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ISBN 978-951-29-9605-6 (PRINT)
ISBN 978-951-29-9606-3 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2024

To my family

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Clinical Medicine
Otorhinolaryngology – Head and Neck Surgery
EERO KYTÖ: Follow-up of Head and Neck Cancer Patients after Treatment
Doctoral Dissertation, 118 pp.
Doctoral Programme in Clinical Research
January 2024

ABSTRACT

Post-treatment follow-up of head and neck cancer patients is crucial due to their high risk of disease recurrence and increased likelihood of developing secondary cancers. Rehabilitation requires multiple visits to different healthcare professionals and addressing challenges with eating, speaking, breathing, and cosmetic concerns caused by treatments. As the number of these cases continues to rise, additional resources are needed for adequate monitoring.

This thesis aimed to investigate the appropriate duration of routine follow-up, the significance of PET imaging at the 1-year mark after treatment completion, the use of telemedicine in surveillance, and the long-term effects of head and neck cancer treatments. The research data included all head and neck cancer patients treated at Turku University Hospital between 1999 and 2008 (I), those under surveillance for head and neck cancer between 23 March and 27 May 2020 (II), patients who received radiation therapy for head and neck cancer between 2010 and 2015 (III), and head and neck cancer patients treated at Turku University Hospital and Tampere University Hospital between 2010 and 2015 (IV).

We found that routine 3-year follow-up was sufficient for head and neck cancers. However, patients should have the opportunity to contact healthcare providers in case of new symptoms even after this period, to promptly arrange appointments and necessary additional examinations (I). After the first year of surveillance, some follow-ups could potentially be conducted by phone without delaying the detection of disease recurrence (II). Difficulty in swallowing and hypothyroidism were the most common of the studied long-term side effects of radiation therapy. The dose of radiation to the neck did not appear to influence the occurrence of side effects. Osteoradionecrosis was observed only in patients with oral cavity cancer (III). Routine PET imaging at the 1-year mark after treatment completion did not improve the 5-year prognosis of the whole imaged patient group or of any particular subgroup (IV).

KEYWORDS: head and neck cancer; squamous cell carcinoma; follow-up; PET imaging; radiation therapy; late effects; telemedicine

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Korva-, nenä- ja kurkkutautioppi
EERO KYTÖ: Pään ja kaulan alueen syövän sairastaneiden seuranta hoidon jälkeen
Väitöskirja, 118 s.
Turun kliininen tohtoriohjelma
Tammikuu 2024

TIIVISTELMÄ

Pään ja kaulan alueen syöpäpotilaiden seuranta hoidon jälkeen on tärkeää, koska heillä on korkea taudin uusiutumisriski sekä suurentunut riski saada toinen syöpä. Potilaan kuntoutus vaatii useita käyntejä monilla eri terveydenhuollon ammattiryhmillä johtuen hoitojen aiheuttamista ongelmista syömisessä, puhumisessa ja hengittämisessä sekä kosmeettisista haitoista. Näiden syöpien määrä on lisääntymässä, joten seurantaankin tarvitaan lisää resursseja.

Tämä väitöskirjatyö pyrki selvittämään rutiininomaisen seurannan sopivaa pituutta, PET-kuvantamisen merkitystä vuoden kohdalla hoitojen päättymisestä, etälääketieteen käyttöä seurannassa sekä pitkäaikaishaittoja pään ja kaulan alueen syöpien hoidon jälkeen. Tutkimusaineistona olivat kaikki Turun Yliopistollisessa keskussairaalassa vuosina 1999–2008 hoidetut pään ja kaulan alueen syöpäpotilaat (I), pään ja kaulan alueen seurannassa olevat syöpäpotilaat 23.3.2020 – 27.5.2020 (II), sädehoidetut pään ja kaulan alueen syöpäpotilaat 2010–2015 (III) sekä Turun Yliopistollisessa keskussairaalassa ja Tampereen Yliopistollisessa keskussairaalassa hoidetut pään ja kaulan alueen syöpäpotilaat 2010–2015 (IV).

Totesimme rutiininomaisen kolmen vuoden seurannan riittävän pään ja kaulan alueen syövissä, mutta potilailla pitää olla mahdollisuus ottaa yhteyttä hoitavaan tahoon uusien oireiden ilmetessä myös tämän jälkeen, jotta voidaan nopeasti järjestää aika vastaanotolle sekä tarvittaviin lisätutkimuksiin (I). Ensimmäisen vuoden seurannan jälkeen osa kontrolleista voitaisiin järjestää puhelimitse ilman, että taudin mahdollisen uusiutumisen toteaminen näyttäisi viivästyvän (II). Sädehoidon yleisimmät pitkäaikaishaittavaikutukset tutkituista olivat nielemisvaikeus ja kilpirauhasen vajaatoiminta. Kaulalle kohdistetun sädeannoksen suuruudella ei todettu olevan vaikutusta haittavaikutusten esiintymiseen. Luukuoliota todettiin vain potilailla, joilla oli suuontelon syöpä (III). Rutiininomainen PET-kuvantaminen vuoden kohdalla hoitojen päättymisestä ei parantanut kuvannetun potilasjoukon eikä myöskään minkään tutkitun alaryhmän 5-vuotisennustetta (IV).

AVAINSANAT: pään ja kaulan alueen syöpä; levyepiteelikarsinooma; seuranta; PET-kuvantaminen; sädehoito; myöhäishaitat; etälääketiede

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Abbreviations

FDG	2-[18F]-fluoro-2-deoxy-d-glucose
COVID-19	Coronavirus 19 / SARS-CoV-2
CT	Computed tomography
DNA	Deoxyribonucleic acid
DFS	Disease-free survival
EBV	Epstein-Barr virus
END	Elective neck dissection
FNA	Fine needle aspiration/fine needle biopsy
Gy	Gray
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell cancer
HPV	Human papilloma virus
IMRT	Intense modulated radiotherapy
IQR	Interquartile range
MRI	Magnetic resonance imaging
NBI	Narrow band imaging
NCCN	National Comprehensive Cancer Network
ND	Neck dissection
NPC	Nasopharyngeal carcinoma
OPC	Oropharyngeal carcinoma
OPSCC	Oropharyngeal squamous cell cancer
ORN	Osteoradionecrosis
OS	Overall survival
PET	Positron emission tomography
RT	Radiation therapy
SPECT	Single photon computed tomography
TNM	Tumour, node, metastasis classification
TORS	Transoral robotic surgery
TTMV	Tumour tissue modified viral
US	Ultrasound/ultrasonography
VMAT	Volumetric modulated arc therapy
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Kytö E, Haapio E, Minn H, Irjala H. Critical review of the follow-up protocol for head and neck cancer patients. *J Laryngol Otol*, 2019; 133(5): 424–429.

II Kytö E, Haapio E, Kinnunen I, Irjala H. Effect of coronavirus disease 2019 on recurrences and follow up of head and neck squamous cell carcinoma. *J Laryngol Otol,*2021; 135(4):344–347.

III Ranta P, Kytö E, Nissi L, Kinnunen I, Vahlberg T, Minn H, Haapio E, Nelimarkka L, Irjala H. Dysphagia, hypothyroidism, and osteoradionecrosis after radiation therapy for head and neck cancer. *Laryngoscope Investig Otolarygol*, 2021; 7(1): 108–116s.

IV Kytö E, Karjalainen M, Markkanen S, Vahlberg T, Raittinen L, Taulu M, Hirvonen J, Isler S, Laranne J, Irjala H, Halme E. Benefit of routine one-year PET/CT in head and neck cancer follow-up (manuscript)

1 Introduction

Head and neck cancer (HNC) is a heterogeneous group of tumours located in the head and neck region. Histologically, over 90% are squamous cell cancers. In this thesis, we concentrate mostly on head and neck squamous cell cancer (HNSCC). The main subsites of HNSCC are the oral cavity, oropharynx, larynx, and hypopharynx. Known risk factors for HNSCC include smoking and heavy consumption of alcohol, and human papillomavirus (HPV) is gaining importance as an aetiological factor, especially in oropharyngeal squamous cell cancer (OPSCC) (Castellsagué et al., 2016).

HNC can be treated with surgery, radiation therapy (RT), chemotherapy, or a combination of these. Generally, early-stage HNSCC patients receive single-modality treatment, whereas advanced stages often require combined therapy. Immunotherapeutic drugs are a novel treatment method for recurrent or metastasised HNC. Adverse effects of treatments are common, especially dysphagia, oral mucositis, and xerostomia often presenting after RT (Pezdirec et al., 2019). Disfigurement and problems with speaking and breathing are common after major surgery and reconstructions are often needed. Optimising treatment is important to save patients from unnecessary adverse effects while treating them effectively.

Follow-up after treatment is under debate. Most major HNC associations and national guidelines recommend post-treatment follow-up for up to 5 years and often annually after that. However, many studies have challenged these protocols, suggesting a length of 3 years instead. Some studies also endorse more tailored follow-up protocols depending on the subsite and stage of the disease.

PET/CT or PET/MRI is known to be beneficial for evaluating the results of treatment 3–4 months after HNSCC treatment. However, as there is no strong evidence for the use of any modality of imaging beyond this period as part of routine surveillance, current protocols recommend it only when there is a suspicion of recurrent disease. Current practices vary, but resources could be saved if later imaging is shown to be unhelpful, or detection improved if it is found to be beneficial.

Telemedicine is surging in popularity for the follow-up of cancer patients, especially in the wake of the COVID-19 pandemic. Among other benefits, it can save resources and patients' travelling time while reducing the risk of infection. However, lack of clinical examination is the major limitation. The optimal use of telemedicine in HNC patients is unclear and needs further investigation.

2 Review of the Literature

2.1 Head and neck cancer (HNC)

2.1.1 Epidemiology

HNC is the sixth most common cancer globally, with 890,000 new cases and 450,000 deaths reported in 2018 (Bray et al., 2018; Ferlay et al., 2019; Siegel et al., 2020; Sung et al., 2021). This contrasts with 650,000 new cases worldwide in 2013, showing that the incidence of HNC is growing (Chaturvedi et al., 2013). In 2021, 950 new cases were diagnosed in Finland and the incidence is trending up by around 2% annually (Seppä et al., 2021).

There are many types of HNC with widely varying histology, but over 90% of occurrences are HNSCC. Typical anatomical sites for HNSCC are the lip and oral cavity, oropharynx, nasopharynx, hypopharynx, sinonasal area, larynx, and upper oesophagus. These arise from the mucosa or lining of the upper aerodigestive tract. Other cancers of the head and neck arise from the skin, salivary glands, soft tissue, bone, thyroid, or parathyroid glands, and the histology varies far more. In 2–5% of cases of HNSCC the primary site remains unknown (Ye et al., 2021). HNC tends to metastasise to the regional lymph nodes of the neck and can generate distant metastases, most commonly in the lungs (Ferlito et al., 2001).

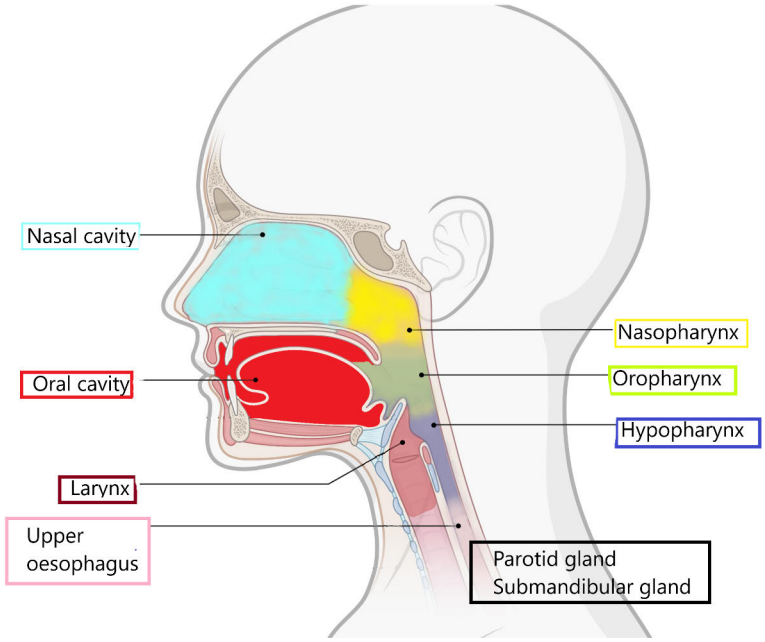

Figure 1. Head and neck cancer sites. Modified from Wikimedia Commons with permission of Creative Commons 4.0

Worldwide, there are major differences in HNC incidence between developing countries and countries with a higher sociodemographic index (Gormley et al., 2022). In the latter, cancer rates in subsites like the larynx and hypopharynx are declining due to cessation or reduction of tobacco and alcohol use (Fitzmaurice et al., 2017).

Cigarette smoking is the most important risk factor for HNC (Lassig et al., 2012). Other substantial risk factors are age and heavy use of alcohol (Denissoff et al., 2022; Hashibe et al., 2007). Cessation of tobacco use around the age of 50 has been found to reduce the risk of upper aerodigestive cancer by 50% and at the age of 30 by 90% (Bosetti et al., 2008). High-frequency alcohol consumption is also known to be an independent risk factor for HNC, and when combined with concurrent smoking the risk is much higher (Denissoff et al., 2022; Hashibe et al., 2007; Lewin et al., 1998). The risk of getting HNC increases with age, but the median age fluctuates depending on the site and epidemiological factors (Rettig & D'Souza, 2015).

Oncogenic viruses like HPV and Epstein-Barr virus (EBV) are also associated with an elevated risk of HNC, the former especially in oropharyngeal and the latter in nasopharyngeal carcinoma (NPC). Some geographical areas are associated with an elevated risk of developing these cancers, especially in the case of NPC which is more common in southern China and some Pacific islands (Lin et al., 2014; Palser et al., 2015).

Mucosal premalignant conditions and poor dental hygiene are risk factors for oral cancer. Exposure to hardwood dust has been linked to a higher risk of NPC and sinonasal

cancer. Immunosuppressive drugs, especially after organ transplants, are known to pose a risk for HNC (K. F. Lee et al., 2016; Taborelli et al., 2018). Consumption of meat has been reported to increase the risk of oral cancer, whereas eating fruits and vegetables has been associated with a reduced risk (Bravi et al., 2012; Edefonti et al., 2012; Pavia et al., 2006). However, evidence for the role of diet in HNSCC incidence is weak and the clinical significance limited (Barasch & Litaker, 2011).

