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Ten-year (2009–2019) epidemiological study of head and neck, salivary glands and upper aerodigestive tract cancers, and overall survival outcomes in the Northern Territory of Australia

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ABSTRACT

Background Head and neck, salivary glands and aerodigestive tract cancers (HNACs) rank sixth in cancer incidence in Australia, posing significant public health and economic challenges. However, data on HNACs in the Northern Territory (NT) are lacking, crucial for healthcare planning.

Objective This study aims to analyse HNACs epidemiology, risk factors and survival outcomes in the NT, focusing on Indigenous and non-Indigenous Australians.

Methods We conducted a retrospective analysis (2009–2019) of HNACs cases from the NT Cancer Registry. Ethically approved, the study assessed incidence, mortality, risk factors and survival across ethnic populations.

Results Of 612 potential cases, 524 were analysed, with 35.5% identifying as Aboriginal or Torres Strait Islanders. Predominantly affecting males (median age: 62 years), HNACs showed an age-standardised incidence of 21.9 per 100 000, with stable trends. The 5-year survival rate was 39.6%, notably lower in Indigenous Australians (25%) and remote areas (18%) vs the national average (68%). Oropharyngeal malignancies were common (36% survival). High-risk behaviours such as alcohol use (73%) and smoking (91%) prevailed. Most patients (73%) presented with advanced disease (stages III–IV), with one-third offered palliative care at diagnosis. P16-negative tumours predominated, with increasing P16-positive cases in non-Indigenous patients.

Conclusion HNACs survival rates in the NT are significantly lower than the national average, especially among Indigenous Australians and remote residents. Targeted interventions are needed to improve service planning and delivery, considering identified risk factors and cultural sensitivities, and promoting Indigenous participation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Before this study, it was understood that HNACs are significant health concerns in Australia, with known prevalence, risk factors and survival outcomes. However, comprehensive data specifically from the Northern Territory, especially concerning Indigenous Australians, are limited. This gap in data is crucial as it hinders the development of targeted healthcare strategies and interventions suitable for this unique demographic.

WHAT THIS STUDY ADDS

⇒ This study provides a detailed analysis of HNACs in the Northern Territory over a 10-year period, focusing on both Indigenous and non-Indigenous Australians. It reveals that the overall 5-year survival rate for HNAC in the Northern Territory is significantly lower than the Australian average, with even lower rates among Indigenous populations and individuals in remote areas. The study also highlights the impact of factors like stage at presentation, treatment intent, P16 status and the high prevalence of risk factors like smoking and alcohol consumption. These findings are instrumental in understanding the specific challenges faced in the Northern Territory, guiding future healthcare planning and interventions.

INTRODUCTION

Head and neck, salivary glands and aerodigestive tract cancers (HNACs) are recognised as the sixth most prevalent cancers globally, with an upward trend in incidence rates.[1] These cancers include malignancies in the oral cavity, nasopharynx, salivary glands, hypopharynx and larynx, but exclude thyroid cancers.[2] Key risk factors encompass lifestyle habits such as tobacco smoking, betel nut chewing, alcohol consumption, and poor nutrition and dentition, predominantly impacting individuals between 50 and 70 years.[3 4]

Recent years have seen a growing link between human papillomavirus (HPV) and head and neck squamous cell carcinoma (HNSCC).[5] P16, a surrogate marker for HPV, is often used in tumour analysis due to constraints related to cost and time.[6] It is noted that in the USA, up to 70%

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The insights from this study underscore the need for targeted healthcare strategies and interventions in the Northern Territory, especially for Indigenous communities. It suggests the necessity for early detection programmes, culturally sensitive healthcare approaches, and enhanced infrastructure and resources in remote areas. The study could influence policy-makers to allocate resources more effectively and encourage further research into the unique healthcare needs of Indigenous Australians. Additionally, it may lead to the adoption of more comprehensive and culturally sensitive healthcare practices, potentially reducing the disparities in HNACs outcomes in the region.

of oropharyngeal SCC cases are P16-positive, indicating a more favourable prognosis.[7 8] This prevalence of P16-positive SCC, however, varies regionally.[9 10]

HNACs are staged using the TNM system as defined by both the Union for International Cancer Control and the American Joint Committee on Cancer (AJCC).[11]

In Australia's Northern Territory (NT), spanning 1 349 129 km^2, the incidence of HNACs is significantly higher compared with the rest of the country. This increase is particularly evident in males (52% higher) and to a lesser degree in females (10.2% higher), as categorised under the Australian Statistical Geography Standard (ASGS).[12–14]

Government statistics from 2013 to 2017 reflect a 72% 5-year survival rate for individuals diagnosed with HNACs, including lip cancer, with women experiencing slightly higher rates than men.[15] However, disparities in outcomes are evident, particularly among Indigenous Australians. A study by Moore *et al* identified socioeconomic status, comorbidities and delayed treatment as key factors influencing survival in HNACs, noting a higher likelihood of death from non-cancer causes among Indigenous patients.[16] Furthermore, a Queensland study (1998–2004) highlighted no significant differences in HNACs incidence between Indigenous and non-Indigenous Australians yet found a markedly higher mortality rate among Indigenous patients.[16]

This study aims to conduct a comprehensive and methodically examination of head and neck cancers in the NT over a 10-year period. We intend to gather detailed epidemiological data focusing on factors such as stage, gender, ethnicity, risk factors and comorbidities at diagnosis. Additionally, the study will analyse overall and disease-specific survival rates, with a focus on identifying modifiable factors that could significantly improve patient outcomes, especially within the Indigenous population.

METHODS

Study setting

The study was conducted in the NT of Australia, characterised by a low population density and a significant proportion of Indigenous residents, many of whom live in remote or very remote communities. This unique demographic and geographical context provides a critical setting for investigating head and neck, salivary glands, and upper aerodigestive tract cancers (HNAC), particularly in relation to Indigenous health outcomes.

Study participants

The study encompassed all adults (18+ years) diagnosed with head and neck, salivary glands, and upper aerodigestive tract cancers from 1 January 2009 to 31 December 2019. The NT Cancer Registry (NTCR) provided the data, from which duplicate records and cases of skin, lip or haematological cancers were excluded, resulting in 524 cases for analysis (186 Indigenous and 338 non-Indigenous patients) (online supplemental material, no. of cases). These data allowed for an in-depth analysis of HNAC incidences, patterns and outcomes in both Indigenous and non-Indigenous populations.

Patient and public involvement

This study was a retrospective analysis based on data from the NTCR. As such, no patients were directly involved in the design, recruitment, conduct or dissemination of the research. The research questions, outcome measures and study design were developed independently by the research team without patient or public involvement.

Data source and collection

The NTCR, it is a comprehensive database that systematically collects information on cancer incidences in the NT. The registry operates on a prospective data collection basis, ensuring timely and accurate recording of new cancer cases. The data encompass demographic details, diagnosis information, staging, treatment modalities and outcomes, providing a rich resource for understanding cancer patterns and impacts in the NT population.

Comorbidity analysis

Comorbid conditions significantly influence the prognosis of HNACs patients. To assess the impact of comorbidities, the Charlson Comorbidity Index (CCI) was employed. The index includes a range of comorbid conditions such as diabetes with complications, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, both mild and severe liver disease, hemiplegia, renal disease, leukaemia, lymphoma, metastatic tumour and acquired immunodeficiency syndrome. This method enables a comprehensive evaluation of comorbidities' effects on patient outcomes, crucial for understanding the complexity of HNACs cases.

