UNIVERSITY OF CAPE TOWN

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MMed Part III (minor Dissertation)

Sino-**N**asal **S**quamous **C**ell **C**arcinoma (SNSCC): a retrospective review of the treatment outcomes of patients treated at Groote Schuur Hospital, Cape Town, South Africa

By

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PART A: STUDY PROTOCOL

Research Title

Sino**N**asal **S**quamous **C**ell **C**arcinoma (SNSCC): a retrospective review of the treatment outcomes of patients treated at Groote Schuur Hospital, Cape Town, South Africa

Purpose of study

A 10 year retrospective folder review of patient treatment outcomes for sinonasal [nasal cavity, maxillary antrum & ethmoid] squamous cell carcinomas (SNSCC) managed at Groote Schuur Hospital (GSH).

Primary Aim

- To evaluate the 2- and 5-year overall survival (OS) rates for patients treated at GSH

Secondary Aims

- To assess patient treatment outcomes in terms of initial treatment intent (radical versus palliative intent)
- To evaluate loco-regional control through Objective Response Rates for patients treated for SNSCC
- To evaluate the incidence of Human Papilloma Virus (HPV) in patients with SNSCC and to determine the effect that HPV has on treatment outcomes

Research Objectives

- To ascertain the 2- and 5-year overall survival rates of patients with SNSCC treated at GSH from 1 Jan 2003 to 31 December 2013
- To determine the 2- and 5-year loco-regional control rates of SNSCC
- To determine the incidence of HPV in this cohort and to evaluate the effect that the presence or absence of HPV has on the overall treatment outcome
- To compare the findings of this study to international literature
- To add to the limited knowledgebase of this rare condition

Definitions

- **Overall survival (OS) Endpoints**

Overall survival is defined as length of time from date of treatment initiation until the date of death from any cause.

- **Objective Response Rate (ORR) Endpoints**

Objective response rate (ORR) will be measured against Response Evaluation Criteria in Solid Tumours v1.1 (RECIST v1.1) as assessed by the primary investigator through review of patient data.

Background

Carcinomas of the nasal cavity and paranasal sinuses are extremely rare with the annual incidence of about 5-10 cases per 1,000,000 individuals [1,2]. Histologically they account for a diverse group of tumours, incorporating neoplasms derived from epithelium, glands, bone, cartilage, soft-tissue, neuroectodermal and haematolymphoid tissues. The commonest histologies observed are squamous cell carcinoma (accounting for 70-80% of cases) followed by adenocarcinoma and adenoid cystic carcinoma (accounting for about 10% of cases each) [3,4].

Sinonasal malignancies account for a mere 3% of all head and neck cancers. The majority (60%) of which arise from the maxillary antra; followed by the nasal cavity, which accounts for approximately 20-30% of cases. Only 10-15% of cancers originate within the ethmoid sinus while cancers of the sphenoid and frontal sinuses are much less common, accounting for less than 1% of the cases [3].

Given the concealed anatomical location from which these malignancies arise and the non-specific symptoms they produce, if any at all, the majority of patients present with locally advanced disease [1]. The mean age at presentation is between 50 to 60 years with an incidence two times greater in men compared to women [3].

Tobacco smoke, air pollution and occupational exposure to leather, textile, wood dust and formaldehyde have been cited in the literature as risk factors for sinonasal malignancies [5]. Co-infection with Human Papillomavirus (HPV) is thought to be associated with malignant degeneration of Schneiderian papillomas (most commonly the inverted papilloma subtype) into squamous cell carcinoma within the sinonasal tract [6]. However, due to the rarity of sinonasal malignancies, despite squamous cell carcinoma being the most common histological variant thereof, not much data is available pertaining to the role that HPV plays in terms of the pathogenesis and treatment of SNSCC.

This proposed study undertaken at one of the two largest cancer treatment units in the Western Cape (South Africa) will provide invaluable information related to patient demographics, stage at presentation and associated treatment related outcomes.

To date there are no studies of this kind that have been conducted within South Africa and only limited information is available from a few sites within Africa. A paper published in 2013 in the Ghana Medical Journal, looking at factors that contributed to poor management outcomes of sinonasal malignancies within southwest Nigeria, found that the majority of patients SNSCC presented with advanced disease (stages 3 and 4) and more than 47% of them in fact presented about a year after the onset of symptoms. Reasons identified for this included prolonged use of self-medication and a strong cultural belief system that promotes traditional healers above western medical practice. They identified the high cost of western medicine, unwelcoming attitudes of medical staff and the distance of health facilities as obstacles to accessing timeous healthcare [7].

The information gained from this study will not only add to this limited African database but will provide tangible insight into the treatment and management options available for this condition within a resource constrained setting, providing a framework further research on this topic both here in RSA and in other developing countries.

Materials and Methods

Study Design

This proposal is for a retrospective folder review of patients treated, with either radical or palliative intent, for Sinonasal squamous cell carcinoma (SNSCC) at Groote Schuur Hospital over a 10-year period commencing in 2003.

Study Population & Socio-demographics

The study will include all patients referred to and treated for SNSCC at Groote Schuur Hospital's Oncology Unit. Groote Schuur Hospital is part of South Africa's public hospital network and is one of two major referral hubs within the Western Cape. The hospital not only serves the greater Cape metropole but also serves patients from neighbouring provinces and occasionally patients from Southern African Development Community (SADC) member states and as such the patient socio-demographic profile is quite diverse.

Recruitment

- All patients with histologically proven Squamous cell carcinomas of the maxillary antrum, nasal cavity or ethmoid sinus, treated at Groote Schuur Hospital between 1 January 2003 to 31 December 2013 will be enrolled into this observational study.
- Subjects will be followed up to the end of December 2018 allowing for the assessment of 5-year overall survival and loco-regional disease control rates.
- Acknowledging the rarity of these cancers, the estimated number of patients to be enrolled during the study period is expected to be about 70 patients.

Inclusion Criteria

- Patients with histologically proven Squamous Cell Carcinomas of the sinonasal tract
- Both HIV positive and HIV negative patients will be included
- The mean age of presentation is in the 6^{th} and 7^{th} decades, and as such minors are not anticipated in the study population

Exclusion Criteria

- Any patient who received treatment, or initiated treatment an institution other than Groote Schuur Hospital or iThemba LABS
- Patients with significant co-morbidities who in the absence of their cancer would not be expected survive more than 12weeks (this being the minimum time period required for the radical treatment of sinonasal squamous cell carcinomas.
- Any histology other than Squamous Cell Carcinoma

Research Procedures and Data Collection Methods

The Groote Schuur cancer registry will be used to identify patients known with sinonasal carcinomas. Patient files will then be sourced from filing archives and will then be individually processed to confirm the histological presence of Squamous cell carcinoma of the sinonasal tract. The number of cases of other histological subtypes will be recorded but only those files with histologically proven squamous cell carcinoma will be reviewed further.
Clinical data, including but not limited to, presenting symptoms, time to presentation, histology, staging investigations, patient demographics, occupational exposures will be recorded and evaluated. Further data pertaining to histology and staging investigations will be obtained from the National Health Laboratory Service's (NHLS) electronic result archive and Groote Schuur's **P**icture **A**rchiving and **C**ommunications **S**ystem (PACS). Pathology reports will be reviewed and HPV status will be recorded. Those specimens in which HPV stains were not performed will be recorded as unknown. The 2-year, 5-year and date to last follow-up will be obtained from the radiotherapy folder. Similarly, date to progression as well as date of death will be obtained from the file records or the Births and Deaths Registry at the Department of Home Affairs.

Data Safety and Protection of Personal Information

No personal information, in the form of patient addresses/ contact details will be collected from the study files selected for analysis inclusion. Any data collected will be entered on to REDCap, a secure platform via a password-protected laptop that will be held in a secure location by the primary investigator (PI).

Only the PI and direct supervisor will have access to this database thereby ensuring protection of all subjects.

