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Health Systems Factors in Advanced Stage Diagnosis of Head and Neck Cancer

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Abstract

Background: Globally, head and neck cancer (HNC), comprising of squamous cell carcinomas of the oral cavity, oropharynx, larynx, and other sites of the head and neck, is the 7th most common cancer grouping by incidence and 9th by mortality. People with HNC have poor overall survival, with an estimated 50% 5-year survival. One of the key prognostic factors is stage at diagnosis, with people diagnosed with advanced stage HNC at diagnosis, categorised as stage III or IV in the Tumour, Nodes, Metastases (TNM) classification, having poorer outcomes than those with early-stage disease (stages I and II). The burden of advanced stage HNC in the UK is not quantified and factors associated with advanced stage at diagnosis, particularly health systems factors, not well researched or understood. There is a paradigm shift happening in health services research with the understanding that pragmatic approaches embracing complexity are needed. With advanced stage HNC presenting a public health challenge in the UK and internationally, ascertaining the full nature of the burden of advanced stage HNC and the factors associated with advanced-stage diagnosis are key to prepare system changes and interventions to improve early detection rates.

Aims: This thesis is split into three separate studies each focussing on specific aims:

i) Chapter Three: To quantify the burden of advanced stage HNC across the countries of the United Kingdom through analysis of routinely collected cancer registry data, and to begin to assess the distribution of stage of HNC by socio-demographic factors.

ii) Chapter Four: To identify health systems factors associated with stage at diagnosis through a novel benchmarking survey of international HNC centres.

iii) Chapter Five: To explore the role of health systems factors in advanced stage diagnosis of HNC through qualitative analysis of two HNC centres: Glasgow, Scotland and Montevideo, Uruguay.

Methods: A mixed-methods approach was undertaken in this thesis. Each study had specific methodological approaches:

i) Chapter Three: Collecting routinely collected, aggregated cancer registry data from the four Cancer Registries of the UK via detailed specification of HNC data requests (2009-2018). Data were collated and harmonised. Descriptive epidemiological analysis of trends and the burden of advanced stage across the four countries was performed by HNC overall and subsite groupings. Additional, analysis was undertaken for the Scottish Cancer Registry stage of HNC and subsites by age grouping, sex, and area-based socioeconomic status measured by the Scottish Index of Multiple Deprivation (SIMD) of home postcode.

ii) Chapter Four: A bespoke health systems questionnaire was sent to 18 international HNC centres, to the Head and Neck Cancer in South America and Europe (HEADSpAcE) Consortium centre leads. The questionnaire included items on various health system domains capturing both quantitative and qualitative data on the local pathways to diagnosis of HNC and burden of advanced stage HNC. These data were collated and categorised into health systems factors and HNC centres were then benchmarked according to the local proportion of advanced stage HNC and the presence/absence of these factors within their local HNC diagnostic pathway. Analysis for each health system factors was undertaken to assess the impact of each factor on the proportion of advanced stage HNC through least square means tests. Qualitative descriptions of the patient pathways to HNC diagnosis for all centres were collated and harmonised into an adapted diagnostic interval model.

iii) Chapter Five: A qualitative follow-on study to the research undertaken in Chapter Four was conducted in two centres (Glasgow, UK and Montevideo, Uruguay) and comprised 29 semi-structured, in-depth interviews undertaken with a range of stakeholders across both sites, including surgeons, oncologists, primary care practitioners, and HNC patients. The interviews used specifically created topic guides; and were undertaken by trained and standardised interviewers. Interviews were recorded, transcribed, and translated where required to enable analysis. A thematic template analysis was undertaken with 16 key health system themes and 45 sub-themes identified across the different intervals of HNC diagnosis and subsequently applied to the framework of the systems engineering initiative for patient safety (SEIPS) 3.0.

Results: Key findings from each study were:

i) Chapter Three: Descriptive analysis revealed that in the UK 59% of HNCs where stage is recorded were found to be at advanced stage at diagnosis in 2016-2018, with stage IV the most common stage at diagnosis for all HNC. Cancer Registry data on stage at diagnosis had improved year on year and was 87% complete by 2018. Further analysis of the Scottish Registry data found males to have higher odds of having advanced stage HNC than females (odds ratio (OR) 1.24, 95% Confidence Interval (CI) 1.05, 1.46), and those who are diagnosed with HNC from the 20% most socioeconomically deprived areas had greater odds of having advanced stage at diagnosis when compared to those in the 20% least socioeconomically deprived areas, although the association was not as strong (OR 1.14, 95% CI 0.89, 1.48).

ii) Chapter Four: Health systems factors were shown to be associated with a lower proportion of advanced stage HNC including formal referral triaging (14%, 95%CI-0.26, -0.03), routine monitoring of time from referral to diagnosis (16%, 95%CI-0.27, -0.05), and fully publicly funded systems (17% 95% CI-0.29, -0.06). Several health system factors were found to have a lack of routinely collected data at HNC centre, including routine reporting of proportion of advanced stage locally, workforce numbers and whole-time equivalent of different specialties and grades, HNC referral source, routine reporting of referrals leading to confirmed HNC diagnosis, and performance indicators relating to referral/pre-diagnosis. Additionally, the variance in pathways to HNC diagnosis across the HNC centres in this study were harmonised into a universal pathway to HNC diagnosis.

iii) Chapter Five: Key health system themes identified included public awareness and ability to act on HNC symptoms (i.e. navigate into and through pathways to diagnosis), the underlying role of socioeconomic/geographic inequalities, and the disconnect/communication barriers between care teams – specifically primary and secondary care. In applying the thematic results to the SEIPS framework, a systems understanding of how the themes relate to the various elements and processes of HNC diagnostic pathways was formed, illustrating the complexity whilst highlighting how these factors may be navigated (through focus on people, tasks, environment, or organisations).

Conclusions: This thesis presents and describes a high burden of advanced stage HNC across the nations of the UK, identifies important health systems factors in advanced stage HNC across international HNC centres, develops a harmonised HNC diagnostic pathway, and further explores the main factors associated with stage at diagnosis of HNC from two HNC centres, Glasgow in Scotland and Montevideo in Uruguay.

This research undertaken in this thesis includes the first fully focused health systems factors investigation into advanced stage diagnosis of HNC through a systems approach to international HNC diagnostic pathways. The findings from this research present key considerations for health system/service change to improve earlier diagnosis of HNC internationally.

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Author's Declaration

This thesis has been submitted by alternative format. I declare that, except where explicitly stated, that this thesis is the result of my own work and has not been submitted, partly or in whole, for any other degree at the University of Glasgow or any other institution.

Publications

Research from this thesis was published in the following peer-reviewed journals:

British Dental Journal – Published November 11th 2022. "Head and neck cancer in the UK: what was the stage before COVID-19? UK cancer registries analysis (2011–2018)" https://doi.org/10.1038/s41415-022-5151-4

Head and Neck - Published February 25th 2025. "Advanced Stage Head and Neck Cancer Diagnosis: HEADSpAcE Consortium Health Systems Benchmarking Survey" https://doi.org/10.1002/hed.28094

Findings synthesised from the literature review undertaken in this thesis contributed towards the following publications:

British Dental Journal – Published November 11th 2022 "Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors" https://doi.org/10.1038/s41415-022-5166-x

The Journal of Laryngology and Otology – Published March 14th 2024. "Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines, Sixth Edition Edited by Jarrod J Homer and Stuart C Winter" https://doi.org/10.1017/S0022215123001615

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HEADSpAcE Scientific Meeting (IARC – WHO): (Remote) HEADSpAcE (IARC-WHO) Annual Meeting, Heidelberg, Germany 11th April 2024. *"Health System Factors in Advanced Stage Diagnosis of HNC"*

International Association for Dental Research HEADSpAcE Symposium: Bogota, Colombia, 23rd June 2023. *"Investigating the Role of Healthcare Systems in Advanced Stage Head and Neck Cancer Diagnosis"*

International Association for Dental Research: Behavioural, Epidemiologic and Health Services Research Forum: Bogota, Colombia, 20th June 2023. *"Investigating the Role of Healthcare Systems in Advanced Stage Head and Neck Cancer Diagnosis"*

The International Centre for Oral Health Inequalities Research and Policy (ICOHIRP) Showcase (Remote) 10th May 2023. *"Investigating the Role of Healthcare Systems in Advanced Stage Head and Neck Cancer"*

HEADSpAcE Scientific Meeting (IARC – WHO) Cartagena 6th October 2022. *"Updates on Head and Neck Cancer Health Systems Analyses"*

HEADSpAcE Scientific Meeting: (IARC – WHO) (Remote) 11th March 2021. *"Incidence and Trends in Advanced Stage Diagnosis of Head and Neck Cancer in the United Kingdom"*

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Three Minute Thesis (3MT) University of Glasgow Finalist 2nd July 2020 *"When Being Late is Never a Good Thing"*

Definitions/Abbreviations

2WW - Two-Week-Wait
AJCC - American Joint Commission on Cancer
ARCAGE - Alcohol-Related Cancers and Genetic Susceptibility in Europe:
ASR - Age-Standardised Rates
CI - Confidence Interval
CRUK - Cancer Research UK
CT - Computerised Tomography
cTNM - Clinical Tumour, Nodes, Metastases Stage
ENT - Ear, Nose, and Throat
FONASA - Fondo Nacional de Salud (National Health Fund of Uruguay)
GDP – General Dental Practitioner
GLOBOCAN – Global Cancer Observatory
GP - General Practitioner
HEADSpAcE - Head and Neck Cancer in South America and Europe
HIC – High Income Country
HN5000 – Head and Neck 5000
HNC – Head and Neck Cancer
HPV – Human Papilloma Virus
HR – Hazard Ratio
IARC - International Agency for Research on Cancer
ICBP – International Cancer Benchmarking Partnership
ICD - International Classification of Diseases
INHANCE - International Head and Neck Cancer Epidemiology Consortium
KPI - Key Performance Indicators
LC - Laryngeal Cancer
LMIC – Low-Middle Income Country
MDT - Multidisciplinary Teams
MRI - Magnetic Resonance Imaging
MVLS - Medicine, Veterinary and Life Sciences
NCCN - The National Comprehensive Cancer Network
NCD - Non-Communicable Diseases
NHS – National Health Service
NICE - National Institute for Clinical Excellence
OCC - Oral Cavity Cancer (OCC)
OPC - Oropharyngeal Cancer (OPC)
OR - Odds Ratio (OR)
PCP – Primary Care Practitioner
PET-CT - Positron Emission Tomography-Computerised Tomography 41
pTNM - Pathological Stage
QPI - Quality Performance Indicators
SCC - Squamous Cell Carcinoma
SDoH - The Social Determinants of Health
SEER - Surveillance, Epidemiology, and End Results
SEIPS - Systems Engineering Initiative for Patient Safety
SIMD - Scottish Index of Multiple Deprivation
SNIS - National Integrated Health System
TNM - Tumour, Nodes, Metastases
UHC - Universal Health Coverage
WHO – World Health Organisation
WOSCAN - The West of Scotland Cancer Network

1 Chapter One: Introduction

1.1 Overview

This chapter begins with a narrative literature review covering the definitions and descriptions of the term head and neck cancer (HNC) used, and the epidemiology of HNC, including the burden of disease (trends in incidence/survival), alongside the risk factors, determinants and health inequalities associated with the disease. Following this disease-specific section, a narrative overview of what constitutes a “health system” and the role of “systems-thinking” in health research is provided, with a brief introduction to general cancer diagnostic systems and pathways from the international literature. This chapter concludes by bringing these two elements together in an overview of HNC diagnostic pathways and provides the rationale for the thesis research questions and studies on the role of health system factors in HNC diagnosis pathways and stage of presentation. The flow for this introductory and background chapter can be seen visualised in Figure 1-1.

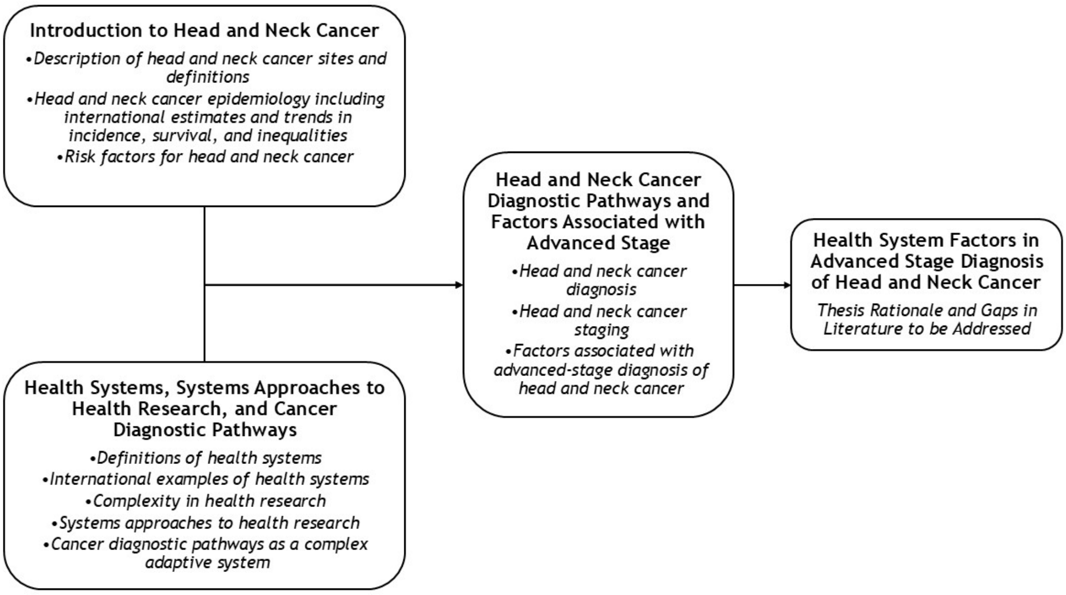

Figure 1-1: Overview of Literature Reviewed and Presented in Introduction Chapter

1.2 Head and Neck Cancer Definition

HNCs are defined as primary tumours arising in the mucosal lining of the mouth, throat and voice-box; with Squamous Cell Carcinoma (SCC) being the most common histologically confirmed cancer, making up 90% of HNCs, and the remaining 10% being other types of cancer such as tumours arising from: lymphoid tissue (Lymphomas), glandular tissue (Adenomas) or muscle tissue (Sarcomas). Excluded from HNCs are brain tumours and skin cancers of the face and neck (Melanomas) (cancer.net, 2021, NHS.UK, 2021).

HNCs are grouped together for clinical and academic purposes due to their common epidemiology, risk factors, and treatment approaches, however, given the complex anatomy of the head and neck, HNCs are divided into grouped sites based on their exact anatomical location. The main sites for HNC are the oral cavity (mouth), oropharynx (throat), the larynx (voice box), hypopharynx, and nose and paranasal sinuses. These sites are further broken down into sub-sites and include organs and tissues essential for many important bodily functions, such as eating, speaking, facial expression, smelling, and senses such as sight, taste, smell and taste (Logan, 2016).

The group name HNC is widely termed by multiple agencies/organisations, including the National Cancer Institute, International Agency for Research on Cancer (IARC), and Cancer Research UK (CRUK), but it remains important to clarify the definition of the sites included based on The International Classification of Diseases and Related Health problems (ICD) codes when discussing literature or interventions based on each specific site grouping (Kaste, 2013). ICD codes are the internationally recognised method for recording types and sites of disease endorsed by the WHO. This offers a standardised method for recording a given diagnosis and allows for efficient data collection and compilation (WHO, 2019).

The oral cavity covers the soft tissues of the mouth and is bordered by the inner aspect of the lips to the posterior border of the hard palate. The specific sub-sites of the oral cavity also include the periodontal tissues (gums), the lining of the cheek (buccal mucosae), the floor of the mouth (the area underneath the tongue), the anterior two thirds of the tongue and the tissue located behind the lower wisdom teeth (retromolar pad). Cancers of the external surface of the lip are not included in the definition of HNC due to having a very different aetiology and disease profile similar to that of non-melanomatous skin cancers, with exposure to UV light being the major risk factor. ICD-10 codes for oral cavity cancer (OCC) include: C00.3 – C00.9 inner aspects of lip; C02 anterior 2/3 tongue; C03 gum; C04 floor of mouth; C05 palate; and C06 inner cheek/other linings of mouth.

The oropharynx encompasses the area immediately posterior to the oral pharynx and includes the soft palate, uvula, tonsillar pillar, tonsils, posterior wall of the oropharynx and the posterior third of the tongue. Together, oral cavity and oropharyngeal cancers have been grouped as “Oral Cancer” but diverging epidemiology for each has resulted in them being considered as distinct disease entities for academic and clinical purposes (Conway et al., 2018). ICD-10 codes for oropharyngeal cancer (OPC) include: C01 base of tongue; C02.4 lingual tonsil; C09 tonsil; C10 oropharynx; and C14.0, C14.2 pharynx

The larynx is the area immediately inferior to the oropharynx and contains three distinct anatomical areas. The supraglottic section contains the epiglottis (a flap of soft tissue that prevents food from entering further into the respiratory tract when eating), the arytenoid cartilage, the aryepiglottic folds and the ventricular bands which enable the function of speech. ICD-10 codes for laryngeal cancer (LC) include those under C32.

The hypopharynx is the area directly posterior to the larynx. It encompasses the pyriform sinus, postcricoid region, hypopharyngeal aspect of aryepiglottic fold, posterior wall and laryngopharynx and includes ICD-10 codes under C13

Nasal cavity and nasopharyngeal cancers have a slightly different aetiology to the other major regions of HNC, with strong evidence pointing to higher risk among those from Chinese/Asian ethnic groups, and Epstein-Barr Virus exposure and a family history of the disease are distinct risk factors (Chen et al., 2019). These tumours are not typically included in definitions of HNCs as a group.

Thyroid cancers also are treated as a separate entity due to a diverging epidemiology and clinical management strategies, with rising incidences but flat mortality rates seemingly due to development in screening and early detection (Seib and Sosa, 2019).

Salivary gland cancers cover a rare and diverse group of non-squamous cell carcinomatous tumours including adenocarcinomas, adenoid cystic carcinomas and acinic cell carcinomas. The diagnostic methods, epidemiology, survival rates, and management strategies differ from the major HNC groups such that they are often not included in the common grouping of HNC (Carlson and Schlieve, 2019).

For the purposes of this thesis, the term HNC is used to encompass SCCs of the head and neck including cancers of the oral cavity, oropharynx, hypopharynx and larynx. This definition is adopted on several grounds, including that these tumours comprise the vast majority of HNCs, their common epidemiology (risk factors), but most importantly that they are managed collectively by head and neck cancer clinical teams in specialist hospital services.

1.3 Head and Neck Cancer Epidemiology

1.3.1 Descriptive Epidemiology: Incidence

Globally, HNC accounts for 4.2% of all new cases of cancer and is the 6th most common in incidence and make up about 4% and 5% of all new cancers in Europe and South America respectively, with the greatest burden ins South East Asia (Bray et al., 2018). The overall incidence of HNC is expected to continue to rise by about 30% by 2030 (Johnson et al., 2020, Sung et al., 2021). Several recent reviews have found that HNCs to be a global epidemic (Simard et al., 2014, Shield et al., 2017) with increased incidence of HNC recorded in both developed (high income) and developing (low and middle income) countries (Bravi et al., 2021). Laryngeal cancers have increased by 23% in the past decade, however, age-adjusted rates for new laryngeal cancer cases have been falling in high-income countries (Global Burden of Disease Cancer Collaboration, 2017). Countries with the highest burden of HNC, in particular OCCs, are found in

South-East Asia or the Asian-Pacific regions, followed then by European countries, where there is a rising burden of OPC, and South America, in particular Brazil (Gormley et al., 2022).

HNC affects males two-to-four times more than females (Miranda-Filho and Bray, 2020). The risk of developing HNC increases with age, with the majority of cases diagnosed in those over 50 years old (Warnakulasuriya, 2009). Interestingly, there has been a rise in reported cases of HNC, particularly oral cavity cancer, amongst younger females in European countries, which may be explained by sex-specific patterns of tobacco and alcohol consumption, but it is a topic of interest in current literature. (Miranda-Filho and Bray, 2020, Bosetti et al., 2020)

HNC rates are rising in the UK, almost entirely due to rising OPC. From 1995-2011, OPC incidence increased by 7.3% for males and 6.5% for women in England, with OCC having a 2.8% rise in men and 3.0% rise in women (Louie et al., 2015). In Scotland specifically, OPC incidence rates increased by 85% from 1975-2012. (Purkayastha et al., 2016). HNC rates in Scotland have had an upwards trend in Scotland over the last 25 years, with routinely reported data from the Scottish Cancer Registry showing a near 50% increase in cases diagnosed in 2017 compared to 1993. Within the UK, Scotland has the highest rates of HNC (Conway et al., 2018).

1.3.2 Descriptive Epidemiology: Mortality and Survival

Across the globe, survival from HNC is poor with only 50% of patients surviving at five years with little change over recent decades for men and women according to WHO death certification data (Warnakulasuriya, 2009, Bosetti et al., 2020). Mortality due to HNC is multifactorial with patient factors (i.e. age, sex, socioeconomic status), treatment factors, smoking/alcohol status, tumour site, and advanced stage diagnosis all important prognostic indicators (Ingarfield et al., 2019a). HNC survival rates vary greatly across geography, tumour sub-site and diagnostic stage, with a global 5-year survival rate of 45.7% (Muller et al., 2016).

The five-year net survival rates for adults with HNC in the UK are 56.1% for oral cavity cancer, 65.6% for oropharyngeal cancers, 66.8% for laryngeal cancers and as low as 30.1% for hypopharyngeal disease. (CRUK, 2020). HNC can be cured if the tumour is diagnosed at an early stage and confined to the head and neck region, but survival is poor if there is advanced stage disease, metastatic spread and recurrence of disease (Marur and Forastiere, 2016).

In 2018 in the UK there were approximately 4000 deaths attributable to HNC which accounted for 2% of all cancer deaths (CRUK, 2021). There exists some variation in national HNC mortality rates (European Age-standardised rates; ASR per 100,000 population) between the four nations of the UK with Scotland (ASR 8.7) and Northern Ireland (ASR 8.4) having worse outcomes than England (ASR 6.2) and Wales (ASR 5.8). Over the past five decades, HNC mortality for men and women combined has fallen by 11% overall (1971; ASR 7.3. 2018; ASR 6.5). The last decade, however, has seen a gradual rise in mortality rates from a low in 2006 (ASR 5.6) possibly reflecting the changes in disease incidence and static survival rates. (CRUK, 2021)

1.3.3 Analytical Epidemiology: Risk Factors

HNC is a disease with numerous attributable risk factors covering behavioural, infectious agent, and socioeconomic factors. The international head and Neck cancer epidemiology consortium (INHANCE) included 35 pooled-case-control studies from across the globe and aimed to better understand the individual-level risk factors for HNC development that consisted of studies from across the globe and met a minimal standard of sample size and data availability. The INHANCE consortium has to-date published 45 peer-reviewed papers which are summarised effectively in two key papers by Winn et al. (2015) and Bravi et al. (2021). Risk factors are common across the sub-sites of HNC, bar a few specific exceptions, but the magnitude of effect for each risk factor can vary across sub-sites. The key findings from the INHANCE consortium and other important studies have been summarised below.

1.3.3.1 Tobacco Use and Alcohol Consumption

The major risk factors for HNC are firmly understood to be the behaviours of tobacco smoking and drinking alcohol, both in isolation and combined (Gormley et al., 2022). Tobacco smoking is a prominent carcinogen with this behaviour alone increasing an individual risk for developing HNC by ten times compared to non-smokers (Jethwa and Khariwala, 2017). In their substantial pooled analysis, Hashibe et al. investigated the effects of tobacco smoking in people who never consumed alcohol and found an increased risk of HNC (Hashibe et al., 2007). Additional pooled analyses have shown the increased frequency and higher dose of smoking is associated with greater risk of developing HNC (Lubin et al., 2009), with duration having a stronger effect than dose, a result that has been consistent over recent decades (Berthiller et al., 2016).The attributable risk of smoking for each HNC subsite group varies and has been found to be most prominent for laryngeal cancer, with significant associated also noted for oral cavity and oropharyngeal cancers (Hashibe et al., 2007). Second-hand smoke carries also carries risk for developing HNC in non-smokers (Lee et al., 2008). Use of smokeless tobacco also increases the risk of developing HNC, most significantly for oral cavity cancer (Wyss et al., 2016).

Alcohol consumption is a behaviour strongly associated with increased risk of developing HNC (Gormley et al., 2022). People who never smoke but regularly and frequently consume alcohol have an increased risk of developing HNC (Hashibe et al., 2007) whilst a shorter time of higher frequency consumption is more harmful than a longer period of lower frequency consumption (Kawakita and Matsuo, 2017). There is limited effusive evidence on the variation in risk between different types of alcohol but the evidence that does exist shows little difference in the overall risk of HNC development between beer and spirits (Purdue et al., 2009).

Although tobacco use and the synergistic effect of smoking tobacco and consuming alcohol has been shown to increase risk of developing HNC by over 35-fold, Hashibe et al (2009), in a subsequent pooled analysis to their 2007 study, showed 72% of HNC cases overall could be attributed to combined tobacco use and alcohol consumption across the INHANCE consortium, and 83%-84% in Latin America and Europe respectively. A large multi-centre study on upper aerodigestive tract cancers from the 2000s was unequivocal in its attribution of risk of HNCs and showed that the multiplicative effect of smoking tobacco and consuming alcohol accounted for 85% of hypopharyngeal/laryngeal cancers, 75% of non-HPV (Human Papilloma Virus) oropharyngeal cancers, and 61% of OCCs (Anantharaman et al., 2011). Although rates of tobacco smoking and alcohol consumption are reducing in high-income countries, rates in developing countries are rising dramatically as commercial entities target new markets (Delobelle, 2019).

1.3.3.2 Human Papilloma Virus

In recent decades, there has been a growing understanding of the role played by HPV in the development and pathophysiology of HNC. Of the many types of HPV, 15 are known to be associated with cancer of the cervix, anus, and oropharynx, with HPV 16 accounting for over 90% of HPV-positive oropharyngeal tumours (Kobayashi et al., 2018). HPV positive HNC has been said to be driving the increase in rates of oropharyngeal cancer but not necessarily with oral cancer (Conway et al., 2018). Prior to 2010, HPV-positive disease was not classified as a distinct aetiological and molecular entity (Ang et al., 2010) but HPV positive and HPV negative squamous cell carcinoma of the oropharynx are now two separate disease entities, as is reflected by the changes in disease staging classification described later in this chapter (See section 1.4.4). HPV positive tumours have been shown to have a better overall prognosis (Ang et al., 2010), with 87% of patients with HPV positive oropharyngeal cancer shown to survive for minimum 10 years post diagnosis compared to those diagnosed with HPV negative oropharyngeal cancer of whom 56% survive for 10 years (Du et al., 2019). The distinct epidemiological differences led to the development of different treatment regimens for HPV-positive HNC so as to reduce the morbidities experienced by these patients associated with conventional treatment (Marur et al., 2010).

1.3.3.3 Additional Risk Factors and Geographic Variance

Other possible risk factors include low dietary fruit/vegetable intake (Boeing et al., 2006, Sapkota et al., 2008), sexual history (Smith et al., 2004), marijuana use (Hashibe et al., 2005), poor oral hygiene (Rosenquist, 2005), family history of HNC (Negri et al., 2009), low body mass index (Kreimer et al., 2006) and exposure to several occupational circumstances such as isopropanol manufacturing and exposure to inorganic acid mists containing sulfuric acid and mustard gas, which are risks thought to be risks for laryngeal cancer (Siemiatycki et al., 2004). Some risk factors are specific to territory such as drinking hot mate in South America (Loomis et al., 2016).

In certain parts of Asia and the Pacific Islands, the chewing of betel quid/areca nut is strongly associated with an increased risk of HNC, specifically oral cavity cancers and forms the basis of the prediction of increasing burden of HNC in these areas in the future (Petti, 2009).

An important pooled analysis of 32 case-control studies undertaken as part of the INHANCE consortium investigated the role of behavioural risk factors in HNC incidence and found stark differences between less developed countries and more developed countries in the role of smoking and alcohol. For smokers of greater than 20 years, there was an increased risk of developing OCC and Hypopharynx cancers in less developed countries compared to more developed countries, and for alcohol consumption of greater than 20 years there was an increased odds ratio for developing all HNC sites bar overlapping sites and OCC in less developed countries (Goyal et al., 2023). This raises interesting questions as to what the cause of these differences is, including the type of tobacco product/alcohol consumed and suggests underappreciated cultural/societal differences that may affect risk of developing HNC.

1.3.4 Head and Neck Cancer Inequalities and Socioeconomic Status

“Health inequalities” is the term commonly used to describe the preventable and adverse discrepancies in health outcomes of different patient populations (Marmot, 2017). Health inequalities exist globally, both in developed and developing countries. They exist between and within countries and do so because of a range of economic, political, commercial, and societal factors. Inequalities between groups can be absolute or relative and are found across the whole spectrum of health and disease, including HNC. The burden of head and neck cancer is strongly socioeconomically patterned, with those in socioeconomically deprived communities having the highest HNC related disease burden (Purkayastha et al., 2016) with recent research highlighting the need for more targeted measures to reach those most at risk of HNC as well as a change in policy to combat the societal causes of inequality (Ingarfield et al., 2019b).

A systematic review and meta-analysis of case-control studies defined the clear risk of developing oral cancers with low socioeconomic status, comparable to the significant risk associated with harmful lifestyle factors (Conway et al., 2008). Similar to oral cavity cancers, oropharyngeal, and laryngeal cancers also demonstrate significant inequality in terms of incidence and risk as shown in a retrospective analysis of a large Scottish cohort (Purkayastha et al., 2016). For HNCs in entirety, a large-scale pooled analysis showed that despite there being variances across geographic regions and site of disease, there were associations between lower educational attainment and higher levels of socioeconomic deprivation with higher risk of developing HNC (Conway et al., 2015).

There are several studies exploring the factors associated with relatively poor survival among people with HNC, including analyses from the Head and Neck 5000 (HN5000) study, a large prospective cohort of over 5000 newly diagnosed HNC patients across the UK (Ness et al., 2014), that have demonstrated significant socioeconomic inequalities in HNC survival in the UK, which cannot be fully explained by behavioural factors (Ingarfield et al., 2021).

Within the analysis of the large, multicentre HN5000 cohort, it was also shown that those at a more financially insecure position are at greater risk of poorer survival outcomes (Ingarfield et al., 2021), however, analysis from a Scottish cohort suggested that there are many complex reasons for inequalities in HNC survival outcomes which could involve various patient, tumour and treatment factors (Ingarfield et al., 2019b).

1.4 Health Systems

A comprehensive approach to searching, identifying and reviewing the literature in relation to health systems (Section 1.4) and head and neck cancer diagnostic pathway (Section 1.5) was taken. The search strategy was developed in conjunction with the College of Medicine, Veterinary, and Life Sciences, University of Glasgow subject librarian (Appendix 1-1). Search terms were applied to multiple databases (Medline, Embase, Pubmed) and supplemented with targeted searches of grey literature (via Google, Google Scholar, and key health and cancer organisation websites including from national governments, the NHS, the AJCC, and Cancer.net). Given the heterogeneity of studies identified a narrative approach was taken to appraising the literature.

1.4.1 Health System Definition and Examples

Defining a health system has historically been a challenging task and has resulted in vast variations across literature, specifically in terms of defining the boundaries of a health system (McKee et al., 2011). The World Health Organisation (WHO) in 2000 produced the now most commonly adopted definition of health systems in its global report in which it defined health systems as “comprising all the organisations, institutions and resources that are devoted to producing health actions” (WHO, 2000). This was subsequently updated in 2007 to include systems as sets of processes, groups, and elements that “consist of all organisations, people and actions whose primary intent is to promote, restore of maintain health” (WHO, 2007).

When considering the components of a health system, Gift and Anderson (2007) proposed that systems can be divided into the following key domains:

- Structure: how the system is structured?
- Functions: what is the system’s purpose and how does it go about achieving this?
- Personnel: who is involved in delivering work in the system?
- Funding: where are the funds derived from?
- Target Population: which groups are to benefit from the system?

In many countries, the organisation, regulation and financing of health services may be centrally controlled at the state or country level. Countries in this situation are often said to have a “national health system”. National health systems often end up requiring some level of governmental involvement due to the volatile natures of economic markets and societal conditions (Somerville et al., 2016a). National health systems such as the Scottish National Health Service

(NHS), are sometimes separated into smaller, territorial bodies that have responsibility for the population of a geographic area and other health bodies that have specific foci, such as public health and health professions education (NHS Scotland, 2024).

Health systems are significantly politically important entities in each respective country/district and are largely driven in their intentional design by the needs of their population, however there is no one country with a health system that has proven to adequately meet the needs of all its citizens (Watt, 2013a). Across the globe, health systems have developed dramatically over the last century from those available to the wealthy few/in place to react to significant events to systems that to systems that form a core part of a nations' social landscape (Somerville et al., 2016b).

1.4.2 Health System Funding Models

National health systems have diverse financing structures that are broadly described as being predominantly in one of two categories: "public" and "private", with many systems having elements of both (Watt, 2013a). Public funding essentially means government organised and available to the whole population, while private funding means payment is left up to an individual to source and access healthcare on their own accord though whatever means are available to them.

In publicly financed services, healthcare is paid for centrally either in full or with subsidisation, out-of-pocket transaction from the patient at the point of care. Financing for these systems usually comes through general taxation, compulsory national insurance, or are social health insurance-based systems (Somerville et al., 2016b). Services financed through taxation are designed to have an equal offer of care no matter who is utilising the system, such as the UK's NHS (Watt, 2013b), although there still exists within these models discrepancies in the care offer for some people, particularly across regional geographic boundaries (Jo et al., 2021), and in the offer of some services such as dentistry, which remains a largely privately financed entity globally (Hugo et al., 2021).

Western European countries, such as France and Germany, operate a social health insurance-based model which, although is also designed to offer affordable care to all, has intricate inequalities associated with different categories of patient demographics. Private-based systems, where patients rely on out-of-pocket payments or privately arranged insurance models, by their nature have significant inequalities for those in those countries where those who can afford to often have the best level of care with many have no access to medical care or have severely limited access to anything other than acute care provision (Somerville et al., 2016b).

Despite the intentions of providing care for all in publicly financed models, there exists the phenomenon of the “inverse care law” by which the availability of quality health care does not match the areas of greatest population need (Tudor Hart, 1971). The inverse care law exists across LMICs with HICs experiencing the “disproportionate care law” in that those with greatest need receive more health care but at insufficient quality to meet their specific needs (Cookson et al., 2021).

1.4.3 Health Service Structure

Health systems have many nuances and intricacies depending on environmental, social, political and economic circumstance but can broadly be categorised into three categories: primary/community care, specialist/secondary care, and tertiary care (Watt, 2013a).

1.4.3.1 Primary Health Care / Community Health Care

Primary Health Care also known as Community Health Care is often the first port of call for people with health concerns and tends to have a more general healthcare offering than specialised services. The major component of primary health care is that of primary medical care provided by generalised medical doctors and nurses. Additionally, pharmacists, optometrists, physiotherapists are also components of primary health care systems. Primary care is almost always provided as an outpatient service.

Primary health care services are an essential component of a functioning, quality health system. The WHO describes the central principles of primary healthcare as person-centred, high-quality, comprehensive and continuous coverage that focusses on intersectional action on health determinants through disease prevention and health promotion in a cost-efficient manner that has equitable coverage across a population (WHO, 2018).

Primary care teams have a wide-ranging role in health systems in preventing disease, managing patients who do not require hospitalisation or whom have been recently discharged from hospital, offering access to population groups who have difficulties accessing other health services, and identifying patients with disease that require specialist input (Starfield et al., 2005). Traditionally, primary care physicians have undertaken this role of "gatekeeping" in health systems, in that they are often the decision maker in who required specialist care and subsequently direct patients towards this care via a referral (Sripa et al., 2019).

Croke et al's cross national survey analysis (2024), which formed part of the Lancet Commission on Health System Performance, focussed on healthcare users' experience of primary care services across 14 countries of varying system structures and economies and showed significant gaps in coverage of population-level screening and preventive services in countries with relatively low overall patient-reported quality ratings. Study participants also rated the quality of primary health care worse than other areas of health care in another study from the commission by Lewis et al (2024).

In addition to the medical element of primary care, dental professionals also operate largely in the primary care service and have a responsibility for repairing and maintaining the dentition and oral health of patients. The extent to which dental services are incorporated into national/regional health services varies massively across the globe. In HICs there is a broad range of systems from the UK where it forms part of the National Health Service and has a large commitment of funding from public-finance in addition to subsidised patient charges (Daly et al., 2013) to Australia where dentistry is a largely insurance based or out-of-pocket type scheme but for some examples where the is specific, comprehensive governmental funding available for groups with significant unmet dental need (Australian Dental Association, 2019).

1.4.3.2 Secondary and Tertiary Care

Secondary care services are usually those which concentrate on diagnoses that require a specialist doctor or team for management. This can be as an inpatient or outpatient. Many different specialities are often collocated in secondary care sites and consultant-level specialists tend to be based here. Traditionally, the majority of specialist investigations and diagnostic tests also happen in secondary care (Watt, 2013a). Tertiary care is a term used to describe centres of clinical excellence in specific disciplines were specialist or sub-specialist care is concentrated. These also tend to be multidisciplinary, and many are involved in national/international training and education (Watt, 2013a).

1.4.4 International Examples of Health Systems

Health systems often reflect the societal values and priorities of a nation; examples of this are the system of the USA where an individual is required to take greater personal responsibility and accountability for the financing and organising of one’s own healthcare which correlates with the national political and societal attitude of individual responsibility and has resulted in a “market-type” approach to healthcare (Levitt and Altman, 2023). Conversely, nations in which there is a more centrally governed approach to society have seen this reflect in their respective health systems such as in China where funding for the national health system has tripled in the last decade and there are ambitious aims to provide financially protected universal healthcare coverage to all citizens by 2030 (Jakovljevic et al., 2023).

In health research, countries are commonly categorised by their World Bank Income classification into two broad descriptions: Low-Middle Income Countries (LMICs) that encompass low-income, lower-middle, and upper-middle income countries; and High-Income Countries (HICs) (World Bank, 2024b). There is some debate and academic controversy over the use of the term LMICs in research, in particular when investigating health services and systems. Lenucha and Neupane (2022) in their editorial suggest that the way that the term LMIC is commonly used and its “unreflexive overuse poses many problems for how we view the world and how we conduct global scholarship” and that it may “serve both to obscure and divide”. Despite this argument, it remains a well-utilised way to group countries according to their national resources and wealth with the caveats that they are broad groupings and there is a lot of heterogeneity within them. These terms are widely used by large funding bodies such as the United Kingdom Research and Innovation (UKRI) council in their most recent funding calls and remains commonly found in current literature (UKRI, 2024). A further classification used to describe nations is the United Nation's Human Development Index (HDI), a metric that covers health, education, and wealth to categorise nations into four categories: low, middle, high, and very high (United Nations, 2024).

In their seminal study in 2006 assessing global disease burden, Lopez et al showed that countries classified as LMIC account for approximately 84% of the world's population and 90% of the global disease burden, although only 24% of the world's GDP and 13% of global health expenditure (Lopez, 2006).

According to the most recent GLOBOCAN data, incidence rates of all cancer types will rise two-to-three times faster in countries classified as low or medium HDI when compared to high or very high HDI countries by the year 2050. Whilst high and very high HDI countries currently have the highest burden of cancer, this is not the case for lip and oral cavity cancers which are more common in low and middle HDI nations (Bray et al., 2024). In recent decades, the burden of disease in LMIC has shifted to an increasing proportion of non-communicable diseases (NCDs). Currently these still account for a minority of total disease burden but are projected to rise to a majority of total disease burden in some LMICs by 2040 and rising fastest in those countries potentially least prepared for the change (Bollyky et al., 2017).

Despite an increased attention to the development of international health systems, there remains some commonly shared and significant differences across health systems of countries categorised as LMIC and between the health systems of LMICs and HICs in modern times (Mills, 2011). In South America in 2019, most countries were classified as LMICs (with the exception of Uruguay, Chile, and French Guiana (World Bank, 2024b)) and there exists a range of differing health systems. Brazil, the largest and most populus country in South America, has an interesting health system structure that has evolved greatly in recent decades. Brazil operates a decentralised, universal health system funded by tax revenue and governmental contributions from federal, state and municipal governments.

Following a significant reorganising of health systems in 1998, all residents and visitors in the country can access comprehensive public health care at all levels of service from primary care to tertiary care (Tikkanen et al., 2020). There are challenges in the system where there is often significant demand which overwhelm the availability of treatment provision, meaning although this care is free to access, many people face extremely lengthy waits for care (Pacheco Santos et al., 2018). There exists in Brazil a significant proportion of care being delivered through privately financed means, with more than 23% of the population access care through private means in 2019 and 80% of medical training providers being private institutions. Interestingly, Brazil operates a primary care model that incorporates a family-focussed approach with access to specialists from various disciplines, including obstetrics, paediatrics, and others depending on the population need (Tikkanen et al., 2020).

Contrasting Brazil, from 2007 following major reforms, Uruguay (a neighbouring country) has had the National Integrated Health System (SNIS) which is funded by the National Health Fund (FONASA) and integrates public and private providers to ensure that every citizen has access to healthcare (Organisation, 2021). This fund is comprised of general state revenue and a contributory component from employers and employees, similar to the governmental funding and National Insurance model in the UK (Watt, 2013b). Global health expenditure as a percentage of GDP was 10.87% in 2020, a sharp increase from 8.6% in 2000 and a full percentage point more than in 2019, likely due to the COVID-19 pandemic. 2019 health spending as a proportion of GDP was 9.89% in Brazil, 11.34% in the UK, and 9.36% in Uruguay. Spending per capita is 761.27 US$ in Brazil, 5138.64 US$ in the UK, and 1620.33 US$ by most recent data available via the World Bank (World Bank, 2024a).

In the recent Lancet Commission on Health System Performance, there were several interesting findings from their impressive, international, multi-centre studies involving a range of key participants, including patients and care providers (Knaul et al., 2021). The primary study from this commission analysed a novel population survey of confidence in health systems, the first such internationally pooled analysis of this kind. Alarmingly, fewer than half of respondents reported confidence in getting and affording good quality healthcare if they were to be sick. Additionally, the lowest levels of endorsement in the national health systems came from Peru, Greece, and the UK (Kruk et al., 2024). Roberti et al. undertook a cross-sectional survey of four Latin American countries (Colombia, Mexico, Peru, and Uruguay) covering population characteristics, health system outcomes, and health system use and sectors. They found that between one quarter and a half of participants had a source of healthcare they considered to be of high quality and that there was significant income inequality across all countries with regards to preventative checks. Uruguay was one of the four nations included and interestingly was found to have the highest rate of telemedicine (40%) but also the highest rate of income inequality in the preventative medical checks (89%) (Roberti et al., 2024). Interestingly, there was a trend of participants within the analysis from the commission believing that systems were improving in LMICs and not so in HICs (Croke et al., 2024). A further analysis from the commission showed that underserved adult groups and users with the highest health needs often scored the quality of their care worse (Lewis et al., 2024). The results from this commission show tremendous variation in population health system confidence across different systems and economies.

