, especially in cancers strongly associated with tobacco smoking and alcohol use, including HNC [145]. A review consisting of 27 studies and over 700,000 cancer patients concluded that increased travel requirements to treatment facilities is associated with advanced stage at diagnosis and inappropriate treatment, prognosis, and QoL [146]. In a large cohort study from England (n = 49,270), low SES was associated with less recognition of cancer symptoms and most reported barriers to presentation to a physician [147].

6.1.5.6 Psychological factors and survival

There is evidence that among psychiatric patients, overall cancer mortality is 30%-50% higher compared to the general population, and psychiatric patients typically present with a higher disease stage and more metastases at diagnosis [148]. Barriers to seeking medical attention that results in delayed presentation and thus more advanced stage, as well as inequalities in received care, have been suggested as possible causes for these differences [148, 149]. Psychological distress (anxiety and depression symptoms) has been associated with increased cancer mortality. A large meta-analysis pooled data on 16

prospective cohort studies investigating psychological distress among cancer patients. This meta-analysis consisted of 163,363 individuals aged 16 and over with a mean follow-up period of 9.5 years, during which there were 16,267 deaths (4343 from cancer) [150]. The study found that death rates for all cancer sites were higher in the most psychologically distressed group compared to the least distressed group (HR 1.32; 95% CI 1.18 – 1.48) even after adjusting for age, sex, education, SES, BMI, tobacco smoking and alcohol use [150]. Another study found that patients with HNC who had psychologic distress presented with more advanced stage disease [151].

HNC patients report high rates of depression and its effect on survival has been studied. In a systematic review, depression was associated with worse survival in two of the three studies [152]. In a large study from the US including 3466 HNC patients, patients diagnosed with depression prior to or after cancer diagnosis had significantly worse survival (HR 1.49; 95% CI 1.27 – 1.76 and HR 1.38; 95% CI 1.16 – 1.65, respectively) compared to patients without depression [94]. In another recent retrospective study consisting of 55,069 patients with HNC, of whom 6345 (11.5%) were diagnosed with depression, patients with pre-cancer depression had worse OS compared to those with no depression (HR 1.18; 95% CI 1.11 – 1.25) [93]. On the other hand, patients who had pre-cancer depression but continued to have regular visits to psychiatric clinics after cancer diagnosis, had better OS (HR 0.78; 95% CI 0.71 – 0.86), underlining the importance of continuous depression treatment following a cancer diagnosis [93].

6.1.5.7 HR-HPV infection, p16 overexpression and survival

There is clear evidence that patients with HR-HPV-related OPSCC have better OS compared to those with HPV-unassociated OPSCC [53-56, 153]. The 3-year OS for HR-HPV OPSCC is over 80%, compared to approximately 50% for HPV-unassociated OPSCC [53]. This might be due to differences in the disease etiologies; HR-HPV OPSCC is currently believed to be caused by the effects of the specific oncogenic viral proteins E6 and E7 [154], while HPV-unassociated OPSCC is related to carcinogen exposure through tobacco smoking and alcohol drinking resulting in widespread DNA damage and inaccurate DNA repair [155]. Better treatment response is being observed among HR-HPV OPSCC especially in its better sensitivity to RT [55, 156].

HR-HPV is also found in other HNC sites besides the oropharynx, but p16-staining isn't routinely used in clinical practice because of the lack of clear

evidence on its clinical impact [157, 158]. Positive HPV or p16-staining is found in 4% of oral SCCs [157, 158], 3.5% of glottic SCCs [157], and 21% of hypopharyngeal SCCs [159]. According to a recent large (n = 9314) register study, HPV-positive hypopharyngeal SCC has been associated with improved survival [159]. Additionally, in a large study of nearly 42,000 patients, better survival was observed among HPV-positive patients in multiple HNC sites including the oral cavity, oropharynx, hypopharynx, and larynx [160].

6.1.5.8 Other prognostic factors

Tobacco smoking and alcohol consumption, the two most important risk factors for HNC, are risk factors for multiple other diseases (high blood pressure, coronary artery disease), explaining the high prevalence of comorbidities among HNC patients. A large Danish population-based patient cohort study including 12,623 HNC patients found that Charlson Comorbidity Index (CCI) was a strong independent prognostic factor for OS among HNC patients [161], similarly to a study from Finland [162].

There is some evidence that gender might be a factor influencing survival in HNC. According to a study by Gatta et al., the 5-year relative survival was significantly better among women compared to men in all HNC sites, except the larynx [7].

6.2 DEFINITIONS OF DIFFERENT DELAYS AND DELAY TIMES

Multiple different definitions for delay intervals have been used in the literature resulting in difficulties when comparing the results of different studies as the measured delay intervals may vary between different studies. In 2009, Olesen et al. proposed the following time periods to be used in studies investigating delay intervals in HNC: patient delay, delay in PHC (which can be divided into physician-related delay and system delay in healthcare) and secondary healthcare delay (which can be further divided into diagnostic delay in secondary healthcare and treatment delay) [163]. Later in 2012, an international Consensus Work Group was formed to further improve and standardize the reporting of studies on delay intervals in cancer research by developing a guideline called “The Aarhus Statement”, which proposed the following changes to the Olesen model: the term “interval” should be used instead of “delay” and “diagnostic interval” was defined as an interval from the first presentation to a physician to diagnosis [164]. In the literature, the term

"diagnostic delay" is used variably sometimes referring to the "diagnostic interval" used in the Aarhus Statement and other times to the "SC diagnostic delay". For clarification, the "total diagnostic interval" (TDI) term is used if referring to the delay from the first presentation to physician to diagnosis and "SC diagnostic delay" when referring to the diagnostic delay taking place in SC. Otherwise, in our studies we have followed the model suggested by Olesen et al., because it allowed more detailed examination of different SC delays.

6.2.1 PATIENT DELAY

Patient delay, sometimes referred to as the "patient interval", is a time interval starting from patient noticing the first symptom or a sign to contacting PHC or other HCP. The distribution of patient delay is generally skewed to the right, meaning most patients report shorter delays than the mean delay. Patient delay is sometimes divided into three parts: an appraisal interval, meaning the interval from the first bodily change to patient inferring the symptom as an illness, followed by a help-seeking interval until the patient contacts medical care and a primary care scheduling interval from the initial contact to the first visit in PHC [165]. However, it is hard to reliably distinguish between appraisal and health-seeking delay because of patients' recall bias and therefore, they are usually coupled together. Furthermore, after a patient has contacted an HCP, the delay isn't any more patient driven, but relies on the resources of PHC. Therefore, in our own studies, this is part of PHC delay.

In a Canadian study, the mean HNC patient delay was 3.9 months [15], while in a Spanish study, the median patient delay was 30 days [166]. A substantially longer median patient delay of 10 months was reported by a Brazilian study [25].

There are more studies on patient delay among oral cancer patients than other HNC sites. According to a systematic review including 18 studies on oral cancer, the mean patient delay was 3.5 – 5.4 months [167], which is substantially more than the weighted average of 80 days reported in more recent systematic review (n = 22 studies) on oral cancer [29]. The median patient delay was just 21 days among patients with OPSCC in a study from the US [24].

For a selective comparison to a few other malignancies, a median patient delay of 44 and 18 days were reported for cancers of colon and rectum, respectively

[168], and 42 days for stomach cancer [169]. In a Finnish study on lung cancer, the median patient delay was 14 days (mean 41 days) [170]. In a Turkish study on lung cancer, the mean patient delay was significantly longer (81 days) [171].

There has been some individual- and community -level interventions to raise cancer symptom awareness to promote early presentation to a physician across multiple different cancers. One such intervention is the MSC that aims at raising awareness of HNC symptoms [32]. However, the effectiveness of these campaigns remains limited. A systematic review, consisting of five randomized controlled trials of individual-level interventions and four community-level trials on multiple different cancers, and studying the effectiveness of campaigns promoting cancer symptom awareness, concluded that the effectiveness of these trials is very limited [20]. The interventions seemed to raise cancer symptom awareness in the short term but there was insufficient evidence that these interventions lead to shorter patient delay [20]. An article on oral cancer awareness concluded that "multi-component, theory-based campaigns, targeted at high-risk groups, may have greater potential for translating knowledge gained into behavior change" [172]. Different community groups should be involved in raising awareness of cancer symptoms and risk factors and the public awareness campaigns need to be coupled with good availability of PHC services [172]. MacPherson suggests that opportunistic screening for oral cancer should be carried out at PHC and routine dental visits and the importance of primary prevention (tobacco and alcohol use) cannot be understated [172].

To conclude, patient delay is patient derived and considered to be the most important contributor to the total delay before the initiation of curative treatment.

6.2.2 PRIMARY HEALTHCARE DELAY

PHC delay, sometimes referred to as "primary healthcare interval" or "healthcare-provider delay", is a time interval starting from the patient contacting PHC or other HCP, to the first referral to SC unit.

A systematic review including 22 studies on oral cancer, reported a mean PHC delay of 16 days [29]. A more recent study from Canada (n = 196, multiple sites), reported a substantially longer mean PHC delay of 10.7 months in the province of British Columbia [15], with 50% of the patients needing to visit an

HCP at least three times before referral to SC. A study from the US reported a significantly shorter median PHC delay of just 8 days for patients with OPSCC [24]. In a Finnish study on lung cancer, median PHC delay was 16 days [170].

In the UK, a national program called the National Awareness and Early Diagnosis Initiative was launched in 2007 to optimize healthcare systems to minimize delays in cancer diagnosis (in all cancers) [173]. The National Audit of Cancer Diagnosis in Primary Care, including data collected from 1200 different practices on 19,500 patients, found that the median PHC delay was 4 days [173]. According to a systematic review (n = 22 articles) on multiple cancers, there was no evidence that additional education aimed at GP's directly reduced PHC delay [174].

The length of PHC delay varies greatly between countries with different healthcare systems and it is much less researched compared to patient and SC delays.

6.2.3 SPECIALIST CARE DELAY

SC delay, sometimes referred to as "secondary care interval", is a time interval starting from receiving the referral from PHC or other HCP to the initiation of definitive treatment. Therefore, patients who receive palliative care do not have SC delay, nor treatment delay.

In a recent prospective Dutch study (n = 173) of oral, oropharyngeal, hypopharyngeal and laryngeal cancer, the median SC delay was 39 days [175]. In comparison, in a Finnish study on lung cancer, the median SC delay was 54 days [170].

Much effort has been placed into shortening the SC delay. The earliest national referral guideline for early cancer detection was formed in the UK in 1995 branded as "two-week-wait" -rule, instructing that patient with symptoms highly suggesting of cancer should be seen by a specialist within two weeks of referral from PHC [176]. In Denmark, a fast-track system was created in 2007 to streamline the clinical pathway of HNC diagnosis and treatment to reduce delays in SC [177]. After the implementation, the median TDI was reduced between 2002 and 2010 from 17 days to 13 days and the median treatment delay from 47 days to 25 days [178]. In another study on the fast-track system,

the median PHC delay was reduced from 21 days to 9 days and the median SC delay was reduced from 26 days to just 15 days [31]. Before the implementation of the fast-track system in Denmark, the total professional delay (PHC + SC delay) was reported to have grown longer from the median of 50 days in 1992 to a median of 72 days in 2002 [179]. This change was largely caused by the increasing use of imaging in the diagnosis and poor availability of it.

The Dutch Head and Neck Society has stated that SC delay should not exceed 30 days for at least 80% of the patients, but this is only achieved in 34% of all HNC patients [120]. A systematic review including 37 studies on different types of healthcare system interventions that are implemented to reduce diagnostic and treatment delay in HNC, concluded that these interventions improve timely diagnosis and treatment of HNC, but there is not enough evidence of long-term impact [180].

SC delay is the most studied delay interval and the second largest contributor to delay before treatment initiation. However, because of the multiple procedures that are needed to ensure best possible care, the effectiveness of different interventions aiming to shorten this delay remains limited.

6.2.3.1 Specialist care diagnostic delay and total diagnostic interval

SC diagnostic delay, sometimes referred to as "diagnostic delay", is a time interval starting from receiving the referral from PHC or other HCP to histopathological diagnosis. Total diagnostic interval is a time interval starting from first presentation to a physician to histopathological diagnosis.

A systematic review article on oral cancer reported a mean TDI of 48 days [29]. A Brazilian study (n = 80) reported a median SC diagnostic delay of four weeks [25]. Seoane et al. studied the contribution of the specialist to the diagnostic delay among oral and oropharynx cancer patients (n = 228) and found that the median delay from the first visit to specialist until histopathological diagnosis was just 6 days [115].

In Denmark, a standardized cancer patient pathway (CPP) was implemented in 2008, through which GPs could refer cancer patients to SC units. A Danish study on five most common cancer groups (colorectal, lung, malignant melanoma, breast, and prostate cancer), involving three patient cohorts (n =

12,558), found that the TDI was substantially reduced from the initial median interval of 49 days to 32 days after implementing CPP [181].

6.2.3.2 Treatment delay

Treatment delay is the time interval starting from histopathological diagnosis to the initiation of definitive treatment. The Finnish Ministry of Social Affairs and Health has proposed in 2010 in its working group report that treatment delay for HNC should not exceed three weeks [182].

A large retrospective study from the US including all HNC sites (n = 37 730) reported that among surgically treated patients, treatment was initiated within 30 days for 45% of the patients, from 30 to 60 days for 41% of the patients and the remaining 14% of the patients had a delay longer than 60 days [183]. A French study including all HNC sites (n = 1667) reported a similar finding, with a median treatment delay of 35 days (27 days for surgically treated and 55 days for those treated with definitive RT) [131]. A similar retrospective Dutch study (n = 2493) reported a median treatment delay of 39 days [120]. Substantially longer treatment delays have been reported. The median treatment delay was 84 days in a study from Brazil (n = 80) [25]. In a study on lung cancer, the median treatment delay was just 15 days among surgically treated patients [170].