Variables Analysed

- Clerical information collected will include hospital folder and radiotherapy (RT) folder numbers and date of registration at the oncology clinic. Upon enrolment, each patient file will be assigned a unique coded number that will ensure anonymity but allow for ease of identification should further information need to be obtained from that particular file at any stage in the future.
- Demographic information will include date of birth, gender, performance status (based on the Eastern Cooperative Oncology Group performance scale), HIV status, smoking habits and occupational exposure to leather, textiles, wood dust or formaldehyde.
- Tumour characteristics: site of tumour (nasal cavity, maxillary antrum or ethmoid sinus), presenting symptoms (pain/ bleeding), tumour histology, HPV status, date of histology and the TNM staging of the disease (as per the 8th edition of the American Joint Committee on Cancer [AJCC]).
- Staging investigations performed: Computerized Tomograpy (CT), Magnetic Resonance Imaging (MRI), PET CT and ultrasound scans.
- Treatment related information:
    - Intent of treatment: radical versus palliative
    - Treatment modality: upfront surgery followed by radiation or definitive radiotherapy with or without concurrent chemotherapy and the type of chemotherapy administered
    - The type of radiotherapy (protons versus photons)
    - Radiation dose prescription and treatment technique (3D- conformal/ intensity modulated)
    - Overall Treatment Time (OTT) will be documented. Any treatment interruption or premature termination of treatment will be recorded together with the reason for and the duration of the said interruption/ termination.

- Objective response rate (ORR) will be assessed at 3 months based upon clinical evaluation as documented within the patient's medical records according to formal criteria as set out in RECIST (Response Evaluation Criteria in Solid Tumours) v1.1:
    - A **complete response (CR)** is defined as the absence of appreciable disease on clinical assessment or radiological imaging with any pathological lymph nodes reduced to <10mm in short axis diameter. **Partial response (PR)** is defined as more than a 30% reduction in the linear dimension of the tumour and/ or associated nodal disease measurements. Less than a 30% reduction in tumour and nodal size or less than a 20% increase in tumour/ nodal size represents refractory/ **stable disease (SD)**. Any new nodes or increase in the size of the tumour by more than 20% will be considered as **progressive disease (PD)** [8].
- Loco-regional control rates will be calculated at two defined intervals, 2-years and 5-years after the completion of treatment, and will be based on clinical and or radiologic assessment as documented in the patient notes according to RECIST v1.1.
- In the event of disease progression, the date at which progression was first suspected and site of relapse/ progression together with the chosen treatment modality will be recorded.
- Overall survival will be determined from the date of treatment initiation to the date of last follow-up within the 10-year study timeframe or up to the date of death.

Statistical Analysis

Demographic data will be analysed using descriptive statistics (mean, median, standard deviations). Survival analysis at 2- and 5-years will be ascertained through the use of Kaplan Meier curves. Survival distribution in HPV positive versus HPV negative tumours will be assessed using the log-rank test. Statistically significant differences in survival is defined as a p-value < 0.05.

Ethical Considerations

This study is a retrospective review of patient records with no direct interaction between investigators and enrolled subjects and poses no harms or risks to participants involved. On these grounds informed consent will not be sought from participants.

Confidentiality and the protection of personal information will be maintained at all times through the anonymisation of all information collected and through the use of unique patient file codes, as was described above.

This study proposal is submitted for a minor dissertation (MMed degree) as part of my specialist oncology training and for the consideration of publication in a reputed peer-reviewed journal. The study is purely observational and requires no monetary funding; furthermore, no conflict of interest has been identified.

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PART B: PUBLICATION-READY MANUSCRIPT

Sino**N**asal **S**quamous **C**ell **C**arcinoma (SNSCC): a retrospective review of the treatment outcomes of patients treated at Groote Schuur Hospital, Cape Town, South Africa

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ABSTRACT

Purpose: Cancers of the sinonasal tract are rare, comprise a diverse group of histologies and are known for their poor prognostic outcomes. The primary aim of this study was to evaluate the 2- and 5-year overall survival (OS) rates in patients treated with radical and palliative intent for sinonasal squamous cell carcinoma (SNSCC).

Methods: A retrospective review of medical records of all patients presenting to Cape Town's Groote Schuur Hospital between January 2003 and December 2013 was carried out. All patients with histologically proven squamous cell carcinoma (SCC) of the maxillary sinus and nasoethmoidal complex who underwent treatment at Groote Schuur Hospital and/or iThemba LABS (Laboratory for Accelerator Based Sciences) were included.

Fifty-five patients with cancers of the sinonasal tract were identified from the electronic patient system; 23 were excluded either because of different histologies, lack of histology or having initiated treatment outside of Groote Schuur Hospital. The medical records of 32 patients were utilised for final analysis. 2- and 5-year OS was calculated using Kaplan-Meier analysis.

Results: The majority (75%) of patients had an ECOG performance status of 1 with facial asymmetry secondary to tumour mass or swelling being the most common presenting symptom (present in 68,75% of cases). 62,50% of cases originated within the maxillary antrum and 56,25% of cases were classified as keratinizing SCC. Twenty-six (81,25%) patients presented with stage IV disease; nodal disease was seen in 13 (40,63%) patients and distant metastasis in 4 (12,50%) patients. Most patients underwent palliative intent treatment with only 11 (34,38%) having radical treatment. The cumulative 2- and 5-year OS from the date of treatment initiation was 26% and 19% respectively. Median OS for the entire cohort was 7,7 months and was statistically significant between intent groups at 5,19 months (95% CI:3.43–

6.95) for palliative compared to 35,45 months (95% CI: 0.00–138.52) for radical patients (χ^2 = 7.80, p = 0.005).

Conclusion: Despite a decline in incidence of disease over the last 30 years and the improved diagnostic and therapeutic modalities available today, the prognosis and survival outcomes for SNSCC remains poor.

Keywords: Squamous cell carcinoma, nasal cavity, paranasal sinuses, radiation, treatment outcomes

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INTRODUCTION

Cancers of the sinonasal tract are rare accounting for between 3–5% of head and neck malignancies and less than 1% of all malignancies.[1,2] The precise incidence for South Africa is unknown; this as the South African National Cancer Registry co-registers them together with those of the oropharynx as 'naso-oropharynx' carcinomas.[3] According to the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database the recorded incidence is 0.36–0.83 cases per 100,000 persons per year,[2,4,5] with slightly higher incidences having being reported in Japan, China, India and certain regions of Africa.[6] However, over the last three decades there has been a significant and steady decline in these incidence rates, with an annual percentage reduction of 2.63% for males and 1.69% for females.[7] Sinonasal cancers (SNCs) have a male preponderance of 1.8:1,[2,4] and 'white' ethnicity, when compared to 'black' and 'other', is the most prevalent.[1,2,5,7,8] These cancers are aggressive, are known to have poor prognostic outcomes and due to their insidious nature are often diagnosed at advanced stages,[9] usually within the 6th and 7th decade of life.[2,4]

Clinical presentation varies with primary tumour site and includes nasal obstruction, rhinorrhoea, epistaxis, epiphora, proptosis, facial pain and asymmetry, paraesthesia and tooth mobility among others.[2,6,10] These non-specific symptoms often lead to delays in diagnosis with the treatment of common aetiologies first.

Sinonasal tumours display some of the most diverse histologic variation when compared to other head and neck subsites: they can arise from the epithelial lining, the supporting soft tissue structures or the haematolymphoid and neuroendocrine systems, and encompass both benign and malignant histologies.[4,6,10] The most common histology by far is squamous cell carcinoma (SCC) with an incidence of anywhere between 35% and 58%.[7] The maxillary antrum accounts for the majority of cases followed, in roughly equal frequency, by the nasal cavity and ethmoid sinus.[7,11] SCC of the sphenoid and frontal sinuses are rare and are not well documented in the literature. The sinonasal tract is lined in its entirety by respiratory epithelium, with exception of

the nasal vestibule, making squamous metaplasia a prerequisite for squamous neoplasia.[10]

The rarity of the disease precludes randomised control trials (RCTs) with management strategies largely being informed by reviews of single-institution retrospective series, analysis of population-based registries and expert opinion.[12–14] The current international mainstream recommendation inclines toward upfront surgery followed by post-operative radiotherapy (PORT),[13] with definitive (chemo)radiation used in situations where surgery is contra-indicated due to underlying co-morbidities, or patient preference, or in instances where complete surgical resection is deemed unlikely due to the anatomic location of the lesion.[14,15]

Despite advancements in radiotherapy with the advent of intensity modulated radiotherapy (IMRT) including volume modulated arc therapy (VMAT) and improved less invasive surgical techniques by endoscopic resection, the overall prognosis for sinonasal squamous cell carcinoma (SNSCC), and sinonasal malignancies in general, remains very poor.
Literature from Africa evaluating treatment outcomes for this malignancy is scarce, with only a few papers from Nigeria exploring its prevalence and clinico-pathologic features.[16–18] In this study, we report the disease outcomes and patterns of failure for patients with SNSCC treated by radical and palliative intent at our centre.

