A DEMOGRAPHIC REVIEW OF STAGE OF PRESENTATION AND SURVIVAL RATES OF HEAD AND NECK CANCER PATIENTS IN THE WESTERN CAPE, SOUTH AFRICA

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Conflict of Interest

The authors have no conflicts of interest to disclose.

DECLARATION

I, *Simon Honnet*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABBREVIATIONS

HNC	Head & Neck Cancer
TNM	Tumour, Nodes, Metastases
HPV	Human Papilloma Virus
NCI	National Cancer Institue
HNCUP	Head & Neck Cancer of Unknown Primary
OPSCC	Oropharyngeal Squamous Cell Carcinoma
SCC	Squamous Cell Carcinoma
LMIC	Low- & Middle- Income Country

1. ABSTRACT

Most literature reports significantly poorer access to healthcare, more advanced cancers, and worse survival in rural and remote populations. This study investigates if significant disparities exist with regard to stage at presentation and overall survival of patients with head and neck cancer (HNC) between geographical areas within the Western Cape Province in South Africa.

A retrospective chart review was conducted on all patients managed with both curative and palliative intent through the Combined ENT/Head and Neck Oncology clinic at Groote Schuur Hospital in the five-year period from January 2010 to December 2014. Ethics approval was granted by the University of Cape Town Human Research Ethics Committee (HREC, 351-2017).

Although we observed no significant difference in TNM clinical stages or overall survival between metropolitan and remote patients, there were statistically and clinically significant differences in terms of both stages of HNC and survival between some individual metropolitan and remote areas. The remote area of Eden had a median overall survival of more than 6 months less than that of the Southern subdistrict of the City of Cape Town. These discrepancies in HNC stages and survival are likely multifactorial, involving socioeconomic and demographic factors in addition to geographic factors.

2. INTRODUCTION

Head and neck cancer (HNC) causes significant morbidity, by impacting bodily functions such as breathing, speech, swallowing and taste, as well as the psychological and social impacts of the disease, and morbidity of treatment. As a public health problem, lower- and middle-income countries (LMICs) not only have the majority and increasing incidence of burden of cancer, but also limited resources for its management (Farmer, 2010).

There is a wide geographical variation in the incidence of HNCs, reflecting distribution of poorer socioeconomic populations, and exposure to carcinogens such as smoking, alcohol and human papilloma virus (HPV) infection. According to data from death certificates and from Statistics South Africa, the Western Cape Province had substantially higher age-standardised mortality from cancers during our study period (118 per 100,000 population), that was close to double the national average of 69 per 100,000 population (Made, 2017).

HNC is different from other cancers in South Africa such as breast, cervical, colorectal and prostate cancers, in that there are no screening tests; diagnosis relies on a good history and specialised clinical examination. Management of HNC is therefore highly specialised and requires multidisciplinary input. With South Africa's constrained financial and staffing resources, this requires that these services are centralised in the metropolitan areas.

According to data from the 2011 Census, 36% of the Western Cape population live outside of the City of Cape Town metropolitan area, some in towns as large as George (population 114,000) and Paarl (population 112,000), and some in smaller towns and rural areas. Many of these non-metropolitan areas have good clinic and hospital infrastructure, but most of the surgery and oncology services for HNC are centralised in the City of Cape Town metropolitan area.

The World Health Organisation's Alma-Ata declaration in 1978 was the first, and now most well-known international declaration identifying the importance of primary health care in attaining ambitious goals of 'health for all' (WHO, 1978). Forty-four years on, many rural and remote areas of South Africa are severely underfunded and understaffed, and unable to provide adequate primary health care. Oral and oropharyngeal cancers ought to be readily diagnosed in primary healthcare settings due to the accessibility of the oral cavity and oropharynx for examination and biopsy. Although laryngeal cancers are not as easily accessible, they certainly cause dysphonia, even from an early stage. In many such cases, these early symptoms are overlooked or neglected by both patients and primary care physicians.

Most literature reports significantly poorer access to healthcare, more advanced cancers, and worse survival in rural and remote populations. Coory (2005) used the Australian Standardised Geographic Classification, and Statistical Divisions to define capital cities, and found that rural and remote patients had higher mortality from prostate cancer. Jong (2004) found that patients with HNC from remote areas of Australia, as defined by the Accessibility/Remoteness Index had higher mortality. Olson (2012) reported that patients from rural populations, as defined by Canadian census data from the patients' postal codes, presented with more advanced breast cancer, but had no difference in survival. Henley (2017) using an arbitrary classification of population sizes of the counties in the United States found age-adjusted disease-specific survivals for various cancers to be 14% worse in patients from rural areas. Onega (2008) estimated patients' travel time by their United States ZIP codes of the patients' residence and geocoded point locations of their National Cancer Institute (NCI)

Hospitals, as a proxy for rurality. They demonstrated significant burdens for access to specialised health care for non-urban populations.

It should, however, be noted that there are some contradictory data on this topic. Unger et al (2018) used the United States' Rural-Urban Continuum Codes that classify metropolitan areas according to their population, and non-metropolitan areas according to both population and proximity to metropolitan areas. They analysed a cohort of 36,995 patients with various cancers and found no significant difference in overall or disease-specific survival.

Kim (2017) reported no significant difference in overall survival of HNC between rural and urban populations in Canada, using community size as a proxy for rurality.

These apparent contradictions may be due in part to the semantic differences in ways that populations are defined; some researchers compared urban and rural populations, while others compared metropolitan and non-metropolitan populations. These comparisons are not necessarily equivalent. Definitions of what constitutes metropolitan, urban, suburban and rural areas vary across different countries. 'Remoteness' in a country like Australia may be very different from that in Western Europe. The European Commission for the World Bank has therefore called for harmonised definitions in this regard (European Union/FAO/UN-Habitat/OECD/The World Bank, 2021).

Anecdotal evidence certainly suggests that remoteness from medical care and poor access to specialist medical centres are associated with advanced disease at presentation and poor overall survival (van Rensburg 2014, van der Hoeven)

3. AIMS & OBJECTIVES

To determine if significant differences exist between metropolitan and remote geographical areas within the Western Cape Province in South Africa, with regard to clinical stage at presentation or overall survival of patients with HNC managed with both curative and palliative intent.

4. MATERIALS & METHODS

A retrospective chart review was conducted of all patients presenting to the Combined ENT/Head and Neck Oncology Clinic at Groote Schuur Hospital in the five-year period from January 2010 to December 2014 managed with both curative and palliative intent. Ethics approval was granted by the University of Cape Town Human Research Ethics Committee (HREC, 351-2017).

Inclusion and exclusion criteria:

Patients were included with squamous cell carcinomas of the oral cavity, oropharynx, larynx, hypopharynx, sinonasal cavities, salivary glands, skin and unknown primary sites.

Patients were excluded for the following reasons:

- Patients living outside of the Western Cape of South Africa, since although some of these were metropolitan areas, they were still geographically remote from Groote Schuur Hospital
- South African patients with no identification documents, and foreign patients, due to our inability to follow up their date of death
- Incomplete records of the nature of their cancer site, type or staging
- Patients with previous medical history of any cancer or radiation therapy before the start of this folder review, and patients developing cancer in non-head and neck areas during the follow-up period, since this may have influenced their survival independently of their HNC
- Patients with benign or premalignant tumours, since this study focuses on HNC
- Patients with sarcoma, lymphoma, Merkel cell carcinoma, and neuroendocrine carcinoma, since these cancers are not staged by the TNM system
- Patients with nasopharyngeal carcinoma and carcinoma of the ear, since these cancers have such completely different natural histories from squamous carcinoma in other HNC sites, thereby creating a much more heterogenous sample, which reduces the statistical power of the study

Data from hospital folders were collected, collated, and reviewed by the first author. Patient anonymity was preserved by allocation and use of a unique patient identification number in the spreadsheet of results, instead of their names, ID numbers, or hospital numbers. Demographic details such as patients' age, gender, residential area and date of registration at the clinic were recorded, as well as cancer site, subsite, histology, and TNM staging.