Stage at presentation

The AJCC eighth edition guidelines were followed for cancer staging. This system classifies cancers into early stages (I and II) with tumours confined to the original site and advanced stages (III and IV) with larger, more invasive tumours.

P16 status analysis and Epstein-Barr virus status analysis

In the context of oropharyngeal SCC, the P16 status was assessed to understand its prognostic implications. P16

serves as a surrogate marker for HPV-associated oncogenic activity, particularly in HNSCC cases. The study focused on P16 status for its relevance in predicting treatment responses and survival outcomes.

The EBV (Epstein-Barr virus) status was collected when available for nasopharyngeal carcinoma cases. However, given the specificity of the study and the broader scope of our analysis, we have chosen not to include a detailed discussion of EBV status in the current results and analysis section. Instead, we plan to explore this aspect in a future article dedicated to a more focused examination of nasopharyngeal carcinoma and its associated factors.

Survival analysis

A comprehensive analysis of 5-year survival rates was conducted, with a focus on progression-free survival (PFS) and overall survival (OS), employing log-rank tests and multivariate regression models to compare primary cancer subsites and patient demographics.

Statistical analysis

In the demographic analysis, key variables such as age at diagnosis, gender, ethnicity (distinguishing between Indigenous and non-Indigenous populations), and the geographical location of the patients at the time of diagnosis (categorised into regional ASGS level 3, rural ASGS level 4 or remote ASGS level 5) were examined. The data was processed and analysed using advanced statistical software, including STATA V.18 (2023) and SPSS V.29. This involved stratifying clinical characteristics based on Indigenous status and applying relevant statistical tests for thorough analysis.

The study also paid close attention to potential risk factors such as tobacco and alcohol usage, employing the Shapiro-Wilks distribution test to assess their distribution and impact. Additionally, the influence of comorbidities on different ethnic groups was rigorously evaluated using multivariate ordered logistic and linear regression models to discern patterns and correlations.

For a more focused analysis, primary cancer subsites were selectively reviewed based on their P16 status, using multivariate regression models to understand the relationship between this biomarker and various cancer characteristics. The survival analysis, a critical component of the study, concentrated on both 5-year PFS and OS. This analysis was facilitated by log-rank tests and supported by a suite of analytical tools including STATA IC V.15, R Project for Statistical Computing V.4.2.0, GraphPad Prism V.9.2.0 and Tableau Software 2022.1, to ensure comprehensive and accurate interpretations of the data.

RESULTS

Overall clinical and demographic data

The research encompassed 524 patients with HNACs, of whom 430 were male (accounting for 82% of the study group) and 94 were female (making up the remaining 18%). Within this cohort, 186 individuals (35.5%) were identified as Indigenous Australians, while the remaining 338 participants (64.5%) were non-Indigenous.

In this cohort, males comprised the majority (82%), and most participants were non-Indigenous Australians (65%). A substantial proportion, over half (55%), were from regional areas as per the ASGS level 3 classification. The median age at diagnosis across the study was 62 years, which remained consistent when comparing Indigenous and non-Indigenous patients. Multivariate analysis revealed a significant difference in the incidence of head and neck aerodigestive tract cancers (HNAC) between the NT and the rest of Australia. Specifically, the OR was 11.23 with a 95% CI of 10.26 to 12.28 (p<0.0001) (as shown in figure 1A).

A

Clinical variables	Patients (n=524)	Indigenous (n=186, 35%)	Non-Indigenous (n=338, 65%)	p-value
Age (years) (median (IQR))	62.1 (57, 60)	62.05 (57, 79)	62.1 (57, 60)	0.651*
Sex (Male)	430 (82%)	141 (27%)	289 (55%)	0.004*
ASGS level 3	289 (55%)	38 (7%)	251 (48%)	0.001*
ASGS level 4	122 (23%)	57 (11%)	65 (12%)	0.642
ASGS level 5	113 (22%)	91 (17%)	22 (4%)	<0.001 *
Remote (ASGS 4 or 5)	235 (45%)	148 (28%)	87 (17%)	0.001*
Smoking history	478 (91%)	176 (34%)	302 (57%)	<0.01*
PYH	39 (30, 40)	37 (30, 39)	40 (35, 45)	0.001*
Alcohol history	381 (73%)	139 (27%)	242 (46%)	<0.01*

B

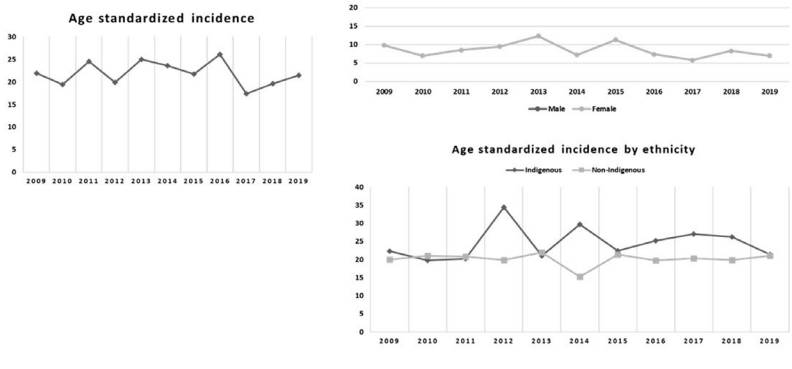


Figure 1 (A) Clinical and demographic profile of patients with Head and neck, salivary glands and aerodigestive tract cancers (HNACs) patients by Indigenous status (B) Age-standardised incidence. Overall incidence, incidence by gender and by ethnicity are represent. P value derived from two-tailed proportions z-test for categorical parameters and Kruskal-Wallis rank test for continuous parameters. *Significance at p<0.05. ASGS, Australian Statistical Geography Standard; PYH, pack-year history.

In the study of HNACs in the NT, the analysis included a breakdown by cancer type and primary subsite. The study examined various primary subsites of HNAC, identified by the TNM, ICD-10-CM Diagnosis Code. These included nasopharynx, sinonasal, oral cavity, oropharynx, major and minor salivary glands, hypopharynx, larynx and unknown primary.

The most common subsite was the oropharynx, which accounted for 205 cases (30%) of the total, comprising 130 non-Indigenous and 75 Indigenous patients. The study also reported survival rates by subsite, revealing significant differences in outcomes depending on the subsite affected. For example, salivary glands showed the highest probability of survival at 61.8%±1.22%, while the nasopharyngeal subsite had the lowest survival rate at 21.4%±0.7%. The oropharyngeal subsite had a probability of survival of 36.3%±2.1%.

These details are crucial as they provide insights into the behaviour and treatment of different types of head and neck cancers, which are essential for planning targeted interventions and improving patient outcomes.

Incidence

During the decade-long investigation in the NT, the age-standardised incidence rate of HNACs stood at 21.9 per 100 000 individuals, with no significant changes observed through the period (figure 1B). A pronounced disparity in incidence rates was apparent between genders, with males presenting a notably higher rate of 36.1 per 100 000, while females had an incidence of 8.5 per 100 000.

The study also found that males are more commonly affected by HNACs in both the NT and the rest of Australia, with a male-to-female ratio ranging from 2:1 to 4:1. However, the incidence rate in NT males was significantly higher than that seen in males across the rest of Australia, while the rates for females were comparable between the NT and the rest of the country.