METHODS

Study aims and objectives

The aim of this study was to assess the treatment outcomes for squamous cell carcinomas of the nasal cavity, maxillary antrum and ethmoid sinus treated by both radical and palliative intent at a specialised oncology unit. Hallmark features associated with these malignancies as well as patient and tumour characteristics are identified and described. Pre-treatment staging was by means of the American Joint Committee on Cancer's (AJCC) 8th edition staging manual [Figure 1].

Primary Tumour (T)

T Category	T Criteria: Nasal Cavity & Ethmoid Sinus	T Criteria: Maxillary Sinus
Tx	Primary tumour cannot be assessed	Primary tumour cannot be assessed
Tis	Carcinoma in-situ	Carcinoma in situ
T1	Tumour restricted to any one subsite, with or without bony invasion	Tumour limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumour invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion	Tumour causing bone erosion or destruction, including extension into the hard palate and/or middle nasal meatus but excludes extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumour extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate	Tumour invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues. floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Moderately advanced local disease >> Tumour invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid, or frontal sinuses	Moderately advanced local disease >> Tumour invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid, or frontal sinuses
T4b	Very advanced local disease >> Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V2), nasopharynx, or clivus	Very advanced local disease >> Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus

Regional Lymph Nodes (N)

N Category	N Criteria
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE (-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE (-)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE (-)
N3b	Metastasis in any node(s) with clinically overt ENE (+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, ENE (extra-nodal extension) should be recorded as ENE (-) or ENE (+).

Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC Prognostic Stage Groups

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1 / T2 / T3	N1	M0	III
T4a	N0 / N1	M0	IVa
T1 / T2 / T3 / T4a	N2	M0	IVa
Any T	N3	M0	IVb
T4b	Any N	M0	IVb
Any T	Any N	M1	IVc

Figure 1: AJCC 8TH edition TNM staging

The primary objective was to determine the 2- and 5-year overall survival (OS) rates for patients with SNSCC. Secondary objectives were to describe treatment outcomes separated by treatment intent (radical vs. palliative) and to evaluate loco-regional control (LRC) and assess patterns of recurrence.

Study design

A retrospective folder review of all patients treated for SNSCC between January 2003 and December 2013 at the head and neck oncology clinic at Groote Schuur Hospital, Cape Town was conducted. All patients with histologically proven stage I to IV SCC of the sinonasal tract were included. Any patients who had received, or initiated, treatment at an institution other than Groote Schuur Hospital or iThemba LABS (Laboratory for Accelerator Based Sciences) were excluded from the study. Ethical approval was obtained from the University of Cape Town's Human Research Ethics Committee (HREC; approval number 139/2020). Anonymised data was collected and stored using REDCap software (version 9.5.36; Vanderbilt University, Nashville, TN, USA), with only the primary- and sub-investigator having access to the database.

Treatment

All patients were reviewed in the head and neck multidisciplinary team meeting to establish consensus on individual treatment plans prior to treatment initiation. The decision for radical intent or palliative intent radiotherapy was determined by characteristics at presentation such as Eastern Cooperative Oncology Group (ECOG) performance status, medical co-morbidities, nutritional status, and general physical condition as well as by disease burden and extent of local invasion. The decision for surgery and the type of surgical resection was based upon the clinical and radiologic assessment of tumour location and invasion of adjacent critical structures and the probability of obtaining complete tumour resection with minimal and acceptable morbidity as determined by the otolaryngologist in consultation with the patient.

The choice of radiotherapy fractionation schedule and treatment technique was at the discretion of the treating radiation oncologist and machine workload. During the study time-period 3D-conformal radiotherapy (3D-CRT) with photons was used for both radical and palliative intent treatments while conventional

(2D) photon techniques were used solely for palliative treatments. Select patients received neutron therapy at iThemba LABS (formerly the National Accelerator Centre) as part of a clinical study for surgically irresectable advanced stage SCCs of the maxillary sinus.[19]

Over the decade beginning 2003, several photon fractionation schedules were used ranging from 4.0Gy x 5# (*EQD2 = 23.33Gy$_{10}$) to 2.1Gy x 31# (*EQD2 = 65.64Gy$_{10}$) among others, assuming an α/β ratio of 10 for tumour cells (*EQD2 being the biologically equivalent dose in 2Gy fractions). Photon therapy was initially delivered as a single fraction daily, Monday to Friday, four days per week as per departmental policy at the time, but in the latter half of the study included treatment five days per week in accordance with a change to this policy. In cases where neutron therapy was used treatment was administered three days per week, Monday to Friday, at 1.36NGy over 15 fractions to a total dose of 20.40NGy. At iThemba LABS neutrons are produced through the collision of a 66MeV cyclotron-generated proton beam upon a thick beryllium target. The dose distribution of this neutron beam is remarkably similar to that of an 8MV photon beam, although with a slightly larger penumbra. Compared to photons, neutrons are high linear energy transfer (LET) radiation associated with reduced dependence on tumour oxygen tension and reduced repair of sub-lethal damage with less variation in terms of radiosensitivity throughout the cell cycle. The relative biological effectiveness (RBE) of this neutron beam is three, with the 20.40NGy administered roughly being equivalent to 61.20Gy of photons.

Patients were treated with various combinations of surgery, radiation, and chemotherapy, or in certain instances with monotherapy alone. Routine follow-up was on a 3-monthly basis for the first 2 years and thereafter on a 6-monthly basis up to 5 years, or sooner where necessary. Follow-up beyond 5 years was on an annual basis.

Treatment response was assessed at a minimum of 12 weeks after completing the treatment plan and was referenced as the first follow-up. Second and third follow-up was at 2-years and 5-years respectively, or as close as possible

thereto. In all cases assessment was based on clinical examination with the use of radiology in select cases. Although radiologic assessment was not performed for all patients the principles of the Response Evaluation Criteria in Solid Tumours (RECIST criteria v1.1) were applied to all three follow-up periods.

Statistical analysis

Primary variables collected were age; gender; ECOG performance status; medical co-morbidities; risk factors; presenting symptoms; tumour site, histology and staging; treatment modality; treatment response and type of treatment failure. Data was analysed using SPSS software (version 28.0; IBM, Armonk, NY, USA).

The objective response rate (ORR) was assessed 12 weeks after treatment completion and was defined as the proportion of patients with complete response (CR) and/or partial response (PR). Locoregional control (LRC) rates were assessed at each of the three follow-up intervals (3-months, 2-years and 5-years post treatment completion or as close as possible thereto) and was defined as the proportion of patients without progressive disease (PD). OS was calculated from the date of treatment initiation until death using Kaplan-Meier survival analysis, censoring at the last attended hospital visit for patients who were lost to follow-up.

RESULTS

Fifty-five patients with SNC were registered on the hospital's electronic patient registry (EPR) between 2003 and 2013; 33 had SCC, 21 had other histologies and one patient had missing records. In total 32 patients with SCC were included for formal analysis; one patient being excluded in accordance with the study criteria after having treatment that was initiated at another facility.

The mean age at the time of registration into the head and neck clinic was 60.16 years (SD $\pm$ 15.80) with a range of 24–93 years (IQR = 19.72). Most patients were male (22/32; 68.75%) and only 10/32 (31.25%) were female, with a male to female ratio of 2.2:1. Seventy-five percent (24/32) of patients were

ECOG performance status 1. The most common co-morbidity was hypertension (14/32; 43.75%) followed by diabetes mellitus (3/32; 9.38%). Only 1/32 (3.13%) patients were HIV positive [Table 1].