1.4.5 Determinants of Health

The factors associated with disease development are commonly known as the "Determinants of Health". Traditionally, and most directly related to an individual, behavioural determinants of health were the main focus of health improvement and policy. Although there is significant evidence for many behaviour-related risk factors (such as diet, smoking and alcohol) and disease development, there has been an ever-increasing acknowledgement and understanding of the wider determinants of health. These wider determinants are fixed in the social, cultural, environmental, and political circumstances of a person or population's life.

The Social Determinants of Health (SDoH) is a concept brought to prominence by Dahlgreen and Whitehead in 1991 in their seminal paper "Policies and strategies to promote social equity in health" (Dahlgren and Whitehead, 1991). Here, the authors lay out the framework for disease development, and the causes of inequalities in health, that pertain to the social environment of a population or an individual and their experiences of living. This framework for health determinants incorporates many aspects that instinctively many would not consider of direct relation to health, but the authors successfully laid the foundations for the strong academic, clinical, and political attention over the last three decades given to this topic and is the basis for many frameworks used to address the SDoH.

Included in Dahlgreen and Whitehead's model, within the context of living and working conditions, is health care services. In cancer care, availability of and access to services has been noted as an important factor in reducing inequalities in patient outcomes in cancer care (Denny et al., 2019) with several reviews indicating that social factors are associated with reduced access to care for several cancer types, including lower education and socioeconomic status for pancreatic cancer (Petric et al., 2022), and rural residence for lung and breast cancers (Conti et al., 2022, Lennox et al., 2023).

In recent years, more discussion has been had on the importance of the political and commercial determinants of health. In their 2005 op-ed, Bambra et al (2005) define the role that politics and policy plays in people's health and argue the importance of acknowledging this going forward, something that Kickbush (2015) in their editorial claims public health has not been successful at doing.

1.4.6 Health Outcomes

In health research, a key outcome is that of population health. Again, there are various definitions in existence for 'population health' throughout literature but the most ubiquitous definition was coined by Kindig et al (2003) as "the health outcomes of a group of individuals, including the distribution of such outcomes within the group". Key to population health are two significant aspects: 'health outcomes' and 'determinants of health'.

Interestingly, in the most widely accepted definitions of health systems, the importance of health improvement is not explicit. Health improvement, the processes and actions aimed at improving the quality of health of a population, has an essential role in reducing the burden of disease within a population and addressing identified inequalities within and between populations. Health improvement, as per the Faculty of Public Health, is one of the cornerstones of the practice of public health (FPH, 2024) with the responsibility for this endeavour not exclusive to public health specialists and bodies, but also to national and local government, educationalists, public institutions, clinicians, and healthcare providers.

When measuring population health, the metrics commonly used are known as 'health outcomes'. These vary depending on the disease and population and are normally aggregated data on a particular status at a population level. As per the Faculty of Public Health: "Health outcomes may reflect a state of health at a point in time; a change in a health state over a period of time; or change in health status as a result of an intervention" (Blackwood et al., 2016). With regards to cancer, there are several health outcomes commonly used in research, government reporting, and intervention evaluation, including:

Survival: The proportion of patients diagnosed with a disease that are still alive at specified intervals following diagnosis, with five-year post diagnosis the most commonly used metric (National Cancer Institute, 2024c).

Mortality: The rate of people diagnosed with a disease that are no longer alive at specific time intervals. This can be disease-specific or due to all causes.

Quality of Life (QoL): This is a quality metric based on patient reported answers to set questions on daily living and bodily function. There are several QoL measures used, with modified Oral Health QOL (OHQOL) measures commonly used in HNC research (Sischo and Broder, 2011).

When measuring health system performance, the WHO in 2022 published a report containing frameworks for approaches to this subject which advanced the base set out in their 2000 publication that introduced a global discussion on measuring health systems (WHO, 2000, WHO, 2022a). When assessing health system performance, the WHO approach looks to the functions and sub-functions of the system being assessed (with a particular focus on finance, infrastructure, data, workforce, and coverage) with an overarching lens of governance for each domain. The specific metrics by which health systems are measured vary depending on the respective function or element of the system of interest with no strict universal approach appropriate to all situations, with the 2022 framework providing an overarching, comprehensive guide that can be adapted as required (WHO, 2022a).

There are other, intermediate, cancer outcomes related to the health system/services such as those proposed by an expert panel in early 2024 as vital to ensuring a sustainable cancer care system in the UK that include time to diagnosis, time to treatment, and other quality metrics (Aggarwal et al., 2024)

1.4.6.1 Stage at Diagnosis

With the ever-developing appreciation that diagnostic stage is a key prognostic indicator of survival across cancer types (McPhail et al., 2015), stage at diagnosis itself is now an important intermediate health outcome measure of importance and can itself be a measure of health system performance. Stage at diagnosis has been included in recently published health outcome descriptors for breast cancer developed by Baldeh et al as part of a review of European breast cancer guidelines (Baldeh et al., 2020). In England in 2023, 58% of all recorded cancers newly diagnosed were at stage I or II, up 8% from pre-pandemic levels. The United Kingdom government have declared the lofty ambition of having 75% of all cancers diagnosed at either stage I or II by 2028 (UK Government, 2018), a target that may be achievable for some cancer types that already have a high early detection, have a high incidence rate, and/or are often detected by established screening programmes, including breast cancer (NHS England, 2024a). HNC staging is described in greater detail later in this chapter (See section 1.4.4).

1.4.7 Complexity in Health Systems

Despite significant advances in our understanding of disease pathophysiology, causes and determinants of ill-health, prevention strategies, and medical interventions/treatments, health outcomes for non-communicable diseases across the globe are not improving (Bennett et al., 2018). One key explanation for this has been the role of complexity in health systems.The topic of complexity in health services was brought to prominence in 2001 by Plsek and Greenhalgh, with complexity being defined as “a dynamic and constantly emerging set of processes and objects that not only interact with each other, but come to be defined by those interactions" (Cohn et al., 2013). While in mechanical systems, entry points and boundaries can be clearly defined and obvious, complex systems have boundaries that are more unclear (Plsek and Greenhalgh, 2001). Complex systems adapt and develop alongside other systems with which they interact in expected and unexpected ways as opposed to mechanical/technical systems that often remain static and individual (Braithwaite et al., 2017). Several factors influence the development and adaptation of health systems/services, including: changing population demographics, evolving patterns of disease and their impacts, expectations and demands from the public, advancing technology, globalisation, and economic changes (Watt, 2013a). HNC systems are an example of a complex adaptive system as will be demonstrated in subsequent sections.

Long et al. (2018) in their op-ed argue for pragmatic approaches to health systems research that consider the complexity of health systems. The authors advocate for an appreciation that health services research cannot by its nature be confined to the same research methods and boundaries as other areas of clinical research due to the lack of ability to control of all factors involved, however the authors proposed that this should not preclude health services research from having important value to improving health outcomes, rather that research should embrace the complexity of services in order to contextualise results. The appreciation of embracing complexity in health systems when trying to improve health outcomes is now a fundamental consideration for the development of interventions as in now included as a key area in the Medical Research Council's guidance of developing and evaluating complex interventions (Skivington et al., 2018).

Given what is now commonly known and understood by academics, clinicians, and politicians on the factors involved in health and disease, there is a current paradigm shift in what the boundaries are for health services and systems research with Galea and Ettman (2021) demonstrating in their commentary that boundaries need to be expanded to acknowledge the interaction health systems have with other elements of society. Traditional health services research has focussed very much on quantitative outcomes from the processes involved once a patient is within a service. Greenhalgh and Papoutsi explore this paradigm shift and demonstrate the new paradigm of complexity-informed approaches and expertly summarised this shift through several lenses (Greenhalgh and Papoutsi, 2018), including:

i) Goal of research: from Establishing the universal, enduring truth and solutions to well-defined problems to exploring tensions, generating insights and wisdom; exposing multiple perspectives; and viewing complex systems as moving targets.

ii) Assumed model of causality: From linear, cause-and-effect approaches to emergent causality: multiple interacting influences accounting for a particular outcome but none can be said to have a fixed ‘effect size’.

iii) Typical format of research question: From focussing on effect size and statistical significance to trying to understand what combination of influences has generated a phenomenon and what does the intervention of interest contribute? Additionally, what happens to the system and its actors if we intervene in a particular way and what are the unintended consequences elsewhere in the system?

iv) Mode of representation: From attempting to represent research in one authoritative voice to attempting to illustrate the plurality of voices inherent in the research and phenomena under study

v) How good research is characterised: From methodological ‘rigour’ and conventional approaches to generalisability and validity to strong theory, flexible methods, pragmatic adaptation to emerging circumstances, and contribution to generative learning and theoretical transferability

When considering the call for pragmatic approaches to complexity in health research, it is also vital to have a realistic understanding of what is practical and feasible within the research field of interest. In their thoughtful opinion piece, Long et al. (2018) argue for the adoption of pragmatism in health services research, with their sentiments of ensuring research considers the real-world and everchanging health systems context also being pertinent to all aspects of public health research.

Greenhalgh et al furthered this argument in their 2022 paper, which was borne of their reflections from the COVID-19 pandemic, which forcefully makes the case for a new paradigm of “evidence-based medicine plus” (including dentistry/other clinical practices). They strongly argue the benefit of harnessing mixed-methodologies and incorporating the views of key informants on systems in research relating to them (Greenhalgh et al., 2022).

1.4.8 Systems Science in Health Research

Systems science offers the opportunity to conduct research that acknowledges and embraces the complexity of health systems (Carey et al., 2015). Systems science approaches have been adopted by the Medical Research Council as a fundamental aspect of developing and evaluating complex interventions in modern health research (Skivington et al., 2021) and the World Health Organisation has also proclaimed the importance of systems thinking to improve international endeavours to reduce the burden of non-communicable diseases (WHO, 2022b).

Systems science approaches have offered deeper understanding and evidence progression of health topics including many behaviour-related non-communicable diseases by providing a whole-systems lens in which to understand the determinants of health and disease, including those socioeconomic, environmental, political, and commercial (Knai et al., 2018). Additionally, these approaches have helped develop understanding and tools for addressing public health challenges in wider sociopolitical contexts, such as the recent “cost-of-living crises” (Höhn et al., 2023).

There are numerous systems approaches to health research, each with its own strengths and weaknesses in attempting to address specific research questions in public health. A qualitative systematic review of systems research approaches to public health research synthesised findings into four main areas: position pieces, analytic lens, benchmarking, and systems modelling (Carey et al., 2015).

I. Position Pieces: These include many articles where systems science is introduced but do not contain detail on specific projects or original research.

II. Analytic Lens: This category includes studies where a systems approach was used to frame research results or projects. Systems science methodologies aren’t used as pure analytical methods but rather to guide results from other methodologies (mainly qualitative) and give context to the results reflecting the complexity of the system in which the research has been undertaken.

III. Benchmarking: This approach included studies where systems concepts and methodologies are used in the design of the research to compare best practice across sites/systems and elucidate factors that contribute towards favourable outcomes. Benchmarking has a strong role as a method for positive change in healthcare quality improvement when focussing on evidence-based quality metrics (Willmington et al., 2022).

IV. Systems Modelling: Research in this category involves the use of a range of qualitative and quantitative methodologies to model systems pertaining to health. This approach allows for consideration of multiple levels of factors that may influence the research question but requires a valid model to be employed so as to ensure research quality.

One well-adopted framework for undertaking health systems research is that of the Systems Engineering Initiative for Patient Safety (SEIPS). SEIPS was originally developed and published in 2006 as a framework for utilising work system design methods to understand the structures, process, and outcomes involved in healthcare outcomes (Carayon et al., 2006). In this first model, Carayon et al break down the components of systems into key groupings of person, organisation, technologies and tools, tasks, and environments whilst also separating outcomes into employee/organisational outcomes and patient outcomes.

Although the authors offer up criticism of their own model for not including enough healthcare specifics, it was successful in providing an overarching framework to guide a systems approach to health services research and was developed further by Holden et al. (2013) to incorporate three novel concepts to the original model: configuration, engagement and adaptation.

Recognising that in healthcare the protagonist of any process and outcome is the patient, the development of the SEIPS model has culminated on the publishing of SEIPS 3.0 by Carayon et al. (2020). In this model, a sociotechnical approach is taken centring on the patient journey as the overarching lens through which the system components can be analysed and better understood. The SEIPS 3.0 model builds on the conceptual framework developed by Ball et al. (2016) which focussed on the diagnostic process within health system work and emphasises the importance of considering the experiences of a wide range of key stakeholders and personnel in a system to truly understand the system as it exists rather than the system purely by design (Figure 1-2).

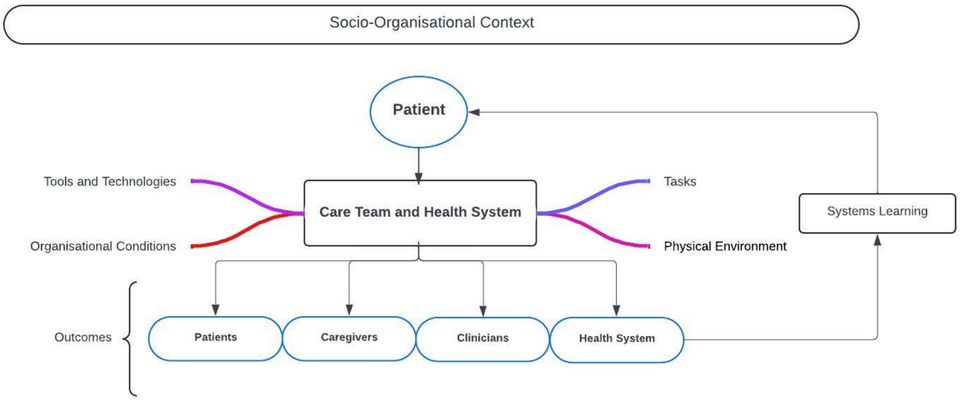

Figure 1-2: Sociotechnical systems approach to patient journey and patient safety adapted from Carayon et al. 2020

The logical, chronological approach taken in this model allows for a pragmatic approach to health measures and outcomes, including diagnosis, considering factors from the intricate technical to the wider organisational and environmental. In recent years, SEIPS has been adopted by large organisations in a drive to improve health outcomes and healthcare quality and included in toolkits such as the Patient Safety Learning Response Toolkit (NHS England, 2022).

1.4.9 Cancer Diagnostic Systems

Building on the literature covered in previous sections, the following section presents the dimensions of the cancer diagnostic pathway from the point of symptom development/detection through to confirmed diagnosis of cancer, with a focus on the systems elements and processes involved that were prominent from the aforementioned literature search.

1.4.9.1 Diagnostic Pathways

Theoretical frameworks for research and strategy development in symptomatic cancer diagnosis have been through several rounds of adaptation and development in recent years. The first commonly applied framework was the Anderson model of total patient delay (Andersen and Cacioppo, 1995) which utilised Psychophysiological Comparison Theory to delineate the patient cancer journey and pathway into the processes involved and correlating these with chronological contributions to “total patient delay”. These “delays” were named:

Appraisal delay: Time between detecting a symptom and inferring illness

Illness Delay: Time between inferring illness and deciding to seek medical attention

Behavioural Delay: Time between Time between deciding to seek medical attention and acting on this

Scheduling Delay: Time between making first appointment and receiving medical attention

Treatment Delay: Time between receiving medical attention and starting treatment

This Anderson model of total patient delay gave a framework for subsequent research to be undertaken but did keep the focus on the individual patient and their respective health journey. The approach taken here was helpful in giving this research basis but perhaps somewhat pejoratively places sole focus on the "cause" of delay with patients, or at least this is how it was subsequently framed in much future research. A subsequent influential model from 2009 is that by Olesen et al. (2009), known as the Danish model, further developed the "delay" model to separate the patient diagnostic journey into intervals of delay that did not all pertain to the patient, including patient delay (first symptom to first contact with general practitioner (GP)), doctor delay (first contact with GP to initiation of investigation of cancer-related-symptoms), and system delay (initiation of investigation of cancer-related symptoms to initiation of treatment). The authors also further broke the diagnostic pathway in the post-patient delay interval into what the aspect of system delay is (primary care, secondary care, and treatment delay) and whether the day is pertained to primary health care or secondary health care (Figure 1-3).

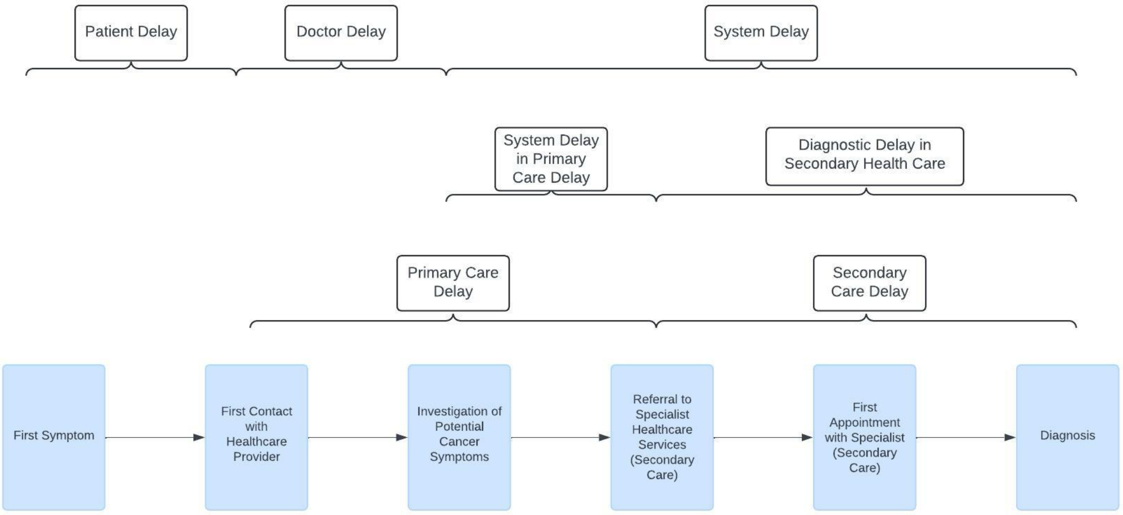

Figure 1-3: Categorisation of Delay Adapted from Olesen et al 2009

Walter et al. (2012) undertook a systematic review of applications of the Anderson model in cancer diagnosis and found some interesting results. Although only including 10 papers from eight studies due to the review's strict criteria of only including studies that explicitly utilised the Anderson model unmodified, there was strong evidence for the role of "appraisal delay" but no certainty of evidence for the other components of "total patient delay" as the main contributors towards total delay. The authors also found, and were somewhat critical of, the variation in approach taken by research teams in that many adapted or reframed the Anderson model to fit their research population, meaning there may be subtle differences and nuances that may preclude true harmonisation of data in this field. This reflection by the authors perhaps does not take into consideration the full complex nature of these pathways meaning that in order for the research to be undertaken, and the results contextualised appropriately, models such as the Anderson model may need to be adapted and not utilised in their strict form. Interestingly, from a narrative synthesis of their review, the authors also reveal their own model of pathways to cancer treatment that expands on the Anderson model with the intent of better defining the stages and processes involved, as well as simplifying the time intervals into four:

Appraisal: Patient appraisal and self-management

Help seeking: Decision to consult healthcare provider and arrange appointment

Diagnostic: Healthcare provider appraisal, investigations, referrals and appointments

Pre-treatment: Planning and scheduling of treatment

With this update, the model from Walter et al removes the element of delay being down to persons (patient, doctor) and additionally offers categories for contributory factors: patient, healthcare provider and system, and disease factors (Walter et al., 2012).

The body of research utilising the Anderson and other models culminated in the Aarhus statement being developed by Weller et al. (2012). The authors, as part of a consensus working group, undertook their own review of cancer diagnostic research and found the same lack of consistency in research approach, specifically in methodology and approach. Recognising further the complexity of cancer diagnostic pathways, the authors set out to provide a checklist than can be used to guide both research design and appraisal by clarifying approaches to different study types and defining timepoints.

Modern literature on cancer diagnostic systems now considers there to be two specific intervals in cancer diagnosis; the “pre-diagnostic” and “diagnostic” intervals. The pre-diagnostic interval contains both an appraisal and help seeking dimension whilst the diagnostic interval is separated into the primary care, referral, and secondary care phases (Brown et al., 2014).

Supporting models such as the iterations of the Anderson model, there has been a developing literature on applying complexity further to cancer pathways research such as that by Black et al. (2023) where the authors propose a systems approach to improve early diagnosis of cancer by removing delay and error in the processes of patient scheduling and reducing administrative responsibilities for clinical staff. This was met with criticism from some clinicians who believed there was blame being placed on those working in systems for errors but systems approaches by their nature do not consider blame as a factor, as argued by the authors in a well-thought rebuttal to criticisms.

1.4.9.2 Workforce and Multidisciplinary Teams

When considering those professionals involved in cancer pathways, disciplines range from general practitioners through to consultant specialists with a range of medical and wider healthcare staff involved at different stages of the cancer care pathway. The exact make up of cancer care teams depends on the cancer type and site but typically many care teams will include surgeons, oncologists and radiologists (Selby et al., 1996).

As with many aspects of healthcare, Tapani et al.'s systematic review (2021) on the distribution of global cancer workforce in 2021 revealed the stark differences between the availability of cancer specialists between HICs and LMICs across medical oncologists, clinical oncologists, and radiation oncologists with some HICs having between 4-30 times as many available specialist clinical staff compared to some LICs.

Multidisciplinary teams (MDTs) have for some time been widely recognised as the gold standard in cancer care delivery. They are formed of clinicians and healthcare professionals relevant to a person's diagnosis, and who are likely to be involved that person's care, at the point of diagnosis to organise that person's treatment plan. It has been shown that MDTs have the benefit of taking a wholistic approach to patient care and improving interdisciplinary communication. The MDT is a developing concept with an ever-growing appreciation and utilisation of modern technologies aiming to streamline their activity (Winters et al., 2021). Patients who go through cancer diagnostic pathways that utilise MDTs have been shown in several systematic reviews to have better overall survival for diseases such as breast, colorectal, and ovarian cancer (Junor et al., 1994, Peng et al., 2021, Pangarsa et al., 2023). Fleissig et al. (2004) in their review of MDTs in the UK note the many benefits of MDTs, including on patient outcome, inter-disciplinary communication, and increased consistency in care, but do note that in order to be successful, strong leadership, governance, and administrative support is required.

1.4.9.3 Centralisation

Centralisation is a process in which services are consolidated and are purposively situated/focused in geographical areas so that healthcare teams are collocated and resource limited to one site. Centralisation has been employed to improve health outcomes and system efficiency but can have unintended negative consequences, including increased inequity in access to services, increasing travel burden for patients, and increasing workload pressures on hospitals (Aggarwal et al., 2022).

Specialist healthcare has always been somewhat centralised but in cancer care there has been a definite shift towards this mode of service design in high-income countries over recent decades, primarily brought about by the developing literature on hospital/physician volume and cancer care outcomes. Significant early reviews on this topic, such as those by Hillner et al. which looked at evidence from a range of countries and cancer types, found a clear association with many cancer types and favourable outcomes for patients (Hillner et al., 2000). However, this review, as with others in the field, only included high-income countries and did not include HNC. There is limited substantive evidence of the effect of centralisation on HNC outcomes, however, some small locoregional studies in the UK have shown centralisation to be more cost efficient (Tzanidakis et al., 2017), result in longer waiting times with no effect on survival (Birchall et al., 2004), but to be associated with increased risk of nodal involvement in disease (Kent et al., 2019). The exact mechanism of how volume affects outcomes though is not exactly clear, as discussed in Mesman et al.’s important review (2015).

National studies such as that by Kilsdonk et al in the Netherlands analysing cancer registry data for oesophageal, pancreatic, and bladder cancers from 2000 to 2013 showing a correlation between introduction of minimum clinical standards and the publication of evidence concluding a positive volume-outcome relationship for some cancer types with the increase in centralisation of services in that country (Kilsdonk et al., 2018). A subsequent study in the Netherlands found whilst centralisation may not have increased the travel burden for the general population of cancer patients, those from more vulnerable patient groups were at greatest risk of increased travel burden (Versteeg et al., 2018).

Although here has been little literature to date on centralisation of services in low-middle income countries, a systematic review by Brand et al on the delays and barriers to cancer care in LMICs from 2019 found rural residence to be a key barrier to diagnosis across cancer types and geographic regions (Brand et al., 2019).

1.4.9.4 Referral Systems and Clinical Guidelines for Suspected Cancer

Referral is a process in which a healthcare practitioner passes on the clinical information of a patient to another service. This can be done in a multitude of ways, including directing patients to a location, telephone calls, letters, email, or through bespoke electronic systems. Referrals for suspected cancer are often the highest priority of referral that is made from primary care to specialist services that does not require an emergency presentation to hospital (Round et al., 2021). Although there has been some evidence on the role of health information technology on cancer prevention that shows a clinical benefit for several applications of technology across the cancer care continuum (Jimbo et al., 2006), there has not been a review to date on the role of technology in cancer referral.

As part of the multicentre, International Cancer Benchmarking Partnership (ICBP), a collaboration aiming to investigate the variation in cancer pathways and outcomes across European and North American health systems, Lynch et al. (2023) undertook a comparative analysis of primary care cancer referral pathways in 10 HICs for lung, colorectal, and ovarian cancers and identified a commonality of primary healthcare clinicians having to refer into specialist services for diagnosis to be made across these cancer sites, but there was great heterogeneity in the exact routes available to primary care and patients, with some areas such as Denmark lacking clear pathways on how to expedite referrals for acutely unwell patients and some areas such as British Columbia in Canda having facilitated referral systems for people with positive abdominal screening results. Interestingly, the authors noted variation of practice and routes available within countries, including England and Scotland.

Over recent decades, the role of clinical guidelines has become ubiquitous in healthcare. Clinical guidelines aim to improve patient care by offering recommended processes and actions for identifying and managing diseases, including cancer (Woolf et al., 1999). With healthcare advancing so quickly, and the ability to share information easier than in the past due to the internet, Grol et al. (2003) undertook a review that acknowledged several problems in the sphere of cancer guidelines including; lack of quality, lack of evidence, interpretation of evidence, feasibility, implementation, and translation into practice. These findings led to the development of the AGREE instrument (AGREE Collaboration, 2003) which ensured clinical guidelines can be an effective tool for improving cancer care by following specific quality criteria in six domains: scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability, and editorial independence.

An evaluation of AGREE showed that following the domains of the tool was associated with greater guideline adoption (Brouwers et al., 2010b) but also revealed areas for further development, which resulted in the AGREE II tool being published in 2010 which included the same original six domains but added extra detail and clarity on how to apply them (Brouwers et al., 2010a).

1.4.9.5 Quality Performance Indicators and Monitoring

A key process that supports the continuous development health systems is that of performance monitoring. Monitoring is normally done through the use of specific indicators known as Key Performance indicators (KPIs) or Quality performance Indicators (QPIs) that record metrics against a set standard/target (NHS Scotland, 2024a). Further indicators used are waiting times by which there are standards and targets for how long a person should be waiting between steps in their diagnostic/treatment journey. An example of this is the two-week-wait

(2WW) used in NHS England whereby a person should be seen by a specialist within two weeks of referral for a suspected cancer. This pathway came under some criticism as it was not believed to be effective at improving cancer outcomes: a systematic review of studies over a 15-year period of 2WW referrals for colorectal cancer found only 10% of people referred on this pathway had confirmed colorectal cancer and that 24% of all colorectal cancer patients diagnosed were referred via 2WW pathways (Langton et al., 2016). Research like this contributed to a report into cancer waiting times in NHS England published in 2021 that recommended the removal of the 2WW pathway resulting in it being removed in favour of more flexible early detection pathways in 2023. Most countries have a form of cancer registry where administrative and demographic data is held on all new cases of cancer diagnosed and often reported on in an aggregated presentation to allow for contemporaneous assessment of a nations cancer burden and to potentially help guide interventions and subsequent evaluations (Piñeros et al., 2021).

1.4.9.6 Cancer Screening

Cancer screening is a process through which people who have specific sociodemographic/behavioural risk factor profiles are selected and invited for clinical examination/investigation to detect asymptomatic cancer, or potentially cancerous conditions, with the aim of identifying disease at an early stage or at pre-cancerous before it has progressed to cancer (Crosby et al., 2022). The UK currently has three targeted cancer screening programmes nationally for breast cancer, lung cancer, and bowel cancer (CRUK, 2024). Screening programmes for these cancers have been shown to be successful in reducing overall mortality and improving early detection rates (Schopper and de Wolf, 2009, (Logan et al., 2012, Amicizia et al., 2023). Many HICs have similar screening programmes but the availability of such programmes is more limited in LMICs and many past attempts have had limited success, possibly due to a failure to understand the social and cultural environment (Sullivan et al., 2021).

1.4.10 “Delays” in Diagnosis of Cancer

Using the models of cancer diagnosis described previously (see section 1.3.9.1) from Andersen et al described previously (Andersen et al., 1995, Olesen et al., 2009, Weller et al., 2012), much literature now focusses on where in the cancer diagnostic pathway can delay be attributed and how does that relate to cancer outcomes.

A large, international, cross-sectional study from the International Cancer Benchmarking Partnership analysed a range of data from routine administration and patient/professional questionnaires for colorectal cancers and found the most common route to entry to the cancer-specialised services was a symptomatic presentation to primary care physicians followed by referral to the specialist service. This study also found the largest interval of time in the diagnostic pathway was the “diagnostic” interval (ranging from 27-76 days) (Weller et al., 2018). This study has a narrow focus in terms of system breadth though as cancer centres included in this study were all from high-income countries with highly developed national health systems.

The literature tends to focus on treatment delay as it is clearer where the individual time points for comparison lie as they are recordable dates often within the same part of a health system (i.e., diagnosis date–treatment start, both traditionally within secondary care). Hanna et al (2020) show in their systematic review of multiple cancer types, not including HNC, show that even a four-week delay can significantly increase the risk of mortality. The literature on how delay relates to stage is curiously less clear, with the exact relationship seemingly equivocal. As Caplan discusses in their narrative review (2014) that covered breast cancer studies from a range of HIC and LMICs, there was not a clear direction in the relationship with some studies showing that there was a longer time prior to diagnosis for those with early stage disease and shorter for stage III or IV cases. This phenomenon has also been shown for other cancer types such as colorectal (Murchie et al., 2014). Attempts to explain the inverse relationship between time and stage have proposed the lack on research on tumour aggressiveness as a potential reason (Neal, 2009).

Attempts to identify factors associated with delay and stage at diagnosis have been made for many cancer types but there remains a lack of clarity on what the important factors that contribute towards delay in diagnosis/advanced stage disease. One seemingly important factor is that of the first presenting symptom reported, with Macleod et al.’s comprehensive systematic review (2009) of factors associated with delayed presentation of symptomatic cancers showing that, even with variance across cancer sites as to what symptoms drive early presentation, there seems to be some consensus across cancer sites that more general/vague symptoms such as fatigue/weakness are associated with a delayed presentation.

Williams et al. (2019) published their systematic review into factors influencing delays in diagnosis of gynaecological cancer which was limited to HICs. The showed a range of factors which they separated into three categories: patient factors (e.g. symptoms and symptom knowledge, patient demographics), primary care factors (e.g. referral process, non-specific symptoms of clinical findings), and system factors (GPs being gatekeepers, poor access to specialist services). Their separation of primary care away from system factors is interesting and perhaps reflects the historical view of health system boundaries for cancer care. A seminal paper by Brown et al. (2014) was the first to review in any way the role that health system factors may influence time to diagnosis across cancer types and different countries which they categorised the health systems factors as: System regulation; financing; Primary care provider; Centralisation of services; Access to primary care; Access to secondary care; Longitudinality of care; First contact in health system; Comprehensiveness of system; and Co-ordination of system.

The issues in identifying factors associated with advanced stage cancer diagnosis and diagnostic delay are an example of how undertaking research in this complex system, where studies are not able to appropriately take complexity into consideration, show that it is unlikely that one study type will ever be sufficient to achieve an understanding of all factors involved. The need for embracing complexity in cancer diagnostic research is succinctly argued by Lyratzopolous et al. (2014) where the authors offer that delays in cancer diagnosis are unlikely to be caused by poor individual clinical performance but rather likely due to the very challenging and complex nature of cancer diagnosis and how patients interact with health systems given the wider role of social, political, and environmental determinants.

1.5 Head and Neck Cancer Diagnostic Pathway

1.5.1 Head and Neck Cancer Prevention

The ultimate way to reduce inequalities, morbidity, and mortality from HNC is to prevent as many cases from developing as possible and to detect and diagnose those who do develop HNC at as early a stage as possible. Current strategies for HNC prevention can be separated onto the following broad categories (Porta, 2014):

Primary prevention: This approach includes processes and interventions that aim to “reduce the incidence of disease by personal and communal efforts” that can be applied across a spectrum of the general population, subgroups with specific genetic characteristics, or those with a higher risk of developing disease due to environmental, occupational, or behavioural risk factors (Porta, 2014).

Secondary prevention: This approach aims to reduce the lifespan of a disease though measures such as early detection or “screening” to minimise treatment burden and increase the likelihood of cure. Screening is the systematic employment of a clinical tests or examination that “can be applied rapidly in a presumptive asymptomatic population, aiming at the presumptive identification of unrecognised defect or defect” (Porta, 2014).

Tertiary prevention: This approach includes “measures aimed at reducing the impact of long-term disease and disability by eliminating or reducing impairment, disability, and handicap; minimising suffering; and maximising potential years or useful life. It is mainly a task of rehabilitation” with a focus on timely, effective healthcare (Porta, 2014).

The recently published Oral Cancer Prevention Handbook from the World Health Organisation International Agency for Research on Cancer (WHO-IARC) comprehensively covers the international strategies employed via primary and secondary preventive measures for oral cavity cancer (Bouvard et al., 2022) although the handbook did not fully consider policy-level interventions such as regulation or pricing of alcohol or tobacco control.

1.5.1.1 Primary Prevention of Head and Neck Cancer

The focus of many primary prevention strategies is on cessation of behaviours known to increase risk of developing HNC. In oral cavity cancer, these include cessation of smoking tobacco, use of smokeless tobacco, chewing betel quid/areca nut, and alcohol consumption. WHO-IARC deemed there was sufficient evidence for recommendations of quitting alcohol consumption, stopping smoking and stopping chewing of areca nut/betel quid to reduce risk of developing oral cavity cancer but there was less evidence available to make a decision for stopping chewing tobacco and preventing oral cavity cancer was less (Bouvard et al., 2022).

The HPV vaccination is primarily delivered as a very effective method of protection against HPV driven cervical cancer in females (Brisson et al., 2020). Recent evidence has shown that these HPV vaccines could also provide protection against HPV driven HNCs, mainly OPCs, due to immunisation coverage of the strains of HPV that drive oropharyngeal cancer; HPV 16 and 18 being the same as cervical cancer (Timbang et al., 2019). It is proposed that the adoption of HPV vaccination schemes to include young males could have a positive effect in reducing HPV driven oropharyngeal disease in the future, with some cohort studies suggesting this to be the case already (Stanley, 2014). This public health measure was introduced in the UK in 2019.

1.5.1.2 Secondary Prevention of Head and Neck Cancer

Screening for HNC is often posited as a crucial way of preventing potentially malignant conditions from developing into HNC and for diagnosing HNC at an earlier stage but it is a topic of great debate on its efficacy (Brocklehurst et al., 2013). Currently, there is no internationally recognized standard in screening programmes for HNC. Research in cancers of the mouth has thus far provided insufficient evidence to meet the requirements of the UK screening committee (Brocklehurst and Speight, 2018). The only routinely used method for opportunistic screening of oral cavity cancers is the clinical oral examination, consisting of visual and palpable examination of the oral cavity and surrounding facial/neck areas. The evidence base for this method is still equivocal, with the suggestion that early detection of high-risk individuals in this manner may reduce mortality from oral cancer caveated by concerns over statistical power, selection bias and lack of clarity over the role of primary prevention within studied cohorts (Bouvard et al., 2022). A Cochrane review of clinical assessments for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults found that an oral clinical examination was an effective way of identifying early oral cancer and OPMDs but that there was low certainty evidence for screening in the general population, with even less certainty over mouth self-evaluation and remote examination (Walsh et al., 2021b).

1.5.2 Head and Neck Cancer Symptoms and Signs

HNC can present in many ways, with a wide range of symptoms, but can also be asymptomatic and only detected through clinical examination/investigation (National Cancer Institute, 2024b). HNC are unique amongst cancers in that they can be detected by dental professionals as well as medical professionals. Presenting symptoms can vary but commonly include a non-healing mouth ulcer, a lump in the neck, hoarseness and can be innocuous. Additionally, there are many potentially-malignant conditions that can be present and identified including mucosal dysplasia in the oral cavity and pharynx, including: leukoplakia, proliferative verrucous leukoplakia, erythroplakia, oral submucous fibrosis, oral lichen planus, actinic keratosis, palatal lesions in reverse smokers, oral lupus erythematosus, dyskeratosis congenita, oral lichenoid lesions, and oral graft versus host disease (Warnakulasuriya et al., 2021). Opportunistic oral soft tissue examination is undertaken by dentists when examining patients and is important in detecting early stage tumours (Lim et al., 2003).

Clinicians, including dental professionals, are advised to have high suspicion of unexplained white (leukoplakia), red (erythroplakia) or mixed white/red (erythroleukoplakia) patches on the mucosae of the oral cavity as well as any lesions that are indurated, have rolled margins, or a non-homogeneous (Speight et al., 2018). Despite this, it is appreciated that given the rarity of these cancers and high number of people diagnosed with oral cancers who have not visited dental/health practitioners prior to diagnosis, a more targeted measure of early diagnosis may be more appropriate (Purkayastha et al., 2018). Most patients present to primary care in the first instance but people with HNC can also present through the emergency department, which is considered a concerning route to diagnosis and has been reported to account for around 10% of HNC cases at a large regional HNC centre in England in 2017 (Rovira et al., 2023).

1.5.3 Referral for Suspected Head and Neck Cancer and Pathways to Diagnosis

1.5.3.1 Head and Neck Cancer Clinical Guidelines:

Clinical guidance in the field of HNC is dependent on local systems currently as there is no internationally agreed guidance for the early diagnosis and referral of HNC. Guidance is usually country specific but also relies upon local policies for referrals which can differ greatly between healthcare systems, even within the same country. The National Comprehensive Cancer Network (NCCN) is a large not-for-profit collaboration of 33 cancer centres in the USA than develop and update clinical guidelines for all common cancer groupings, including HNC (NCCN, 2024). The NCCN guidelines on HNC are a comprehensive set of standard procedures for working up and treating HNCs of all subsites and stages and includes guidance on appropriate clinical and radiographic tests to be performed prior to treatment. Although comprehensive in this regard, the guidelines do not cover what should happen in primary care or when a person presents to a healthcare provider with a suspected HNC (Caudell et al., 2022).

At present, the UK has two guidelines available to medical and dental practitioners relating to the detection and referral of suspected HNC; the National Institute for Clinical Excellence (NICE) suspected cancer: recognition and referral document published in June 2015 (NICE, 2015) and the Scottish Referral Guidelines for Suspected Cancer (Scottish Government, 2020). Both guidelines take a symptom-plus-duration approach and advise clinicians to refer onwards if there is a non-resolving red, white, or mixed red-white patch present with unknown cause for greater than three weeks, and any ulcer than lasts more than three weeks.

These guidelines are inconsistent, and sometimes conflict, in terms of actions for symptoms such as hoarseness, mucosal swelling/lumps, and in the NICE guidelines advising that referral to a dentist for suspicious lesions is appropriate. The guidelines in the UK have been questioned as to their effectiveness, with delay possible as a result of doctors being recommended to refer to a dentist in the first instance (Grimes et al., 2017).

The differences exhibited in these two guidelines applicable to the same country, Scotland, are an example of the heterogeneity in what clinicians are advised to undertake for suspicion of HNC in terms of the processes involved.

Some of the methods/investigations for diagnosing HNC (e.g. pathology and radiology) are included in clinical management guidelines (Caudell et al., 2022), however, they do not consider pathways or routes to diagnosis.

1.5.3.2 Head and Neck Cancer Referral Processes

Referrals for suspected HNC come predominantly come from primary care medics with some also coming from dental practitioners. The exact proportion from dentists is not routinely reported but Grafton-Clarke et al. (2019) in their systematic review showed 44% of referrals for suspected oral cavity cancer come from dentists in the UK. In England, urgent referrals for a suspicion of HNC were the fourth most common amongst all cancer types, despite it being the eighth most common cancer in incidence (NHS England, 2024b).

Referral processes for HNC are similar to that of other cancers described previously. A retrospective study in Glasgow from June 2015 – May 2016 investigating the outcomes of urgent suspicion of cancer referrals found that only 152 of the 2116 (7.6%) referrals resulted in a diagnosis of primary HNC, with a further 81 cases of other cancer types being diagnosed. Nearly half of urgent suspicion of cancer referrals were discharged after one appointment with reassurance only (851 of 2116, 42.6%) (Douglas et al., 2019).

HNC services are primarily in secondary and tertiary care multidisciplinary care centres in the UK, with large elements of centralisation, where specialist investigations and treatment are undertaken (Homer et al., 2024). There exists large international variation in how HNC services are structured.

HNC are confirmed with a range of diagnostic tests. Primarily, the disease is confirmed with a biopsy of the suspected tumour which then undergoes histopathological analysis by a pathologist to confirm the cellular and epithelial changes consistent with invasive cancer. Additionally, patients may have aspiration biopsies of suspicious neck or facial nodes if no primary tumour is clinically identifiable (Homer et al., 2024).

Another key step on the road to diagnosis is the undertaking of clinical imaging. Imaging offers the opportunity to identify the local extent of primary disease, the presence of multiple primary disease locations, and the presence of nodal involvement or metastatic spread. Commonly for most HNC sites, the standard imaging of choice is computerised tomography (CT) as it provides high quality anatomical depiction. It is a reliable and accurate method of imaging but does come with a high radiation cost, far surpassing the total background radiation exposure for one calendar year experienced on average by a UK citizen (UK Government, 2021). A further mode of imaging commonly used is Magnetic Resonance Imaging (MRI). Whilst carrying no radiation risk, it provides excellent detail on soft tissues examined, including extents of disease but is operationally more challenging and sensitive to small movements made by the patient mid-investigation. Other modes of imaging commonly used are ultrasound, plain radiographic imaging and positron emission tomography, the latter particularly when the primary site of disease is unknown (Vishwanath et al., 2020). If there is a confirmed HNC but no primary tumour is identified (often due to the presenting symptom being enlarged, suspicious nodes in the neck), patients will often undergo a Positron Emission Tomography (PET)-CT to identify areas of active mucosal or and nodal disease (Homer et al., 2024).