In terms of ethnicity, the Indigenous population in the NT had a median HNAC incidence of 24.5 per 100 000, which was higher than the 20.1 per 100 000 observed in the non-Indigenous population. Further analysis using a multivariate approach showed an OR of 1.22 (p=0.0037 [95%CI 0.62 to 2.40]), suggesting that Indigenous individuals have a 22% higher probability of developing HNAC compared with non-Indigenous individuals in the NT.

Overall survival

Figure 2 presents the 5-year survival rates for head and neck cancer patients in the NT, as determined by Kaplan-Meier analysis. The OS rate for these patients was 39.6% (with a margin of error of ±2.9). A breakdown by gender revealed that males had a lower survival rate of 36.3% (±4), while females had a notably higher rate of 48.3% (±4). When considering ethnicity, the survival rate for Indigenous patients was 25.6% (±1.8), significantly lower than the 46.0% (±2) survival rate observed in non-Indigenous patients.

Survival by stage at presentation

Our analysis revealed that a minority of the study participants, specifically 27.67%, were diagnosed at the early stages (I and II). In contrast, a significant majority, 72.33%, presented with cancer at the advanced stages (III and IV), as illustrated in figure 3A. Notably, within the Indigenous subgroup, which constitutes 32.33% of the study population, there was a pronounced tendency for advanced-stage diagnosis; 86% of these patients were found to be in the advanced stages, with stage IVa being the most frequently observed stage at the time of diagnosis. This was in comparison to the non-Indigenous population, where 66.4% were diagnosed at advanced stages.

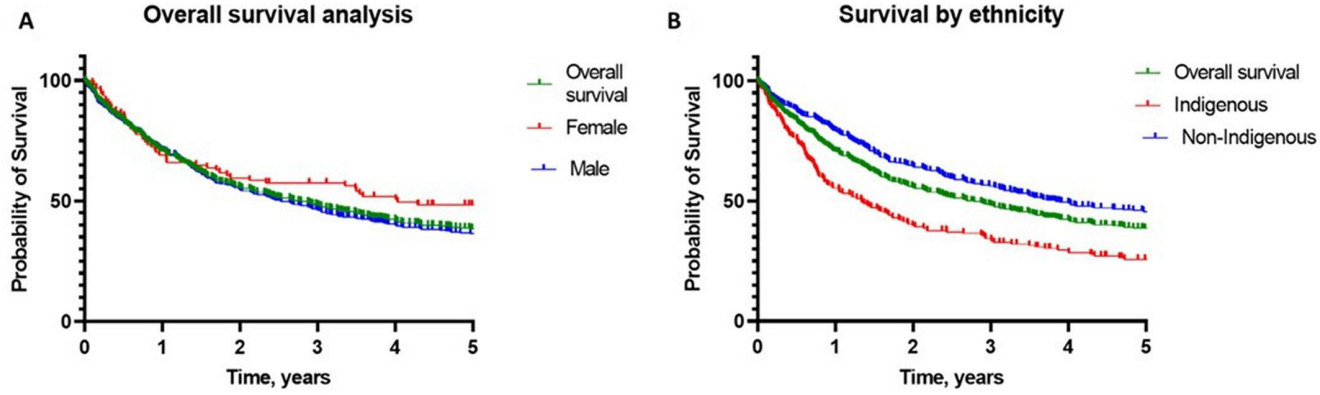
Further, figure 3B delineates the 5-year survival rates based on the stage of disease. The data indicated that patients diagnosed at later stages (III and IV) had notably lower survival rates (42.4% for stage III and 19.4% for stage IV) compared with those diagnosed at earlier stages (76.5% for stage I and 67.3% for stage II). This pattern suggests a grimmer prognosis for patients with advanced-stage cancer. Significantly, the 5-year survival rate for Indigenous patients was substantially lower at 25.6%, compared with 46.0% for non-Indigenous patients. This disparity is attributable, in part, to a higher incidence of advanced-stage diagnosis among Indigenous patients (86% in stages III and IV) as opposed to 66.4% in the non-Indigenous group. These findings underscore the critical importance of early detection and intervention, particularly in the Indigenous community, to enhance patient outcomes.

Survival by treatment intent: curative versus palliative

An analysis of different treatment approaches revealed that at the time of diagnosis, 38.6% of patients received palliative care. Among these patients, a higher percentage were Indigenous (22.4% among Indigenous patients compared with 16.2% among non-Indigenous patients). Interestingly, Indigenous patients were twice as likely to receive palliative care (with an OR of 2.159, and a p<0.0001) as shown in figure 3C. Additionally, patients who received palliative care had worse survival rates (11.4% compared with 53.4%), as depicted in figure 3D.

figure 3D,E illustrates the impact of excluding patients offered palliative care from the analysis. This exclusion resulted in an overall 5-year mean survival rate of 53.4%, which is more consistent with the overall 5-year survival rate for head and neck cancers in Australia. According to the latest data from the Australian Institute of Health and Welfare from 2016 to 2017, the national survival rate for head and neck cancers in Australia is 64%.[17]

Patients who received curative intent treatment had better survival outcomes, underscoring the importance of timely and appropriate treatment for head and neck cancers. The most common curative treatments included chemoradiotherapy, followed by trimodality therapy and surgery with postoperative adjuvant radiotherapy. Only a small percentage (7.25%) of patients received primary



C

Variables	KM Five-year survival	p-value
Overall	39.6% ±2.9	<0.001*
Males	36.3% ± 4	0.001*
Females	48.3% ± 4	0.001*
Indigenous	25.6% ± 1.8	<0.01*
Non-Indigenous	46.0% ± 2	0.001*
P16 Positive	51.9% ± 2.3	0.001*
P16 Negative	31.2% ± 1.7	<0.01*
RA3. Outer Regional Australia	46.8% ± 2.1	0.774
RA4. Remote Australia	52.5% ± 1.3	0.079
RA5. Very Remote Australia	18.1% ± 2.8	0.001*

Figure 2 Five-year relative mean survival. (A) Overall survival for Head and neck, salivary glands and aerodigestive tract cancers (HNACs), male, female and combined. (B) Five-year survival analysis comparing Indigenous, non-Indigenous population and combined. (C) Table showing clinical variables and Kaplan-Meier's 5-year survival. P value derived from two-tailed proportions z-test for categorical parameters and Kruskal-Wallis rank test for continuous parameters against the Australian mean 5-year survival. *Significance at p<0.05. P16: Cyclin-dependent kinase inhibitor 2A highly correlated with human papillomavirus infection in head and neck squamous cell carcinoma.[47]32 RA, remoteness area.

radiotherapy alone, as shown in figure 3F. The choice of treatment takes into account individual factors such as tumour characteristics, comorbidities and patient preferences.

Survival by subsite

In this study, we examined cases of HNACs using eight primary subsites as defined by the ICD-10-CM Diagnosis Code. These subsites include the nasopharynx, sinonasal, oral cavity, oropharynx, major and minor salivary glands, hypopharynx, larynx and cases where the primary site was unknown. Among these subsites, the oropharynx was the most common, accounting for 205 cases (30%) in total, with 130 cases among non-Indigenous patients and 75 among Indigenous patients, as shown in figure 4A.

We conducted a 5-year survival analysis for each subsite, which is presented in figure 4B using Kaplan-Meier analysis. Salivary gland cases had the highest probability of survival, at 61.8%±1.22%, while cases originating from the nasopharynx had the lowest survival probability, at 21.4%±0.7%. Oropharyngeal cases (the most frequent subsite) showed a survival probability of 36.3%±2.1%.