6.3 FACTORS INFLUENCING DELAY

6.3.1 PATIENT DELAY

The reasons for a delayed presentation in HNC are multifaceted and overall more poorly understood than the SC delay [167].

6.3.1.1 Sociodemographic factors

It is well established in the literature that patient age and sex are not associated with patient delay [14, 21, 184-187], although in a study on nasopharyngeal cancer, patient delays of over 6 months were significantly more common among females [116]. Furthermore, most studies have found no association between marital status and patient delay [14, 21, 185], although living situation has been shown to be associated with patient delay. A longer patient delay has

been reported among patients who live alone, compared to patients living in household of two or more, or in a household with children [14, 15, 19, 21, 22]. In a study by Rozniatowski et al., patients who presented with a large primary tumor (T3 – T4) were more often single, separated, divorced, or widowed [188]. Advice from a partner was an important motivating factor for seeking medical consultation and over 3-month delay in seeking medical advice was observed more in those living alone [188]. A Finnish study investigated the characteristics of patients with HNC and concluded that HNC patients largely resembled the general population with regards to sociodemographic factors [189].

6.3.1.2 Socioeconomic status

One might assume that a patient's socioeconomic situation could influence their search for medical attention, because the better the financial situation, the larger the array of available options. There have been multiple studies investigating the association between SES and patient delay [21]. Some studies have reported a positive correlation between shorter patient delay and higher SES [16, 17], but in other studies no association was found between SES and patient delay [14, 22, 185]. A Danish study, which included all cancers except non-melanoma skin cancers, found that retired female patients had a shorter patient delay than employed female patients (OR 0.35), but among males this association was not observed [187]. It is important to note that in most studies deprivation is measured according to a the place of residence, which creates bias as the majority of deprived individuals do not live in deprived areas [36].

The association between educational level and patient delay is complex [21]. A study from the UK on oral cancer reported education as being an important factor that affects how patients seek medical care [17], but in Dutch study on oral and pharyngeal cancer, no association was found between education and patient delay [14].

6.3.1.3 Tobacco and alcohol use

Smoking is more common among HNC patients than the general population [189]. Interestingly, in a Finnish study, only half of the surveyed patients with HNC recognized tobacco smoking as a risk factor for HNC [189]. The literature on the effects of health-related behavior on patient delay is inconclusive. A few studies found no association between health-related behaviors (tobacco smoking and alcohol use) and patient delay [14, 184]. In a study by Tromp et

al., heavy alcohol drinkers (more than 5 drinks per day) tended to show more patient delay compared to non-heavy drinkers [19], which is a finding supported by a few other studies [18, 190], but not all [186]. Regarding tobacco smoking, some studies report no association between heavy smoking and patient delay [18, 191]. Furthermore, in a Finnish study published by Väisänen et al., smoking was not related to patient delay [189]. However, a study from the UK reported shorter patient delays among smokers and drinkers [185]. In a Danish study on all cancers, smoking female patients had longer patient delays (OR 2.42) compared to non-smokers, but this was not found among males [187].

6.3.1.4 Psychological factors

It is well established in the literature that psychosocial and psychological factors affect health and are associated with cancer incidence and survival, as described above. Therefore, it is reasonable to assume, that some part of this effect comes from differences in healthcare seeking behavior. Nevertheless, only few studies have investigated this matter.

A study by Tromp et al. (n = 277 HNC patients), found that patients who delayed seeking medical care for over three months generally had less optimism, less health hardiness, less active coping, and less support seeking as a coping style [19]. The authors note "the way people cope with a symptom is very important for the decision whether or not to seek professional medical consultation" [19]. Another study on HNC found that fear of physicians was more common among patients who postponed their medical care seeking for over 3 months [189]. A study by Rozniatowski et al., found no association between patient delay and depressive symptoms among HNC patients [188]. There are a few studies on breast cancer that support the notion that optimism is related to short patient delays [192], while denial can lead to prolonged patient delays [193].

6.3.1.5 Symptoms and symptom awareness

A symptom refers to a bodily sensation that the experiencing individual regards as abnormal, thereby it is important to understand that it is clearly affected by the individual's interpretation. This interpretation takes place in social and cultural context on what is regarded as normal [194, 195]. People can interpret similar bodily sensations very differently, which can lead to

differences in self-reported delay intervals between respondents. This creates bias in research studying patient delays [13].

There are multiple studies on symptoms' relation to healthcare seeking among HNC patients. In pharyngeal cancer, patients with sore throat as an initial symptom had longer patient delays compared to patients with dysphagia or a neck mass [14]. Similarly in another study, a neck lump was associated with shorter a patient delay [191]. The initial symptom and patient delay were also associated with each other in oral cancer [14]. In a Finnish study, a patient delay of over 3 months was associated with having a symptom other than pain [189]. In a study from the UK on oral and oropharyngeal cancer, swelling was associated with a shorter patient delay [185]. In a Brazilian study, a high number of symptoms was associated with advanced stage at diagnosis [23]. Conversely, in a study from the UK, no association was observed between symptoms and patient delay [196].

Furthermore, many studies on HNC have found an association between longer patient delay and patients' knowledge of cancer symptoms: their false interpretation of symptoms being benign [14, 16, 20-22, 189, 197]. A large English study on cancer symptom awareness (including HNC symptoms) among the general population, including nearly 50,000 people, found that lower symptom awareness was significantly associated with those who were single, unemployed, or had a lower SES [147]. In another study from the UK, only 50% of the patients with HNC regarded their symptoms as benign and stated that they would have sought medical care sooner if they had had a suspicion of malignancy [198].

6.3.1.6 Site of the primary tumor

Site determines the quality of symptoms that a growing tumor causes, which eventually leads to a patient seeking medical care. According to the literature, patient delays differ substantially between different tumor sites. A Dutch study reported a median patient delay of 10 weeks for glottic cancer compared to 4 weeks for supraglottic cancer [22]. Another study on pharyngeal and oral cancer reported mean patient delays of 45 and 28 days, respectively [14]. Patients with nasopharyngeal cancer are reported to have significantly longer patient delays [116]. In a large study (n = 4768) from Hong Kong, the mean patient delay for nasopharyngeal cancer was 10 months [116]. A Finnish study on SCC of tongue, pharynx, and larynx, observed a trend ($p = 0.08$) of longer patient delays amongst patients with laryngeal cancer [119].

6.3.1.7 TNM and stage + HPV status

Tumor size has been associated with patient delay in some studies. A study by Brouha et al. on oral and pharyngeal cancer reported that T3-T4 Class tumors were associated with longer patient delay compared to T1-T2 tumors, but N Class had no association [14]. Conversely, in a study from the UK, higher T and N Class were associated with a shorter patient delay [185]. In a Dutch study, patient delay of over three months was significantly associated with advanced stage at diagnosis (n = 306 HNC patients), but no association was found between T Class and delay [114]. Similarly, in another study on oral and pharyngeal cancer, advanced stage was associated with patient delay in oral, but not pharyngeal cancer [14]. Conversely, a Brazilian study on HNC (n = 679) reported an inverse relationship between patient delay and disease stage: patients who postponed their search for medical care for over 3 months were less likely to be diagnosed with an advanced stage (III-IV) disease compared to patients who contacted a HCP within one month [23]. In other studies, no association was observed between tumor-related factors and patient delay [9, 22, 184, 191].

According to a recent study on OPSCC, two-thirds of patients with HPV-associated OPSCC presented with an asymptomatic neck mass as the initial symptom [199]. Another study showed that among patients with HPV-unassociated OPSCC, symptoms were more often related to the primary tumor site, including sore throat, dysphagia and odynophagia [200], but no studies have investigated the association between HPV-status and patient delay.

6.3.2 PRIMARY HEALTHCARE DELAY

6.3.2.1 Patient-related factors

There are only a handful of studies investigating the journey through PHC of patients with HNC. Regarding sociodemographic factors, a few studies have found no significant association between PHC delay and sociodemographic factors or patients' health-related behavior (tobacco and alcohol use) [26, 201]. Although, in a large Danish study (n = 1252), which included all cancers except non-melanoma skin cancers, male patients had longer PHC physician-related delays compared to female patients (OR 1.65) [187]. Moreover, a Finnish study on pharyngeal cancer reported that current smokers experience shorter PHC delays [191].

SES has been associated with PHC delay in a few studies. In a Finnish study, low SES was associated with tumors being overlooked at the initial visit, resulting in longer PHC delays [201]. According to a Danish study looking at all cancers, male patients with high educational levels experienced shorter PHC physician-related delays compared to those with a low educational level (OR 0.40). Similarly, females with high SES had shorter PHC physician-related delays than those with a low SES (OR 0.07) [187]. In a study on pharyngeal cancer, occupational status did not affect PHC delay [191].

Certain symptoms have been associated with an increased delay in PHC. Patients with voice change as a symptom, experienced longer PHC delays [26]. Furthermore, upon the persistence of a symptom after the initial PHC appointment, if a patient regarded the symptom as benign, there was prolongation of the patient's return to PHC, thus prolonging the PHC delay [26].

6.3.2.2 Tumor-related factors

Only a few studies examine the association of tumor-related factors and PHC delay. According to a study including all types of HNC (n = 306), patients with glottic or supraglottic tumors experienced longer PHC delay [26]. However, according to another study on the same patient cohort, disease stage was not significantly associated with PHC delay [114], a finding similar to a study on oral cancer [202], and another study on all HNSCCs [201]. Conversely, in a Finnish study on tongue cancer, compared to patients referred at the initial visit, patients who weren't referred to SC at the initial visit and thus who had longer PHC delay, had more advanced tumors at diagnosis [27]. In a Finnish study on pharyngeal cancer, patients with oropharyngeal cancer had significantly shorter median PHC delays (0.9 months), compared to those with nasopharyngeal (1.9 months) and hypopharyngeal (1.6 months) cancer [191].

6.3.2.3 Healthcare-related factors

HNCs are rare. The worldwide incidence of HNC was just over 10 per 100,000 in 2018 [1], and due to this low incidence, the number of HNC patients a physician encounters during their career is limited. A study by Alho et al., investigating the incidence of HNC and the different symptoms associated with it among individuals visiting 24 randomly selected PHC centers found that HNC was diagnosed approximately once for every 63,000 visits and 11% of patients visiting PHC centers had symptom related to HNC [201]. According

to the same study, on average, Finnish PHC physicians encounter two new HNC cases during their careers [201]. In a British study, HNC was found among 9.5% of patients referred through a fast-track system implemented there [203].

GPs play a crucial role in HNC detection and referral to SC [204]. Most HNC patients are referred to SC by a GP [204, 205]. In a study by Ligier et al., 86% of all HNC patients had consulted a GP and 21% a dentist before the referral to SC [206]. However, in the case of oral cancer, the role of dentists is more pronounced. According to a systematic review including 16 studies on oral cancer, 44% of oral cancer patients were referred to SC by a dentist [207]. There was no difference in PHC delay between patients referred by dentists compared with GPs [207]. Correspondingly, in a Finnish study on HNSCC, the initial location visited was not significantly associated with the number of visits before referral to SC [201].

Both the contents of the initial visit to a HCP, and whether a suspicion of malignancy arose, greatly affected PHC delay [201]. Misdiagnosis plays a part in the contribution to PHC delay and TDI. A study from the US (n = 100) investigating different diagnostic errors by the referring physician, found that 22% of HNC symptoms were initially treated as an infection [28], which is slightly less than in a Finnish study on pharyngeal cancer (33%) [191]. Further reasons for delay were failure to employ appropriate diagnostic test in time (15%) and failure to act on test results (14%) [28]. According to a Finnish study on HNC (n = 221), insufficient physical evaluation by the physician was significantly associated with the disease being overlooked (no referral or follow-up) [201].

It is logical that the number of visits to PHC affects delay, as many studies have reported [26, 201]. In a Finnish study by Koivunen et al. on pharyngeal cancer, around half of the patients were referred to SC at their first visit to PHC [191], similar to a study by Alho et al. (on all HNC sites) [201]. In another study on tongue cancer, the proportion of patients referred to SC on the initial visit was 65% [27]. Among the non-referred patients, PHC delay was significantly longer if no follow-up was scheduled [27]. A similar finding was reported in a study including all HNC [26]. In a systematic review of OPSCC (n = 16 studies), patients had average of two to three visits to a GP or dentist before referral to SC [207]. In two studies from the UK on oral cancer, the proportion of patients referred to SC at the initial visit to an HCP were 78% and 53% [185, 208] compared to 38% reported in a study on all HNC [26]. Furthermore, death HR

was significantly higher among patients with tongue cancer who were not referred and had no scheduled follow-up compared to those who were referred to SC [27], a finding similar to that of a study including all HNSCCs [201]. According to another Finnish study on laryngeal cancer, longer PHC delay was associated with worse prognosis [209].

6.3.3 SPECIALIST CARE DELAY

In most studies, SC delay is divided into SC diagnostic delay and treatment delay, with most studies focusing on treatment delay. In a few studies, socioeconomic deprivation or low SES has been associated with longer SC delay [121, 126, 131]. The studies argue that one contributing factor might be spatial access to treatment. A Canadian study found that the most deprived patients had the longest travel times to HNC treatment centers both in rural and suburban areas [210].

6.3.4 DIAGNOSTIC DELAY

Regarding factors associated with diagnostic delay, a Finnish study on SCC of the tongue, pharynx, and larynx, reported longer median TDI (from the first visit to a HCP to diagnosis) among laryngeal cancer patients (2.1 months compared to median of 0.7 months for tongue and 1.1 months for pharynx) [119]. In a study from the US, HPV-status did not affect diagnostic delay among patients with OPSCC [24].