2.1.1.1 Role of HPV in HNC

Alongside the traditional risk factors of tobacco and alcohol, HPV is one of the major risk factors for OPSCC. Although HPV is also a factor in oral cavity and laryngeal cancers, its role is much weaker than in oropharyngeal cancer (Castellsagué et al., 2016). HPV and smoking are also known to interact and further increase the risk (Anantharaman et al., 2016; Tumban, 2019).

The incidence of HPV-related OPSCCs is growing fast and is thought to be behind the observed surge in HNC. Globally, 33% of OPSCCs have been reported as HPV-positive, but there is wide global variation in prevalence depending on the geographical region (Anantharaman et al., 2017; Carlander et al., 2021; Mehanna, Franklin, et al., 2016). In a recent study by Carlander et al., the prevalence was 70% in Sweden and 22% in Japan (Carlander et al., 2021). Although there are many types of HPV, subtype 16 poses the greatest risk for HPV-positive OPSCC. This, together with the second most common subtype, 18, accounts for around 90% of HPV-related oropharyngeal and oral cavity cancers (de Sanjosé et al., 2018; Hobbs et al., 2006).

The median age of patients first presenting with HPV-related HNSCC is much lower than among those with HPV-negative HNSCC, 53 years versus 66 years (Chaturvedi et al., 2008). The prevalence of HPV-related HNSCC has previously been reported to drop with increasing age, but in a review of recent studies, Lechner et al. noted that the burden of disease has begun to shift towards older men (Lechner et al., 2022). A risk factor for HPV-positive OPSCC is sexual behaviour, the most consistently identified factor being the number of oral-sex partners (Gillison et al., 2015; Gooi et al., 2016; Heck et al., 2009). The HPV vaccine is considered effective against HPV infection, and the incidence of cervical cancer, in which HPV is known to be a factor, is decreasing. Initially, the vaccine was available only to girls but now is given also to boys, as it is known to be linked to OPSCC and male genital cancers. Although the incidence of HPV-positive OPSCC has overtaken that of cervical cancer, the beneficial effect of HPV vaccinations on HNSCC is expected to be seen by 2060, given that the average latency from HPV infection to OPSCC is assumed to be 10–30 years (Gillison et al., 2015).

HPV positivity is a well-known favourable prognostic factor for HNSCC patients treated with standard chemotherapy and RT (Argiris et al., 2014; C. H.

Chung et al., 2014; Fakhry, Psyrri, et al., 2014), but its value as a predictor of immunotherapy response remains unclear (Roof & Yilmaz, 2023). Due to the better response to RT and chemotherapy and because the patients are generally younger and fitter with fewer comorbidities, the prognosis is usually better in HPV-related cancers (Chaturvedi et al., 2011). In a review by VanderWalde et al., older people with HNC did not have worse survival rates. Instead, comorbidities and functional age were a better prognostic factor of treatment outcome (VanderWalde et al., 2013).

2.1.2 Diagnosis

The symptoms of HNC vary depending on the site of the primary tumour, regional or distant metastases, and possible secondary tumours. HNC may also be asymptomatic. Symptoms can be caused by local effects of the primary tumour, such as pain in an ulcerative tongue tumour, repetitive epistaxis in sinonasal tumours, difficulty swallowing because of a mass in the base of the tongue, or hoarseness due to a tumour in the larynx. Metastases can cause symptoms like a mass in the neck from enlarged lymph nodes. Asymptomatic tumours may sometimes show up as part of an unrelated examination.

Suspicion of HNC usually arises from a patient's symptoms, and referral to a head and neck surgeon should be arranged without delay. Previous risk factors are very important to consider. Primary clinical examination including palpation, mirror examination, and flexible nasofiberoscopy should indicate a need for further examinations.

If possible, a needle biopsy should be taken from the primary tumour as a first step to diagnosis and should be relatively easy in an outpatient clinic if the tumour is visible. Fine-needle aspiration (FNA) is a common procedure when there is a palpable mass in the neck, and it can also be guided by ultrasound. If it does not provide enough information, a biopsy can be done next. If a node biopsy is needed, complete nodal resection is preferable to prevent extracapsular metastatic spread (L. Q. M. Chow, 2020).

Imaging modalities when HNC is suspected or diagnosed include ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) combined with CT or MRI. US is appropriate for characterising a neck mass; CT and MRI are used to define the extent of the primary tumour and possible locoregional metastases. MRI is superior to CT when evaluating soft tissues and local bone marrow involvement, while CT is better for evaluating lung metastases or metastatic bone involvement (Chong & Fan, 1997b; N.-N. Chung et al., 2004; Eisen et al., 1996; J. Sun et al., 2015). MRI is also better for defining extracapsular nodal extension, which has a prognostic value (Mesia et al., 2021; J. Sun et al., 2015).

Positron emission tomography (PET)/CT has become increasingly important in the care of patients with HNSCC, and HNC was one of the first indications for PET (VanderWalde et al., 2014; W. L. Wong et al., 1997). PET/CT is now a key diagnostic tool for HNC and provides more accurate staging of disease (Ceylan et al., 2018; Wai Lup Wong, 2021). It is especially important for detection of the primary site in patients who present with a malignant neck lymph node and no evidence of primary cancer in the upper aerodigestive tract mucosa (Dong et al., 2008; Rusthoven et al., 2004; W. L. Wong et al., 2012). PET/CT has led to more accurate diagnoses and has contributed to improved outcomes in HNC patients (Ceylan et al., 2018).

Endoscopic examinations are needed especially when the primary site is unknown or a primary tumour is invisible. These include flexible bronchoscopy, rigid oesophageal examination, and gastroscopy under general anaesthesia. Endoscopic examinations provide an opportunity to take a biopsy from a suspect site or, in an unknown primary case, to perform a tonsillectomy and mucosectomy of the root of the tongue, these being the most common primary sites when a tumour is not visible. Narrow Band Imaging (NBI) is an endoscopic technique that only allows the passage of blue and green light. As the vasculature and architecture of tumours change during carcinogenesis, NBI enables early identification of mucosal tumours by recognising these vascular alterations (Kumagai et al., 2002).

Early recognition of symptoms and signs is important for prompt diagnosis. A delay in diagnosis in the care pathway of HNC usually leads to progression of the cancer and worsening of prognosis (Murphy et al., 2016; Patel & Brennan, 2012; Seoane et al., 2016; Teppo & Alho, 2008). In developing countries, diagnosis is often relegated to advanced stages of the disease due to a lack of adequate medical services (Vartanian et al., 2004).

A novel method for diagnosing cancers is liquid biopsy, which measures circulating cell-free tumour tissue DNA from plasma. This is easily done from a blood sample or other body fluids. It could increase the efficiency of the diagnostic process, reducing diagnostic delay and cutting the number of unnecessary diagnostic procedures. It could also be used, for example, during screening and follow-up (Connal et al., 2023).

2.1.2.1 Staging and TNM

Staging of HNC is based on the site of the primary tumour and follows the TNM (Tumour, Node, Metastasis) classification developed by the Union for International Cancer Control (UICC), of which the most recent 8th edition was published in 2017 (UICC, 2017). Accurate staging is the most important factor guiding therapeutic decision making (Argiris et al., 2008). Stages I and II are early stages and III and IV advanced. The T class describes the extent of the primary tumour. If there is no

metastatic spread, T1-T2 tumours are usually described as early stage and T3-T4 as advanced stage tumours. The N class describes lymph node involvement and the M class distant metastases. The most significant update in the 8th edition creates a separate staging algorithm for high-risk HPV-associated cancer of the oropharynx, distinguishing it from oropharyngeal cancer (OPC) with other cause (Lydiatt et al., 2017). The 8th edition of the TNM classification seems to lead to better pre-treatment staging for both HPV-positive and HPV-negative diseases (Dal Cin et al., 2023). Unknown primary was also staged for the first time in the 8th edition.

Table 1: Clinical TNM classification for lip and oral cavity cancers according to the **a)** 7th, **b)** 8th edition of UICC. (ENE = extranodal extension, DOI = depth of invasion) (UICC, 2009, 2017).

a) Lip and Oral cavity TNM 7th edition

T	Primary tumour	N	Regional lymph nodes	M	Distant metastasis
X	Primary tumour cannot be assessed	**X**	Regional lymph nodes cannot be assessed	**0**	No distant metastasis
0	No evidence of primary tumour	**0**	No regional lymph node metastasis	**1**	Distant metastasis
1	≤ 2 cm	**1**	Ipsilateral single ≤ 3 cm		
2	> 2–4 cm	**2a**	Ipsilateral single > 3–6 cm		
3	> 4 cm	**2b**	Ipsilateral multiple ≤ 6 cm		
4a	Lip: invades through cortical bone, inferior alveolar nerve, floor of mouth or skin	**2c**	Bilateral, contralateral ≤ 6 cm		
	Oral cavity: invades through cortical bone, deep/extrinsic muscle of tongue, maxillary sinus or skin of face	**3**	> 6 cm		
4b	Invades masticator space, pterygoid plates, skull base or encases internal carotid artery				

b) Lip & Oral cavity TNM 8th edition

T	Primary tumour	N	Regional lymph nodes	M	Distant metastasis
1	≤ 2 cm and DOI ≤ 5 mm depth of invasion*	**X**	Regional lymph nodes cannot be assessed	**0**	No distant metastasis
2	2–4 cm and DOI ≤ 10 mm	**0**	No regional lymph node metastasis	**1**	Distant metastasis
3	> 4 cm or DOI > 10 mm depth of invasion	**1**	Ipsilateral single ≤ 3 cm, without ENE		
4a	Lip: Tumour invades through cortical bone, inferior alveoral nerve, floor of mouth, or skin (of the chin or nose)	**2a**	Single ipsilateral 3–6 cm, without ENE		
	Oral cavity: Tumour invades through cortical bone of the mandible or maxillary sinus, or invades the skin of face	**2b**	Ipsilateral multiple, none > 6 cm, without ENE		
4b	Lip and oral cavity: Tumour invades masticator space, pterygoid plates, or skull base, or encases internal carotid artery	**2c**	Bilateral or contralateral, none >6 cm, without ENE		
		3a	> 6 cm, without ENE		
		3b	Single or multiple, with clinical ENE		

* Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumour as T4a.

Table 2. Clinical staging for **a)** lip and oral cavity **b)** cervical node unknown primary according to the 8th edition of UICC (UICC, 2017).

a)

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1,T2,T3	N1	M0
IVa	T4a	N0, N1	M0
	T1,T2,T3,T4a	N2	M0
IVb	Any T	N3	M0
	T4b	Any N	M0
IVc	Any T	Any N	M1

b)

Stage	T0	N	M0	Stage
III	T0	N1	M0	III
IVa	T0	N2	M0	IVa
IVb	T0	N3	M0	IVb
IVc	T0	N1,N2,N3	M0	IVc

2.1.3 Treatment modalities

Selection of the treatment modality depends on many different factors such as the patient's condition, tumour specificity, stage of the disease, and modalities available. The head and neck region is complex and the type of treatment should be optimised considering anatomic, functional, and cosmetic outcomes. If possible, single-modality treatment is preferred because of its lower morbidity compared to multi-modality treatment. This is usually possible in early-stage tumours, but advanced disease almost always requires combined treatment when curative intent is feasible. In early-stage tumours, single-modality treatment can be surgery only or RT. When surgery as a single-modality treatment is not sufficient, for example when the disease is at an advanced stage, RT should be combined, with or without concurrent chemotherapy, to achieve a curative result. Other risk factors that increase the risk of local recurrence are perineural invasion, lymph vascular invasion, and extranodal invasion. Decisions on the most appropriate treatment are made by a multidisciplinary tumour board according to the Finnish national treatment recommendation which has been made for all different subsites of HNCs (Example in Table 3).

The target of RT is to damage cellular DNA and the cell membrane, leading to death of the tumour cells. Around 80% of all HNC patients will receive RT at least once during their disease (Borras et al., 2015). Nowadays, intense modulated radiotherapy (IMRT) and its more advanced technique, volumetric modulated arc therapy (VMAT), is the main approach. When RT is combined with chemotherapy, the effect is superior but there are more side effects. The most common chemotherapeutic agent used is cisplatin. Chemotherapy alone is usually used as a

palliative treatment for incurable disease, but it can also be used for induction treatment (Y. Sun et al., 2016). Reirradiation can also be used in selected cases but is often a part of palliative treatment.

The efficacy of surgery and RT is thought to be the same in early-stage tumours, but late toxicities occur less with surgery. Surgery is usually chosen as first-line therapy for oral cavity tumours to avoid the side effects of RT. However, in early-stage oropharyngeal and hypopharyngeal carcinomas RT has generally been presented as the first option, since it results in cure rates comparable to surgery and is usually associated with lower morbidity (Mendenhall et al., 2006). Transoral robotic surgery (TORS) has been adapted over the past two decades and is currently widely used especially in early-stage oropharyngeal tumours that do not have marked lymph node involvement. In laryngeal tumours there is a greater divergence of practice, especially in the early stages. RT can be focused on a small area and the side effects are fairly mild, but in some studies the transoral laser microsurgical approach is thought to be superior in early-stage laryngeal tumours (Baird et al., 2018). In advanced-stage laryngeal tumours chemoradiation is the first-line treatment, but when the disease involves the cartilage, surgery must be performed when curative intent is feasible. When possible, single-modality treatment is chosen because of better functional outcomes (Jepsen et al., 2003).

Table 3. Example of Finnish treatment recommendation for tongue, floor of mouth, and buccal mucosa cancer. Modified from the Finnish Society for Head and Oncology treatment recommendations.

Tongue, floor of mouth, buccal mucosa	**T1-2N0**	**T1-2N1**	**T3-4N0**	**T3-4N1**	**T1-4N2-3**
Primary tumour	Surgery	Surgery	Surgery	Surgery	Surgery
Neck treatment	T1: sentinel/no*/L I-III	L I-III(IV)	L I-III	L I-III/IV	L I-IV(V)
	T2: L I-III/sentinel				
Postoperative oncology treatment	No	When necessary	Yes	Yes	Yes

* A small, superficial (infiltration <3mm) primary tumour does not necessarily require treatment of the neck

In case of recurrence or residual cancer, the primary option is salvage surgery if the tumour is resectable. It is more challenging and related to a high complication rate because of previous treatment causing scarring, and anatomic landmarks can be different (Pang et al., 2011). Palliative surgery is performed when the tumour is not curable but symptoms can be alleviated and the remaining life quality improved.