Figure 4C provides a comparison of the 5-year survival rates across the different subsites, indicating an OS probability of 39.6%±2.9% and a median survival duration of 2.75 years. Statistical analyses using p values derived from two-tailed proportions z-tests for categorical parameters and Kruskal-Wallis rank tests for continuous parameters revealed significant differences in survival rates among the various subsites, with a significance threshold of p<0.05.

Risk factors

Alcohol and smoking history

The study identified smoking and alcohol consumption as primary factors associated with HNACs. Among individuals with HNACs, 91% were smokers, with a median pack-year history (PYH) of 39 (range: 30–40), and 73% had a documented history of alcohol consumption.

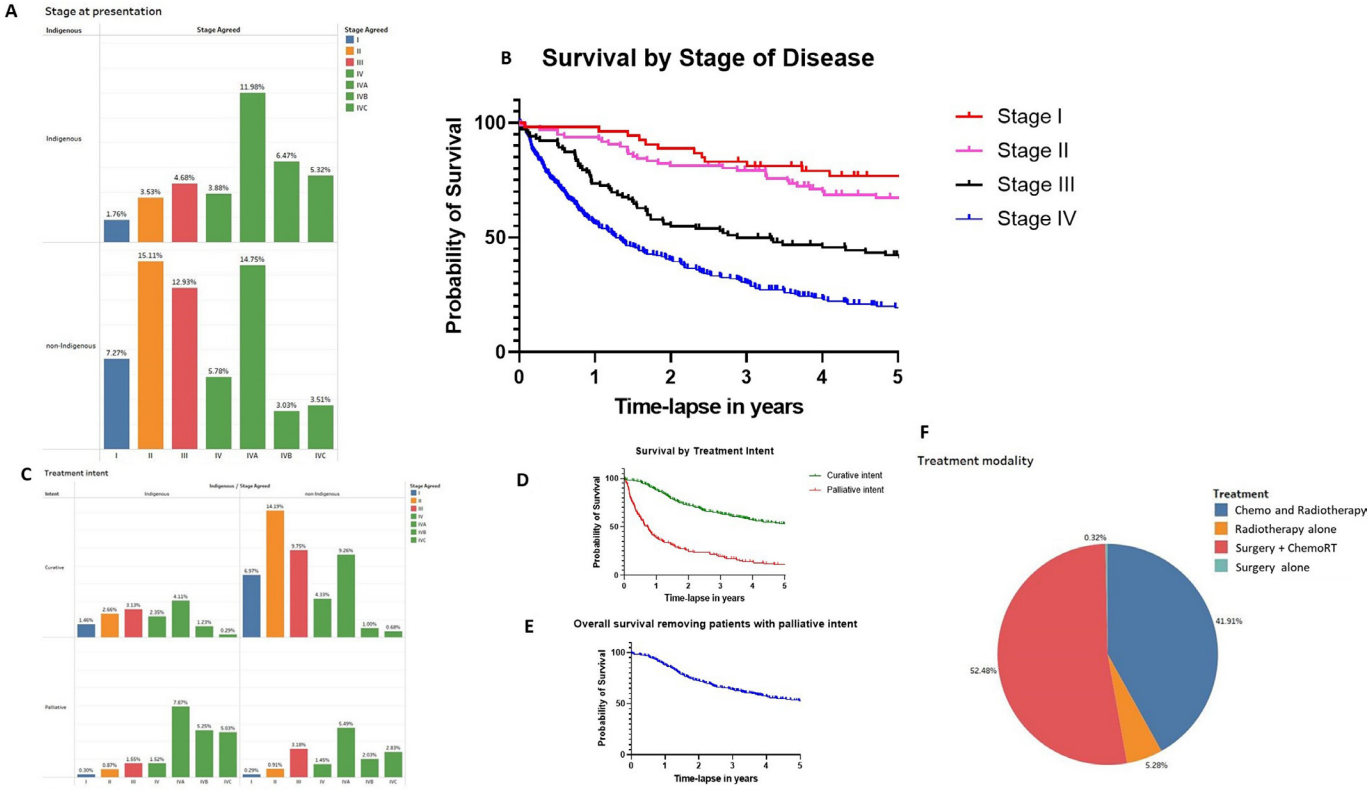


Figure 3 This figure presents an analysis of the stage of cancer presentation broken down by ethnicity. (A) Colour table with details of the staging by grades and ethnicity. (B) Five-year mean survival by stage of disease. In regard of the analysis of treatment modalities by ethnicity and corresponding 5-year survival rates. (C) Staging by curative intent and ethnicity. (D) Kaplan-Meier 5-year mean survival rates by treatment intent. (E) Effect of excluding palliative intent patients on 5-year survival rates in head and neck aerodigestive tract cancer study. (F) The treatment modalities for patients with curative intent.

Additionally, a high median PYH of 39 was observed, indicating an association with a higher HNAC risk (see figure 1A).

Comorbidities

In our study, we found that the average CCI was 7.4±1.23, indicating a substantial comorbidity burden within the entire population under examination. Notably, there was no significant distinction in CCI between the Indigenous and non-Indigenous groups, implying that comorbidities may not be a prominent contributing factor to the differences in survival rates.

P16 status (in oropharyngeal subsite)

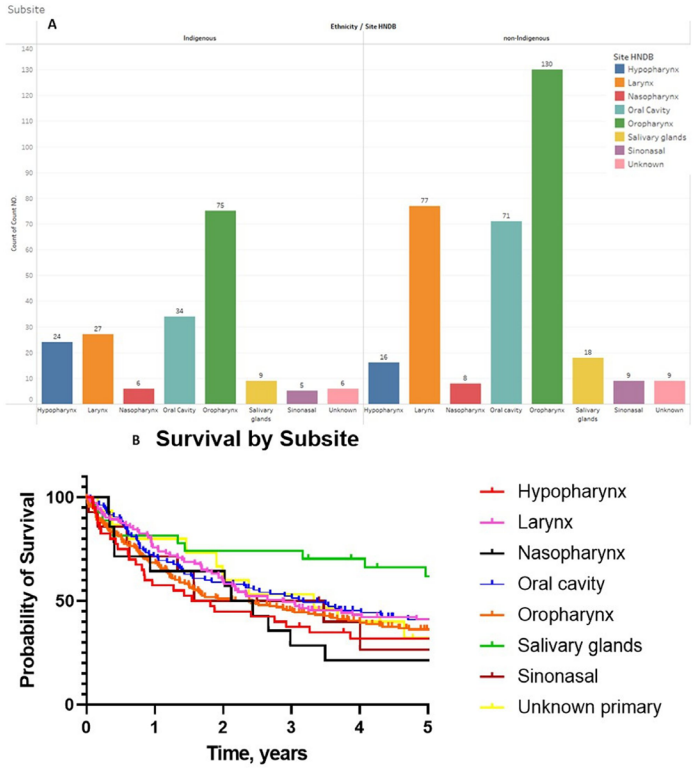
Our findings showed that among the 205 patients with oropharyngeal SCC in the NT, 61.88% were P16-negative, while 38.12% were P16-positive. Importantly, P16-positive tumours were associated with significantly better survival rates, ranging from 50% to 57%, compared with 21% to 29% for P16-negative tumours (p<0.0001). This highlights the prognostic importance of P16 in oropharyngeal SCC (figure 5A,B).