Residential areas, as defined by the Western Cape Municipality (*Figure 1*) included: City of Cape Town Metropole, with the following subdistricts: Northern, Southern, Eastern, Western, Tygerberg, Klipfontein, Mitchells Plain and Khayelitsha. The remainder of the Western Cape Province is divided into the following districts, which for the purpose of patient management, are remote: West Coast, Cape Winelands, Overberg, Eden, and Central Karoo.

Figure 1: Residential areas

City of Cape Town Metropolitan Subdistricts Remote Districts of the Western Cape

Dates of death were in some cases recorded in the hospital records, but the majority were obtained from the open access registry at the Department of Home Affairs of South Africa. As the majority of patients had no record of the cause of death, we measured overall survival instead of disease-specific survival. We used a simple subtraction of the number of days between the date of registration with the clinic from the date of death to calculate the overall survival in days. The starting date was the first week of January 2010, when the first patients were registered and seen in the clinic, and data collection was terminated on 5 March 2020 due to the start of Covid-19 in South Africa, as the Covid-19 pandemic has had a major impact on survival of patients with comorbidities such as cancer.

All statistical analyses were performed in R (version 4.1.1). We used Kaplan-Meier curves to graphically demonstrate the cumulative survival, and log-rank tests for comparison of strata to determine independent predictors of overall survival, since crude survival figures do not take censored data into account. We also calculated median overall survivals and 5-year overall survivals for comparison to international literature.

5. RESULTS

A total of 1,287 patient charts were reviewed, and 269 were excluded for the following reasons (*Table 1*):

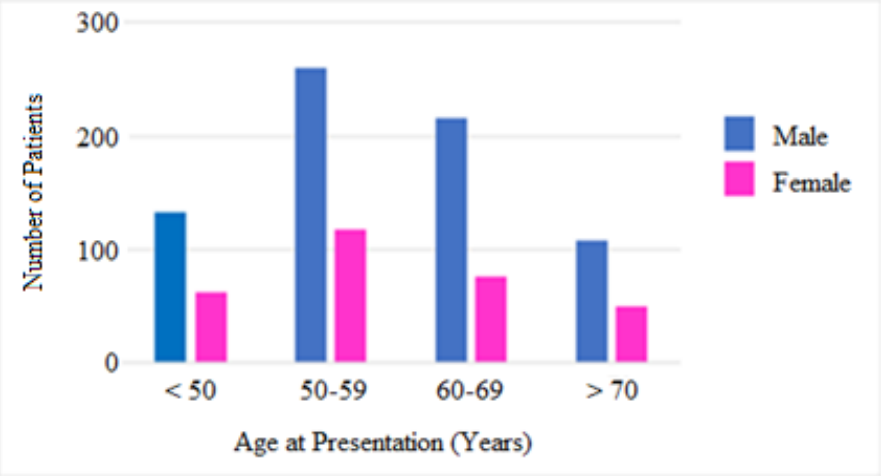
Table 1: Reasons for patient exclusions

Number (%)	Reason for Exclusion
22 (2.2%)	Patients living outside of the Western Cape of South Africa
48 (4.8%)	Patients with no South African identification documents
22 (2.2%)	Incomplete records of the nature of their cancer site, type or staging
79 (7.8%)	Patients with previous medical history of any cancer or radiation therapy before the start of this folder review
5 (0.5%)	Patients developing cancer in non-head and neck areas during the follow-up period
34 (3.3%)	Benign and premalignant tumours
17 (1.7%)	Sarcoma, Lymphoma, Merkel cell carcinoma, and Neuroendocrine carcinoma
42 (4.1%)	Nasopharyngeal carcinoma, Carcinoma of the ear

General Epidemiology

The study included 1,018 patients, ranging in age from 8 to 103 years (median age 58.1 years), and including 714 males and 304 females (male-to-female ratio of 2.3:1). (*Figure 2*).

Figure 2: Distribution of ages of study cohort



The numbers of new patients attending our clinic from metropolitan and remote areas was consistent from year to year, with the metropolitan areas having approximately double the number of patients, which is a reflection of the total population numbers in these areas.

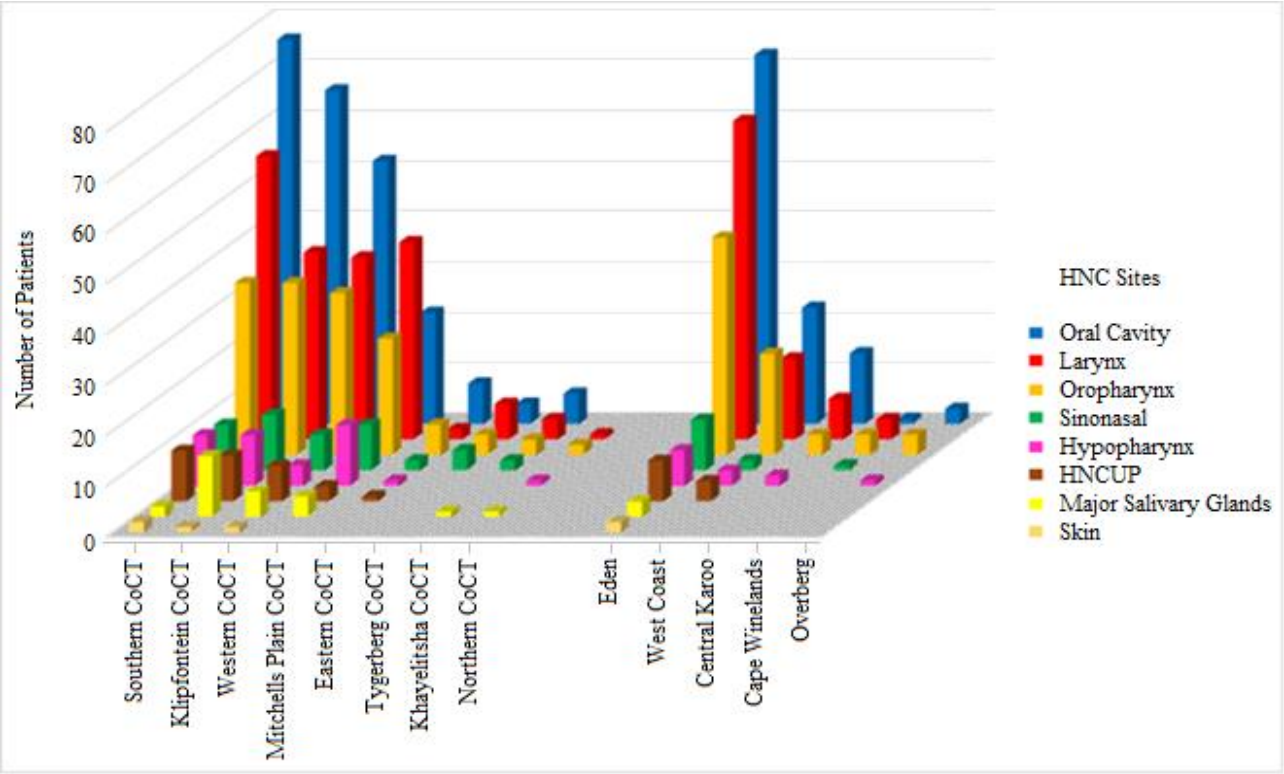
Patients living in remote areas were slightly younger (median 55.6 years) than those living in metropolitan areas (median 58.7 years). This is in keeping with the overall age distribution of the provincial population (according to the Department of Cooperative Governance and Traditional Affairs, South Africa)

Squamous cell carcinomas accounted for 94.3% of patients, and adenocarcinomas for 3.3%. Other subtypes of salivary carcinomas accounted for 1.1%, other sinonasal carcinomas for 0.8%, melanomas for 0.3%, and rare tumours for 0.2% of patients.