Multi-Disciplinary Teams (MDTs) are commonly used in HNC management to reach consensus between the various clinical teams on patient care. They are made up of a group of professionals from the various specialist teams involved in the care of HNC patients and use the available information from clinical, pathological and imaging investigations to devise diagnosis, staging and prognosis of a patient and their disease. MDTs are a vital measure in the safe and efficient progression of a patient's care (De Felice et al., 2018). It is recommended that the HNC MDT should consist of professionals involved in the direct management of HNC patients, with the exact make-up dependant on locally available specialist clinicians. MDT-led care has been shown to improve outcomes for those patients diagnosed with advanced stage disease (Friedland et al., 2011) but their role in early diagnosis is unclear. HNC MDTs are held in the specialist services of health systems and commonly include head and neck surgeons, radiologists, oncologists and pathologists and may include additional roles such as clinical nurse specialists, restorative dentists, speech and language professionals, and palliative care teams (Homer et al., 2024). There have also been strong arguments, such as those by Taberna et al. (2020) in their narrative review of MDTs, for the role of specialised dieticians and psychosocial support to be integral in HNC MDTs based on their integral role throughout treatment and onwards survivorship from HNC.

1.5.4 Head and Neck Cancer Staging

In order to confirm a diagnosis of HNC, and determine the extent of disease, clinical investigative processes must be undertaken. Pathological investigation is when a sample of tissue is taken from the site of disease, known as a biopsy, which is then carefully analysed in a laboratory through microscopic means with the aid of various chemical agents (Helliwell and Giles, 2016). The type of biopsy required depends on the clinical presentation and site of disease but often include incisional biopsies performed under local anaesthetic for oral cavity cancers, and the same for other sites but with the addition of endoscopic devices and sometimes under general anaesthesia (cancercenter.com, 2021). Another effective type of biopsy commonly undertaken is the Fine Needle Aspirate (FNA). This involves the insertion of a very thin needle into the tissue of interest, typically with the assistance of ultrasound imaging, where cells are gathered for pathological analysis and is commonly undertaken when assessing lymphatic nodes and solitary neck lumps/masses (Tandon et al., 2008). If initial pathological analyses are inconclusive, they may be repeated or progressed to excisional biopsies if clinically justified.

Following investigation and confirmation of a diagnosis of HNC, the disease is then staged. Cancer staging is a key proponent of diagnosis and treatment planning within HNC patient care. Staging defines the state of disease with regards to how locally advanced it is and whether it has spread to other parts/systems of the body through metastases. HNC, similar to all solid cancer types, is staged dependent on clinical examination, radiological and pathological evaluation. Diagnostic stage is categorised into four categories, I, II, III and IV, which are formed depending on a combination of the anatomical sub-site and the disease progression in the TNM classification (tumour, nodes, metastases). Stage I being commonly described as the most "early" or minimally progressed disease normally limited to local tumour of no significant size/spread to lymphatic nodes or distant sites, and stage IV being the most advanced level of cancer progression. and is a major prognostic factor in HNC (Seoane et al., 2016). Commonly, stages I and II are grouped as "early" stage cancers, with stage III and IV cancers grouped as "late" (National Cancer Institute, 2024a). There has been debate recently on the terminology of "late-stage" diagnosis as this comes with pejorative connotations of intentional non-action and as such the term "advanced stage" has been adopted in modern research on this subject.

Released in 2017, the eight edition of the Union for International Cancer Control (UICC) and American Joint Commission on Cancer (AJCC) Cancer Staging Manual contained some key changes to HNC staging (Amin et al., 2017). The most significant of these included separating HPV positive and HPC negative OPC into distinct disease entities with unique staging classifications, with HPV positive OPC having a revision of nodal classification to reflect the improved prognosis for patients who have confirmed nodal disease when tumours are positive for P16, the protein commonly expressed in HPV-positive HNC and often used as a proxy for HPV serology testing, compared to those with HPV negative disease.

Diagnostic stage is separated into two categories; clinical stage (cTNM) and pathological stage (pTNM). cTNM is the staging confirmed following clinical examination, biopsy, and imaging and is normally the first confirmed diagnosis a patient will have. pTNM is normally only available once a full tumour +/- any appropriate nodes have been resected and analysed completely. There is a documented discordance between clinical and pathological staging of HNCs, where Hondorp et al demonstrated a 33% discordance in their cohort with a Cohen's kappa agreement of 0.55. This shows the importance of having high quality diagnostic examinations and investigations to ensure appropriate treatment for patients with HNC. There was variation between HNC subsites across TNM categories with clear early or advanced disease presentations more concordant than those in the middle ranges of T and N (Hondorp et al., 2024).

Advanced stage at diagnosis of HNC is understood to be one of the key predictors of patient mortality. An analysis of the INTERCHANGE South American cohort study from 2011-2017, conducted by Abrahao et al (2020), showed that patients with stage IV OCC had a hazard ratio (HR) of death of 11.7 compared to those with stage I disease in a multivariable model. This higher risk of mortality was also seen in OPC cases where people with stage IV disease having a HR of 3.71.

Analysis also conducted by Abrahao et al (2018) of a large European case-control study, ARCAGE (2002-2011), showed similar results, with a HR of death of 3.71 for patients with stage IV when compared to stage I OCC. In an analysis of European cancer registries form the early 2000s, as few as 38% of HNCs are diagnosed at an early stage (Gatta et al., 2015). HNC stage was not routinely reported on by national cancer registries in the UK as of 2019. Advanced stage HNC is a significant public health problem but is one that has not been quantified or qualified internationally or nationally in the UK.

1.5.5 Time to Head and Neck Cancer Diagnosis and Stage at Diagnosis

1.5.5.1 Head and Neck Cancer Diagnostic “Delays”

The relationship between time and stage of HNC diagnosis is equivocal with a summary of the available review literature provided here.

Goy et al. (2009) with their quality systematic review were the first to review diagnostic delay and stage in HNC. The main finding from the analysis of the 27 studies included in the review was the lack of correlation between delay and stage at diagnosis across HNC subsites and in totality. When considering studies of all sites in HNC and those that looked at subsites only, mainly OCC, OPC, and laryngeal cancer, only six of the 27 studies showed a relationship between delay and stage at diagnosis, with most of these not having significance and there was no consistent relationship between stage and time with some studies, such as that by Kaufmen et al. (1980) showing an inverse relationship between time and stage.

Schutte et al. (2020) in their paradigm challenging review on impact of time to diagnosis and treatment on HNC found no significant evidence that delay of any kind was associated with TNM stage at diagnosis. However, the authors did find one study by Tromp et al. (2005) that showed a significant correlation with advanced T-stage and time-to-primary healthcare professional and a further study that identified an inverse relationship between time and tumour size, with those people who had large oral cavity tumours having shorter time intervals between first presentation to a primary health professional and confirmed diagnosis (WILDT et al., 1995), a phenomenon that may be related to aggressiveness of tumour or patient attributions of risk, however further research is required to better understand this inverse relationship.

The effect of diagnostic delay in HNC on survival and quality of life has been strongly shown. Seoane et al. (2012) in their systematic review and meta-analysis of 10 studies, identified diagnostic delay as a moderate risk factor for mortality from HNC, with patient delay, professional delays, and referral delays all contributing to overall delay in a fixed effects model.

A subsequent systematic review by Seoane et al. (2016) looked to evaluate the application of the Aarhus statement in oral cancer early diagnosis research and found that increased time from symptom development to referral is a significant risk factor for advanced stage diagnosis and mortality from HNC. The authors criticised the quality of studies that were able to be included in the review but were retrospectively applying the checklist to studies undertaken long before the checklist's development and publication. Historically, there has been debate similar to that of other cancer types in the relationship between stage and time for HNC in that there does not seem to be the expected longer time leading to more advanced disease finding (Guggenheimer et al., 1989, McGurk et al., 2005).

Graboyes et al. (2019) published a relatively limited systematic review on the association of treatment delays with survival for patients with head and neck cancer in which the authors focus on delays from the point of diagnosis to treatment initiation/completion. The review suggested that there was a strong relationship between increased time to treatment initiation and worse oncological outcomes, but all of the studies included in the review were limited to those from the United States only.

Across all the reviews noted, there was discussion as to the lack of homogeneity in study design and analyses precluding the ability to undertake meta-analysis. Specifically, there was little cohesion on the time points in the cancer care system used. With these points in mind, caution should be taken when interpreting these results however perhaps this heterogeneity itself is due to the variance in HNC systems globally and that existing models of "delay" do not truly account for the complexity in these systems or the environments in which they exist. Interestingly, these reviews also show clearly the lack of a true relationship between time and stage, despite the seemingly direct relationship between time and survival.

Within the literature, the terminology for defining advanced stage is heterogeneous with many studies defining stage III and IV disease as "late stage". Additionally, the literature on factors associated with stage is limited with most focus being placed on diagnostic delays.

1.5.5.2 Factors Associated with Head and Neck Cancer Delayed Diagnosis and Stage at Diagnosis

Worsham's editorial review (2011) was the first attempt to consolidate the literature on factors associated with advanced stage HNC where it was found that there was as strong association with race and advanced stage HNC, with African Americans being diagnosed with a greater proportion of advanced disease than Caucasian American, and within the African American population, those in lower-income groups had an even greater burden of advanced stage disease.

The role of race is one that has been further explored in the literature since within the lens of other factors such as health-insurance coverage. Osazuwa-Peters et al, in their 2020 analysis of State Medicaid coverage of patients for HNC, utilised registry data across the USA to assess the impact of State Medicaid expansion on rates of early stage HNC. The authors showed a statistically significant percentage increase in early stage detection of HNC overall of 2.37%, but this was markedly higher for several populations within their data set, including females (7.54%), young people (<35yo, 17.2%), those who identify as non-Hispanic blacks, and for residents in counties of mid-high education. Although the data analysed in this study and the named review are from HICs, and are retrospective looks at routine administrative data, this work contributes towards the potential role of universal health care in improving early stage diagnosis and reducing HNC inequalities with regards to advanced stage at diagnosis (Osazuwa-Peters et al., 2016).

In Schoonbeek et al.'s insightful systematic review (2021) on the determinants of delay and association with outcome in head and neck cancer, they add to the existing review literature on time to treatment in HNC by encompassing the different time elements in diagnosis and treatment within their search that ultimately included 57 studies. Across the four common sites for HNC, the authors found strong correlation that Hispanic and African Americans/Hispanics had an increased risk of delay, and that people who had diagnosis and treatment through Medicaid in the US as opposed to other forms of healthcare access were more likely to experience delays. The authors also interestingly found that there was conflicting evidence for the role of comorbidities in delay of diagnosis and treatment for HNC. Although the authors excluded studies on the pre-hospital contributions to delay in diagnosis, this review still adds valuable results to the literature by conforming the role of financial elements of health systems as contributing to delay.

Considering oral cavity cancers in isolation, a narrow systematic review on delay in diagnosis, Marcia de Cunha Lima et al (2021) neatly present the various factors identified from a range of studies from developed and developing countries. The authors portray the main finding as being a lack of population and professional awareness of HNC as the overarching finding from the papers included, which came from a range of developing and developed nations. The heterogeneity of study design and data included, as well as the focus on elderly populations, preclude any significant utility to the findings however they remain useful as an important factor to consider as one of the few pieces of existing literature on the topic.

Despite the understanding that stage at diagnosis is a key prognostic indicator for HNC, the evidence base for factors associated with diagnostic stage, and especially health system factors, is limited and largely focussed on HICs other than for OCCs.

1.6 Summary and Study Rationale

1.6.1 Thesis Rationale

This chapter has reviewed the literature pertaining to advanced stage HNC, including the definitions, burden and trends of disease, pathways and processes involved in obtaining a diagnosis, and introduced the role that various factors, such as the role of sociodemographic and tumour-related factors (e.g. HPV status) have in relation to advanced stage disease. The literature presented in this chapter has highlighted the emerging appreciation of health systems in the context of addressing complex health challenges and identifies the need to explore and investigate the potentially important role health system factors may have in advanced stage diagnosis of HNC in order to better understand the complexities involved in the significant public health challenge of the advanced stage HNC. At the time of embarking on this thesis and series of studies (October 2019) the health systems role and indeed a health systems approach to studying advanced stage HNC was scarcely discussed in the peer-reviewed literature.

From the literature available at the time prior to undertaking the research that forms this thesis, the evidence base for health system factors in HNC diagnosis was very limited and heterogenous. The role of health systems factors in wider cancer diagnosis more generally is still a developing area of health research with limited consensus on approaches to identifying or evaluating health system factors in cancer diagnosis, and no literature relating to HNC specifically. This scarcity of evidence, and the requirements set out for the output and timescale of this PhD, precluded any formal systematic review or synthesis from being an achievable aim within the timescale of this period of study.

Despite some evidence and wide acknowledgement that advanced stage HNC diagnosis is a key prognostic indicator for cancer outcomes, the actual burden of advanced stage HNC is not well described in the UK (and Scotland) and in the international data – with stage not typically recorded in cancer registries for HNC. With HNC incidence rates rising across the world, and with the associated significant burden that advanced stage disease brings, knowing the burden of this disease is critical to plan public health prevention strategies and health system/services developments to meet this challenge.

Much of the research to-date in cancer diagnosis more generally, and in particular HNC, is limited to analysing routine administrative data with limited understanding on factors, (especially health system related) associated with diagnosis from HNC patients and professionals from multiple perspectives. Greenhalgh and Papoutsi (2018) propose that to improve the quality and applicability of health systems research, studies must embrace complexity and engage with a wider range of stakeholders.

In addition to quantifying the burden of advanced stage HNC, and in order to address this problem, it is important that a more holistic/health system level perspective to understanding of the factors associated with advanced stage diagnosis of HNC is developed. Currently, there remains quite a limited understanding of the factors that influence stage of HNC diagnosis, with literature mainly emanating from HICs (especially USA), and it tends to focus on a polarised view of “patient” delay or “professional” delay with much of the explanation (or blame) being pointed towards patient related factors in seeking care. There is a clear need to explore a wider range of factors, across the behavioural, biological, and health systems as well as socioeconomic determinants to better understand reasons behind advanced stage HNC diagnosis. This understanding is particularly absent and important from a health system perspective. But there is also a need to understand with a depth that is missing in the literature from patients’ perspectives their “journeys” – pathways to diagnosis. While these stories may be unique to individuals – there are likely common barriers and facilitators and lessons that could shape the improvement of routes to HNC diagnosis. Moreover, there is rarely an international perspective taken to understanding HNC diagnosis - with opportunities to research and learn from across the world, not with a North (HIC) to South (LMIC) learning, but rather with an upfront openness to two-way learning.

With what is now known in terms of the many outcomes related to those factors in the social and environmental aspects of a population/individual, there is the additional need to include these factors in health services and systems research moving forward. A better understanding of how systems relate to each other and how people relate to those systems is needed if progress is to be made in improving health outcomes.

1.6.2 The Head and Neck Cancer in South America and Europe (HEADSpAcE) Collaboration and Consortium

The HEAD and neck cancer in South America and Europe (HEADSpAcE) Consortium is an EU Horizon 2020-funded, international collaboration of international researchers coordinated by the WHO International Agency for Research on Cancer (IARC). The consortium consists of a range of research organised as work packages aiming to identify factors associated with advanced stage diagnosis of HNC including tumour, demographic, behavioural, and systems factors. HEADSpAcE aimed to investigate the reasons for the poor prognosis of HNC across patient, tumour, and systems reasons for a diagnosis of advanced stage diagnosis; the influence of behavioural, infectious, and genetic factors on poor outcomes; and the adherence to available clinical guidelines across international HNC centres. The consortium also had additional aims of identifying the best way to clinically diagnose HPV-positive HNC and understanding genomic markers that were associated with poorer outcomes (IARC, 2020).

HEADSpAcE Consortium member institutions and researchers are situated in HNC centres from countries across the continents of South America and Europe, with HNC centres from Iran and Pakistan joining more recently after conception and additional analytical support for some elements of the consortium provided by researchers in the USA.

Work package two of HEADSpAcE has the focus of better understanding the factors involved and reasons behind advanced stage HNC and this PhD theses was undertaken as part of this work package with a specific focus on investigating the health system factors involved. This research was led by the University of Glasgow with close collaboration from researchers in Montevideo, Uruguay from the University de la Rey, along with others from across the consortium.

2 Chapter Two: Thesis Aims, Objectives, and Methodological Considerations

In this chapter, the overarching aims and objectives for the thesis are stated alongside specific aims, objectives, and methodological considerations for each of the study chapters. Informed by the overview of the literature in chapter one pertaining to HNC epidemiology, advanced stage at diagnosis of HNC, HNC systems, and factors associated with stage at diagnosis of HNC, the thesis undertakes a mixed-methods approach to answer the research questions stated.

2.1 Overarching Aims

The overarching aims of this thesis are to assess the burden of advanced stage HNC in the UK and to explore the potential role of health systems factors in diagnosis of advanced stage HNC. These aims will be accomplished by achieving the specific research aims and objectives for each subsequent chapter as detailed below.

2.2 Chapter Aims and Objectives:

2.2.1 Chapter Three: Head and Neck Cancer in the UK: What Was the Stage Before COVID-19? UK Cancer Registries Analysis (2011-2018)

Research Question: What is the burden of advanced stage head and neck cancer in the United Kingdom?

The aim of this chapter is to describe the burden of advanced stage head and neck cancer in the UK through analysis of national cancer registry data from 2009-2018 (before the COVID-19 pandemic).

The objectives of this chapter are:

- To request, collect, and collate cancer registry data on head and neck cancer incidence from the four national cancer registries of the UK.

- To undertake descriptive analysis of head and neck cancer incidence from 2009-2018 by HNC subsite (oral cavity, oropharynx, larynx, other) and UK country.

- To undertake descriptive analysis of incidence of head and neck cancers by stage at diagnosis across the four nations of the UK and HNC subsite.

- To undertake further analytical analysis of head and neck cancer by stage at diagnosis across age, sex, and area-based socioeconomic status for Scotland to assess relative importance of sociodemographic factors.

2.2.2 Chapter Four: Advanced Stage Head and Neck Cancer Diagnosis: HEADSpAcE Consortium Health Systems Benchmarking Survey

Research Question: What is the potential role of health systems factors in advanced stage diagnosis of head and neck cancer?

Aim: To explore the role of health systems factors in the diagnosis of advanced stage diagnosis of head and neck cancer across international specialist head and neck cancer centres via benchmarking data from a health system centre survey.

The objectives of this chapter are:

- To create bespoke health systems questionnaire to obtain quantitative and semi-qualitative data on head and neck cancer pathways to diagnosis and incidence at 18 head and neck cancer centres from the HEAD and Neck Cancer in South America and Europe (HEADSpAcE) consortium.

- To collate questionnaire responses, check data quality and completeness, with further rounds and checks with HNC centre leads.

- To formulate health system factors from responses where data were available and identify health system factors where data were not available.

- To benchmark head and neck cancer centres by proportion of advanced stage head and neck cancer and the presence/absence of health system factors within local head and neck cancer diagnostic systems.

- To undertake exploratory analysis on the role of each health system factor and the proportion of advanced stage head and neck cancer diagnosis.

- To collate information on the care pathway to head and neck cancer diagnosis from each of the 18 centres, and to harmonise these data into a standardised head and neck cancer diagnostic pathway.

2.2.3 Chapter Five: Health System Factors in Head and Neck Cancer Advanced Stage Diagnosis: A HEADSpAcE Consortium Qualitative Study in Glasgow and Montevideo

Research Question: What are the factors associated with stage at diagnosis of HNC and how do these prevent or facilitate early diagnosis?

Aim: To explore in-depth the health systems factors in advanced stage diagnosis of head and neck cancer in two specialist centres, Montevideo in Uruguay and Glasgow in Scotland, through a qualitative research study involving semi-structured interviews with a range of key informants and evaluate these factors using a systems approach

The objectives of this chapter are:

- To create thematic interview topic guides based on literature and findings from HEADSpAcE Benchmarking Survey (Chapter Four).

- To recruit 6-12 head and neck cancer patients in both Glasgow and Uruguay for semi-structured qualitative interviews.

- To recruit 6-12 clinicians and professional / management staff involved in the head and neck cancer systems in both Glasgow and Uruguay for semi-structured qualitative interviews.

- To undertake semi-structured interviews with consented participants.

- To thematically analyse the interview transcripts in order to assess the roles of health system factors in head and neck cancer stage at diagnosis.

- To apply a systems lens to the analysis of the emerging health system factor themes.

2.2.4 Chapter Six: Discussion

The objectives of this chapter are to:

- Present the key findings from this thesis as a body of work.

- Discuss these findings in the context of the wider international literature.

- Discuss the strengths and limitations of the data analysed and methodological approaches taken, considering alternative possible strategies.

- Present suggested areas for future research and propose recommendations for clinical practice and health system policy.

2.3 Methodological Considerations

The subsequent chapters in this thesis are presented, following receipt of appropriate approvals, in the alternative submission format for the College of Medicine, Veterinary and Life Sciences, University of Glasgow (in which chapters are presented in the style of the peer-reviewed journals that have already accepted/published the chapter-associated paper or in the style of the journal of intended submission). Each chapter contains details on the methods used in the respective studies. Whilst each chapter will cover, in detail, the methods used, and discuss the limitations of each, there is an appreciation that some of the traditionally included methodological and theoretical considerations found in a traditional PhD thesis may be beneficial for readers of this thesis in its entirety. In this section some further detail of the methodological and theoretical considerations for the thesis and each included study are presented to aid the contextualisation, understanding and interpretation of the finalised study chapters.

2.3.1 Overarching Thesis Methodology

The work undertaken in this thesis, specifically Chapters Four and Five, was undertaken as part of the aforementioned HEADSpAcE Consortium which has the overarching aim of investigating what tumour, behavioural, and health systems factors may be associated with advanced stage HNC (largely in South American and European settings). The area of health systems factors in diagnosis HNC, as described in Chapter One, is an emergent area of research in cancer diagnosis with this thesis aiming to explore this field for HNC for the first time.

Guided by the overarching theory of pathways to cancer diagnosis introduced in Sections 1.4 and 1.5, this thesis utilises a mixed-methods approach comprising of both qualitative and quantitative approaches to achieve the research aims and answer the thesis research questions. Mixed methods research approaches, widely accepted as a research methodology in which “the investigator collects and analyses data, integrates the findings, and draws inferences using both quantitative and qualitative approaches or methods in a single study or program of study” as defined by Tashakkori and Creswell (2007) provide researchers with a pragmatic and effective approach to answer research questions within a single study or series of studies. Within health research, especially those focussing on outcomes, mixed-methods approaches have been increasing as the realisation that acknowledging and embracing the complexity of health challenges can be better understood through traditionally quantitative only means (Tariq and Woodman, 2013, Wasti et al., 2022,).

In this thesis, an explanatory-sequential approach has been used (Shorten and Smith, 2017) as: first the burden of advanced stage HNC for in the United Kingdom is described (with sub-analysis investigating the role of demographic factors); then health systems factors identified and their effect on centre-level proportion of advanced stage HNC calculated across 18 international HNC centres; and culminating in a qualitative exploration of health systems factors through interviews with HNC patients and health professionals.

2.3.2 Chapter Three: Head and Neck Cancer in the UK: What Was the Stage Before COVID-19? UK Cancer Registries Analysis (2011-2018)

In order to answer the research question for this study the most complete set of data from all HNC cases in the UK lies within the national cancer registries of each country. Cancer registry data for HNC epidemiological study have been a successful avenue for previous analysis including in showing trends in incidence and mortality rates and in population demography (Ingarfield, 2019) but their role in understanding burden of advanced stage disease had not, at the time of this study, been assessed.

2.3.3 Chapter Four: Advanced Stage Head and Neck Cancer Diagnosis: HEADSpAcE Consortium Health Systems Benchmarking Survey

Benchmarking, as introduced in Chapter One, is an emerging methodology for health systems research. Other consortia researching health systems and cancer outcomes, mainly from the ICBP, have focussed on individual-level data direct from health professionals or routinely collected cancer registry data for benchmarking (Weller et al., 2018, Torring et al., 2019, Menon et al., 2019). Whilst this is a highly valuable approach, this was not something possible to the same degree for HNC (which is not included in the ICBP research programme) as the depth of routinely available data at the national level is less complete and in this study, we have included HNC centres from a broad range of countries, not solely HICs with largely publicly-funded national health systems as in ICBP.

The literature review in Chapter One identified an emerging appreciation for the need of pragmatic systems approaches to health research (Plsek and Greenhalgh, 2001, Greenhalgh and Papoutsi, 2018). In this study, devised as the first explorative investigation of health systems in relation to pathways to HNC diagnosis and stage of presentation, there is an initial data scoping and gathering exercise through a centre-level questionnaire completed by research leads at 18 HNC centres from across the world (in the HEADSpAcE consortium). This health systems questionnaire was based on the wider health systems literature and contained a large mixture of qualitative closed and open questions in addition to requests for aggregated estimates and counts of new HNC diagnoses and proportion of advanced stage. From the data collected, health system factors were identified and used for analysis by calculating the difference in proportion of advanced stage HNC by the presence/absence of each health system factor; a novel approach not seen in the literature to date.

2.3.4 Chapter Five: Health System Factors in Head and Neck Cancer Advanced Stage Diagnosis: A HEADSpAcE Consortium Qualitative Study in Glasgow and Montevideo

For this study, which aimed to understand how health systems affect the stage at diagnosis of HNC from people involved in the HNC diagnostic pathway and those diagnosed with HNC, a qualitative approach was chosen due to the ability of qualitative research to provide a rich, deep understanding of specific issues and the ability to answer more of the "how" than quantitative approaches allow (Pope and Mays, 1995).

Adopting a qualitative case-study approach was deemed most-appropriate here given the research focus on health systems factors and their relationship with stage at diagnosis of HNC stage (Renjith et al., 2021) and that the study was theoretically underpinned rather than aiming to develop new theory. Similarly, although ethnography could have been a methodological option, the highly sensitive nature of a HNC diagnosis and complex nature of HNC pathways led to interviews with key informants being chosen as the best approach to ensure a whole-systems view was obtained (Bannister-Tyrrell and Meiqari, 2020). This led to the purposive sampling of people with diagnosed HNC being included for participation and the inclusion of a broad range of HNC care professionals that reflected the wider range of clinical team members involved in the HNC diagnostic pathway.

The expressed need by the EU Horizon 2020 Programme, from which the funding that supported these studies was obtained, for the research to cover both Europe and South America presented the novel opportunity to undertake primary qualitative research in two centres concurrently with the interesting challenges of ensuring methodological rigour in the approach taken. The detailed methods used are described in Chapter Five section 5.3.

A brief overview of the content of each of the chapters included in this thesis and how they relate can be seen in Figure 2-1 with the studies being undertaken in chronological order with each result chapter partially informing the next and Chapter Five being informed by both Chapters Three and Four.

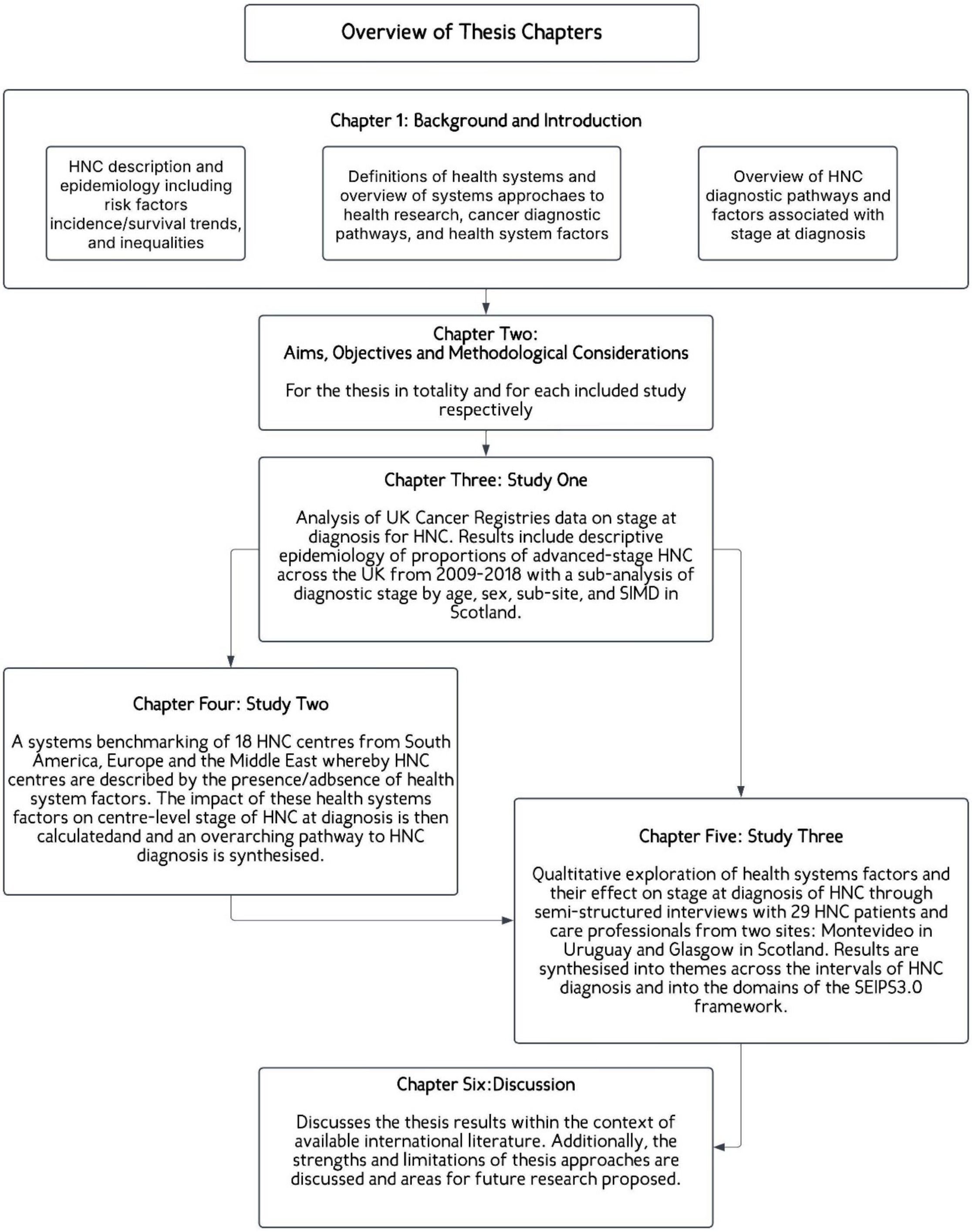

Figure 2-1: Project Flow Diagram of Thesis Chapters

3 Chapter Three: Head and Neck Cancer in the UK – What Was the Stage Prior to COVID-19? UK Cancer Registries Analysis (2011-2018)

This chapter was published in the British Dental Journal on 11th November 2022 and is presented in the format of the submission guidelines for the journal.

Creaney G, et al. Head and neck cancer in the UK: what was the stage before COVID-19? UK cancer registries analysis (2011-2018). Br Dent J. 2022 Nov;233(9):787-793. doi: 10.1038/s41415-022-5151-4. Epub 2022 Nov 11. PMID: 36369569; PMCID: PMC965017

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Key Words: Head and Neck Cancer, Cancer Stage, Oral/Oropharyngeal Cancer, Incidence, Population

Key Messages: -

From 2009 to 2018, 59% of patients with head and neck cancer in the UK were diagnosed with advanced stage disease where stage was recorded in national cancer registries.

The proportion of cancers diagnosed with advanced disease in 2016-2018 was highest in Wales (69%), followed by Northern Ireland (67%), Scotland (65%), and then England (58%) where stage was recorded.

Patients with oral cavity cancer or oropharyngeal cancers were more likely to have advanced disease than early disease.

Data on head and neck cancer stage in UK cancer registries has improved in completeness in recent years, with 87% known by 2018.

3.1 Abstract

Introduction

People who present with more advanced stage head and neck cancer (HNC) are associated with poorer outcomes and survival. The burden and trends of advanced stage HNC are not fully known at the population level. The UK national cancer registries routinely collect data on HNC diagnoses.

Aims

To describe trends in stage of diagnosis of HNCs across the UK prior to the COVID-19 pandemic.

Methods

Aggregated HNC incidence data were requested from the national cancer registries of the four UK countries for the 10 most recent years of available by subsite and American Joint Commission on Cancer (AJCC) stage at diagnosis classification. Additionally, data for Scotland were available by age-group, sex, and area-based socioeconomic deprivation (SIMD) category.

Results

Across the UK, rates of advanced stage HNC had increased, with 59% of patients having advanced disease at diagnosis from 2016-2018. England had a lower proportion of advanced disease (58%) than Scotland, Wales or Northern Ireland (63-69%) where stage data were available. The completeness of stage data had improved over recent years (87% by 2018).

Conclusion

Prior to the COVID-19 pandemic, diagnoses of HNC at an advanced stage comprised the majority of HNCs in the UK – representing the major challenge for the cancer healthcare system.

3.2 Introduction

Head and Neck Cancer (HNC) – the collective terms for cancers of the oral cavity, oropharynx, larynx, and other sites of the head and neck – is the 8th most common cancer globally with incidence rates either static or rising over recent decades, and the 9th highest cause of cancer-related mortality (Sung et al., 2021). In the UK, it is estimated that approximately 12,200 people have a new diagnosis of HNC every year, a 33% rise in incidence since the early 1990s (CRUK, 2020), which seems to be largely driven by dramatic increases in oropharyngeal cancer. The five-year survival for patients with HNC, although improving, remains poor globally (Pulte and Brenner, 2010), with only 28%-67% chance of survival at 5 years in the UK, depending on the subsite (CRUK, 2020), and mortality rates in Scotland rising 12% higher in women and 22% higher in men over the last decade. Many patient, tumour, and treatment factors contribute towards survival outcomes with HNC with a key prognostic tumour indicator being stage of disease at diagnosis (Ingarfield et al., 2019a).

Early stage HNC, where there is no loco-regional spread, is associated with relatively more straightforward treatment and better prognosis. Conversely, advanced stage HNC is associated with more complex / involved treatment and management, or in some cases palliative care (Worsham, 2011). Advanced stage disease also substantially impacts on quality of life and poorer survival outcomes (Mahul B. Amin, 2017).

Globally, a number of studies have shown high proportions of HNC diagnosed at advanced stage has remained high – including a large cohort from South America (2011-2017) with 75% advanced stage (Abrahão et al., 2020); and a multicentre European case-control study (2002-2004) with 54% (Abrahão et al., 2018).In the UK, two historic large clinical cohorts – one in Scotland 1999-2000 (Ingarfield et al., 2019b) and one in South West England 1996-2003 (Drugan et al., 2013) reported 56% and 56-59% advanced stage HNC respectively. More recently the UK wider HN5000 cohort 2011-2014 recruited 59.6% people with advanced stage disease (Ness et al., 2016). However, thus far population cancer registry data have not been utilised to examine stage of HNC in the UK.

Opportunistic oral soft tissue screening is undertaken by dentists when examining patients and is important in detecting early stage tumours (Lim et al., 2003), however, it is appreciated that given the rarity of these cancers and high number of sufferers who visit dental/health practitioners infrequently prior to diagnosis mean that more targeted measures of early diagnosis may be more appropriate (Purkayastha et al., 2018b). HNC can be cured more readily if the tumour is diagnosed at an early stage and confined to the head and neck region, but survival is poor if there is late-stage disease, metastatic spread and recurrence of disease (Marur and Forastiere, 2016).

We aimed to describe the stage at diagnosis of head and neck cancers in the UK at the population level prior to the COVID-19 pandemic by subsite, age, sex, socioeconomic factors, and over time. We also aimed to assess the completeness and availability of HNC stage data held by the cancer registries of the UK.

3.3 Methods

Information requests were submitted to the Scottish Cancer Registry (Public Health Scotland), English Cancer Registry National HNC report (Public Health England), Welsh Cancer Intelligence and Surveillance Unit (Public Health Wales), and the Northern Ireland Cancer Registry (Queen's University, Belfast). Data were requested where available on the numbers of cases and both the crude and European age-standardised incidence rates (per 100,000 population) of HNC over the most recent 10-year period (2009-2018), by HNC subsite, and stage of diagnosis. Subsites were defined via the International Classification of Diseases (ICD) , 2013) as: oral cavity cancers (C00.3, C00.4, C02.0, C02.1, C02.2, C03.0, C03.1, C04.0, C04.1, C05.0, C06.0, C06.1, C06.2); oropharyngeal cancer (C01, C02.4, C05.1, C05.2, C09.0, C09.1, C09.9, C10.0, C10.1, C10.2, C10.3); laryngeal cancer (C32.0, C32.1, C32.2); and for other sites of the head and neck (C07, C08.0, C08.1, C08.8, C08.9, C11.0, C11.1, C11.2, C11.3, C12, C13.0, C13.1, C13.2, C14.0, C14.8, C30.0, C31.0, C31.1, C73X).

HNC is staged using the AJCC TNM Classification of Malignant Tumours (TNM) classification of Malignant Tumours (Christian Wittekind, 2016, Mahul B. Amin, 2017) in order to categorise an individual's disease into one of four stages from stage I to stage IV at the time of diagnosis. TNM is used in treatment planning and gives a clinical description of the disease by tumour size, whether there is nodal involvement, and whether the cancer has metastasised to another site in the body. Stage I and II HNCs are considered early stage disease and are associated with more straightforward treatment and better prognosis, while stage III and IV HNCs are late, or more accurately termed advanced stage disease.

The Scottish Cancer Registry head and neck cancer data were also available by the additional demographics of age (5-year age bands), sex (male, female), and area-based socioeconomic measure – Scottish Index of Multiple Deprivation (SIMD) fifths – where SIMD-1 is the most deprived and SIMD-5 is the least deprived, (Scottish Government, 2016).

Crude incidence rates of HNCs were collated by stage for 2009-2018 where data were available. Age-standardised rates (ASR) were available for England, Scotland, and Northern Ireland. Where data were incomplete, this was factored into analysis in the description. ASR provide the incidence rate of a disease per 100,000 person-years within a population standardised to a standard population (EASR being standardised to a European population), which allows comparison between different regions and countries which might have different underlying population age-structure.

Further aggregated data were available for Scotland from years 2016-2018 covering age, sex, stage at diagnosis and SIMD quintile. Odds Ratios (OR) and 95% Confidence Intervals (95%CI) were calculated for this data set to ascertain any inequalities that could exist. Only cases where stage was known were included for analysis.

Least Square Means were calculated for ASR data from England, Northern Ireland and Scotland using SAS 16.

3.4 Results

Incidence by crude count was available for all four nations for all HNCs, however, data for Wales were only available for a slightly different ICD specification (C00-C14, C30-32). Incidence by subsite was available for England, Northern Ireland, and Scotland. Incidence by EASR was available for stage of diagnosis from England, Northern Ireland, and Scotland. Scotland had no data on stage available prior to 2016. Staging data were incomplete for all countries. For staging collations and comparisons, data from 2016-2018 has been used. All data utilised for stage analyses are shown in Supplementary Table 1 (Appendix 3-1).

Country	Counts	Crude Rate	EASR	Years Available	Subsite	Stage Data Routinely Published	Socioeconomic Status	Age	Sex
England	Yes	Yes	Yes	2009-2018	Yes	Partial	No	No	No
Northern Ireland	Yes	Yes	Yes	2009-2018	Yes	Partial	No	No	No
Scotland	Yes	Yes	Yes	2016-2018	Yes	No	Yes*	Yes*	Yes*
Wales	Yes	No	No	2011-2018	Yes	Partial	No	No	No

***Specifically requested**

Table 3-1: HNC Stage Related Data Available for Analysis from Information Requests

A total of 104,913 cases of HNC were diagnosed across England, Scotland, Wales and Northern Ireland from 2011 to 2018. Diagnosis across all subsites was more common to be at an advanced stage rather than early stage apart from for laryngeal cancers. Across all nations and subsites together, 59.0% of new HNCs were diagnosed at an advanced stage where stage was known from 2016 to 2018 (Figure 1).

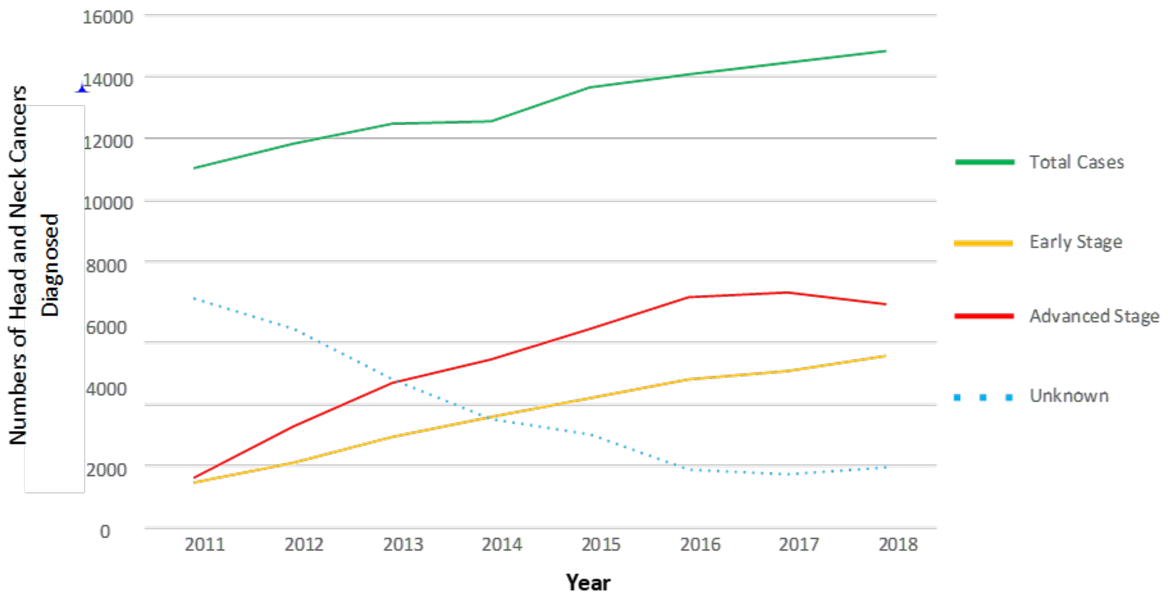

Figure 3-1: Numbers of New Head and Neck Cancers in the United Kingdom from 2011-2018 by Stage at Diagnosis

In 2011, only 32.6% of new HNC cases recorded in cancer registries had a stage at diagnosis recorded. This improved to 86.9% by 2018. As stage data became more complete over the seven years, rates of advanced disease rose much more quickly than early stages (Figure 2).