The analysis of P16 status in the NT oropharyngeal SCC cohort highlights significant differences between Indigenous and non-Indigenous groups. Overall, 38.12% of the cohort tested positive for P16. However, a distinct pattern emerged showing a lower prevalence of P16 positivity among Indigenous patients as compared with their non-Indigenous counterparts. This disparity in P16 status distribution is statistically significant, as evidenced by a χ^2 test result of 14.36, which notably exceeds the critical value of 3.841 at a 0.05 significance level. This statistically significant finding underscores a substantial difference in the molecular characteristics of oropharyngeal SCC between these two populations.

Rurality

In our study, the majority of participants resided in either inner or outer regional areas; however, a noticeable discrepancy emerged between Indigenous and non-Indigenous patients. Notably, a higher proportion of Indigenous patients lived in areas classified as very remote (ASGS level 4 or 5) in comparison to non-Indigenous patients (28% vs 17%, p<0.001), as illustrated in figure 5C and figure 1.

Furthermore, when we conducted a survival analysis based on geographical location, a noteworthy trend emerged. Patients residing in very remote areas exhibited significantly lower survival rates, with a 5-year survival rate of only 18%, in contrast to the 45%–54% survival rates observed for those residing in rural or regional locations (p=0.0005) as shown in figure 5D. These findings emphasise the substantial impact of geographic location



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Survival comparison by subsite	5-year probability of survival	Median survival in years	p-value
Overall	39.6% ±2.9	2.75	<0.001*
Hypopharynx	31.9% ± 1.1	1.68	0.05*
Larynx	41.1% ± 1.7	2.87	0.001*
Nasopharynx	21.4% ± 0.7	2.77	<0.05*
Oral cavity	42% ± 1.2	3.17	0.001*
Oropharynx	36.3% ± 2.1	2.38	<0.05*
Salivary glands	61.8% ± 1.8	>5 years (8.81)	0.001*
Sinonasal	26.6% ± 1.7	2.52	<0.001*
Unknown primary	32% ± 2	3.32	<0.001*

Figure 4 (A) Subsites of aerodigestive cancer of the head and neck showing the oropharynx as modal. (B) Kaplan-Meier (KM) curves by subsites of aerodigestive cancer of the head and neck. (C) Table representing KM's 5-year survival analysis by subsite. Survival is expressed in probability of survival (%) and in median survival years. *Significance at p<0.05.

and access to healthcare resources on the prognosis and treatment outcomes for individuals with head and neck cancer.

DISCUSSION

This study is the first comprehensive investigation of head and neck salivary glands and upper aerodigestive tract cancers (HNACs) in the NT, examining patient demographics, incidence, risk factors and survival outcomes for Indigenous and non-Indigenous Australians. It uses data from the NTCR database, covering the Top End and Central Australia Health Services during the study period. The research reveals significant disparities in HNACs outcomes due to the unique features of the NT. These disparities highlight health inequalities compared with the rest of Australia and differences between NT Indigenous and non-Indigenous patients, building on previous studies on HNACs among Indigenous Australians.[14 16 18] The NT's distinct features, such as its vast land area covering one-sixth of Australia, sparsely populated regions with only five remote urban centres (two of which have populations exceeding 10 000), and a significant Aboriginal and Torres Strait Islander population (28%, the highest in Australia, with 70% residing in remote communities), make it a crucial context for studying HNAC trends among NT Indigenous Australians.[19]

This study generates significant data to address key research questions regarding HNAC in the NT:

1. It examines a 10-year epidemiological analysis, including age-standardised incidence.
2. It conducts survival analysis, encompassing OS and subsite-specific survival.
3. It investigates risk factors influencing stage at presentation and survival in HNAC, including alcohol and smoking, comorbidities, P16 status, stage at presentation and treatment intent.

This study stands apart from previous research by encompassing a wide time frame and evaluating age-adjusted incidence rates, while also comparing risk factors and survival outcomes across diverse groups, including Indigenous and non-Indigenous Australians and individuals from regional, rural and remote areas. Out of the 524 patients diagnosed with head and neck aerodigestive tract cancers (HNAC) during the study period, the majority (82%) were male and non-Indigenous (65%), with a median age of 62 years, which is consistent with the Australian Government's 2022 data indicating that around half of the newly diagnosed patients with head and neck cancer are male and over the age of 60.[20 15 21] Notably, the study also incorporated a substantial cohort of Indigenous patients, numbering 186 or 35.5% of the total.

In 2017, the age-standardised incidence of head and neck cancer was reported at 16 cases per 100 000 people, with a higher incidence in males (25 per 100 000) compared with females (7.7 per 100 000).[22 15] By 2022,