The oral cavity, larynx and oropharynx were the most common HNC sites, together accounting for 82% of cases. The remaining 18% were cancers of the sinonasal cavities, hypopharynx, major salivary glands, skin and HNC of unknown primary (HNCUP). There were only 6 patients with skin cancers, as the clinic only manages advanced cases requiring complex resections and reconstruction, parotidectomy and/or neck dissection.

Although all metropolitan and remote districts were represented, some areas like the Eastern, Northern, Tygerberg and Khayelitsha subdistricts of the City of Cape Town are served primarily by Tygerberg Hospital. Likewise, some areas of the Winelands and Malmesbury are served by Paarl and Tygerberg Hospitals, and some areas of the Overberg are served by Hottentots Holland and Tygerberg Hospitals (*Figure 3*).

Figure 3: Burden of HNC in different referral areas

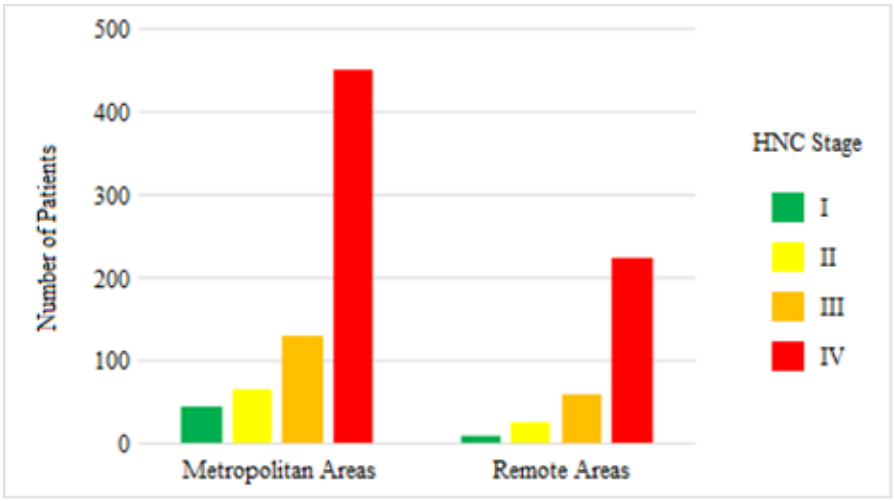


All tumour sites had approximately double the number of patients from metropolitan areas compared to remote areas.

TNM Stages according to geographical region

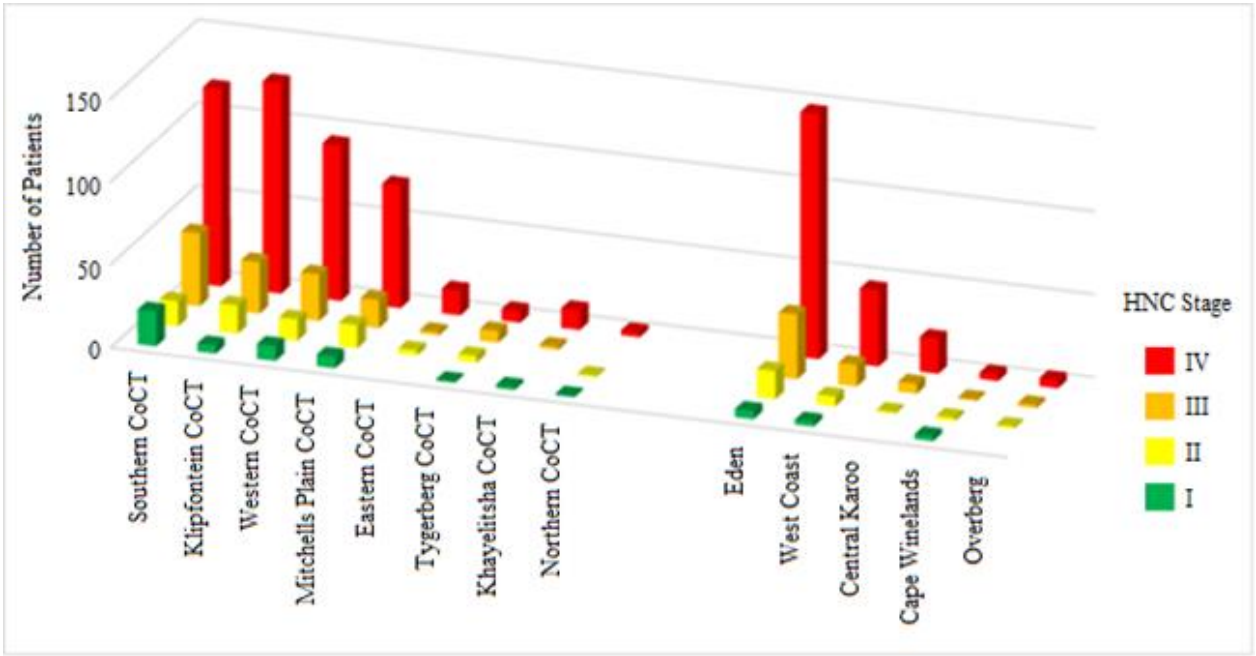
Most patients from both metropolitan (84%) and remote areas (88%) presented with advanced (stage III – IV) disease. There was no significant difference in Chi-squared analysis of the stages of cancer between all the metropolitan areas compared with all the remote areas (P = 0.16) (*Figure 4*).

Figure 4: TNM stage according to metropolitan vs remote



There were, however, some significant differences in cancer stages between different districts and subdistricts (P = 0.0123). Of stage I cancers, 37% originated in the Southern subdistrict of City of Cape Town, while all the remote areas *combined* had only 19% of stage I cancers. The Eden area (includes Oudtshoorn, George, Knysna, Plettenberg Bay and Mossel Bay) had a high burden of advanced (stages III and IV) cancers (187 cases); this represents 66% of all the remote areas' advanced cancers (*Figure 5*).