Reconstruction of tissues is often needed in conjunction with surgery. With small tumours, the resection site can usually be covered by primary closure, local flaps, or

a split-thickness skin graft, or sometimes it can be left open and allowed to heal by secondary intention. In advanced stages, where reconstruction typically requires more tissues to cover the site, it can be achieved with pedicled flaps or microvascular free-tissue transfer which may include skin, muscle, and/or bone depending on the site and size of resection.

Neck dissection (ND) is combined with surgical treatment when there is a clinical suspicion of lymph node metastasis in the neck area. Elective neck dissection (END) can be done prophylactically when there is no suspicion of nodal metastasis but the probability of occult metastasis exceeds 15–20%. HNSCC frequently metastasises to the cervical lymph nodes, and distribution to regional lymph nodes of the neck is the most important prognostic factor (Ferlito et al., 2002). The risk of developing nodal metastasis varies by tumour site and other tumour-specific factors. In both ND and END all lymph nodes from the specific levels of the neck are removed, not only to prevent cancer spread but also to send them for pathological evaluation. If metastatic cancer is found in the lymph nodes, additional treatment can be combined.

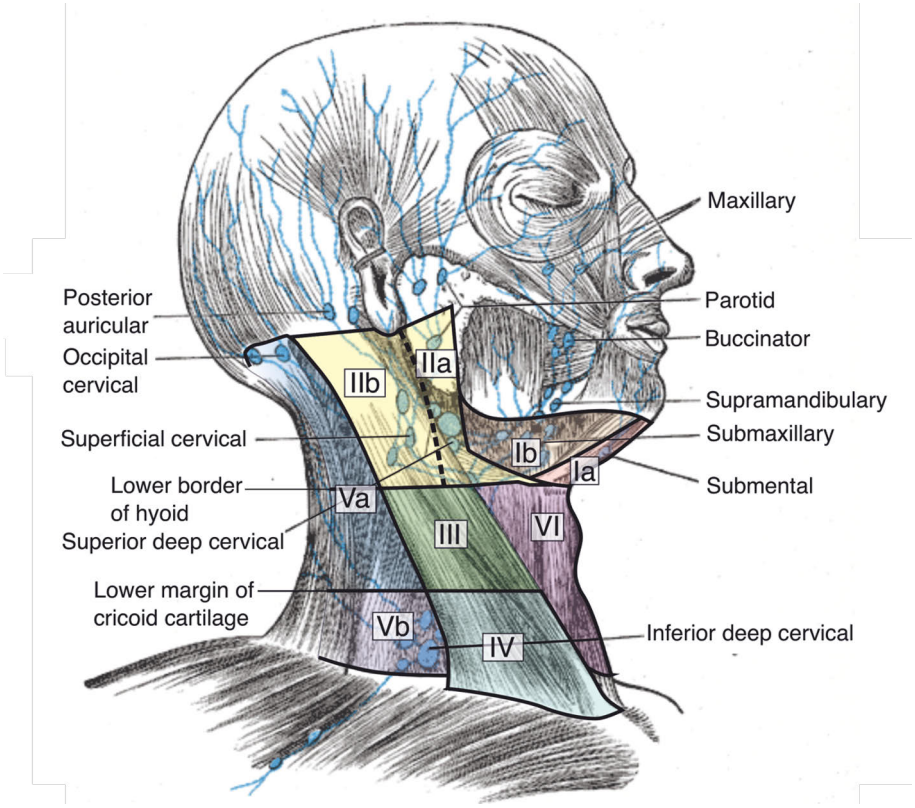

Figure 2. Lymph node levels of the neck. Image by Mikael Häggström. Public Domain (CC0 1.0).

Sentinel lymph node biopsy can be performed if the primary tumour is relatively small (T1/T2) and reachable by injection and there is no clinical suspicion of metastatic disease in the neck. A radioactive substance is injected around the primary tumour and spreads to the sentinel nodes, which are located first on SPECT/CT (Fig. 3) and then during surgery using a special gamma detector probe. Usually, the primary tumour is operated on at the same time. Pathologists examine these lymph nodes more carefully than in normal ND, thus smaller metastases can be found with this procedure. Sentinel lymph node biobsy has shown oncologic equivalence to ND in these small tumours (Garrel et al., 2020).

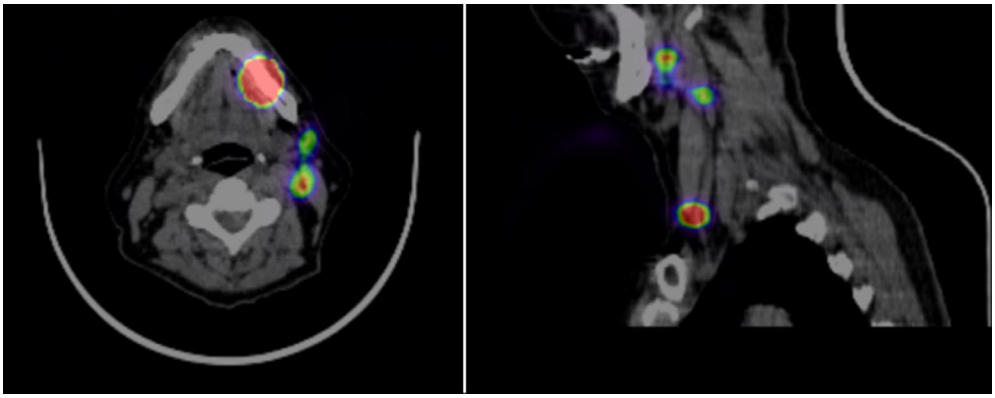

Figure 3. SPECT/CT of sentinel nodes (picture by Heikki Irjala).

Immunotherapy is a novel treatment offering new advances in the treatment of recurrent and metastatic HNSCC, which has led to remarkable benefits and prolonged remissions for some patients (Fasano et al., 2022). Before immunotherapy became an approved treatment for HNSCC, targeted therapy was the preferred modality. The most commonly used drug for this, cetuximab, has been used for about 20 years in HNSCC patients and targets tumour growth receptors. It is the most studied agent in HNSCC. Currently, pembrolizumab and nivolumab are the most studied and used immunotherapeutic agents for HNCs. These new immune check-point inhibitors use the patient's own immune system to fight the tumour. Immune cells that have been suppressed by cancer cells can be re-activated under the influence of immunotherapeutic agents, enabling the patient's own system to fight off the tumour. Numerous studies and clinical trials are ongoing around the topic of immunotherapy and biomarkers with the aim of finding the optimal treatment for every patient (Fasano et al., 2022).

De-intensification of treatment is also under investigation. Some studies show promising outcomes with de-intensification of treatment in HPV-positive OPSCC early-stage tumours (Yoshida et al., 2020). HPV-positive HNC is more

radiosensitive than HPV-negative, and OPSCC has a better prognosis when the disease is HPV-positive (C. H. Chung et al., 2014; Jouhi et al., 2018; Kimple et al., 2013). Also, the latest tumour TNM classification has made major changes to HPV-related OPSCC staging (UICC, 2017). However, the results of de-intensification studies are conflicting, and in a retrospective study of stage I HPV-positive OPSCC, definitive RT was associated with poorer survival compared to any multimodality treatment (Cheraghlou et al., 2018; Yoshida et al., 2020). HPV-positive disease can also recur in high-risk treatment volume areas (Nissi et al., 2021). In a recent review article, the safety of de-intensification of radiation in HPV-positive disease could not be verified (Petrelli et al., 2022).

2.1.4 Recurrence

Among patients with locally advanced disease, more than 50% develop locoregional or distant relapses and even early-stage diseases recur (Argiris et al., 2008; J. H. Lee et al., 2013). Field cancerisation is a common feature in HNC and was described in the literature already in 1953 (Slaughter et al., 1953). It refers to the whole mucosal area being exposed to carcinogenic agents, for example when tobacco smoke spreads throughout the upper aerodigestive tract or the entire mucosa is exposed to the alcohol metabolic carcinogen acetaldehyde. This contributes to a high risk of recurrent tumour and even second primary cancer (Leemans et al., 2011).

If a patient is still smoking or consuming alcohol heavily, they should be encouraged and helped to stop (Do et al., 2003; León et al., 2009). Concurrent smoking is a strong risk factor for recurrent tumour, but cessation less than 1 year before or after diagnosis is still a good prognostic factor (Karlsson et al., 2021). Locally advanced disease carries a high risk of local recurrence of 15–40%, and with distant metastases prognosis is poor, with systemic therapy, the median OS is 10 months (Braakhuis et al., 2012; Vermorken et al., 2008).

HNCs are heterogeneous and the tendency to recur varies depending on the location of the original tumour. Even HPV-positive OPSCC recurs differently than does HPV-negative. One option for detecting recurrence of an HPV-positive tumour is to measure circulating Tumour Tissue Modified Viral (TTMV)-HPV DNA in plasma. This method is called liquid biopsy. In a study by Berger et al., the overall positive predictive value of TTMV-HPV DNA testing for recurrent disease was 95% (Berger et al., 2022). Likewise, plasma EBV DNA can be used in NPC screening and its surveillance (A. K. Chan et al., 2017).

2.1.4.1 Second primary

A second primary tumour originates from a different site than the primary tumour. Patients with HNSCC are also at risk of secondary primary cancers, such as lung or oesophageal cancer, or a second HNC. This has been attributed to field cancerisation. A second primary tumour is a second prominent cause of death after the primary tumour itself (Baxi et al., 2014). Around 10–20% of HNCs develop a second primary cancer (Atienza & Dasanu, 2012; Hujala et al., 2005; Priante et al., 2010; Rennemo et al., 2008). In a review by Coca-Pelaz et al., the most frequent site of a second primary was the head and neck area, followed by the lungs and oesophagus (Coca-Pelaz et al., 2020). The larynx and hypopharynx are associated more with a second primary in the lung, and the oral cavity and oropharynx with one in the head and neck (Atienza & Dasanu, 2012). In a study by Douglas et al., 14% patients with HNC developed lung cancer, 31% of which were synchronous (Douglas et al., 2003). PET/CT has an important role in detecting second primaries; Strobel et al. reported that a synchronous second primary occurred in 9.5% of HNSCC patients and that 84% of these tumours had been detected by FDG PET/CT (Strobel et al., 2009).

2.1.5 Follow-up

Due to the tendency of cancer to recur, it is important to monitor patients after completion of treatment, primarily to detect potentially curable locoregional recurrences, distant metastasis, or second primary malignancies. In a survey for HNC survivors, 75% of patients reported detecting possible recurrence to be the most important priority of surveillance (Pagedar et al., 2020). Other reasons are physical and psychological rehabilitation, which commonly involves other healthcare workers. How to do this, however, can be controversial. Some of the studies suggest de-escalating strict surveillance, while others prefer more intensified surveillance (Ilmarinen et al., 2019; Meregaglia et al., 2017; Su et al., 2018; Trinidade et al., 2012). Follow-up protocols vary greatly around the world, even within the same countries. The National Comprehensive Cancer Network (NCCN), along with the major head and neck oncology societies, the American Head and Neck Society (AHNS), the British Association of Head and Neck Oncology (BAHNO), and the European Society of Medical Oncology (ESMO), recommend a minimum follow-up length of 5 years (Machiels et al., 2020; Pfister et al., 2022; Roman et al., 2016; Simo et al., 2016) (Table 4.). Although this duration has been questioned by many researchers, the different national recommendations still endorse 5 years as the minimum, and most of them even annually for life (De Felice et al., 2021; G. Liu et al., 2012; Ritoe et al., 2004). In Finland, 5-year follow-up was used until 2019, when a 3-year routine follow-up protocol was adopted.

The recurrence incidence of HNSCC is maximal within 2 years, with most recurrences occurring within 3 years after treatment (Argiris et al., 2008; Kumar et al., 2013). Given the rising incidence and improving techniques of treatment, more resources are needed for follow-up and survivorship issues. Head and neck malignancies vary substantially in their histology and can act differently at different sites. The similarity in the follow-up guidelines of different associations means that almost all HNSCCs are compressed into the same protocol. Furthermore, many HNSCC follow-up studies describe different tumour sites and heterogeneous groups of patients as a single group. However, one protocol for follow-up may not fit all HNSCCs and more tailored approaches are needed (De Felice et al., 2021; G. J. Hanna et al., 2023).

More tailored protocols have been suggested for different HNSCC sites and OPSCC with or without HPV-association also by Lee et al., who used parametric modelling for optimising the outpatient visit intervals of follow-up. According to the study, the shortest interval between follow-up visits should be for hypopharyngeal SCC and the longest for HPV-positive OPSCC. (H. I. Lee et al., 2022) De Felice et al. have proposed different follow-up protocols when the site of the tumour is or is not clinically evaluable, basing their recommendations on current national guidelines and their own clinical experience. The number of imaging exams was notably higher when the tumour was not clinically evaluable, but there was no difference in intensity of clinical visits between these two groups. (De Felice et al., 2017)

De-escalation of the follow-up protocol has been proposed for patients with HPV-associated OPSCC, where in a study by Ilmarinen et al. not a single recurrence was found during routine visits with patients without symptoms (Ilmarinen et al., 2019). Fakhry et al. found the 2-year OS to be much better with recurrence of HPV-positive OPC (54.6%) than HPV-negative OPC (27.6%) (Fakhry, Zhang, et al., 2014). Likewise, follow-up de-escalation is being considered for glottic cancer. In a study of glottic SCC, no recurrences of T1 disease were found after 36 months when the primary tumour was successfully treated (Haapaniemi et al., 2017). Ritoe et al. found that routine follow-up after treatment of laryngeal carcinoma did not enhance the survival of asymptomatic patients with tumour recurrence (Ritoe et al., 2004). In addition to the site, stage, and HPV status, patient adherence to outpatient visits, life management skills, smoking, and alcohol consumption should also be considered when planning the potential de-escalation of follow-up.