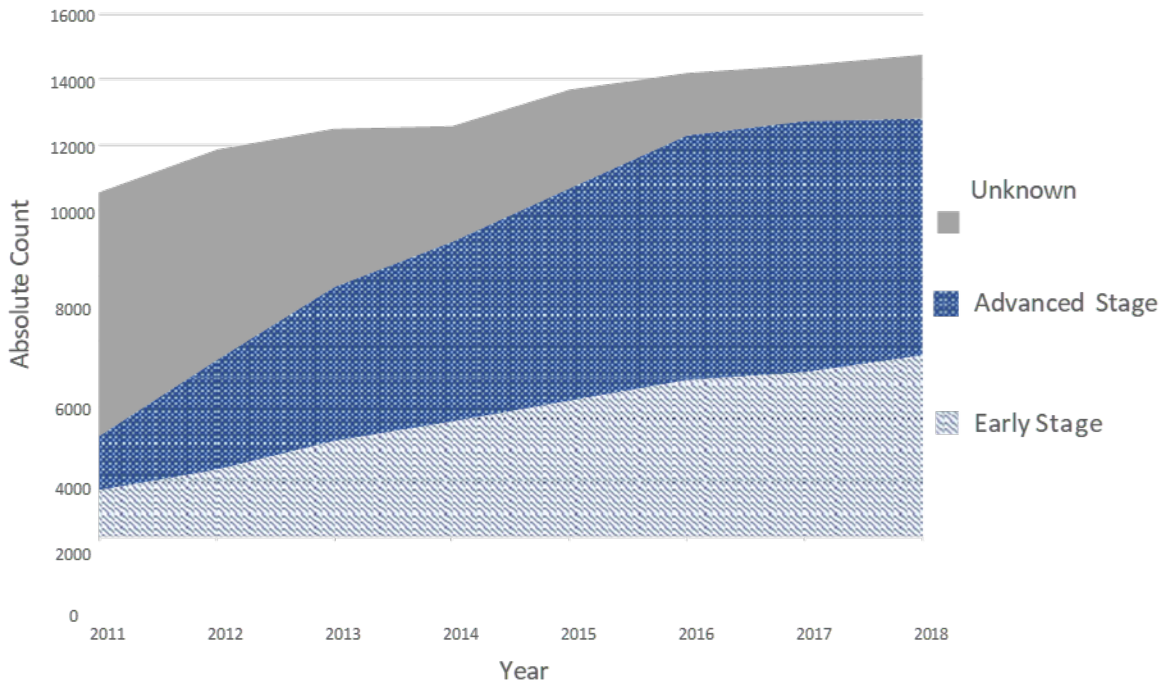

Figure 3-2: Proportion of Head and Neck Cancers in the United Kingdom from 2011-2018 by Stage at Diagnosis

Across the four nations, proportions of HNCs diagnosed at an advanced stage range from 50.5% in England, 52.6% in Scotland, 61.6% in Wales and 63.1% in Northern Ireland. When only analysing cases where stage is recorded, these rates increase to 57.6% in England, 65.4% in Scotland, 68.9% in Wales, and 66.9% in Northern Ireland. (Figure 3)

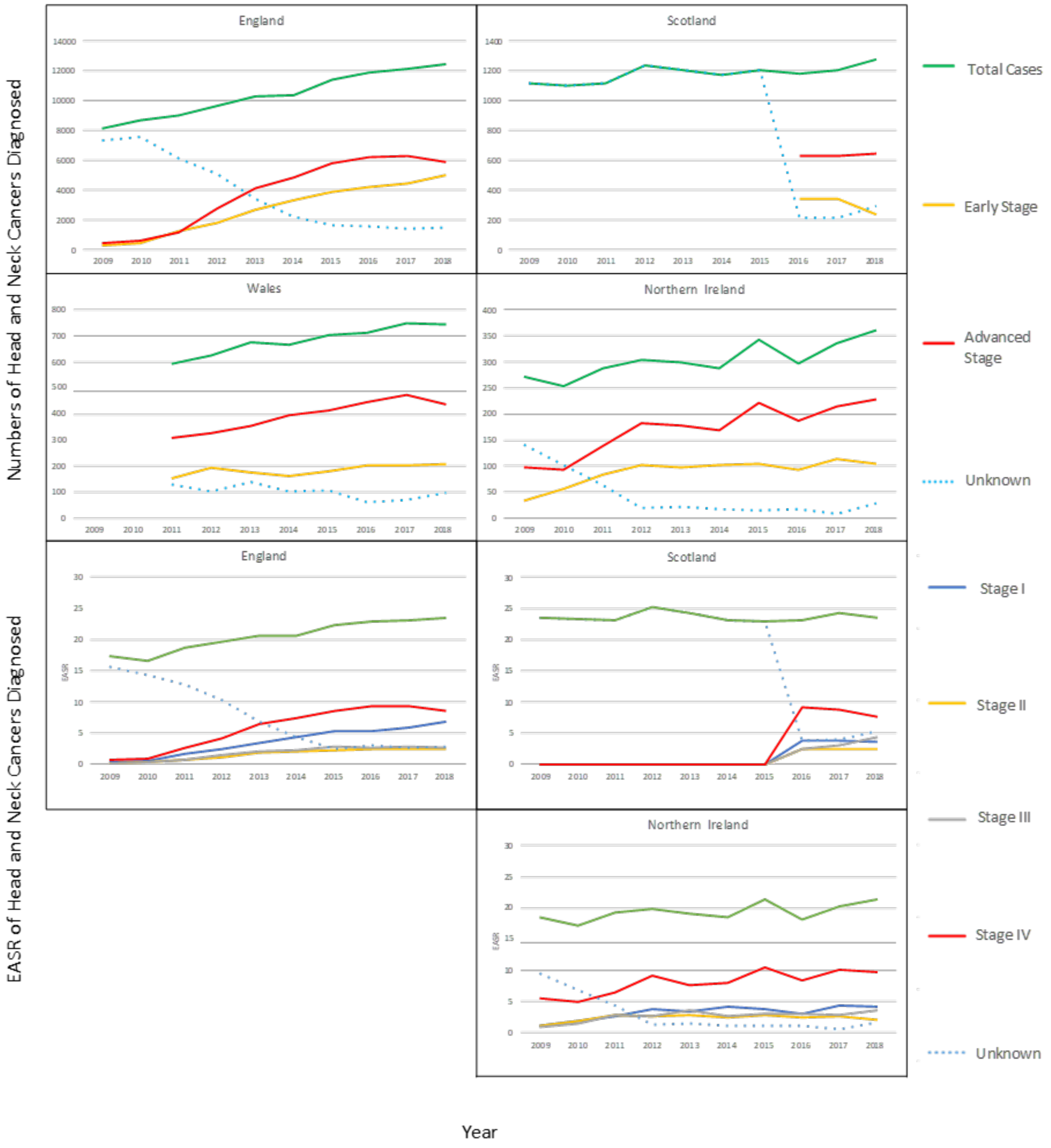

Figure 3-3: Head and Neck Cancer Incidence Counts and European Age-Standardised Rate (EASR) by Stage at Diagnosis for Each Home Nation for Years 2009-2018

In terms of site groupings, oropharyngeal cancers have the highest proportion of advanced stage at diagnosis. Stage IV tumours account for the significant majority of new oropharyngeal disease in England. In Scotland, 61.3% of new oropharyngeal tumours are diagnosed at an advanced stage. This rises to 80.7% when only considering cases where stage has been recorded (Table 3). Additional analysis utilising Least Square Means shows oropharyngeal cancers to be the highest rate of cancer subsite across the UK, and stage IV the most common stage at diagnosis.

Variable		EASR (95% Confidence Interval)	Difference Between Means (95% Confidence Interval)
HNC Subsite	Larynx	0.75 (0.58, 0.92)	1.00(Referent)
	Oropharyngeal	0.91 (0.74, 1.08)	0.16 (0.08, 0.41)
	Oral Cavity	0.73(0.55, 0.90)	-0.02 (-0.26, 0.22)
	Other sites of Head and Neck	0.76 (0.59, 0.94)	0.02 (-0.22, 0.26)
Stage at Diagnosis	I	0.74 (0.59, 0.89)	1.00 (Referent)
	II	0.44 (0.29, 0.59)	-0.31 (-0.52, -0.10)
	III	0.49 (0.34, 0.64)	-0.25 (-0.47, -0.04)
	IV	1.48 (0.33, 1.63)	0.74 (0.52, 0.95)

Table 3-2: Least Square Means Tests for Selected Variables for European Age Standardised Rates (EASR) of New HNCs in England, Northern Ireland and Scotland 2009-2018 Where Stage Known

When considering cases in Scotland (Table 3), being aged 50 years or more (relative to under 50 years) at diagnosis was not associated with risk for presenting with advanced stage disease (OR 1.10, 95%CI 0.86-1.42). Males tended more likely to be diagnosed at an advanced stage compared to females (OR 1.24, 95%CI 1.05-1.46). Although those from the most deprived areas (SIMD5) were not found to have a statistically significant higher risks of advanced stage HNC (OR 1.14, 95%CI 0.89-1.48), they did have a higher proportion of advanced stage disease (68.9%) compared to those in the least deprived areas (63.7%). People diagnosed with oropharyngeal disease were statistically more likely to have advanced disease when compared to oral cavity disease (OR 3.14, 95%CI 2.54-3.89).

		Early Stage		Advanced Stage		Ratio Advanced to Early	Univariate Model		
		N= 1016	**34.57%**	**N=1923**	**65.43%**	**1.89**	**P Value**	**Odds Ratio (to Reference Category)**	**(95% CI)**
Age at diagnosis	**<50** (Ref)	104	36.62%	180	63.38%	1.73	-	1.00 (Referent)	-
	50+	912	34.35%	1743	65.65%	1.91	0.222410	1.10	0.86-1.42
Sex	**Female** (Ref)	324	38.03%	528	61.97%	1.63	-	1.00 (Referent)	-
	Male	692	33.16%	1395	66.84%	2.02	**0.005919**	**1.24**	**1.05-1.46**
Site Grouping	**Oral Cavity** (Ref)	392	42.98%	520	57.03%	1.33	-	1.00 (Referent)	-
	Oropharynx	169	19.34%	705	80.66%	4.17	**<0.0001**	**3.14**	**2.54-3.89**
	Larynx	331	48.53%	351	51.47%	1.06	0.013853	0.80	0.65-0.98
	Other sites of Head and Neck	124	26.33%	347	73.67%	2.80	**<0.0001**	**2.11**	**1.65-2.69**
SIMD	**5: Least Deprived** (Ref)	132	36.26%	232	63.74%	1.76	-	1.00 (Referent)	-
	4	175	37.72%	289	62.28%	1.65	0.333869	0.94	0.71-1.25
	3	213	36.66%	368	63.34%	1.73	0.374067	0.96	0.73-1.26
	2	227	34.08%	439	65.92%	1.93	0.241447	1.10	0.84-1.44
	1	296	31.13%	595	68.87%	2.21	0.151167	1.14	0.89-1.48

Table 3-3:HNC diagnoses by Early/Advanced Stage in Scotland by Age, Sex and SIMD 2016-2018 where stage known

Discussion

These results show that the proportion of HNCs diagnosed with advanced disease has not improved across the UK in recent years with 59% of people with HNC presenting with advanced stage disease. In addition, data held by the national cancer registries show oropharyngeal cancer to be the most common subsite of HNC from 2009-2018 in the UK. There have been several large cohort studies incorporating stage at diagnosis into their investigations in recent decades. Our analyses show that from 2016-2018, 65% of HNCs with known stage were diagnosed with advanced disease in Scotland, a higher proportion than that shown by the Scottish Audit of Head and Neck Cancer in 1999-2000, where 56% of HNCs were stage III or IV at diagnosis in the national population (Ingarfield et al., 2019b). The change has not been as pronounced in England where the South West Audit of Head and Neck Cancer (1996-2003) had a 56-59% advanced stage diagnostic rate (Drugan et al., 2013) which is similar to that found here foe England of 57% from 2009-2018. The UK-wide Head and Neck 5000 study (HN5000) undertaken in 2011-2014 had 59.6% of all HNCs were diagnosed at an advanced stage, which again is similar to our findings for the UK with 59% of HNCs diagnosed at advanced stage in the national registries (Ness et al., 2016). Care must be taken when interpreting these data however, as there is a notable difference between the four nations, described above. The data presented in this paper show that there has been no improvement in rates of advanced disease in the last 20 years, with current rates far higher currently in Scotland, Wales, and Northern Ireland than in England. These rates across the UK fall short of the UK target of 75% cancers being diagnosed at early stage is to be met by 2028 (McCormack and Aggarwal, 2021).

Cancer Registries are population-level databases normally hosted within a public health system. They provide high quality population coverage data on cancer incidence related to key demographics (Brewster et al., 2005). With cancer registry data on HNCs becoming more complete over time, as demonstrated in this analysis, further opportunities emerge for better understanding the trends and burden of HNC in the UK. Appropriate understanding and use of cancer registry data has been demonstrated to be a very valuable asset for health providers and public bodies in reducing the burden of disease (Bouchardy et al., 2014). Cancer stage at diagnosis is routinely recorded in registries for some major cancer sites such as breast, colon and lung, but only recently has begun to be recorded for HNCs as demonstrated here.

Although a rich and very useful source of population level data, cancer registry databases do have limitations. Registries rely on accurate data being recorded and entered from the clinical locations and while there are high levels of quality and completeness in cancer registries overall, some fields, particularly stage, have been incomplete (Brewster et al., 1994, Brewster et al., 1997, Brewster et al., 2002). Analysis of cancer registry data for other types of cancer has suggested that those cases with missing stage within cancer registries may be more likely to be from people diagnosed with later stage disease, meaning that proportion of advanced disease may in fact be underreported. This has not been shown for HNCs to-date however, although it may suggest some underestimation of our study findings (Di Girolamo et al., 2018).

Advanced stage at diagnosis of an HNC is defined as Stage III or IV according to the TNM 8th Edition (Christian Wittekind, 2016). There was one significant change in the transition from TNM 7th edition to the current volume involving P16 positive tumours of the oropharynx. This change, a downstaging for certain P16 positive oropharyngeal tumours given the more favourable prognosis of these compared to p16 negative tumours, was able to be adopted by all registries from January 2018 and will inevitably cause some heterogeneity in data recording processes. This change could have resulted in disease being classified as early rather than advanced stage, meaning that any reduction in rate of advanced stage at diagnosis observed in 2018 may be in part a disease classification phenomenon as opposed to a true reduction in severity of disease presentation.

The importance of stage at diagnosis as a prognostic factor cannot be understated. Stage at diagnosis is one of the key prognostic indicators of mortality in people with HNC (Ingarfield et al., 2019a) with an increase in morbidity and reduction in post-treatment quality of life also observed. (De Melo et al., 2018) There are many factors that influence the stage at diagnosis of HNC, including patient-related factors, tumour-related factors, HPV infection and socioeconomic factors (Auluck et al., 2016, Carvalho et al., 2002, Anantharaman et al., 2013, Lechner et al., 2022, Worsham, 2011). While not found to be statistically different, the result that those in the most socioeconomically deprived areas of Scotland (SIMD1) have a higher proportion of advanced stage disease when compared to those in the least deprived areas (SIMD5) suggests that there are wider socioeconomic environmental factors that potentially influencing stage at diagnosis of HNC. A key area for further research is that of health-system factors in stage of diagnosis. It is widely reported that delay in diagnosis of HNC can have significant impact on the tumour-related and patient-related outcomes, with delay coming from both the patient interval and professional interval (Schutte et al., 2020b). In order to improve rates of early diagnosis, more understanding is required as to how these delays can be addressed; something that a major WHO International Agency for Research on Cancer led initiative, the Head and Neck Cancer in South America and Europe (HEADSpAcE) study is currently investigating (IARC, 2021).

A key reason for the importance of this study to understand the pre-pandemic situation with regards to stage at diagnosis of HNC is to accurately ascertain the effect that the pandemic has had on the HNC system in the UK. It is possible that rates of advanced disease will rise given the well-documented issues of limited access to health services and reported lower rates of diagnosis generally, however emerging research from European countries has not demonstrated this (Popovic et al., 2022). While HNC services have been able to continue diagnosing and treating patients throughout the COVID-19 pandemic (Walker and Paterson, 2021), there is concern that the pandemic may have led to more patients presenting with advanced disease, or not at all, to health services. It will be important to monitor the impact of the COVID-19 pandemic on the incidence of advanced stage HNC, and we have shown there is improving data available via the UK cancer registries which can be used to monitor this and inform service recovery.

For dentists, oral cancer is a key topic for ongoing Continuing Professional Development (General Dental Council, 2018). Most patients first present to primary care in the first instance with a HNC but there is more that can potentially be done in raising awareness across health professionals (Fanaras and Warnakulasuriya, 2016) and also in the general public (Macpherson, 2018) in order to reduce rates of advanced disease. Dentists can play a very important role in early detection of HNC through opportunistic screening and more frequent recall intervals for patients who may be at higher risk of developing

HNC despite low-detection rates in primary care (Purkayastha et al., 2018a). An updated recent Cochrane Review reiterated the important role frontline that oral health teams play in detecting oral malignancies (Walsh et al., 2021b). However, for this to be the case, clear pathways and guidelines have to be available for referral of suspicious signs and symptoms to secondary care settings, as advised in the recent Delivering Better Oral Health guidelines (Office for Health Improvement and Disparities, Updated November 2021). National guidelines also exist to facilitate this pathway, such as NICE Guideline 12 (NICE, 2015 [updated 2022]) and the Scottish Cancer Referral Guidelines (Scottish Government, 2020).

3.5 Conclusions

Prior to the COVID-19 pandemic, based on available population data, diagnoses of HNC at an advanced stage comprised the majority of HNCs across the UK – representing the major challenge for the cancer healthcare system, including the need for better clarification of the role of the dental team and their links with/referral pathways to HNC services. Understanding the reasons behind the high levels of advanced HNC at presentation is vital in order to reduce the substantial impact of this disease and the poor survival rates experienced in the UK and internationally.

The future trends of advanced stage HNC as we emerge from the COVID-19 are not yet known, but these data demonstrate a pre-pandemic baseline level which highlights this as a significant public health challenge.

3.6 Ethics Declaration

The University of Glasgow Medicine, Veterinary and Life Sciences (MVLS) Research Ethics Committee were approached and advised formal ethical approval was not necessary for this analysis of aggregated, routine administrative data. The authors declare no conflict of interest.

3.7 Author Contribution

DC and GC, with AR, conceived and designed this study. LB collated and provided enhanced data for Scotland. GC with AM analysed data. CP provided clinical oncology input. GC wrote the first draft of manuscript. All authors contributed to the final draft and reviewed prior to submission.

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4 Chapter Four: Advanced Stage Head and Neck Cancer Diagnosis: Headspace Consortium Health Systems Benchmarking Survey

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4.1 **Abstract**

Background: Globally, most people with head and neck cancers (HNCs) are diagnosed with advanced stage disease. HNC diagnostic stage has multifactorial explanations, with the role of health system factors not yet fully investigated.

Methods: HNC centres (n=18) from the HEADSpAcE Consortium were surveyed via a bespoke health system questionnaire covering a range of factors. Centres were compared using the least square means for the presence/absence of each health system factor to their proportion of advanced stage HNC.

Results: Health system factors associated with lower proportion in advanced stage diagnosis were formal referral triaging (14%, 95%CI-0.26, -0.03), routine monitoring of time from referral to diagnosis (16%, 95%CI-0.27, -0.05), and fully publicly funded systems (17% 95% CI-0.29, -0.06). Several health systems factors had a lack of routine data available.

Conclusions: Through identifying health systems factors associated with lower proportions of advanced stage HNC, interventions can be developed, and systems redesigned, to address this significant issue.

Keywords: Health Systems, Head and Neck Cancer, Diagnostic Pathway, Stage at Diagnosis

4.2 Background

Head and neck cancers (HNCs) comprising cancers of the oral cavity, pharynx, and larynx are the 6th most commonly diagnosed cancer group globally with 90% of HNCs being squamous cell carcinoma (SCC) (Bray et al., 2024). Mortality rates are high (Gormley et al., 2022), and extensive multi-modal treatment is usually required, but often results in significant morbidities (Semple et al., 2023). Stage at diagnosis influences treatment planning and is a key prognostic factor (Worsham, 2011, (Mahul B. Amin, 2017), with advanced disease (Stage III and IV as per TNM 7th and 8th editions (Christian Wittekind, 2016, Brierley, 2021) resulting in poorer survival. Estimates from large international cohort studies have shown the proportion of advanced HNC to range from 54% in Europe (Abrahão et al., 2018) to 75% in South America (Abrahão et al., 2020). Cancer registry analysis has shown that 59% of newly diagnosed HNCs in the United Kingdom were recorded as TNM stage III or IV in the national cancer registries in 2016-2018 (Creaney et al., 2022). Despite advances in understanding the causes and risks of developing HNC (Gormley et al., 2022), preventative and early detection measures (Brocklehurst et al., 2013), and progress in treatments for HNCs including technological advances in radiotherapy and new immunotherapy regimens (Amaral et al., 2022), there has been minimal improvements in survival from HNC observed in recent decades (Bray et al., 2024, Gormley et al., 2022).

Health systems are known to be complex with many challenges arising from dynamic interactions between patient factors, operational procedures, and organisational demands (Plsek and Greenhalgh, 2001). Currently, the literature investigating factors associated with diagnosis of advanced HNC does not include health system factors, and is limited to findings on individual race, type of health insurance, and is based in the United States of America (Worsham, 2011, Osazuwa-Peters et al., 2020, Schoonbeek et al., 2021), or is for the oral cavity subsite only where the main finding was the role of patient and professional awareness of oral cancer (Lima et al., 2021). Recent studies investigating the role of health systems and diagnosis of cancer (but not including HNC), identified the potential role of technology, gatekeeping, finance, and centralisation of services on diagnostic pathways and patient experience towards diagnosis (Brown et al., 2014, Rose et al., 2015, (Schoonbeek et al., 2021). This study aims to explore the potential role for health system factors on the stage at diagnosis of HNCs. exploring the different pathways to diagnosis across HEADSpAcE centres.

4.3 Methods

4.3.1 Study Design and Setting

The HEADSpAcE (HEAD and neck cancer in South America and Europe) Consortium is an international multicentre research programme coordinated by the International Agency for Research on Cancer – World Health Organisation (IARC-WHO) focused on investigating factors associated with advanced stage at diagnosis of HNCs including genomic, patient, socioeconomic, and health system factors (IARC, 2021). The HEADSpAcE Consortium includes 18 HNC tertiary treatment centres: 10 from South America, 6 from Europe, and 2 from the Middle East (Table 1).

This study utilized a systems survey approach through a self-completed questionnaire, specifically designed for the centre leads of the HNC centres within the HEADSpAcE Consortium. Data collection was focussed on the health system in the year prior to the COVID-19 pandemic (i.e. in 2019), questionnaires were returned between November 2020 and November 2022, with subsequent rounds of follow up with centres to check data quality and completeness. Each HEADSpAcE centre is linked with local HNC clinical centres

HEADSpAcE Centre	Location	Country	Region	United Nations Human Development Index	World Bank Economy Ranking	HNC Cases Diagnosed in 2019 (n)
Tehran University of Medical Sciences (TUMS)	Tehran	Iran	South Central Asia	High	Low-Middle Income	56
Aga Khan University (AKU)	Karachi	Pakistan	South Central Asia	Low	Low-Middle Income	602
Santa Fe de Bogotá Foundation University Hospital (FSFB)	Bogota	Colombia	South America	High	Low-Middle Income	123
A.C. Camargo Cancer Centre (AC-CCC)	Sao Paulo	Brazil	South America	High	Low-Middle Income	823
Barretos Cancer Hospital (HCB)	Barretos	Brazil	South America	High	Low-Middle Income	704
University of the Republic (UdelaR)	Montevideo	Uruguay	South America	Very High	High Income Country	110
National University of Cordoba (UNC)	Cordoba	Argentina	South America	Very High	Low-Middle Income	20
Hospital Santa Rita de Cassia - Women's Association of Education and Fight against Cancer (AFECC)	Vitoria	Brazil	South America	High	Low-Middle Income	341
Goiânia Cancer Registry (GCR)	Goiânia	Brazil	South America	High	Low-Middle Income	650
University of Buenos Aires (IOAR)	Buenos Aires	Argentina	South America	Very High	Low-Middle Income	443
Brazilian National Cancer Institute (INCA)	Rio	Brazil	South America	High	Low-Middle Income	1296
National University of Asuncion (NUA)	Asuncion	Paraguay	South America	High	Low-Middle Income	155
Léon Bérard Centre (CLB)	Lyon	France	Europe	Very High	High Income Country	403
University of Bristol (UBRIS)	Bristol	UK	Europe	Very High	High Income Country	210
Catalan institute of Oncology (ICO)	Barcelona	Spain	Europe	Very High	High Income Country	333
University of Turin (UNITO)	Turin	Italy	Europe	Very High	High Income Country	171
Charles University (CUNI)	Prague	Czechia	Europe	Very High	High Income Country	266
University of Glasgow (UGLA)	Glasgow	UK	Europe	Very High	High Income Country	543

Table 4-1: HEADSpAcE Head and Neck Cancer Centres

4.3.2 Data Sources and Measurement

A bespoke questionnaire was developed with reference to the literature (Brown et al., 2014) and in consultation with clinicians, healthcare managers, and administrators and collaborators from the HEADSpAcE Consortium (Appendix 4-1). The questionnaire included both closed and open-ended questions to assess the availability of data on health system domains and open-ended questions to gather detailed information on the healthcare pathway to diagnosis; alongside data on the number of HNC cases diagnosed in 2019 and the proportion of these that were advanced stage at diagnosis. Additionally, local protocols or guidelines for referral and diagnosis of HNC where available were requested from each centre. Project leads in each of the 18 HNC centres were responsible for the completion of the questionnaire for their respective centre.

4.3.3 Health System Domains

Health system domains covered in the questionnaire included items on the availability and nature of: Referral Systems (assessing electronic pathways and triaging); Quality/Performance Indicators (monitoring referral to diagnosis times); Diagnostic Processes (ensuring centralised diagnoses, are integral); Multidisciplinary Teams (assessing comprehensiveness of care); Technology (in relation to communication across system); Financial Models (evaluating funding structures); and Centre Activity (measuring case-load volume), and Service Structures (assessing degree of centralisation of services).

Following collation of the questionnaire responses; health system factors deriving from responses to each respective questionnaire domain with data available for benchmarking across all centres were identified (Table 2). Centres were categorised by the presence of the health system factor in their local HNC system (yes/no).

Health System Domains	Topics in Health System Questionnaire	Benchmarking Health System Factor	Description of Health System Factor
Referral System	Referral Guidance Referral Volume Referral Categories Referral Methods and Processes Triaging	Bespoke Electronic Referral Pathway	Bespoke electronic referral system used as main method of referral into specialist care
		Referral Guidance	Guidance on referral processes and criteria is available for primary care/community care teams
		Triaging System	Formalised referral triaging/vetting of received referrals by specialist team
Quality/Performance Indicators	Waiting Time from Referral to Diagnosis Waiting Time from Referral to First Appointment Diagnostic Investigation Reporting Time Targets Routinely Monitored Performance Indicators	Referral to Diagnosis Waiting Time Targets/Monitored	Routinely monitored and reported from date of referral through to diagnosis date in entirety
Diagnostic Processes	Diagnostic Confirmatory Procedures	Diagnosis Made Exclusively by HEADSpAcE Centre	Diagnosis is usually only made at the HEADSpAcE centre for all patients and not at another service prior to referral
Multidisciplinary Teams	Frequency of Meetings Multidisciplinary Composition of Members	Comprehensive Multi-Disciplinary Team (MDT)	MDT Includes representation from wide variety of specialists and health professionals and meets regularly
Technology	Communication Methods Common Electronic Medical Records	Common Medical Record	Shared record accessible by all health practitioners across primary care and secondary care
Workforce	Numbers/Full-Time Equivalent Primary Care Clinicians in Local System Numbers/Full-Time Equivalent Specialist/Secondary Care in Local System	Specialist HNC Pathologists and Radiologists	Both radiology and pathology specialists are available locally
Financial Models	Additional Patient Costs Public/Private/Mixed/Insurance	Fully Publicly Funded HNC Centre	Fully Publicly Funded HNC Diagnosis and Treatment, including Dental Checks
Centre Activity	New Cases Diagnosed Source of Referrals Proportion of Advanced HNC	Large HNC Patient Volume	Centre treats >= Mean Number of Cases per Annum (402, from the 18 centres)
Service Structure	Location of Services "One-Stop" Clinics	All Diagnosis and Treatment Undertaken at One Location in HEADSpAcE Centre	All aspects of diagnosis and treatment happen in one hospital/physical site

Table 4-2: Healthcare System Questionnaire Domains

4.3.4 Centre Health System Benchmarking Analysis

The centres were sorted by their proportion of advanced stage HNC diagnosed in 2019 (Table 3). Least Square Means tests were performed to calculate the absolute percentage difference and standard deviation in the proportion of advanced stage HNC for each health system factor (along with 95% confidence intervals and p-values). Subgroup analyses and sensitivity analyses were also performed to ensure robustness of the findings (Table 4). All statistical analyses were performed using R software (R version 2022.02.2).

4.3.5 HNC Diagnostic Pathway Description and Harmonisation

Open questions were included in the questionnaire which asked for descriptions of each centre's pathway to HNC diagnosis. These responses were clarified with follow up online discussions with centre leads where required. The interval approach that forms the Aarhus pathway for cancer research (Coxon et al., 2018, (Seoane et al., 2016, (Weller et al., 2012) was used as a framework to collate and harmonise the range of diagnostic pathways across centres for all HNC subsites with the aid of Lucidchart (lucid.co) digital mapping software.

Health System Factor	**HEADSpAcE Centre**																	
	CLB	**UBRIS**	**ICO**	**FSFB**	**AC-CCC**	**UNITO**	**TUMS**	**HCB**	**UdelaR**	**CUNI**	**UNC**	**UGLA**	**AKU**	**AFECC**	**GCR**	**IOAR**	**INCA**	**NUA**
Estimated Proportion of Advanced Stage HNC 2019	27%	38%	45%	46%	48%	50%	50%	50%	52%	55%	59%	65%	65%	69%	70%	76%	77%	90%
Electronic Referral System for HNC	No	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	No
Common Primary-Secondary Care Medical Record	No	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No	No
Higher Patient Volume (>Mean)	Yes	No	No	No	Yes	No	No	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	No
Single Centralised Site	Yes	No	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes
Referral Waiting Times Monitored	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Yes	No	No
Initial Diagnosis Made Exclusively at Centre	No	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No	No	No	No	No
Comprehensive MDT	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No
Specialist HNC Radiologists and Pathologists	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
Referrals Formally Triaged	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No
Referral Guidance	No	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	No	Yes	No	No	No	No
Exclusively Publicly Funded System	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No	Yes	No	No	No	No	No	No

Table 4-3: Benchmarking Proportion of Advanced Stage HNC Against Presence of Health System Factor

4.4 Results

4.4.1 Centre Health System Benchmarking

The centres were ranked and benchmarked by the proportion of advanced stage HNC in 2019 which ranged from 27% (CLB, Lyon, France) to 90% (NUA, Asunción, Paraguay), along with the presence or absence of health system factors (Table 3). Nine out of 18 centres have electronic referral systems, while only five have integrated common primary-secondary care medical records. Eight centres manage a higher number of patients per year than the mean (mean n=402, range 20-1296), and nine operate from a single centralised site. Monitoring referral to diagnosis waiting times is undertaken in 12 centres. Eleven centres employ comprehensive multidisciplinary teams, and 12 have specialist HNC radiologists and pathologists. Formal triage of referrals occurs in 13 centres, but only seven have formal referral guidance. There were diverse funding models for the health systems with seven exclusively publicly funded centres. No centre exhibited all of the health system factors assessed and all centres had at least one of the assessed health system factor present.

The presence of several health systems factors within the HNC centres included in this analysis were associated with a lower proportion of advanced stage HNC (Table 4). Of all the factors analysed, three were strongly associated with a lower proportion of advanced stage HNC diagnoses when they were part of a centre's HNC system: i) routine monitoring of waiting times from referral to diagnosis had a 16% lower proportion in advanced stage HNC (95% Confidence Interval (CI) -0.27, -0.05; p-value 0.007); ii) having a formal referral triaging process showed a 14% lower proportion (95% CI -0.26, -0.03; p-value 0.0179); and iii) centres with a publicly funded patient finance model/universal health coverage had a 17% lower proportion (95% CI -0.29, -0.06; p-value 0.008).). Centres with higher patient volume (2% (95% CI -0.13, 0.16)) and centralisation of centre services (*% (95% CI -0.19, 0.19) showed no evidence of a higher proportion of advanced stage HNC while the remaining health system factors showed no evidence of association with HNC stage at diagnosis.

Overall, centres in HICs (mean=47%) had a 17% lower proportion of advanced stage HNC than centres in LMICs (mean=64%) (95% CI -0.30, -0.03 p-value 0.022).

Several of the domains included in the questionnaire were found to have no routinely available data across HEADSpAcE centres, meaning that several gaps in health system factors were identified (Table 5). This may be important to contextualise the results of this study and aid discussion on the potential role of health systems factors and HNC diagnosis. For example, while the stage at diagnosis is recorded individually for each patient, it is not routinely aggregated and reported/monitored as a management system measure; there was also no formal routinely reported data on the source of suspected cancer referrals in any centre. Additionally, data on workforce composition and availability in both primary and secondary care is not routinely available. Quality Performance Indicators (QPIs) in HNC were primarily focussed on post-diagnostic events and treatment. In addition, total diagnostic time (from referral to diagnosis) is not commonly reported; instead, centres more commonly report sub-time points such as the first appointment at the HNC specialist centre and treatment initiation.

Health System Factor	**Y/N**	**Mean Proportion Advanced Stage HNC 2019 (SD)**	**Difference in Means (95% Cis)**	**P-Value**
HNC Electronic Referral System	N	0.59 (0.19)	-	-
	Y	0.56 (0.13)	-0.03 (-0.18, 0.13)	0.7023
Common Primary/Secondary Medical Record	N	0.60 (0.17)	-	-
	Y	0.51 (0.10)	-0.10 (-0.23, 0.03)	0.1221
Higher Patient Volume (>Mean)	N	0.55 (0.15)	-	-
	Y	0.60 (0.17)	0.02(-0.13, 0.16)	0.8111
Single Site/Location	N	0.57 (0.11)	-	-
	Y	0.58 (0.20)	0.00 (-0.19, 0.19)	0.9584
Routine Monitoring of Referral Waiting Times	N	0.68 (0.15)	-	-
	Y	0.52 (0.13)	-0.16 (-0.27, -0.05)	0.0069
Initial Diagnosis Within Centre	N	0.60 (0.18)	-	-
	Y	0.53 (0.10)	-0.08 (-0.21, 0.06)	0.2357
Comprehensive MDT	N	0.63 (0.16)	-	-
	Y	0.55 (0.15)	-0.08 (-0.20, 0.04)	0.1564
Specialist HNC Pathologists and Radiologists	N	0.63 (0.24)	-	-
	Y	0.55 (0.11)	-0.07 (-0.24, 0.11)	0.4319
Referral Triaging System	N	0.70 (0.18)	-	-
	Y	0.54 (0.13)	-0.14 (-0.26, -0.03)	0.0179
Referral Guidance	N	0.60 (0.18)	-	-
	Y	0.53 (0.11)	-0.08 (-0.22, -0.06)	0.2458
Entirely Publicly Funded Patient Finance	N	0.64 (0.14)	-	-
	Y	0.47 (0.12)	-0.17 (-0.29, -0.06)	0.008

Table 4-4: Least Square Means Analysis of Healthcare System Factors

Health System Domain	Missing Health System Factor	Explanation of Missing Data
Centre Activity	Proportion of Advanced Stage HNC	Stage at Diagnosis recorded individually for each patient but not routinely reported as a system measure
	"One-Stop" Clinics	Only present in two centres and only for some subsites
	Source of Suspected Cancer Referrals	No formal routinely reported data on referral source
Workforce	Number of Primary Care and Specialist Clinicians in Local System	Data on workforce composition and availability is not formally routinely available
Referral System	Proportion of Suspected Cancer Referrals with Confirmed HNC Diagnosis	Often Audited but not formally routinely reported
	Guidelines for Referral Processes	Guidance for diagnostic procedures near universally available but seldom for referral
Quality Performance Indicators	QPIs Relating to Referral/Pre-Diagnosis	Few or none across centres, QPIs largely focussed on treatment/post-diagnosis events
	Referral Waiting Times	Total diagnostic time not commonly reported: sub-time points such as first appointment and time to treatment more commonly used
	Targets/ Waiting Times Reporting for Specialist Investigations	Not formally reported in most centres

Table 4-5: Gaps in Healthcare System Questionnaire Responses

4.4.2 Harmonised Head and Neck Cancer Diagnostic Pathway

A simple HNC diagnostic pathway was harmonised from the HEADSpAcE HNC centre pathways to capture and collate the variation in diagnostic pathways across all HNC centres in the HEADSpAcE consortium (Figure 1). This pathway defines the various routes through which people are diagnosed with HNC, including direct presentation to specialist hospital services and acute presentations to emergency departments. The dominant pathway across centres was that of a hybrid model where diagnosis is made either at the centre itself or within primary care/community care before being referred on, which was more prominent in South American centres (n=10), with other centres having a specialist-only diagnostic model with patients presenting to primary/community health services and subsequently being referred to a hospital specialist for further investigation and diagnosis(n=8). Routes through primary care were split between patients who went to dental services and those who went to medical services. This pathway also captures the potentially varying routes that a patient might traverse to getting a diagnosis of HNC depending on the cancer subsite with some OCCs being initially detected by dental clinicians. This HEADSpAcE Head and Neck Cancer Diagnostic Pathway provides a formalised description of the contextual work system ("work as done" (Anderson et al., 2016)) to capture the heterogeneity of pathways from the international health systems included in the consortium.

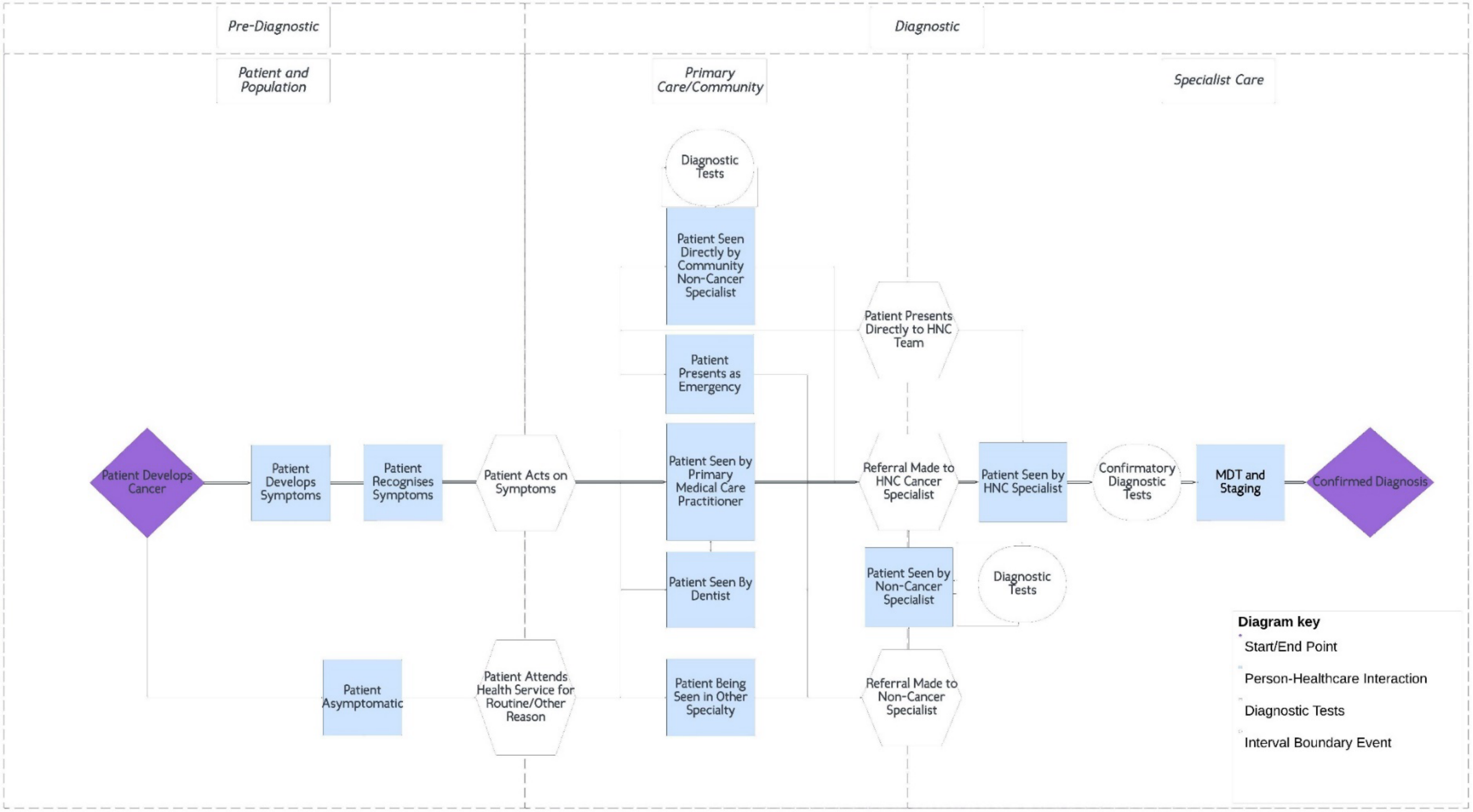

Figure 4-1: HEADSpAcE Head and Neck Cancer Diagnostic Pathway

4.5 Discussion

This study explored for the first time the role of health system factors associated with the diagnosis of advanced stage Head and Neck Cancer (HNC) across various international centres, encompassing both low-middle income and high-income countries. Key findings indicate that three health system factors are associated with a lower proportion of advanced stage HNC diagnoses: routine monitoring of waiting times from referral to diagnosis, having a formal referral triaging process, and being fully publicly funded.

The findings align with previous research that highlights the importance of accessible and efficient healthcare systems in improving cancer outcomes (Sungwalee et al., 2016, Panth et al., 2020, Zhao et al., 2022, Smith et al., 2023). The significant lower proportions in advanced stage HNC associated with monitoring waiting times, formal referral triaging, and publicly funded health systems underscore the potential benefits of these practices. However, the lack of impact from service centralisation and higher patient volumes suggests that these factors may not be as crucial in the context of HNC diagnosis. The impact of centralisation of services, which is closely linked with higher numbers of cases, has previously been found to be associated with better survival outcomes in oesophageal cancers at a regional level (Boddy et al., 2012) but it is not clear whether this is through improved diagnostic pathways or in relation to other treatment/care services. An analysis of national trends in breast and ovarian cancers in France found centralisation to be associated with increased quality of care but increased inequalities in access to care (Huguet, 2020). A modelling of centralisation of specialist cancer services for rectal cancer in the UK at the national level showed the potential travel impacts on patients but showed limited impact on stage at diagnosis (Aggarwal et al., 2022).