Figure 5: TNM Stage according to residential districts

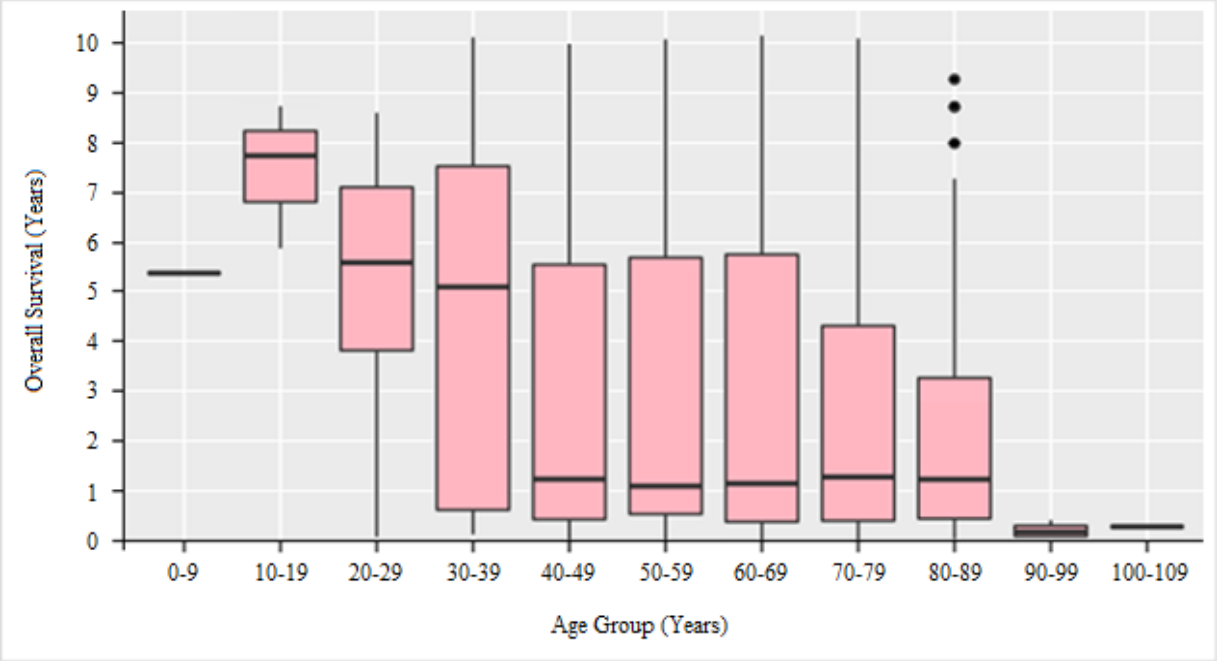


Overall survival

At the end of the study period, 231 of 1,018 patients (22.7%) were still alive; for purposes of statistical analysis, these were recorded as censored data. The median follow-up time for these

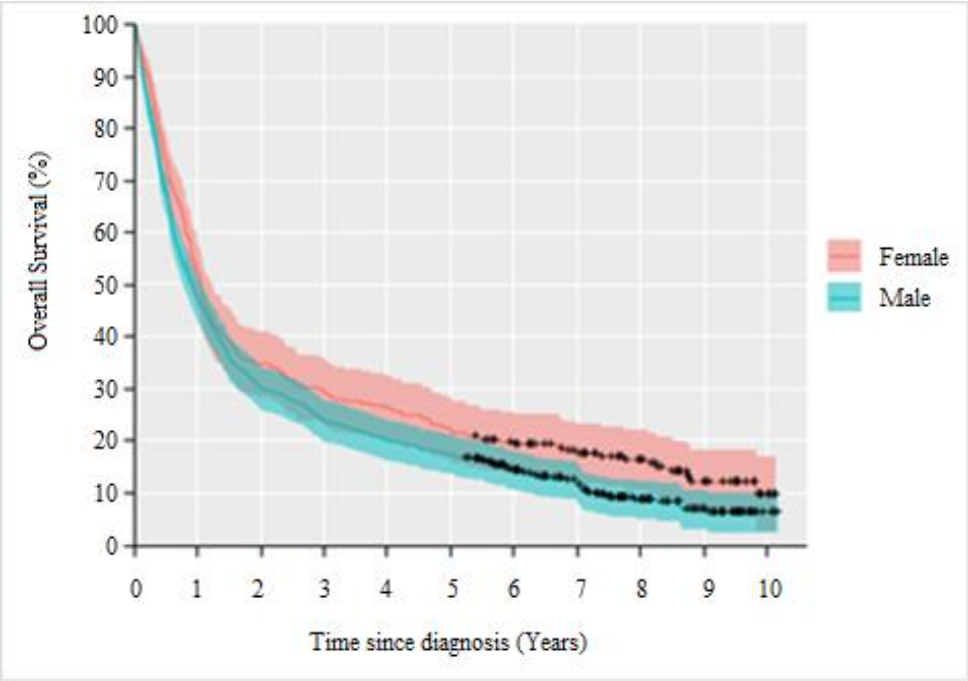
patients was 7.6 years. A major reduction in overall survival occurred from as early as 40 years. Advanced age at the time of diagnosis was clearly associated with significantly worse overall survival (P < 0.0001) (*Figure 6*).

Figure 6: Overall survival related to age



The median overall survival for males was 1.17 years and for females 1.23 years, which was not significantly different (P = 0.056) (*Figure 7*).

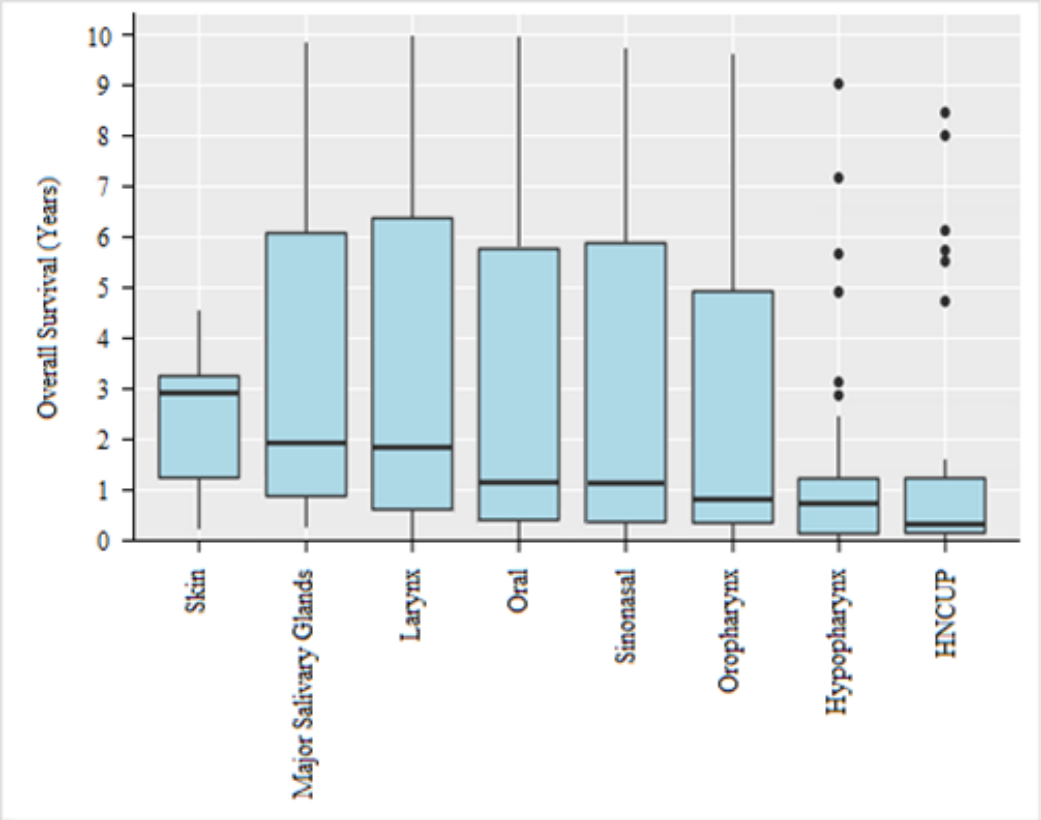
Figure 7: Overall survival related to gender



Overall survival according to tumour site

There was a significant difference in overall survival of cancers of different head and neck sites (P < 0.0001) (*Figure 8*). The 5-year overall survival ranged from 25% to 39% for cancers of the oral cavity, larynx, oropharynx, major salivary glands, and sinonasal cavities. Cancers of the hypopharynx and HNCUP had poor outcomes, and none of our skin cancer patients survived 5 years, but it should be noted that 5 of the 6 skin cancer patients had presented with stage IV disease.