In a study by Pulte et al., the 5-year relative survival rate among HNC patients in the United States improved from 52.7% to 65.9% between 1982–1986 and 2002–2006. The greatest improvements were observed in tonsillar carcinoma (22.2%) and carcinoma of the tongue (14.4%), but HPV status was not available. (Pulte & Brenner, 2010) Haas et al. noticed that 87% of patients who survived their recurrence

of HNSCC had a T1 or T2 tumour, and only 30% had nodal disease (Haas et al., 2001). Agrawal et al. found that survival with recurrence was significantly better with original prior early-stage disease and if the recurrence was at a local-only site. However, if a primary tumour was found in an advanced stage or in cases with regional recurrence, the survival was extremely poor. In their study, there was no improvement in survival of patients who had undergone salvage surgery for the original primary. (Agrawal et al., 2009) Nevertheless, in later studies, salvage surgery did have superior outcomes in recurrent HPV-positive OPCs (Fakhry, Psyrri, et al., 2014; Leeman et al., 2017). According to a study by Trosman et al., HPV-positive OPSCC distant metastases occur later than in HPV-negative OPSCC and metastases can occur at rarer sites than usual in HNSCC. (Trosman et al., 2015). Given that most distant recurrences are asymptomatic and only appear with PET/CT surveillance, even more intense follow-up of these HPV-positive OPSCC patients has been considered (Su et al., 2018; Szturz et al., 2020). Intensified follow-up has been suggested especially because single-organ oligometastatic disease is potentially curable using surgery or RT in one-third of patients (Huang et al., 2014).

Regular hospital-based follow-up may also amplify some patients' anxiety resulting from constant reminders of the disease and fear of recurrence. It is known that a prolonged follow-up interval may delay detection of recurrence (Kumar et al., 2013). Patients with symptoms may also postpone contacting the clinic while waiting for a scheduled visit.

Table 4. Intervals of follow-up protocols, time in months. NCCN=National Comprehensive Network, EHNS = European Head and Neck Society, AHNS = American Head and Neck Society, BAHNO = British Association of Head and Neck Oncology, BCCANCER = British Columbia Guidelines, DHNS = Dutch Head and Neck Society (Dutch Head and Neck Society, 2014; Gilbert R, Devries-Aboud M, Winquist E, Waldron J, McQuestion M, 2009; Machiels et al., 2020; H Mehanna et al., 2016; Pfister et al., 2022; Roman et al., 2016).

FOLLOW-UP	NCCN	EHNS	AHNS	BAHNO	BCCANCER	DHNS
1st year	1–3	2–3	1–3	1–2	2	2–3
2nd year	2–4	2–3	2–4	1–2	2	3
3rd year	4–6	6	3–6	3	3	4–6
4th year	4–6	6	4–6	6	Stop	6
5th year	4–6	6	4–6	6		6
>5 year	6–12	12	12	12		Stop

2.1.5.1 Clinical follow-up

Outpatient visits with clinical examination are a mainstay of follow-up and are arranged for all patients treated for HNC. In a study by Ng et al., a clinical finding

was detected in 80% of locoregional relapses (Ng et al., 2019). In Finland, the frequency of routine follow-up visits is typically every 3rd month during the first year and every 4th month during the second and the third years. A clinical appointment with a head and neck surgeon includes both an interview and clinical examination. It is important to evaluate the patient's symptoms, state of mind, and concerns regarding recurrence of the disease and physical rehabilitation. A comprehensive head and neck examination must be done that includes neck palpation, careful visual examination and palpation of the mucous membranes, floor of the mouth, tongue, tonsillar fossae, and buccal and gingival mucosa, and examination of the ears and nose. Mirror examinations and nasofiberoscopy are essential to fully evaluate the site of the tumour. Some tumours, like some hypopharyngeal and upper oesophageal cancers, are invisible in an office setting. Endoscopic examinations under general anaesthesia are occasionally required. Follow-up and rehabilitation are multidisciplinary and consist of multiple different healthcare workers including, for example, dentists, dietitians, and speech therapists. The need for rehabilitation is greatest in the early stages of the post-treatment period and gradually decreases over time.

2.1.5.2 Imaging modalities in follow-up

Different imaging modalities can be used as a part of follow-up of HNC. US, CT, MRI, or PET all have their own benefits. Depending on the site, stage, and histology of the tumour and previously used imaging modalities, an adequate option is chosen by a multidisciplinary tumour board. Practices of imaging during follow-up vary widely and there is no consensus on this. When there is a suspicion of recurrence or some other specific problem in the recovery, the imaging modality is quite easy to select.

Sometimes visual examination is most accurate, like in early mucosal changes, where both CT and MRI have poor sensitivity in detecting these changes (Chong & Fan, 1997a). In a retrospective study of the follow-up of T2 and T3 glottic cancers treated with transoral laser microsurgery, there were no significant differences in OS or DSF between follow-up using only endoscopy or endoscopy and follow-up with imaging using CT or MRI. (Marchi et al., 2017).

The use of imaging during routine follow-up must strike a balance between benefits and drawbacks. In post-surveillance imaging, care should be taken that the number of CT and PET scans is limited to those that are strictly necessary, as radiation increases the risk of secondary malignancies, especially in younger patients (Shao et al., 2020). Ng et al. found that routine imaging after 2 years is not effective; although asymptomatic recurrences were found earlier with imaging than clinically, there was no statistical difference in survival (Ng et al., 2019).

Different guidelines make no official recommendations for surveillance imaging in an asymptomatic patient beyond 6 months after treatment, except for the NCCN, which suggests a protocol for imaging smokers with chest CT (Wierzbicka & Napierała, 2017). A recent article by Chen et al. compared post-treatment imaging-based surveillance (CT, MRI, or PET) of HNC with scanning only for clinical indications in patients who showed a complete response on PET within 6 months after RT. There were no differences in 3-year local-regional control, OS, progression-free survival, or freedom from distant metastases (Chen et al., 2023). Nor did Anzai et al. find better survival with surveillance imaging in their retrospective study when all HNC histologies were investigated as one group. However, PET/CT surveillance was associated with lower mortality among patients with HNSCC with regionalised or metastatic disease. (Anzai et al., 2023)

The advantage of US is lack of radiation and the opportunity to take fine needle biopsies (FNA) at the same time. Likewise, the low cost and easy in-office availability of US favours its use in routine follow-up. Hwang et al. compared US and PET in the detection of cancers of the head and neck and found them to be comparable, especially when US is combined with FNA (Hwang et al., 2009). The drawback of US is that it lacks documentation for comparison, unlike PET/CT imaging.

CT has displaced chest X-ray because of its superiority in detecting recurrent tumours (Bradley et al., 2019). The problem with CT is exposure to radiation. Taghipour et al. found CT and PET/CT to have comparable accuracy in the evaluation of primary tumour sites but CT was inferior in assessing cervical node involvement (Taghipour et al., 2017). For detecting a second primary lung cancer CT is superior to MRI, and the NCCN guidelines recommend CT annually for HNC patients with a history of 20 pack-year smoking due to the high risk of developing lung cancer (Pfister et al., 2022). Even though CT is sensitive in detecting lung tumours, Ritoe et al. failed to show an improvement in OS with CT screening for second primary in the lung after laryngeal cancer (Ritoe et al., 2007).

MRI has better resolution when scanning soft tissue and is the best modality for detecting perineural or dural invasion, and the radiation exposure is absent. In a study by Anzai et al., MRI and/or CT were superior to PET/CT in surveillance imaging of other histology HNC than squamous cell cancer, and surveillance imaging with MRI and/or CT was associated with better survival among patients with non-SCC (Anzai et al., 2023). MRI is also better than PET/CT, for example, in the diagnosis and follow-up of some salivary gland tumours because of their paucity of FDG avidity, and perineural invasion cannot be detected reliably with PET/CT (Wai Lup Wong, 2021).

PET/MRI gives detailed anatomical information at lower radiation and combines metabolic data from PET, though PET/CT is better at detecting lung metastases (Szyszko & Cook, 2018). In practice they are equal, but PET/MRI is still quite rare

in clinical use compared to PET/CT. PET imaging for surveillance has good sensitivity and negative predictive value but only a moderate positive predictive value, whereas CT and MRI have lower sensitivity but higher specificity (J. C. Lee et al., 2007; Roman et al., 2016). PET/CT or PET/MRI is widely used to assess treatment response and is typically done 3 months after treatment, called the baseline PET scan. PET during follow-up of HNC treated with chemoradiation up to 3–6 months after treatment is efficient and is principally used for advanced stage HNSCC. In a study by Kao et al., 2-year survival was 100% with negative 6-month PET/CT, whereas survival was only 32% when there was a positive result at PET/CT (Kao et al., 2009). Especially in hypopharyngeal cancer, PET/CT was useful in surveillance imaging (Anzai et al., 2023). Mehanna et al. found that PET/CT is comparable to planned ND 12 weeks after chemoradiation therapy (Mehanna, Wong, et al., 2016). The accuracy of PET increases with time, and repeated PET/CT imaging is beneficial to differentiate inflammation from the cancer process. After radiation there is unspecified activity in the treated area due to an inflammatory process that can last for months. Repeated imaging reveals the slowly diminishing activity (Iovoli et al., 2021). Especially in HPV-positive OPSCC, imaging after 4 months instead of 3 could spare patients from unnecessary surgery if the inflammatory process were given enough time to heal (H. Y. H. Liu et al., 2019).

PET is effective and sensitive for follow-up of advanced stage HNSCC within 2 years post-treatment (Anzai et al., 2023; Sheikhbahaei et al., 2022). Some institutes perform a new PET/CT around 1 year after treatment but there is no routine protocol described in the literature. In a prospective study by Perie et al., routine PET/CT for asymptomatic patients 1 year after treatment was associated with a much higher incidence of subsequent futile procedures compared to patients with imaging because of clinical suspicion of recurrence (Périé et al., 2007). There is no evidence for using PET/CT for routine surveillance after baseline post-treatment examination, therefore NCCN and other guidelines recommend using PET/CT later only if there is a suspicion of recurrence.

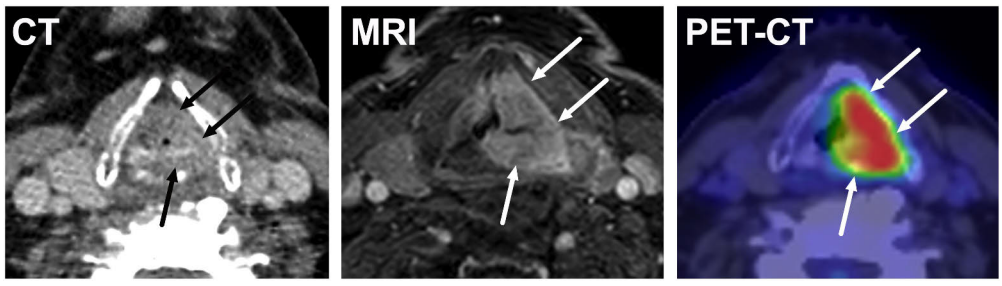

Figure 4: Different imaging modalities of the same subglottic squamous cell carcinoma (picture by Jussi Hirvonen).

2.1.5.3 Telemedicine / e-health

New technological improvements are providing opportunities to rearrange follow-up. A variety of methods such as telephone, video calls, or internet-based questionnaires can be used as follow-up instruments alone or adjunct to face-to-face appointments. The advantage of telemedicine is that the patient avoids an in-person visit to the hospital, reducing the need for resources, lowering the patient's anxiety, and allowing more time for new patients. In the wake of the COVID-19 pandemic and the need to avoid infections, telemedicine, which was once barely used for cancer patients, has spread across the globe.

An article by Stewart et al. on HNC patient satisfaction with telephone consultations showed that patients found it beneficial in 98% of cases, and that 30% of patients were relieved not to have to visit the hospital (Stewart et al., 2021). Likewise, Zhu et al. report high patient satisfaction among telemedicine users especially in the COVID era, but also concerns among some of them that there is no physical examination (Zhu et al., 2021). Patients' quality of life is one aspect of follow-up, but effectiveness in detecting recurrent disease is the main point of arranging it. There are not enough studies on the effectiveness of using telehealth in the HNC survivor population, or studies that would reveal when and in what types of HNC telemedicine could be used.

2.2 Adverse effects of treatment

Treatment of HNC is complex, often requiring major surgical intervention combined with RT and chemotherapy or some of these as a single-modality treatment. Adverse effects of treatment are almost invariably present and are classified as acute or long-term. Improvement of therapies has enhanced the opportunity to preserve organ function and reduce morbidity and mortality. However, adverse effects are still abundant.

2.2.1 Acute (short) term

Acute adverse effects can include pain, skin reactions, mucositis, swallowing and nutrition problems, breathing problems, disfiguration, problems with speaking and communication, psychosocial distress, and even death. Most HNC patients, especially those treated with RT alone or combined with some other treatment modality, reported high pain scores within 1 year post-treatment (Allen-Ayodabo et al., 2019). Typical RT-associated acute adverse effects are mucositis, increased secretions, dysphagia, loss of taste, hoarseness, and dermatitis (Rosenthal et al., 2006; Trotti et al., 2003).

Despite improvements in surgical techniques, disfiguration is common. Because treatment usually involves visible areas of the body, it can have devastating effects

on a patient's recovery and social life. The side effects of surgery are usually acute and can become long lasting. Decent treatment of side effects is crucial to prevent acute symptoms from developing into late ones.

2.2.2 Long term

Long-term side-effects of RT are generally defined as symptoms starting more than 90 days after completion of treatment (Cox et al., 1995). Known long-term adverse effects of RT are xerostomia due to impaired function of the salivary glands, hypothyroidism, osteoradionecrosis (ORN), dental caries, swallowing difficulties, aspiration, pharyngoesophageal stenosis, trismus, neck fibrosis, lymphoedema, and chronic skin changes (Hamilton et al., 2019). According to the literature, the most common long-term adverse effects are xerostomia, dysphagia, hypothyroidism, and ORN (Dirix et al., 2006; Martin et al., 2018; Patterson et al., 2018; Pezdirec et al., 2019; Ranta et al., 2021). The most disturbing symptoms are xerostomia and dysphagia (Carmignani et al., 2018; Roe et al., 2014). Sensorineural hearing loss is linked especially to cisplatin (Laurell & Jungnelius, 1990; Musio et al., 2022). Thanks to the use of IMRT, the late toxicity profile has decreased, especially regarding xerostomia (Muzumder et al., 2021; Saarilahti et al., 2005).