While there was a 17% lower proportion of advanced stage HNC in centres located within HICs when compared to LMICs, care should be taken when interpreting this result as some centres as there was wide variation - e.g. within HIC, UoG in Glasgow, Scotland (65%), had a higher proportion of advanced stage HNC than those in LMICS, such as those in AC-CCC, Sao Paulo, Brazil (48%). These differences could also relate to within country inequalities and the socioeconomic profile of people with HNC and other determinants of advanced stage disease at the centre level (Braveman and Gottlieb, 2014).

One of the key data gaps identified was the lack of routinely reported data on the proportion of advanced stage at diagnosis within each centre. This measure was not readily available or used in management / service monitoring. Centres had to either calculated or clinically estimated from clinical records/lists. This was surprising given the important relationship of stage at diagnosis in determining treatment (service) planning and in prognosis (Brown et al., 2018, Abrahão et al., 2018, Ingarfield et al., 2019a, Ingarfield et al., 2019b, Ingarfield et al., 2021,). Similarly, stage of HNC is not a routinely reported measure in cancer registries. This has only recently been captured in the UK with analyses showing that 59% of HNC cases are diagnosed as stage III or IV (Creaney et al., 2022) which puts the UK target of 75% of cancers being diagnosed at stage I or II by 2028 very unlikely to be achieved for HNC (UK Government, 2021).

Additional important findings in this study were health system domains in which data were unavailable from any centre, these included routine information on workforce and source of referral. These domains had previously been identified as potential health systems factors in cancer diagnosis (Brown et al., 2014, Harris et al., 2018). The lack of these data highlight gaps in monitoring of the diagnostic pathway in all centres which could be utilised for health system quality improvement. These variations in structural and operational characteristics could impact the quality and efficiency of care.

The focus of research to date in health systems factors in cancer diagnosis has mainly been on other cancer groups such as breast, lung, and colon cancers (Weller et al., 2016, Weller et al., 2018, Menon et al., 2019, Torring et al., 2019, Vedsted et al., 2022,). These studies were the primary source of the health system domains that informed the questionnaire developed for this study. This prior research focus may be reflective of the higher disease burden and more ready availability of high-quality reported data for these cancer groups historically (White et al., 2017).

Our newly devised HEADSpAcE HNC Diagnostic Pathway, synthesised from the consortium centres' individual pathways to diagnosis, offers a novel lens through which future HNC research and intervention development can be undertaken. It provides a real-world framework that is likely to cover the majority of patients' diagnostic journeys and can aid in planning and evaluation of interventions aiming to address variation and inequalities in the pathway.

To our knowledge, this is the first study addressing centre-level health system factors on stage at diagnosis in HNC, and the results are strengthened by inclusion of data from a number of HNC systems from across the world. The centres included in this study were heterogeneous in their geography, healthcare system structure, World Bank economic ranking, and United Nations Human Development Index, allowing for a broader analysis of health system factors, but my not reflect the total range of HNC systems internationally.

This study has a number of limitations. As noted by Brown et al in their narrative review, attributing causality to an outcome due to any particular health system factor is challenging due to the significant complexity and socio-organisational environment in which healthcare systems exist (Brown et al., 2014). Our study has only begun to explore the potential influence these factors but had limited access to wider socioeconomic system data, however, further triangulation with other data and ongoing approaches within the HEADSpAcE consortium including analysis of prospective individual patient HNC cohort and qualitative centre case-studies (IARC) will enhance the literature on this subject. Similarly, not considering health/cancer policy related information is another limitation. The International Cancer Benchmarking Partnership (ICBP), which does not include HNC, has shown that policy has a crucial role to play in cancer outcomes (Nolte et al., 2022). The wider cancer/public health system could be defined as starting with the self-detection of a health problem and subsequent health seeking element of a patient's interaction with services was not fully captured here (Walter et al., 2012). This could include screening services/activities, although, there is limited current evidence for formal screening programmes for HNC (Brocklehurst and Speight, 2018, Walsh et al., 2021b) and improvements in early detection of HNC may have come from opportunistic screening, e.g. in primary care dental services (Walsh et al., 2021b), and in better joined up primary and secondary/tertiary services and care pathways.

This study considers only the cancer system to the point of diagnosis, but investigation of the role of health system factors in HNC treatment and survivorship should also be a priority for future research in order to have a comprehensive whole-system approach to reducing the devastating burden of HNC.

4.6 Conclusions

This study reveals the role that health system factors play in the burden of advanced stage HNC diagnosed; with processes that monitor referral to diagnosis waiting times and formally triage referrals, along with systems within a fully publicly funded model being associated with lower centre-level proportion of advanced HNC.

It is key that in order to shift the burden of disease from advanced to early stage, more attention should be given to routinely monitoring the burden of advanced disease. A diagnostic pathway for HNC has been proposed to allow better planning for future development of interventions or health system/policy change or innovation to improve the diagnostic care pathway for HNC.

4.7 List of abbreviations

HNC: Head and Neck Cancer

HEADSpAcE: Head and Neck Cancer in South America and Europe consortium

HIC: High Income Country

ICBP: International Cancer Benchmarking Partnership

IARC: International Agency for Research on Cancer

LMIC: Low-Middle Income Country

WHO: World Health Organisation

4.8 Declarations

Provisional results from this study were presented at the International Association for Dental Research General Assembly, Bogota, June 2023

Ethics approval and consent to participate: No ethical approval required as no patient/individual level data are involved.

Disclaimer Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Availability of data and materials: All study data are included within the paper. Materials are available upon request.

Competing interests/Conflicts of Interest: The authors have nothing to declare

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Authors' contributions

GC: Data collection, collation, conceptualisation, analysis, primary manuscript draft and revisions, qualitative analysis.

SP, LW, LA, LMRA, PAR, TD, MV, SALdB, JCdO, ShP, PS, MC, JB, LFRP, MPC, KZ, LR, MP, JRdP, SVvZ, RMM, SV: Data Collection

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5 Chapter Five: Health System Factors in Head and Neck Cancer Advanced Stage Diagnosis: A HEADSpAcE Consortium Qualitative Study in Glasgow and Montevideo

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5.1 Abstract

Background

Head and Neck cancer (HNC) is a devastating diagnosis with advanced stage disease leading to poorer outcomes. This study aims to identify health system factors associated with advanced stage HNC through a qualitative approach.

Methods

Qualitative semi-structured, in-depth interviews with key stakeholders, including HNC patients and clinicians, were undertaken in two HNC centres: Glasgow, Scotland, and Montevideo, Uruguay. Transcripts were analysed thematically through a template analysis with sub-themes and themes framed by a HNC diagnostic pathway and the Systems Engineering Initiative for Patient Safety (SEIPS) 3.0 framework.

Results

Interviews (n=29) were completed with 16 key health system themes and 45 sub-themes identified. Key themes included public awareness and ability to navigate through HNC pathways, the underlying role of socioeconomic/geographic inequalities, and the disconnect between primary and secondary care teams/services.

Conclusions

Health system factors associated with advanced stage HNC were identified across centres and participant types that could contribute to informing service changes/interventions that could improve earlier stage diagnosis of HNC.

Keywords

HNC, Health Systems, Qualitative Methods

5.2 Background

Head and Neck Cancer (HNC) is a significant and increasing global public health problem ranking as the 7th highest cancer in incidence, with over 800,000 newly diagnosed cases of oral cavity, oropharynx, hypopharynx, and larynx cancer annually, and an estimated 400,000 deaths annually, making HNC the 9th highest cancer in mortality globally (Sung et al., 2021). It has been shown that more than half of HNC cases are diagnosed at advanced stage disease (Abrahão et al., 2018, Creaney et al., 2022), defined as stages III and IV according to the TNM 8th Edition (Christian Wittekind, 2016). Diagnosing HNC at an early stage is important for improving outcomes, including treatment-related morbidity, quality of life, and survival (Ingarfield et al., 2019a, Sharma et al., 2019).

Local and national health systems and infrastructures are involved in diagnosis and treatment of HNC with both human (specialist multidisciplinary teams) and technical (diagnosis services and equipment) resources important elements (Blankart, 2012). For HNC diagnosis, tissue biopsy for histopathological specialist analysis remains the gold-standard, supplemented by imaging and enhanced visualisation for clinical staging (Walsh et al., 2021a). Additionally, there is a potential role for a well-developed, clear care pathway from referral to diagnosis in improving efficiency of diagnosis (Richards et al., 2023).

Factors that influence the stage at diagnosis of HNC include individual sociodemographic, health and behaviours, and tumour related factors such as subsite, with HPV associated with oropharyngeal tumours (Worsham, 2011). The role of health systems factors has not been fully investigated for HNC, with existing literature on health systems largely focusing on other solid tumour cancers such as breast, lung, and colon (Weller et al., 2016, Weller et al., 2018, Torring et al., 2019), identifying factors such as availability and accessibility of diagnostic facilities as important to stage at diagnosis.

There seems to be an evidence gap in relation to improving the diagnostic care pathway for HNC through understanding the role of health system factors. A recently published systematic review on inequalities in advanced stage HNC identified a number of studies which included health system variables as potential factors, however, in the review synthesis, health system factors did not go beyond identifying individual health insurance and individual ability to access healthcare services (Ioerger et al., 2024).

The emerging role of systems science in health systems research offers a lens through which a holistic view can be taken on the complexities of health systems (Höhn et al., 2023a). The Head and Neck Cancer in South America and Europe (HEADSpAcE) multicentre consortium (IARC) provides the opportunity to investigate health systems factors in advanced stage diagnosis of HNC. This study aims to take a qualitative research approach identify factors in advanced stage diagnosis of HNC in two centres that form part of the HEADSpAcE consortium: Glasgow, Scotland, and Montevideo, Uruguay.

5.3 Methods

5.3.1 Setting and Study Design

The setting for this study was two purposively selected regional major cancer centres: The West of Scotland Cancer Network (WOSCAN) in Glasgow, Scotland, and the Hospital de Clinicas in Montevideo, Uruguay. The study was a cross-sectional qualitative study drawing from theory-informed, semi-structured interviews with multiple stakeholders based on non-probabilistic quota sampling (Deville, 1991). Sampling, based on the non-homogenous participant type, underpinning theory, the narrowly defined objectives, and the objective of achieving adequate data to meet the research aims, was set at an overall target of 24 interviews with flexibility to adapt and expand to developing themes from interview data (Vasileiou et al., 2018, Hennink and Kaiser, 2022). The centres were selected from the HEADSpAcE Consortium, where they both are the major HNC centre in their respective countries, and where the countries are of similar size and with Uruguay being the only high-income country from South America in the Consortium (World Bank, 2024b).

5.3.2 Procedures

In order to be eligible, HNC patients had to (a) have been diagnosed with a new, primary HNC in the preceding 2 years; (b) be physically and cognitively able to give informed consent and participate in the study; (c) be at least 18 years of age; and (d) have gone through the diagnostic processes at the respective HNC centre.

HNC patient participants were approached in the first instance by local cancer treatment teams and given a high-level project overview. Those willing to be contacted by the research team were then approached in-person at a subsequent clinical appointment, or at the same appointment when possible, and given a participant information sheet and the opportunity to ask questions. Interview arrangements were made by email, telephone, or made to coincide with a subsequent appointment.

Multidisciplinary clinician participants were key informants, identified through local clinical teams due to their ability to inform the research via professional expertise and knowledge of local HNC systems (Pahwa et al., 2023). They were purposively sampled to ensure diversity of clinical roles/positions and were contacted via email plus attached participant information sheet. Following initial interviews, further clinical/administrative participants were identified through a snowball strategy to obtain a breadth of perspectives. Fully informed, written consent was obtained at time of interview for all participants.

5.3.3 Participants

There were 29 interviews undertaken in total: n=17 in Glasgow (seven HNC patients, 10 professionals); and n=12 in Montevideo (five HNC patients, seven professionals). Summary details of participants are shown in Tables 5-1 and 5-2. The researchers were not known to the HNC patient participants prior to the study but were to some of the professional participants due to the highly specialised nature of the HNC teams.

Participant	Montevideo, Uruguay	Glasgow, Scotland	Total
Primary Care Medic	2	2	4
Dentist	0	2	2
Radiologist	0	1	1
Nurse Specialist	0	1	1
Speech Therapist	0	1	1
Surgeon	3	2	5
Oncologist	2	1	3
Head and Neck Service Lead	1 (Also Oncologist)	1 (Also Surgeon)	2*
HNC Cancer Survivor	5	7	12
Total	12	17	29

*Head and Neck Service Leads both had clinical roles

Table 5-1: Profile of Participants

Location	Sex	Age (Years)	Tumour Site	T	N	M	Early/Advanced Stage TNM 8th Edition
Montevideo	Male	64	Oral Cavity	2	2	0	Advanced
Montevideo	Male	65	Hypopharynx	3	2	0	Advanced
Montevideo	Male	67	Oral Cavity	4	0	0	Advanced
Montevideo	Female	42	Oropharynx HPV-Negative	4a	2b	0	Advanced
Montevideo	Male	69	Larynx	3	1	0	Advanced
Glasgow	Male	67	Larynx	4	0	0	Advanced
Glasgow	Female	60	Oropharynx HPV-Positive	2	2	0	Early
Glasgow	Male	61	Oropharynx HPV-Positive	3	1	0	Early
Glasgow	Male	53	Oral Cavity	4	0	0	Advanced
Glasgow	Female	38	Oral Cavity	3	0	0	Advanced
Glasgow	Female	61	Larynx	4	0	0	Advanced
Glasgow	Male	59	Oropharynx HPV-Positive	3	2	0	Early

Table 5-2: Profile of Patient Participants

5.3.4 Interviews

This study was undertaken over an 18-month period from early 2022 to mid-2023. Interviews were undertaken either face-to-face (in a University room or local clinical setting of convenience for the participant) or online via ZOOM (Zoom Video Communications Inc. version 5.11.0) depending on participant preference and the local COVID-19-related mitigation measures in place at the time (and given that this was deemed an appropriate software for qualitative interviews (Archibald et al., 2019). Interviews lasted on average 42 minutes with the longest lasting 75 minutes.

Interviews were undertaken by a dedicated clinical researcher in each centre (GC and ILG). They were trained in qualitative interviewing techniques and standardised in approach by an experienced qualitative researcher (AR) and had experience of working with HNC patients but were not part of the centres' HNC clinical teams (GC is a Dental Public Health Registrar and Lecturer and ILG a bilingual (Spanish and English) Oncologist who is not part of the HNC team). Interviews were undertaken at a time and location of the participants' choosing with support from the clinical team available through facilitated contact if required for HNC patient participants given the sensitive nature of the topic. Interviews were guided by topic guides that were created following literature review and covered findings from the HEADSpAcE Benchmarking study (Thesis Chapter Four).

Two templates were applied in developing interview guides and guiding interpretation: a) the temporal frame of cancer diagnostic intervals from the Aarhus Statement on cancer diagnostic research (Coxon et al., 2018) that was modified into the HEADSpAcE HNC Diagnostic Pathway in the HEADSpAcE Benchmarking study (Figure 5-1) (Thesis Chapter 4). These intervals were the patient and population interval; the Primary and Community care Interval; and the Secondary care Interval; b) The Systems Engineering Initiative for Patient Safety (SEIPS) 3.0 model of the complex socio-technical interactions and processes in the diagnostic journey (Carayon et al., 2020). This combination of templates allowed for probing along known diagnostic intervals and timelines and for recognised health system factors such as staff, technology, procedure, environment.

Topic guides containing high-level open questions with subsequent probing questions and prompts were piloted with non-participant clinicians in Glasgow prior to commencement of the study (Appendix 5-1). Topic guides were available for all interviews but flexibility was afforded within interviews to follow a productive line of participant response. Participants were alone apart from two whom had a partner join in the room during the interview. Single interviews were recorded for each participant except one participant who contacted the research team to clarify some of their responses and had a shorter follow-up interview recorded (Glasgow, Patient). No additional field notes were made.

Each interview was recorded on an audio digital recorder or via record function on ZOOM depending on how the interview was facilitated and transcribed verbatim in the language undertaken (English in Glasgow, Spanish in Montevideo). Transcripts were checked back against original recordings to reduce transcription bias and, where necessary, were translated into English via a digital translation technology (Sonix Inc), which was then checked by the researchers (GC, ILG) for accuracy. Scripts were not returned to participants prior to analysis.

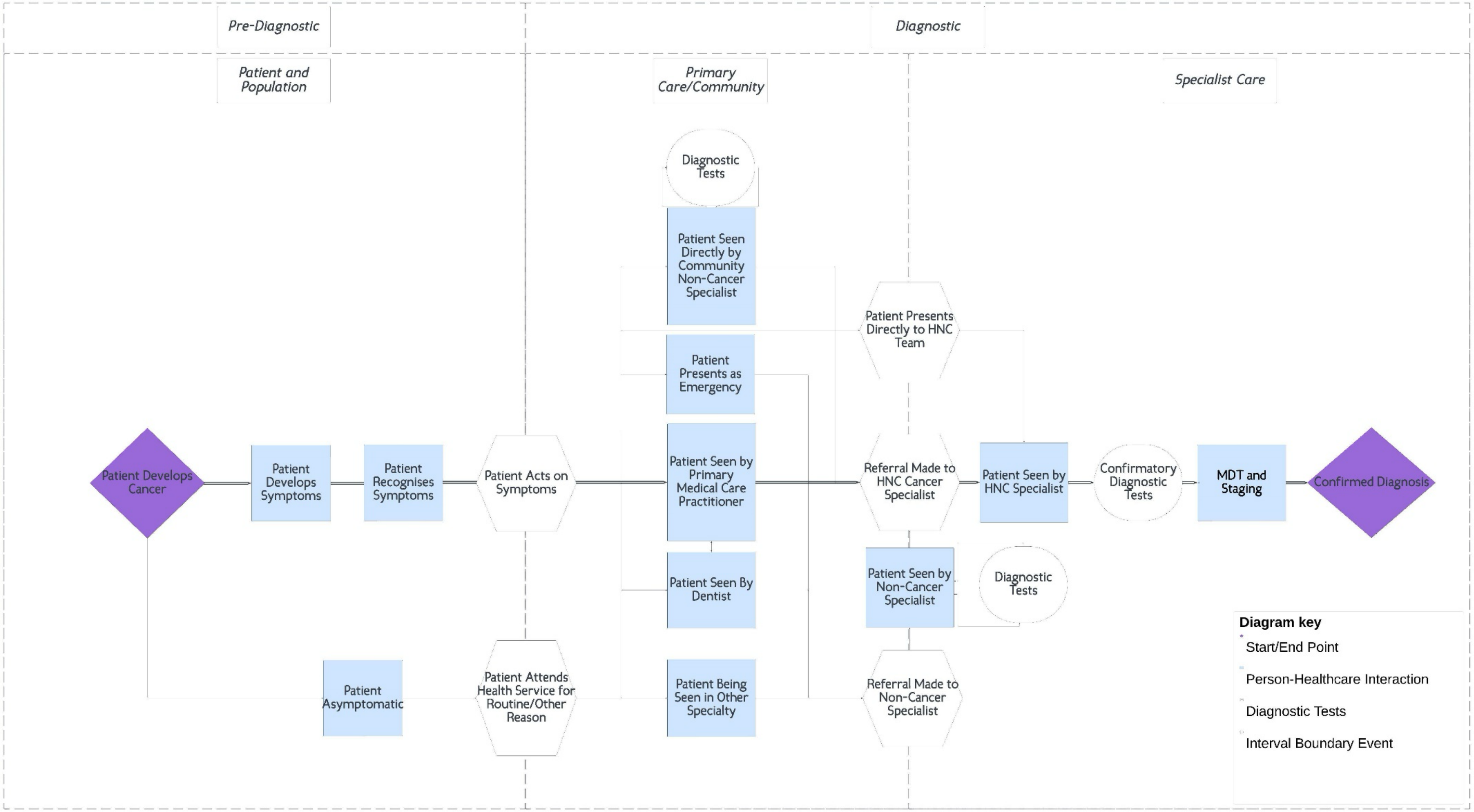


Figure 5-1: HEADSpAcE Head and Neck Cancer Diagnostic Pathway

5.3.5 Analysis

An adapted template analysis was facilitated through uploading interview transcripts to Lumivero NVivo 14.0 qualitative data management software (NVivo 14 for Windows, Lumivero). Strong and meaningful concepts and sub-themes that related to the aims of this study were identified through template analysis: a form of thematic analysis that allows interpretation of qualitative data using a priori themes (the 'template' (Brooks et al., 2015)) to guide interpretation while still allowing for flexibility and for subthemes and patterns to emerge (Appendix 5-2).

In this study, the templates were those of the HNC diagnostic intervals and SEIPS 3.0 framework applied deductively as described above. The sub-theme analysis was undertaken via a traditional inductive approach drawing from participant narratives. A sample of initial codes was developed by the primary researcher (GC) into provisional themes and checked independently by a senior researcher (AR) for consistency and quality checking. Analysis was concurrent with ongoing data collection in order to facilitate the purposive sampling of alternative perspectives and to ascertain data adequacy for the narrow and specific research aims of this study. When no new thematic groupings were forthcoming in the interviews (Saunders et al., 2018) due to the data being rich, relevant and of sufficient quality, data adequacy was deemed to be reached for this study (Vasileiou et al., 2018, Hennink and Kaiser, 2022, Sims and Cilliers, 2025). Participants did not provide feedback on results prior to publication.

5.4 Results

Results are presented here in terms of the three main interval domains of the HNC diagnostic pathway: Patient/Population; Primary/Community Care; Specialist (Supplementary tables can be found in Appendix 5-3). There then follows brief further analysis by participant types and country/location. Finally, two linked overarching themes emerged across all intervals and participant types/locations and are detailed below: 1) the complex nature of the HNC diagnostic system and 2) the importance of communication in driving diagnostic goals within this complex health system landscape.

5.4.1 Interval Domains

5.4.1.1 HNC Patient / Population Interval

The dominant themes and sub-themes in this diagnostic interval pertained to patient and population HNC awareness and agency. There was consensus on the importance of improving public awareness of HNC symptoms and supporting people to navigate initial access points into the local health system when seeking to act upon symptoms:

> "To the patient who has a discomfort, difficulty in swallowing, consult immediately"
>
> (Montevideo, Patient)

> "That… that is key and that goes with early detection campaigns and going out to explain to people that if they have such and such characteristics of symptoms or signs, to consult quickly."
>
> (Montevideo, Clinician)

Many patients do not act on symptoms when they first arise and may wait for a significant time before first contacting health services. Sometimes, they are concerned the symptom might indicate cancer but they can be fearful on first attending health services:

> "At the back of my mind I kept thinking, I wonder if this is cancer. I kept ignoring it."
>
> (Glasgow, Patient)

> "I probably knew deep down what it was, but it is quite a scary thing to face up to that."
>
> (Glasgow, Patient)

Another strong theme was the role of family and friends in prompting and facilitating these early steps in the diagnostic pathway. It was noted that friends and family can both positively and negatively impact individual decision making, with spouses/partners playing an important role in encouraging presentation to health services:

> "…my wife was with me and she insisted on having it done there and then and I thank her for it."
>
> (Glasgow, Patient)

> "It was worrisome, I consulted with my children and they decided to have me seen."
>
> (Montevideo, Patient)

One patient mentioned previous negative experience of the service as partly contributing to delay in initial access, saying

"My GP [General Practitioner] […] didn't give the best of treatment to my husband"

(Glasgow, Patient).

This role of trust in health organisations and public bodies was an apparent issue in how people engage with health services and make decisions on accessing them:

> "That was subconsciously my plan, rather than going to a GP, which I don't have huge faith in. It was always my plan is to check with my colleague"
>
> (Glasgow, Patient)

> "I think for the better, in all aspects, improve the approach to bureaucracy… maybe today there is no doctor."
>
> (Montevideo, Patient)

There was a clear understanding, particularly from professionals, of the role of complex social geographic and financial inequalities and how they may affect an individual's interaction with health services. This was noted as applying to HNC but also across the wider range of health issues and health services landscape. People who develop HNC disproportionately come from areas of higher socioeconomic deprivation which gives rise to complicated social and economic barriers at the community level access to health services, but also further difficulties in navigating from initial access through to specialist services:

> "…above all the approach to the social part of these patients, who are extremely complex and it is a deficit that we have. They are patients who come from extremely complicated backgrounds…"
>
> (Montevideo, Clinician)

In terms of proposals to reduce the levels of advanced stage HNC diagnosis, there was an appreciation that public health approaches were needed for improving access to the care pathway to diagnosis. This would cover public health action to address underlying socioeconomic inequalities as well as communicating this pathway in an open way to patients. Communication to clinical teams in primary and secondary care was also proposed as beneficial as was developing data monitoring capability and harnessing existing data:

> "We have improved a lot and we have a very good cancer registry because in order to make health policy on cancer you have to have and know what the incidence and mortality in this case of localization is." (Montevideo, Clinician)

5.4.1.2 Primary / Community Care Interval

Knowing which health service to attend in the first instance for symptoms of potential HNC was an issue, highlighting overlapping roles of dentists and general medical practitioners in this role in the system:

> "…patients are maybe phoning their doctor for things to do with their mouth but there's been things to do with like throat or maybe like neck and things and they're told to come to their dentist."
> (Glasgow, Clinician)

> "Dentists do not refer anywhere…they say 'I have this patient, I am going to refer him to you' and then we (general medical practitioner) are the ones who make the referral."
> (Montevideo, Clinician)

Once individuals have made the decision to contact and engage with health services there were several important themes. There was a clear expression that HNC is a poorly recognised and understood disease at the primary care level, particularly in primary medical care, as the symptoms are often potentially attributed to other diseases that are less serious and more routinely seen. There were many strong expressions of reported misdiagnosis, including several repeat prescriptions for antibiotics when patients attended primary care:

> "From the moment they consult with their first symptom, go through a series of general practitioners who give them different treatments, antibiotics, painkillers".
> (Montevideo, Clinician)

> "I finished the course of antibiotics and then went back again and then got another set of antibiotics"
>
> (Glasgow, Patient)

Not having standardised equipment, such as scopes to visualise the oropharynx, was said to be a barrier in examining in primary care, which points to a desire for an enhanced diagnostic role in primary/community care:

> "Yes, there are things ... Not all places have the equipment, such as endoscopes, to make a diagnosis"
>
> (Montevideo, Clinician)

There is a reported need for training and education for primary care practitioners on HNC and how it presents, symptoms and signs, and on the criteria for urgent referral for suspected cancer. It was suggested the training should be delivered by the specialists from HNC treatment centres, which would also improve primary care and specialist engagement:

> "Obviously there is always room for improvement, and I think it would be another point that would be good to think of improvements in terms of training for everyone and on a more frequent basis."
>
> (Montevideo, Clinician)

> "I think that there is a lot of potential I would imagine in increased awareness among GPs."
>
> (Glasgow, Clinician)

There were also reflections on options for screening of HNC targeted to those highest risk (those with traditional smoking/alcohol risk factors and or from particular areas/backgrounds) although there was acknowledgement that there was a need to build the evidence base for a formal screening programme:

> "There is no way to see that without a clinic exam. So that would be the part of screening that you would need if you were doing it clinically… there are blood tests and things that are currently under research… I think it would have to be extremely targeted."
>
> (Glasgow, Clinician)

> "I have been taking part in some sort of screening events over the years where most of the stuff you see is benign, so I'm not quite sure how effective it is"
>
> (Glasgow, Clinician)

Finally, the issue of honest, frank communication was noted. Patients and professionals felt that the risk of developing HNC was not explicitly discussed during healthcare appointments prior to diagnosis and there were potential missed opportunities for interventional discussions/referrals to services that may support modifying certain lifestyle behaviours such as smoking and/or alcohol consumption, relating to the theme of trust presented earlier:

> “Maybe a bit more forthrightness with each other. Sometimes we do things, and we don’t want to hurt people’s feelings…”
> (Glasgow, Clinician)

> “…if the dentist would be more forthcoming with a wee bit of information about what could potentially happen.”
> (Glasgow, Patient)

5.4.1.3 Specialist Services Interval

The main themes expressed related to the specialist services interval were related to referral processes/systems. There was an expressed need for formalised referral systems that were open to wider health teams, not only primary care medical practitioners:

> “for people presenting with concerning signs to community pharmacies… make sure that they have an established pathway to report their concerns.”
> (Glasgow, Clinician)

In addition, there were calls for clearer, more accessible referral guidance to enable the referral pathway to be better utilised. There were frustrations at the heavy volumes of bureaucracy which impact efficiency and the referral processes particularly when it comes to the ability to share clear information, such as having to include information that is already available through medical records and not being able to easily upload photographs to referrals. Clarity of information was seen as key for reducing any potential delays in referral processing:

> “They have to be quite clear and concise of all the symptoms”
>
> (Glasgow, Clinician).

The benefits of referral triaging and time monitoring for ensuring that appropriate patients are seen as quickly as possible were also expressed:

> “I believe that in this sense, some kind of articulating personnel between both levels would be very useful who could filter, to some extent triage, the patients who have some element of organicity and who require a quicker consultation”
> (Montevideo, Clinician)

These referral aspects were part of a wider disconnect between primary care- and specialist services where the health system for the pathway to HNC diagnosis is seen as challenging for primary care professionals as specialist services are the sole gatekeepers for cancer diagnosis and there is no shared ownership over the diagnostic pathways:

> “I believe that there is a devaluation of the first level of care physicians, there is a devaluation of family and community medicine…” (Montevideo, Clinician)

> “Potentially...unintentionally and subconsciously having a change or shift in referrers’ behaviours so that gatekeeping is essentially being moved into secondary care where they have, I am pretty sure, unintentionally taken on that role of gatekeeping.”
> (Glasgow, Clinician)

It was also suggested that patients could have their journeys to diagnosis better supported and facilitated to counteract some of those earlier expressed complexities. This could for example be done through the role of a patient coordinator/facilitator for those being referred for suspected HNC:

> “There has to be a nurse in charge of coordinating everything for the patient or someone who coordinates everything”
> (Montevideo, Clinician)

> “…a patient navigator essentially to try and make sure that people are accepting the earlier scans and everything that they can.” (
> Glasgow, Clinician)

Similarly to primary care, the availability of resources for undertaking and reporting specialist diagnostic investigations was considered essential in facilitating early diagnosis. There was also the suggestion of increasing access to histopathology and radiology services directly from primary care/ community care:

> "I think if you had your radiology and scanners and all these types of things not necessarily in GP practices, but in community-based healthcare facilities, you might get somewhere."
> (Glasgow, Clinician)

The importance of having immediate investigations without delays following presentation to specialist services was emphasised; with several diagnostic improvements to the process for requesting and automating some aspects of this process rather than relying on human prompts:

> "… it would be lovely if there was one unified request, that I could move that patient along the system… I should just be able to press a button and move that sequentially along the system."
> (Glasgow, Clinician)

More broadly, there were reported challenges in terms of demand on the overburdened health systems and availability of HNC specialists. On occasion this had impacted where specialist clinicians would bypass existing systems to get things done:

> "Capacity is the main barrier, yes, without a doubt yes"
> (Glasgow, Clinician)

> "We try to expedite… I give them the phone number so that they can go to the consultation or consult me"
> (Montevideo, Clinician)

There was also the expressed wish for utilising a wider workforce skill mix and the diagnostic care pathway so that specialists/senior staff are not overly burdened with tasks that could be readily undertaken by other specialists:

> "The specialist does not fulfil the function of a specialist only… have to do research, to do epidemiology or to do social work"
> (Montevideo, Clinician)

Regarding HNC service structure and design, there were conflicting suggestions as to the utility of centralisation, with specialists considering a centralised service as the gold standard as it meant better access to full multidisciplinary team, yet challenging in terms of physical access to the service and in relation to geographic inequalities:

> "I think it's, I guess, quite a good thing to have it all centralised because then if it's centralised everyone knows everyone"
> (Glasgow, Clinician)

> "…we also have to take into account the distances in which each of the people live and where they must be attended."
> (Montevideo, Clinician)

There were additionally conflicting opinions on the role of the multidisciplinary team whereby it may improve treatment delivery but may not have any positive impact on the stage of diagnosis:

> "…as a specialist looking after a patient you probably feel less able to make your own decisions and get the ball rolling…"
> (Glasgow, Clinician)

> "in terms of then getting through the pathway, I do think there are ways that we can probably make that quicker… the meeting is once a week and often we find that nothing gets done between the meetings." (Glasgow, Clinician)

Finally, the role of technology and diagnosis on improving communication in the HNC diagnostic pathway was highlighted, including the potential of artificial intelligence aiding diagnostic reporting.

> "if we could have more technology it would make it much easier for, for those coming up the learning ladder to see better and learn better."
> (Montevideo, Clinician)

There was some caution from a patient perspective given in relation to some technological approaches such as difficulties with remote online consultations and how they could contribute towards misdiagnosis:

> "I mean how can you make a diagnosis over a telephone call?"
> (Glasgow, Patient).

5.4.2 Overarching Themes Across the Diagnostic Pathway

5.4.2.1 Communication

Across all aspects of the diagnostic pathway (interval domains) the main overarching theme was that of communication issues and barriers both between health service and patients and also between components of the health system/services. Achieving accurate and timely diagnostic outcomes through this dynamic work and community system substantially relies upon communication, which must be optimised through formal stakeholder links and through nurturing interpersonal relationships with trusted partners:

> "I believe that the links with second level specialists [and primary care teams] need to be improved. That would go a long way toward shortening times and improving patient care."
>
> (Montevideo, Clinician)

> "Well, communication, I think, is fundamental in these patients and it is also fundamental to personalize it."
>
> (Montevideo, Clinician)

Many of the communication barriers described related to the role of processes and technologies including difficulties accessing and sharing relevant information and this issue was particularly relevant to the referral processes from primary care into specialist services:

> "I think pathways between us can be much, much better. Quite often professionals will just hang up the phone and can't wait for ten minutes for somebody to answer the phone. Quite right, I wouldn't do either."
>
> (Glasgow, Clinician)

> "It seems to me this whole referral system is set up to suit secondary care and certainly not to suit primary care and not to suit the patient. The patient journey is non-existent with their referral mechanisms."
>
> (Glasgow, Clinician)

Additionally, due to the complex and untransparent nature of the diagnostic pathway, there were several perceived issues with communicating with HNC patients on how best to navigate that pathway with an associated need to do more in public health terms to communicate risk with HNC patients who have traditional behavioural and socioeconomic risk factors for developing HNC. This of course illustrates another complexity of the system in that the outcomes emerge from interactions with these community factors.

5.4.2.2 The Complex Head and Neck Diagnostic System

The application of the SEIPS systems model illustrates the complex nature of the diagnostic landscape that patients and staff have to negotiate and navigate, with these thematic results naturally sitting within the SEIPS 3.0 domains (Figure 5-2). The work system can be conceptualised as a collection of elements: persons with roles and responsibilities (e.g., patients, oncologist, PCPs), performing tasks (e.g., ordering a test), while using various tools/technologies (e.g., electronic health records, human resource, decision support), working in an environment (e.g., office, clinician workroom, home), and sitting in an organizational context (e.g., practice, guidance, staffing). There are professional aspects (e.g., primary care using guidance to inform clinical decision making, communication between clinicians), patient aspects (e.g., management of activity and diet as a contribution of health maintenance, attending services, undergoing recommended opportunistic cancer screening) and shared work processes (e.g., shared decision making between clinician and patient). Often, this system requires tasks that may not be entirely delineated and may be shared and equally actionable between multiple individuals.

It can be observed from patient and staff interviews that HNC patients interact with multiple health system elements and external environments in their non-linear pathways to diagnosis.

> "To me, the system of having this to do that, to do that, to do that, is putting too many obstacles in the way of seeing someone who knows what they're talking about from day one, right at the beginning."
> (Glasgow, Patient)

Family, community and work influences, including geographical and financial inequalities, set norms and form dynamic initial conditions through which health issues and symptoms are experienced and understood, and engagement with the health system is initiated (or otherwise).

> “Pains appear, symptoms appear and suddenly you assimilate them because of the experience you have from other people or from relatives or acquaintances.”
>
> (Montevideo, Patient)

Service access and engagement is complex due to a number of interactions including: knowledge of appropriate services; unclear responsibilities of medical and dental professionals in primary care; emergent risk from a lack of professional case-based experience and/or training; and difficult screening decisions including efficiency-thoroughness trade-offs.

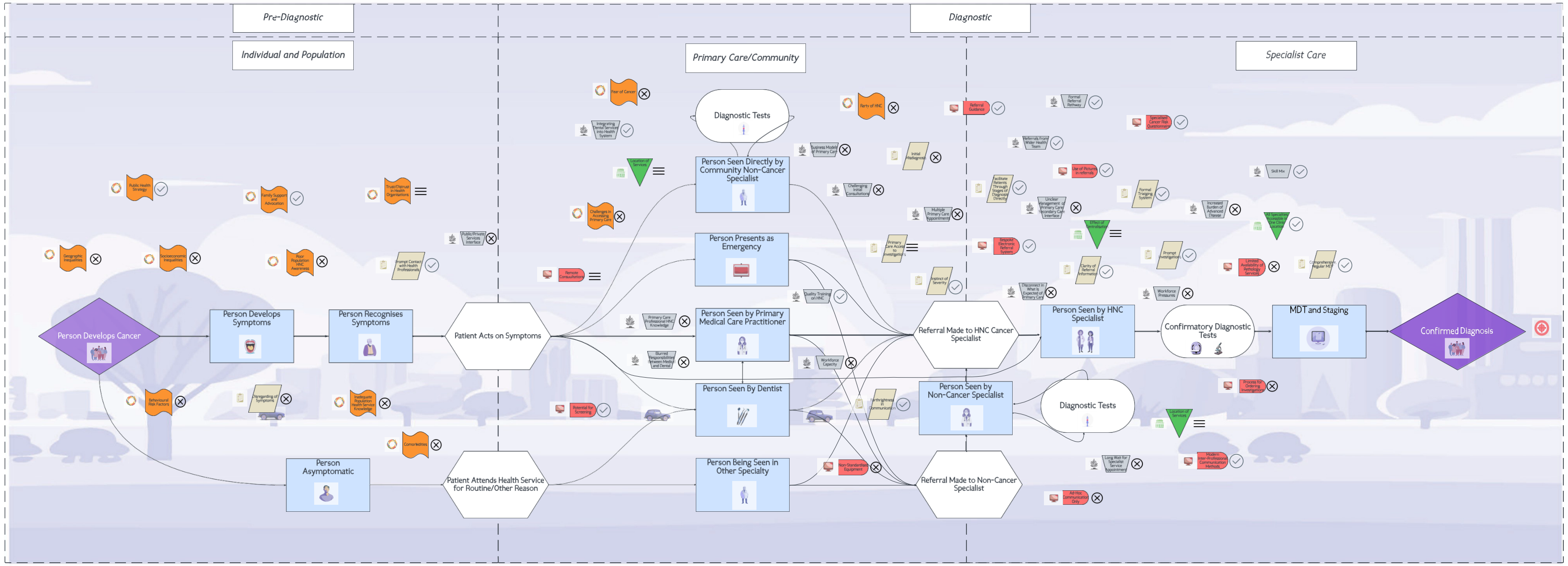
> “I see probably about one a month where they tell me that they saw their GP with throat pain and it was dismissed. Or it was reassured that the pain didn’t get better and then they went back and they got some antibiotics and maybe another course of antibiotics. Then when you see them there is nothing you can do there.”
>
> (Glasgow, Clinician)

There is further complexity in referral and investigative processes which bring in some further context in tools and technologies, tasks and the organisation of work, for example: staffing pressures which might indicate benefit in the use of the wider skills of the team; lack of clear guidance for efficient referral is a known issue; the need for data and optimal governance, monitoring and oversight; specialist investigations are resource-pressured and could benefit from widening staff access and incorporating better feedback and feedforward loops .

> “I think that the bureaucracy, the bureaucracy of public health and of each institution does not work in a coordinated way, there is no smooth coordination”
>
> (Montevideo, Clinician)

System Factors in Advanced Stage Diagnosis of Head and Neck Cancer: A HEADSpAcE Qualitative Study Across Glasgow, UK, and Montevideo, Uruguay.

HEADSpAcE



This diagram is a product of the Qualitative Study involving Semi-Structured Interviews with key stakeholders, incuding patient survivors, acrsoss two Head and Neck Cancer (HNC) centres in the HEADSpAcE Consortium: Glasgow, UK and Montevideo, Glasgow. The results were thematically analysed following a template analysis using a modified version of the Aarhus cancer statement (created following the HEADSpAcE Benchmarking Study which ran in parallel with this study) to define the chronological steps involved in diagnosing HNC. Subsequently, the themes were then applied to the domains of the SEIPS 3.0 model of systems enginering in health services pertaining to patient diagnostic journeys to reflect what the potential barriers to and facilitators of early HNC diagnosis are and where they lie in the context of the HNC diagnostic athway. This helps visualise the potential issues existing and helps focus further research and intervention ideas.

Pascale Carayon, Abigail Wooldridge, Peter Hoonakker, Ann Schoofs Hundt, Michelle M. Kelly, SEIPS 3.0: Human-centered design of the patient journey for patient safety, Applied Ergonomics, Volume 84, 2020, 103033, ISSN 0003-6870, doi.org/10.1016/j.apergo.2019.103033.
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Diagram Key for Patient Journey and Interactions with Staff

- 🟦 **Person-Healthcare Interactions**
- ⬭ **Diagnostic Tests**
- ⬡ **Interval Boundary Event**
- ◆ **Start/End Point**

Diagram Key for System Factor Classification

- Tools and Technology
- Tasks
- Socio-Organisational Context
- Organisational Conditions
- Physical Environment
- ✓ Facilitator to Early Diagnosis
- ≡ Mixed Barrier-Facilitator
- ⊗ Barrier to Early Diagnosis

Figure 5-2: Thematic Results Applied to Templates of HEADSpAcE Head and Neck Cancer Diagnostic Pathway and SEIPS 3.0

5.4.3 Interpretation by Participant Type and Location

5.4.3.1 Differences Between Glasgow and Montevideo.

A key difference between HNC centres was the overall sense of the main contributors towards the high levels of advanced stage diagnosis. In Glasgow, the general feeling was that the major issues were related to initial access to primary care, accurate initial detection, and in the process of referral to specialist services. However, in Montevideo it was felt that there were significant issues in the specialist services themselves, including in the organisation and structure of specialist clinics (and availability of specialist services more generally).

Another key difference was the availability of and access to diagnostic investigations. In Glasgow, it was noted that these happened rapidly once an HNC patient was referred. However, in Montevideo there were significant bureaucratic and human resource limitations resulting in long waits for pathology diagnostic services in particular.