6.3.5 TREATMENT DELAY

6.3.5.1 Location of the primary tumor

There is evidence that site of the primary tumor is associated with treatment delay. The median treatment delay according to tumor site for cancers of the larynx, tonsil, oral tongue, hypopharynx, and non-tonsil oropharynx were 23, 26, 28, 29, and 30 days, respectively ($p < 0.001$) according to a large ($n = 51,655$) US study using the National Cancer Database (NCDB) [30]. Conversely, in a Dutch study, a longer SC delay was associated with glottic cancer [211]. In another Dutch study with 2493 HNC patients, the tumor site was significantly associated with treatment delay, with the shortest median delays reported among patients with hypopharyngeal (35 days) and laryngeal cancer (35 days), while patients with oral and oropharyngeal cancer reported

significantly longer median treatment delays (38 days and 41 days, respectively) [120]. This finding is supported by another Dutch study by Van Harten et al. (n = 13,140) [121].

6.3.5.2 TNM and stage

A large retrospective study from the US (n = 51,655 patients with HNC), found that treatment delay was significantly associated with stage. In the previously mentioned study using the NCDB patient material, the median treatment delays according to stages I, II, III and IV were, 20, 26, 27, and 28 days, respectively [30]. Similarly in a Dutch study, the median treatment delays for stage I, II, III, and IV were, 31, 39, 40, and 40 days, respectively [121]. As mentioned previously, the relationship between delay and advanced Stage at diagnosis is well documented in the literature [11, 14, 112-115], although in a Dutch study, no association was found between treatment delay and stage [120].

6.3.5.3 Treatment modality

The treatment modality has been shown to affect treatment delay. Significantly longer treatment delays have been observed among patients primarily treated with (C)RT compared to surgery [10, 30, 120, 121, 131]. The median treatment delays for patients treated primarily with surgery, RT, and (C)RT were 17, 31, and 34 days, respectively [30]. In another French study the median treatment delay for RT among HNC patients was 44 days [212].

6.3.5.4 Socioeconomic status

There is evidence that SES and other sociodemographic factors might be associated with treatment delay. A study from the US (n = 1802) reported that black patients with HNC had more treatment delay compared to others [126]. In a Dutch study, a high SES was significantly associated with slightly shorter median treatment delay (36 days vs. 38 days for low SES) [121]. This is in line with the findings of a US study, where private hospitals had significantly shorter mean treatment delays compared to safety net hospitals (44 days vs. 58 days), and people treated at private hospitals were more often insured and had higher SES [213].

An association between SES and treatment delay has also been observed in other cancers. In large retrospective study on colorectal cancer (n = 71,917), deprived patients were less likely to receive treatment, and if treated, received it significantly later compared to the more affluent ones, and had significantly worse survival [214]. In a Danish study on all cancers, different socioeconomic variables were related to system delays favoring patients with higher SES [187].

6.3.5.5 Other factors

In a large Dutch study (n = 13,410), young patients (<40 years old) had shorter median treatment delays (28 days), compared to patients aged 40 or older (37 days) [121]. However, in most studies this association has not been reported [14, 21, 184-186]. The use of alternative medicine was found to prolong treatment delay by an average of 22 days in a study from the US [215]. Treatment location affected treatment delay according to a French study; patients treated at regional care centers had longer treatment delays compared to patients treated at university hospitals, general hospitals, and private clinics [131]. The same study also found an association with higher CCI and longer treatment delay [131].

7. AIMS OF THE STUDY

Because the treatment outcomes for advanced stage HNCs are worse and treatment is more demanding, which leads to a worse functional result, our aim was to study different factors influencing delay, across patients' whole medical care-seeking pathway, up until the initiation of definitive treatment. Firstly, we analyzed the lengths and causes of patient- and healthcare-related delays in the Helsinki and Uusimaa healthcare district (Studies I and II). Secondly, we focused on sizeable tumors (T3 and T4) of the oral cavity, oropharynx, and larynx with two nationwide studies (Studies III and IV). Lastly, we studied the challenges in diagnosing HNC in Helsinki's healthcare centers (Study V).

The specific aims of the studies were:

I. To study the lengths and causes of patient and PHC delays in all new HNC patients treated at Helsinki University Hospital, Department of Otorhinolaryngology - Head and Neck Surgery during a one-year period.
II. To study patient, PHC and SC delays in patients with OPSCC and to investigate whether p16 status bears any significance in the delays.
III. To investigate the reasons behind delays in large (class T3-4) oral, pharyngeal, and laryngeal cancers.
IV. To study psychological and socioeconomic factors and their associations with patient delay in large (class T3-T4) oral, pharyngeal, and laryngeal cancers.
V. To study the different challenges PHC physician faces in diagnosing HNC from the general patient population.

8. MATERIALS AND METHODS

8.1 PATIENTS AND STUDY DESIGN

8.1.1 STUDIES I AND II

Study I was a prospective patient cohort study that covered all new HNC patients treated at the Department of Otorhinolaryngology – Head and Neck Surgery at the Helsinki University Hospital between January 14th 2015, and January 14th 2016, resulting in a total of 202 patients with newly diagnosed HNC, of whom 6 patients refused to participate, 22 didn't return the questionnaire, and 32 patients failed to meet our inclusion criteria for several reasons: dementia (n = 12), could not read Finnish or Swedish (n = 8), had a previous HNC (n = 6), due to poor overall health (n = 3), or for other reasons (n = 3). The remaining 142 patients formed our study cohort.

Study II was a prospective patient cohort study that covered all patients with newly diagnosed OPSCC treated at our tertiary care center between January 14th 2015, and January 14th 2017, resulting in a total of 111 patients, of whom 17 did not return our questionnaire. A further 11 patients were excluded for the following reasons: dementia (n = 4), could not read Finnish or Swedish (n = 3), had a previous HNC (n = 2), or other reasons (n = 2). The remaining 83 patients formed our study cohort.

Data were obtained from patients using semi-constructed, multiple-choice questionnaires, and from the hospital medical records. The questionnaire was distributed after the cancer diagnosis during a nurse visit, but before the initiation of curative treatment. If the patient did not return the questionnaire within a reasonable time, we sent a reminder by mail. The questionnaire included a fixed-choice questions on cancer signs and symptoms, the time of the appearance of the initial symptom/sign, the time of contact to PHC or other HCP, the number of PHC or other HCP visits before the referral to SC, the patient's employment status and education, as well as the patient's perception of whether the HCP had had regarded his/her symptoms as potentially caused by a malignancy. For the second year of data collection in

Study II, we added three more questions regarding a visit to a nurse prior to a GP, whether an oral examination was performed at the initial visit and the patient's impression of the physician's clinical examination.

The data collected from hospital medical records included patient and tumor-related factors. The patient-related variables were age, sex, smoking history, alcohol consumption habits, education, employment, and place of residence. For excessive alcohol use, we used commonly applied dose limits; 15 or more alcohol drinks per week for men, and 8 or more drinks for women. The tumor characteristics included tumor site according to ICD-10 classification codes, and TNM and stage classification according to UICC TNM Classification of Malignant Tumors (7th edition in study I, and 7th and 8th edition in Study II). For the analysis in Study I, tumor sites were grouped as follows: oral cavity, oropharynx, nasopharynx, hypopharynx, supraglottic, glottic, subglottic, transglottic, nose and paranasal sinuses, and major salivary glands. The following tumor subsites in OPSCC (Study II) were used: anterior wall (base of the tongue and vallecula), lateral wall (tonsillar pillars and palatine tonsils), superior wall (soft palate and uvula), and posterior wall.

8.1.2 STUDIES III AND IV

Studies III and IV were prospective, nationwide, patient cohort studies comprising all five university hospital districts in Finland. We included consecutive patients with a new T3–T4 oral, oropharyngeal, or laryngeal SCC without a previous HNC treated at the university hospitals between 1st of September 2017 and 31st of August 2020. In total, 528 patients met the inclusion criteria of whom 108 were not recruited due to our inability to administer the questionnaire to all the patients. Ten patients refused to participate and a further 62 patients were excluded for the following reasons: incapability to understand the questionnaire (n = 31), poor overall health condition (n = 19), could not read Finnish or Swedish (n = 5), and for other reasons (n = 7). Of the remaining 348 patients who received the questionnaire, 145 did not return it.

Data were collected using semi-structured questionnaires that were distributed to patients after their cancer diagnosis but before the initiation of curative treatment. If patient didn't respond within a reasonable time, a reminder was sent via mail. The questionnaire included multiple-choice questions on the patients' symptoms and the time of symptom onset, previous knowledge about HNC risk factors, the patient's socioeconomic

characteristics, their health-related behavior (tobacco and alcohol use), the time of initial contact with an HCP. Psychological factors were assessed using commonly used and validated questionnaires, including the Beck's Depression Inventory (BDI), Social Support Questionnaire (SSQ), Cynical Distrust Scale (CDS), and the Three-Item Loneliness Scale.

Data collected from hospital medical records included patient- and disease-related factors and the time points relevant to our studies (when the referral was received by SC, the time of histopathological diagnosis and the start of curative treatment. Additionally, we used patient hospital medical records to cross-check the delay data reported by the patient to the specialist about the time of symptom onset. If a major discrepancy was found between the patient-reported symptom onset and the hospital medical record, the latter was used, as it was noted closer to the time of symptom onset thus less prone to recall bias.

8.1.3 STUDY V

We retrospectively collected data on all outpatient visits at the 28 PHC centers located in the city of Helsinki in 2016. We did not include emergency room visits. The data were collected from the Social Services and Health Care Division of Helsinki's centralized database. The data we collected included the number of patients and visits to PHC centers based on the ICD-10 diagnosis codes used at the appointment, grouped according to the patients' age and sex.

We had previously selected a set of 57 different ICD-10 diagnosis codes we felt to represent a sign/symptom that might be caused by HNC. We chose the year 2016, because we had previously collected a patient cohort (Study I) that included all new HNC's diagnosed at our tertiary care center that year. We also collected data on patients with HNC who were treated at the Department of Oral and Maxillofacial Surgery to ensure full coverage. Consequently, we were able to confirm which diagnosis codes were used at the PHC centers for all patients with new HNC, all of which were included in the chosen 57 ICD-10 codes. In total, 111 new HNC's were diagnosed from the Helsinki population of 635,181 in 2016.

The data on patients with HNC were collected from hospital medical records and complemented with PHC center medical records, from where we extracted

the exact date of the initial visit to PHC and date of referral to SC, as well as the ICD-10 diagnosis code used at the initial visit.

8.1.4 STATISTICAL ANALYSIS

Statistical analyses were performed using IBM's SPSS Statistics version 26 for Windows (IBM Corp., Armonk, NY, USA). Most patients (in Studies I-IV) reported shorter delay times than the average, resulting in a right-skewed distribution of delays. Because the delays were not normally distributed, univariate associations for patient-, tumor-, and healthcare-related variables and symptoms with patient, PHC and SC delays were analyzed using nonparametric Mann-Whitney *U* test and the Kruskal-Wallis test, applying the Dunn-Bonferroni correction for pairwise comparisons. Delays were reported using median values to better represent the data.

For multivariable analysis (Studies I-III), factors that were significantly associated with delays identified through univariate analysis were included. As the delay distribution skewed to the right, a natural log-transformation (a constant of 0.5 was added to patient and PHC delay values before transformation because delays contained values 0) was performed for delay variables. We used a stepwise backward method (exclusion criteria, $P \geq 0.05$) in Study III to select the factors included in the final multivariable model. Results were back-transformed to the original scale and reported as adjusted geometric means (with 95% CI). The patients who were either excluded from the studies or did not return the questionnaire, and the study cohorts were analyzed using the chi-square test. We considered $p < 0.05$ as statistically significant.

8.1.5 ETHICAL CONSIDERATIONS

These studies obtained institutional study permissions and approval from the Research Ethics Board at the Hospital District of Helsinki and Uusimaa (record number: 398/13/03/02/15). In study III, a study permission was obtained from the Helsinki Social and Health Care Services. In studies IV and V, all university hospitals obtained their own institutional study permission.

9. RESULTS

9.1 CAUSES FOR PATIENT, PHC, AND SC DELAYS AMONG PATIENTS WITH HNC (STUDIES I-III)

In Study I, our patient cohort consisted of 142 patients with newly diagnosed HNC, treated at our tertiary care center, whereas Study II included only patients with OPSCC (n = 83), and Study III focused on large (T3-T4) oral, oropharyngeal, and laryngeal SCC (n = 203), and the data were collected from all five University Hospital Districts.

9.1.1 PATIENT DELAY

The median patient delays were 35 days (mean 128 days), 30 days (mean 56 days), and 58 days (mean 103 days) in Studies I, II, and III, respectively. The big difference between median and mean values is because of a few patients who reported delays of multiple years. Especially in Study I, exceptionally long patient delays of over one year were reported by 11 patients, the longest being 9 years. Three of the 11 longest delays, including the longest one, were reported in nose cancer, another three in salivary gland tumors, four in laryngeal cancers, and one in a cancer of tonsil. In comparison, the longest patient delay in Study II was 12 months. A comparison of patient, PHC, and SC delays of Studies I, II; and III, are presented in Figure 1.