Dysphagia usually develops in older patients and is more common in higher T-class diseases (Aylward et al., 2019; Baudelet et al., 2019). Difficulty swallowing is caused by weakened function of the throat muscles, scarring, xerostomia, and lymphatic swelling (Strojan et al., 2017). There is a 2.5-fold risk of developing dysphagia in patients treated with chemoradiation compared to those treated with surgery alone (Francis et al., 2010). Swallowing problems were reported in a study by Roe et al. in 44% of patients 1 year after IMRT-treated OPC (Roe et al., 2014). Treatment of dysphagia can consist of different swallowing exercises, dilatations, and surgery depending on the underlying cause. Malnutrition and weight loss worsen the treatment results, and the patient's energy intake must be secured (van Bokhorst-de van der Schueren et al., 1999). For a short time, such as after surgery, nutrition can be managed via nasogastric tube. If parenteral nutrition is needed for a longer period, a PEG tube is usually inserted either prophylactically or during treatment.

ORN is most common in oral cavity cancer. It arises from radiation-induced damage to the bone tissue, and symptoms often appear within 3 years after treatment (Sroussi et al., 2017; Studer et al., 2016). The mandible is the bone most affected, and in a review article by De Felice et al., mandibular ORN secondary to IMRT for HNC ranges from 0% to 14% (De Felice et al., 2020). ORN is less common in maxillary bone because of good collateral blood circulation. Tooth extraction and dental diseases in the area of radiation are major contributing factors. To prevent occurrence of ORN, oral care is the most important prophylactic procedure, and oral

disease should be treated before receiving RT. If teeth must be removed before treatment, this should be done at least 7–14 days before treatment (Kojima et al., 2017). Treatment options for ORN are antibiotics and surgical removal of damaged tissue. Hyperbaric oxygen is commonly used as well, although the clinical benefit is questionable (Jacobson et al., 2010; Lyons & Ghazali, 2008).

RT of the neck affects the thyroid, which is a radiation-sensitive tissue. Hypothyroidism is therefore a common side-effect of RT and can result from radiation-induced autoimmunity or directly from tissue fibrosis or atrophy (Nagayama, 2018). In the literature, the dose of radiation to the thyroid correlates to the incidence of hypothyroidism. Chow et al. summarise that the prevalence of hypothyroidism after RT varies from 10% to 57%. (J. C. H. Chow et al., 2022) Symptoms can vary and most of them are due to the slowing metabolic process. RT-induced hypothyroidism is treated with synthetic thyroid hormone, and thyroid-stimulating hormone levels should be measured in all patients treated with RT.

2.3 COVID-19

2.3.1 COVID and otorhinolaryngology

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2, COVID/-19) caused a worldwide pandemic and overburdened healthcare systems all over the world. The COVID virus settles in the upper aerodigestive tract, from where it is spread by aerosols into the environment. It is highly contagious, and healthcare workers were at high risk of infection early in the pandemic when caring for large numbers of infected patients. Otolaryngologists, whose work brings them into close contact with the area where the virus is located, are exposed to the aerosols and are therefore at higher risk of infection compared to some other subspecialities of medicine. Anosmia and dysgeusia were identified as primary symptoms which usually redirect these patients to otolaryngologists. Flexible nasofiberoscopy, which is a very common procedure on a visit to an otolaryngological clinic, is an aerosol-generating procedure creating a high risk of viral infection for the examiner (O'Connell et al., 2020). By 2020, almost all oncological organisations and otolaryngology clinics had developed their own or collective treatment protocols for COVID patients and patients with HNC both with and without COVID (AAO-HNS Position Statement, 2020; J. Y. K. Chan et al., 2020; Kowalski et al., 2020; Simo et al., 2020). Recommendations were quite variable, but the main purpose of all of them was to diminish COVID infections and ensure treatment safety for both healthcare workers and patients.

2.3.2 COVID and cancer

COVID-19 is not associated with cancer genesis and is not a specific risk factor for HNC. Due to the immunosuppressive state caused directly by tumour growth and indirectly by the effects of anticancer treatment, cancer patients are a highly vulnerable population for SARS-CoV-2. Frequent causes of morbidity and mortality among HNC patients are respiratory complications (Silverman et al., 2020).

The pandemic changed the treatment and follow-up protocols of cancers due to overloading of hospitals and concerns over infection risk among patients and healthcare workers. This led to some expansion of new protocols in the practice of telemedicine, especially regarding follow-up. According to the existing literature, in some studies diagnoses of cancer were partly delayed due to patients' concerns over infection and limited healthcare resources, but other studies did not find any influence on delay in detecting HNC or progress in the stage of disease when detected (Clements et al., 2023; Heckel et al., 2023; Kanatas et al., 2021; Mack et al., 2023). At the time of writing, the COVID era is not yet over, and further investigations and results are expected.

3 Aims

The general objective of this study was to evaluate the optimal follow-up protocol and to investigate late adverse effects in HNC patients treated with curative intent.

The specific aims of the four studies were:

1. To find out the modalities by which and time points when recurrences are found in the follow-up of patients with HNSCC.
2. To evaluate whether using telemedicine for follow-up of HNSCC patients during COVID-19 caused delay in detecting recurrences and if telemedicine could be used as a part of follow-up in future.
3. To analyse the prevalence of three common long-term side effects (dysphagia, osteoradionecrosis, and hypothyroidism) of RT for HNC.
4. To investigate the benefit of routine PET/CT imaging in HNSCC patients 1 year after completion of treatment.

4 Materials and Methods

4.1 Study designs

4.1.1 Study I

This study was a retrospective single-centre study on the modalities and time from treatment of finding a recurrence of HNC. All new diagnosed head and neck malignancies identified during a 10-year period (1999–2008) at the Department of Otorhinolaryngology–Head and Neck Surgery, Turku University Hospital, tertiary academic centre, were analysed. The main search criterion was accomplished panendoscopy, which was a routine examination at the time for all new mucosal head and neck malignancies. Site of primary tumour, treatment modality, date of treatment completed, date of finding recurrence, method of finding recurrence, and site of recurrence were recorded.

Exclusion criteria were missing data, non-curative intent of treatment, histology other than squamous cell carcinoma, residual tumour less than 3 months after completion of treatment, recurrence after 5 years classified as a new primary cancer, and former head and neck malignancy.

4.1.2 Study II

Study II was a prospective and descriptive study of all cases of HNSCC undergoing follow-up at Turku University Hospital over a 2-month period. Regular in-office visits were changed to phone appointments from 23 March to 27 May 2020 due to the COVID-19 pandemic. Patients were informed about the new practice by a registered nurse. Only one routine follow-up visit per patient was replaced in this way. For patients who were treated less than a year previously, follow-up visits remained unchanged. All patient contacts, reasons for contact, and detected recurrent cancers were carefully recorded over a 7-month period after May 2020. Possible associations between delayed diagnosis because of the pandemic and changing outpatient visits to phone appointments were investigated.

4.1.3 Study III

In this retrospective study of adverse effects of RT, all HNC patients treated with RT/chemoradiotherapy at Turku University Hospital during a 6-year period (2010–2015) were included, except for patients who had died within 1 year after treatment. This information was collected from the Finnish Population Register Centre. IMRT with standard fractionation was applied in each case. Patients' HPV status, smoking, alcohol use and presence of dysphagia, hypothyroidism, and ORN were noted from medical records. Correlations between population-based factors, treatment, and late toxicities were identified.

4.1.4 Study IV

Study IV was a retrospective, study on the feasibility of routine PET imaging in two tertiary academic centres, Turku University Hospital and Tampere University Hospital. The search criteria were ICD-10 codes C00-C14, C30-C32, and C77 at both locations. The study population included patients with HNSCC diagnosed between 2010 and 2015 and treated with curative intent at these centres. Patients with tumour of the skin, salivary glands, and upper oesophagus were excluded. Patients who died or had recurrent disease within 10 months after treatment were excluded from further analysis.

At Tampere University Hospital, PET/CT was used as a routine follow-up examination and at Turku University Hospital only if needed. OS when using or not using PET for follow-up after 10–14 months was the primary endpoint. DFS was also determined. Clinical data were collected separately from the two centres in similar digital data format when reading through the medical histories. Dates and causes of death were obtained from the Finnish Population Register Centre.

4.2 Patient population

4.2.1 Study I

In all, 456 patients were diagnosed with new HNC during the period 1999–2008, of whom 425 (93%) were treated with curative intent and 23 with palliative care. The total number of recurrences was 197 in 140 (31%) patients. In all there were 94 (21% of all patients) true first relapses when excluding patients who did not meet the inclusion criteria.

Table 5. Inclusion criteria of Study I. Modified from Study I.

Inclusion	Exclusion
New head and neck cancers in 1999–2008 **n=456**	23 palliative intent
	8 data missing
Treated with curative intent **n= 425**	
Suspicion of recurrent cancer **n= 197** in 140 patients	13 false alarms
Verified recurrence **n= 184** in 133 patients	16 other cancer than HNSCC
	7 data missing
	36 residual
	3 new primary cancer >5 years
	1 previous head and neck malignancy
121 recurrences in 94 patients	22 2nd recurrence
	5 3rd recurrence
94 first recurrences in 94 patients	

4.2.2 Study II

In Study II, the total number of patients with HNC who were followed up from 23 March to 27 May 2020 was 209. Histologically other than squamous cell carcinomas were excluded, leaving 178 (85%) patients. After the lockdown period, 169 (94%) of these patients visited the outpatient clinic during the study period, which was nearly 7 months. For 76 (45%) patients whose treatment had ended less than a year previously, the established follow-up protocol with outpatient visits was followed. For 90 (88%) of the 102 (60%) patients whose treatment had ended more than a year earlier, one outpatient visit was changed to a phone appointment. If there was a suspicion of recurrent cancer via phone appointment, an outpatient visit was arranged.

4.2.3 Study III

The total number of HNC patients who received RT was 307, which was 44.6% of the whole population of HNC patients in the study. Survival 1 year after treatment was used as an inclusion criterion, leaving 233 (75.9%) of all RT treated patients. The median follow-up duration was 5 years. The length of follow-up was 5 years for patients who survived (n= 149), and in patients who died before September 2020, when the data was gathered, the median follow-up was 30.34 months (n=84).

Table 6. Overview of participant characteristics in Study III. Modified from Study III.

Overview of participants	**n (%)**	
Duration of follow-up	233 (100)	Median 5 y (IQR 1.12), mean 4.31y
Age at diagnosis (mean +/- SD)	61.4 +/- 10.1	
Gender female/male n (%)	62 (26.6) / 171 (73.4)	
Smoking		
Recent smoker	75 (32.2)	
Early quitter	53 (22.7)	Cessation 1 year or earlier before diagnosis
Recent quitter	50 (21.5)	Cessation less than 1 year earlier or later
Never smoker	52 (22.3)	
Heavy alcohol use		>16 drinks/week for female, >24 drinks/week for male
Yes	45 (19.3)	
Before	25 (10.7)	
Never	136 (58.4)	
Information missing	27 (11.6)	

Table 7. Tumour characteristics and treatments in Study III. Modified from Study III.

Tumour characteristics and treatment			
Primary tumour site	**n (%)**	**Treatment modality**	**n (%)**
Oral cavity	92 (39.5)	Definitive RT	21 (9)
Oropharynx	61 (26.2)	Definitive RT, concomitant chemotherapy	97 (41.6)
Nasopharynx or nasal cavity	13 (5.6)	Preoperative RT	3 (1.3)
Hypopharynx	4 (1.7)	Postoperative RT	15 (6.4)
Larynx	49 (21)	Preoperative RT + chemotherapy	39 (16.7)
Parotid gland	2 (0.9)	Postoperative RT + chemotherapy	54 (23.2)
Paranasal sinuses	1 (0.4)	Palliative RT +/- chemotherapy	4 (1.8)
Multiple head and neck primaries	1 (0.4)	**RT of the neck**	
Neck metastasis	10 (4.3)	No	14 (6)
HPV (p16) status		Ipsilateral	12 (5.2)
Positive	23 (9.9)	Bilateral	207 (88.8)
Negative	15 (6.4)	**Chemotherapy drug**	
Information missing	195 (83.6)	Cisplatin	166 (86.0)
Stage (TNM 7th edition)		Cetuximab	16 (8.3)
I	25 (10.7)	Paclitaxel	1 (0.5)
II	49 (21)	Information missing	10 (5.2)
III	52 (22.3)		
IV	90 (38.6)		
Missing (unknown primary)	17 (7.3)		

4.2.4 Study IV

The total number of new HNC patients at these two hospitals was 1,246. Criteria for inclusion were no previous HNC, curative intent treatment, squamous cell cancer, no salivary gland or oesophageal cancer, and data available. After exclusions the sample was reduced to 833 patients. The most common sites for tumours were the oral cavity, oropharynx, and larynx. The groups at both hospitals were in many ways equal, but significant differences were also found and are shown in Table 8. Difference in alcohol use can be attributed partly to incomplete entries in the medical history.

Table 8. Patient characteristics from two hospitals. TYKS = Turku University Hospital, TAYS = Tampere University Hospital. Modified from Study IV manuscript.

Total n=833	**TYKS**	**TAYS**	**p-value**
Included	391	442	
Age (mean)	62.9	63.2	.191
Sex female	131 (33.5%)	141 (31.9%)	.622
Alcohol yes/no*	115(29.5%) / 275	97(22.9%) / 327	.032
Site			
Oral cavity	201	194	.030
Oropharynx	81	108	.201
Hypopharynx	12	24	.094
Larynx	68	82	.663
Nasopharynx	11	4	.039
Sinonasal	6	11	.331
Unknown primary	11	19	.251
Stage (1 / 2 / 3 / 4)	97 / 66 / 81 / 146	90/58/80/204	.041
T (0 / 1 / 2 / 3 / 4)	12 / 127 / 129 / 70 / 53	19 / 121 / 130 / 57 / 114	<.001
N (0 / 1 / 2 / 3)	207 / 59 / 116 / 9	223 / 57 / 151 / 10	.518
Recurrence	152 (38.9%)	180 (40.7%)	.586
Treatment modality			<.001
Surgery	115	78	
RT	20	38	
CRT	99	121	
Surgery + RT	26	96	
Surgery + CRT	129	108	
Overall survival			
Alive	53.2%	49.5%	
Alive at 5 years	63.4%	61.1%	

4.3 Ethical considerations and funding

All studies comply with the Declaration of Helsinki as revised in 2002. The study I protocol was approved by the Hospital District of Southwest Finland (record number: T227/2014) and was funded by the Kirsti and Tor Johansson Heart and Cancer Foundation and a grant from Merck KGaA, Darmstadt, Germany. The study II protocol was approved by the Institutional Research Ethics Board of Turku University Hospital (record number: T248/2020) and was funded by the State Research Fund and the Cancer Foundation of Southwest Finland.