With regards to referral systems, in Montevideo there was an expressed need for referral guidance and clear protocols whereas these already existed in Glasgow at the time of the study. The feeling and experiences of those in Glasgow was that the guidance was useful but not well utilised due to poor awareness/understanding from clinical teams (and not awareness from patients) and that there was still a need for training, particularly of primary care clinicians. Glasgow already has in place a bespoke electronic referral system for suspected patients with HNC, available to primary care medical doctors and dentists to refer into specialist services, however there were significant frustrations expressed particularly by primary care clinicians of both the bureaucracy and operational effectiveness of the system. In Montevideo, clinicians expressed a strong need for an electronic referral process system for patients with suspected HNC.

Other themes expressed solely in Montevideo were the significant travel distances experienced by patients in accessing specialist care, as the HNC here accepts referral nationwide, which did not exist in Glasgow to the same extent, which is a regional referral centre. In Glasgow, but not in Montevideo, there was explicit discussion given to the important role of dentists and how they integrate into health systems. Additionally in Glasgow there was attention given to the increasing incidence of HNC and to the role of HPV and changing the profile of HNC (i.e. more oropharyngeal cancer cases), which would impact on both specialist care services and potentially on referral pathways, which has yet to be observed in Montevideo.

5.4.3.2 Differences Between Participant Types

More differences were observed between patients and clinicians, as might be expected given the different roles in the HNC diagnostic pathway of those going through the diagnostic pathway compared to those delivering it- and between primary care and specialist clinicians due to the knowledge and expertise in different areas of the intervals and the HNC systems.

Patient participants were forthright in their views over the lack of explicit cancer discussions and risk factors in their early interactions with health services prior to their diagnosis. Patient participants generally feel the diagnostic pathway is longer and slower from start to finish than professionals do, and stress the difficulties of multiple healthcare visits and navigating challenging barriers to access the right services. Patients generally stressed the important of the role of family and friends in prompting initial attendance to health services and supporting them through diagnosis. Patients also shared that their perception of the severity and importance of symptoms played into how they assessed when they should contact health services. Almost unanimously, patients did not immediately act on the initial health concern because they didn't think it was significant.

A key theme to come from the patient participants that was not fully appreciated by the clinician participants was one of trust and attitude towards health organisations and authority more generally. This was evident across patient interviews where an existing distrust or previous negative experience was a barrier to them engaging with health services promptly.

For professional participants the key issues were much more in the processes of the health system pathways to diagnosis, particularly with regards to how patients go through the health system from primary care to specialist services and are provided with specialist diagnostic investigations. Much comment was made on the organisation of clinics and having all equipment and staffing resource available. Clinicians expressed the need for a national strategy including clear protocols and harnessing data to improve services, in addition to improving HNC population knowledge through improved communication strategies targeted to both the general population and primary care clinicians.

5.5 Discussion

To our knowledge, this is the first study to investigate barriers and delays in the diagnostic pathway for HNC through a health systems approach using qualitative methods with patients and staff. We aimed to understand health system factors associated with advanced stage HNC diagnosis in two centres embedded in an international HNC consortium. The reason for selecting two high income countries was to limit (to some degree) the potential impact of the wider socioeconomic context, and to enable the focus on local/centre level health system factors. We interviewed both patients and multidisciplinary clinicians to ascertain their perspectives on HNC diagnostic pathways. We identified the key themes of population perspectives of HNC and navigating health systems, the role of family/friends, socioeconomic and geographic inequalities, the disconnect between primary and secondary care, and professional perspectives of agency were those most strongly expressed universally.

There were a number of strengths to this study, including obtaining a whole-health systems view to the HNC diagnostic pathway through including patients and a range of clinicians as participants. Additionally, undertaking this study in two centres gives a unique insight into some of the findings from an international perspective. Applying the findings to the framework of SEIPS 3.0 helped form a system level interpretation of results to facilitate potential intervention and this very complex health issue.

This study adds to the existing literature on factors associated with stage of diagnosis and HNC, highlighting, for the first time, the explicit role that health systems play in addition to patient related factors. Previously, the emphasis has been placed on patients in these time intervals to diagnosis, defined pejoratively as “patient delays (Schoonbeek et al., 2021). However, when considered as part of the health system, there is responsibility for systems to consider patient agency and ease of access to services, as well as considering how smoothly these systems can be navigated through until the point of diagnosis of HNC. Our findings suggest that the issues in the patient interval or more socio-organisational rather than individual. This study is innovative in combining the structural model of the diagnostic pathway with the systems lens of SEIPS which is a validated theory-based tool embedded within healthcare systems, including the NHS in the UK (NHS England, 2022).

Limitations to this study include: only patients with head and neck cancers who had survived treatment were able to be interviewed given the timings of receiving a diagnosis, starting treatment and being fit enough to participate in an interview. This means that HNC diagnostic pathways for patients who did not survive or were on a palliative care pathway were not included (and those patients could have even greater barriers to early diagnosis and accessing healthcare), nevertheless it is likely that many of the findings would apply. Another limitation is that interviews were carried out in the common language of the centre, Spanish in Montevideo and English in Glasgow. This means that the potentially important factor in HNC patient ability to navigate health systems, the role of language barriers, which can be an access to an issue in accessing healthcare and a factor in poor health outcomes (Cano-Ibáñez et al., 2021), was not covered in additional depth. Interventions to mitigate language barriers in research have been well evidenced in existing literature (Whitaker et al., 2022), which could be applied to HNC. Access to potential participants was made more challenging due to the COVID-19 pandemic and associated mitigations were introduced just as this study was beginning, resulting in challenges in study approvals and recruitment of participants. A further limitation is that we were unable to include participants from more than two centres with this depth of qualitative study, or from health systems that are funded through different models/ have radically different pathways to HNC diagnosis such as through community specialists. However, by having two centres that are publicly funded in a similar fashion, both in high income countries, we enabled comparisons to be made.

The wider range of HNC centres (n=18) from the HEADSpAcE Consortium were analysed in the HEADSpAcE Benchmarking study (Thesis Chapter Four) and this study correlates with the findings from that study in several important ways. Firstly, the expression in this study that socioeconomic factors play a key role in stage of HNC diagnosis is linked to the role of having a publicly-funded health system which aims to mitigate the role of financial costs in navigating the pathway to HNC diagnosis. Additionally, having a formalised referral triaging system and routinely monitoring referral waiting times relate to the themes here of utilising data and formalising referral pathways.

Improving population knowledge and awareness of HNC has been described as a key factor in reducing advanced stage diagnosis (Varela-Centelles et al., 2021, Baumann et al., 2023,), although the literature is conflicted as previous evidence relating to population awareness campaigns shows there is no impact on stage (Macpherson, 2018). The findings from this study suggest that knowledge and awareness of HNC alone is perhaps insufficient and we were able to be more specific here in that there is a need for health literacy and agency in accessing and navigating health services through the diagnostic pathway. More than knowledge and awareness, there were suggestions raised for facilitating/supporting patients through the diagnostic care pathway with referral coordinator/support worker to help navigate the seemingly complex system.

Additionally, the utility of referral guidance/ protocols is also an interesting finding. Even in Glasgow, where such guidance exists, some clinician participants were not aware of them (Scottish Government, 2020). Studies have shown that although guidance has an important role to play, it must be implemented/ utilised and fully communicated in order to have the desired aim of improving the referral/diagnostic pathway (Grafton-Clarke et al., 2019).

Despite some participants calling for HNC screening programmes, there is insufficient evidence to support formal screening programmes for HNC's

(Brocklehurst and Speight, 2018). There is some evidenced recognising the role of opportunistic screening by health professionals, particularly dentists for detecting oral potentially malignant disorders or early stage oral cavity cancer via routine clinical oral examinations (Purkayastha et al., 2018b, Walsh et al., 2021a). As there are wide socioeconomic inequalities in the burden and outcomes of HNC (Purkayastha et al., 2016, Ingarfield et al., 2019b, Ingarfield et al., 2021) “upstream” policy-level changes will be essential to address these inequalities and reduce the population disease burden.

These study findings of a disconnect between primary care and specialist care, the need for clinician training, and limited knowledge/lack of guidelines are similar to that of a large systematic review from 2016 across the cancer spectrum, though not specifically HNC, (Lawrence et al., 2016) which identified the need for training and clear pathway guidance from international primary care practitioners as barriers to effective provision cancer care. The blurring of the role of dentists and medics in primary care was highlighted as a factor in this study, which also adds to the evidence for the need for clear roles in HNC diagnostic pathways, a factor raised in a 2019 systematic review which found variance between both sets of professionals with regards to HNC referral patterns (Grafton-Clarke et al., 2019).

The role of modern technologies and processes involved in the diagnostic HNC patient diagnostic pathway may also play a key role in prompt diagnosis and early detection of HNCs. The emergence of telemedicine has been proposed as a possible route to improve early diagnosis rates and the use of modern electronic HNC patient records can improve inter-professional workflow reducing friction and delay in the HNC patient journey, and even predict future diagnosis by identifying changes in healthcare use (Dickson et al., 2022, White et al., 2022) but care must be taken to consider the potential negative effects of telemedicine on affecting pathways to HNC diagnosis as raised in this study.

5.6 Conclusions

This study offers, from both patient and clinician perspectives, a deep insight into health system factors associated with the HNC diagnostic pathways leading to advanced stage disease in two centres that are part of the HEADSpAcE Consortium, Glasgow, Scotland, and Montevideo, Uruguay. There are key themes and issues associated with advanced stage HNC diagnosis pertaining to all areas of the referral to diagnosis pathway, including the ability of individuals to access and navigate health services, the structure and organisation of health services and challenges in communication between key people in the diagnostic journey to HNC diagnosis that could prove beneficial for future research areas and health service/system change to reduce the burden of advanced stage HNC.

5.6.1 Reflexivity

The primary researcher in this study, GC, is a dentist and registrar in dental public health with experience in the direct care of patients with HNC from referral through to patient care in primary care and specialist services in the UK and New Zealand. GC has personal experience of a close relation who was diagnosed with cancer (Non-HNC) at Stage IV as a young adult. Patient participants were not explicitly made aware of this latter fact unless it came up in discussion at interview time. ILG is an Oncologist but is not part of an HNC team. Potential impacts of the professional roles in interview consistency were mitigated through the use of standardised topic guides and regular discussions following interviews on findings to help achieve saturation.

5.7 List of Abbreviations

GP: General Practitioner

HEADSpAcE: Translational Studies of Head and Neck Cancer in South America and Europe

HNC: Head and Neck Cancer

HPV: Human Papilloma Virus

NHS: National Health Service

PCP: Primary Care Practitioner

SEIPS System Engineering Initiative for Patient Safety

TNM: Tumour, Nodes, Metastasis

WOSCAN: West of Scotland Cancer Network

5.8 Declarations

The authors declare no conflict of interest

5.8.1 Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer /World Health Organization.

5.8.2 Ethics approval and consent to participate

This study was approved by local ethical approval including from the NHS WOSREC 3 21/WS/0038. All participants provided informed consent at the time of interview (Appendix 5-4).

5.8.3 Availability of data and materials

Interview transcripts are not publicly available but may be upon appropriate request to the main author.

COREQ-Checklist can be found in appendices (APPENDIX 5-5).

5.8.4 Competing interests:

There are no completing interests to declare

5.8.5 Funding

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5.8.6 Authors' Contributions

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5.8.7 Acknowledgements

5.8.7.1 HEADSpAcE Consortium

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6 Chapter Six: Discussion

In this chapter, the findings from the studies included in this thesis are summarised and the strengths and limitations of the study approaches and data analysed expanded upon from those set out within the study chapters. The results are contextualised against the wider literature on HNC diagnosis and, potential areas and avenues for future clinical practice, health system policy, and research are proposed.

6.1 Findings and Comparisons with International Literature:

This thesis has described the burden of advanced stage HNC in the UK and explored the potential role of health systems factors in HNC diagnosis and stage of disease – identifying advanced stage HNC as a significant public health issue. The thesis also showed that health system factors seem to be associated with stage at diagnosis and need to be more explicitly considered in approaches to address the high burden of advanced stage head and neck cancer.

6.1.1 The Burden of Advanced stage Head and Neck Cancer in the UK

What is the burden of advanced stage head and neck cancer in the United Kingdom?

6.1.1.1 Summary of Thesis Results and UK Context

The study undertaken in Chapter Three of this thesis, Head and Neck Cancer in the UK – What Was the Stage Prior to COVID-19? UK Cancer Registries Analysis (2011-2018), involved analysis of collated, aggregated data from the four cancer registries of the UK and showed for the first time the proportion of advanced stage HNC in the UK, which was found to be 59% when stage was recorded for all nations combined. Until this study, the only estimates available for proportion of stage at diagnosis came from large cohort studies, such as the HN5000 study from 2011-2014 which showed similarly that 59.6% of patients with HNC were diagnosed with advanced stage disease (Ness et al., 2016), or single-nation studies such as from Scotland alone that again found 55% advanced stage HNC at diagnosis in 1999-2001 where stage was known (Ingarfield et al., 2019a). The thesis analysis found that across the nations of the UK individually, England had the lowest proportion of advanced stage HNC with 58%, followed by 65.4% in Scotland, 66.9% in Northern Ireland, and 68.9% in Wales. The results from this study show that proportion of advanced stage HNC is generally at similar levels to the existing literature, however the new thesis data from Scotland noted a nearly 10% higher proportion of advanced stage HNC from the level previously reported in 1999-2001 (Ingarfield et al., 2019a)

Of the subsites of HNC, Oropharyngeal Cancer (OPC) had the highest proportion of advanced stage with 80.7% at stage III or IV in the UK where stage is known. Those with OPC had a strongly associated higher odds of advanced disease when compared to OCCs (OR3.14, 95%CI 2.54, 3.89), suggesting that OPC is not only driving the rapid increases in HNC incidence rates observed, but also potentially driving the higher proportion of advanced stage HNC (Gormley et al., 2022).

More detailed analysis of the Scottish data (due to data availability) revealed that males were strongly associated with a higher odds of advanced stage disease compared to females (OR1.24, 95%CI 1.05, 1.46), but less strong were the odds of advanced disease in people aged over 50 years compared to those under 50 years old (OR1.10, 95%CI 0.86, 1.42). Additionally, those diagnosed with HNC in the most socioeconomically deprived areas (according to the SIMD) had a higher odds of advanced stage compared to those from the least socioeconomically deprived areas (OR1.14, 95%CI 0.89, 1.48) although this was not as strongly associated.

These findings of this study concur with the existing understanding of males having the highest incidence of HNC overall (Gormley et al., 2022) and add to the evidence of HNC being a socioeconomically patterned disease. Significant inequalities in incidence and survival are well described in the literature, with those from the most deprived socioeconomic areas with lowest level of educational attainment at much higher risk of developing HNC and having worse cancer outcomes (Johnson et al., 2008, Conway et al., 2015, Purkayastha et al., 2016, Conway et al., 2021, Ingarfield et al., 2021,).

6.1.1.2 International Epidemiology of Advanced stage Head and Neck Cancer in the Literature

The findings from Chapter Three in this thesis offer an interesting comparison to the proportion of advanced stage HNC reported internationally.

Cancer registries offer a wealth of accessible data for HNC monitoring and analysis but are underutilised as a source for assessing proportion of advanced stage HNC. Registry-informed, national proportions of advanced stage HNC are scarce in the literature for South American and European countries with best results often coming from large, international cohort studies. In South America, the INTERCHANGE cohort study which included patients from a diverse group of HNC centres from 2011-2017 showed that 75% of recruited patients were diagnosed with advanced stage HNC (Abrahão et al., 2020) whilst in Europe, the ARCAGE multicentre European case-control study (2002-2004) showed a proportion of advanced stage HNC of 54% across constituent centres (Abrahão et al., 2018). These proportions highlight a difference between countries from South America and Europe that was one of the main basis for establishing the HEADSpAcE consortium to examine advanced stage HNC disease in both South America and Europe, and thus the rationale and focus of the health systems work in Chapters Four and Five. Incidentally, the estimated proportion of advanced stage HNC provided by centres across the consortium also broadly is in keeping with the literature observation of higher proportions among countries in South America compared with Europe.

One European country cancer registry study is available in the published literature, from Germany, in which researchers undertook analysis of national cancer registry data from 2002-2017. This study showed a proportion of advanced stage HNC of 69% in the registry at stage III or IV according to TNM 8th edition where stage was recorded, but a significant 45.1% of cases in the registry had incomplete staging data and could not be analysed (Vahl et al., 2023).

Internationally, there are few other examples of cancer registry data being used to assess the burden of advanced stage HNC, with studies limited to those from registries from HICs. In the US, analysis of Surveillance, Epidemiology, and End Results (SEER) data assessing epidemiological changes pre and post the SARS-

CoV-2 pandemic (2017-2022) showed no change in advanced stage disease, with 62% of cases shown either regionally and distant advanced-disease, although the classifications used preclude a direct comparison with the results from this thesis given the lack of clarity as to how they directly relate to TNM classifications (Semprini et al., 2024).

When considering the sub-analysis undertaken in Chapter Four on the Scottish data, our findings of males and those in more deprived socioeconomic groups is consistent with the findings of a comprehensive systematic review by Ioerger et al (2024) where the authors found persuasive evidence across the 50 studies included of male sex and low socioeconomic status as risk factors for advanced stage HNC. Even though the majority (92%) of studies were deemed low risk of bias, these results must be caveated by the sole inclusion of studies from the USA and may also not reflect populations with limited access to health services.

6.1.2 Health System Factors in Advanced stage Head and Neck Cancer

What is the potential role of health systems factors in advanced stage diagnosis of head and neck cancer?

6.1.2.1 Summary of Thesis Results

Chapter Four, Advanced Stage Head and Neck Cancer Diagnosis: HEADSpAcE Consortium Health Systems Benchmarking Survey, employed a novel, pragmatic approach to understand the potential role of health systems factors in stage at diagnosis of HNC, an area of the literature that is scarce to date. Through undertaking least square means tests on the presence/absence of individual health systems factors against the mean proportion of advanced stage HNC, this study showed the association of specific health systems factors with stage at diagnosis of HNC, contributing towards the emerging appreciation for the role of health systems factors in stage at diagnosis of HNC. In particular, three health systems factors showed a strong association with absolute lower proportion of advanced stage HNC at the centre level: formal referral triaging (14%, 95% CI -0.26, -0.03), routine monitoring of time from referral to diagnosis (16%, 95% CI -0.27, -0.05), and fully publicly funded systems (17%, 95% CI -0.29, -0.06).

Other health systems factors analysed but not showing strong association with stage were centres with higher patient volume with a 2% higher proportion of advanced stage HNC (95% CI -0.13, 0.16), centralisation of centre services to one location with no change (95% CI -0.19, 0.19). Remaining health system factors were associated with a lower proportion in advanced stage diagnosis, but none showed a strong association with stage at diagnosis. These include electronic referral system, common primary-secondary care medical record initial diagnosis made exclusively at centre comprehensive MDT specialist HNC radiologists and pathologists; and referral guidance for HNC.

Notably, there were several health systems factors that could not be included in analysis due to an absence of data from all centres, including: source/origin of HNC referral; counts and whole-time equivalent workforce within HNC system; performance indicators relating to referral pathways; and routinely reported proportions of stage at diagnosis.

The additional creation of the HEADSpAcE HNC diagnostic pathway as part of this study, dividing the pathway into “pre-diagnostic” (pertaining to patients and populations) and “diagnostic” (pertaining to interactions with health services) intervals, could be considered a valuable framework for undertaking and evaluating future HNC diagnostic research – including for planned analysis of the HEADSpAcE new prospective cohort which has been collected by centres in the consortium to examine individual patient and tumour level factors associated with HNC. While this framework already exists for cancers more generally through the Aarhus statement (Weller et al., 2012), HNC has added complexities that are absent from Aarhus and require consideration. These were identified in this chapter as including the role of dental care teams, the multiple routes to diagnosis, and the multiple health services providing diagnosis and care services for HNC. In addition, the international diversity of HNC diagnostic pathway/health systems was also captured through this chapter.

6.1.2.2 Factors in Advanced stage HNC

To date there is limited evidence on the role of health systems factors in HNC diagnosis but there have been some reviews covering advanced stage HNC and wider factors involved. A recent, insightful systematic review of HNC inequalities took a broad lens to the role of different factors in HNC advanced stage at presentation or delayed diagnosis. The review included 50 studies and did not have a health systems focus, but found that those of black, native American, and native Hawaiian/other pacific islander were all more likely to be diagnosed with advanced stage disease when compared to white counter parts. Additionally, the review reported that men had a higher risk of advanced staged disease compared to women in all but one study. Furthermore, socioeconomic status was strongly related to stage at diagnosis, with lower socioeconomic status associated with advanced stage at diagnosis (Ioerger et al., 2024). The review has one significant flaw for generalising results however as only studies conducted on populations within the United States of America were included, meaning that these results may only be applicable to the specific nature of the health systems of the USA where healthcare is largely funded through a mixed-insurance-based health model, which itself is associated with inequality (Dickman et al., 2017).

There have been some qualitative studies that have elucidated on aspects of health systems and their role in advanced stage HNC, such as those by Venchiarutti et al (2022a, 2022b) that raised the variation in travel distances to access HNC care required by some patients, particularly in rural areas, as a possible inequality relating to diagnostic stage. Inequalities was a strong theme from Chapter Five’s results, both in geographic and socioeconomic terms.

6.1.3 Health System Factors in Head and Neck Cancer Advanced Stage Diagnosis: A HEADSpAcE Consortium Qualitative Study in Glasgow and Montevideo

What are the health system factors associated with stage at diagnosis of HNC and how do they affect stage at diagnosis?

6.1.3.1 Summary of Thesis Results

Chapter Five employed a traditional qualitative methodology with a modern template analytical approach to the subject of advanced stage HNC. The results from this study shed light on how people, both HNC patients and clinicians, have difficulties in navigating the complex diagnostic pathway with the importance of communication demonstrated along the entirety of the HNC diagnostic pathway. Key thematic findings were the role of inter-disciplinary communication between primary care and secondary care, socioeconomic and geographic inequalities, HNC awareness and patient agency in accessing care, and referral processes. Through applying the lens of the SEIPS 3.0 framework (Carayon et al., 2020) the findings from this analysis were framed into system domains that will help inform future research and intervention development.

6.1.3.2 Head and Neck Cancer Awareness and Accessing Care

In Chapter fFve, awareness of HNC symptoms was raised as a key factor in stage at diagnosis. Disease-specific awareness of symptoms is often posited as a key factor in delayed diagnosis (Macleod et al., 2009) and as such arguments are made for focussing on increasing awareness as a way of addressing delays (Richards, 2009). While this has proven to have some positive effect on presentation time for cancers such as breast and colon cancers (Richards, 2009) the same cannot be said for HNCs where efforts to raise population awareness of symptoms have not translated into long term improvement in early diagnostic rates or better patient outcomes (Macpherson, 2018).

Ford and Farah (2013) reviewed the literature on early detection and diagnosis of oral cancer in 2013 and offered suggestions for improvement strategies. The authors discussed the multitude of complex factors in play and the potential role for targeted screening but emphasised that the benefit of patient awareness campaigns is not clear despite there still being a role for this if better understanding was available of what messaging could provide benefit.

A review of systematic reviews by Macleod et al (2009) that synthesised factors associated with delayed presentation of symptomatic cancer to primary care produced some very sobering findings. The main theme was non-recognition of cancer symptoms across cancer groups. Fear of cancer was also a strong finding from patient perspectives, whilst misdiagnosis was the common theme in primary care, which correlates with the finding in Chapter Five of poor recognition of HNC in primary care. Complementary studies employing primary and secondary analysis of qualitative data by the same authors investigated symptom appraisal and found when attributing risk to symptoms, the social context and shared cancer narratives affect decisions to access health services (Macleod et al., 2009, Macdonald et al., 2019), strengthening the results in Chapter Five that show, when considering the findings in a systems-context through the SEIPS framework, many of the factors associated with stage in the pre-diagnostic interval pertain to the socio-organisational context.

Awareness of HNC symptoms remains key but alone awareness is unlikely to transmit into longer term change. Rather than focus on population or individual behaviour change through symptom awareness, the findings from this thesis suggest that awareness of how to navigate health systems may have an added beneficial effect.

The results from this thesis largely correlate with research from other fields of health where, despite some limitations in terms of bias within studies, improved health literacy has been shown to lead to better patient outcomes (Walters et al., 2020, Coughlin et al., 2020). However, where the literature to-date has discussed a more general awareness of oral/HNCs in terms of knowledge of symptoms and signs and risk factors (van der Waal et al., 2011, Macpherson, 2018), the thesis findings from Chapter Five which identified the need for more clear understanding of what patients (and indeed clinicians) should do in terms of clarity of referral guidelines and diagnostic pathways provides useful insight for future work in this area.

Results from this thesis suggest that there is perhaps a role for more active facilitation/support for patients through the HNC pathway, which might involve support to navigate the health system from primary care to specialist care, also shows that simple messaging awareness may not be enough and that a more active/supporting function to support patients is needed. Such patient navigation interventions have been shown to have positive effect in the US on bowel cancer screening and treatment (Escoffery et al., 2015) with persuasive evidence from recent systematic reviews showing a strong positive effect on cancer treatment pathways in non-HNC cancers (Chan et al., 2023, Chen et al., 2024). Patient navigation interventions for HNC are limited in the literature to narrow, locally-devised schemes for diagnosis such as that presented by Ohlstein et al (2015) where a community partnership was formed between clinicians and third sector organisations to counteract system disruption in the wake of a natural disaster or pertain only to treatment and focus on clinical roles of the role of the clinical nurse specialist (Homer et al., 2024).

One important nuance raised in Chapter Five was the role of family and friends in having a role in prompting, and facilitating initial presentation to health services through enabling contact with and attendance to appropriate care providers. Whilst there is a body of research into the positive and protective role that friends and family members have in supporting cancer patients peri/post treatment (Gilliss et al., 2019), there is nothing in published literature evidencing the facilitatory role that loved ones can play in early diagnosis of cancer.

6.1.3.3 Patient-Clinician Relationship

A revealing finding from Chapter Five was the importance of the patient-clinician relationship, particularly in the early aspects of HNC diagnosis, and that how a patient perceives health services and/or their relationship with their general health care providers can influence decisions to access healthcare. Thought-provoking qualitative studies have given insight into the factors that affect patient experience with primary care in HNC cancer pathways. In a study from Australia, 39 patients and 17 carers were interviewed with the resulting thematic analysis showing a perceived lack of emotional investment from clinicians by patients, which relates to the issues of trust from patients in health organisations and clinicians raised in this thesis (Venchiarutti et al., 2022a).

From the primary-care perspective in cancer generally, the role of “Gut feelings” from patient-clinician interactions has been shown to improve cancer detection, but only when there is an existing relationship between patients and clinicians, which highlights the importance of the clinical interaction (Smith et al., 2020). However, it has also been shown that misdiagnosis, e.g. with prescription of antibiotics, can increase time to diagnosis, as demonstrated by

Gallogly et al in their cohort study of nearly 8000 patients that revealed that a prescription for antibiotics in the three months prior to diagnosis was associated with increased overall time to diagnosis in HNC in the USA (Gallogly et al., 2023). These findings, combined with those from this thesis, suggest there is a need for specific, high-quality HNC referral and diagnostic guidance.

6.1.3.4 Pathways between Primary and Secondary Care

This thesis has shown insight into the importance of pathways between primary care and secondary care teams and services with Chapter Four highlighting the importance of system-steps in the referral processes between primary care and secondary care services (i.e. referral waiting time monitoring and triaging) and Chapter Five highlighting a perceived and experienced disconnect between the levels of healthcare within the researched systems. Considering HNC, there have been two insightful qualitative studies on this topic. A study of HNC patients and healthcare workers on timely HNC care in Boston, USA identified four major themes across participant groups: the fragmented HNC referral and triage pathway; primary medical and dental care have a key role in referring in a timely manner; and care can be expedited if coordination between clinicians is smooth (Batool et al., 2024). Another study which interviewed HNC surgeon specialists in England and the Netherlands highlighted the frustration at poor communication from primary care and the need for professional education (Langton et al., 2019). The correlation of these findings with the major finding of a disconnect between care teams in this thesis are startling in their similarity.

The broader challenges in communication between these primary care and secondary care in cancer pathways is a compelling topic in the literature with a revealing systematic by Lawrence et al. (2016) highlighting poor quality of communication and lack of guidance as key factors in the disconnect between services. Additionally, questions over trust between care teams was shown to be a key factor finding that chimes with the raising of trust between patients and health teams in this thesis.

An interesting survey from the ICBP investigated factors that influence primary care practitioner referral activities across several health systems within HICs with results revealing the ability to refer, perceptions of pressure, and varying expectation of primary care roles as key (Harris et al., 2018), correlating with the themes from Chapter Five of overloaded primary care services and the disconnect between care teams with the role of primary care providers requiring clarity. Another key study from the ICBP assessed referral variation across constituent jurisdictions, analysing pathways for colorectal, lung, and breast cancers, and revealed interesting insight into the heterogeneity in referral pathways between and within countries. Inflexible pathways, primary care practitioner autonomy, and direct access to special investigations were all common issues raised in the study, correlating also with the findings from this thesis (Lynch et al., 2023).

While Sripa et al (2019), in their somewhat limited systematic review on the role of gatekeeping by general medical practitioners found overall positive impacts on health expenditure and reduced use of specialist care in general, for cancer care in particular greater one-year survival was in patients that had direct access to cancer specialists. There were only two studies on cancer included however, with one having inconclusive results.

The role of dentists in HNC diagnostic pathways was raised in Chapter Five, something that has been well researched, particularly with the potential positive role for brief interventions aimed at reducing harmful behaviours (Mathur et al., 2022). Opportunistic screening for HNCs at routine dental appointments to diagnose asymptomatic disease has also been posited as a potential way for detecting HNCs at an earlier stage, given that there is a significant link between regular dental attendance and reduced risk of HNC incidence, as shown by Gupta et al (2019) in their systematic review, with earlier stage at diagnosis of HNC also found to be associated with regular dental attendance in several population and cohort studies, including those by Groome et al, (2011) and Farquhar, et al (2020) who showed in their large cohort of patients from a HIC that regular dental visits were protective against advanced disease at diagnosis.

6.1.4 Combined Results from Chapters Four and Five

Given the research subject and methodologies employed in Chapters Four and Five, there were several resulting themes that were common between both, with the themes of referral processes, clinical guidance, system monitoring, and models of health system finance and associated inequalities.

6.1.4.1 HNC Referral and Diagnostic Guidance

The lack of a strong association between the availability of referral guidance and stage at diagnosis was an interesting and surprising finding of the thesis. The availability of guidance is a useful metric but does not assess quality of guidance documents and tools, however there are tools available, such as the AGREE II framework described earlier in this thesis, to do this (Brouwers et al., 2010a). An explanation to the lack of relationship between presence of guidance and lower proportion of advanced stage HNC in the centres included in Chapter Four may be the concept of adherence to guidance, meaning that just because guidance is available, does not mean it is being utilised or complied with. A retrospective study of cancer patients in England analysed the patient diagnostic journey for people with major cancer symptoms (i.e.; dysphagia, haematuria) presenting to primary care teams and assessed the incidence rate of cancer in non-referred patients. Through linkage with cancer registry data, analysis revealed that 4% of people not referred despite having these symptoms developed cancer within 1 year suggesting that if guidance was followed, their cancer could have been diagnosed earlier (Wiering et al., 2022).

A recent scoping review of international HNC treatment guidelines, the first review of its kind, found differences in clinical practice guidelines that suggested inequity in health system conditions, namely the availability of resources such as imaging, clinical professionals, and modern technologies. The review also revealed that Latin America was one of only two regions, alongside Oceania, that did not have a treatment guideline for HNC originating from that area (Arboleda et al., 2023). However, these guidelines were focussed on clinical management of HNC patients and pre-treatment workup and did not include pathways to diagnosis or referral guidance.

6.1.4.2 Monitoring of HNC Diagnostic Pathways

Waiting times from referral to diagnosis and diagnosis to treatment are an area of focus in literature – mainly from the UK. In England, waiting times to first appointment in specialist services have been governed by the “two-week-wait”

(2WW) approach whereby a person with suspected cancer is referred through a specific pathway so that they are seen within this time window (Department of Health, 2000). A thorough analysis of individual-level data from the English Cancer Registry, assessing cases from 2006-2014, revealed several interesting findings, including that people referred through the 2WW pathway were more likely to be diagnosed with stage III or IV disease than those referred through other primary care pathways, although emergency presentations were the most associated with stage III or IV disease (Deane et al., 2022).

Other examples of initiatives to improve early detection of HNC include the Danish program for fast-tracking cancer referrals which, from introduction in 2007, has provided clear referral guidance for cancers (including HNC) and targets for time between referral and first appointment (six calendar days) and referral and diagnosis (21 calendar days) and employs the clinical examination of a patient with suspicious signs or symptoms of HNC by a ‘private’ ENT (Ear, Nose, and Throat) specialist within 24 hours of initial presentation to primary care which dictates the need for onwards referral to HNC specialist services. (Roennegaard et al., 2018). Analysis from a large HNC tertiary centre in Denmark has shown that over 90% of patients with diagnosed HNC are seen within this timeframe but the effects on stage at diagnosis since the implementation of this program has not been quantified (Roennegaard et al., 2018).

The results from this thesis suggest that monitoring time to diagnosis may be an important factor in reducing advanced stage disease. A unique systematic review of delays in primary care of oral cancer diagnosis by Grafton-Clarke et al. (2019) covered a broad range of international studies and had interesting findings on there being no discernible difference in time to diagnosis between medical and dental primary care routes, however, data were limited by clear descriptions of primary care services. In Chapter Four of this thesis, it was found that source of referral was not routinely reported by any HNC centre included in the study, perhaps indicating that this is not a health system factor that would affect proportion of advanced stage in international-HNC diagnostic pathways, despite the importance of dental routes being highlighted by (Mathur et al., 2022). Interestingly, this review by Grafton et al. show that patients often required two or three appointments in primary care before a referral for onward investigation was made.

6.1.4.3 Models of Healthcare Finance

The benchmarking survey in Chapter Four raised the important finding of the difference in proportion of advanced stage HNC reported between centres that were based in fully public funded health systems and those from either mixed public/private or fully private/insurance-based models. Unfortunately, this could not be probed in more detail in the case studies of Chapter Five – as both Glasgow and Montevideo are set in fully publicly funded health systems in high income countries. In HNC research, there is little in the way of analysis of this health system factor specifically, but there is some evidence from the US that suggests an association between affordable care and earlier diagnosis. In Panth et al.'s (2020) cohort study of over 90,000 HNC patients, there was improved early detection of HNC following the affordable care act USA in 2014 for those with Medicaid health cover (aOR = 1.12, 95 % CI 1.03, 1.21; p = 0.007).

The topic of universal health coverage (UHC) is a high priority of the World Health Organisation (WHO, 2024) with the acceptance that UHC has the ability to mitigate some of the social determinants of health and disease (Marmot, 2013). A key element of UHC is reducing the out-of-pocket financial costs to people (Mathur et al., 2015) which is a feature of publicly funded health systems (McKee et al., 2013); a health system factor analysed in Chapter Four of this thesis. A major study by Kruk et al (2018) showed how important quality health systems are in modern day society, with an estimated 8 million deaths globally attributed to poor-quality health services.

Whilst the findings of this thesis suggest that publicly-funded health systems/universal health coverage could reduce the burden of advanced stage disease with those centres that exist within publicly-funded health systems showing a lower proportion of advanced stage HNC, care must be taken to consider the quality of these systems should they be introduced where they do not exist already to ensure equitable allocation of resources and healthcare access (Bloom et al., 2018). Chapter Five of this thesis revealed the importance of knowing how to initially access and then subsequently navigate through the complex HNC diagnostic pathway, both from a patient and professional perspective, in order to detect HNCs earlier. This raises the question of wider primary-care access where, even in health systems such as the UK's NHS, there exists inequalities of access where services are harder to access in areas of greatest health need – an example of the “inverse care law” in action (Watt, 2018). Linked to this is the issue of overburdened primary healthcare providers in these areas of greatest need, which has led to creative and impactful projects and collaborations, such as the Deep End GPs, aiming to improve patient outcomes (Watt et al., 2012, Watt, 2018, Butler et al., 2022). Incorporating the learning from successful examples such as this initiative would help develop interventions to aid patients in navigating HNC diagnostic pathways to improve early detection of HNCs whilst also supporting primary care practitioners.

6.2 Limitations of Thesis Approaches

6.2.1 Cancer Registries and Epidemiology

In Chapter Three, the data utilised were routinely collected, aggregated data held within the four cancer registries of the UK (NCRAS, 2021, WCISU, 2021, NICR,2021, SCR, 2021).

A limitation of the data analysed in this study was the lack of separation between HPV-positive and HPV-negative OPCs. It has been suggested that HPV is driving the dramatic rise in OPC, with as much as 60% of OPC patients in a cohort from Scotland being HPV-positive in 2013-2015 (Wakeham et al., 2019) and up until 2018, the different stage classifications for OPC depending on HPV status were not included in cancer registry data. With the 8th edition of the AJCC TNM staging classifications (Christian Wittekind, 2016) updating classifications to downstage HPV-positive OPC that were previously stage III to stage II, and leaving only cases that are metastatic as stage IV, it is possible that should the registry data be reevaluated with the newest staging classifications, the proportion of advanced stage OPC would not be as high, reducing the overall HNC proportion of advanced HNC.

However, another finding from Chapter Three was the incomplete nature of diagnostic stage data, which although improving drastically in the last decade, was still only 87% complete by 2018. The incomplete nature of registry data can lead to potentially incorrect depictions of the national cancer burden, however, as Di Girolamo et al. (2018) have shown for other cancer types (colon, lung, and breast), those with missing stage at cancer registry level are more likely to have advanced-disease than early, which suggests that through analysing cancer registry data we are unlikely to be underestimating the burden of advanced stage disease. Despite limitations of cancer registries in not often having the depth required to undertake comprehensive analytical epidemiological research (Jones et al., 2019), cancer registries do have a vital role in monitoring cancer through descriptive epidemiology including the disease burden and trends (Bouchardy et al., 2014), and offer, as results from this thesis show, an opportunity to better understand the public health challenge of advanced stage HNC. Therefore, despite these data limitations, the proportion of advanced stage HNC remains substantial with significant impacts on patients and clinical services alike, and this remains a public health/health service challenge that needs to be addressed.

6.2.2 Health System Factors and Methodologies Used

In Chapter Four, a bespoke questionnaire was developed that aimed to capture centre data on local routinely collected data and with qualitative data to capture the centre pathways to HNC diagnosis. The questionnaire had to be developed from scratch as there were no validated question items available, which leaves it at risk of bias or lack of utility (Ranganathan and Caduff, 2023). Care was taken to ensure readability, answerability, and analytical utility: a significant challenge given the topic was itself a complex and an underexplored research area. Following the recommendations of Boynton and Greenhalgh (2004), the questionnaire was developed based on general health system literature and involved several rounds of consultation with a range of clinical, administrative, and academic colleagues from the Glasgow HNC Centre and with the wider HEADSpAcE consortium.

The benchmarking study in Chapter Four is explorative by design and as such the data collected were in different formats. Additionally, the HNC centres included in this study were not randomly sampled but rather opportunistically and conveniently selected from the established HEADSpAcE consortium of HNC centres. The intention in this benchmarking study was to attempt to quantify the relevant importance of specific health systems factors within the studied centres, and, in some ways more importantly, to assess what the health systems factors that were measurable in the first place were available. Whilst there was an absence of data pertaining to health system domains identified as potentially important in advanced stage HNC, including data on workforce and referral sources (meaning that analysis of corresponding health system factors could not be undertaken), the identification of health system domains where there is no routinely collected analysable data available was also an important finding from this study.

An important data limitation in the benchmarking survey was the lack of routine data on the main outcome variable – the proportion of advanced stage HNC. Centres reported they had to identify or estimate these data from heterogenous sources including annual reports, local audits, research studies, and professional estimates. This heterogeneity creates opportunity for recall, participation, and confirmation bias (Althubaiti, 2016). However, highlighting that HNC stage data were not routinely available as a system monitoring measurement is an important thesis finding.

In Chapter Five, traditional in-depth, semi-structured qualitative interviews were employed with a range of kay stakeholders in HCN diagnosis in two centres (Montevideo, Uruguay and Glasgow, Scotland). Although these centres did not have identical HNC systems, they were similar in terms of being the major HNC centres in a HIC and existing in countries with similar models of health funding and had similar pathways to HNC diagnosis, differing mainly in the role of dental professionals. Whilst this means that both centres were not completely comparable, given the heterogeneity in HNC centre design and activity as demonstrated in Chapter Four, these two centres offered an opportunity to include international centres as case studies.

The range of interviewees was purposively recruited, initially targeting key personnel in the HNC systems, then opportunistically through snowball sampling. Despite efforts to ensure participation, some key administrative and non-clinical management personnel within local systems did not consent for participation in this study, in Montevideo this was primarily due to the relative absence of such non-clinical roles in HNC, meaning non-clinical professional experiences and insights were not able to be analysed within this study. However, data-saturation was reached, and measures to include administrative and management elements were covered in topic guides and by interviewing clinical service-leads. Further work with management and policy personal at the local centre, regional, and governmental level could elucidate further perspectives of health systems and barriers/facilitators to change. Nevertheless, a focus on the clinical pathways from clinician and patient perspectives is an important basis for identifying issues related to pathways to diagnosis.

With my clinical role as a dental professional, there may have been a bias towards covering the role of dentists in HNC diagnosis more in Glasgow than in Montevideo-based interviews, however with this in mind, topic guides were structured to cover the multiple routes to diagnosis, including dental routes.

In analysing these case study centre interview data, we employed a template analysis. While there are limitations of this approach including a potential loss of understanding of issues raised in individual accounts, this is an unavoidable limitation of the thematic approach (Brooks et al., 2015). We have sought to counter this by adding depth to the findings through the thematic synthesis of the results using the SEIPS3.0 framework; highlighting how these themes relate to the patient journey in a systems engineering model (Carayon et al. 2020).

6.2.3 Impact of COVID-19 on Undertaking the Thesis Research

The outbreak of the COVID-19 pandemic, and the associated measures of mitigation against disease transmission that existed for the years following in various ways internationally, impacted on this thesis in two ways: i) directly, in terms of the ability to undertake clinical research; and ii) indirectly, with the disruption and rapid transformation of health systems during the pandemic and in its recovery.