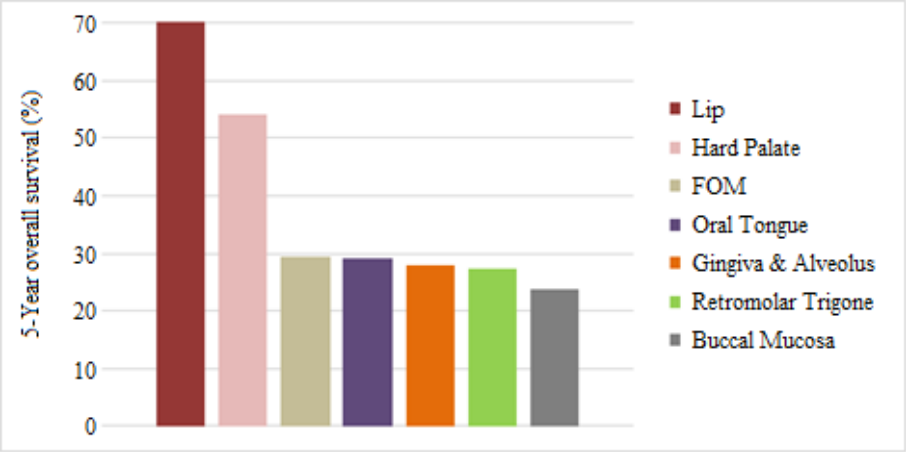
Figure 8: Overall survival according to tumour site



Oral cancer

Squamous cell carcinoma accounted for 97% of cases, and adenocarcinomas and mucosal melanoma for the remaining 3%. The most affected subsites were oral tongue (39%) and floor of mouth (36%). The 5-year overall survival for oral cancer subsites was significantly better for lip and hard palate (71% and 54% respectively) than other subsites (P < 0.001) (*Figure 9*). There was no clinically significant difference in 5-year overall survival between males and females (31% vs 30% respectively), or between the metropolitan and remote areas (31% vs 29% respectively).

Figure 9: 5-year overall survival of oral SCC according to tumour site



Larynx cancers

The number of referrals of larynx cancer decreased over the study period in both the metropolitan and remote areas (*Figure 10*). As expected from international literature (Ferlay, 2015), the male-to-female ratio (5:1) was higher than for cancers at other sites. The majority arose from the supraglottis and glottis (51% and 45% respectively), and only 4% from the subglottis. The 5-year overall survival was better for glottic and subglottic cancers (50% and 45% respectively), compared to supraglottic cancers (22%) (*Figure 11*), and it was better in females than males (47% vs 33%). There was no clinically significant difference in the overall survival between the metropolitan and remote areas (37% vs 33% respectively), or over the study period.

Figure 10: Number of laryngeal cancer referrals

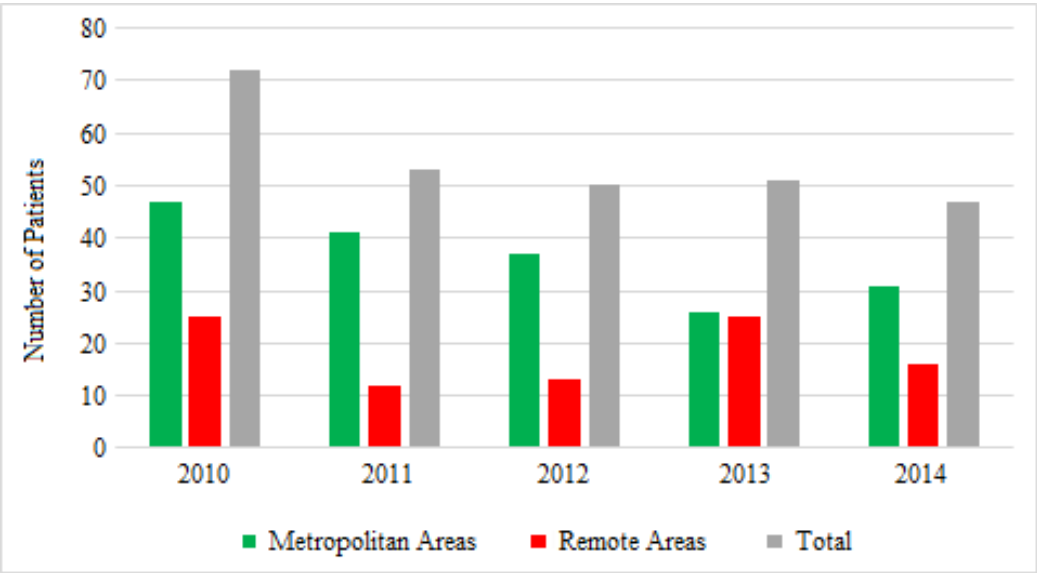
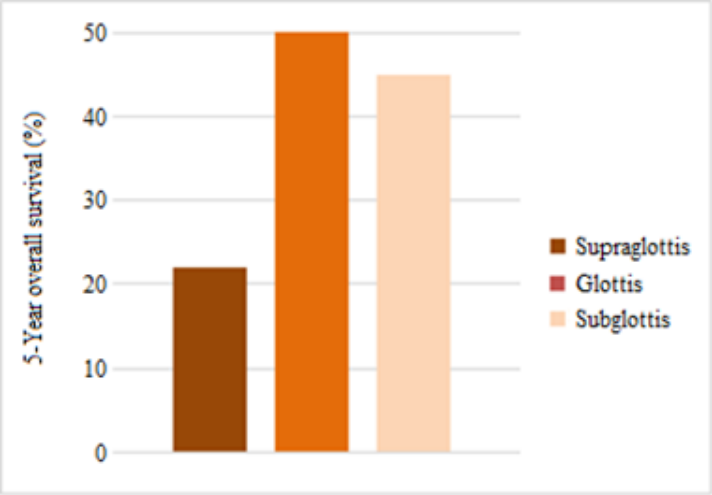


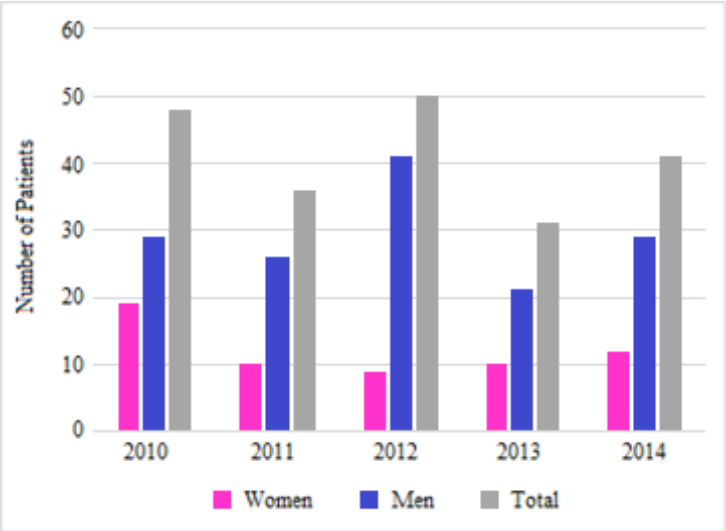
Figure 11: 5-year overall survival (%) of larynx cancer according to tumour site



Oropharyngeal squamous cell carcinoma (OPSCC)

The number of OPSCC referrals almost halved in females (19 in 2010 to 12 in 2014) but was consistently higher in males (average of 29 per year) (*Figure 12*). There was no clinically significant difference in 5-year overall survival between metropolitan and remote patients (24% vs 23% respectively). The 5-year overall survival was 19% in 2010 and 34% in 2014; this was not statistically significant (P = 0.41), but this may be due to the small sample size, and on-going surveillance in this regard may show a trend toward increasing survival.