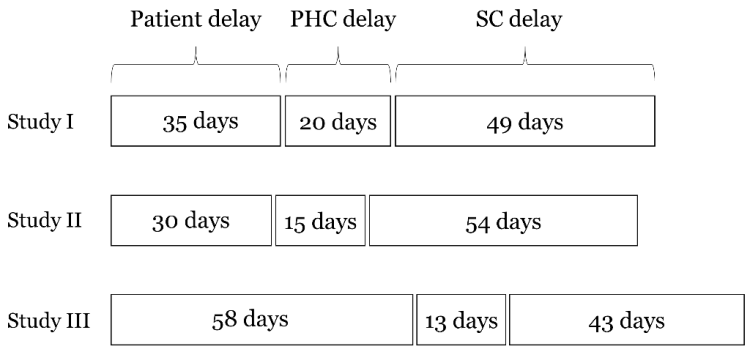

Figure 1. *The Median patient, PHC, and SC delays in Studies I, II, and III.*

9.1.1.1 Patient characteristics in Studies I-III

Most patients were male (73% in Study I, 72% in Study II, and 70% in Study III), with a mean age of 62 years in Study I, 61 years in Study II, and 67 years in Study III. Most were current or previous smokers (71% in Study I, 70% in Study II, and 75% in Study III), and some had a history of current or former heavy use of alcohol (30% in Study I, and 37% in Study II). However, in our nationwide patient cohort of large HNC's, current or previous heavy alcohol use was significantly more common (48% in Study III). In Study II, heavy alcohol use and tobacco smoking were significantly associated with the p16-negative patient group (Table 1), whereas they were somewhat less common among patients with HR-HPV-related OPSCC.

The majority of patients with HNC were either retired or unemployed in all three studies (61%, 64%, and 76% in Studies, I, II, and III, respectively), with only a small proportion of the cohort having a postsecondary education (university or university of applied sciences): 23%, 24%, and 18%, in Studies I, II, and III, respectively. The most common educational level was secondary education in Studies I and II (44% and 43%, respectively), but among patients with large tumors, primary education was more common (42%).

9.1.1.2 Tumor characteristics in Studies I-III

In Study I, most of the tumors were SCCs (82%), and the most common tumor site was the pharynx (45%), followed by larynx (18%), oral cavity (12%), nose and paranasal sinuses (10%), and major salivary glands (9%). Of the OPSCCs included in Study II, the most common subsite was the lateral wall (57%), followed by anterior wall (39%). In Study III, 48% had oral, 34% oropharyngeal, and 18% laryngeal cancer.

In Studies I and II, most of the tumors were small (T1-T2; 65% in Study I, and 74% in Study II). In Study III, 43% were T3, and 57% were T4 tumors. In Studies I and III, slightly over half of the patients had regionally advanced disease (53% in Study I, and 57% in Study III). However, regional advancement was significantly more common in the patient cohort only including OPSCC (81% in Study II). Most HNC's were diagnosed at an advanced stage (stages III-IV; 59% in Study I and 87% in Study II, according to 7th edition of UICC TNM Classification), but distant metastases were rare (2% in Studies I and III, 5% in Study II). Regarding p16 status, most of the OPSCCs were p16-positive (79% in Study II and 68% in Study III). The differences between the p16-positive and p16-negative patient groups in Study II are presented in Table 1.

Table 1. *Patient characteristics according to p16 status (n = 81 patients)*

	p16-positive (n = 64)	p16-negative (n = 17)	*P* value	All (n = 83)
Sex				
Male	46 (72%)	12 (71%)	1.000	60 (72%)
Female	18 (28%)	5 (29%)		23 (28%)
Mean age (in years)	59.7	66.6	**0.023**	61.4
History of smoking				
Never smoked	23 (36%)	2 (12%)	**<0.001**	26 (31%)
Former smoker	33 (52%)	5 (29%)		39 (47%)
Current smoker	8 (12%)	10 (59%)		18 (22%)
Excessive use of alcohol				
No	46 (72%)	4 (24%)	**<0.001**	52 (63%)
Yes	11 (17%)	6 (35%)		17 (21%)
Previous use	7 (11%)	7 (41%)		14 (17%)
T class**				
T1-2	47 (73%)	13 (76%)	1.000	61 (74%)
T3-4	17 (27%)	4 (24%)		22 (27%)
N class**				
N+	10 (16%)	6 (35%)	0.090	16 (19%)
N0	54 (84%)	11 (65%)		67 (81%)
Stage**				
I-II	6 (9%)	5 (29%)	**0.047**	11 (13%)
III-IV	58 (91%)	12 (71%)		72 (87%)

**According to UICC, seventh edition

***n = 81; p16-positive (n = 63), p16-negative (n = 16)

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9.1.1.3 Symptoms in Studies I-III

Pain was reported as the most common symptom in Studies I and III, affecting 51% and 63% of patients, respectively. In Study II, a lump in the neck was the most common symptom (69%), followed by pain (48%). A lump in the neck was also a common symptom in Study I (42%), but less common in Study III (29%), possibly reflecting the lower number of oropharyngeal cancers and larger number of oral cancers in Study III compared to Studies I and II. Other symptoms were difficulties swallowing (25%, 36%, and 36% in Studies I, II, and III, respectively), hoarseness (25%, 16%, and 35%), mucosal ulcer or other lesion (17%, 16%, and 27%), weight loss (8%, 11%, and 19%), difficulties breathing (9%, 5%, and 11%), bleeding (9%, 5%, and 8%), and facial swelling (5%, 2%, and 6%). Regarding the number of different symptoms, some patients reported having one symptom (38%, 34%, and 28%, in Studies I, II, and III, respectively), some had two symptoms (29%, 30%, and 30%, in Studies I, II, and III, respectively), and some had three or more symptoms (31%, 36%, and 42%, in Studies I, III, and III, respectively). In Study I, three patients (2%) reported having no HNC symptoms. Notably, patients with large tumors (Study III), had on average a higher number of symptoms compared to those in Studies I, and II, possibly because a larger tumor produces more pronounced symptoms compared to a smaller one.

9.1.1.4 Patient characteristics and patient delay

In studies I, II, and III, patients' age and sex were not associated with patient delay. Of the other patient characteristics, employment status was associated with patient delay in Study II; unemployed or retired patients reported longer median patient delays (34 days vs. 20 days). However, no association regarding employment status were found in Studies I and III. In Study III, lower education was associated with a longer median patient delay (62 days for patients with a primary education and 31 days for patients with a postsecondary education), although no association was found in Studies I and II. Regarding health-related behavior, tobacco smoking was not associated with patient delay in any of the three studies, but in Study III, a longer patient delay was significantly associated with current heavy use of alcohol (median delay of 75 days vs. 35 days for no current/previous heavy alcohol use). However, in Studies I and II, alcohol use did not affect patient delay.

9.1.1.5 Tumor characteristics and patient delay

Regarding disease-related factors, tumor site was associated with patient delay in Study I, with glottic tumors having a significantly longer median patient delay (133 days). Similarly, in Study III, laryngeal cancer patients reported a significantly longer median patient delay of 92 days, compared to patients with oropharyngeal (43 days), or oral (44 days) cancers. In Study II, higher T Class (T3-T4) was associated with a longer median patient delay (59 days, vs. 22 days in T1-T2), but Studies I and III did not report similar findings. This might be because of the larger number of disease entities in Study I, and only T3-T4 cancers were included in Study III. In Study I, patients with regionally advanced disease had a shorter median patient delay of 28 days compared to 57 days for patients with N0 disease, similar to the findings in Study II. However, in Study III no association was found between N Class and patient delay. In Studies I and II, higher stage was associated with a shorter patient delay; this finding remained significant in the multivariate analysis in Study II. T, N, and M class did not associate with patient delay in the multivariate analysis (Study II). In Study III, stage did not affect patient delay, most likely since only large tumors were included, thus most patients had advanced stage disease. p16 status was not associated with patient delay in any study.

9.1.1.6 Symptoms and patient delay

Certain symptoms were associated with patient delay. A lump in the neck was associated with shorter median patient delay in Study I (28 days vs. 48 days), but no association was found in Studies II and III. Pain was not associated with

patient delay in any of the studies. Hoarseness (yes vs. no) was associated with a longer median patient delay in Study I (60 days vs. 21 days) and Study III (78 days vs. 45 days). This most likely explains, at least in part, why laryngeal cancer patients had longer patient delays. Patients with difficulties breathing reported longer median patient delays in all three studies: 113 days vs. 31 days in Study I, 151 days vs. 29 days in Study II, and 91 vs. 51 days in Study III. This might be due to inverse causality; a longer patient delay may have led to tumor growth and consequent disease advancement, eventually resulting in breathing difficulties. It is important to note that if the patient reported multiple symptoms, we were not able to identify the time interval for every specific symptom, which causes bias of the results and might explain why a symptom as grave as difficulty breathing was associated with a longer patient delay. This is supported by the fact that in the univariate and multivariate analysis in Study II, a higher number of symptoms was associated with longer patient delay (although in Studies I and III, this association was not found). Further, longer median patient delay was associated with weight loss (75 days vs. 24 days) in Study II. Other symptoms did not associate with patient delay.

9.1.2 PHC DELAY

The median PHC delays were 20 days, 15 days, and 13 days in studies I, II, and III, respectively. None of the patient- or tumor- related variables were associated with PHC delay, except for salivary gland carcinomas, in which there was a significantly longer median PHC delay of 96 days vs. 17 days for SCCs. In Studies I and II, symptoms were not associated with PHC delay. However, a lump in the neck and facial swelling were associated with a shorter PHC delay (6 days vs. 18 days and 0 days vs. 14 days, respectively) in Study III.

The initial point of contact was associated with PHC delay; patients who initially contacted a private otorhinolaryngologist (ORL), had a significantly shorter median PHC delay compared with patients who contacted a GP (4 days vs. 21 days; $P = .027$) in Study I. Similarly, in Studies II and III, trends were observed between having a shorter median PHC delay and visiting a private ORL-specialist instead of a GP (1 day vs. 16 days, $p = 0.09$ in Study II and 6 days vs. 18 days, $p = 0.06$ in Study III). Furthermore, if the patient initially visited a nurse, the PHC delay was longer (34 days vs. 6 days, $p=0.02$), according to Study II.

The proportion of patients who were referred to SC at the initial visit was 39% in Study I, 45% in Study II, and 35% in Study III. Logically, patients who were referred to SC at the initial visit had shorter PHC delays compared to patients

who had multiple visits. The median PHC delays for one, two, three, four, and five or more visits in Study I were 11, 20, 35, 50, and 175 days, respectively ($p<0.001$). Similarly, the median PHC delays for one, two, and three or more visits were 1, 20, and 33 days in Study II, and 5, 18, and 27 days in Study III. Moreover, a scheduled follow-up visit was associated with PHC delay in Studies I and II. Patients with no follow-up visit scheduled had a significantly longer median PHC delay compared to patients who were referred to SC or who had a follow-up visit scheduled (in Study I 102 days vs. 14 days, $p<0.001$ and in Study II 14 days vs. 37 days, $p=0.012$). However, in Study III, only referral to SC was significantly associated with shorter PHC delay, and no association was found between PHC delay and whether a follow-up visit was scheduled or not.

The patient's impression of the physician's initial clinical evaluation was associated with PHC delay in Study II: patients who reported a poorer impression of the initial clinical evaluation, experienced longer PHC delays. This might be because of a bias resulting from the fact that patients who had experienced longer PHC delays might have felt that the clinical examination was inadequate, after finding out that the symptoms were caused by HNC. If the physician mistakenly treated the symptoms as an infection (31% of the cases), the median PHC was significantly longer (26 days vs. 11 days) in Study III. One-fifth of all patients with HNC received antibiotics in Study III, but it did not affect PHC delay. In Studies I and III, we investigated patients' impressions on whether his/her symptoms were initially considered to be caused by a malignancy at the PHC center. In total, 21% and 22% (Study I and III) of patients reported that the treating physician regarded the symptoms as potentially malignant, 39% and 27% (Study I and III) of patients thought they were considered benign, and 40% and 49% (Study I and III) had no clue. However, this was not associated with PHC delay in either study. Furthermore, we wanted to investigate whether patients who eventually received palliative care, had had a long PHC delay. This was not the case, as patients who were treated with palliative intent had short median PHC delay in Studies II (0 days vs. 17 days, $p = 0.03$) and III (1 day vs. 17 days, $p = 0.005$).

Most of the patients (97%, 93%, and 88% in Studies I, II, and III, respectively) were treated with curative intent. The lower percentage in Study II might reflect the higher numbers of distant metastases (5% vs. 2% in Studies I and III). In Study III, we focused on large T3-T4 tumors, so the higher number of patients treated with palliative intent was expected.

9.1.3 SC DELAY

The median SC delays were 49 days (unpublished data), 54 days, and 43 days in Studies I, II, and III, respectively. In Study II, we looked more closely at the different time intervals that contribute to SC delay. The median delay from the referral to first visit to an ORL-specialist was 7 days, the median SC diagnostic delay (from referral to histopathological diagnosis) was 16 days, of which 4 days were delay caused by pathologist reviewing the sample. Similarly, in Study III the median SC diagnostic delay was 13 days. The median delay from diagnosis to the initiation of curative treatment (treatment delay) was 29 days in Study II and 30 days in Study III.

The chosen treatment modality was significantly associated with SC delay in Study I (unpublished data): patients treated with surgery had a significantly shorter median SC delay (41 days) compared to patients treated with RT (63 days), or CRT (56 days) $p = 0.04$. Similar findings were observed in Study III, where median SC delay was 35 days for the surgically-treated, and 55 days for patients treated with (C)RT ($p<0.001$). Logically, the treatment modality also affected treatment delay: surgically treated patients had a median treatment delay of 15 days (Study II) and 25 days (Study III) compared to 36 days (Study II) and 34 days (Study III) for (C)RT. Similarly, in Study I, the mean treatment delay for surgically treated patients was 10 days, compared to patients treated with RT (21 days) or CRT (36 days) [unpublished data].

If the patient was referred to a Central Hospital prior to the University Hospital, the median SC delay was significantly longer in Study III (49 days vs. 40 days, $p = 0.009$) and a similar trend was observed in Study II (63 days vs. 49 days, $p = 0.066$).