Table 1: Patient and tumour characteristics

Characteristics	Number (n = 32)	Percent
Gender		
Male	22	68.75
Female	10	31.25
ECOG status		
PS 0 – Completely normal	2	6.25
PS 1 – Symptomatic ambulatory	24	75.00
PS 2 – In bed < 50% of day	4	12.50
PS 3 – In bed > 50% of day	1	3.13
PS 4 – Bedbound	1	3.13
Co-morbidities		
None	11	34.38
Hypertension	14	43.75
Diabetes	3	9.38
HIV	1	3.13
Other	15	46.88
Risk factors		
Tobacco smoker	22	68.75
Wood dust	2	6.25
Organic compounds	3	9.38
Alcohol	6	18.75
Unknown	8	25.00
Symptoms		
Nasal obstruction	12	37.50
Epistaxis	13	40.63
Facial mass/ asymmetry	22	68.75
Facial pain	18	56.25
Neck nodes	3	9.38
Weight loss	10	31.25
Change in phonation	1	3.13
Decreased sensation	2	6.25
Loose teeth	4	12.50
Visual disturbance	4	12.50
Epiphora	1	3.13
Headaches	3	9.38
Tumour site		
Nasal cavity	11	34.38
Maxillary sinus	20	62.50
Ethmoid sinus	1	3.13
Staging investigation		
CT	29	90.63
MRI	10	31.25
Chest X-ray	21	65.63
Bone scan	1	3.13
T stage		
T1	2	6.25
T2	0	0.00
T3	6	18.75
T4	24	75.00
N stage		
N0	19	59.38
N1	3	9.38
N2	8	25.00
N3	2	6.25
M stage		
M0	28	87.50
M1	4	12.50
Stage group (AJCC 8th edition)		
Stage I	1	3.13
Stage II	0	0.00
Stage III	5	15.63
Stage IV	26	81.25
Histology		
Keratinizing SCC	18	56.25
Non- keratinizing SCC	8	25.00
Poorly differentiated SCC	4	12.50
Carcinoma in-situ	2	6.25
Tumour grade		
Well differentiated	4	12.50
Moderately differentiated	12	37.50
Poorly differentiated	6	18.75
Unknown	10	31.25
Lymphovascular invasion		
Yes	0	0.00
No	18	56.25

Unknown	14	43.75
Perineural invasion		
Yes	0	0.00
No	18	56.25
Unknown	14	43.75
HPV		
Positive	0	0.00
Negative	3	9.38
Unknown	29	90.63

Facial mass/ asymmetry (22/32; 68.75%) followed by facial pain (18/32; 56.25%) and epistaxis (13/32; 40.63%) were the leading presenting complaints [Table 1]. The mean duration of symptoms from the time of onset to the date first seen in the oncology unit was 17.23 weeks (SD ± 12.55; range 3–52). The average time from symptom onset to histological diagnosis was 14.19 weeks (SD ± 11.06; range 1–50). The maxillary antrum was the primary tumour site in 20/32 (62.50%) cases and keratinizing squamous cell carcinoma was the predominant histologic subtype (18/32; 56.25%) [Table 1]. Only 3/32 (9.38%) specimens were tested for human papilloma virus (HPV) and 1/32 (3.13%) was tested for Epstein-Barr virus (EBV) all of which were negative [Table 1]. 26/32 (81.25%) patients had stage IV disease. Staging was by means of CT-scan in 90.63% of cases, MRI and bone scans were used in select cases. Predominant risk factors were tobacco and alcohol use each accounting for 68.75% and 18.75% of cases. Occupational exposure to organic solvents and wood dust was documented in 9.38% and 6.25% of cases, respectively [Table 1].

Table 2: Treatment strategy by intent

	Number	Details
Radical intent group	n = 11	
Surgery alone	3	1 patient diagnosed with mesothelioma 6 months after surgery.
Surgery / Holding Chemo / PORT	1	
Holding Chemo / Surgery / PORT	1	
Surgery + PORT	3	1 patient demised 9 days after surgery*
Induction Chemo + definitive concurrent chemo-RT (IC + dCCRT)	2	
Definitive Radiotherapy (dRT)	1	
Palliative intent group	n = 21	
Best supportive care	1	
Neutron RT	5	2 patients had holding chemo.
Radiotherapy	12	1 had WBRT + spine RT€; 1 demised before starting RT*; 1 demised after second fraction.
High dose palliative RT	1	Palliative chemo + consolidatory high dose RT.$
High dose palliative concurrent chemo-RT	1	Patient diagnosed with lung cancer during radiation treatment.
Palliative chemotherapy	2	1 absconded^; 1 had palliative chemo + consolidatory high dose RT$

$ Denotes treatment in the same patient
* 2 patients demised before starting RT
€ 1 patient had both whole brain RT (WBRT) 20Gy/5# and spinal RT 20Gy/5#
τ 1 patient absconded palliative chemotherapy

Most patients were treated with palliative intent with only 11/32 (34.38%) being managed radically [Table 2]. The distribution of disease by site for these radical patients was 63.64% (7/11) nasal cavity, 27.27% (3/11) maxillary sinus and 9.09% (1/11) ethmoid sinus.

In total, eight patients underwent surgery: 5/32 (15.63%) had surgery followed post-operative radiotherapy (PORT) and 3/32 (9.38%) had surgery alone [Table 2]. The majority (6/8; 75.00%) had open resection of the tumour. Only three (37.50%) had neck dissections, one of which was a bilateral neck dissection [Table 3]. While definitive radiotherapy (dRT) was only administered to 1/32 (3.13%) patients [Table 3].

Induction chemotherapy (IC) followed by definitive concurrent chemoradiotherapy (dCCRT) was used in two cases (2/32; 6.25%) [Table 2]. IC consisted of four cycles of carboplatin + 5-fluorouracil + paclitaxel for the one patient, and three cycles of cisplatin + 5-fluorouracil for the other patient followed by dCCRT.
In total three patients received CCRT [Table 2], one had three cycles of concurrent carboplatin and the other had two cycles of concurrent carboplatin, both of which were administered over a 21-day cycle. The third patient received three cycles of concurrent cisplatin over a 21-day cycle.

Of the four (12.50%) cases where holding chemotherapy (HC) was used, two had HC + palliative neutron RT and two had HC incorporated into their surgery + PORT treatment plans [Table 2]. Three patients received cisplatin + 5-fluorouracil as HC two of whom received a single cycle and one of whom received two cycles. In a single case, three cycles of carboplatin + 5-fluorouracil was used as HC.

Palliative radiotherapy and best supportive care were administered for 18/32 (56.25%) and 1/32 (3.13%) cases respectively [Table 3]. Of the 2/32 (6.25%) patients who were scheduled for palliative chemotherapy, one patient completed six cycles of carboplatin + 5-fluorouracil given as a 21-day cycle followed by consolidatory RT to 46.20Gy, and the other declined palliative chemotherapy before its commencement.

Table 3: Treatment details

	Number	Percent
Surgery		
Technique	n = 8	
Open	6	75.00
Endoscopic	2	25.00
Neck dissection	n = 3	
Unilateral	2	66.67
Bilateral	1	33.33
Resection margin status	n = 8	
R0 – microscopically clear	4	50.00
R1 – microscopically involved	2	25.00
R2 – gross residual	0	0.00
Unknown	2	25.00
Radiotherapy		
Technique	n = 25 (27-2)*	
2D-conventional	n = 9	
Palliative	9	100.00
3D-conformal (3D-CRT)	n = 16	
Palliative 3D-neutron RT	5	31.25
Palliative 3D-CRT	4	25.00
Radical 3D-CRT	7	43.75
***Demised prior to RT**	n = 2*	
Palliative	1	50.00
Radical	1	50.00
RT dose: Radical		
60.00Gy/24#	2	8.00
63.00Gy/30#	1	4.00
64.00Gy/32#	1	4.00
65.00Gy/26#	2	8.00
65.10Gy/31#	1	4.00
RT dose: Palliative		
20.4NGy/15#	5	20.00
20.00Gy/5#	7[€]	28.00
30.00Gy/10#	3	12.00
36.00Gy/12#	1	4.00
46.20Gy/22#	1	4.00
50.00Gy/20#	1	4.00
Chemotherapy		
Induction	2	-
Holding	4	-
Concurrent	3	-
Palliative	1 (2–1)[τ]	-
Miscellaneous		
Best supportive care	1	-

* 2 patients demised before starting RT
€ 1 patient had both whole brain RT (WBRT) 20Gy/5# and spinal RT 20Gy/5#
τ 1 patient absconded palliative chemotherapy

Table 4: Radiotherapy treatment delays

	Number (n = 25)	Percent
Treatment toxicity	3	12.00
Transport problems	2	8.00
Social issues	1	4.00
National holiday	5	20.00
Machine service	7	28.00

Regarding the radiotherapy technique, conventional 2D-RT was used for 9/32 (28.13%) of the cases. 3D-CRT was used for 16/32 (50.00%) of the cases. Two (2/32; 6.25%) patients succumbed prior to radiotherapy initiation and 5/32 (15.63%) patients did not have radiotherapy as a part of their treatment plan [Table 3]. Photon radiotherapy was used for all cases except for five where neutron therapy was used as part of an actively recruiting study at the time. For this paper, all five of these cases were classified under the palliative intent group in accordance with their original in file classification of 'high-dose palliative radiation' for the neutron study.