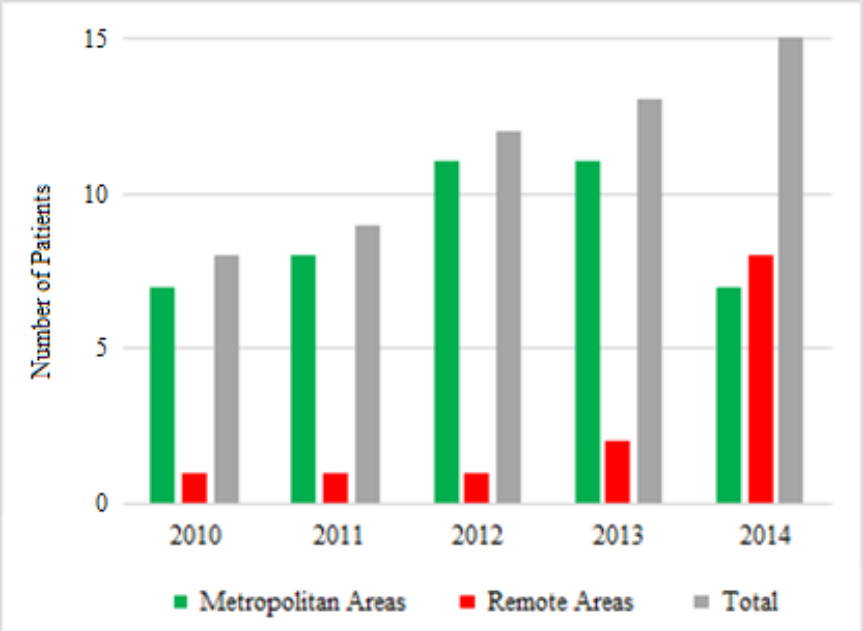
Figure 12: Number of OPSCC referrals per year



Sinonasal cancer

The number of sinonasal cancer referrals increased steadily every year, from 8 in 2010 to 15 in 2014, especially in remote areas (*Figure 13*). Only 4 of 57 cases (7%) of were diagnosed at an early stage, and all of these were from metropolitan areas. The 5-year overall survival was better in females than in males (36% vs 25%, respectively), and more than double in metropolitan compared to remote patients (34% vs 15%, respectively). SCC accounted for the majority (70%) of cases, and had a 5-year overall survival of 20%. The less common histological types included olfactory neuroblastoma, adenoid cystic carcinoma, adenocarcinoma not otherwise specified, sinonasal undifferentiated carcinoma, and mucosal melanoma.

Figure 13: Number of sinonasal cancer referrals per year



Overall survival according to TNM stage

The overall survival for the combined cohort of all tumour sites, in all residential areas was clearly related to the stage of the cancer at presentation ($P < 0.001$) (*Figures 14 and 15)*.

The box-and-whisker graph shows the significant difference of survival according to TNM stage, but also shows numerous outliers in terms of survival of some stage IV patients: of the 675 patients with stage IV cancers, 119 (17%) had overall survival greater than 5 years.

Figure 14: Overall survival according to TNM stage

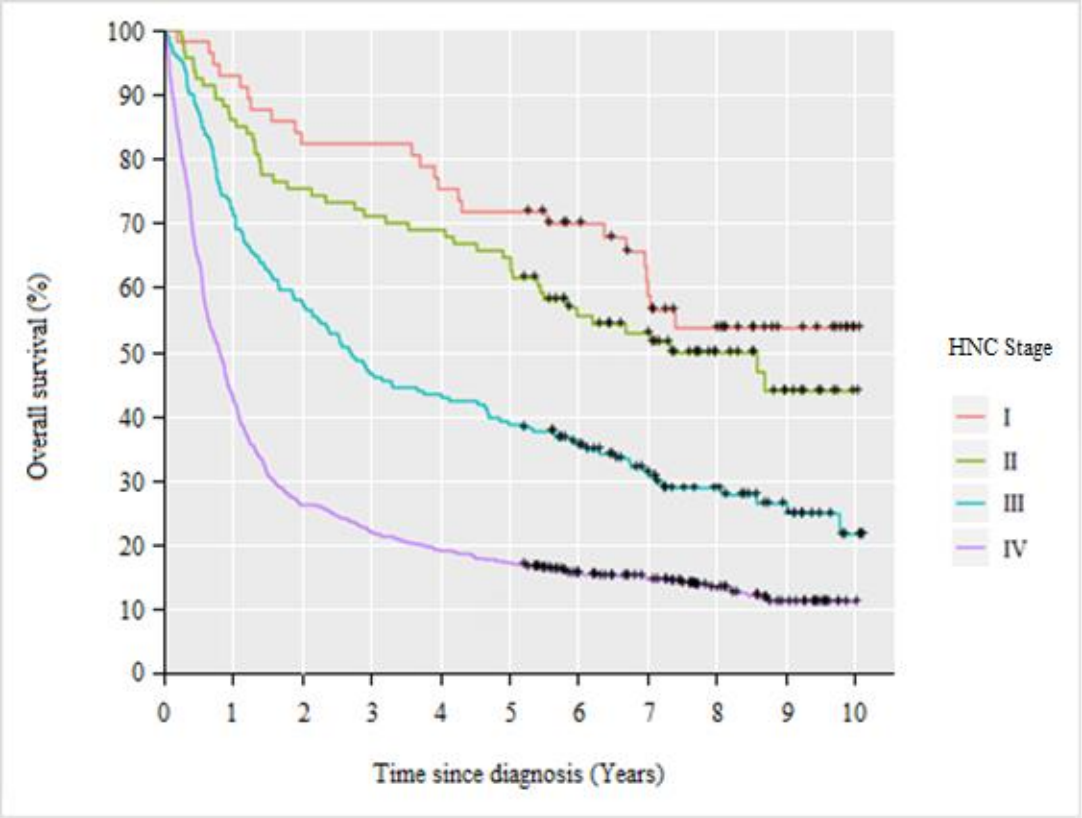
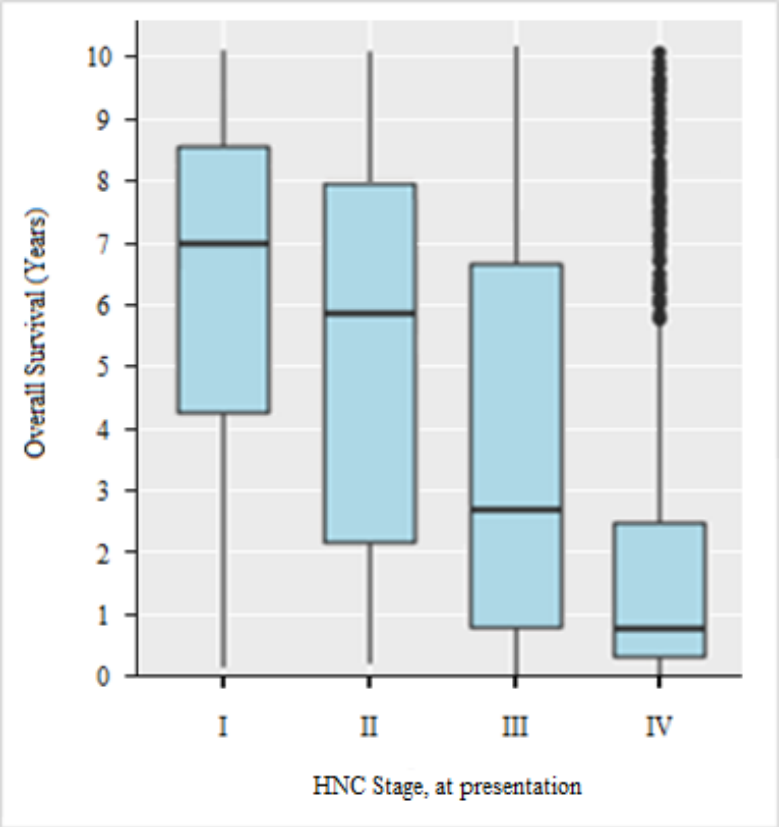