The Study III and IV protocol was approved by local Clinical Research Centres (record numbers: T06/049/20, T54/2021, and R20611) and study permission was granted. Study III was funded by the Kirsti and Tor Johansson Heart and Cancer Foundation, the Finnish Association of Otorhinolaryngology–Head and Neck Surgery, the Vaasa Medical Foundation, and the State Research Fund. Study IV was funded by the Finnish Cancer Foundation, the State Research Fund, the Finnish Association of Otorhinolaryngology–Head and Neck Surgery, the Paulo Foundation, the Päivikki and Sakari Sohlberg Foundation, and the TYKS Foundation.

4.4 Statistical analyses

4.4.1 Study I

In Study I, the statistical analyses were performed with SAS 12.1 statistical software (SAS Institute Inc, Cary, North Carolina) and the material compiled using Microsoft Excel. The Chi-Square nonparametric test was used for comparisons between groups of symptomatic and asymptomatic outcomes. The correlation of tumour identification with time was calculated with Fisher's exact test. Statistical significance was set at p-value <0.05.

4.4.2 Study II

Study II was a descriptive analysis without any statistical comparison or correlation between groups and no p-value was used. Data was compiled, and descriptive statistics performed, in Microsoft Excel.

4.4.3 Study III

In Study III, crosstabs, the Chi-Square test, and Fisher's exact test were used to find any differences in the incidence of RT side effects between smoking, gender, alcohol consumption, primary tumour site, cancer stage, p16, surgery modality, neck RT,

and chemotherapy. One-way ANOVA was used to assess how age at diagnosis impacted the RT side-effect incidence. The Mann-Whitney U test and Kruskal-Wallis tests were used to assess whether the radiation dose or fraction was different in groups with hypothyroidism, dysphagia, dietary change, dysphagia treatment, ORN, and ORN treatment. Age at diagnosis was normally distributed according to the histograms, but radiation dose and fraction were skewed. Linear regression was used to test the trend in median TSH levels between time points. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistic software version 27 (SPSS, IBM).

4.4.4 Study IV

Patient groups were compared with a two-sample T-test for continuous variables and a Chi-Square test for categorical variables. Kaplan-Meier curves were constructed to display the time-to-event relationship for the occurrence of death and recurrent disease in survival analyses. Cox regression was used to find statistical significances between interactions and routine PET imaging. A p-value of less than .05 indicated statistical significance. Material was gathered with Research Electronic Data Capture (REDCap®) with similar data collection platforms at both hospitals and all statistical analyses were performed with SPSS statistical software version 28 (SPSS, IBM).

5 Results

5.1 Follow-up duration (Study I)

Fifty-two (55%) of 94 recurrences were detected at the primary site (Table 9). The most common site of recurrence was the oral cavity, in 29 (31%) patients. The second most common site was the larynx, in 18 (19%) patients. Twenty-two (23%) patients had metastatic lymph nodes in the neck, the oral cavity being the commonest primary site in these patients. Distant metastases were found in 12 (13%) patients. Simultaneous recurrences at two or more sites were found in four (4%) patients.

Table 9. Sites of recurrences. Modified from study I.

Primary site	Recurrence site					
	Local	Neck	Distant	Second primary	Multiple	Total by site
Oral cavity	29	17	6	1	1	54
Oropharynx	2	2	2	1	2	9
Nasopharynx or cavity	2	0	1	0	0	3
Hypopharynx	1	2	1	0	0	4
Larynx	18	1	2	2	1	24
Total	52	22	12	4	4	94

Ninety percent of recurrences were found within 36 months after treatment (Fig. 5). All recurrent tumours without patient-reported symptoms were detected within 34 months; 16% of recurrences were found based on patients' questions about symptoms during extra follow-up visits, 37% during routine visits by symptomatic patients, and 30% at routine visits by asymptomatic patients. In 14% of cases the data was insufficient. There was no significant difference in time from treatment to diagnosis of recurrent disease between groups of patients with no symptoms, patients with symptoms at routine visit, or patients with extra follow-up visits due to symptoms ($p=0.52$).

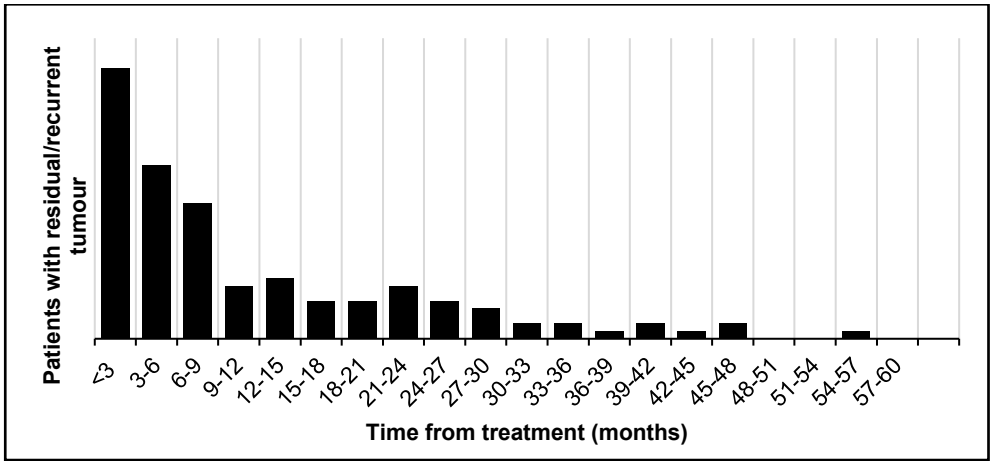

Figure 5. Number of recurrences over time. Note: Findings at less than 3 months were excluded as residual tumours. Modified from Study I.

With hypopharyngeal and laryngeal cancers, the follow-up protocol was different than for other sites. The schedules were similar, but in these groups endoscopic examination was performed under general anaesthesia. In these groups 11 (12%) recurrences were detected, eight (9%) of which were laryngeal carcinomas. Six recurrences (6%) were found upon routine examination and five by the patient making contact between routine visits.

The commonest symptoms in groups of symptomatic patients were local pain, mucosal lesion, or a palpable mass. If the patient did not have any symptoms, mucosal lesion or palpable mass on routine examination were the most common findings indicating recurrent disease. Routine imaging found recurrence only in two patients.

Treatment of recurrence with curative intent is summarised in Table 9. In 22 (34.3%) cases the treatment was considered successfully curative at 5-year follow-up.

Table 9. Treatment of recurrences with curative treatment and survival at 5-year follow-up. Results from Study I.

Recurrence treatment with curative intent	n=64 of 94	Successful	Unclear/lost in follow-up
Surgery	42	23.8%	5
(C)RT	3	100%	0
Surgery + (C)RT	19	57.9%	2

5.2 Selection of type of follow-up and delay caused by COVID-19 (Study II)

5.2.1 Patients with HNSCC treated less than a year earlier

The study included 76 patients whose treatment had ended less than a year previously and 102 whose treatment had ended more than a year previously (Figure 6). In 14 (18%) of the 76 patients whose treatment had ended less than year previously, a recurrent tumour was detected. In all, 39 patients contacted the hospital and nine (23%) of them had recurrent disease. Eight of these nine patients with recurrence had completed treatment less than a year previously (Table 11). Three (21%) of the 14 recurrences were found at routine control and all were symptomatic. One of these three patients did not wish to visit the outpatient clinic due to the COVID-19 pandemic, thus the recurrence was only discovered at the second visit after a telephone appointment; the symptoms had developed during the period between visits. Another three (21%) of the 14 recurrences were distant metastases without symptoms, detected either on the baseline or 1-year PET/MRI.

Table11. Recurrences in patients with HNSCC treated less than a year earlier.

14 recurrences <1 year after treatment
8 contacted the hospital
3 at routine control, symptomatic (one of these at a second visit after phone appointment)
3 distant metastases, asymptomatic, detected by PET-MRI (baseline or 1-year routine)

5.2.2 Patients with HNSCC treated more than a year earlier

Only in three (3%) patients of 102 whose treatment had been completed more than a year earlier were recurrences found. Two of these were patients whose outpatient visit had been changed to a phone appointment. One of the two had been treated earlier for laryngeal cancer and had no symptoms to report on the phone, but 1 month later came for a visit because of fatigue, upon which a second primary tumour was found in a lung. The other patient had had a previously treated tonsillar cancer, and a second primary tumour was detected in the nasal cavity at an additional visit arranged because of symptoms. One of the three above attended a follow-up visit for sinonasal SCC at the clinic instead of a phone appointment, because metastasis had been detected at routine PET-MRI when the patient had no symptoms.

In our study, there was no delay in detecting recurrences because of COVID-19 or changing the outpatient visits to a phone appointment. Phone contact was found

to be effective in screening symptomatic patients and none of the recurrences were detected at the next routine visit after the phone appointment.

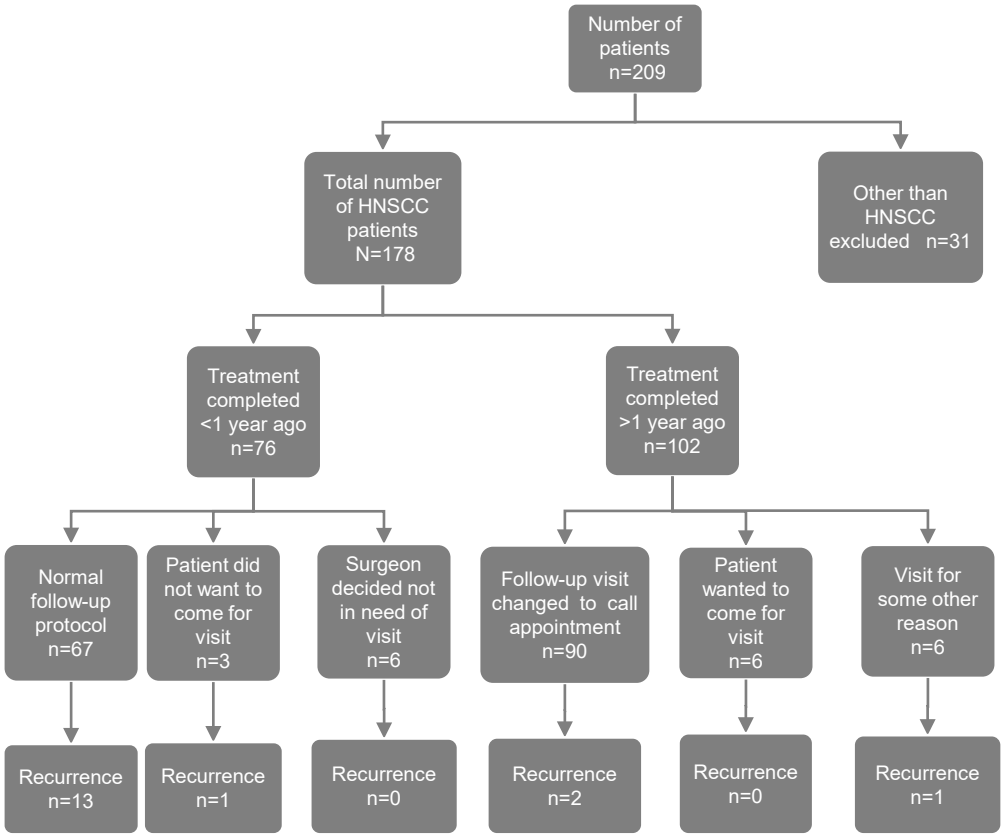

Figure 6. Flowchart of patients in Study II. Modified from Study II.

5.3 Late effects of radiation (Study III)

The total number of included patients was 233. Dysphagia was the most common of the 3 investigated long-term side effects and was reported in 106 (45%) patients as continuing for more than a year after treatment. Twenty-two (21%) of these 106 patients had undergone upper sphincter dilatation at least once; the maximum number of dilatations was 14. Twenty-four (23%) of the 106 patients were permanently dependent on a PEG tube, of whom 20 were able to swallow some purees and liquids, three only small amounts of liquid, and one was not able to swallow at all.

Hypothyroidism was diagnosed in 67 (29%) of the 233 patients after HNC treatment. The median time from end of RT to starting thyroxine substitution was

2.5 years, the earliest being 15 days and the latest 9.1 years. Eighteen patients had thyroxine-treated hypothyroidism already before RT. TSH values trended upwards in all patients after treatment and, comparing the TSH trend in patients who had and had not prescribed thyroxine treatment after the RT, elevated TSH trends were significant in both groups ($p = .037$ and $p = .001$).

ORN was diagnosed in 29 (12%) patients. Ten of them underwent surgery under general anaesthesia, whereas 13 were treated by a dental specialist using local anaesthesia. Six patients were treated with hyperbaric oxygen. Three patients received parenteral antibiotics and nine were treated with oral antibiotics only. For two patients, follow-up by a dental specialist was enough.

5.3.1 Patient features in relation to side effects

Age had a significant impact on hypothyroidism; it was more common in younger patients (p=.01), the mean age of those diagnosed with hypothyroidism after HNC treatment being 58.4 years (SD 9.8). Hypothyroidism was also more common in females (p<.001), being diagnosed in 52.8% of female patients but only in 23.5% of males. Age and gender did not have a statistically significant impact on dysphagia or ORN.

60.9% of RT-treated patients had stage III-IV disease, but higher stage did not have a statistical impact on the incidence of side effects under investigation. Of all the patients who received RT, 71.3% received RT of the neck, 63.4% received definitive RT to metastatic areas of the neck (median dose 65 Gy), and 36.6% received only elective neck RT (median dose 50Gy). RT of the neck was the only significant treatment-related factor behind dysphagia. There was no statistically significant difference between definitive and elective neck RT groups in terms of side effects.