Doses for palliative photon treatment ranged between 20Gy and 50Gy, with the most common palliative fractionation schedules being 20Gy/5# and 30Gy/10# each respectively administered to seven and three of the 21 palliative patients. While the dose for radical treatment ranged between 60Gy to 65.1Gy.

Radiotherapy treatment delays were reported in 11/25 (44%) cases. Machine services and national holidays were the most common reasons for these treatment delays. Treatment was only interrupted in 3/25 (12%) cases for acute side effects [Table 4]. The median delay in RT treatment time was two days (range 1–7days; IQR 2).

Most patients 28/32 (87.50%) completed their treatment plans; three patients died prior to completing their intended treatment and one patient declined treatment with palliative chemotherapy. The median overall treatment duration, inclusive of any treatment delays, was 17days (range 2–243; IQR = 28 days) and 117 days (range 1–234; IQR 175 days) for palliative and radical patients, respectively.

Table 5: Treatment assessments at follow-up

	Numbers and percent (%)		
	1st follow-up	2nd follow-up	3rd follow-up
RADICAL (n = 11)			
Alive	8 (72.73)	6 (54.55)	3 (27.27)
Demised	3 (27.27)	5 (45.45)	6 (54.55)
Lost to follow-up	0	0	2 (18.18)
Treatment response			
Complete Response (CR)	5 (45.45)	6 (54.55)	3 (27.27)
Partial Response (PR)	2 (18.18)	0	0
Stable Disease (SD)	0	0	0
Progressive Disease (PD)	1 (9.09)	0	0
PALLIATIVE (n = 21)	10 (47.62)	5 (23.81)	0
Alive	7 (33.33)	13 (61.90)	18 (85.71)
Demised	4 (19.05)	3 (14.29)	3 (14.29)
Lost to follow-up			
Treatment response	0	0	-

Complete Response (CR)	4	(19.05)	0		-
Partial Response (PR)	1	(4.76)	0		-
Stable Disease (SD)	5	(23.81)	5	(23.81)	-
Progressive Disease (PD)					
PATTERNS OF PROGRESSIVE DISEASE (n = 32)					
Local	3	(9.38)	4	(12.50)	0
Regional	2	(6.25)	1	(3.13)	0
Local + Regional	1	(3.13)	0		0
Distant	0		0		0

Local disease accounted for (3+4/11) 63.64% of treatment failures.
Regional disease accounted for (2+1/11) 27.27% of treatment failures.
Local + Regional disease accounted for (1/11) 9.09% of treatment failures.

First follow-up / Initial treatment response assessment

The median time from treatment completion to first follow-up was three months (range 2–11) for palliative patients and four months (range 2–7) for radical patients.

With respect to palliative patients, 10/21 (47.62%) were alive at first follow-up, four of whom had partial response (PR) and five had PD with a median time to disease progression of 101 days (range 92–108) from date of treatment completion. Four (4/21; 19.05%) palliative patients were lost to follow-up [Table 5]. With respect to the 11 radical patients, eight (72.73%) were alive at the first follow-up: five patients had CR and two had PR. Only one patient had PD with a time to progression of 101 days from the date of treatment completion.

The ORR and LRC rate for palliative patients were 19.05% (4/21) and 23.81% (5/21), respectively. By contrast, the ORR and LRC rate in the radical intent group were both 63.64% (7/11) [Table 5].

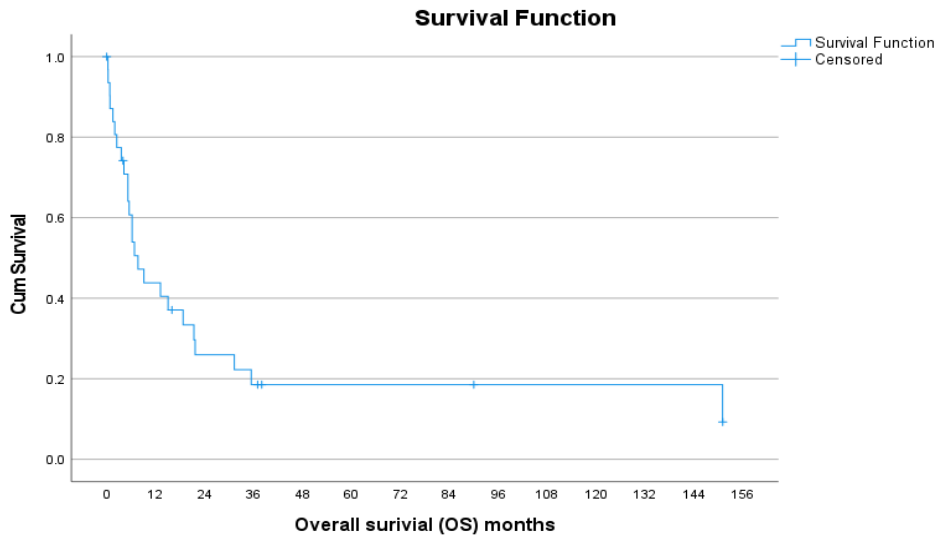
Second follow-up

Median time from treatment completion to 2nd follow-up was 7.23 months (range 5.06–25.64) for palliative patients and 26.30 months (range 22.88–30.28) for radical patients. The ORR and LRC for the palliative group were both zero percent, with all five palliative patients having PD; median time to disease progression from end of treatment was 6.97 months (range 5.09–11.38). At the time of 2nd follow-up 13/21 (61.90%) palliative patients had demised, compared to 5/11 (45.45%) from the radical group. The remaining six radical patients all had complete responses (CR). The ORR and LRC were 54.55% for both measurements [Table 5].

Third follow-up

At the time of 3rd follow-up 3/21 (14.29%) palliative patients were lost to follow-up and the remaining 18/21 (85.71%) had succumbed to disease. For radical patients, median time to 3rd follow-up from the time of treatment completion was 5.14 years (range 5.04–5.36). Of the 11 radical patients, three (27.27%) were alive, two (18.18%) were lost to follow-up and six (54.55%) had demised by the time of 3rd follow-up. CR was noted in all three patients, and the ORR and LRC rates were both 27.27% [Table 5].

Median overall survival, as measured from the time of treatment initiation, for the entire cohort was 7.69 months (SE ± 1.95; 95% CI: 3.86–11.51), and the 2- and 5-year cumulative OS was 26% and 19%, respectively [Figure 2]. Split by treatment intent, palliative patients had a median OS of 5.19 months (SE ± 0.89; 95% CI: 3.43–6.95) compared to 35.45 months (SE ± 52.59; 95% CI: 0–138.52) for radical intent patients [Figure 3]. The log-rank test showed that the survival distributions of the palliatively and radically treated patients were statistically significant (χ^2 = 7.80, p = 0.005).



The median survival time of all patients from the start of treatment was 7,69 months (95% CI, 3,86 to 11,51). Cumulative 2- and 5-year survival was 0,26 (26%) and 0,19 (19%) respectively at 24 months and 60 months from time of treatment initiation.

Figure 2: Kaplan Meier survival curve for entire cohort

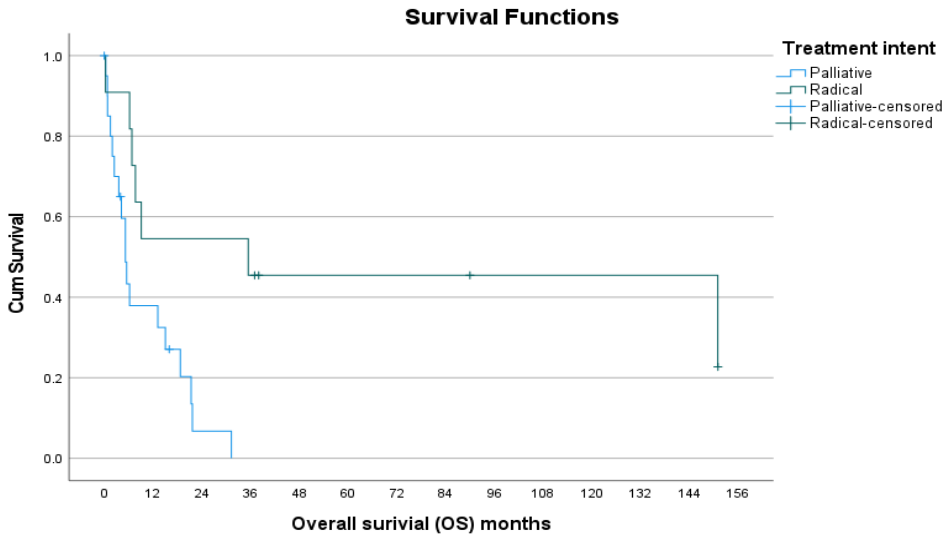


Figure 3: Kaplan Meier survival curves separated by treatment intent

DISCUSSION

The diagnosis and management of sinonasal squamous cell carcinoma (SNSCC) presents a major therapeutic challenge. They are rare malignancies lacking randomised control data to conclusively guide management strategies, and comparisons between case series is often difficult due to varied treatment approaches and tumour site heterogeneity.[14] Furthermore, the anatomic location of the sinonasal tract and its proximity to the orbit, base of skull and central nervous system, complicates management and accounts for their poor outcomes and low 5-year survival rates.[8]

The mean age at presentation (60.16 years) and male preponderance (M:F ratio = 2.2:1) in our study was in keeping with known epidemiological data.[2,4,7,8] The maxillary sinus accounts for the highest incidence (approximately 60%) of SCC within the sinonasal tract followed by the nasal cavity and the ethmoid sinus, each accounting for approximately 25% and 15% of cases respectively.[20] We report similar disease distributions for our cohort with 62.50% and 34,38% of cases originating within the maxillary sinus and nasal cavity respectively.