On the first matter, the studies that form this thesis, as part of the wider work packages of research being undertaken by the HEADSpAcE consortium, were conceptualised and designed prior to the COVID-19 pandemic and were due to begin in March 2020 – right at the time of the first lockdown in the UK and across Europe (Plumper and Neumayer, 2020). All aspects of clinical research were heavily disrupted, with researchers and clinicians redeployed to pandemic-related endeavours and research infrastructure pivoted entirely to COVID-19 related projects, and associated impacts variable depending on what country the services were in (Faulkner-Gurstein et al., 2022). In cancer care services, pathways and treatment regimens had to be reconsidered and the workforce were in some places redeployed where deemed necessary (Mayor, 2020). In the UK, a survey by Cancer Research UK in 2021 of cancer patients showed disruption to clinical pathways and even the pausing of clinical research, including drug trials, for indefinite time periods (Greenwood and Swanton, 2021). A survey from the European Society of Medical Oncology also revealed that cancer workforces were at risk of poor wellbeing and burnout due to overwhelming workloads at this time (Lim et al., 2022).

In the research related to the thesis, these impacts and challenges were replicated in the centres across the HEADSpAcE consortium. Furthermore, these impacts in each of the HEADSpAcE centres were occurring at different calendar times, meaning that the ability to engage with this research project was limited for many centres until deep into 2022. This affected the ability to contemporaneously undertake the benchmarking study from Chapter Four. However, in order to be able to analyse data from a non-pandemic affected time, data from 2019 were used from each centre so that HNC systems and pathways to diagnosis were being analysed and benchmarked as they existed prior to the pandemic.

Additionally, due to restrictions on clinical access to both clinicians and patients, the qualitative interviews undertaken in Chapter Five were not all able to be undertaken in the preferred, face-to-face method resulting in some heterogeneity in approach of a mix of online/in-person interviews being undertaken. Online-video based methods have been shown to be appropriate and useful for undertaking qualitative interviews (Archibald et al., 2019) and, despite there being some limitations, specifically in terms of non-verbal communication cues from both participants and researcher (which have been said to be more relevant to focus-groups than one-to-one interviews (Lobe et al., 2022)), the mix of in-person and online interviews improved the availability of potential participants. Although the direct effects of the COVID-19 pandemic did not fundamentally affect the analytical methodology of the research, or the results shown, it did complicate the undertaking of these projects and require careful consideration.

A major element of the HEADSpAcE Consortium is a prospective cohort of over 1000 newly diagnosed HNC patients across the centres. The two primary research studies included in this thesis, Chapters Four and Five, were initially intended to be linked directly, and started subsequent to, this cohort but due to unavoidable significant global delays in the initiation and recruitment of this cohort this was not feasible.

6.2.4 Impact of COVID-19 Pandemic on Interpreting Thesis Findings

At the onset of the COVID-19 pandemic, a strategically significant population-based modelling study in the UK estimated an increase in deaths due to cancers, including colorectal (15.3-16.6%), oesophageal (5.8-6.0%), and lung (4.8-5.3%) up to 5 years after diagnosis (Maringe et al., 2020). Expert opinion at the time suggested significant impacts in all elements of the cancer care pathway and suggested strategies for mitigating the potential worst effects of COVID-19 and associated measures on cancer diagnosis and treatment, including case/resource prioritisation and active waiting list monitoring (Richards et al., 2020).

Although the COVID-19 pandemic had, and continues to have, disastrous impacts on health and cancer services globally, both in terms of healthcare access and patient outcomes (Richards et al., 2020), the anticipated impact of increased advanced stage HNC diagnosis did not seem to have been realised. HEADSpAcE consortium studies from HNC centres in Turin, Italy and Glasgow, Scotland reported no significant stage shift from early to advanced stage immediately following the early phases of the pandemic and public health mitigation measures (Popovic et al., 2022, Clements et al., 2023). Moreover, a systematic review by Pereira et al (2023) showed no statistically significant changes in stage at diagnosis in all but one study (a retrospective observational analysis of a relatively small number of cases (Wai et al., 2021). Although this review only included nine studies, the results did involve findings from a diverse group of countries included with representation from HICs (e.g. USA), and low- and middle-income countries (e.g. India) (World Bank, 2024b).

In the literature post-pandemic, there were conflicting reports on changes in HNC diagnostic pathways, treatments, and outcomes observed in retrospective observational and survey studies (Brody et al., 2020, Lein et al., 2024). This included specifically a shift to more radical radio-oncological treatment approaches in place of some surgical approaches; however, there was also evidence that experienced surgical teams and adaptation of procedures could help reduce any potential impacts (Colin et al., 2024). To date, there has been no thorough review or meta-analyses of the overall impacts particularly in relation to cancer outcomes in HNC as a result of the COVID-19 pandemic.

From the literature available, it does not seem that the COVID-19 pandemic has had significant, lasting impact on HNC pathways to diagnosis and wider HNC systems, which gives some encouragement to view the results of the studies undertaken in this thesis as remaining relevant to informing future health system improvements and optimal cancer diagnostic/care pathway developments.

6.3 Strengths of Thesis Approaches

6.3.1 Cancer Registries and Epidemiology

The ultimate strength of using data from Cancer Registries, as in Chapter Three, is the ability to analyse large population datasets that have a high degree of quality and completeness, that can be used to monitor cancer disease burden (Brewster et al., 1994, Brewster et al., 1997, Brewster et al., 2005). This study was able to utilise data from cancer registries of the four countries of the UK and synthesise results despite heterogeneity in what is routinely collected and reported, something successfully done in past literature for overall HNC incidence and trends (Conway, 2018). This is the first study however to analyse stage of HNC through utilising cancer registry data and shed light on the improving completeness of diagnostic stage of cases within registries. This study has proven the utility of cancer registry data as a method for monitoring stage of HNC as part of future trends and incidence analyses.

The results from the sub-analysis of Scottish Cancer Registry results also gives insight into the inequalities and demographics of people with advanced stage HNC. HNC is intrinsically linked to socioeconomic status, with those from the lowest socioeconomic groups or living in the most socioeconomically deprived areas having greatest risk of developing HNC, and having the poorest outcomes

(Conway et al., 2008, Ingarfield et al., 2019b, Ingarfield et al., 2021, Gormley et al., 2022). As a result of this study, we have gained additional insight into the potential role of area-based socioeconomics in stage at diagnosis in Scotland

6.3.2 Systems Benchmarking Survey

The data analysed in Chapter Four is a unique, purposively collected set of qualitative and quantitative data that is not represented in any other literature for HNC. While existing examples of benchmarking studies in international cancer have covered a mix of routinely collected quantitative and purposive qualitative data for other groups, such as breast, colon, and lung (Rose et al., 2015, Weller et al., 2018, Menon et al., 2019, Vedsted et al., 2022, Lynch et al., 2023) these have not included HNC and are limited to systems from HICs. Chapter Four of this thesis includes data from a range of HNC systems from a variety of countries across the world, from High-, Middle- and Low-Income Countries, allowing for results to be interpreted in the context of a variety of health systems, not solely HICs.

In undertaking a pragmatic, systems approach to the topic of HNC diagnosis (Long et al., 2018), we have been able to elicit previously unexplored findings on what aspects of local HNC health systems may be important in reducing advanced stage HNC diagnoses; namely quality data monitoring in referral pathways through monitoring waiting times to diagnosis and formally triaging referrals. At the current time where bureaucracy and paperwork are reported as barriers to implementing quality, patient-centred care (Wang et al., 2023), it is vital to understand which administrative exercises improve health outcomes, with the results from Chapter Four identifying aspects of diagnostic pathways that may enable a reduction in advanced stage HNC if adopted.

6.3.3 Case Study Qualitative Methods

Qualitative research is an important aspect of health services research and gives deep insight into how people experience and interact with healthcare within their sociocultural context (Pope and Mays, 1995, Tenny et al., 2024). The study in Chapter Five has the strengths of including participants from two HNC centres in different countries from similar publicly funded national health systems but differing local HNC pathways. Additionally, by undertaking in-depth, semi-structured interviews with participants from a variety of clinical roles and HNC patients, a whole-systems lens is able to be gained from the results, something that Greenhalgh and Papoutsi have said is essential in navigating the complexity of health systems (2018).

Qualitative research serves a different purpose to traditional quantitative approaches and as such is not as “generalisable” as other methods, however, the purpose of qualitative approaches in health research is not to provide standardised results but to provide insight and context to a phenomenon or system (Isaacs, 2014). This thesis provides deep understanding from a range of stakeholders on the system of HNC diagnosis across two centres, Montevideo in Uruguay and Glasgow in Scotland, that can inform system changes, and interventions in these areas but also provide an insight into potential health systems factors in advanced stage HNC diagnosis to consider more generally.

In order to ensure a rigorous approach to the qualitative analysis, the recommendations of Braun and Clarke (2023) and Roberts et al. (2019) were followed when constructing the analytical codebook and undertaking thematic analysis, culminating in the use of template analysis (Brooks et al., 2015) to go beyond the basic description of data and provide reflexive interpretation of the data.

In undertaking this qualitative study that was informed in both design and analysis by the findings from Chapter Four, this thesis is able to correlate the real-life experiences of key stakeholders in HNC diagnosis with the health system as understood by what data is readily available at the centre-level so that a broader, system level understanding can be made. The undertaking of these two studies together has allowed for deeper understanding of the context of this thesis’ findings within the wider literature on advanced stage HNC.

6.4 Reflexivity

As a researcher undertaking qualitative research in the topic of cancer, it is important to consider reflexivity in the scope of this thesis and as such I would like to focus on personal contextual reflexivity (Olmos-Vega et al., 2023). In my life, I have had significant personal experiences through close family experiences of different cancer types, and also professional experience through working in dental and maxillofacial clinical jobs. These experiences have given me a deep understanding of the impact of cancer on people and their families. Through my partner’s diagnosis with stage IV Non-Hodgkin’s Lymphoma in July 2015 when she was 23 years old and recently graduated, my personal relationship with cancer developed into something existential. Thankfully, she remains in remission following completion of her treatment. Through and since this experience, I witnessed the major life-changing effects of a cancer diagnosis and treatment at this time of life and, via various support networks, we have made great friends with many other young people impacted by cancer - including HNC. Those near two years of anxious uncertainty stay with me to date and going through this extremely difficult lived experience with my partner (now wife) remain a constant motivation in all of my academic and NHS public health work.

I was conscious of my personal history with cancer and my clinical role as a dentist as being potentially influential in steering the research included in this thesis, in particular Chapter Five, down specific routes based on my experience. To ensure that the research was rigorous, an experienced qualitative researcher (Professor Alastair Ross) helped guide the research and interview topic-guides, whilst also reviewing interviews contemporaneously to ensure the structured approach desired was being undertaken in both HNC centres included as case-studies.

I was aware of the perceived and experienced power-imbalances as a researcher, from a clinical background, with patient interviewees, which was almost reversed in some interviews with some clinician interviews where I was the “young trainee”. I ensured where possible to build rapport to break down those imbalances, an important factor in successful qualitative interviews (Dicicco-Bloom and Crabtree, 2006), by sharing my personal reasons for undertaking this research but without sharing the exact nature of my wife’s history. While the information on my personal experiences was not explicitly stated before each interview, it was not kept secret if probed by participants.

6.5 Conclusions and Recommendations

6.5.1 Conclusions

This thesis has supported the finding that advanced stage diagnosis of HNC is a substantial public health challenge, which is faced by countries across the world. Substantial because the proportion/burden of advanced stage HNC remains high, but also because the impacts of advanced stage HNC are substantial on individuals, their families, and populations – including more and complexity of treatment and lower prognosis poorer outcomes. The converse is also true the impacts can be reduced if these cancers are detected earlier. With this thesis showing that 59% of HNCs in the UK diagnosed at advanced stages there is scope for vast improvement. The thesis also identified important health system factors that could inform implementation of interventions and health system changes to reduce advanced stage HNC diagnoses.

Within country socioeconomic inequalities were noted in the distribution of advanced stage diagnosis across the population. Ensuring that stage data are included in routine cancer registry collections and reports can help monitor and intervene in reducing the burden of advanced stage HNC.

Through the systems benchmarking study, and which individual health systems factors were found to be associated a lower proportion of advanced stage HNC at the centre level, specifically referral triaging systems, monitoring waiting times from the point of referral to diagnosis, and having systems that exist within fully publicly financed models, consideration can now be given as to how HNC systems can be shaped towards earlier diagnosis of HNCs, although more research in this area is required to build on these exploratory and measure findings. Improving the use of routinely collected data, and collecting data readily available from clinical pathways, may strengthen future research and improve decision making and pathway development in HNC systems.

Through the qualitative analysis on HNC patient and care provider experiences of pathways to diagnosis, the themes of patient and health professional awareness of HNC and how to navigate HNC diagnostic pathways, and the disconnect between care teams, has powerfully been shown to have a role in diagnostic stage. The findings from this thesis reflect the need for clear pathways and well-defined roles in HNC systems so that systems can account where possible for the complex nature of HNC diagnosis. Additionally, these results suggest that the challenge of preventing advanced stage diagnosis of HNC will not be met without addressing the underlying social and economic inequalities that exist in society.

6.5.2 Recommendations

This section proposes recommendations for future practice and policy from a health systems perspective and suggests avenues for future research in HNC and health systems factors. Additionally, research areas that are being undertaken as part of the wider HEADSpAcE Consortium are described briefly.

6.5.2.1 Health System and Policy Recommendations

Cancer registry data are essential for governments, health bodies, and researchers to understand the evolving epidemiology of cancers nationally and at regional levels (Bouchardy et al., 2014). As at the time of this thesis, stage at diagnosis is not routinely reported in all cancer registries in the UK despite the reduction of advanced stage cancers being a priority for the UK government and associated cancer bodies (McCormack and Aggarwal, 2021). The results of this thesis have shown the utility in including stage data in cancer registries for disease monitoring and planning/improving health services and therefore it would be recommended to improve the completeness of stage at diagnosis data for HNCs and include disease stage in routine cancer monitoring reports, something that has since been implemented by the National Cancer Registration and Analysis Service of England (NCRAS, 2021) where stage is included in the annual reporting and public database for HNC. This recommendation could also be extended in time to cancer registries across the world through GLOBOCAN (which currently captures data on incidence and mortality) although it should be noted that not all countries have population level Cancer Registries with some still relying on hospital-based registries and therefore on-going more general efforts that support the development of Cancer Registries is also recommended (Siddiqui and Zafar, 2018).

With regards to local/regional HNC systems, the thesis research has shown the potential benefit of high-quality referral monitoring and triage systems. While these are in place already in some HNC centres internationally, it would be prudent to consider adopting and adapting processes like these into all HNC systems with a view of improving the efficiency of the HNC diagnostic pathway with a focus on easing communication between clinical teams. Ultimately, the reporting on stage at diagnosis of patients within HNC systems should be routine and included as a performance indicator as a measure of the pre-specialist centre performance.

The complexity of HNC diagnosis has been shown through two studies in this thesis looking at the pathways to diagnosis and how people interact with these pathways. A key finding from this thesis is the heterogeneity in how people initially access and experience the early steps of the diagnostic pathway. From these findings, a prudent consideration would be to formalise the pathways to HNC for wider health professionals including dentists and pharmacists. It has been shown that dentists are successful in referring early stage HNC through thorough analysis of cancer registry data in England, with referrals from dentists on the 2WW pathway are more likely to result on diagnosis of stage I or II disease than those from other primary care referral routes (Deane et al., 2022). Moreover, there is evidence from qualitative studies in the UK to suggest that pharmacists may be an accessible entry point for people with suspicious symptoms to be referred for onward investigation for HNC with appropriately designed schemes (Bissett et al., 2023, Sturrock et al., 2023).

Consideration should be made to empowering primary care teams, including widening of access to special investigations to primary care teams. Direct access to investigations for colorectal cancer has been shown in small, loco-regional studies to reduce time to diagnosis in England (Orchard et al., 2021) and primary care doctors have also been shown to have comparable levels of accuracy in appropriate investigation requests as specialist clinicians (Smith et al., 2018). An insightful review of changes to health systems along these lines has shown that carefully planned changes aiming to reduce delays in diagnosis offered some modest reduction in time but no effect on stage has been measured (Venchiarutti et al., 2023). Any potential changes to health systems should be comprehensively planned with focus on resource availability and equality of access.

An educational programme for primary care professionals, led by HNC specialists and patients, where the reasons for referral of patients with suspicious symptoms and clear training on the local referral pathway would be something to consider. This thesis has additionally shown the importance of family and friends as a positive force for encouraging early diagnosis of HNC. Consideration should be made for future public health campaigns and interventions to target the role of advocating for friends and family in addition to self-responsibility for health. With regards to HNC pathways, clear guidance and structures should be provided to aid clinicians in the tasks of HNC diagnosis. Ensuring clarity in referral criteria, where to refer, how diagnosis is undertaken, and what process are required for diagnosis across national/regional areas is to be encouraged to ensure homogeneity in patient care and reduction of health inequalities.

In Scotland, very recently, the Optimal Head and Neck Cancer Diagnostic Pathway has been developed (CFSD, 2023). Some (although not all) of the thesis findings have fed into this process including setting out a clear pathway (guidance) for referral from primary care to secondary care for diagnosis, with some elements of the process monitoring (particularly around waiting times), and a triage system for suspected lesions. In some ways this is not a big change from the previous system although having this is a standardised pathway for the whole of (“Once for”) Scotland – rather than multiple regional variations of pathways to diagnosis – is a good next step. Some of the radical proposals such as community-based diagnostics (rather than centralised) may take more time and may need further evidence or perhaps piloting. Some of the more routine monitoring of stage of diagnosis and source of referral might be more readily implementable in the short to medium term.

The findings from this thesis provide a systems context to the challenge of advanced stage HNC. Results from Chapter Five in particular, refer to the wider social organisational context of HNC diagnosis and add to the need to preserve and enhance access to primary care medical and dental services (Aminu et al., 2023, Evans et al., 2023, Iacobucci, 2023). When health systems experience shock, it is often those in the most challenging socioeconomic circumstances that suffer most (Watt et al., 2022). Policy makers should take a systems approach and employ a local health system contextualised candidacy approach to enabling access to primary care and specialist care services (Sinnott et al., 2024).

6.5.2.2 Research Recommendations

As part of the wider HEADSpAcE Consortium, the findings from this thesis will be triangulated with additional analyses of the HEADSpAcE new international prospective HNC cohort - to better understand the factors involved in advanced stage diagnosis of HNC and inform further development of recommendations to improve routes/pathways to diagnosis. A natural next step is to further analyse elements of the cohort dataset that are novel in the literature of HNC, particularly patient perceptions and attitudes to health and cancer, which will provide a thoroughly interesting insight into how HNC engaged with health services up to their diagnosis and the motivations behind their decisions. The ultimate aim of HEADSpAcE is to create a series of recommendations in the form of an internationally applicable guidance tool to reduce advanced stage HNC diagnosis, the production of which should be a priority for the near future. However, care must be taken to assure that any guidance tool is of high quality and clinical utility. An analysis of international treatment guidelines for HNC has already been produced by the HEADSpAcE consortium (Arboleda et al., 2023), with a similar review of international referral and diagnostic guidelines a necessary future study.

There is an emerging body of evidence into health systems and cancer diagnosis/outcomes through benchmarking research; largely led by the ICBP where metrics and clinical practice for different cancer groups, although not HNC, were analysed to assess variation in survival and the differing pathways to diagnosis across the health systems of international countries, however only HICs have been included in analyses to date (Weller et al., 2016, Weller et al., 2018, Pedersen et al., 2018, Nicholson et al., 2018, Torring et al., 2019, Vedsted et al., 2022). These efforts are to be lauded given the logistic difficulties and methodological challenges they necessitate; however, they do not include LMICs nor HNC. In a consensus statement from global cancer researchers, health systems research and strengthening cancer registries have been included as priorities for cancer research in LMICs to reduce the burden of advanced stage cancer (Pramesh et al., 2022). This study is the first to explore health systems factors in HNC across international health systems and further efforts to utilise this consortium, through research in other parts of the HNC care pathway, should be undertaken. This could be further expanded to include more HNC centres from diverse systems from LMICs and especially from South-East Asia where the burden of HNC is greatest (Bray et al., 2024).

The results of Chapter Five pertaining to HNC awareness and patient agency to navigate pathways imply the need for further research in this area. Further studies on patient experience of accessing HNC services from primary care through to specialist care should be considered, with the potential framework of candidacy as a feature which is unexplored in this domain but has been successfully employed in research into patient access to general practitioners (Sinnott et al., 2024). Exploratory studies aiming to develop patient navigation interventions should also be conducted, with care taken to ensure local/regional systems and sociocultural norms and behaviours are considered as part of these. Results from this thesis could help inform a framework for patient navigation intervention, something that has the potential to aid the implementation, evaluation, and sustainability of such interventions in LMICs where interventions to date have not had long-lasting effects (Dalton et al., 2019). More qualitative work with cancer policy leads at the regional and national level would also be important to understand system challenges – barriers and facilitators – from their perspective (including but not limited to links to wider systems, priorities, financial, along with processes to make/implement system change).

The constant theme of inequalities through HNC literature and this thesis show the distinctive determining relationship between poverty (socioeconomics) and HNC – impacting across the cancer continuum from access to services, diagnosis, and through to treatment/care and cancer outcomes. As a research community, we must aim to better understand the mechanisms behind this phenomenon and be ambitious in our determination to find solutions with multimodality approaches from investigating factors at the micro-level (e.g., genetics, tumour environment, immunological patters, and microbiome); through to the patient-level (e.g., behaviours, health attitudes, life circumstances experiences); and to the macro-level (e.g. health systems, cultural, societal structures, poverty, and inequalities). For such a wicked intransigent problem as inequalities in head and neck cancer, there is a real need to embrace the complex nature of interactions between different factors operating at multiple levels, to reduce and tackle these inequalities and to ultimately prevent this devastating disease.

6.5.3 Final Remarks

At the beginning of this PhD, I believed myself to be in a prime position to undertake this research and was highly motivated to do it. In truth, there was a huge learning curve associated with managing these experiences and motivations. In my current and future career it is my ambition to contribute to preventing and reducing the heavy burden of HNC in both the population and in individuals and their families. The combination of my professional understandings, personal experiences and the professional learning from undertaking this research has hopefully placed me in a stronger position for progress in this field.

In this thesis the term “advanced stage” has been purposively adopted to describe locally advanced or regionally spread (stage III and IV) head and neck cancer. At the outset of this PhD (and in the HEADSpAcE Consortium – where this PhD originated and is embedded) the term “late-stage” HNC was the commonly used description. An early conversation with a clinical colleague shed light on their reluctance to use this term in practice. The clinician reported that when patients hear it, the pejorative nature of the word “late” can provoke, understandably, very strong emotions and feelings of patients blaming themselves for the delay. In the literature, “late-stage” was and is still the predominantly used term to describe stage III/IV HNC - and even can explicitly blame patients for this rather than take a health system approach (Gómez et al., 2010). Moreover, the same literature still has a heavy focus on “delay” and is loaded with connotations of deliberate inaction, especially when termed together with personal identifiers such as “patient” and “professional” – although there is a much stronger focus in the literature on “patients”. Given the equivocal nature of the relationship between time and stage in the current literature (Goy et al., 2009, Schutte et al., 2020a), the direct terms of “patient delay” or “professional delay” and “late-stage” has been avoided in this thesis.

The approach of the thesis has been consistently to contextualise the intervals of diagnosis through a health systems lens or perspective (including pre-diagnostic and diagnostic intervals). The findings of this thesis, in addition to the literature reviewed, show that to attribute “blame” on any individual, or any one part of the diagnostic pathway, is to misunderstand the true dynamic and complex nature of HNC diagnosis.

In addition to supporting the change of language around advanced stage head and neck cancer, it is a hope that the contribution of this thesis is to shine a light on the importance of the whole health system on head and neck cancer diagnosis. It is how people (patients), clinicians and other stakeholders interact with and within the health system that is essential. Addressing the public health challenge of high levels of advanced stage head and neck cancer will only come with deeper understanding of and improvements to the health system concerned with the pathway and process to diagnosis.

Appendices

Appendix 1-1: Literature Search Strategy

1) Head and Neck Cancer OR Oral Cancer OR Larynx Cancer OR Laryngeal OR Oropharyngeal Cancer Or Oropharynx Cancer AND (“diagnostic pathway*” OR “Patient Journey*” OR “Patient Trajectory*” OR “system level factors*” OR “healthcare system*” OR “System factors*” OR “delayed diagnosis*” OR “diagnostic delay*” OR “diagnostic system*” OR “cancer system*” OR “Patient Knowledge*” OR “Patient Access*” OR “Service Availability*” OR “2ww” OR “Two week wait*” OR “Waiting times*”) in Title or Abstract

2) Healthcare Research AND ("systems science*" OR "Systems Engineering*" OR "Systems Methods*") in Title or Abstract

3) Purposive grey literature searches on documents/reports pertaining to HNC

Databases searched: Scopus, Pubmed, Web of Science

1122 results found in total

Duplicates removed: leaving 847

After reviewing titles/abstracts 328 full texts were read were relevant articles included in Chapter One.

Appendix 3-1: Supplementary Table

		Numbers of Cases by Stage						ASR by Stage			
		I	II	III	IV	Unknown	I	II	III	IV	Unknown
England											
Subsite all years available	**OCC**	4511	1904	1200	5782	6509	N/A	N/A	N/A	N/A	N/A
	OPC	1298	1554	2914	13690	7660	N/A	N/A	N/A	N/A	N/A
	Larynx	4144	2068	2100	3173	6281	N/A	N/A	N/A	N/A	N/A
	Other	9313	2845	3181	7150	24515	N/A	N/A	N/A	N/A	N/A
	All HNC	19266	8371	9395	29795	45010	N/A	N/A	N/A	N/A	N/A
Year	**2008**	193	103	114	272	6979	0.4	0.2	0.2	0.5	10.7
	2009	211	116	107	331	7368	0.5	0.3	0.2	0.7	12.5
	2010	308	162	184	450	7614	0.6	0.3	0.4	1.0	11.2
	2011	841	402	395	1267	6131	1.7	0.9	0.8	2.7	10.4
	2012	1233	585	722	2068	5065	2.5	1.2	1.5	4.3	9.2
	2013	1784	906	1007	3160	3435	3.5	1.8	2.1	6.4	6.2
	2014	2277	1034	1159	3736	2212	4.5	2.1	2.3	7.5	3.9
	2015	2732	1195	1432	4368	1682	5.3	2.4	2.8	8.6	2.9
	2016	2853	1247	1417	4796	1574	5.4	2.4	2.7	9.3	2.7
	2017	3133	1298	1463	4834	1425	5.9	2.5	2.8	9.3	2.4

	2018	3701	1323	1395	4513	1525	6.9	2.5	2.7	8.6	2.5
Northern Ireland											
Subsite all years available	**OCC**	181	79	58	327	156	N/A	N/A	N/A	N/A	N/A
	OPC	45	69	155	502	78	N/A	N/A	N/A	N/A	N/A
	Larynx	241	161	145	179	81	N/A	N/A	N/A	N/A	N/A
	Other	46	70	72	268	125	N/A	N/A	N/A	N/A	N/A
	All HNC	513	379	430	1276	440	N/A	N/A	N/A	N/A	N/A
Year	**2009**	16	17	15	82	141	1.2	1.2	1.0	5.6	9.6
	2010	29	27	23	71	103	1.9	1.8	1.5	5.0	6.9
	2011	41	44	43	96	64	2.8	2.9	2.8	6.4	4.3
	2012	59	43	40	142	20	3.8	2.8	2.6	9.2	1.3
	2013	52	46	57	120	23	3.3	2.9	3.6	7.7	1.5
	2014	64	39	43	125	17	4.1	2.5	2.7	8.0	1.2
	2015	61	44	51	171	16	3.8	2.8	3.1	10.6	1.1
	2016	51	41	50	136	18	3.1	2.5	3.0	8.4	1.1
	2017	70	43	46	168	9	4.3	2.6	2.8	10.1	0.6
	2018	70	35	62	165	29	4.2	2.0	3.6	9.8	1.7
Scotland											

Subsite all years available	**OCC**	271	121	110	410	88	1.7	0.8	0.7	2.6	0.6
	OPC	83	86	182	523	276	0.5	0.5	1.1	3.3	1.7
	Larynx	203	128	169	182	161	1.3	0.8	1.1	1.2	1.1
	Other	57	67	76	271	195	0.4	0.4	0.5	1.8	1.3
	All HNC	614	402	537	1386	720	3.9	2.6	3.4	8.9	4.6
Year	**2016**	207	132	137	492	211	4.1	2.5	2.7	9.5	4.1
	2017	205	137	167	478	216	3.9	2.6	3.2	9.2	4.2
	2018	202	133	233	416	293	3.8	2.5	4.3	7.9	5.6
Sex	**Males**	403	289	389	1006	496	5.4	3.8	5.1	13.3	6.7
	Females	211	113	148	380	224	2.5	1.3	1.7	4.4	2.6
SIMD Category	**SIMD1**	155	114	165	430	226	5.6	4.1	5.9	15.4	8.2
	SIMD2	125	102	120	319	152	4.0	3.3	3.9	10.4	5.1
	SIMD3	145	68	99	269	148	4.4	2.1	3.0	8.1	4.5
	SIMD4	107	68	80	209	114	3.2	2.0	2.4	6.4	3.4
	SIMD5	82	50	73	159	80	2.6	1.6	2.3	5.2	2.5
Age	**0 to 4**	0	0	0	0	1	0.0	0.0	0.0	0.0	0.1
	5 to 9	0	0	0	1	0	0.0	0.0	0.0	0.1	0.0
	10 to 14	0	0	1	0	1	0.0	0.0	0.1	0.0	0.1
	15 to 19	0	1	0	1	0	0.0	0.1	0.0	0.1	0.0

	20 to 24	4	0	1	2	2	0.4	0.0	0.1	0.2	0.2
	25 to 29	2	4	1	2	0	0.2	0.4	0.1	0.2	0.0
	30 to 34	5	1	2	6	8	0.5	0.1	0.2	0.6	0.7
	35 to 39	10	2	4	23	3	1.0	0.2	0.4	2.3	0.3
	40 to 44	13	8	17	35	16	1.3	0.8	1.7	3.6	1.6
	45 to 49	31	23	27	57	43	2.7	2.0	2.3	4.9	3.7
	50 to 54	52	37	64	136	60	4.3	3.0	5.3	11.2	4.9
	55 to 59	75	54	79	193	78	6.6	4.8	7.0	17.0	6.9
	60 to 64	102	58	82	228	125	10.3	5.9	8.3	23.1	12.7
	65 to 69	95	73	97	232	115	10.3	7.9	10.5	25.1	12.5
	70 to 74	78	57	69	180	98	10.1	7.4	9.0	23.4	12.7
	75 to 79	78	43	51	136	64	13.8	7.6	9.0	24.0	11.3
	80 to 84	45	26	23	90	64	10.9	6.3	5.5	21.7	15.4
	85 to 89	19	9	14	42	23	7.9	3.8	5.8	17.5	9.6
	Over 90	5	6	5	22	19	4.0	4.8	4.0	17.6	15.2
Wales											
Subsite all years available	**OCC + OPC**	424	280	153	1210	410	N/A	N/A	N/A	N/A	N/A
	Larynx	329	185	244	296	114	N/A	N/A	N/A	N/A	N/A
Year	**All HNC**	858	623	601	2567	821	N/A	N/A	N/A	N/A	N/A

	2011	98	54	69	242	129	N/A	N/A	N/A	N/A	N/A
	2012	109	85	48	280	102	N/A	N/A	N/A	N/A	N/A
	2013	85	90	46	311	142	N/A	N/A	N/A	N/A	N/A
	2014	85	78	74	324	105	N/A	N/A	N/A	N/A	N/A
	2015	97	85	79	334	110	N/A	N/A	N/A	N/A	N/A
	2016	124	79	85	363	63	N/A	N/A	N/A	N/A	N/A
	2017	133	71	100	374	73	N/A	N/A	N/A	N/A	N/A
Sex	**2018**	127	81	100	339	97	N/A	N/A	N/A	N/A	N/A
	Males	573	418	447	1895	550	N/A	N/A	N/A	N/A	N/A
	Females	285	205	154	672	271	N/A	N/A	N/A	N/A	N/A

Supplementary Table 3-1: Counts and Age-Standardised Rates (ASR) for New HNCs by Stage at Diagnosis by variables available.

Appendix 4-1: Health Systems Questionnaire

Health Systems Questionnaire

Thank you for your participation in the HEADSpAcE study. This questionnaire aims to provide an understanding of how the Head and Neck Cancer (HNC) healthcare systems function up to the point of **pre-treatment diagnosis** in each participating HEADSpAcE centre.

Please complete each section with the best information you can. You may require input from different people within your respective organisational structures to fully complete this questionnaire. If the answer to a question is not found in routine data (or otherwise readily accessible) then please provide best estimate (indicating that this is an estimate), or if you cannot estimate or do not have this information please indicate that you not have this information. There is a mixture of numerical and narrative questions.

We are interested in the description of the healthcare services until the end of 2019 (i.e. prior to the Covid-19 pandemic) but do have a question at the end of the document related to Covid-19.

If you have any questions, please contact the research team in Glasgow, UK through the details below:

Grant Creaney
University of Glasgow
Grant.creaney@glasgow.ac.uk
+xxxxxxxxxxxxx

HEADSpAcE Centre: [Insert Location]
PI: [Insert Name]

1 Description of Local Head and Neck Cancer System

Could you please describe your “Normal” Head and Neck Cancer system in a paragraph? (Please include whether it is a publicly-funded service/ mixed public and private for example)

…

2 Referral to Diagnosis Process

For the purpose of this research, we will be using the term “Diagnosis” to represent the point at which a patient receives their “Definitive Diagnosis” following initial consultation and investigation but prior to commencement of treatment. “Referral” represents the point at which the primary practitioner (Dental OR medical) makes contact through any means with the specialist care team. Unless specified, the questions relate to the processes regarding referrals of suspected cancers

2.1 What guidelines for referral and diagnosis of HNC do you operate under if any? (can you please append these guidelines)

…

2.2 Do you have any performance indicators or regularly audited items related to diagnosis of Head and Neck Cancer? If there are quality/ performance indicators for the head and neck service, provide the data available for the past 3years: (for example, waiting time from referral to appointment?)

…

2.3 What cancers do you include in your Head and Neck Cancer service (Please use the WHO ICD-10 Site codes if possible)

…

2.4 How do you define a diagnosis as "late stage" in your system?

…

2.5: Complete the following table to the best of your ability using data available to you, indicating the source of your data (if providing answers based on an estimate, please indicate using an "E" in the relevant boxes):

Year Cases		2019
Total Numbers of New Head and Neck Cancer Cases		
Number of cases per Subsite	Oral	
	Oropharynx	
	Larynx	
	Other	

2.6:Complete the following table to the best of your ability using data available to you, indicating the source of your data (if providing answers based on an estimate, please indicate using an "E" in the relevant boxes):

		Year	2019
Source of Referral (%)	General Medical Practitioner	Oral	
		Oropharyngeal	
		Laryngeal	
		Other	
		TOTAL (All HNCs)	
	Dental Practitioner	Oral	
		Oropharyngeal	
		Laryngeal	
		Other	
		TOTAL (All HNCs)	
	Emergency Department	Oral	
		Oropharyngeal	
		Laryngeal	
		Other	
		TOTAL (All HNCs)	
	Other Medical/Surgical Specialty	Oral	
		Oropharyngeal	
		Laryngeal	
		Other	
		TOTAL (All HNCs)	
	Other	Oral	
		Oropharyngeal	
		Laryngeal	
		Other	
		TOTAL (All HNCs)	

2.7: If you receive referrals through the "other" category, what are these routes?

…

2.8: Complete the following table to the best of your ability using data available to you, indicating the source of your data (if providing answers based on an estimate, please indicate using an “E” in the relevant boxes):

	Year	2019
Number of Cases Diagnosed with *Early Stage Disease*	Other	
	Laryngeal	
	Oropharyngeal	
	Oral	
	TOTAL (All HNCs)	
Number of Cases Diagnosed with Late Stage Disease	Other	
	Laryngeal	
	Oropharyngeal	
	Oral	
	TOTAL (All HNCs)	

2.9 Do you have thresholds/targets for the following waiting times? If yes, can you please specify what they are in days/weeks):
(a) Time from referral to first appointment? … days/weeks
(b) Time from first appointment to diagnosis? … days/weeks
(c) Time from referral to diagnosis? … days/weeks

2.10 For 2019
(a) Do you record the time from referral to first appointment? Yes/No
(b) If so, what is the median time in days? … days
(c) What is the shortest time recorded in days? … days
(d) What is the longest in the most recent calendar year in days? … days

2.11 For 2019
(a)Do you record the time from first appointment to diagnosis? Yes/No
(b) If so, what is the median time in days? … days
(c) What is the shortest time in days? … days
(d) What is the longest time in days? … days

2.12 How is pre-treatment diagnosis confirmed within your system?

…

2.13 Do you have waiting time targets/thresholds for receiving reports from the following specialties and if so, what are they (In days)?

(a) Pathology: Yes/No … days
(b) Radiology: Yes/No … days
(c) Other (Please name the service): … days

2.14 (a) Do you operate a "One-stop" clinic for suspected cancer cases? Yes/No

(b) If yes, can you please describe what happens at these clinics?

…

2.15 Can you provide us with the median wait you have in receiving results from the following specialties, indicating the source of your data (if providing answers based on an estimate, please indicate using an "E" in the relevant boxes):

Report Format Specialty	Formal Report (i.e., written and placed within patient's record)	"Informal" Report (i.e. phone call from reporting clinician)
Pathology		
P 16 (If not included in pathology)		
HPV DNA/RNA		
Radiology		
Haematology/Biochemistry Lab		

Source of data (i.e., audit/quality performance indicator): …

………
………..

2 Workforce

2.1 How are your staff structured? If this this data that is not readily available, it is acceptable to complete the gross numbers and indicate any reasons for data not being available.

(a) How many of the following staff in each category work in your service and, where applicable, **to what discipline to they belong** (For example; Oral and Maxillofacial; Ear, Nose and Throat; Plastic Surgery; Oncology; Radiology; Pathology; Restorative Dentistry, etc)?

	Gross Number	Whole-Time Equivalent
Senior Clinical Staff		
Mid-level Clinical Staff		
Junior Staff		
Healthcare Support Staff		
Allied Health Professionals		
Nursing Staff		
Administrative Staff		
Managerial Staff		

(b) Do you have Head and Neck Specialists in the following specialties?

(i) Pathology: Yes/No
(ii) Radiology?: Yes/No

………..

3 Healthcare System Area

3.1 What is the geographical area serviced by your HNC team? (If you have a map/picture depicting this, could you please attach this in addition to answering the question)

…

3.2 (a) What is the ratio of primary care dentists per population in your serviced area according to your most up to date levels of information?

…

(b) When was this recorded?

…

3.3 (a) What is the ratio of primary care doctors per population in your serviced area according to your most up to date levels of information?

…

(b) When was this recorded?

…

3.4 What is the population of the area that you service according to most recent survey/estimates?

…

3.5 What level of centralisation does your system exhibit (i.e. to what level is your serviced directed towards one central site)?

…

3.6 (a) Are Head and Neck Cancer operations/surgeries performed in one centralised site? Y/N

(b) If so, where is this? …

(c) If not, at how many sites are surgeries undertaken and where are these located? …

3.7 (a) Are radiotherapy and/or chemotherapy treatments undertaken in one centralised site? Y/N

(b) If so where is this? …

(c) If not, at how many sites is radiotherapy and chemotherapy undertaken and where are these located? …

3.8 (a) Are other treatment options available in your service such as immunotherapy? Y/N

(b) If so, what are they? …

(c) Where are they undertaken? …

………

4 Multi-Disciplinary Team

4.1 (a) Does your service operate a Multi-Disciplinary Team (MDT) meeting? Yes/No

(b) If so, how many MDTs exist? …
(c) How often do they meet?...
(d) What specialties are part of the MDT? …

4.2 Do you routinely use teleconferencing/video as part of the MDT process? Yes/No

4.3 (a) Do you have any formal governance for your MDTs? Yes/No

(b) If yes, could you please describe that here or attach any documents used to govern MDT?

……….

5 Referrals:

5.1 What are the different referral categories in your system? (i.e. Routine/Urgent/Urgent Suspicion of Cancer)

…

5.2 How many of your newly diagnosed cases of HNC are referred with the following urgencies, indicating the source of your data (if providing answers based on an estimate, please indicate using an "E" in the relevant boxes) you may change the referral categories to match those used in your service:

Referral Category	Site	2019	
		Number of cases	Proportion of total cases
Routine	Oral		
	Oropharyngeal		
	Laryngeal		
	Other		
Urgent	Oral		
	Oropharyngeal		
	Laryngeal		
	Other		
Urgent-Suspected Cancer	Oral		
	Oropharyngeal		
	Laryngeal		
	Other		
Presented Without Referral	Oral		
	Oropharyngeal		
	Laryngeal		
	Other		

5.3 What proportion of patients referred urgently for suspected cancer go on to develop a HNC cancer?

Site	Proportion of Urgent Suspicion of Cancer referrals (Or local equivalent) that are diagnosed with cancer (%):
Oral	
Oropharyngeal	
Laryngeal	
Other	

5.4 Is your referral system electronic (facilitated using a computer system)?

…

5.5 Do you still receive referrals by:

- **(a) Email? …**
- **(b) Mail?...**
- **(c) Telephone?...**

…

5.6 How are referrals triaged in your department?

…

5.7 How do you manage patients referred through each respective category that you have mentioned? (Example categories can be replaced with respective categories as necessary)

- **(a) Routine Referral:**
  - (i) How are patients contacted? …
  - (ii) What is undertaken at the patient's first appointment? …
  - (iii) Which category of professional is the patient most likely to be seen by? …
  - (iv) Are short-notice appointments kept free for referrals of this category? …
- **(a) Urgent Referral:**
  - (i) How are patients contacted? …
  - (ii) What is undertaken at the patient's first appointment? …
  - (iii) Which category of professional is the patient most likely to be seen by? …
  - (iv) Are short-notice appointments kept free for referrals of this category? …
- **(c) Urgent Suspicion of Cancer:**
  - (i) How are patients contacted? …
  - (ii) What is undertaken at the patient's first appointment? …
  - (iii) Which category of professional is the patient most likely to be seen by? …
  - (iv) Are short-notice appointments kept free for referrals of this category? …

……

6 Communication

6.1 What IT/ computer systems are used in the process of gaining a diagnosis for a patient and what is their function? Please describe:

…

6.2 How do you normally communicate with primary care if required? Please describe:

…

6.3 Are hospital staff able to access primary care records/test result undertaken in primary care? Please describe:

…

…….