None of the patient- or tumor-related variables were associated with SC delay in Studies I and II, although a trend ($p = 0.07$) of a shorter median SC delay was observed among current smokers (49 days) compared to never smokers (62 days). Conversely, the opposite trend ($p = 0.08$) was found in Study III, where current smokers experienced longer median SC delays (46 days), compared to never smokers (37 days). The median SC delay was shorter in Study III for patients with oral cancer (35 days), compared to patients with oropharyngeal (48 days), or laryngeal (58 days) cancer. This difference was mostly due to a shorter median diagnostic delay (9 days vs. 14 days for oropharyngeal, and 21 days for laryngeal cancer), but might have been partly due to patients with oral cancer being treated more often with surgery,

compared to (C)RT (data not shown). Accordingly, patients with an ulcer or other mucosal lesion experienced shorter median diagnostic, treatment, and SC delays (Study III), while patients with hoarseness had longer diagnostic and treatment delays mirroring the differences in SC delay between patients with oral and laryngeal cancer. In Study II, patients who reported a neck lump as a symptom experienced a shorter SC delay in the univariate analysis (49 days vs. 64 days), even though N Class was not associated with SC delay. However, in the multivariate analysis, this association was not present.

9.1.4 WITHDRAWAL ANALYSIS IN STUDIES I-III

We also reviewed patient-, and tumor- characteristics from patients who were excluded or did not complete the questionnaire-part of the study for whatever reason. The coverage for Studies I and II was better (70% and 75%) than in Study III (38%). There were no differences in age and sex distributions between non-included and included patients. In Study I, there were no differences between the included and non-included patients with regards to tumor site, histology, and N Class. However, T4 tumors were more common among the non-included patients (33% vs. 20%), who also generally had more advanced stage (III-IV) disease (67% vs. 59%), and greater occurrence of distant metastases (7% vs. 2%). Similarly, in Study II, patients who were not included had a larger T Class (T3-T4; 39% vs. 27%), more advanced stage (III-IV; 43% vs. 20%) and HPV-unassociated (p16-negative) OPSCC was more common (39% vs. 21%). In Study III, there were no differences regarding tumor site, T or N Class, or stage, but the non-included patients had a greater occurrence of distant metastases (6% vs. 2%; $P = 0.04$). Palliative treatment was more common among non-included patient group (27% vs. 3% in Study I, 25% vs. 7% in Study II, and 27% vs. 12% in Study III).

9.2 PSYCHOSOCIAL FACTORS AND DELAYS IN HNC (STUDY IV)

In Study IV, we investigated the psychological and socioeconomic factors amongst patients with a large oral, oropharyngeal, or laryngeal SCC, and their relation to different delay intervals. We also compared the patient cohort to the age- and sex- matched Finnish general population using the FinTerveys 2017 report. This is the same patient cohort as in Study III.

Regarding socioeconomic factors, patient education, but not employment, was associated with patient delay, as reported earlier in Study III. In total, 51% were married or in a relationship and 8% had children living in the same household. Similarly, 46% lived in one, 44% in two, and 8% in three or more persons households. Regarding the household financial situation, 59% reported having adequate funds, 29% needed to limit expenditures and 7% received financial support (5% did not report these data). Relationship status, living arrangements, and household financial situation was not associated with patient, PHC, or SC delays. However, a trend ($p = 0.06$) was observed for a shorter median patient delay among patients living with children (25 days vs. 59 days).

We also inquired about the patient's impression on his/her general health. In total, 12% felt their health was excellent or very good, 30% good, 26% moderate to poor while 32% did not report these data. Perceived functional capacity on scale of 1-10 was "good to excellent (6-10)" among 58% and "poor to moderate (1-5) among 18 percent, while 24 percent did not report these data. Perceived general health and functional capacity was not associated with patient, PHC, or SC delays.

Depressive symptoms were investigated with the BDI-questionnaire. Most patients, 69%, reported normal results (a score of 0-13), while 13% had mild (14-19), and 17% moderate to severe (20 and over) depressive symptoms (1% did not report these data). The CDS was used to investigate cynical hostility among this patient group: 60% had low to moderate (0-16) and 21% had moderate to high (17-24) scores on the CDS. The SSQ was used to figure out the patient's social support. Many patients (49%) had a very low to low (0-4) score in SSQ, 18% had a moderate (5-7), and 32% had a high to very high scores (over 8) while 1% did not report these data. Perceived feeling of loneliness was investigated using the Three-Item Loneliness Scale, in which 45% of the patients reported that they never felt themselves lonely, 30% felt loneliness sometimes and 19% were often lonely (6% did not report these data). Most patients (94%) had someone they could talk to, and 23% had someone close diagnosed with cancer. Depressive symptoms, cynical hostility, social support, and loneliness were not associated with patient, PHC, or SC delays in our patient cohort.

Most patients reported as knowing about HNC risk factors to at least some degree (76%), while 10% said they knew very little and 12% were completely unaware of cancer risk factors. Most patients did not suspect that his/her

symptoms would be caused by cancer (57%). Patient knowledge and suspicion of cancer was not associated with patient delay in our cohort. Over half (59%) of the patients were told to seek medical attention by someone else and surprisingly, these had a longer median patient delay (73 days vs. 31 days) compared to patients who were not prompted to seek medical care. This is most likely due to inverse causality; patients who delayed seeking medical care were eventually told to do so by someone else.

Compared to the age- and sex- matched Finnish general population, patients with large oral, oropharyngeal, or laryngeal cancers were more often unmarried, divorced or widowed (59% vs. 29%), living alone (59% vs. 25%), and far fewer lived in a household of three or more (8% vs. 31%). Compared to the general population, primary education was more common, and post-secondary education rarer among patients with HNC, in both men and women, between the ages of 40 and 80. Furthermore, far fewer patients with HNC aged between 40–69 were currently employed, and patients aged 40–69 reported more often having "inadequate funds" compared to the Finnish general population. HNC patients were more often current smokers and heavy users of alcohol, although total alcohol abstinence was also more common among HNC patients compared to the Finnish general population. Symptoms of depression were more common among male patients with HNC aged between 30-64 (27% vs. 9%) as well as over 65 years old (25% vs. 7%), compared to the general population. This difference was even more pronounced among women with HNC: 52% vs. 13% for 30-64 years old, and 35% vs. 11% for over 65 years old, compared to general population. Male patients with HNC aged over 50 were less trusting of other people compared to the Finnish general population, but there were no differences among women. The average reported functional capacity was somewhat similar among male, but lower among female patients with HNC, compared to the general population.

9.3 CHALLENGES A GP FACES WHEN DIAGNOSING HNC (STUDY V)

In Study V, we investigated the patient material from which a GP working in a healthcare center needs to identify HNC patients. We included all 28 PHC centers, employing a total of 380 GPs, in the city of Helsinki, with a population of 635,181 in 2016. From this patient population, 111 new HNCs were diagnosed in 2016, of which 40 (36%) were referred to SC from Helsinki's PHC centers. The complete list of all places of referring instances is presented in Figure 2.

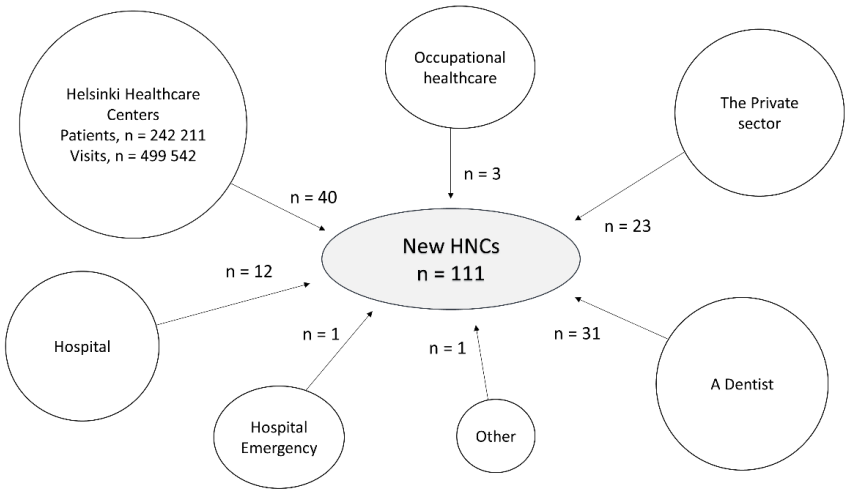

Figure 2. *New HNCs in the Helsinki area according to the place of referral.*

OPSCC was more common among patients referred to SC from PHC centers compared to some other referring instances, while only a small proportion of patients with oral cancer (16%) contacted PHC. Instead, most patients with oral cancer had visited a dentist (64%). The comprehensive list of all HNCs according to tumor site and place of referral is presented in Table 2.

Half of the PHC patients who were referred to SC at the initial visit, 43% at the second, and 7% at the third visit. Two-thirds of these additional visits were related to an FNAC, the remaining being clinical follow-ups or other visits. The median physician-related PHC delay (from the initial appointment to the referral to SC) was 5 days and 73% of patients were referred to SC within two weeks. Only three patients had a PHC longer than two months.

Table 2. *Number of HNC patients diagnosed in the Helsinki area in 2016 according to site and place of referral.*

Tumor site	Total	PHC center	Dentist	Private MD*	Other
Oral Cavity	45	7	29	3	6
Oropharynx	31	15	2	10	4
Larynx	10	4	-	3	3
Hypopharynx	9	6	-	2	1
Nose and nasal cavities	8	5	-	2	1
Major salivary glands	5	1	-	3	1
Unknown primary	3	2	-	-	1
Total	111	40	31	23	17

*Medical doctor

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In comparison, a total of 242,211 individuals, of whom 60% were female and 45% were under 40 years old, visited a PHC center in the City of Helsinki during 2016, resulting in nearly 500,000 outpatient visits. Of these, 11,896 (5% of all patients) visited a physician because of a symptom that might be caused by a HNC (with at least one of the chosen 57 ICD-10 diagnosis codes). From these patients, 33 new HNCs were diagnosed. The remaining 7 did not have an ICD-10 diagnosis code related to a possible symptom/sign caused by HNC.

We then focused on these 11,896 patients and compared the age-, and sex-matched patient groups, according to the different ICD-10 codes, to the actual number of HNCs found from that patient population. For example, 233 male patients aged over 60 visited PHC center in 2016 because of a neck lump, and from these patients, 7 new HNCs were diagnosed resulting in an incidence rate of 3% in this patient group. All these data are presented in Table 3.

One out of every 6000 patients visiting a PHC center in 2016 had HNC. However, stratification according to certain clinical traits results in a higher detection rate of HNC. If we rule out patients younger than 40, the ratio rises to 1:3300. If we consider that most HNC patients are male (68% in this series), the likelihood for HNC in male patients visiting a PHC center aged 40 or older

is 1:2000. If we add HNC symptoms to the equation, the likelihood of HNC rises to 1:90. This is impressively high ratio considering that the most known HNC risk factors (tobacco and alcohol) were not considered, and no information about symptom duration or other apparent causes for the signs/symptoms was available.

Table 3. *Total number of patients that visited a PHC center in the city of Helsinki during 2016 with HNC-related symptom*

Sign or symptom		ICD-10 codes used	Total number of patients (M/F[a]%)	Number of patients, M/F			Number of HNC patients, M/F (n = 33)		
				Age			Age		
Symptoms related to HNC				**<40**	**40-59**	**≥60**	**<40**	**40-59 (%[c])**	**≥60 (%[b])**
1.	Sore tongue, non-healing mouth ulcers and/or red or white patches in the mouth	K12, K12.01, K12.10, K12.18, K13.2-13.4, K13.6, K13.7, K13.78, K13.79, K14, K14.0-09, K14.6, K14.60-69, K14.88, K14.9	306 (37.6/62.4)	50/60	31/31	34/100	0/0	1/1 (3.2/3.2)	1/2 (2.9/2.0)
2.	Pain in the throat	R07.0	1157 (35.1/64.9)	257/451	79/149	70/151	0/0	1/0 (1.3/0.0)	2/1 (2.9/0.7)
3.	Hoarseness	J04, J04.0, R49.0, R49.8	976 (36.6/63.4)	231/316	38/143	88/160	0/0	0/0 (0.0/0.0)	2/0 (2.3/0.0)
4.	Painful and/or difficulty swallowing	J02, J02.9, J03, J03.9, J31.2, R13	3004 (40.4/59.6)	937/1318	137/242	140/230	0/0	1/0 (0.7/0.0)	3/0 (2.1/0.0)
5.	Lump on the neck	D23, D23.4, I88, I88.8, I88.9, R22, R22.0, R22.1, R59.0, R59.9	2267 (34.8/65.2)	387/600	168/355	233/524	0/0	1/0 (0.4/0.0)	7/2 (3.0/0.4)
6.	Blocked nose and/or bloody discharge from the nose	J31.0, J33, J33.0, J33.9, R04.0	1172 (47.9/52.1)	260/227	99/119	202/265	0/0	1/1 (1.0/0.8)	1/1 (0.5/0.4)
7.	Difficulty breathing and/or hemoptysis	R06, R06.0, R06.1, R04.2, R58	3014 (38.3/61.8)	305/541	221/262	628/1057	0/0	1/0 (0.5/0.0)	2/1 (0.3/0.1)
	Total		11 896 (38.6/61.4)	2427/3513	773/1301	1395/2487	0/0	6/2 (0.8/0.2)	18/7 (1.3/0.3)

[a] Male/Female

[b] The percentage of cancer in this age and sex group

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10. DISCUSSION

Delays before the initiation of curative treatment lead to disease progression and worse survival [9, 112, 122, 123]. These delays can be patient- or healthcare-related. By investigating the factors associated with patient, PHC, and SC delays, we can find different ways to mitigate delay intervals leading to better care for patients with HNC.