Tumour stage is defined by the extent of invasion into adjacent structures and not by dimensions.[11] The large air-filled cavities of the paranasal sinuses allow

for sub-clinical disease progression with invasion into adjacent structures and characteristically present as advanced-stage disease with non-specific symptoms when compared to nasal cavity tumours which generally produce noticeable symptoms earlier during the disease course given the narrower confines of the airway space in which they occur.[8,21] Our findings are consistent with this: T4 tumours were 1.5 times more common in the maxillary sinus compared to the nasal cavity; and the nasal cavity was the only subsite to harbour T1 disease.

Relative to primaries of other head and neck subsites, metastases to cervical lymph nodes and distant spread are generally not common. However, compared to other histologies affecting the sinonasal tract, SCC is associated with higher incidences of nodal metastases and neck failure, and when present at diagnosis is a poor prognostic indicator linked to inferior loco-regional control (LRC) and disease-specific survival (DSS).[6,21,22] Smith et al. reported a node positivity rate of 40.22% for SNCs as a whole and higher rate of 46.52% specific to SNSCCs.[5] Our finding of 40.62% node positive disease at presentation was similar to these findings but is notably higher than the observed 10–20% in other reported data.[10] Altogether, more than 96% of our cases were advanced stage disease (15.63% stage III, and 81.25% stage IV) with the nasal cavity accounting for the highest proportion of stage III disease.

The role of HPV co-infection in SCCs of the sinonasal tract is not completely understood.[10] It is reported that approximately 20–25% of SNSCCs are positive for HPV, the majority of which are of the non-keratinizing subtype, which histomorphologically is similar to HPV positive SCCs of the oropharynx.[10,20] The implication of this association is not entirely clear – it is thought that like with oropharyngeal carcinoma HPV co-infection confers a more favourable prognosis – and has been the subject of investigation in recent studies. Chowdhury et al. demonstrated a statistically significant survival advantage of 54 months for HPV-positive SCCs of the nasal cavity compared to 12 months for HPV-negative tumours (log-rank test $p < 0.003$).[23] In their recent systematic review and meta-analysis of SNSCCs, Sharma et al. observed a significant association between HPV positivity and overall survival (HR = 0.51,

95% CI: 0.38–0.70), indicating that HPV was a significant predictor for more favourable survival outcomes.[24] This data illuminates HPV as a useful biomarker for prognostication and with time, once further data becomes available, could potentially underpin changes in treatment with respect to dose modulation for chemotherapy and radiotherapy.
At present the routine testing of SNSCC for HPV, or its surrogate marker p16, has not been validated but may soon become standard practice. The limited specimens tested for HPV in our study (3/32; 9.38%) were all negative precluding further evaluation.

The relationship between EBV and SNSCC is less clear. Notwithstanding a statistically significant association between EBV and sinonasal inverted papillomas (SIPs), a positive association was not observed for EBV and SNSCC.[25] Current literature suggests that EBV is unlikely to be a causative agent in the pathogenesis of SIP or SNSCC, but when present in established disease promotes disease progression.[25,26]

Although SCC can develop in any one of the three Schneiderian papilloma subtypes (viz. exophytic, oncocytic and inverted) malignant transformation is most common for the SIP subtype with rates ranging from 2–27%.[10] Tobacco smoking is thought to promote their malignant transformation, with 15% of all SNSCCs occurring either synchronously or metachronously to papillomas. By contrast, alcohol consumption has not been proven as a risk factor.[20]
Occupational exposure to arsenic, asbestos, welding fumes, nickel / chromium compounds, chlorophenols, formaldehyde, and wood, textile and leather dusts have a causal role in the development of sinonasal malignancies.[27,28] For our study population exposure to organic compounds and wood dust was respectively documented in 9.38% and 6.25% of cases, while tobacco smoking was the most prominent risk factor with a prevalence of 68.75%. On univariate analysis, Russo et al. identified smoking to be predictive for poorer LRC with active smokers having a 5-year LRC rate of 23% compared to 83% for non-active smokers ($p = 0.004$).[29]

The predominant pattern of treatment failure is local relapse.[14,30] Disease progression was noted in 11/32 (34.38%) patients; 10 of whom were palliative. 7/32 (21.88%) had local site progression; 3/32 (9.38%) had regional adenopathy; and only 1/32 (3.13%) had both local and regional failure. The pattern of failure for the only radical patient with progression was regional disease. Distant metastatic recurrence was not observed in our cohort. Slevin et al. reported their outcomes for locally advanced SNSCC managed by radical intent with either definitive RT or adjuvant RT at four tertiary cancer centres across the United Kingdom. They noted rates for local, regional, and distant failure of 33%, 33% and 16% respectively. Their median duration of follow-up was 3.8years (IQR 2.0–4.7 years) and estimates for 5-year OS and progression free survival (PFS) were 30.2% and 24.2% respectively.

Estimated cumulative OS for the entire cohort was 26% and 19% at 2- and 5-years respectively. Specific to radical patients, these rates were 55% and 45% each, and is in keeping with observed survival rates in the literature of 25–50% at 5-years.[30,31] With respect to palliative patients, we recorded a 2-year estimated cumulative OS of approximately six percent, with no survivors beyond 31 months. For patients treated radically, LRC rates at 3-months, 2-years, and 5-years of 63.64%, 54.55% and 27.27%, were observed respectively.

Reported outcomes from previous studies vary widely and inter-study comparisons are challenging because of tumour site heterogeneity, changes to the staging system over the years, the varied treatment approaches between institutions and the incorporation of modern radiotherapy and surgical techniques. Russo et al. reported on outcomes of 54 patients with stage III and IV SNSCC who were treated with either surgery + proton beam RT or definitive proton beam RT where they observed 2- and 5-year OS rates of 67% and 47% respectively, and LC rates of 80% at both 2- and 5-years.[29] This data seems to suggests that recurrences beyond 2 years are uncommon. In their study comparing definitive RT to surgery + adjuvant RT for SNSCC treated with radical intent, Duru Birgi et al. managed 84% of their patients with 3D-CRT, 9% with IMRT 7% with electron field RT. Their reported rates for 2-year local

control, regional control, and OS were 81%, 90% and 80% respectively, and 5-year rates were 76%, 90% and 71% respectively; furthermore they found no significant difference in the 2-year locoregional disease free survival between treatment arms (70% for definitive RT vs 75% for surgery + adjuvant RT; p = 0.98).[14]

Proton radiation was not used for any of these cases. While protons are advantageous for minimising dose to adjacent critical structures by the Bragg peak phenomenon, the 200 MeV horizontal proton beam at iThemba LABS was limited by a maximum field diameter of 10cm and had a RBE of 1.1 holding little therapeutic advantage when compared to photons.[32] Proton therapy was therefore only used for smaller tumours, mostly intracranial lesions, where a rapid dose fall-off was desired.

LIMITATIONS

Based on the low number of cases encountered over the study period, investigators included all registered patients with confirmed SNSCC for evaluation. This mix of palliative and radical patients may prevent direct comparison of certain outcomes between our study and others.
The concealed nature of the sinonasal tract necessitates radiological evaluation in conjunction with clinical examination for complete assessment; while all patients underwent baseline radiology for staging purposes only radical patients had subsequent radiological re-evaluation at follow-up assessments. Tumour response evaluations for most of the palliative patients was by means of clinical examination alone, and due to the retrospective nature of this study authors were exclusively reliant upon the documented information within patient medical records.