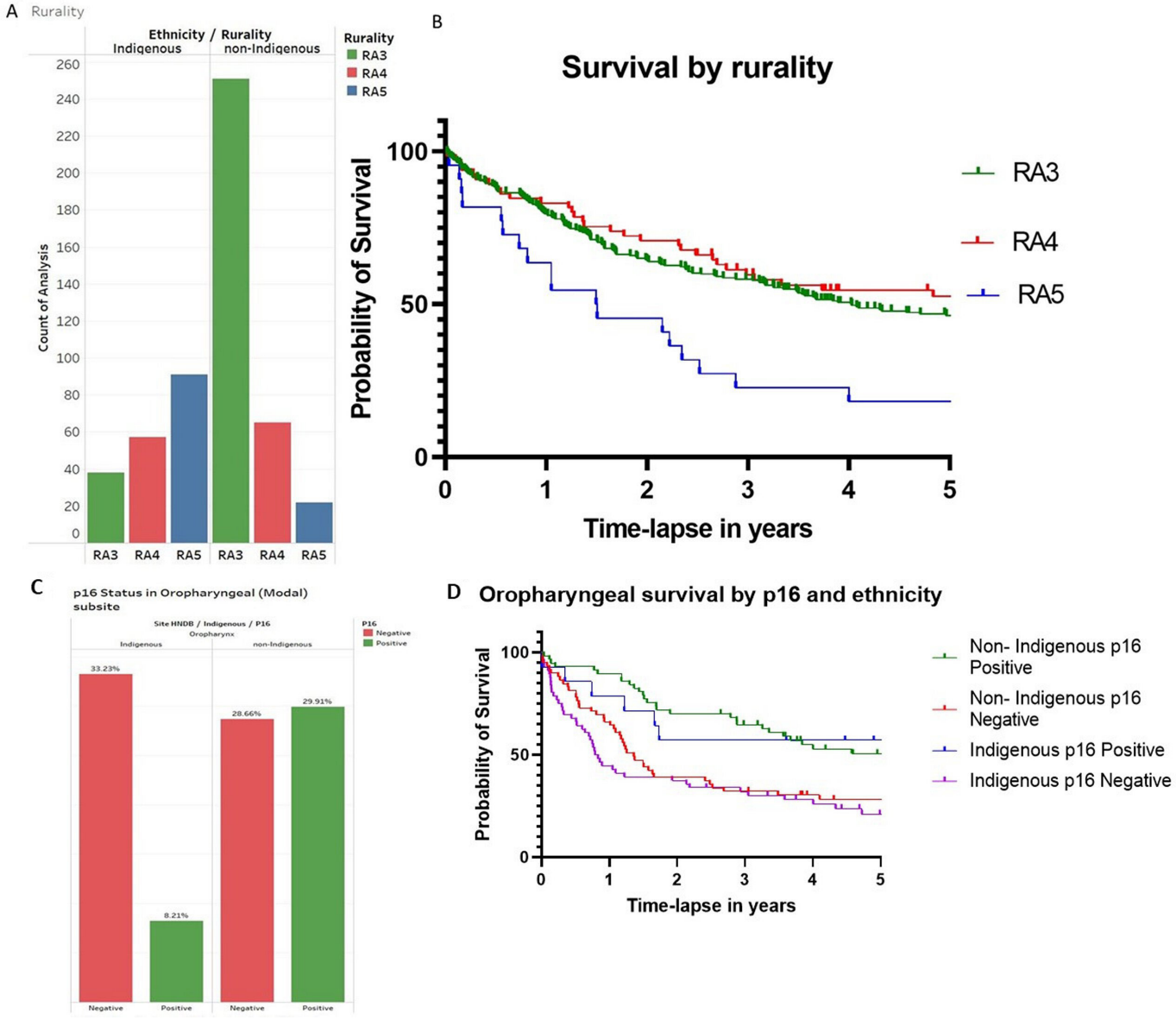

Figure 5 (A) Analysis of rurality broken down by ethnicity. (B) Survival by rurality. Colour shows details about rurality: RA3 (outer regional) in blue, RA4 (remote) in orange and RA5 (very remote) in red. (C) The coloured table describes the analysis of P16 status in the oropharyngeal (modal) subsite broken down by ethnicity. (D) Survival analysis by ethnicity and P16 status for oropharyngeal subsite. RA, remoteness area.

the estimated lifetime risk of being diagnosed with head and neck cancer by age 85 was 1 in 58 (1.7% overall), with the risk being greater for males (1 in 39 or 2.6%) than for females (1 in 112 or 0.89%).[18] In the NT, the incidence of head and neck cancer was notably higher, 325% greater than in other parts of Australia.[23 14] Our study over a 10-year period found an incidence of 21.9 new HNAC cases per 100 000 population in the NT, without a discernible trend over time. Significantly, an OR of 11.23 with a 95% CI of 10.26 to 12.28 (p<0.0001) indicates that NT residents are more than eleven times as likely to develop HNAC compared with those in other Australian regions.

Further analysis within the NT reveals a marked difference in HNAC incidence between Indigenous and non-Indigenous populations. Specifically, Indigenous Australians in the NT have an incidence of 24.5 new cases per 100 000 population. A relative risk calculation shows that Indigenous Australians are approximately 2.3 times more likely to suffer from HNAC compared with their non-Indigenous counterparts in the NT, emphasising the heightened risk in this demographic.

The Australian Government[24] reported that in 2014–2018, individuals diagnosed with HNACs (including lip) had a 72% chance (71% for males and 74% for females) and 68.2% chance in 2006–2010 (without including lip)[15] of surviving for 5 years.[18] In America, the 5-year survival between 1992 and 1996 was 55% without including lip. A report for the period of 2002–2006 noted survival improvement to 66%; a finding attributed to better treatment outcomes of HPV-associated HNSCC.[19] Our study reveals significantly different overall 5-year survival

rates: 39.6% (36.6% for males and 48% for females) overall, 25.6% for Indigenous Australians, and 46% for non-Indigenous counterparts. Five-year survival rates by subsite ranged from 21.4% for nasopharyngeal to 61.8% for salivary gland malignancies. Oropharyngeal malignancies, the most common subsite, had a 5-year survival rate of 36.3%. Lip malignancies, which usually have good survival rates, were not part of this study. Compared with studies outside the NT, our findings indicate lower survival rates for both Indigenous and non-Indigenous HNAC patients, with Indigenous patients experiencing the poorest outcomes.[25]

Alcohol and tobacco use are well-known risk factors for HNACs, leading to a 2.5-fold increase in the risk of head and neck cancer compared with non-smokers and non-drinkers.[26 21] Despite the long-term downward trend in tobacco smoking and alcohol abuse in Australia since 1991 (from 24% to 11% in 2019), there is still a high prevalence of smoking and alcohol consumption in remote areas of Australia (19.6%) compared with inner regional areas (13.4%) and major cities (9.7%).[27] In our study on HNACs, we found a high prevalence of tobacco and alcohol use, with 91% of patients being smokers and 73% reporting excessive alcohol consumption. This trend contrasts with the national decrease in smoking and alcohol abuse in Australia, particularly highlighting the need for targeted interventions in high-risk, remote areas.[28 29] While our data shows these risk factors are significantly present in the HNACs patient population, it does not specifically differentiate between Indigenous and non-Indigenous groups. Given the poorer outcomes in Indigenous populations, further analysis is necessary to determine if these risk factors are more prevalent among Indigenous patients, which would be crucial for understanding and addressing the disparities in HNAC outcomes in the NT[30] .

HNACs patients often have associated comorbidities, influenced by behaviours like smoking and high alcohol consumption, which increase disease risk.[21] To assess the risk of death within 1 year of hospitalisation due to specific comorbidities, CCI is used, validated for HNAC.[31] Comorbidity severity is categorised as mild (CCI 1–2), moderate (CCI 3–4) and severe (CCI>5). Patients with severe comorbidities tend to have worse survival outcomes and more complications.[31 32] Our study found a mean CCI of 7.4 (indicating severe comorbidities) at presentation, with no significant difference between Indigenous and non-Indigenous patients. This underscores the need to address comorbidities in HNAC management, particularly in patients with severe comorbidities. Importantly, it challenges the common belief that worse outcomes for Indigenous patients can be solely attributed to higher comorbidities compared with non-Indigenous counterparts.

HPV-associated HNACs, especially oropharyngeal SCC, is on the rise in Australia, particularly among younger, educated and healthy individuals, potentially contributing to better survival rates in this group.[33 34] Interestingly, we found no studies reporting the prevalence of P16 status in HNAC among the Indigenous population in Australia. P16 data were available for the oropharyngeal subsite in 93% of the patients studied, with 61.88% being P16-negative and 38.12% P16-positive. Patients with P16-positive disease had a 5-year survival of >50%, nearly double that of P16-negative disease (<28%). This aligns with Australian data.[25] Analysis by ethnicity revealed a significant difference in disease aetiology between Indigenous and non-Indigenous groups, with only 9.21% of Indigenous patients having P16-positive disease compared with 29.91% in the non-Indigenous group. Overall, the NT population with HNACs is predominantly identified with P16-negative disease, associated with smoking and alcohol intake.