10.1 CAUSES OF PATIENT, PHC, AND SC DELAYS AMONG PATIENTS WITH HNC (STUDIES I-III)

In Study I, we focused on an unselected patient series of all new HNCs diagnosed at our tertiary care clinic in 2016, whereas in Study II we recruited only patients with newly diagnosed OPSCC to better focus on the aspects of p16 status and HR-HPV-related disease. In addition, we wanted to further investigate the lengths and reasons behind delays among patients who present with a large T3-T4 Class tumor, to better understand why these tumors get to grow so large despite causing distinct and easily noticeable signs and symptoms.

10.1.1 LENGTHS AND CAUSES OF DELAYS

10.1.1.1 Patient delay

The median patient delays were 35 days, 30 days, and 58 days in Studies I, II, and III, respectively, while the mean patient delay was between 1.9 months and 4.3 months. The median patient delay was similar to a study from Spain, that reported a median of 30 days for all HNC [166], but was longer than in a study from the US including only OPSCC (21 days) [24]. Although, similarly to the US study, median patient delay was shorter in our Study II, which focused solely on OPSCC. The mean patient delays were in accordance with the weighted average of 2.7 months reported in a systematic review on oral cancer [29], but a bit shorter than in another review on oral cancer (3.5 – 5.5 months) [167]. We have used median values instead of means to present our delay data, as it is a more useful and representative value since most patients have shorter delays than the mean (delay data are skewed to the right), and very long delays (even multiple years) occurred in only a few patients, significantly influencing the mean values.

Similar to the literature, patients' age and sex was not associated with patient delay in any of our studies [14, 21, 184, 185]. Regarding socioeconomic variables, employment was associated with a shorter patient delay in Study II, but no association was found in Studies I and III. We had hypothesized that employment would affect patient delay as employed patients had access to occupational healthcare. Only a few studies have investigated the association between different socioeconomic variables and patient delay. In an Indian study by Akram et al. lower SES was associated with a longer patient delay [16]. However, they do not to present how this SES was measured in the study. A study from the UK showed that "low social class" was associated with longer patient delay, but also do not present how this "social class" was measured [17]. Furthermore, in both previously mentioned studies, patient delay was addressed as a class variable with a cut-off point of 3 months [16], and 3 weeks [17], instead of being a continuous variable. Similar to our findings in Studies I and III, a Dutch study on laryngeal cancer found no association between employment and patient delay [22], and a study from the UK found no association between the Index of Multiple Deprivation 2000 (where employment is weighted as 22.5% of the final value) and patient delay [185]. Lower education was associated with a longer median patient delay (62 days for patients with primary education and 31 days for patients with post-secondary education) in Study III, similarly to a study from the UK [17]. However, no association was found in Studies I and II, in accordance with a Dutch study on oral and pharyngeal cancer [14]. We had hypothesized that higher levels of education would be associated with a shorter patient delay as highly educated individuals are more aware of different HNC symptoms [147].

Regarding health-related behaviors, tobacco smoking was not associated with patient delay in any of the three studies, which is in line with multiple studies that have found no association between smoking and patient delay [14, 18, 184, 189, 191]. Conversely, a study from the UK reported shorter patient delays among smokers [185], and a Danish study reported longer patient delays among female smokers, but not male smokers [187]. In studies I and II, alcohol use was not associated with patient delay, a finding similar to some studies [14, 184, 186]. However, in Study III current heavy alcohol use was associated with a longer patient delay (75 days vs. 35 days). This was an expected finding as heavy alcohol use can mask HNC symptoms and this patient group might generally be less interested in their general health. A few other studies have reported longer patient delays among heavy users of alcohol [18, 19, 190].

Certain symptoms are associated with patient delay. A lump in the neck was associated with a shorter median patient delay in Study I (28 days vs. 48 days),

but not in Studies II and III. A few other studies have reported an association between a neck mass and shorter patient delay [14, 191]. This might be because a lump in the neck is abnormal, and an easily noticeable sign for the patient. Pain was not associated with patient delay in any study, a finding similar to the literature [14, 189, 191, 196]. Hoarseness was associated with a longer median patient delay in Study I (60 days vs. 21 days), and Study III (78 days vs. 45 days), most likely explaining at least in part the long patient delays of glottic cancer. Hoarseness has not been associated with a longer patient delay [22], although it has been associated with longer PHC [26] as well as treatment delay [211]. Hoarseness is common among smokers and in many benign conditions, and therefore might not raise a suspicion of malignancy and prompt patients or physicians to investigate the etiology quickly. Difficulty breathing was associated with longer patient delay in Studies I, II, and III. However in the literature, difficulty breathing has not been associated with patient delay [22]. This might be due to an inverse causality; longer patient delay might have led to tumor growth and consequent disease advancement, eventually resulting in breathing difficulties. It is important to note that due to our study setting, we were not able to identify the time interval for each individual symptom, in the case that a patient reported multiple symptoms, which might at least partly explain why difficulty breathing was associated with a longer patient delay. This is supported by the fact that in the univariate and multivariate analysis in Study II, a higher number of symptoms was associated with longer patient delay (although in Studies I and III, this association was not found), which is further supported by a finding of a Brazilian study, that reported an association between a higher number of symptoms and higher disease stage [23]. Furthermore, a longer median patient delay was associated with weight loss (75 days vs. 24 days) in Study II, which is usually related to a more advanced disease. Similarly to the literature, other symptoms were not associated with patient delay [196].

Laryngeal, and especially glottic, tumors had longer median patient delays in Studies I and III. This is most likely because hoarseness, the most common symptom of glottic tumors, was associated with longer patient delay in these studies. Similar to our studies, a Dutch study on laryngeal cancer observed a similarly longer median patient delay for glottic (10 weeks), compared to supraglottic (4 weeks) cancer [22]. Some other studies have supported the notion that tumor site affects patient delay [14, 119].

Tumors tend to grow and therefore we hypothesized that patients who present with a large tumor at diagnosis have postponed seeking medical care, allowing the tumor to grow larger. In Study II, higher T Class was associated with a longer median patient delay and correspondingly, in Study III that included

only large T3-T4 tumors, the median patient delay was twice as long compared to our other two studies. T Class was not associated with patient delay in Study I, possibly because of the large number of different tumor sites and histological types. Most studies have found no association between T Class and patient delay [9, 22, 114, 184, 191]. A study on oral and pharyngeal cancer reported, similarly to Study II, an association between higher T Class and longer patient delay [14], but conversely another study from the UK reported that patients with larger tumors had a shorter patient delay [185]. In Study I, patients with regionally advanced disease (N+), had a shorter median patient delay of 28 days compared to 57 days for the N0 patients, similar to findings reported in Study II (only in the univariate analysis). These were most likely because a lump in the neck was also associated with shorter patient delay and prompted patients to seek medical care quickly. In Study III however, no association was found between N Class and patient delay. In the literature, N and M Class have not been associated with patient delay [9, 14, 22, 184, 191].

In Studies I and II, higher stage was associated with shorter patient delay, a finding that remained significant in the multivariate analysis in Study II. In Study III, stage did not affect patient delay, most likely since almost all patients had a high stage cancer. These findings may seem counterintuitive since higher T Class was associated with longer patient delay. However, in Studies I and II, higher stage was mediated more through N, instead of T, Class. The literature around this matter remains inconclusive. Some studies have reported an association between higher stage and longer patient delay [14, 114], while some have found an opposite association [23]. However, most studies have found no association between disease stage and patient delay [9, 184, 191]. p16 status was not associated with patient delay and, as far as we know, no other studies on this matter have been published. We hypothesized that patient delay might have been shorter due to the differences in patient material (younger non-smokers, less alcohol use), symptoms (a lump in the neck), and tumor characteristics (higher N Class) [53, 199]. The varying results between TNM and stage and patient delay reported in the literature are most likely due to the individual differences in tumor aggressiveness and their varying tendencies for causing symptoms. The growth rate between individual HNCs varies greatly [9, 111]. Aggressive tumors can grow rapidly and spread to local lymph nodes early, causing notable symptoms leading patients to seek medical attention promptly, whereas less aggressive tumors usually cause milder symptoms, but due to their slow growth, they may present with a low T Class despite a long delay. This might explain why some studies have reported an association between short patient delay and higher stage, while others have found the opposite findings. However, in Studies II and III, patients who eventually received palliative care, had significantly longer median patient

delays (119 days vs. 28 days in Study II, p = 0.02 and 88 days vs. 51 days, p = 0.02 in Study III), but shorter PHC delays (0 days vs. 17 days in Study II, p = 0.03 and 1 day vs. 17 days in Study III, p = 0.005), meaning that the delay that possibly led to tumor growth and might have eventually led to the patient receiving palliative care, was more patient-related than PHC-related.

10.1.1.2 PHC delay

The median PHC delays were 20 days, 15 days, and 13 days in studies I, II, and III, respectively, which is a bit more than in a systematic review of oral cancer [29]. A study from Canada reported a substantially longer mean PHC delay of over 10 months, measured in the province of British Columbia [15]. This is most likely due to poor availability of PHC services due to very long distances between patients and HCPs. However, a substantially shorter median PHC delay of just 9 days has been reported in a Danish study, after the implementation of their fast-track system [31].

In Studies I-III, none of the sociodemographic variables were associated with PHC delay, similar to some studies [26, 201]. We found no association between a patient's employment status and educational level, and PHC delay, similar to a Dutch and a Finnish study [26, 191], whereas a Danish study on all cancers (including HNC), found that well-educated males and females, with a high family fortune, experienced shorter PHC physician-related delay (the time interval from the initial visit to PHC physician to the referral to SC) [187]. They argued that this might be due to more available resources and better capabilities to describe symptoms accurately, which might lead to shorter PHC delay [187]. Furthermore, in a Finnish study on HNC, low SES was associated with disease being overlooked (i.e. no referral or follow-up appointment arranged), which was further associated with longer PHC physician-related delay and poorer outcomes [201]. Tobacco smoking and alcohol consumption were not associated with PHC delay in our studies. However, in a Finnish study on HNC, tobacco smoking was associated with shorter PHC delay [191]. This might be because tobacco smoking is the most important risk factor for HNC, so the physicians' suspicion for malignancy is accurately higher when considering different HNC-related symptoms among smokers.

In Studies I and II, symptoms were not associated with PHC delay, but a lump on the neck and facial swelling were associated with shorter PHC in Study III. Facial swelling and a lump in the neck are abnormal, and perhaps, more easily visible signs for the physician to notice, which might lead to shorter PHC delay. In a Dutch study on HNC, hoarseness, but not swelling or other HNC

symptoms, was associated with a prolonged PHC delay [26]. Regarding tumor factors, salivary gland carcinomas were associated with a longer PHC delay compared to HNSCCs. Malignant salivary gland tumors are relatively rare compared to benign tumors, and generally grow slowly, which might add to the delay in PHC. We found no other study on PHC delay, that included salivary gland carcinomas.

Patients who had initially visited a private ORL-specialist, had a shorter PHC delay compared to patients, who had contacted a GP. This finding was significant in Study I, and similar trends were also observed in Studies II and III. This was an expected finding as ORL-specialists have more extensive education and experience on HNCs and clinically evaluating patients with HNC. Furthermore, HNCs are presumably more common among the patient population of an ORL-specialist, compared to an unselected patient population of a GP. According to a Finnish study, a new HNC is diagnosed approximately once in every 63,000 visits to a GP, while 11% of their patient population presents with symptoms possibly caused by a HNC [201]. There were no differences between PHC delay among patients who had initially visited dentists compared to GPs (Study III), which was expected and in line with the literature [207]. Patients who initially visited a nurse instead of a GP, had longer PHC delay, which was to be expected, as the number of visits is strongly associated with PHC delay.

The portion of HNC patients who were referred to SC at the initial visit was between 35% and 45%, in Studies I-III, which is similar to a Dutch study on all HNC [26], but lower than in two studies from the UK on patients with oral cancer and OPSCC [185, 208]. Logically, the number of visits to PHC was associated with PHC delay in Studies I-III, similarly to the literature [26, 201]. Patients with no follow-up visit scheduled had a significantly longer median PHC delay, compared to patients who were referred to SC or had a follow-up visit scheduled in Studies I and II (but not in Study III). Again, this is a very logical finding as if no referral or follow-up appointment is scheduled, the symptoms are most likely considered to be benign by the physician, and with no follow-up appointment, it is entirely dependent on the patient when he/she will return to PHC when the symptoms persist.

Insufficient clinical evaluation by the physician has been associated with a higher risk of the disease being overlooked (no referral or follow-up) [201]. In Study II, patients who reported a poorer impression of the initial clinical evaluation, experienced longer PHC delays. However, this might be at least partially because patients who experienced longer PHC delays, might have felt

the clinical examination as inadequate after receiving the HNC diagnosis. Furthermore, a patient's perception of the physician's impression of whether he/her thought the symptom to be malignant or benign, did not affect the PHC delay, contrary to our hypothesis. We assumed that if the physician considered the symptom as possibly malignant, it would result in a shorter PHC delay. Notably, a large portion of the patients were unsure whether his/her physician considered his/her symptom as malignant or not (40% in Study I and 49% in Study III), which might impact the results. It seems that the suspicion of malignancy is not clearly communicated to the patients, which could lead to further PHC delay. In a Dutch study, patients who considered their symptom to be benign prolonged their return to PHC, upon persistence of the symptoms [26]. Misdiagnosis plays a part in PHC delay among patients with HNC [28]. In Study III, 31% of the HNCs were mistakenly treated as infections, similarly to a study from the US (22%) [28]. Logically, this resulted in longer PHC delay as oral and pharyngeal infections are common and symptoms may persist for over a week or even multiple weeks before raising the concern of the treating physician.