ORN was more common in patients with tumours in the oral cavity (20.7%, n=92) compared to all other sites of the primary tumour (7.2%, n=141) (p=.003). The site of the primary tumour did not have a significant impact on the incidence of hypothyroidism or dysphagia.

Surgical treatment modalities as a part of treatment did not increase the incidence of dysphagia (p=.247), hypothyroidism (p=.673), or ORN (p=.562). Radiation dose or fraction did not have a statistically significant impact on the incidence of side effects or their treatment. The chemotherapy itself, the drug used (cisplatin vs. cetuximab), and the number of cycles did not have a statistically significant impact on side effects either. For comparison, we analysed in addition to the study population eight patients with surgery as the only treatment modality with stage III or IV disease, of which one was excluded because of prior dysphagia before HNC diagnosis. No dysphagia was present in these seven patients.

In heavy alcohol users, hypothyroidism was less common (19.0%) than among participants with no history of heavy alcohol use (31.1%) or those with a history of

heavy alcohol use before the HNC diagnosis (48%). Consumption of alcohol did not have a statistically significant impact on the incidence of other side effects or their treatment. For smoking and p16, there was too much missing data and/or the late toxicity subgroups were too small for reliable analysis.

5.4 Benefit of routine PET/CT after 1 year of treatment (Study IV)

In further analyses comparing patients who had undergone routine PET/CT imaging with those who had not, patients with recurrence or death within 10 months post-treatment were excluded, bringing the sample to 590. The number of stage I diseases was notably higher in the non-PET-imaged group. More detailed comparisons are provided in Table 12.

Table 12. Patient characteristics when comparing routinely performed PET imaging. Modified from Study IV manuscript.

Total n=590	**Routine 1y PET**	**No PET**	**p-value**
Hospital TYKS/TAYS	13/228	276/73	<.001
Age (mean)	60.8	63.3	.208
Sex female	72 (29.9%)	122 (35.0%)	.197
Alcohol yes/no*	59/171	89/258	.999
Site			
Oral cavity	90	194	<.001
Oropharynx	73	65	.001
Hypopharynx	10	8	.197
Larynx	42	57	.726
Nasopharynx	5	8	.860
Sinonasal	8	5	.125
Unknown primary	12	11	.260
Stage (1/2/3/4)	42 / 34 / 49 / 111	123 / 63 / 65 / 97	<.001
T (0,1,2,3,4)	11/ 69 / 76 / 32 / 52	12 / 145 / 109 / 48 / 35	<.001
N0/N+	114 / 126	227 / 122	<.001
Recurrence	61 (25.3%)	93 (26.6%)	.716
Treatment modality			<.001
Surgery	27	133	
RT or CRT	94	96	
Surgery + (C)RT	120	119	
Overall survival			
Alive	70.1%	63.3%	
Alive at 5 years	82.6%	76.8%	

The OS did not show a statistically significant difference between patients treated in these two hospitals (p=0.273). Nor did we find in our study a statistically significant improvement in 5-year survival (p=0.89) or in disease-free survival (DFS) at 5 years (p=0.924) among those who underwent PET/CT (or PET/MRI) after 1 year of treatment (Fig. 6). When examining survival, we were unable to identify any specific subgroup as an independent factor that would have benefitted from routine PET imaging 1 year after treatment. (Table. 13).

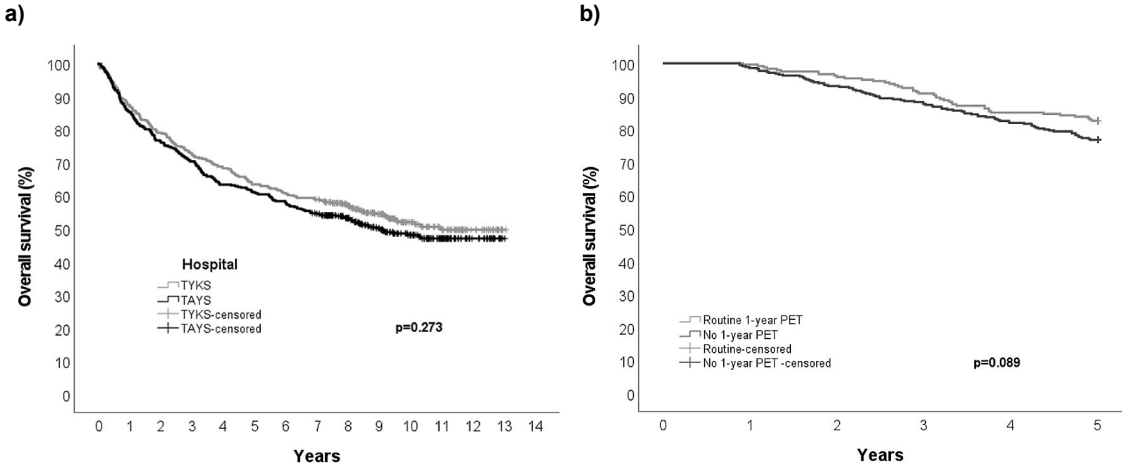

Figure 7. **a)** Kaplan-Meier curve of overall survival between hospitals (HR 0.90, 95% CI 0.74–1.09, p=0.273) **b)** Kaplan-Meier curve of 5-year survival in patients who routinely underwent 1-year PET/CT or PET/MRI and patients without imaging (HR 0.73, 95% CI 0.50–1.05, p=0.089). Modified from Study IV manuscript.

Eight recurrences were detected from PET/CT images and six following unclear findings on the 1-year PET/CT. Two of the six already had some symptoms when diagnosis was confirmed. Curative intent salvage therapy was performed for eight of these 14 recurrences, but one was lost during follow-up. The 2-year OS was 38%. Three of the 14 recurrences were local, three regional metastases, five distant metastases, two second primaries, and one both regional and distant metastases.

Table 13. Cox regression for subgroup analyses affecting survival with or without routine 1-year PET/CT. Modified from Study IV manuscript.

Factor	p-value
Hospital	0.770
Sex	0.216
Stage	0.542
T class	0.594
N class	0.590
Oral cavity	0.242
Oropharynx	0.418
Hypopharynx	0.177
Larynx	0.769
Nasopharynx	0.965
Sinonasal	0.873
CUP	0.965

6 Discussion

The incidence of HNC is increasing, with a trend towards younger patients. This rise is reflected in our data, which compared 425 HNSCC patients treated with curative intent over a 10-year period (Study I) with 352 patients treated over a 6-year period (Study IV) (mean values 42.5/year and 58.7/year). According to the literature, the proportion of OPSCC cases has also risen (Näsman et al., 2020). Lundberg et al. confirm this, demonstrating a rise in OPSCC incidence in Finland along with an increase in the relative frequency of p16-positive HNSCC tumours (Lundberg et al., 2011).

Advances in treatment have improved survival rates, leading to a higher number of patients in surveillance as well. This requires more resources to meet the demands of follow-up and care for late toxicities. It is known that approximately 50% of HNC tumours recur (Argiris et al., 2008; Rettig & D'Souza, 2015). The most important aim of follow-up is to find these recurrences early enough while they are still potentially curable. Residual disease is defined as the presence of cancer cells or tissue remains after initial treatment, and recurrence as cancer found later after treatment although there were no detectable or actively growing tumour cells immediately after treatment. In Study I, we defined residual disease as a relapse of cancer within 3 months, while in later studies we defined it as a relapse within 6 months. Although there is no official time-interval defined in the literature, 6 months is more commonly used. Theoretically, recurrent disease can always be considered either residual or second primary, but there is a consensus on using the term 'residual disease' in cases of rapid recurrence.

Our research focused primarily on squamous cell cancer of the head and neck due to its prevalence (over 90% of HNCs) and the heterogeneity already present within this category.

6.1 Duration of follow-up

Because follow-up protocols for HNC patients are subject to debate, in Study I we investigated how and when HNSCC recurrences can be detected. We found that 90% occur within 3 years after treatment. This trend has been supported by earlier studies and more recent research as well (Autio et al., 2023; Boysen et al., 1992; de Visscher

& Manni, 1994; Kumar et al., 2013). Additionally, we found that all asymptomatic recurrences were detected within 34 months. Similar results have been reported in the literature, such as in the study by Kumar et al. in which patients with new cancer events developed a symptomatic recurrence within 3–5 years (Kumar et al., 2013).

Boysen et al. described self-reported symptoms in 67% of recurrences, while in our study symptoms were present in 56% (Boysen et al., 2016). Our finding is slightly lower than in other studies, for example by Zatterström et al. and Flynn et al., where symptomatic patients made up 78% and 66% of recurrence cases, respectively (Flynn et al., 2010; Zatterstrom et al., 2014). Notably, in 14% of our recurrences no data on symptoms was available. In Study II, despite the small sample size, the proportion of symptomatic patients was 71%, consistent with other studies.

In our population in Study I, the 5-year DFS rate was 69%, which aligns with international studies (Gatta et al., 2015). The 5-year OS for patients with detected recurrence treated with curative intent was 34.3%. Five-year survival rates in the literature vary by site and stage of tumour. Rates of 35% for early stage locally recurrent tumours, 16% for advanced stage locally recurrent disease, 35% for radically resected second primaries, 27% for laryngeal tumours, and 28–44% for oropharyngeal tumours when salvage surgery is feasible have been reported (Hay et al., 2019; van der Putten et al., 2015; L. Y. Wong et al., 2003; Zafereo et al., 2009).

Nonetheless, most follow-up protocols recommend a minimum of 5 years and some even suggest annual visits beyond that. For example, the European Head and Neck Society (EHNS) justifies a minimum length of 5 years for detecting second primary tumours and rehabilitation (Machiels et al., 2020). Pagh et al. also recommend 5 years of follow-up in order to treat sequelae as well (Pagh et al., 2013). Other literature supports the cessation of routine follow-up visits after 3 years, a conclusion echoed in our study (Autio et al., 2023; Boysen et al., 2016; de Visscher & Manni, 1994; Ritoe et al., 2007). It is crucial for patients to have prompt access to a clinic when needed, and appointments should be arranged swiftly in case of symptoms, even beyond 3 years. However, routine follow-up visits may not be necessary after this. In a study by Stone et al., following the NCCN post-treatment guidelines in the first year was linked to improved 5-year overall and disease-specific survival. However, this notable connection was not observed in individuals who maintained consistent adherence over the course of 5 years (Stone et al., 2023). A study by Boysen et al. in 1992 already demonstrated that successful treatment of recurrent carcinoma was limited primarily to cases of local recurrence, especially in laryngeal carcinoma initially treated with RT, and in cancers of the oral cavity treated with or without limited surgical resection (Boysen et al., 1992). The intensity of follow-up does not correlate with survival, and the optimal interval remains an open question (Brennan et al., 2018; Hall et al., 2019; Roman et al., 2016). Recent studies propose more tailored follow-up protocols because of the heterogeneity of tumours,

but there is still a need for more research in this area (H. I. Lee et al., 2022). Ongoing prospective and randomised studies of follow-up, such as SURVEILL'ORL (NCT03519048), may provide further insights.

6.2 Symptoms and imaging in follow-up

The most common symptoms of recurrent HNSCC in our studies were pain, palpable mass, or mucosal lesions, which aligns with the previous literature (Agrawal et al., 2004). In Study I, if a tumour was discovered during a routine visit without any symptoms, survival for recurrence after treatment was 40%, slightly better than in cases where symptoms were present (33%). However, this difference was not statistically significant (p=0.61). In De Visscher and Manni's study, patients who were found to have recurrent tumours during routine visits had almost twice the survival rate of those whose recurrent tumours were discovered during unscheduled visits due to new symptoms (de Visscher & Manni, 1994). Conversely, in a study by Boysen et al., patients with self-reported symptoms had better outcomes after salvage therapy for oral cavity and larynx cancers (Boysen et al., 2016). A recent study by Brands et al. found that asymptomatic detection of new disease during routine visits did not lead to improved OS, suggesting that the follow-up focus should be on providing psychosocial care and rehabilitation (Brands et al., 2023). According to the recent literature, perhaps a strict in-office protocol with a head and neck surgeon does not provide the best solution, and more autonomy could be given to patients. Ilmarinen et al. propose de-escalation of the follow-up protocol in HPV-associated OPSCC (Ilmarinen et al., 2019).

Using PET/CT imaging as a baseline to assess response to treatment is well proven in many studies and is also recommended in guidelines (Gupta et al., 2011; Machiels et al., 2020; Mehanna, Wong, et al., 2016; Pfister et al., 2022). In HPV-positive OPSCC, increased metabolic activity of the tumour can last longer than in HPV-negative OPSCC. Therefore, it is beneficial not to perform baseline PET/CT imaging before 4 months post-treatment in HPV-positive OPSCC. The use of PET/CT is valuable in evaluating the treatment result and for repeating imaging when the result of the treatment is incomplete (Iovoli et al., 2021). In a study by Gore et al., PET/CT was valuable even beyond 6 months to detect recurrences in both symptomatic and asymptomatic patients, but there was no evidence of its benefit for survival (Gore et al., 2020). The value of imaging for detecting recurrences later than 6 months after treatment has been confirmed in several studies (Anzai et al., 2023; Sheikhbahaei et al., 2022).

The clinical benefit of PET/CT 1 year after treatment and its impact on survival was a primary question in our Study IV. We excluded patients with symptoms or clinical suspicion of recurrence. In the routinely PET-imaged group, we did not

notice a significantly improved impact on OS or 5-year DSF. The OS was the same at both hospitals despite the different follow-up protocols for imaging. In a study by Ng et al., no effect on survival was noticed with any imaging modality after 2 years of treatment, which was expected due to most recurrences being found within 2 years after treatment (Ng et al., 2019). Nor did Imbimbo et al. find any difference in survival between symptom-detected and clinically or radiologically detected recurrences, even if more recurrences were identified with clinical and radiological follow-up (Imbimbo et al., 2019).