7 Patient Finances

7.1 (a) Is medical primary care provision publicly funded in your area for patient? Y/N/Partly

(b) Is it free for all patients? Y/N

(c) If not, for whom is medical primary care free of charge? …

7.2 (a) Are dental examinations publicly funded for the entire population in your area? Y/N/Partly

(b) Are they free for all patients? Y/N

(c) If not, for whom are dental examinations free of charge? …

7.3 (a) Is HNC treatment publicly funded in your area? Y/N/Partly

(b) Is it free for all patients? Y/N

(c) If not, for whom is HNC treatment free of charge? …

7.4 Are there any direct patient costs associated with the process of receiving a diagnosis of Head and Neck Cancer (For example, medical fees, dental fees)? Please describe:

…

7.5 Are there any private healthcare providers/parallel systems available that depend on a patient's ability to pay for treatment? Please describe:

…

……

……….

8 Final Comments

8.1 Could you please describe, as best as you can, the impact that the Covid-19 pandemic is having to your Head and Neck Cancer system and how it is affecting the process to the point of diagnosis? Have you had to adopt any specific measures/re-organise as a result of the pandemic?

...

8.2 Is there anything that we haven't covered that you think it is important to inform us of?

…

8.3 If there are any relevant documents that you would like to attach you can do so here or email them to the address on page 1:

…

Thank you sincerely for completing this document.

………
……….

Glossary of Terms:

Area: The physical geographic locations/regions for which your service is responsible for Head and Neck Cancer patient care and/or treatment.
Publicly funded: Provided by the local or central government/state
Multi-Disciplinary Team: Designated team of individuals from different specialties/professional types tasked with diagnosing and treatment planning patient care.
Managerial: Non-clinical healthcare staff tasked with oversight of system.
Social Care: a term that generally describes all forms of personal ***care*** and other practical assistance for those in need
Welfare Support: a type of government support for the citizens of that society. It is usually intended to ensure that people can meet their basic human needs such as food and shelter.
Senior Clinical Staff: Top level medical/surgical/dental staff
Mid-level Clinical Staff: Medical/surgical/dental staff neither entry level or top level
Junior Staff: Entry level medical/surgical/dental staff
Allied Health Professionals: Please see the following link for a list: https://www.england.nhs.uk/ahp/role/
Healthcare Support Staff: A member of staff who has the awareness and ability to address the basic care needs of individual patients/ clients under the direction and supervision of healthcare professionals but is **not** medically, dentally, surgically or nursing qualified.
"One-Stop" Clinic: A clinic where the initial examination and any appropriate investigative procedures or imaging are taken at a single visit.
Formal Report: Formal results posted onto/placed in patient's medical record
Informal Report: Contact from the Radiologist/Pathologist through face-to-face contact/telephone/email but not in formalised health-record form
Short-Term Contract: Employed for a time period not more than 1 year
Long-Term Contract: Employed for a time period not defined/no fixed term.

Appendix 5-1: Interview Topic Guides

HEADSpAcE

University of Glasgow

NHS Greater Glasgow and Clyde

Healthcare Systems Qualitative Interview Guide: HNC Healthcare System Worker Perspective

Topic	Main Question	Follow Up Questions
Role in Head and Neck Cancer Pathway	Can you first describe your role within the Head and Neck cancer pathway?	*What was your reason for coming into this field?* *How long have you been involved in the care of Head and Neck Cancer patients?* *What are your professional duties with regards to Head and Neck Cancer Patients?*
Patient pathway to hospital service	What is your first contact with a potential Head and Neck Cancer patient?	*Are there any common themes to what patients say or how they behave at these initial appointments, in your experience?* *How many suspected head and neck cancers would you expect to see in an average week?*
Communication between primary care and secondary care	What do you think about the way primary care practitioners and hospitals communicate with each other?	*What works well?* *Where could improvement be made?* *What stops it from being more efficient?*
Communication between teams in hospital care	What are your thoughts on communication between the different teams in the hospitals?	*What works well?* *Where could improvement be made?* *What stops it from being more efficient?* *Do you note any advantages or disadvantages to having purely consultant-to-consultant discussions about head and neck cancer patients?* *What role would a junior clinician play in the communication pathway?*
MDT	Do you regularly attend an MDT?	*Who is usually there?* *Where is it held and how often?* *What is your role there?* *What do you think works well about the process?* *Is there anything that could be made better about the MDT?*

Physical facilities	Can you please tell me about the physical environment in which you work?	*Is there anything about this that you feel inhibits your ability to see patients efficiently?*
Time	What are your feelings about the time taken to get a diagnosis of Head and Neck Cancer in your department?	*Are there any notable points of delay?* *What do you think causes this delay?* *What could be done, in your opinion, to resolve this?* *Is there anything that you feel works particularly well?*
Support	How would you describe the support you receive from your non-clinical/managerial colleagues?	*Is there anything about this relationship that could be improved to allow for a more efficient diagnostic pathway?*
Staffing levels	Do you feel that you have an adequately staffed team to provide the level of care you wish for these patients?	*Are there any roles which you feel could be better utilised or more abundant to improve the diagnostic pathway?*
Barriers	What do you think are the potential barriers to receiving a diagnosis of early stage disease?	*Why do you think that we are still seeing such a high proportion of late-stage diagnoses of Head and Neck Cancer?*
Communication with patients	In what ways do you have direct communication with patients?	*What do you find works well?* *Is there anything that does not yet happen in this regard but which you would like to do?* *Who would you say has the most and best communication with patients from your team?*
Improvements/ Recommendations	Are there any areas in the diagnostic pathway of Head and Neck cancer that you feel could be improved?	*Is there anything that you would like to see implemented to improve the resilience of the pathway?*
Covid-19	What has been the impact of Covid-19 on the Head and Neck Cancer system?	*What concerns, if any, do you have about the system in the coming years as a result of this?* *Do you foresee any changes to the system's structure?*

Healthcare Systems Qualitative Interview Guide: Primary Care Worker Perspective

Topic	Main Question	Probes
Role in Head and Neck Cancer Pathway	Can you first describe your role within the Head and Neck cancer pathway?	*What was your reason for coming into this field?* *How long have you been involved in the care of Head and Neck Cancer patients?* *How would you describe your professional duties with regards to Head and Neck Cancer Patients?*
Patient pathway to hospital service	What is your first contact with a potential Head and Neck Cancer patient?	*Are there any common themes to what patients say or how they behave at these initial appointments, in your experience?* *How many suspected head and neck cancers would you expect to see in an average week?*
Communication between primary care and secondary care	What do you think about the way primary care practitioners and hospitals communicate with each other?	*What works well?* *Where could improvement be made?* *What stops it from being more efficient?* *Do you feel that you have adequate communication from secondary care once you have sent a referral?*

Communication between different primary care teams	What are your thoughts about how different primary care practitioners communicate with each other?	*What works well?* *Where could improvement be made?* *What stops it from being more efficient?* *For example: dentists and general practitioners?*
Communicating with patients	How do you find consultations with patients where the possibility of a cancer arises?	*What challenges arise in these situations?* *Does the dynamic change if there are family members/friends with the patient?* *How comfortable are you in broaching the subject of cancer?* *Are you aware of any specific tools or training with regards to these consultations?*
Physical facilities	Can you please tell me about the physical environment in which you work?	*Is there anything about this that you feel inhibits your ability to see patients efficiently with regards to Head and Neck Cancers?*
Time	What are your feelings about the time taken to get a diagnosis of Head and Neck Cancer in your area?	*Are there any notable points of delay?* *What do you think causes this delay?* *What could be done, in your opinion, to resolve this?* *Is there anything that you feel works particularly well?*
Support	How would you describe the support you receive from your specialist/non-clinical/managerial colleagues?	*Is there anything about this relationship that could be improved to allow for a more efficient diagnostic pathway?*

Staffing levels	Do you feel that you have an adequately staffed team to provide the level of care you wish for these patients?	*Are there any roles which you feel could be better utilised or more abundant to improve the diagnostic pathway?*
Barriers	What do you think are the potential barriers to receiving a diagnosis of early stage disease?	*Why do you think that we are still seeing such a high proportion of late-stage diagnoses of Head and Neck Cancer?*
Improvements/ Recommendations	Are there any areas in the diagnostic pathway of Head and Neck cancer that you feel could be improved?	*Is there anything that you would like to see implemented to improve the resilience of the pathway?*

HEADSpAcE

Healthcare Systems Qualitative Interview Guide: Patient Perspective

Topic/ Main Question	Prompts
Journey to Diagnosis Can you tell me about yourself and your story?	*Can you tell about what happened in the lead up to the diagnosis of your cancer?* *What made you seek a healthcare professional in the first instance?* *Was there anything that encouraged you to seek help or inhibited you from doing so?* *How long did you wait after first noticing a symptom and contacting a healthcare professional?* *Where your symptoms obvious?* *Did you feel that there was any delay in getting to see the doctor/dentist at first?* *Did your health get worse, better or stay the same while you were waiting for first appointment?* *Were there any major life events/stresses happening for you at this time?*
Prior Knowledge of Head and Neck Cancer What did you know about your cancer of the head and neck prior to your diagnosis?	*Had anyone ever spoken to you about head and neck cancer before?*
Access to Healthcare How did you to get to see a dentist/GP?	*Did you find it easy or difficult to get an appointment?* *Who did you see?* *Did someone go with you?* *When and where did you see them?*
Primary Care What happened when you saw doctor/dentist for the first time?	*What happened when you were there?* *How were you feeling at the time before and after this appointment?*

	Did your dentist/doctor mention the possibility of head and neck cancer to you? *Did they refer you after this first appointment? If not, how many more appointments did you have before you were referred and what happened at these?* *Did you know where they had referred you to?* *Did you have much contact with your GP/Dentist after they referred you?*
Hospital Care What happened when you visited the hospital for your consultation and tests?	*How did you feel before and after this first appointment?* *How long did you wait for a hospital appointment? How did the length of your wait feel?* *Where there any aspects of this that took a longer or shorter amount of time than you expected?* *Had you any idea of what to expect?* *Did you feel that there was any overlong delay in between your appointments/tests?* *Was there anything you felt affected the time you waited to receive a diagnosis either positively or negatively?* *Were you given complete explanation of test results in understandable way?* *Who first told you that you had cancer? How do you feel about the way you were told that you had cancer?*
Family What role have family, friends and work colleagues played on your journey to your diagnosis?	*Do you feel that they were helpful and supportive?* *Who? How? What? When?*
Barriers Was there anything that you can think of that may have prevented you from getting your diagnosis earlier?	*Personal things, Family, Work, Health Service*
Support Before your diagnosis, what methods of support did you need and have access to?	*Were there services that you felt you would have benefitted from but you did not receive/have access to? Social, Psychological, Financial*
Improvements / Recommendations If you were able to go back in time, what do you think	*Personal? Habits?* *What about the pathway through the healthcare system?*

could have been done differently to make the process easier and quicker?	

Appendix 5-2: NVivo Codebook

HEADSpAcE Qual Interviews

Name	Files	References
1 PATIENT + POPULATION	28	354
POPULATION HNC AWARENESS AND AGENCY	23	91
Commercial elements influencing patient mindset	1	1
Consumption of cancer-related media	1	1
Correlating HNC to Environmental Factors such as Chernobyl	2	3
Existing Awareness of HNC or Other Cancers May Prompt	8	13
HNC Not Well Known in Public Population	3	6
Improving Public Awareness of HNC Symptoms and Risks, and on Navigating Health System Through Multiple Methods and Across Settings	18	35
Patient Linking diagnosis with that of a public figure	1	1
Patient sense of risk in everything so risk discussions may not have affected behaviour	1	1
Pop Culture references to Throat Cancer in patient thinking	1	1
ROLE OF BEHAVIOURAL RISK FACTORS	11	28
Alcohol	2	2
patient perception Smoking and Alcohol	1	1
ROLE HPV, OCCUPATIONAL EXPOSURE, AND GENETICS	6	11
Genetics	1	1
HPV, Role in changing rates and demography, patients not aware	6	9
Occupational Exposures	1	1
Smoking and HNC, Patients aware of risk but more so other cancers, affects rates of disease possibly	8	14
Younger patients not paying attention to their health as much as older adults	1	1
ROLE OF FAMILY AND FRIENDS	9	31
Family and Friends play important role in prompting, supporting, facilitating diagnosis and journey and advocating for patient	9	24
Family can negatively affect journey through their own thoughts on healthcare, past experiences or supporting self-monitoring, or patient wanting to protect family	5	6
Switch in family perceived roles and responsibilities	1	1
ROLE OF PUBLIC HEALTH AND STRATEGY	11	55
Behaviour Change Programmes or Groups to Reduce HNC Associated Risks	4	6

Name	Files	References
Delayed Diagnosis is Due to Combination of Factors	3	3
National approach taking clinical, political, economic and public context into account across stakeholders	4	12
Not a prioritised cancer type	1	1
Perception of Stagnant Development and Lack of Strategy	1	5
Public Health Approach Including Reducing Underlying Inequalities, Universally Applied with Targeted Elements, Involving Patient Groups, Utilising Quality Data	7	15
ROLE FOR DATA INTELLIGENCE	6	10
Cancer Tracking and Waiting Time Monitoring	5	8
National and Local Audit	2	2
Strengthening Public Sector by way of Support and Conditions	2	3
ROLE OF SOCIOECONOMIC INEQUALITIES AND COMORBIDITIES	17	47
Complex Medical and Social Needs for Some Increase Risk of Advanced Disease, Despite Often Being in Health System	9	12
EFFECT OF GEOGRAPHIC INEQUALITIES	9	19
Geographical Discrepancies of Ability to Access Services and Means of Transport	9	19
Financial Inequalities on Personal or Demographic Level Affect Access to Services and Mean More Deprived Presenting Later, Seems to be Worsening	7	16
SYMPTOMS	21	90
Patient Contacted Primary Care Immediately When Symptom Arose	2	2
Patient Had Symptoms that Prompted Concern	9	14
Patients ignore symptoms, have lack of concern and or and or think they will go away, waiting weeks to months before contacting, even if cancer is thought of as possibility. Wait until pain or adapt to symptoms	20	66
Range of Vague Pre-Presentation Symptoms and Signs	5	8
TRUST IN HEALTHCARE ORGANIASTION AND CLINICIANS	10	40
Existing Relationships with Primary Care Teams and Experiences of Health Service Key both Positively and Negatively	8	33
Frustration and Distrust in Government and Health Service	4	7
2 ACCESS AND PRIMARY CARE	29	233
EXPERIENCES OF PC ACCESS AND INITIAL ACTION	24	106
Challenges in Accessing Primary Care and Knowing Where to go for Most Patients, They need to be Explicit	12	14
Fear of Cancer possibly delaying healthcare engagement	5	9
Patient feels access to primary care was as quick as could be	5	5
PC MEDICAL AND DENTAL INTERFACE	10	26

Name	Files	References
Empowering Dental Teams and Integrating Dentistry into Health System Fully	4	6
Linked up systems for dentists and medics would be ideal	1	1
Unclear and Blurred Responsibilities and Capabilities of Primary Care Physicians and Dentists	8	19
Potential role for risk calculator	1	1
Primary Care Initial Consultations often Challenging due to Cancer Fears, Patient Attitude, and Multiple Presenting Complaints	6	12
Primary care Model has Pressures that can Impede Early Access and Referral, such as Business Elements and Models of Funding	3	3
Primary Care Staffing and Clinical Capacity Creates Challenges due to Workload, Non-Clinical Responsibilities and Current Model	4	7
PROFESSIONAL INSTINCT	10	14
Beneficial to send patient to emergency room to be seen by specialist rather than wait for referral	1	1
Immediately transferred from emergency department to ENT	1	1
Indication to Refer Often Instinctual	4	5
Patient encouraged to bypass normal system by emergency doctor	1	1
Practitioner often refers for peace of mind	1	1
Went straight to Emergency Service or Bypassed Primary care	4	5
Prompt Professional Action	5	7
Reminder from dentist to attend for check-up prompted attendance	1	1
Role for triaging cancer concerns to then be seen urgently in primary care	2	7
FORTHRIGHTNESS IN COMMUNICATION	11	25
Inter-Specialist Communication Strong Due to Personal Responsibility and Solid Relationships	3	8
More Forthright Discussions with Patients About Risk, Between Colleagues on Service Issues, and on Public Level on Health Service Expectations	2	4
Patient-Professional Conversation Not Explicitly Discussing Cancer Risk	3	5
Sense of Possible Cancer but not Explicitly	6	8
PC EQUIPMENT RESOURCE	4	5
No standardised equipment across service	1	1
Not having appropriate equipment in primary care to clearly examine	3	3
Resources scarce	1	1
PC HNC KNOWLEDGE	21	79
Cancer Not Recognised Early, Misdiagnosis in Primary Care or at First Opportunity, Often with Infection and Given Antibiotics, First Appointment is Crucial	16	42
Discrepancies in clinician experience with HNC and sense of risk	2	3

Name	Files	References
HNC is Rare for Primary Care to see and Training is Minimal (GP) but Awareness of Increasing Issue	5	8
Improving primary care HNC knowledge does not improve early detection	3	3
Primary Care Aware of HNC Sign	1	1
Training for Primary Care and Wider Health Teams on HNC, including signs and symptoms of HNC, Risks and how to Approach Potential Diagnosis, led by HNC Specialists.	10	22
SCREENING POTENTIAL	8	18
Development of New Screening Tools Incorporating AI	2	4
Screening Difficult as a lot of early disease can be asymptomatic or painless	1	1
Screening Difficulties in screening for HNC	2	2
Screening role for Dentists	8	9
Screening Would need to be easy for patient and reliable	1	1
Screening Would need to be very targeted	1	1
3 INTERFACE AND SECONDARY CARE	29	518
ACCESS TO AND EFFICIENCY OF SPECIAL INVESTIGATIONS	21	84
Direct access to radiology available but uncommon	1	1
Important to Protect Specialist Investigation Resource for Suspected Cancers and Constantly Review Protocols	2	7
Investigations are Non-Automatic and Have Several Human-Dependant Action Points that Can Delay but Lack Flexibility in Request System	1	6
Investigations were done immediately or within days	6	7
Key to have Investigations Undertaken Promptly, If not Same Day	4	7
Lack of histopathology resource and wait to get biopsies reported	5	12
Need for better access to specialist clinics and investigations	1	1
Primary Care Could Have More Diagnostic Responsibility, but this Brings Challenges	4	7
Quicker Access to Special Investigations, Quicker Communication of Results and Better Availability of these in Primary and Community Services, Potentially Through One-Stop Clinic	11	30
Significant time between diagnostic steps	1	1
Some Element of Local Investigations and Treatment as part of Centralised System can Work Well	2	4
Sometimes over reliance on single investigations	1	1
EXPERIENCES OF SC CLINIC STRUCTURE	26	108
Ensure Fundamentals are In Place and Expectations are Clear and Achieved, Learning from other Services	3	3
EXPERIENCE OF ENTRY TO SC SYSTEM	9	12

Name	Files	References
Large waiting times and difficulty perceived difficulties accessing for specialist services	4	7
Need to rethink training schemes	1	1
Patient Contacted Directly with Appointment from Specialist Services	1	1
Patient perception that time getting diagnosis is shorter in Europe and America compared to Montevideo	1	1
Patient received phone call from Specialist Services	1	1
SC Initial appointment received after months of delay and going to ED	1	1
Facilities should be appropriate	2	2
Flexibility of appointment times is beneficial	1	1
Key to have Intelligently Planned, Well Resourced Clinics that Focus on Suspected Cancer Patients and have Multiple Specialties Available On Site	8	22
Majority of patients at clinic do not have cancer	1	1
Non-cancer patients taking up appointments when definitely not with cancer	1	1
PERCEPTION OF SC SYSTEM	13	38
Once in secondary care system things happen quickly	1	1
Process for diagnosis once in Specialist Service very quick and Smooth	7	9
SC Diagnosis is a complex, slow process or took a long time due to appointments at different locations, multiple appointments and bureaucracy	9	27
SC Pace of Appointment Scheduling Adding to Anxiety Regarding Diagnosis	1	1
ROLE AND EFFECT OF CENTRALISATION	7	20
Centralisation Can Impose Large Travel Burdens on Patients and Measures to Overcome Need to be Integral	4	10
Centralisation has benefits for Treatment and Service, Allows for improved Team Working and Allows Universal Access to Specialist Pathologists and Radiologists	5	10
SC No continuity in person seen at hospital	1	4
Specialist pathway for unknown primaries to reduce delay	1	1
Standardised Protocols for All Teams in Same Service Can Help	2	3
PC-SC DISCONNECT	19	81
Better improved first level second level communication	3	3
Change in gatekeeping role towards secondary care	1	2
Disconnect regarding what is expected of primary care	1	5
Facilitating Patient Journey from Primary Care Through to Diagnosis with Patient Coordinator, Proactive Communication, Active Follow Up and Transport	11	19
First level physicians not kept in loop	1	1

Name	Files	References
Frustration with Management and Process of Primary Care Secondary Care Interface but Does Work for Some	7	10
GP representatives linked in with cancer service	1	1
Primary Care - Specialists Path Does Not Work Well for Primary Care, Difficult to Access Specialists and is Ad-Hoc through Phone or Letter with Delays in Contact	9	24
Primary Care Secondary Care Disjointed	5	9
Primary care should not just be referral doctor, should be involved in care	1	1
Secondary care critical of Primary Care ability and Potential Role	3	4
Special dental services referred direct to ENT	1	1
Specialists thinking GP should have more responsibility in screening	1	1
REFERRAL SYSTEM DESIGN	20	101
Bespoke Referral System Standardises Process but is Challenging from Primary Care, more set up for Specialist End	5	25
Current Referral System seems Poorly Organised	5	6
Frustration at Bespoke Referral System	1	1
Health has cost and cost high due to poorly planned referral processes	1	1
Ref System Good	7	8
REFERRAL CLARITY AND INFORMATION CONTAINED	5	15
Knocked back referrals due to some missing info	1	1
Need to clearly contain Key Information and Photographs	4	9
Pictures helpful	1	1
Specialised cancer risk questionnaire sent to patients when referral received by specialist care	1	1
Specific Detail Necessary, Facilitated though Questionnaire to Aid Primary care	1	3
REFERRAL SYSTEM GOVERNANCE AND TRIAGE	11	27
Designated triagers of appropriate skill and daily checking important to have	2	4
Formalised Referral System, Available to Other Health Professionals, Such as Pharmacists, and Managed by a Coordinator with Unambiguous Vetting and Triaging Protocols	8	11
Increasing number of private referrals	1	1
No remuneration for Referrals	1	3
Non-direct referrals (Management)	1	1
Patients primarily referred via primary care	1	1
Referral Management Groups	2	3

Name	Files	References
Triaging referrals can be very pressurising	1	1
Vetters able to upgrade or downgrade	2	2
Referrals Sense that things could be more smooth	1	1
Significant time between referral and ENT appointment	2	2
UTILITY OF REFERRAL GUIDANCE	7	14
Guidance Wanted, Needs to be Readily Available, Can Be Useful if Symptoms Neatly Fit	4	8
No Guidance Available	1	1
Professionals Unaware of Existing Guidance or it is Hard to Come By	4	5
When patient is referred, they don't see HNC specialist first, more likely a generalist	1	1
ROLE MDT	9	36
MDT Well-Organised, Regular, Governed, Wider Specialist Inclusion Can Benefit Diagnosis, But is Ultimately Aimed at Treatment Decisions	9	25
No Formal MDT can Impede Decision Making	3	4
Unclear Benefit on Early Diagnosis as Sometimes Nothing Happens Until Next MDT	2	7
SC PROFESSIONAL'S EXPERIENCE OF HNC PRESENTATION	12	29
10% of cancer referrals are true cancers	1	1
Change in demographic, no known risk factors	1	1
Delay worsens outcomes and can leave disease untreatable	2	2
Dysplasia being treated more radically now	1	1
Early stage patients more simple to proceed to treatment	1	1
High levels of palliative care and need to diagnose faster	1	1
If cancer obvious, it's too late	1	1
Increase in both palliative and early disease	1	1
Mainly Advanced Disease being Diagnosed	2	3
Many OPC patients not in regular dental attendance	1	1
OPC now more common than laryngeal now	1	1
Patients Present With Disease that is Already Advanced	4	4
Patients seen with Oral Cancer by Dentists tend to have traditional risk factors	1	1
Professional wish that more could be done to reduce advanced stage HNC burden	1	1
What is being seen in clinics	1	1

Name	Files	References
When Symptoms are Noticeable, Often disease is Already Advanced, Missing Early Signs and Symptoms	6	8
SC STAFFING AND RESOURCE	12	52
Good administrative support is key	1	1
Overburdened System Leading to Clinicians Having to React to Situations	4	5
Physicians working in multiple organisations	3	7
Significant demand	1	1
Staffing, Skill Mix, Team Working and Specialist Team Resilience	11	38
TECHNOLOGY IN COMMUNICATION AND DIAGNOSTICS	13	27
IT systems better but still don't always match up	1	3
Modern technology has enhanced	1	1
Narrow-banding imaging could be potential help	1	1
National Imaging IT system	1	1
Only offered telephone consultation	2	3
Physical letters communication from specialist services	1	1
Potential for misdiagnosis with telephone consultations	1	1
Use of Modern Technologies to Improve Patient Access, Reduce Inequalities, Share Medical Records, Diagnostic Tools and Communication	7	16
MISC and OTHER	19	81
COVID-19	8	20
COVID-19 Pandemic Affected Health Services and Patient Access either Directly or Indirectly	7	17
COVID-19 Pandemic did not affect Diagnosis and May Have Helped	2	3
IMPACT OF DIAGNOSIS	10	16
Delays affecting mental health of clinicians	1	1
Devastating Impact of Diagnosis Which is Often a Complete Shock	8	12
Don't want to worry patients unnecessarily	1	1
Patient made aware of life-changing impacts	1	1
Patients with traditional risk factors more expectant of diagnosis	1	1
PATIENT REFLECTION ON DIAGNOSIS	9	20
Negative experience of Emergency Service Access, Sense of Being Annoyed patient Presented There	1	2
No groups for patients sharing experience	1	1

Name	Files	References
Patient Appreciation for Health Service and Professionals	5	11
Patient feels fortunate that right specialty was there as they did not know if they would be	1	1
Patient had doubts and fears at time of diagnosis	1	1
Reluctance to Think of What Could Have Been if Wasn't for External Intervention	1	1
Remembers significant possible outcomes initially told	1	1
Sense of Remorse for others who may not be able to Understand or Navigate System	1	2
Private System Better Remunerated but does not Work as Well	2	5
TREATMENT	9	20
Treatment	9	20

Appendix 5-3: Supplemental Tables

Theme	**Prominent Sub-Theme**	***Illustration***
Patient and Population HNC Awareness and Agency	Need for Improved Public Awareness of HNC Symptoms and Health System Navigation	*"That, that is key and that goes with early detection campaigns and going out to explain to people that if they have such and such characteristics of symptoms or signs, to consult quickly." Montevideo, Clinician*
	Risk Factors and Relating to Cancer	*"The west of Scotland has the highest endemic rate of smoking in the UK. That behaviour is going to take time to come down." Glasgow, Clinician*
Role of Family and Friends	Family and Friends have Important Role in Prompting and Facilitating Early Steps	*"…my wife was with me and she insisted on having it done there and then and I thank her for it." Glasgow, HNC Patient*
	Negative Experiences of Family and Friends Can Impact Decision to Access Health Services	*"My GP is…I will tell you here and now, my son and my brother do not like him. He didn't give the best of treatment to my husband." Glasgow, HNC Patient*
Socioeconomic and Geographic Inequalities	Complex Social and Medical Needs Increase Risk of Advanced Disease	*"…above all the approach to the social part of these patients, who are extremely complex and it is a deficit that we have. They are patients who come from extremely complicated backgrounds…" Montevideo, Clinician*
	Geographic Inequalities	*"Distances. The distances too. It is not the same living in Montevideo, where everything is more or less close by. Here the distances are brutal" Montevideo, Clinician*

	Financial Inequalities	*"So if you are somebody who's got very little money and, you know, you can't afford a bus to a site or struggle to get to an appointment… that's definitely a factor."* Glasgow, Clinician
Symptoms and Initial Action	Symptoms ignored, downplayed, or adapted to	*"I thought it was temporary, that it was just a sore throat… that's why I didn't see a doctor." Montevideo, HNC Patient* *"At the back of my mind I kept thinking, I wonder if this is cancer. I kept ignoring it, which I should never have done, but hindsight is a wonderful thing." Glasgow, HNC Patient*
	When concerned, prompt action taken	*"The neck lump had grown quite substantially by this point, hence why I had thought to say to him" Glasgow, HNC Patient*
	Fear of cancer delaying presentation	*"That is probably, if I'm honest with you, part of my procrastination and my fear of…I think I knew in my head where we were and I was just finding excuses not to deal with it." Glasgow, HNC Patient*
Trust in Health Organisations and Health Personnel	Existing Relationships with and Experiences of Healthcare Providers Affects Patient Decision Making	*"That was subconsciously my plan, rather than going to a GP, which I don't have huge faith in. It was always my plan is to check with my colleague" Glasgow, HNC Patient*
	Trust in Government and Large Organisations can Affect Patient Attitude	*"Well, the government's mistrusted" Glasgow, HNC Patient*
Utilising Public Health and Strategy	Need for National Approaches to Addressing Universal Issues	*"Therefore, in order to make decisions, all realities must be brought together." Montevideo, Clinician*
	Adopting Public Health Approach	*"That's the biggest thing that anybody could do – spend more money on public health. More bang for your buck, all that, stuff that everybody knows, that people are still in denial about." Glasgow, Clinician*

	Data Harnessing	*"We have improved a lot and we have a very good cancer registry because in order to make health policy on cancer you have to have and know what the incidence and mortality in this case of localization is." Montevideo, Clinician*

Supplemental Table 5-1: Themes Pertaining to Patient and Population Interval

Theme	**Prominent Sub-Theme**	***Illustration***
Access to Primary Care and Initial Action	Clinician Instinct for Referring	*"if you see a patient and you see something that you're looking at it in their mouth and thinking, I am 90 per cent certain that that is oral cancer, then that's when you would do the urgent referral"* Glasgow, *Clinician*

	Challenges in Accessing Services and Knowing Where Best to Go	*"…for the first discomfort I went to the local polyclinic and they told me that it was not for them, that I should see an otolaryngologist without knowing what was there, because they did not know either. Well, that's when I decided to come to the hospital emergency room." Montevideo, Patient*
	Fear of Cancer	*"I probably knew deep down what it was, but it is quite a scary thing to face up to that." Glasgow, Patient*
	Unclear and Blurred Responsibilities Between Medical and Dental Services	*"…patients are maybe phoning their doctor for things to do with their mouth but there's been things to do with like throat or maybe like neck and things and they're told to come to their dentist." Glasgow, Clinician*
	Non-Standardised Equipment and Resources	*"Yes, there are things … Not all places have the equipment, such as endoscopes, to make a diagnosis" Montevideo, Clinician*
Primary Care Knowledge of HNC symptoms, signs and system	HNC Often Misdiagnosed or Not Recognised	*"From the moment they consult with their first symptom, go through a series of general practitioners who give them different treatments, antibiotics, painkillers" Montevideo, Clinician*
	Need for Training for Primary Care and Wider Health Teams on HNC	*"I believe that education is critical for both physicians and patients" Montevideo, Clinician*
Potential for Screening	Potential for Clinician Screening	*"There is no way to see that without a clinic exam. So that would be the part of screening that you would need if you were doing it clinically… there are blood tests and things that are currently under research… I think it would have to be extremely targeted." Glasgow, Clinician*
	Difficulties in Effective Screening	*"I have been taking part in some sort of screening events over the years where most of the stuff you see is benign, so I'm not quite sure how effective it is" Glasgow, Clinician*
Forthrightness in Communication	Cancer and Risks not Explicitly Discussed	*"I think in the clinical and even in the dentist's surgery as well. Even if the dentist would be more forthcoming with a wee bit of information about what could potentially happen, just as a general chat" Glasgow, Patient*

	Inter-Clinician Communication needs to be more Forthright	*"Maybe a bit more forthrightness with each other. Sometimes we do things, and we don't want to hurt people's feelings, or we don't want to…there's a lot of benefit to actually saying no, but this is the reason why. We're not brilliant at that." Glasgow, Clinician*

Supplemental Table 5-2: Themes Pertaining to Primary/Community Care Interval

Theme	**Prominent Sub-Theme**	**Illustration**

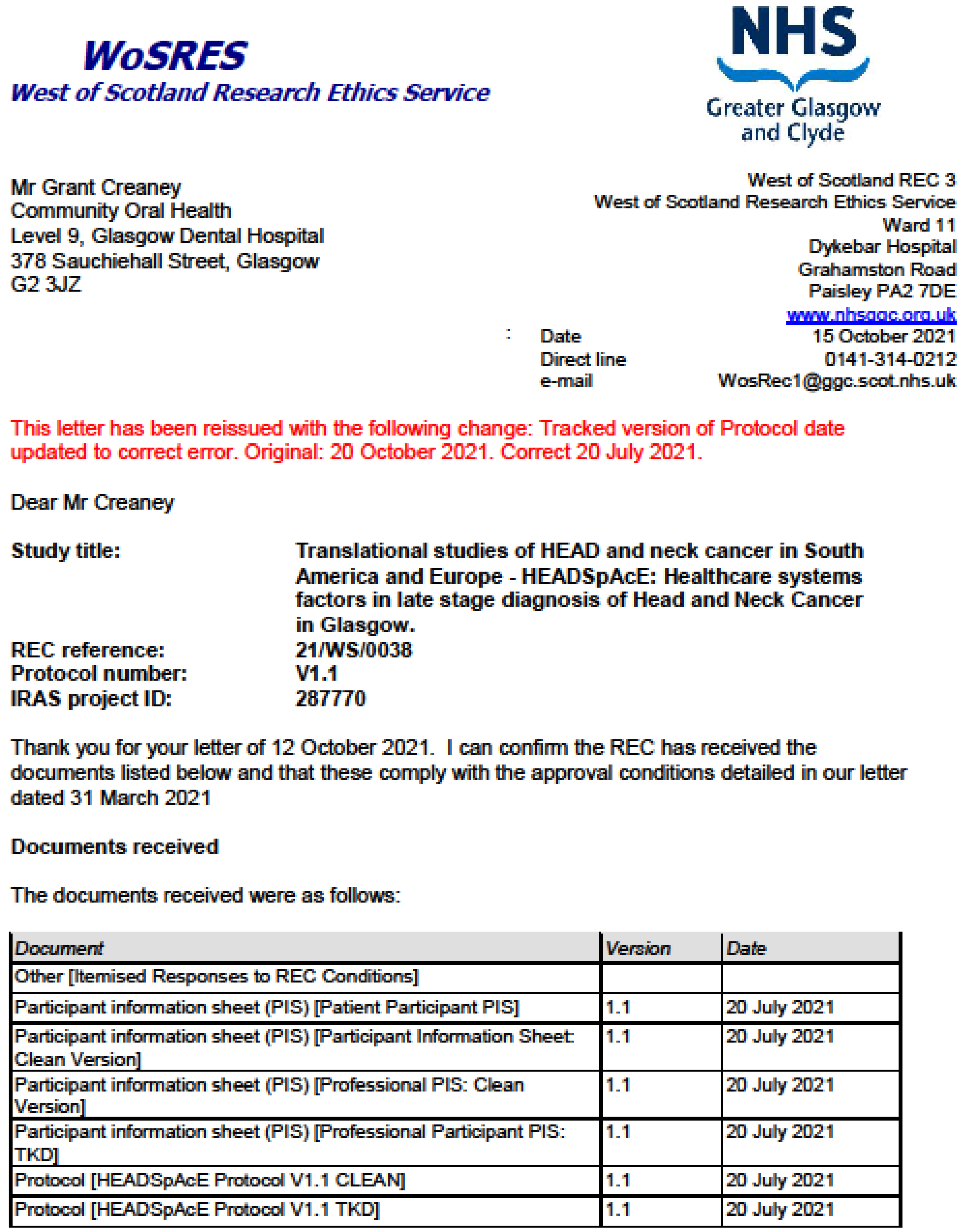
Referral Processes	Need for Formalised Referral Systems Open to Wider Health Teams	*"for people presenting with concerning signs to community pharmacies… make sure that they have an established pathway to report their concerns." Glasgow, Clinician*
	Referral Guidance has Utility if Available and Accessed	*"I think the referral guidelines are pretty clear, you know, what are red flag symptoms… it's just the fact that these primary care remits have been, for different reasons, under the cosh" Glasgow, Clinician*
	Heavy Bureaucracy Affects Efficiency	*"And it is sad because of that, because in reality it could be much more oiled, much more dynamic, much more fluid and of benefit to all." Montevideo, Clinician*
	Need for Clarity and Efficiency	*"They have to be quite clear and concise of all the symptoms." Glasgow, Clinician*
	Referral Monitoring	*"So if the referral has been received but maybe that patient has not had an appointment yet, it's like chasing that up." Glasgow, Clinician*
	Role of Referral Triaging	*"I believe that in this sense, some kind of articulating personnel between both levels would be very useful who could filter, to some extent triage, the patients who have some element of organicity and who require a quicker consultation" Montevideo, Clinician*
Specialist Investigations	Limited Resource and Personnel for Reporting Investigations	*"At the moment we are with a too long time … in reality the common factor is the times in pathological anatomy" Montevideo, Clinician*
	Role for Wider Access to Histopathology and Radiology	*"I would like to have much wider access to diagnostic testing…* *That is obviously a significant investment and work load and then to transfer all of that into primary care would be essentially a paradigm shift of the way that primary care works." Glasgow, Clinician*
	Investigations Processes are Non-iterative	*"Currently what we have is…what we have to have is somebody expecting the result, sitting watching it. We don't have…we call it a failsafe alert system." Glasgow, Clinician*

	Having Immediate Investigations	*"I saw [a Doctor], in Glasgow Royal, and [they] biopsied my tonsil on that very first visit, and so I found out within days that I had squamous cell cancer"* Glasgow, Patient
Professional Role	Shift in role of Primary Care	*"The GP has always been the gatekeeper to the NHS as a whole and properly functioning general practice works well in that role. I had briefly mentioned before the back to referrer and that increasing rejection of referrals and things like that. My own impression is that that essentially is potentially…unintentionally and subconsciously having a change or shift in referrers' behaviours. So that gatekeeping is essentially being moved into secondary care where they have, I am pretty sure, unintentionally taken on that role of gatekeeping."* Glasgow, Clinician
Primary Care Secondary Care Disconnect	System is Challenging for Primary Care Clinicians	*"I believe that there is a devaluation of the first level of care physicians, there is a devaluation of family and community medicine…"* Montevideo, Clinician
	Unclear Oversight and Management of Pathway from Primary Care to Secondary Care	*"There is no relationship, nor is there a correct referral from the first level to the second or third level. There is not a very good relationship, let's say… there is no communication."* Montevideo, Clinician
	Patients Should Have Their Journeys to Diagnosis Facilitated and Managed by a Coordinator	*"The patient is disoriented in the middle of the system and the idea is that he/she can access the specialist as quickly as possible to carry out the corresponding study and diagnosis"* Montevideo, Clinician
Resource and Personnel	Utilising Skill Mix and Incorporating Resilience	*"… in clinics, and doing the ultrasound and biopsies, we can get sonographers to do them… that would free us up to report more diagnostic scans."* Glasgow, Clinician

	Overburdened Systems Affecting Behaviour	*"Many times we multitask and you lose time to concentrate on what you really have to do." Montevideo, Clinician*
Service Structure and Design	Conflicting Role of Centralisation	*"I think a referral centre would be ideal. Uruguay should have a reference centre for head and neck… it would improve a lot," Montevideo, Clinician*
	MDT improves quality of diagnosis but unclear role on stage	*"Those are the more proactive people. There are other specialists and I think it is the majority that do sit back and feel that the MDT is the decision maker. So, don't go requesting the next step in the pathway…" Glasgow, Clinician*
	HCN System Gatekeeping	*"So that gatekeeping is essentially being moved into secondary care where they have, I am pretty sure, unintentionally taken on that role of gatekeeping." Glasgow, Clinician*
Technology in Communication and Diagnosis	Role for utilising Modern Technologies for Patient and Clinician Communication	*"IT is so poor, but the number of different systems and things that are used and that don't talk to each other is ludicrous. Going back to how that single shared record, as you say, could be with certain restrictions on access for patients makes so much sense." Glasgow, Clinician*
	Risk of Misdiagnosis with Remote Initial Consultation	*"…they were doing telephone appointments… after the first one I thought they might have seen me, being of the fact it was in my mouth and my neck but they maybe didn't take it…didn't take any significance from my mouth part." Glasgow, Patient*

Supplemental table 5-3: Themes Pertaining to Specialist Services Interval

Appendix 5-4: Ethical Approval Letter



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This letter has been reissued with the following change: Tracked version of Protocol date updated to correct error. Original: 20 October 2021. Correct 20 July 2021.

Dear Mr Creaney

Study title:	**Translational studies of HEAD and neck cancer in South America and Europe - HEADSpAcE: Healthcare systems factors in late stage diagnosis of Head and Neck Cancer in Glasgow.**
REC reference:	**21/WS/0038**
Protocol number:	**V1.1**
IRAS project ID:	**287770**

Thank you for your letter of 12 October 2021. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 31 March 2021

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Other [Itemised Responses to REC Conditions]		
Participant information sheet (PIS) [Patient Participant PIS]	1.1	20 July 2021
Participant information sheet (PIS) [Participant Information Sheet: Clean Version]	1.1	20 July 2021
Participant information sheet (PIS) [Professional PIS: Clean Version]	1.1	20 July 2021
Participant information sheet (PIS) [Professional Participant PIS: TKD]	1.1	20 July 2021
Protocol [HEADSpAcE Protocol V1.1 CLEAN]	1.1	20 July 2021
Protocol [HEADSpAcE Protocol V1.1 TKD]	1.1	20 July 2021

Appendix 5-5: COREQ Checklist

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	8
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	1
Occupation	3	What was their occupation at the time of the study?	8
Gender	4	Was the researcher male or female?	1
Experience and training	5	What experience or training did the researcher have?	8
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	5
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	8
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	19
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	4, 5, 8, 9
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	5
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	5
Sample size	12	How many participants were in the study?	5-7
Non-participation	13	How many people refused to participate or dropped out? Reasons?	N/A
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	9
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	8
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	6-7
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	8-9
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	8-9
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	8-9
Field notes	20	Were field notes made during and/or after the inter view or focus group?	8-9
Duration	21	What was the duration of the inter views or focus group?	8-9
Data saturation	22	Was data saturation discussed?	11
Transcripts returned	23	Were transcripts returned to participants for comment and/or	8-9

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	11
Description of the coding tree	25	Did authors provide a description of the coding tree?	11
Derivation of themes	26	Were themes identified in advance or derived from the data?	11
Software	27	What software, if applicable, was used to manage the data?	11
Participant checking	28	Did participants provide feedback on the findings?	8-9
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Yes
Data and findings consistent	30	Was there consistency between the data presented and the findings?	Yes
Clarity of major themes	31	Were major themes clearly presented in the findings?	Yes
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	Yes

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

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