10.1.1.3 SC delay

The median SC delays were 43 – 54 days in Studies I-III, which is slightly longer than in a recent Dutch study on oral, oropharyngeal, and laryngeal cancer (39 days) [175]. However in the Dutch study, the start of SC delay was defined as "the first consultation of ORL-specialist at their tertiary care center [175], instead of referral, which explains the difference, as in Study II the median delay from the referral to the first appointment with an ORL-specialist was 7 days. The median delay of 7 days from the referral to first visit may sound rather long, as potential malignancies should get an appointment within one week of referral. One possible reason explaining this is that the suspicion of a malignancy might not have been clearly articulated in the referrals. This might falsely add to the SC delay, even though the delaying factor might have occurred in PHC. Another possible reason could be that some patients did not show up on the scheduled appointment.

The median SC diagnostic delay was 16 and 13 days in Studies II and III, respectively, which is substantially shorter than the median of four weeks reported by a Brazilian study [25]. Most studies have investigated the TDI (PHC + SC diagnostic interval), so comparison to the literature is more difficult. A systematic review on oral cancer reported a mean TDI of 48 days [29], but even shorter TDIs have been reported. A Finnish study reported a TDI of 21 days, 33 days, and 63 days for cancer of tongue, pharynx, and larynx, respectively [119]. The median treatment delay was 29 days in Study II and 30

days in Study III, which is slightly longer than in a study from the US [30], but shorter than reported in French (35 days), Dutch (39 days), and Brazilian (84 days) studies [25, 120, 131]. The Finnish Ministry of Social Affairs and Health has issued a report stating that the treatment of HNC should start within three weeks of diagnosis [182]. Clearly, only a small portion of the patients is treated according to the recommendation. The Danish fast-track system has even stricter recommendations of seven calendar days for patients having surgical treatment and 11 calendar days for patients having treatment with (C)RT [177].

In our series, patients treated with (C)RT had longer SC delay and twice as long treatment delay compared to patients treated with surgery, which is in line with the literature [30, 120, 121]. This might be due to (C)RT treated patients possibly needing more imaging in planning of the treatment, and dental evaluation and -care must be done well before the initiation of RT. A closer look at the different factors contributing to delays is warranted among this patient group.

If the patient was referred to a Central Hospital prior to the University Hospital, median SC delay was longer in Studies II and III, a finding quite similar to a French study that reported a longer treatment delay for patients treated in Regional Care Centers instead of University Hospitals, General Hospitals, and Private Clinics [131]. However, it is important to notice that all HNCs are treated at the five University Hospitals in Finland, so there are clearly differences in the organizational aspects of HNC treatment between Finland and France. The median delay difference of 9 days between patients referred through Central Hospitals was smaller than we had anticipated. Nevertheless, there is an opportunity for improvement.

The median SC delay was shorter in Study III (but not in Studies I and II) for patients with oral cancer compared to those with OPSCC or laryngeal cancer, a finding similar to a Dutch study [211]. This difference was mostly due to a shorter median diagnostic delay (9 days vs. 14 days for oropharyngeal, and 21 days for laryngeal cancer), a finding similar to another Finnish study [119]. Conversely, many studies have associated glottic tumors with shorter treatment delays compared to oral, and oropharyngeal cancers [30, 120, 121]. In Study III, stage IVA disease had a slightly shorter median SC delay compared to stages II-III, conversely to that, which has been reported in the literature regarding treatment delay [30, 121]. The clinical interpretation of this finding remains unclear. Furthermore, p16 status did not affect SC delay, similar to a study from the US [24]. The associations between different HNC symptoms and SC delays reported in our studies are most likely related to

tumor site and are not independent factors.

None of the patient-related variables were associated with SC delay in Studies I-III. On the other hand, two studies from the US [126, 213] and one Dutch study [121] reported an association between low SES and longer treatment delay. This might be because of the differences of our healthcare systems, especially compared to the insurance-based system used in the US. In Finland, the municipality in which the patient live covers a large portion of the expenses of the patient, and there is also a yearly out-of-pocket cap of 692 euros for all healthcare services and 592 euros for medication expenses for each patient. Therefore, monetary incentives play a much smaller role in the Finnish healthcare system, which possibly explains this difference.

10.1.2 REPRESENTATIVENESS OF OUR PATIENT COHORTS

In our studies, most patients with HNC were male (70-73%), with a mean age of 61–67 years, which is close to the global HNC statistics (75% male) [1], as well as the current situation in Finland (66% male) [33]. In a study by Rogers et al. on oral and oropharyngeal cancer, the portion of males was lower (61%), but the mean age (61 years) was similar to our study [185]. Similarly to our studies, a large study from the US reported that the mean ages for individuals with HPV-related OPSCC (n = 17,625) and HPV-unrelated OPSCC (n = 28,144) were 61 years and 64 years, respectively [59].

Most patients in our studies were current or previous smokers (70-75%), which is greater than in the Finnish general population [39], and quite similar to a finding reported by another study on HNC from Finland (67%) [189]. The percentage of current heavy alcohol users (16%, 21%, and 32% in Studies I, II, and III, respectively) was similar to a study on oral cancer (22% were current, and 12% previous heavy drinkers) [202], but lower than reported in some studies [18, 133]. In a Dutch study on HNC, heavy use of alcohol was reported among 41% of HNC patients [18] and in another study on hypopharyngeal and laryngeal cancer, current heavy use of alcohol (over 5 drinks/day) was present among 49% of the patients [133]. The lower prevalence of heavy alcohol use in Study II among individuals with HR-HPV-related OPSCC compared to HPV-unassociated OPSCC was an expected finding, because of the differences in disease etiologies. The role of tobacco and alcohol as an HNC etiological factor is smaller amongst younger patients, where HR-HPV-related disease is more prevalent [216].The fact that alcohol and tobacco use were more common in our study population compared to the general population was an expected

finding, as tobacco smoking and alcohol consumption are two of the most important etiological factors of HNC, estimated to account for the development of 72% of HNCs, with some variation according to subsite (64% for oral cavity, 72% for pharynx, and 86% for larynx) [216].

The majority of patients with HNC were retired: about half in Studies I and II, and two-thirds in Study III, and around 10% were unemployed in all three studies, similar to findings in another study from Finland [189]. The number of retired patients was as expected considering the mean age of patients with HNC and the usual age of retirement in Finland. The higher number of retired patients in Study III is explained by the higher mean age of the patients compared to Studies I and II. These data are in accordance with another Finnish study on HNC [189]. Primary education was relatively common in our studies (33% in Studies I and II, and 42% in Study III), which is a bit lower than reported in a Finnish (49%), and a Dutch (48%) study on HNC [19, 189]. However, it is important to note that the data were collected over 10 years prior to our research in both of the previously mentioned studies, which might affect the results, as the educational level has gradually increased over time among the Finnish general population [217].

In study I, 82% of HNCs were SCCs, which is lower than reported in the literature and there was a significantly smaller proportion of oral cancers (12% vs. 37-46% reported in the literature) [1, 6]. This was due to our study setting: we only included patients with HNC treated at the Department of ORL. However, a large portion of oral cancer patients diagnosed at our University Hospital District are treated at the Department of Oral and Maxillofacial Surgery, thus leading to a lower number of oral cancer patients recruited, which further explains the lower than usual ratio of SCCs compared to other histologies. In Study III, OPSCC was a bit overrepresented compared to data found in Finnish Cancer Registry [33].

Most HNC patients (65%) had a T1-T2 Class primary tumor, which is similar to a study by Rogers et al. (61%) [185]. In Study II, an even larger portion of the patients (74%) had T1-T2 disease, compared to 61% among patients with OPSCC reported by Jouhi et al. [106]. This might be because p16-positive OPSCC was substantially more common in our patient series compared to Jouhi et al. (79% vs. 58%) [106], and given that HR-HPV-related OPSCCs have generally smaller primary tumors [53]. A little over half of patients with HNC had regionally advanced disease in Studies I and III, similarly to a study investigating HNC survival in 20th and 21st century (n = 52,020), that reported

54% of HNCs as having regional metastases between the years 2002-2006 [6]. Similar to the literature, regional metastasis was more common among HR-HPV-related OPSCC [53, 54]. Distant metastases were considerably rarer in all of our Studies (2-5%), compared to 13% reported in the literature [6]. This is at least partly because distant metastases were more common among the non-included patient group, and a larger portion of these patients were not included because of poor overall health, or they were not interested in participating in the study.

Most patients had advanced stage (III-IV) disease at diagnosis (59% in Study I, and 87% in Study II), similar to a large study (n = 51,655) of unselected HNCs [30], and another study focusing on OPSCC (n = 152) [24]. The differences in stage between Study I and II, is explained by the higher stage at diagnosis among HR-HPV-related OPSCC (91%), which is in accordance with the literature [53, 54, 106].

Furthermore, most OPSCCs (79% in Study II and 68% in Study III) were p16-positive, which is higher than reported by studies from Finland (58%) and Canada (57%) [106, 218]. The prevalence of HR-HPV infection has increased over the years and varies among different populations, possibly explaining these differences. HR-HPV-related OPSCC is more common in Northern Europe and North America, where it is estimated to cause over 70% of all OPSCC [219], but lower incidence rates are observed in Southern Europe and Asia [220]. The lower number of p16-positive patients in Study III compared to Study II was expected and is explained by the differences in the inclusion criteria. In Study III we included only T3-T4 Class tumors, and the fact that p16-positive OPSCCs generally have a smaller primary tumor [53, 106] results in overrepresentation of HPV-unassociated disease. We compared the p16-positive, and p16-negative patient groups in Study II and found that smoking and alcohol use was more common among p16 -negative patients, but p16-positive patient group had more advanced stage at diagnosis, similar to that, which has been reported in the literature [53, 106, 220]. The frequency of different HNC symptoms was similar to the literature [9].

Most of the patients (88-97%) were treated with curative intent. The lower number of patients treated with curative intent in Studies II and III might reflect the higher number of distant metastases in those studies. Furthermore, in Study III we focused on large T3-T4 tumors, so higher number of patients receiving palliative care was expected. Palliative care was more common among excluded patients, which can create biased results as a larger

proportion of patients with more extensive disease and worse overall health conditions are not included.

10.2 PSYCHOSOCIAL FACTORS AND DELAYS IN HNC (STUDY IV)

Multiple psychological and socioeconomical factors have been associated with OS in patients with HNC [93, 94, 141, 142]. Therefore, in Study IV we investigated the psychosocial factors among patients with a large oral, oropharyngeal, or laryngeal SCC, and their relation to delays. Furthermore, we compared the patient cohort to the age- and sex- matched Finnish general population using the FinTerveys 2017 report.

Regarding socioeconomic factors, primary education was more common, and post-secondary education rarer among our patient cohort, in both men and women, between the ages of 40 and 80, compared to the Finnish general population [217]. Unemployment was more common among our patient cohort (between the ages 40–69) compared with the Finnish general population [217]. The lower educational level among HNC patients compared to the general Finnish population was a somewhat expected finding, as a lower educational level has been associated with an increased incidence of oral cancer [84]. The effect of educational level and employment status on delays is reported in Study III. Significantly more patients in our study cohort were unmarried, divorced, or widowed, compared with the Finnish general population (49% vs. 29%), and a greater proportion were living alone (46% vs. 25%), or in households of three or more (8% vs. 31%) [217], similar to a study by Rozniatowski et al. [188]. A study by Väisänen et al. published in 2006, reported similar findings to ours regarding educational level, except that higher proportion of the patients had a spouse (69%) [189]. Furthermore, contrary to our findings, they reported that HNC population did not drastically differ from the Finnish general population [189]. A closer look at the data reveals that the educational level of patients with HNC has not increased between 2006 and 2017, meanwhile the educational level of the Finnish general population has. The differences in marital status between our studies might be because we only included large (T3-T4) tumors. We found no association between marital status, household size, and delays, but a trend of a shorter median patient delay among patients living with children was observed ($p = 0.06$), similar to multiple other studies [15, 21, 22, 185], but not all [188]. Individuals living with children are generally younger and might be more aware of their own health, since they have someone who is dependent on them. The majority of patient's households had adequate funds (59%), similar to the general population (62%) [217]. Financial situation was not associated

with patient, PHC, or SC delays, similar to some studies [22, 185], but not all [16, 21]. As proposed in Study III, this might be because of the differences in the healthcare system between countries, and the comprehensive social support provided by the Finnish government. As expected, smoking and heavy alcohol use were more common among patients with HNC than the Finnish general population [217]. In summary, patients with HNC seem to have lower SES compared to the general population, which was to be expected since lower SES has been associated with increased incidence of smoking [71], and increased incidence of multiple different cancers, including HNC [82-84].

Contrary to our expectations, perceived general health was "good to excellent" among 62% of the patients who answered to this part of the questionnaire, and the average functional capacity was somewhat similar among male, but lower among female HNC patients, compared to the general population [217]. This was unexpected considering these were patients with large T3-T4 primary tumors, with higher numbers of smokers and heavy alcohol users, and a lower SES. Most patients knew about HNC risk factors at least to some degree (76%), although only 40% suspected they might have a cancer, which is still substantially higher than reported in a study from England (13%) [198]. This difference might be because we only included large tumors, that usually cause more notable symptoms. However, knowledge of symptoms and suspicion of cancer was not associated with patient delay in our patient cohort, in contrast to the literature [14, 16, 21, 22].

Regarding psychological variables, patients' social support was measured using the validated SSQ. Half of the patients had a very low to low score in the SSQ, while the remaining half had a moderate to high score. Almost half (45%) of the patients reported never feeling lonely, a third were lonely sometimes and a fifth were often lonely. Almost all patients (94%) had someone close they could talk to (a friend or a family member). A study by Väisänen et al. reported that 87% of patients with HNC had at least two friends and 59% felt they got social support from close people [189]. However, social support and social connections, were not associated with patient delay, similar to findings in the study by Väisänen et al. [189]. Furthermore, in our patient cohort, feelings of loneliness did not affect patient delay. We had suspected that patients with higher social support and more social connections would have sought medical attention sooner, as advice from a partner has been associated with shorter patient delay [188]. Conversely, patients who were told to seek medical attention by someone else had a longer median patient delay (73 days vs. 31 days) in our patient cohort. However, this was most likely due to inverse

causality; patients who delayed seeking medical attention were eventually told to do so by someone else.