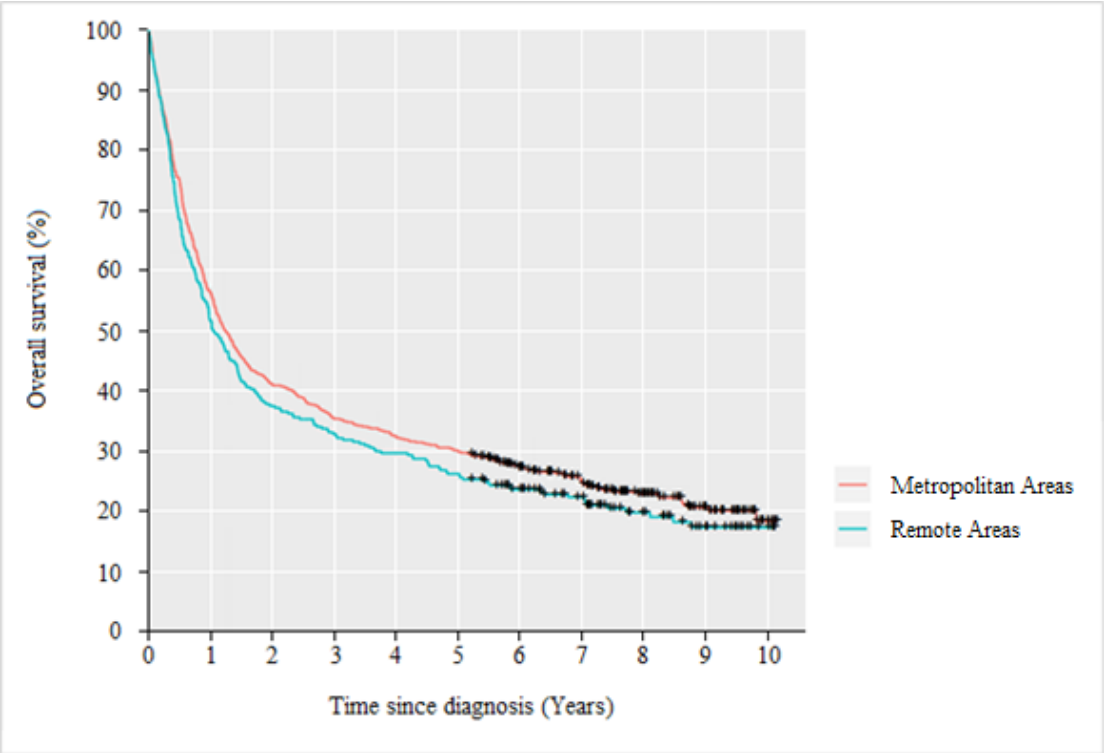
Figure 15: Overall survival according to TNM stage



Overall survival according to geographical region

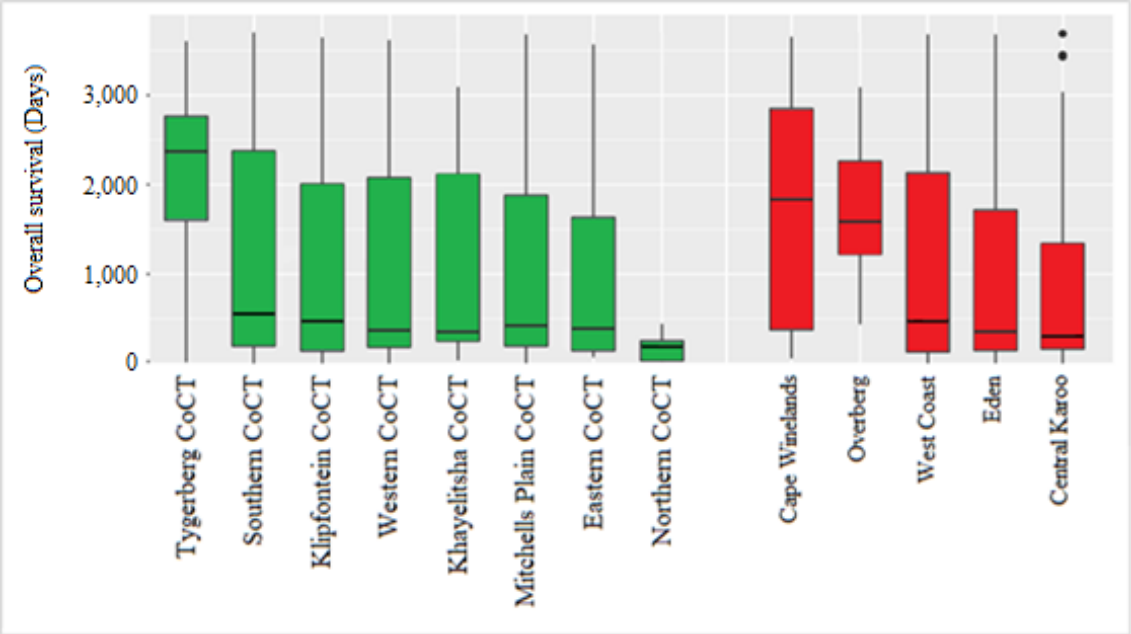
There was no significant difference in median overall survival between all the metropolitan areas combined, compared to all the remote areas combined (1.25 years vs 1.06 years, P = 0.18) (*Figure 16*).

Figure 16: Overall survival according to metropolitan vs remote



There were, however, significant differences in overall survival between specific metropolitan and remote districts (P = 0.015) (*Figure 17*). Although the City of Cape Town Tygerberg subdistrict, Cape Winelands and Overberg areas had much better overall survivals, and the City of Cape Town Northern Subdistrict had much worse overall survival, one should again bear in mind that these specific areas had a very low burden of disease being managed at the clinic, possibly due to being served primarily by other hospitals.

Figure 17: Median overall survival according to geographical region



We illustrated these clinically important differences in a box-and-whisker format, since the Kaplan-Meier graph had numerous overlapping lines making the interpretation difficult.

Atlantis is a town in a small part of the Western subdistrict of the City of Cape Town Metropolitan area, which had 52 patients with a similar median age (57.1 years), similar spectrum of HNCs, and the same proportion of advanced cancer (87%) as patients in the rest of the province. The median survival for patients from Atlantis was only 320 days, compared to 420 days for patients from the rest of the Western subdistrict of City of Cape Town, and 477 days for patients from the rest of the subdistricts of City of Cape Town metropolitan areas. These apparent differences in survival were, however, not statistically significant (P = 0.133 and P = 0.079, respectively).

6. DISCUSSION

Advanced HNC is associated with significant morbidity related both to the disease and in some cases, the treatment, and the long-term survival is poor, especially in LMICs like South Africa (Farmer, 2010 & Patterson, 2019). Disparities in access to healthcare between high- and LMICs are a well-known and long-standing public health concern and are certainly not unique to South Africa. The Millennium Development Goals aspire to achieving equitable access to healthcare; this includes not only geographical proximity, but also economic affordability and cultural acceptability (Dussault, 2006). This study describes the geographic distribution of the burden of HNC in the Western Cape, as well as demonstrating statistically and clinically significant differences in overall survival in specific metropolitan and remotes residential areas.