Foley and Varinder emphasised rurality as a significant risk factor for disparities in head and neck cancer diagnosis and treatment.[35] Patients with HNAC in rural or remote areas face challenges in accessing initial care, emotional support, rehabilitation and follow-up services, exacerbated by long distances. The entire NT is classified as regional, remote or very remote (ASGL level>3), with a higher proportion of Indigenous patients in very remote areas. Our study revealed a significant trend (p=0.001) of lower survival rates (18%) for patients in very remote areas compared with rural (46%) or regional (52%) areas. Patients in very remote areas had 28% lower odds of survival (OR (95% CI) 0.72 (0.57 to 0.90)) compared with those in rural and regional areas. These findings align with Kaur et al. and underscore the need for targeted interventions to improve outcomes for remote HNAC patients.[36]

HNACs are severe diseases with significant morbidity and mortality. Clinical stage at diagnosis is a crucial predictor of patient outcomes. Stages I and II offer a 60%–95% chance of cure, while stages III and IV present a greater than 50% risk of recurrence or distant metastasis, leading to higher morbidity and mortality. Late-stage diagnosis and treatment delays contribute to these disparities.[37] Indigenous patients are often diagnosed with advanced-stage HNAC compared with non-Indigenous patients, with studies indicating these differences.[38]

A study in a Northern Queensland regional hospital found 77% of Indigenous patients had advanced-stage cancer, contrasting with 66% of non-Indigenous patients.[39 40] A report from the NT's palliative care department noted that 70% of HNAC patients between 2011 and 2014 had advanced-stage disease, leading to palliative care as the primary approach.[36 40] Our study showed that only 7.67% of patients were diagnosed at early stages (I–II), while the majority (72.33%) were diagnosed at stages III and IV. Indigenous patients were more likely to present at advanced stages (86%) compared with non-Indigenous patients (66%), resulting in over one-third of the population being offered palliative care at diagnosis, with a higher proportion among Indigenous patients (19%) than non-Indigenous patients (16%).

When we excluded patients who commenced palliative intent treatment in our OS rates for HNACs we realised a figure of 53.4% which is still lower to but more comparable to the survival outcomes reported by the Bureau Australian Statistics.[41] We appreciate that reported results will likely include some patients with palliative intent treatment, but the exercise is simply to demonstrate the potential impact of early detection and timely management, which could help reduce the burden of HNACs and improve patient outcomes.[17]

Patients receiving curative intent treatment had a better survival rate of 53.4%, highlighting the importance of timely diagnosis and access to modalities like surgery, radiotherapy and chemotherapy. Early detection is crucial for improving HNAC outcomes. Unfortunately, many Indigenous HNACs patients in the NT present at advanced stages, leading to higher morbidity and mortality. Understanding the reasons and developing early detection strategies are vital. More Indigenous patients receive palliative care due to factors like at-risk behaviours, limited healthcare access, distrust of the system and cultural perspectives. Accessible local treatment options can encourage Indigenous patients to seek care, allowing them to stay close to family members.[42–44]

Addressing outcome disparities in NT's HNACs patient population is an urgent public health priority. Identifying at-risk patients in early disease stages through prevention and potential screening measures is crucial. Research has demonstrated that simple oral cancer screening, like mouth examinations, can significantly enhance early detection and outcomes.[45] Novel developments such as Point-of-care Analysis for Non-invasive Diagnosis of Oral Cancer (PANDORA) screening kits, designed for oral cancer detection in primary care for high-risk patients, hold promise for early identification, as demonstrated in the PANDORA study).[46] Educating primary care providers in remote areas can aid in early patient identification and screening. Access to specialist nurses and clinicians is essential for provider support, and leveraging digital image capture and telehealth services can further enhance patient management.

Expertise and infrastructure are crucial for local treatment. Culturally sensitive care, local community engagement and involving Indigenous ambassadors can build trust and improve early presentation. While all these points of intervention can be instituted there is a cost implication to an already financially stretched NT Healthcare system. Protected funding to facilitate these targeted improvements to local service provision is imperative at both local government and federal level to achieve better outcomes for our patients and help close the healthcare gap. In summary, addressing the issue of late presentation of HNACs in NT requires a multifaceted approach that involves early detection, specialist engagement at primary care level, understanding the barriers to early presentation, and providing culturally safe and sensitive care. Improving trust and building relationships with Indigenous patients and communities can help break down barriers to early presentation, leading to improved outcomes for patients with HNACs (online supplemental addendum 1). HNACs is a flow diagram the authors hope will help achieve an efficient care model for all HNACs patients inclusive of cultural sensitivities that incorporates the findings and discussion points of this study.

Limitations

This retrospective study has inherent limitations, including potential biases, incomplete or inaccurate data and challenges in ascertaining disease-specific mortality. The data are specific to the NT, which has a unique population and geography that may not represent the broader Indigenous population in other Australian states and territories.

Australia's Indigenous population is diverse, with varying cultural and linguistic backgrounds, potentially impacting the presentation, treatment and outcomes of head and neck cancer (HNACs). Unfortunately, similar studies among Indigenous Australian HNAC patients in other regions and Indigenous populations worldwide are lacking, limiting direct comparisons.

Nonetheless, this study provides valuable detailed demographic and clinical information, including survival analysis, presentation stages, treatment intent and HNAC risk factors in the NT.

CONCLUSION

In conclusion, this comprehensive study of Head and neck, salivary glands and aerodigestive tract cancers (HNACs) in Australia's NT reveals significant challenges, particularly lower survival rates influenced by factors like late diagnosis, aggressive P16-negative disease profiles, and prevalent lifestyle risk factors such as smoking and alcohol use. Our findings underscore the urgent need for targeted public health interventions focusing on lifestyle modification, especially smoking cessation and alcohol use reduction, to improve patient outcomes in the NT. These strategies are vital, as they directly address modifiable risk factors that significantly impact the incidence and prognosis of HNACs.

We advocate for a patient-centred care model specifically designed for HNACs (online supplemental addendum 1), which respects the unique cultural and social backgrounds of Indigenous patients. This model should integrate the expertise of senior clinicians, foster collaborations with local elders and healthcare teams, and include Indigenous ambassadors to ensure comprehensive and culturally sensitive treatment. By enhancing early detection and treatment, this approach aims to improve survival rates and overall health outcomes for patients.

Moreover, in light of the critical role of lifestyle factors in HNACs prevalence and prognosis, we emphasise the importance of public health campaigns and education programmes in high-risk and remote areas. These interventions could substantially reduce the incidence of HNACs and lead to better health outcomes. In addition, continued research and investment are necessary to

develop more effective strategies for managing HNACs, particularly for Indigenous communities in the NT. By implementing these measures, we can move towards a more equitable healthcare system that not only addresses the immediate needs of HNACs patients but also works proactively to prevent the disease and improve the quality of life for all affected individuals, especially those in marginalised communities.