Almost a third (30%; 13% mild, 17% moderate to severe) of our patient cohort reported having symptoms of depression, which is in line with the literature [93, 94, 98, 99]. Symptoms of depression were three times more common among male patients with HNC, and three to four times more common among female patients with HNC, compared to the general population [217]. Not surprisingly, since the patients answered the questionnaire after the cancer diagnosis, during which depression symptoms have been observed to be fairly common (13% - 40%) [98]. Symptoms of depression were not associated with patient, PHC, or SC delays, a finding similar to a study by Rozniatowski et al. [188]. This was an expected finding, since due to our study setting, we were not able to gather information about depression symptoms prior to the HNC diagnosis, which might have influenced patient delay. The small size of our patient cohort might further explain why we did not find statistically significant differences. Cynical hostility was not associated with any delays, and no other studies have investigated this matter. However, cynicism towards other people was a bit more common (around 10%) among male patients with HNC aged over 50, compared to the Finnish general population [217]. Since cynical hostility usually remains constant throughout an individual's life course, we expected to observe longer patient delays among patients with higher score in cynicism, since trust for authorities is generally lower among these individuals, which might lead to the prolongation of seeking medical attention.

10.3 CHALLENGES A GP FACES WHEN DIAGNOSING HNC (STUDY V)

In study V, we investigated the patient material from which a GP working in a healthcare center needs to identify HNC patients. A total of 111 new HNCs were diagnosed from the Helsinki population of 635,181 during 2016. Of the patients with HNC, 36% had contacted PHC center, 28% a dentist, 21% were referred by a private physician, 11% were referred from hospital, and the remaining 4% from elsewhere. Dentists referred almost two-thirds of oral cancer cases to SC. These findings are in line with the literature [204, 205]. In a study by Ligier et al. 21% of HNC patients were referred to SC by a dentist [206], and in another study on oral cancer, 44% of oral cancer patients were referred to SC by dentists [207].

The median PHC physician-related delay (from the initial appointment to the referral to SC) was only 5 days, and only three patients had very long physician-related delays of over three months. This is substantially low, as most other studies investigating PHC delay instead report PHC physician-related delay, without considering the system delay that happens prior to the first appointment. The shortest median PHC delay found in other studies seems to be 8 days in a study from the US on OPSCC [24]. A closer look reveals that they have investigated PHC physician delay, as we have in this Study V. In our study, half of the HNC patients were referred to SC at the initial visit, 43% at the second, and 7% at the third visit, which is similar to two other studies investigating HNC and oral cancer [201, 208], but less than in a systematic review on OPSCC [207]. Most of these additional visits were related to a FNAC, the remaining being clinical follow-ups or other visits. Even though PHC physician-related delay was substantially low, differences in clinical practice occurred regarding where the FNAC was taken. To further shorten these delays, a clear division of labor between PHC and SC, should be implemented.

In comparison to the 40 new HNCs, a total of 242,211 patients visited PHC center in the City of Helsinki, resulting in nearly 500,000 outpatient visits in 2016. Therefore, one new HNC was detected for every 6000 patients or 12,500 visits to a PHC center. This is significantly higher than in a study by Alho et al., which reported a detection rate of one new HNC in every 63,000 visits [201]. This difference might be due to the differences between our study methodologies: we collected all HNCs diagnosed in the city of Helsinki during 2016 and all patients and outpatient visits to PHC during the same year. Alho et al. collected data on 24 different randomly selected PHC centers in Finland over four separate weeks, and compared that with data on patients with HNC diagnosed in Northern Finland between 1986 and 1996 [201]. If these outpatient visits were evenly distributed across all 380 GPs working in the PHC center in the city of Helsinki, each GP would have 1315 appointments with 637 different patients during a calendar year. This would result in, on average, a GP detecting one new HNC per every 10 years of practicing, which is a higher rate than that reported by Alho et al. [201].

Of these 242,211 patients, 11,896 patients (5%) visited a GP because of a symptom that might be caused by HNC, which is significantly lower than 11% reported by Alho et al. [201]. This is most likely due to differences in ICD-10 diagnosis code selection and our study design. From these 11 896 patients, 33 new HNCs were diagnosed, while the remaining 7 did not have a relevant ICD-10 diagnosis code used.

Stratification according to certain clinical traits results in a higher detection rate of HNC, and certain cancer risk groups emerged. The prevalence of HNC among 60-year-old or older male patients seeking medical care with one of the six symptoms mentioned in MSC varied between 0.5% and 3%, depending on the symptom (Table 3). This is impressively high, considering that the most known HNC risk factors (tobacco and alcohol) were not taken into consideration, and there was otherwise no information available about symptom duration or other apparent causes for the signs/symptoms. This is important information for GPs for them to be able to better estimate the likelihood of HNC, considering the patient's age, sex, and main symptoms. However, it is important to distinguish the difference between an ICD-10 diagnosis code used during an appointment, and the overall prevalence of a certain HNC symptom. HNC symptoms are more common than the reported 5% in our study, because a GP usually uses only a single ICD-10 code even if the patient has multiple symptoms. This bias is also present if the patient visited a GP for multiple different reasons. Patient population between the urban city of Helsinki and the rest of Finland might differ, which must be considered when generalizing these results. Furthermore, the higher ratio of MDs to patient population in Helsinki area and the generally good availability of SC resources, might further affect these results. Therefore, too precise estimates based on this study should not be made. However, this is currently the only viable way to study the epidemiology of HNC symptoms in large patient populations, until the emergence of properly working, structured medical record systems.

10.4 STUDY STRENGTHS AND LIMITATIONS

In Studies I-IV, we collected prospective patient cohorts and identified all patients who fulfilled the inclusion criteria. The study recruitment rate was fairly good in Study I (70%) and II (75%), but significantly worse in Studies III and IV (38%). The data were collected using fixed, multiple-choice questions and from the hospital medical records. In Study IV regarding the psychological data, validated questionnaires were used. Delays were analyzed as continuous variables, and multivariate analyses were performed in Studies I-III. The patients were asked to provide the most accurate data on the onset of signs/symptoms and of the initial contact to an HCP, and these data were double-checked from the hospital medical records to check for discrepancies to minimize recall bias. No major discrepancies were found. This further allowed us to perform a comprehensive patient withdrawal analysis.

The biggest limitation in Studies I-IV was our small sample size, which might explain why some associations were not statistically significant. This is a notable limitation affecting all HNC related research as it is a rare malignancy. Furthermore, the tumor characteristics between different HNCs vary greatly depending on tumor histopathology, tumor site, and aggressiveness, which further affect the results emphasizing the effect of small patient cohort, especially in Study I, which focused on an unselected set of HNC patients. The low recruitment rate in Studies III and IV was most likely because of the difficulties in recruitment due to a nationwide multicenter approach, resulting in a lower number of administered questionnaires to the patients who fulfilled the inclusion criteria (20% did not receive the questionnaire), and a further 27% did not return it, despite receiving a reminder via mail. Distant metastases and palliative care were significantly more common among the non-included patients, indicating that these patients had more advanced disease and poorer general health, creating bias to our results. However, it is understandable that patients with very poor general health, might not be able to fill out a rather long patient questionnaire shortly after receiving a cancer diagnosis.

The patients' perception of different bodily sensations and signs vary, creating bias in the reported patient delay. Similarly, the motivation to answer long questionnaires varies between patients, also creating bias. However, these biases are unavoidable in a questionnaire-based study and the motivational bias was minimized by double-checking responses against all available data from the hospital medical records. The retrospective nature of questionnaire-studies might affect a patient's ability to accurately recall the onset of their symptoms, as time passed, creates bias to the results (recall bias). We tried to minimize this by checking the delay data on hospital medical records, where usually the ORL-specialist asks about the symptom onset during the initial visit to SC. Because of the study setting, we were only able to study associations between different variables and delays, not causality.

In Study V, we thoroughly investigated the hospital medical records, and PHC medical records for all 40 patients referred to SC from Helsinki PHC centers, and PHC delay times were accurately gathered from these databases. One limitation of this study is the varying tendency to use the most accurate ICD-10 diagnosis code that represents the patients sign/symptom, and the use of multiple such diagnosis codes by the GPs. Among 18% of the HNC patients, no diagnosis code was used at all, or it was completely uninformative regarding the patient's signs/symptoms. This creates bias in our results. Furthermore, ICD-10 diagnosis codes are not very accurate even if properly used. For

example, breathing difficulties can be due to an array of clinical scenarios like myocardial infarction, asthma, or an item blocking the airway.

10.5 FUTURE ASPECTS

Patient delay is an important factor influencing delay before the initiation of curative treatment, and finding different ways to shorten it might result in better prognosis, QoL, and lower treatment costs. Patients reacted quickly to a lump in the neck, but hoarseness resulted in longer patient delay. Patients with HNC typically have lower educational level, are more often unemployed, live in smaller households, are more often tobacco smokers, and heavy users of alcohol; these factors need to be considered when figuring out effective ways to promote knowledge on HNC in an effort to shorten patient delay. Information campaigns aimed at the public have been shown to be ineffective, and primarily provide health benefits to individuals with high SES [36]. Therefore, a more tailored approach towards high-risk HNC groups might end up being more effective. This should be preferably done in a way that minimizes the need for patients' own initiative, to further improve the effectiveness. Opportunistic interventions during other visits to HCPs (nurse visits, dental visits, pharmacy) might be good places to intervene for patients belonging to high-risk groups, however, more research is needed around this matter.

PHC seemed to work effectively, and GPs referred patients with HNC promptly to SC. To further streamline this process, a clear division of labor between different diagnostic procedures (FNAC and imagining) must be settled. It seems that most of the PHC delay is system-related (a median PHC delay of 13-20 days vs. 5 days for PHC physician-related delay), so more effort should be placed on ensuring better availability of PHC services for the at-risk patients who seek medical care because of a symptom/sign potentially caused by a malignancy. This can be achieved by educating nurses who book the physician appointments, and/or by increasing PHC resources, but more research around PHC system delay is needed.

SC delay was long, especially among patients with HNC treated with (C)RT, compared with Denmark, where much effort has been placed on investigating and improving the processes for fast diagnosis and treatment of HNCs in both PHC and SC. However, the direct implementation of the Danish model is not feasible in Finland, as it relies heavily on the high number of private ORL-specialists available in Denmark. Furthermore, the aging of the Finnish population raises the need and expenses of all healthcare services, which may

reflect on HNC treatment, even though fast treatment of malignancies is still prioritized. This is further impacted by the rising incidence of HR-HPV-related OPSCC, and even though the prevalence of tobacco smoking is reducing, the risk of developing a HNC stays elevated among the ex-smokers. Furthermore, the health effects of other upcoming nicotine and tobacco products are still fairly unknown. Future research is needed to find cost-effective ways to further improve HNC management across the entire cancer continuum.

Depression is common among patients with HNC. Depression has been shown to be associated with worse survival, so it needs to be considered in clinical practice to ensure effective treatment. Larger patient cohort studies are needed in the future to study the medical care seeking of patients with HNC with regards to different psychological conditions, preferably in a study setting, where these aspects can be measured before HNC diagnosis.

Systematic monitoring of different healthcare-related delays would be important when assessing the quality of care among patients with HNC, as it affects prognosis and QoL. This should be done in an automated way using the hospital and PHC medical records, and in a way that minimizes the need for additional workforce and resources. The measured time intervals, and the acceptable delays for each interval, should be clearly defined, and the system should have an automated notification system for when these time intervals are being frequently exceeded.

11.CONCLUSIONS

I. The median patient, PHC, and SC delays were 35, 20, and 49 days, respectively. A lump in the neck got patients to seek medical care promptly, whereas hoarseness and difficulties breathing were associated with longer patient delay. Regarding tumor-related factors, the primary tumor site and presence of regional metastases were associated with patient delay. The number of visits, whether a follow-up appointment was scheduled or not, and whether the patient initially sought medical attention from a private ORL-specialist, were associated with PHC delay.

II. The median patient, PHC, and SC delays among OPSCC patients were 30, 15, and 54 days, respectively. p16 status did not affect delays. A high number of symptoms was associated with a longer patient delay. Unemployed or retired patients also had longer patient delays. The number of visits to PHC, and whether a follow-up visit was scheduled, affected PHC delay. Patients treated with (C)RT, had significantly longer SC delay compared patients treated with surgery.

III. The median patient, PHC, and SC delays among patients with large (T3-T4) oral, oropharyngeal, and laryngeal cancer were 58, 13, and 43 days, respectively. Patients with lower levels of education and heavy use of alcohol reported longer patient delays. Hoarseness and difficulties breathing were also associated with longer patient delay. Treating HNC symptoms as an infection led to longer delays in PHC. Patients treated with surgery had significantly shorter SC delays. Patients who were treated with palliative intent had long patient delays, but short PHC delays.

IV. Depression was common among patients with HNC. Compared to the Finnish general population, patients with HNC had a lower educational level, a lower employment rate, were more often tobacco smokers, and heavy users of alcohol. However, we found no association between psychosocial factors and patient delay.

V. Of all HNCs diagnosed at the Helsinki area, a little over a third of the patients initially sought medical attention from a PHC center. For each of these patients with HNC, a GP working at the PHC center sees 6000 other patients, of whom a hundred have sought medical attention because of a sign/symptom that might be caused by HNC. Still, the median physician-related PHC delay was just 5 days.

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