We measured overall survival of HNC patients managed with both curative and palliative intent, partly due to the limitations in our database and medical records, and partly since HNC recurrence

usually occurs within the first few years after treatment (Ingarfield, 2019), so the two measures of survival should be similar in the context of our follow-up period. Intuitively, one may assume that disease-specific survival would be more relevant to assess cancer mortality, but this is not necessarily so. Non-surgical treatment of advanced HNC is often complicated by a high risk of microaspiration and recurrent chest infections. In LMICs without social service support, patients may become impoverished by having to pay for surgery (Shrime, 2015) or because of the sequelae of the cancer, or of its treatment. Therefore, if the underlying cause(s) of death are not interrogated, disease-specific survival may under-report the true mortality of the disease *and* its treatment. Overall survival, on the other hand, considers death by any cause.

The global incidence of HNC is significantly higher in males than in females, with the ratio varying from 2:1 to 4:1 in different tumour sites and different geographical regions of the world (Stenson, 2021), and our data were in keeping with this literature. Very little literature exists on the impact of gender on mortality of HNC. We found no significant difference in overall survival between males and females attending our clinic. Park (2018) found that females with HNC in California had 1.92 times higher cancer to noncancer mortality compared to males, but they had also been undertreated, having been significantly less likely to have received intensive CRT than males. Roberts (2010) compared survival in male and female HNC patients matched for age, race, smoking status, tumour site, TNM stage, and treatment, and found no significant difference in overall or disease-specific survival.

In our study, advanced age at the time of diagnosis was clearly associated with significantly worse overall survival ($P < 0.0001$) (Figure 6). Advanced age is known to be one of the most important prognostic factors for HNCs: not only by impairing the immune response against carcinogenesis, but also being associated with increasing numbers and severity of comorbidities, and elderly patients are less able to withstand the toxicities of anaesthesia, surgery, chemotherapy and radiation therapy.

The clinical stage of HNC at presentation is also an important prognostic factor for HNC, independent of factors such as age, gender, and tumour location (Ildstad, 1989 and Pera, 1986). Early diagnosis of HNC allows shorter durations of treatment (Kowalski, 1994), lower morbidity (Dolan, 1998) and better prognosis (Janot 1996, Shah 1995, Shah 2006, Mashberg 1995); advanced stages of HNC limit treatment options, and reduce overall survival (Kowalski, 2001). Organ-preservation treatment of HNC is only feasible if the diagnosis is made early. The results in this study certainly support this literature. The Southern subdistrict of City of Cape Town (with the most stage I HNCs) had a median overall survival of 550 days, while the remote Eden area (with two thirds of the remote areas' advanced HNCs) had a median overall survival of 357 days. Atlantis in the Western subdistrict had a median survival of only 320 days, which may partly reflect it's remoteness, since public transport between Atlantis and Woodstock was only introduced in April 2014, toward the end of our study period. It is also likely that this reflects the extremely poor socioeconomic circumstances in the area, with high levels of unemployment, poverty, homelessness, and malnutrition.

Delays in treatment, especially for some sites of HNC such as cancers of the oral cavity, oropharynx, and larynx, are therefore particularly tragic since most of the oral cavity and oropharynx can be viewed and palpated without special instrumentation, and laryngeal cancers generally present with voice symptoms at an early stage.

HPV infection is an important prognostic factor for OPSCC. Although p16 testing for HPV in OPSCC was not widely available during the period of our study, the improved overall survival of OPSCCs over this period possibly reflects an increasing incidence of HPV-related OPSCC.

Our data show that a substantial portion (17%) of stage IV HNCs had an overall survival of greater than 5 years, showing that even advanced HNCs do not necessarily have uniformly poor outcomes.

These data on overall survival can be compared to the Western Cape's life expectancy at birth (Stats SA, 2015) of 63.7 years for men and 66.0 years for women. The median age at death or termination of the investigation was 61.0 years for men and 61.1 years for women, but hundreds of men and women were censored at this time, as follow-up of longer than 5 years would not have added more useful information to this study.

Even though we found no significant difference in median overall survival between all the metropolitan areas combined, compared to all the remote areas combined (P = 0.18), there were significant differences in overall survival between specific metropolitan and remote districts (P = 0.015). One of the difficulties hampering comparative research in this field is the lack of standardised definitions as to exactly what constitutes 'urban' and 'rural', or 'metropolitan' and 'non-metropolitan' populations. Wikipedia defines 'urban' as being a built-up area with high population density and infrastructure of built environment, and 'rural' as having low population density, often with agricultural or forestry land usage. On the other hand, a metropolis is any major city, together with its nearby towns and environs. In South Africa (and many other countries), it would be an over-simplification for this type of research to categorise populations simply as urban and rural alone, since there is a broad continuum between these two extremes. For example, many South African townships have sufficient population densities to be classified as urban but lack any economic core to be functionally urban. Likewise, many formally structured small towns are so geographically remote, that they cannot be truly urban.

One can also use the distance between towns and hospitals to assess remoteness, but again, for a small town 100km from the hospital, this may be quite remote for a patient using a weeks' wages in travel costs but may not be so remote for a patient who uses their own transport.

It is difficult to determine what factors negatively affect outcomes in remote, rural or non-metropolitan populations. It is likely not only the longer distances that deter travel to tertiary hospitals, but also lower levels of formal education, lower socioeconomic status, greater poverty and malnutrition, higher levels of smoking and alcoholism, different attitudes toward healthcare, and cultural practices for example traditional healthcare, that play a role. (Peltzer 2019, Sabesan 2011, Yu 2008, Mitchell 2006). It is also likely that these same factors are associated with more undiagnosed and untreated comorbidities, reducing general life expectancy, which impacts to some extent on overall survival.

Strengths and limitations of the study

The strengths of this study are the large sample size of 1,018 consecutive patients, all of whom were managed by the same multidisciplinary medical team, and the long duration of their follow-up of 7.6 years (of patients still alive at the end at the end of our study period). The weaknesses are the absence of measures of socioeconomic status, which may be more relevant than a patient's address. Future studies should investigate this, as well as prospectively enquire as to the underlying cause of

delays in diagnosis at primary health care levels, and to determine the cause of death. Future studies may also identify whether treatment intents are curative or palliative and analyse these subgroups separately.

7. CONCLUSIONS

Outcomes related to HNC depend on multiple factors, one of which is access to multidisciplinary healthcare. Advanced age and clinically advanced cancer stage are associated with reduced overall survival. While there are significant differences between some metropolitan and remote areas in terms of clinical stage at presentation and overall survival, this is likely due to many factors, such as socioeconomic factors and other hospitals serving some of these areas.

The bulk of HNC managed at Groote Schuur HNC clinic originates from the City of Cape Town Metropole; yet there is a significant burden of disease in the remote Eden area (includes Oudtshoorn, George, Knysna, Plettenberg Bay and Mossel Bay), and in Atlantis in the Western subdistrict of the Cape Town metropolitan area. The difference in median overall survivals between the Southern subdistrict of City of Cape Town (550 days) and Eden (357 days) is not only statistically significant, but is also clinically relevant. Despite these disparities at a district level, there was no significant difference in TNM clinical stages or overall survival between metropolitan and remote patients.

In Australia, where similar problems of geographic isolation of remote communities previously limited access to care, Regional Cancer Centres of Excellence were established, with multidisciplinary staffing, and links to major urban Hospitals. A similar project is being planned in Addis Ababa, Ethiopia (https://www.ircce.org). Perhaps this sort of model could be considered in South Africa.

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