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REFERENCES

1 Ward E, Jemal AS, Xu R. Cancer Statistics 2010. *CA Cancer J Clin* 2011;61:133–4.
2 Gao J, Panizza B, Johnson NW, *et al*. Basic consideration of research strategies for head and neck cancer. *Front Med* 2012;6:339–53.
3 Ferlay J, Shin H-R, Bray F, *et al*. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–917.
4 Agaimy A, Hartmann A. Head and neck Neoplasms: news from the WHO classification of 2017. *Pathologe* 2018;39:1–2.
5 Kreimer AR, Clifford GM, Boyle P, *et al*. Human Papillomavirus types in head and neck squamous cell Carcinomas worldwide: a systematic review. *Cancer Epidemiol* 2005;14:467–75.
6 Chaturvedi AK, Anderson WF, Lortet-Tieulent J, *et al*. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. *J Clin Oncol* 2013;31:4550–9.
7 Kato MG, Baek C-H, Chaturvedi P, *et al*. Update on oral and oropharyngeal cancer staging - International perspectives. *World J Otorhinolaryngol Head Neck Surg* 2020;6:66–75.
8 Wu J, Xiao F, Zheng Y, *et al*. Worldwide trend in human Papillomavirus-attributable cancer incidence rates between 1990 and 2012 and Bayesian projection to 2030. *Cancer* 2021;127:3172–82.
9 Miah MS, McCowan C, Crosbie RA, *et al*. Human Papillomavirus Association in epithelial cancers: a systematic review of the literature. *Oncol Discov* 2013;1:5.
10 Fakhry C, Westra WH, Li S, *et al*. Improved survival of patients with human Papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst* 2008;100:261–9.
11 Iro H, Waldfahrer F. Evaluation of the newly updated TNM classification of head and neck carcinoma with data from 3247 patients. *Cancer* 1998;83:2201–7.
12 Zhang X, Condon J, Dempsey K, *et al*. *Cancer in the Northern Territory 1991 - 2010: Incidence, mortality and survival*. Northern Territory, 2014.
13 Singh J, Jayaraj R, Baxi S, *et al*. Incidence and mortality from Mucosal head and neck cancers amongst Australian States and territories: what it means for the Northern territory. *Asian Pac J Cancer Prev* 2013;14:5621–4.
14 Condon JR, Zhang X, Dempsey K, *et al*. Trends in cancer incidence and survival for indigenous and non-indigenous people in the Northern territory. *Med J Aust* 2016;205:454–8.
15 Welfare. Head and neck cancers in Australia. reports & data. 2014. Available: https://www.aihw.gov.au/reports/cancer/head-neck-cancers-australia/contents/table-of-contents
16 Moore SP, Green AC, Garvey G, *et al*. A study of head and neck cancer treatment and survival among indigenous and non-indigenous people in Queensland, Australia, 1998 to 2004. *BMC Cancer* 2011;11:460.
17 Australia, A.G.C. *Cancer in Australia 2019*. Camberra, 2019.
18 Australia, A.G.C. Head and neck cancer, A.I.O.H.A. welfare, editor. 2022.
19 Zanoni DK, Montero PH, Migliacci JC, *et al*. Survival outcomes after treatment of cancer of the oral cavity (1985-2015). *Oral Oncol* 2019;90:115–21.
20 Australian Institute of Health and Welfare. Canberra, A., profile of Indigenours Australians. 2021.
21 Beynon RA, Lang S, Schimansky S, *et al*. Tobacco smoking and alcohol drinking at diagnosis of head and neck cancer and all-cause mortality: results from head and neck 5000, a prospective observational cohort of people with head and neck cancer. *Int J Cancer* 2018;143:1114–27.
22 Huria T, Palmer SC, Pitama S, *et al*. Linda Tuhiwai Smith Consolidated criteria for strengthening reporting of health research involving indigenous peoples: the CONSIDER statement. *BMC Med Res Methodol* 2019;19:19.
23 Government, N.T. Northern territory cancer Registry. 2021.
24 Government, N.T. Story of our children and young people. 2020. Available: https://dcm.nt.gov.au/generational-change/story-of-our-children-and-young-people

25 Kędzierawski P, Huruk-Kuchinka A, Radowicz-Chil A, *et al*. Human Papillomavirus infection predicts a better survival rate in patients with oropharyngeal cancer. *Arch Med Sci* 2021;17:1308–16.
26 Australian Bureau of Statistics. Regional population growth, Australia, 2017-18. 2019. Available: https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3218.02017-18
27 Eswaran Waran MYZ. Niamh O'Connor, stage at presentation for head and neck cancer in the top end of the Northern territory. *Aust J Rural Health* 2018:10.
28 Council, N.H.a.M.R. Ethical conduct in research with aboriginal and Torres Strait Islander peoples and communities: guidelines for researches and Stakeholders. 2018.
29 Bouland C, Dequanter D, Lechien JR, *et al*. Prognostic significance of a scoring system combining P16, smoking, and drinking status in a series of 131 patients with oropharyngeal cancers. *Int J Otolaryngol* 2021;2021:8020826.
30 Australia, N.T.G.o. *The Northern Territory Environment, P.a.W.S*. Department of Environment, 2022.
31 Singh B, Bhaya M, Stern J, *et al*. Validation of the Charlson Comorbidity index in patients with head and neck cancer: a multi-institutional study. *Laryngoscope* 1997;107:1469–75.
32 Ruud Kjær EK, Jensen JS, Jakobsen KK, *et al*. The impact of Comorbidity on survival in patients with head and neck squamous cell carcinoma: A nationwide case-control study spanning 35 years. *Front Oncol* 2020;10:617184.
33 Piccirillo JF. Importance of Comorbidity in head and neck cancer. *Laryngoscope* 2015;125:2242.
34 Hashmi AA, Younus N, Naz S, *et al*. P16 immunohistochemical expression in head and neck squamous cell carcinoma: association with Prognostic parameters. *Cureus* 2020;12:e8601.
35 Adoga AA, Kokong DD, Ma'an ND, *et al*. The predictive factors of primary head and neck cancer stage at presentation and survival in a developing nation's tertiary hospital. *SAGE Open Medicine* 2018;6:205031211879241.
36 Kaur V, Rooney A, Desai RP. Outcome disparities in rural versus urban patients with head and neck cancer: leveling the playing field. *JCO* 2021;39:e18529.
37 Zhou J, Zhou L, Tao L, *et al*. Oncological outcomes of surgical treatment for T3 supraglottic Laryngeal squamous cell carcinoma patients. *Acta Otolaryngol* 2018;138:1028–34.
38 Cervenka BP, Rao S, Farwell DG, *et al*. Efficacy of Laryngectomy alone for treatment of locally advanced Laryngeal cancer: A Stage- and Subsite-specific survival analysis. *Clin Otolaryngol* 2018;43:544–52.
39 Smith J, Nastasi D, Tso R, *et al*. The effects of continued smoking in head and neck cancer patients treated with radiotherapy: A systematic review and meta-analysis. *Radiother Oncol* 2019;135:51–7.
40 Tan JY-A, Otty ZA, Vangaveti VN, *et al*. A prospective comparison of times to presentation and treatment of regional and remote head and neck patients in North Queensland, Australia. *Intern Med J* 2016;46:917–24.
41 Statistics, A.B.o. Australian statistical geography standard (ASGS). 2013.
42 Ritchie T, Purcell T, Westhead S, *et al*. Enablers and barriers to primary Healthcare for aboriginal and Torres Strait Islander adolescents: study protocol for Participatory mixed-methods research that builds on WHO global standards. *BMJ Open* 2021;11:e046459.
43 Yashadhana A, Fields T, Blitner G, *et al*. Trust, culture and communication: determinants of eye health and care among indigenous people with diabetes in Australia. *BMJ Glob Health* 2020;5:e001999.
44 Dimitropoulos Y, Gunasekera H, Blinkhorn A, *et al*. A collaboration with local aboriginal communities in rural New South Wales, Australia to determine the oral health needs of their children and develop a community-owned oral health promotion program. *Rural Remote Health* 2018;18:4453.
45 Sankaranarayanan R, Ramadas K, Thomas G, *et al*. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. *Lancet* 2005;365:1927–33.
46 Hughes MP, Labeed FH, Hoettges KF, *et al*. Point-of-care analysis for non-invasive diagnosis of oral cancer (PANDORA): A technology-development proof of concept diagnostic accuracy study of Dielectrophoresis in patients with oral squamous cell carcinoma and dysplasia. *J Oral Pathol Med* 2023;52:305–14.
47 Stephen JK, Divine G, Chen KM, *et al*. Significance of P16 in site-specific HPV positive and HPV negative head and neck squamous cell carcinoma. *Cancer Clin Oncol* 2013;2:51–61.