In our Study IV only 14 recurrences were found, eight directly on routine PET/CT and six on further examination. In eight of these 14 recurrences curative treatment was possible. The 2-year survival of curative-treated patients was 38%, which aligns with previous literature-reported 2-year OS rates of e.g. 18% for isolated neck recurrence, 31–64% for oropharyngeal cancer, and 60% for laryngeal cancer (E. J. Chung et al., 2020; Nichols et al., 2011; Righini et al., 2012; van der Putten et al., 2015). Eight recurrences treated with curative intent is a small sample, but similar proportions have been reported by Pagh et al., who estimated that curative intent is reasonable for half of patients with recurrence and that half of them achieve tumour control (Pagh et al., 2016).

PET/CT significantly improves detection of asymptomatic lesions, and surveillance imaging demonstrates very good sensitivity and negative predictive value but only moderate specificity and positive predictive value (Roman et al., 2016). Conversely, evaluation through physical examination, CT, and MRI has much lower sensitivity but higher specificity and positive prediction value (J. C. Lee et al., 2007). In the literature, an annual thorax CT is recommended for patients with a history of heavy smoking and is superior to a chest X-ray, which misses about 25% of cancer lesions (Bradley et al., 2019; Pfister et al., 2022).

Routine-surveillance PET/CT imaging 1 year after treatment was unbeneficial in our study for asymptomatic patients. In the literature, PET/CT is still considered useful when there is a suspicion of recurrence based on a clinical examination or symptoms (Goel et al., 2017). Such a suspicion is usually at a specific location, and CT or MRI is often used as the imaging modality, as they are more readily available and cost less than PET. In Study I, radiological imaging proved to be effective in confirming a suspicion of recurrent disease. However, as there was no established routine imaging protocol at the time, the significance of routine imaging in diagnosing recurrences could not be observed.

6.3 Delay and telemedicine

The COVID-19 pandemic forced the adoption of new ways to approach the follow-up of cancers. Due to the fear of infection, telemedicine became better approved and

some in-person visits were changed to phone appointments, which created a challenge relating to physical examination. Nonetheless, during the pandemic we did not observe any delays in the detection of recurrent disease in our study, regardless of how long it had been since the end of treatment. Observing delay is important because it impacts negatively on prognosis (Murphy et al., 2016; Teppo & Alho, 2008) Fortin et al. found a 15% reduction in survival rate for HNSCC patients if the waiting time from diagnosis to RT was over 40 days (Fortin et al., 2002). Similar results were found in a study by Hanna et al., where the risk of death from HNC increased by about 10% with every 4-week delay (T. P. Hanna et al., 2020). Denmark instigated national fast-track procedures in 2007 with the purpose of reducing delays in diagnostics and treatment to improve survival in HNC (Roennegaard et al., 2018).

In Study II, only three recurrences were observed later than 1 year after treatment. While patients can convey their symptoms over the phone, it is crucial to ask targeted and precise questions. It is also possible that patients may downplay their symptoms, underscoring the importance of urging them to come in for a clinical visit if any symptoms arise. In our Study II, only a minority of recurrences (17%) were detected in patients who had been treated more than a year earlier. Notably, none of these diagnoses were delayed due to phone consultations. Although the number of recurrences in the study is modest, this finding is encouraging.

Only three patients requested phone calls instead of clinical visits in the group treated less than a year earlier. In the same group, clinical visits were changed to phone appointments for six patients upon our recommendation, as underlying disease put them at higher risk of severe outcomes from COVID infection.

In the literature, studies of patient compliance and telemedicine give divergent results. Fassas et al. found that HNC patients prefer in-office visits over telemedicine if given a choice, the major reason being lack of physical examination (Fassas et al., 2021). In a study by Mueller et al., 89.1% of patients preferred self-referral for regular follow-up, 57% favoured fewer visits than the current standard, and 85.1% endorsed regular imaging. Women and patients with a high fear-of-recurrence score were more inclined towards intensive follow-up. However, 2/3 would not want to participate in a randomised follow-up study (Mueller et al., 2019). According to Stewart et al., 30% preferred telemedicine over face-to-face appointments (Stewart et al., 2021). Conversely, Larson et al. found that the quality of life was quite similar in patients whose follow-up was conducted through telemedicine compared to those who attended clinical visits (Larson et al., 2018). In a study by Dhillon et al., 95% of HNC patients had a positive experience with telemedicine appointments and were willing to continue with them in the future (Dhillon et al., 2022).

6.4 Adverse effects of treatment

In Study III, we found that late adverse effects such as dysphagia, hypothyroidism, and osteoradionecrosis are common after treatment with RT of HNC. Nearly half of the patients reported persistent dysphagia, which is consistent with earlier literature; for example, Carmignani et al. found it in 45% of patients and Roe et al. in 44% (Carmignani et al., 2018; King et al., 2016; Martin et al., 2018; Patterson et al., 2018; Roe et al., 2014). This is more prevalent in patients who have received chemoradiotherapy due to mucosal injuries, damage to connective tissue, and xerostomia (Pezdirec et al., 2019). In our study there was no dysphagia in patients treated with surgery alone in advanced stage disease.

Dysphagia significantly impacts the quality of life of patients, especially when they become dependent on PEG tubes because of it (Carmignani et al., 2018; Ranta et al., 2021). Adequate nutrition is important for recovering from treatment. In our study, 10.3% of all RT-treated patients were dependent on a PEG tube, but only 1.7% were unable to swallow anything other than liquids. In the literature, the percentage of permanent feeding-tube dependency (4–12.1%) in disease-free patients is consistent with our results (Beitler et al., 2014; Wopken et al., 2014). Dilatations are recommended for HNC patients with radiation-induced oesophageal stricture, although the rate of complications such as perforations and infections is relatively high at 10.6% (Agarwalla et al., 2015; Moss et al., 2018).

In our study, age or stage of disease had no correlation with dysphagia. Conversely, in a study by Baudelet et al., patients with a higher T classification and older patients had higher dysphagia scores (Baudelet et al., 2019). We found that the only significant treatment-related factor behind dysphagia was neck RT. However, unlike in other studies, in our study there was no statistically significant difference in the proportion of existing dysphagia between definitive and elective neck treatment (Jiang et al., 2018; Kannan & Arul Ponni, 2019). One limitation of our study was lack of data on specific doses to musculature and nerves, which might have contributed to our results. Gharzai et al. suggest that radiation dose to the tongue musculature may be associated with very late dysphagia, and to the hypoglossal nerve with late progressive dysphagia (Gharzai et al., 2020).

Recognised risk factors for radiation-induced hypothyroidism include being female, younger age, having a smaller thyroid, prior neck surgery, and receiving higher radiation doses (Zhou et al., 2020). In our data, we observed a clear influence of female gender and younger age on hypothyroidism, but a greater radiation dose did not show a corresponding increase in incidence, contrary to the findings of Chow et al. (J. C. H. Chow et al., 2022). Unfortunately, specific doses to individual thyroid glands were unavailable for analysis in our study. Nevertheless, IMRT effectively limits radiation exposure to the thyroid gland (Zhou et al., 2020). As described earlier in the literature, we also found that hypothyroidism was less common among heavy

alcohol users (19.0%) than among patients with no history of heavy alcohol use (31.1%) or those with a history of heavy alcohol use before HNC diagnosis (48%) (Balhara & Deb, 2013; Carlé et al., 2012). We noted an elevation in TSH levels following radiation exposure. However, it is worth noting that TSH levels naturally tend to increase with age, which led us to conclude that this finding holds limited additional significance (Surks & Boucai, 2010).

In our study, patients with oral cavity cancer had a higher risk of mandibular ORN (20.7%); 12% of RT-treated patients had mandibular ORN, which is in line with previous literature (4–14%) (Beadle et al., 2013; De Felice et al., 2020; Kubota et al., 2021; Moon et al., 2017). Certain factors like tooth extraction, smoking, and treatment dose are associated with development of mandibular ORN (Aarup-Kristensen et al., 2019). Our data included only a small number of mandibular ORN cases (n=29), which limited assessment of further correlations.

Chemotherapy alongside hyperfractionated RT does not seem to worsen late toxicities, aligning with our findings (Haussmann et al., 2019).

6.5 Strength and limitations

The strength of these studies and this thesis lies in the fact that the population examined consisted of real-world HNC patients, unaffected by socioeconomic background or selection bias. One of the studies was multicentred, which offered a larger sample size and an interesting possibility to compare different follow-up protocols in two otherwise rather similar departments.

However, due to the retrospective setting, it was not possible to have exact information, for example, on cigarette smoking history and alcohol consumption. Lack of data is a feature of retrospective studies, and when patients are followed up for several years some are bound to be lost to the study through incomplete adherence to follow-up.

Interpreting patients´ medical history is not always equal when data collection is done by multiple investigators. In a multicentre study there may also be varying practices in recording patient data. Even if the multicentre study offered a good sample of patients, a larger sample of asymptomatic PET-detected recurrences might have provided even more informative results.

6.6 Future perspectives

In this thesis, we focused on the follow-up and adverse effects of HNC patients after treatment. The role of imaging in follow-up will be within our scope of study in the future. One question is whether patients with a totally clear baseline PET/CT need follow-up at same intensity as other patients. Searching for an optimal imaging

modality for surveillance of salivary gland cancer patients is a topic of interest in the future as well.

The role of HPV-associated OPSCC in post-treatment imaging protocols is also interesting due to its tendency to recur later, and figuring out an optimal protocol for these patients needs further investigation. Use of liquid biopsy in HPV and EBV-involved HNSCCs shows promising outcomes in detecting recurrent disease. It is interesting to see how liquid biopsy will change the follow-up protocols of HNCs once it is taken into wider use.

Treating HNC is concentrated to five departments in Finland. Our multicentre study looked at two of them, but in future it could well be possible to combine the power of all five departments to get a larger sample for follow-up studies.

7 Conclusions

1. Three years of routine clinical follow-up of HNSCC patients after curative intent treatment seems to be long enough. It is important that patients can contact the clinic in case of symptoms after routine follow-up has ended.
2. No delay was found in detecting recurrences even if telephone follow-up was used during the COVID-19 pandemic. Telephone or telemedicine may be used as a part of routine follow-up of HNSCC patients. However, more studies are needed.
3. Late toxicities of RT in HNC are prevalent, dysphagia and hypothyroidism being more common than ORN.
4. Routine PET/CT or PET/MRI at follow up 1 year after treatment of HNSCC does not improve 5-year OS or DSF.

Acknowledgements

This study was conducted at the Department of Otorhinolaryngology – Head and Neck Surgery of Turku University Hospital and at the University of Turku during 2015–2024.

I would like to thank Professors Heikki Irjala, Jaakko Pulkkinen, Jussi Jero, and Reidar Grenman for providing me the opportunity to complete my PhD studies during my time at the clinic.

I wish to express my deepest gratitude to my supervisor, Professor Heikki Irjala. You introduced me to the world of science, challenged me to do my best, and guided me through this at times exhausting thesis. You always had time for endless questions. Many thanks also for your clinical guidance on head and neck surgery.

I am very grateful to all my co-authors for their valuable contribution to the publications of this thesis: Adjunct Professor Ilpo Kinnunen, Eeva Haapio PhD, and Professor Heikki Minn for your input in Studies I and II. Thanks especially to Pihla Ranta MD for your contributions to Study III. Thanks to Matti Karjalainen MD and the TAYS "tuumoritiimi" for helping design the project and collect the data for Study IV. Warmest thanks also to Elina Halme PhD and Professor Jussi Hirvonen for your hard and valuable work when I needed it most. I also wish to thank all the other co-authors of Studies III and IV. Thanks to Tero Vahlberg MsC for your help and work with my statistics.

I wish to thank Adjunct Professor Patrik Lassus and Adjunct Professor Harri Keski-Säntti for reviewing this thesis. I also want to thank the members of my monitoring group, Adjunct Professor Paula Lindholm, Adjunct Professor Samuli Vaittinen, and Adjunct Professor Ilpo Kinnunen.

I would like to thank Adelaide Lönnberg (MapleMountain Editing) for revising the English of this thesis.

I would like to thank all my dear colleagues and other staff at the ENT-Clinic of Turku University Hospital. You are all the best colleagues ever. Every day working with you is a pleasure, and your support is always available when needed. Adjunct Professor and Head of the Department Ilpo Kinnunen, thank you for your support and guidance throughout the clinical work, research, and numerous discussions about medicine, life and everything in between. Special thanks to the group

“Tulevaisuuden tohtorit”, who always shared the ups and downs of my thesis and helped me carry on without getting totally depressed through this project. Professor Jaakko Pulkkinen, special thanks for your understanding of the importance of skiing for well-being at work!

I am privileged to have so many dear friends who have been a strong asset in my daily life and work. Touko, Juho, and Lauri, thank you for your friendship ever since primary school. Thank you also for regularly reminding me that there is life beyond medicine. To the group "Salipunttimaksimipenkki" and all my other friends, your friendship has been very important to me in all aspects of my life. At university, at work, in science, in hobbies, in music and travel or in everything we have done together, and of course skiing. Special thanks to the Joutsens: Jenny for her enthusiasm and encouragement in science, and Alvi, who on the other hand reminded me that real life lies outside of science.

Thanks to one of the most overeducated bands: Professor Jarmo Gunn, Professor Jussi Hirvonen, Adjunct Professor Heikki Lukkarinen, Jami Rekola PhD, and Jan-Erik Wikström PhD. I am very grateful for your friendship and especially for sharing your musical interests. The only sadness is that the level of education is not always reflected in our musical performances!

I am deeply grateful to my family. To my parents Marja and Pekka, you have always loved, supported, and believed in me and helped me find my own path. Your help to our family has been tireless. To my big brothers Heikki and Aleksi, thanks for so many reasons, and especially for your support throughout my life. To my in-lawns Maisa and Juhani, thank you for all your help to our family throughout all these years.

Finally, I express my warmest thanks to my lovely wife, Jutta. Your love and support are evident everywhere in my daily life, and even this thesis would never have been completed without you. To our lovely children Aapo, Elli, and Aili, you are the most precious ones in my life and the only thing that really matters.

This work was financially supported by the Kirsti and Tor Johansson Heart and Cancer Foundation, the Merck KGaA, the State Research Fund, the Turku University Foundation, the Cancer Foundation of Southwest Finland, the Finnish ORL-HNS Foundation, the Finnish Cancer Foundation, the TYKS Foundation, the Paulo Foundation, and the Päivikki and Sakari Sohlberg Foundation.

Eero Kytö

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TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2024

ISBN 978-951-29-9605-6 (PRINT)
ISBN 978-951-29-9606-3 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)