CONCLUSION

To our knowledge this is the first study of its kind in Sub-Saharan Africa to evaluate treatment outcomes for SNSCC and will contribute to the African literature database for this very rare malignancy. In keeping with known data, this single institution retrospective study has identified poor survival outcomes and low rates of locoregional control for patients with locally advanced SNSCC,

where the main pattern of treatment failure remains local disease recurrence. Our findings support the need to evaluate intensified local treatment through IMRT and VMAT further to improve upon these outcomes. The current standard of care for radiation treatment of SNSCC at our institution has shifted from 3D-CRT to VMAT and this study will allow for comparison of treatment outcomes with these newer and more dose-intense techniques.

Ethical considerations

This study was approved by the University of Cape Town's Human Research Ethics Committee. The retrospective design of this study did not impede, alter, or influence treatment decisions or patient care.

Study data was collected and managed using REDCap electronic data capture tools hosted at the University of Cape Town.[33,34] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing: 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Dr Bhavesh Nagar was responsible for review of the literature, data collection and interpretation as well as for drafting the manuscript. All authors were responsible for reviewing and approving the manuscript prior to submission.

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ABBREVIATIONS

Abbreviation	Meaning
AJCC	American Joint Committee on Cancer
CCRT	Concurrent chemoradiation
CR	Complete response
CT scan	Computerised Tomography scan
dCCRT	Definitive concurrent chemoradiation
dRT	Definitive radiotherapy
DSS	Disease Specific Survival
EBV	Epstein-Barr Virus
ECOG	Eastern Cooperative Oncology Group
EPR	Electronic Patient Registry
EQD2	Equivalent dose in 2Gy fractions
Gy	Gray
HC	Holding Chemotherapy
HPV	Human Papilloma Virus
HREC	Human Research Ethics Committee
IC	Induction Chemotherapy
IMRT	Intensity Modulated Radiotherapy
IQR	Interquartile range
LC	Local control
LET	Linear Energy Transfer
LRC	Loco-regional control
MRI	Magnetic Resonance Imaging
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PORT	Post-operative Radiotherapy
PR	Partial Response
PS	Performance Status
RBE	Relative Biological Effectiveness
RCT	Randomised control trial
RECIST	Response Evaluation Criteria in Solid Tumours
RT	Radiotherapy
SCC	Squamous cell carcinoma
SD	Stable Disease
SD	Standard Deviation
SEER	Surveillance Epidemiology and End Results

SIP	Sinonasal Inverted Papilloma
SNC	Sinonasal carcinoma
SNSCC	Sinonasal squamous cell carcinoma
SPSS	Statistical Package for the Social Sciences
VMAT	Volume Modulated Arc Therapy
2D	Two-dimensional
3D	Three-dimensional
3D-CRT	3D-conformal radiotherapy

PART C: APPENDICES

REDCap data capture instrument

Sinonasal Cancer

Record ID	_____
RT Number	_____
Hospital Number	_____
Date of Registration	_____
Date of Birth	_____
Gender	○ Male ○ Female ○ Other
ECOG Perfomance Status	○ Completely normal ○ Symptomatic Ambulatory ○ In bed < 50% of the day ○ In bed > 50% of the day ○ Bedbound
Co-morbidities	☐ None ☐ Hypertension ☐ Diabetes ☐ HIV ☐ Other
If other co-morbidities, specify	_____
Presenting Symptoms	☐ Nasal obstruction ☐ Epistaxis ☐ Facial asymmetry/ mass/ swelling ☐ Facial pain ☐ Neck Nodes/ mass ☐ Weight loss ☐ Change of phonation ☐ Loss/ change of sensation ☐ Loose teeth/ toothache ☐ Visual disturbance ☐ Tearing eyes (epiphora) ☐ Unknown ☐ Other
If other presenting symptom, specify	_____
Duration of Symptoms (weeks)	_____

Time to diagnosis (weeks)	_____
Tumor Site	○ Nasal Cavity ○ Maxillary Antrum ○ Ethmoid Sinus ○ Sphenoid Sinus ○ Frontal Sinus
Date of Histology	_____
Histology	○ Keratinizing squamous cell carcinoma ○ Non keratinizing Squam Ca (Transitional cell Ca) ○ Ca-In-Situ ○ Poorly diff/ undiff Ca ○ Other
If Other Histology, specify	_____
Tumor Grade	○ I - well differentiated ○ II - modd differentiated ○ III - poorly differentiated ○ unknown
Lymphovascular invasion	○ Yes ○ No
Perineural Invasion	○ Yes ○ No
HPV status	○ Positive ○ Negative ○ Unknown
EBER	○ Positive ○ Negative ○ Unknown
Cytokeratin	☐ CK1 ☐ CK 5/6 ☐ CK7 ☐ Other ☐ Unknown
If other CK, specify	_____
Epithelial Membrane Antigen	○ Positive ○ Negative ○ Unknown

Risk Factors	☐ Tobacco smoker ☐ Wood dust ☐ Leather ☐ Textiles ☐ Formaldehyde ☐ Glues ☐ Organic Solvents ☐ Other ☐ Unknown
If other Risk factor, specify	_____
Staging Investigations	☐ CT ☐ MRI ☐ PET- CT ☐ Sonar ☐ CXR ☐ Other
If other staging investigation, specify	_____
Tumor Stage	○ T1 ○ T2 ○ T3 ○ T4a ○ T4b
Nodal Stage	○ Nx ○ N0 ○ N1 ○ N2a ○ N2b ○ N2c ○ N3a ○ N3b
Mets Stage	○ M0 ○ M1
TNM Stage	○ Stage I ○ Stage II ○ Stage III ○ Stage IVa ○ Stage IVb ○ Stage IVc
Treatment intent	○ Radical ○ Palliative

Treatment modality at baseline	☐ Surgery ☐ Postop RT ☐ Postop CRT ☐ Definitive RT ☐ Definitive CRT ☐ Induction Chemotherapy + Definitive CRT ☐ Preoperative chemotherapy ☐ Postop/ Adj chemotherapy ☐ Palliative chemotherapy ☐ Holding chemotherapy ☐ Palliative RT ☐ BSC
Brief treatment plan summary	_____
Date of Surgery	_____
Type of surgery	☐ WLE ☐ Endoscopic ☐ Other
If other surgery, Specify	_____
Neck dissection	○ Yes ○ No
Type of neck dissection	☐ bilateral ☐ unilateral
neck node status on dissection	○ positive ○ negative
Surgical Resection status	○ neg margin (R0) ○ pos margin (R1) ○ gross residual (R2) ○ unknown
Chemo regimen used for CCRT	○ Cisplat Q21d ○ Carbo Q21d ○ Cisplat weekly ○ Carbo weekly ○ Other
If other chemo regimen, specify	_____
No of chemo cycles for CCRT	_____

Induction chemo regimen	○ Cisplat + 5FU + Docetaxel ○ Cisplat + 5FU + Paclitaxel ○ Carbo + 5FU + Docetaxel ○ Carbo + 5FU + Paclitaxel ○ Cisplat + 5FU ○ Carbo + 5FU ○ Other
If other Induct regimen, specify	_____
No of chemo cycles for induct chemo received	_____
Preop chemo regimen	○ Cisplat + 5FU + Docetaxel ○ Cisplat + 5FU + Paclitaxel ○ Carbo + 5FU + Docetaxel ○ Carbo + 5FU + Paclitaxel ○ Cisplat + 5FU ○ Carbo + 5FU ○ Other
If other preop chemo, specify	_____
No of chemo cycles of preop chemo received	_____
Postop/ adj chemo regimen	○ Cisplat + 5FU + Docetaxel ○ Cisplat + 5FU + Paclitaxel ○ Carbo + 5FU + Docetaxel ○ Carbo + 5FU + Paclitaxel ○ Cisplat + 5FU ○ Carbo + 5FU ○ Other
If other postop/ adj chemo, specify	_____
No of chemo cycles of postop/ adj chemo received	_____
Palliative Chemo regimen	_____
No of pall chemo cycles	_____
Completed pall chemo	○ Yes ○ No
Reason not completing pall chemo	☐ Treatment toxicity ☐ Patient withdrew chemo consent ☐ Progressive disease ☐ DNA ☐ Death

Holding chemo Regimen	_____
Number of holding chemo cycles	_____
Induct/ preop/ postop/ pall/ holding chemo start date	_____
Induct / preop/ postop/ pall/ holding chemo end date	_____
Delays in Chemo	○ Yes ○ No
Reason for delays in chemo	☐ Toxicity ☐ DNA ☐ Omitted to allow CCRT ☐ Transport/ social ☐ Other
Toxicity related chemo delays	☐ Neutropaenia ☐ Low HB ☐ Low platelets ☐ Other
If other chemo toxicity	_____
If other reason for chemo delay	_____
Radiation Technique	○ 3D- CRT ○ VMAT ○ IMRT ○ Palliative 2D ○ Absconded
Radiotherapy Type	☐ Photons ☐ Protons ☐ Electrons ☐ Neutrons
If electrons specify if used for boost	○ Yes ○ No
RT dose to primary tumor/ HIGH DOSE	_____
RT dose to involved nodes/ INT DOSE	_____
RT dose to elective nodes/ LOW DOSE	_____
total number of RT fractions planned	_____

Planned number of fractions per week	_____
total number of RT fractions patient received	_____
RT Start date	_____
RT end date	_____
RT treatment delays	○ Yes ○ No
Reason for RT Rx delays	☐ Treatment toxicity ☐ Transport issues ☐ Social issues ☐ National holiday ☐ Machine service ☐ Other
If other RT Rx delay, specify	_____
RT treatment delay duration (days)	_____
Intended RT time (days)	_____
Total RT time (days)	_____
Completed Initial Treatment Plan	○ Yes ○ No
Reason why initial treatment not completed	○ Absconded ○ Disease progression on treatment ○ Treatment toxicity ○ Patient withdrew consent ○ Death
Description of Rx Toxicity	_____
Treatment start date (initial)	_____
Treatment end date (initial)	_____
Overall Treatment Time (OTT - days) INITIAL Rx	_____

Alive at 3month / 1st FU?	○ Yes ○ No
Response at 3 months / 1st FU	○ CR ○ PR ○ SD (aka persistence) ○ PD ○ Lost to follow-up
Method used to establish 3 month / 1st FU response	○ clinical examination ○ radiology ○ both
Date of 3 month/ 1st follow up	_____
Date of Progressive Disease noted @ 1st FU	_____
Time to progression after initial treatment (days)	_____
Site of Progressive Disease @ 3month/ 1st FU	☐ Local (primary tumor site) ☐ Loco-regional LNs ☐ Distant
If distant PD @3 month / 1st FU, where	_____
Treatment modality for Progressive disease (i.e 1st salvage manoeuvre)	☐ Surgery ☐ Chemotherapy ☐ Radiation ☐ BSC
If further rx indicated after initial assessment; Response to 1st salvage manoeuvre	○ Disease Controlled ○ Uncontrolled disease ○ No treatment needed, clinical f/u only
If response to 1st salvage is uncontrolled, What was offered?	○ BSC ○ Other
if other Rx after 1st salvage, what?	_____
Alive/ attended 2yr/ 2nd FU?	○ Yes ○ No
Response at 2years/ 2nd FU	○ Ongoing uncontrolled disease for BSC ○ CR ○ PR ○ SD ○ PD ○ Lost to Follow-up
Method used to establish 2yrs/ 2nd FU response	○ clinical examination ○ radiology ○ both

Date of 2yr/ 2nd follow up	_____
Date of Progressive Disease noted as noted @2yr/ 2nd fu	_____
number of salvage manoeuvres used to date of 2yr/ 2nd FU	_____
Time to progression after initial treatment response (months) Diff btwn date of PD and date documented response to inital rx	_____
Time to progression after last known salvage treatment response (months) Diff btwn date of PD and date documented response to last known salv rx	_____
Site of Progressive Disease @2yrs/ 2nd FU	☐ Local (primary tumor site) ☐ Loco-regional LNs ☐ Distant
If distant PD, where (2yr/ 2nd FU)	_____
Treatment modality for Progressive disease (2yrs/ 2nd FU)	☐ Surgery ☐ Chemotherapy ☐ Radiation ☐ BSC
Response to last known salvage manoeuvre (@2yrs)	○ Disease Controlled ○ Uncontrolled disease ○ N/a
If response to last known salvage is uncontrolled, What was offered?	○ BSC ○ Other
if other Rx after last known salvage, what?	_____
Alive/ attended 5yr fu/ 3rd FU?	○ Yes ○ No
Response at 5years/ 3rd FU post initial Rx	○ Ongoing uncontrolled disease for BSC ○ CR ○ PR ○ SD ○ PD ○ Lost to Follow-up
Method used to establish 5yr / 3rd FU respose	○ clinical examination ○ radiology ○ both
Date of 5yr/ 3rd follow-up	_____

Date of Progressive Disease noted @5yr/ 3rd fu	_____
5yr-Time to progression after initial treatment response (months) Diff btwn date of PD and date documented response to inital rx	_____
5-YR Time to progression after last known salvage treatment response (months) Diff btwn date of PD and date documented response to last known salv rx	_____
Site of Progressive Disease @5yrs/ 3rd FU	☐ Local (primary tumor site) ☐ Loco-regional LNs ☐ Distant
If distant PD @5yr/ 3rd FU, where	_____
Treatment modality for Progressive disease @5yrs/ 3rd FU	☐ Surgery ☐ Chemotherapy ☐ Radiation ☐ BSC
number of salvage manoeuvres used to date of 5yr fu	_____
Response to last known salvage manoeuvre at 5yr/ 3rd FU	○ Disease Controlled ○ Uncontrolled disease ○ N/a
If response to last known salvage is uncontrolled, What was offered?	○ BSC ○ Other
if other Rx after last known salvage, what?	_____
Survivorship	○ Alive ○ Dead ○ Unknown
Date of last follow-up	_____
Date of death	_____
Overall survival (OS) months	_____
Survival to last known follow up (months)	_____
Time from Biopsy to starting Treatment (days)	_____

Reason for delay in Rx initiation (if any)

Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

11 March 2020

HREC REF:139/2020

Dr S Dalvie
Division of Radiation Oncology
LE 34, L -Block, GSH

Dear Dr Dalvie

PROJECT TITLE: SINONASAL SQUAMOUS CELL CARCINOMA (SNSCC): A RETROSPECTIVE REVIEW OF THE TREATMENT OUTCOMES OF PATIENTS TREATED AT GROOTE SCHUUR HOSPITAL, CAPE TOWN, SOUTH AFRICA (MMED DEGREE - DR BHAVESH NAGAR)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 March 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Bhavesh Nagar will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

pp TBurgess
PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

HREC 139/2020sa

Hospital Approval

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: GSHResearch.Request@westerncape.gov.za

Dr Sameera Dalvie
RADIATION ONCOLOGY

E-mail: s.dalvie@uct.ac.za / NGRBHA002@myuct.ac.za

Dear Dr Dalvie,

RESEARCH PROJECT: Sinonasal Squamous Cell Carcinoma (SNSCC): A Retrospective Review of The Treatment Outcomes Of Patients Treated At Groote Schuur Hospital, Cape Town, south Africa

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 March 2022.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) **Confidentiality must always be maintained.**
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) **Kindly submit a copy of the publication or report to this office on completion of the research.**
n) **At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**
o) **Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 30 July 2021

C.C. Mr. L. Naidoo / Dr H. Aziz / Mr A. Mohamed / Professor J. Parkes

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Departmental Approval

Radiation Oncology

Professor Jeannette Parkes
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Groote Schuur Hospital, Observatory, 7925, South Africa

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E-mail: Jeannette.parkes@uct.ac.za

19 March 2020

Dear Dr S Dalvie

Permission is hereby granted to Dr S Dalvie and Dr B Nagar for the following MMED study to be conducted in the department of Radiation Oncology.

MMed Title: SINONASAL SQUAMOUS CELL CARCINOMA (SNSCC): A RETROSPECTIVE REVIEW OF THE TREATMENT OUTCOMES OF PATIENTS TREATED AT GROOTE SCHUUR HOSPITAL, CAPE TOWN, SOUTH AFRICA (MMED DEGREE - DR BHAVESH NAGAR)

Please note that permission is also required from the institutional research committee and from th ethics committee before commencing the research study.

Yours sincerely

Professor Jeannette Parkes
Head of Division
Radiation Oncology Division

Criteria for submission to South African Journal of Oncology

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format. Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings, clearly present the overall results and any meta-analysis.

Word limit	3500-4000 words (excluding the structured abstract and references)
Structured abstract	250 words to include a Background, Aim, Setting, Methods, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate