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TREATMENT OUTCOMES OF EPSTEIN-BARR VIRUS ASSOCIATED NASOPHARYNGEAL CARCINOMA WITH THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY: A RETROSPECTIVE REVIEW

by

Dr Santhuri Viranna

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Supervisor: Dr Sameera Dalvie

Department of Radiation Oncology, University of Cape Town

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DECLARATION

I, Dr Santhuri Viranna, declare that the work on this study is my original work except where acknowledgements are indicated. This is an unsponsored study and was carried out for educational purposes only and towards a postgraduate MMed degree. I therefore declare no conflict of interest whatsoever.

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PUBLICATION-READY FORMAT

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PART A: ABSTRACT

TREATMENT OUTCOMES OF EPSTEIN-BARR VIRUS ASSOCIATED NASOPHARYNGEAL CARCINOMA WITH THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY: A RETROSPECTIVE REVIEW

Santhuri Viranna, Sameera Dalvie

Department of Radiation Oncology, University of Cape Town

Background: Data on treatment outcomes of Epstein-Barr virus (EBV) associated nasopharyngeal carcinoma (NPC) largely comes from endemic regions. There is limited literature available regarding the epidemiology and treatment outcomes of EBV associated NPC in South Africa.

Aim: The primary aim of the study was to determine overall survival (OS) of patients with EBV associated NPC treated over an 11-year period.

Setting: Groote Schuur Hospital, between January 2003 and December 2013.

Methods: This is a retrospective observational study. Medical records of all patients with histologically confirmed NPC were reviewed. EBV staining was requested on all available archived specimens. All radical patients were treated with three-dimensional conformal radiotherapy (3DCRT). This review assesses the prevalence of EBV associated NPC, OS, disease-free survival (DFS), loco-regional control (LRC), and impact of treatment interruptions on OS.

Results: The study population comprised 53 patients. Non-keratinizing carcinoma was the primary histological subtype (86.8%). 25 patients (47.2%) had histologically confirmed EBV positive NPC. The 2-and 5-year OS of radically treated EBV positive patients were significantly higher than EBV negative patients, 84% versus 34% and 45% vs 17% respectively (p=0.002). Two-year DFS was 55% vs 43% (p=0.38) and 2-year LCR were 76.2% vs 46.2% (p=0.13) for EBV positive and EBV negative patients respectively. The mean OS of patients with treatment interruptions was lower compared to those without interruptions (1249 days vs 1440 days).

Conclusion: Treatment of EBV associated NPC is associated with superior OS, with a non-significant trend for improved DFS and LRC, compared to EBV negative tumours.

PART B: PUBLICATION-READY MANUSCRIPT

Introduction

Nasopharyngeal carcinoma (NPC) is a rare malignancy in most parts of the world with incidence rates of less than 1 per 100 000 people in non-endemic regions(1). Endemic regions include Southern China and Hong Kong, with incidence rates of more than 20 cases per 100 000 reported(2). In South Africa, NPC is rare with a 5-year prevalence of 0.88 cases per 100 000 according to GLOBOCAN 2020 statistics(3). The incidence of NPC is two to threefold higher in males than females and displays a bimodal age distribution in non-endemic areas(4).

The specific geographical distribution of NPC is reflective of its complex aetiology which include viral, environmental, and genetic factors. Epstein Barr virus (EBV) infection plays a critical role in the pathogenesis of NPC and there is evolving interest in EBV-associated NPC as a prognostic biomarker(5). Studies document superior outcomes in terms of survival and local control for patients with EBV-associated carcinomas(6,7). The World Health Organization (WHO) classification of NPC encompasses three histological subtypes: keratinizing squamous carcinoma (1978 WHO classification type I), non-keratinizing carcinoma and basaloid carcinoma(8,9). Non-keratinizing carcinoma is further subdivided into differentiated (WHO type II) and undifferentiated tumours (WHO type III). EBV is invariably associated with the non-keratinizing carcinoma subtype seen in both endemic and non-endemic regions(10).

Concurrent chemoradiation (CCRT) is the standard of care for locally advanced disease but treatment may include induction chemotherapy prior to CCRT or adjuvant chemotherapy following CCRT(11). Intensity modulated RT (IMRT) is the preferred RT technique for the treatment of NPC because of distinct dosimetric advantages over 3D conformal RT (3DCRT), including superior tumour coverage and greater sparing of organs at risk(12). Despite these technological advantages, the clinical benefit of IMRT on local control, survival and reducing long term toxicity compared to 3D CRT is still being investigated(13). In many developing countries access and training to advanced techniques such as IMRT are limited and 3DCRT remains the main RT technique available.

There is a dearth of literature regarding the prevalence of EBV-positive NPC in South Africa and information regarding the prevalence from non-endemic regions comes mainly from retrospective studies. In a study from Mexico investigating nonendemic NPC over a 10-year period, the rate of EBV posittivity was 92%(14). In a retrospective study from Pakistan evaluating 100 cases of NPC, 92 cases of non-keratinizing carcinoma were found over a 3-year period, of which 81.5% were EBV positive(15). Only one study evaluating EBV strain characterization in South African patients with NPC found a strong association of 82% between EBV positivity and NPC(16). There is a paucity of data for South Africa regarding the

epidemiology, prevalence and outcomes of EBV associated NPC. We aimed to assess EBV prevalence and treatment outcomes, including comparing overall surival of EBV positive and EBV negative patients treated at a single inistitiution over an 11-year period.

Methods

Study Aims and Objectives

The aim of the study was to determine treatment outcomes of EBV associated NPC patients treated at Groote Schuur Hospital (GSH) between 2003 and 2013.

The primary objective was to determine the 2- and 5-year overall survival (OS) of patients with EBV associated NPC compared to EBV negative NPC treated at GSH. Secondary objectives were to determine disease-free survival (DFS), loco-regional control rates (LRCR), prevalence of EBV associated NPC and impact of treatment interruptions on treatment outcomes.

Study Population

The records of all new patients who presented with NPC to the oncology clinic at GSH between January 2003 and December 2013 were reviewed. Only patients with histologically confirmed NPC, patients treated with radical and palliative intent, including patients younger than 18 years of age and HIV positive patients were included. Patients treated at an institution other than GSH were excluded. Palliative patients were included in the study to determine OS and prevalence of EBV associated NPC treated at GSH. A total of 57 folders were retrieved during the study period however, 4 patients were excluded, one patient was treated at another institution and 3 patients demised before receiving any treatment. The remaining 53 patients were eligible for review.

Scientific Design

This was a retrospective observational study.

Data Collection Methods

Patient demographics, histology, staging, treatment and follow up data were collected. EBV staining using EBV-encoded RNA (EBER) in-situ hybridization (ISH) was documented from pathology reports or requested on available archived specimens. Pre-treatment evaluation included history and examination, indirect laryngoscopy, chest X-ray, computed tomography (CT), magnetic resonance imaging (MRI), bone scan or fluorodeoxyglucose (FDG)-positron

emission tomography (PET). As the staging system for NPC changed during the study period, all tumours were staged using the American Joint Committee on Cancer (AJCC) 8th edition 2017 Tumour Node Metastasis (TNM) staging system. Assessment of response to treatment was based on clinical assessment or imaging as documented in the patient's folder.

Treatment

All patients were reviewed at the multidisciplinary team clinic to determine the treatment intent and management plan. Radiotherapy was the sole modality of treatment for stage I disease. Locally advanced disease was treated with either induction chemotherapy followed by chemoradiation, chemoradiation alone or radiotherapy alone. Induction chemotherapy included a platinum agent, namely cisplatin or carboplatin depending on renal function, and 5 fluorouracil (5FU) chemotherapy. All radical patients were treated using 3D conformal RT. All patients were setup and immobilized in a custom-made thermoplastic mask. The radiotherapy prescription ranged between 60 to 70Gy to the gross tumour and 50Gy to the prophylactic nodal areas. The patients were assessed with imaging 3 months after completing treatment and thereafter assessed clinically for locoregional recurrence and metastatic disease at 3 to 6 monthly intervals. Radiology was used only for symptomatic patients and not routinely during follow up.

Palliative patients were treated with either palliative radiation, chemotherapy, or supportive care. The dose of palliative radiation ranged between 20 to 36Gy using hypo- fractionated regimens.

Statistical Analysis

In view of the rarity of NPC, an 11-year study period was chosen to accrue enough participants to meet the study objectives. The data collected was stored in the REDCap (Research Electronic Data Capture) database and was used to analyze variables relevant to the study. SPSS version 27 software was used for descriptive and inferential statistics to analyze the data.

Kaplan-Meier survival analysis was used to determine OS (defined as time from starting treatment until the date of death or last follow up), DFS (defined as time from end of treatment until the date of relapse at any site) and LRCR (defined as time from end of treatment until locoregional relapse). To compare groups, the log-rank test was used and p-values ≤ 0.05 were considered statistically significant. The Chi-square test was used to determine the association between 2-year local control and EBV status. Only univariate analysis was performed due to small number of subjects.

Ethical Considerations

The Human Research Ethics Committee of the University of Cape Town approved the proposed study. HREC REF 671/2018. Informed consent was not required as this was a retrospective review of medical records only. All collected data was stored on a password protected laptop.

Results

Patient characteristics

A total number of 53 patients were eligible for the study. The demographic data of the study population is included in Table 1. Forty-one (77.4%) patients were treated with curative intent and twelve (22.6%) patients were treated palliatively. Forty (75.5%) patients presented with locally advanced disease (stage III-IVA). Only six (11.3%) patients had metastatic disease at presentation. The median age was 43 years (range 11-87 years). The age-distribution for both sexes showed a peak between the ages of 40-59 years, which accounts for 41.5% of cases. Twelve (22.6%) patients were younger than 25 years of age. A male predominance of patients was observed, 42 males (79.2%) versus 11 females (20.8%). Most patients (66%) had a good Eastern Cooperative Oncology Group (ECOG) performance status (PS) of one. Thirty-six (67.9%) patients were smokers at presentation. Seven patients (13.2%) were HIV positive at diagnosis. Four (57.1%) of the HIV positive patients were treated with curative intent and 3 patients were treated palliatively. Only one patient that was HIV positive had metastatic disease at presentation.

Table 1: Demographic data of study population.

Variable	*n* Value	Percentage (%)
Treatment intent		
Curative	41	77.4
Palliative	12	22.6
Gender		
Male	42	79.2
Female	11	20.8
Age (years)		
Mean	43	
Under 25	12	22.6
25-39	8	15.1
40-59	22	41.5
60-69	7	13.2
≥ 70	4	7.6
Performance Status (ECOG)		
0	1	1.9
1	35	66
2	7	13.2
3	7	13.2
Unknown	3	5.7
HIV status at presentation		
Positive	7	13.2
Negative	29	54.7
Unknown	17	32.1
Smoking status		
Smoker	36	67.9
Nonsmoker	14	26.4
Unknown	3	5.7
Stage		
I	2	3.8
II	5	9.4
III	8	15.1
IVA	32	60.4
IVB	6	11.3
Histology		
Keratinizing carcinoma	6	11.3
Non-keratinizing carcinoma	46	86.8
Basaloid carcinoma	1	1.9
EBV status		
Negative	19	25.8
Positive	25	47.2
Unknown	9	17

Non-keratinizing carcinoma was the predominant histological subtype in 46 patients (86.8%). Keratinizing carcinoma accounted for 11.3% of cases and 1.9% of cases were basaloid carcinoma. Of the 44 patients whose EBV statuses were known, 25 patients (56.8%) were EBV associated versus 19 patients (43.2%) which were EBV negative. Non-keratinizing carcinomas had the highest rate of EBV positivity (92%) compared to other histological subtypes and is displayed in Table 2.

Table 2. Histological subtypes according to EBV status.

Histology	EBV Positive No. (%)	EBV Negative No. (%)	EBV Unknown No. (%)
Non-keratinizing carcinoma	23 (92%)	16 (84.2%)	7 (77.8%)
Keratinizing carcinoma	2 (8%)	3 (15.8%)	1 (11.1%)
Basaloid carcinoma	0	0	1 (11.1%)

Treatment

At presentation, the most common imaging modalities used included CT (94.3%) and bone scan (54.7%). MRI was used in 20.8% of cases and only 18.9% of patients had FDG-PET imaging.

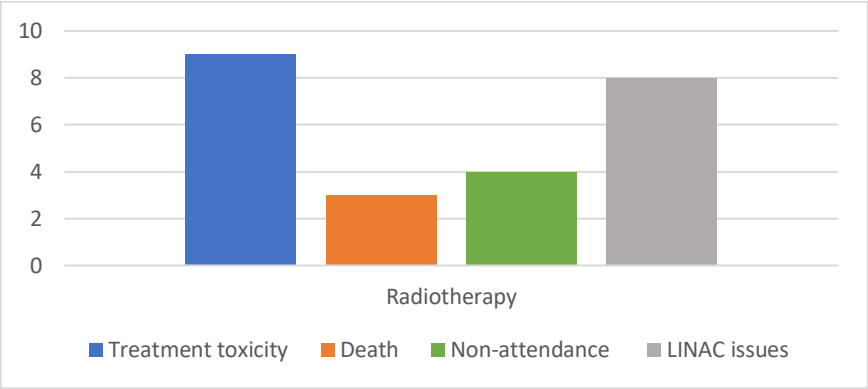
Patients deemed fit for curative treatment (41 patients) received either induction chemotherapy followed by CCRT, CCRT alone or RT alone. The most common treatment modality used was induction chemotherapy followed by CCRT (90%). Two patients did not receive CCRT after induction chemotherapy due to defaulting treatment. Most patients (39 patients, 95.1%) received between one to four cycles of induction chemotherapy with a dual-drug regimen of cisplatin or carboplatin and 5FU. Only one patient was treated with CCRT alone and one other patient received RT alone. The chemotherapy regimens used concurrently with RT included carboplatin area under the curve (AUC) 5 given 3-weekly, cisplatin 75-100mg/m² 3-weekly or weekly carboplatin AUC 2. The average number of concurrent chemotherapy cycles received was 3 (range 1-7 cycles).

Thirty-two (78%) patients experienced radiotherapy and/or chemotherapy treatment interruptions during their planned course of radical treatment. Four patients demised during treatment. One patient died of a traumatic event after receiving 13 fractions of RT. Another patient died of pneumonia during RT. Two patients demised from treatment toxicity, one developed electrolyte abnormalities after the first cycle of induction chemotherapy and died shortly thereafter, and another died after developing grade 3 dysphagia and trismus.

Twenty-four patients experienced RT interruptions, with the average length of RT delays being 9.1 days (range 2-19 days). Data on radiotherapy treatment interruptions are shown in Figure

1. The most common reasons for radiotherapy interruptions were treatment toxicity (37.5%) followed linear accelerator (LINAC) related issues (33.3%). The average dose of radical RT received was 59.4Gy (range 6.3-70Gy). The reasons for patients receiving a lower RT dose than prescribed included treatment interruptions due to treatment toxicity (36.4%), machine breakdown (27.3%), non-cancer related deaths (18.2%) and patients defaulting treatment (18.2%). In terms of patients that received chemotherapy, 9 patients experienced treatment toxicity. Neutropenia was the most common reason chemotherapy was delayed.

Figure 1. Bar chart showing reasons for radiotherapy treatment interruptions in radical patients.



Treatment modalities used in the palliative setting included palliative radiotherapy, palliative chemotherapy, and supportive care. Seven patients received palliative RT. Three hypo fractionated regimens were used to deliver palliative RT, namely, 20Gy in 5 fractions (42.9%), 30Gy in 10 fractions (28.6%) and 36Gy in 12 fractions (28.6%). Seven patients received palliative chemotherapy using a platinum agent with 5FU.

Treatment Outcomes

In terms of the primary endpoint, 2-and 5-year OS after radical treatment of EBV positive and EBV negative patients was 84% versus 34% and 45% versus 17% respectively (p=0.002). The mean OS of radically treated EBV positive patients was 1582 days compared to 661 days in EBV negative patients (Figure 2). This significant survival benefit in EBV associated NPC was demonstrated irrespective of treatment intent in the entire study population, with 2-year OS of 52% versus 21.1% (p<0.001) for EBV positive and EBV negative patients respectively.

The median OS time of all patients included in the study from the start of treatment was 1088 days (95% CI, 505.47 to 1670.53). The cumulative OS two years after treatment was 63% and 37% at five years. The median survival time of radically treated patients was 1671 days compared to 231 days for palliative patients.

The cumulative 2- and 5-year DFS of EBV associated NPC compared to EBV negative cases was 55% and 43% respectively (Figure 3). DFS of EBV positive patients was 12% higher than EBV negative patients but was not found to be statistically significant (p=0.38).

Figure 2. Kaplan-Meier survival curve for OS in radically treated patients according to EBV status (p=0.002).

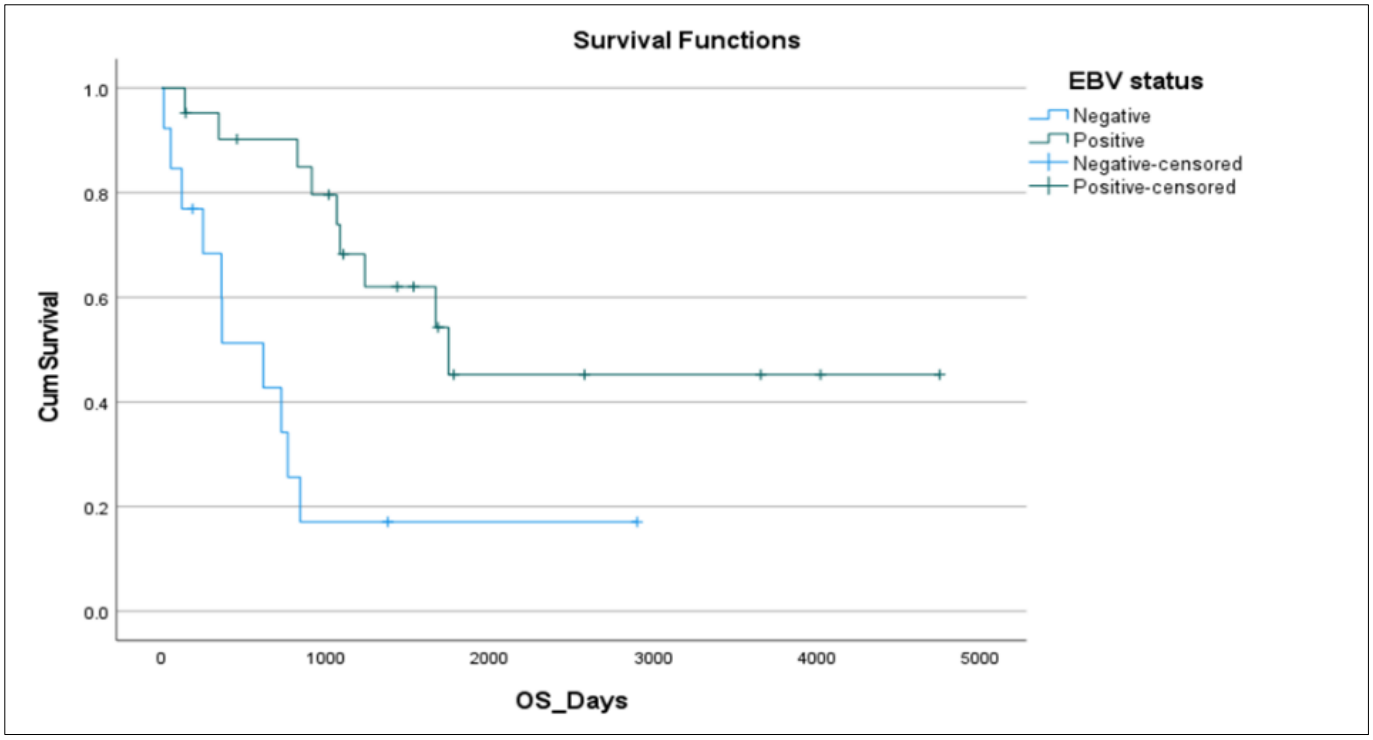
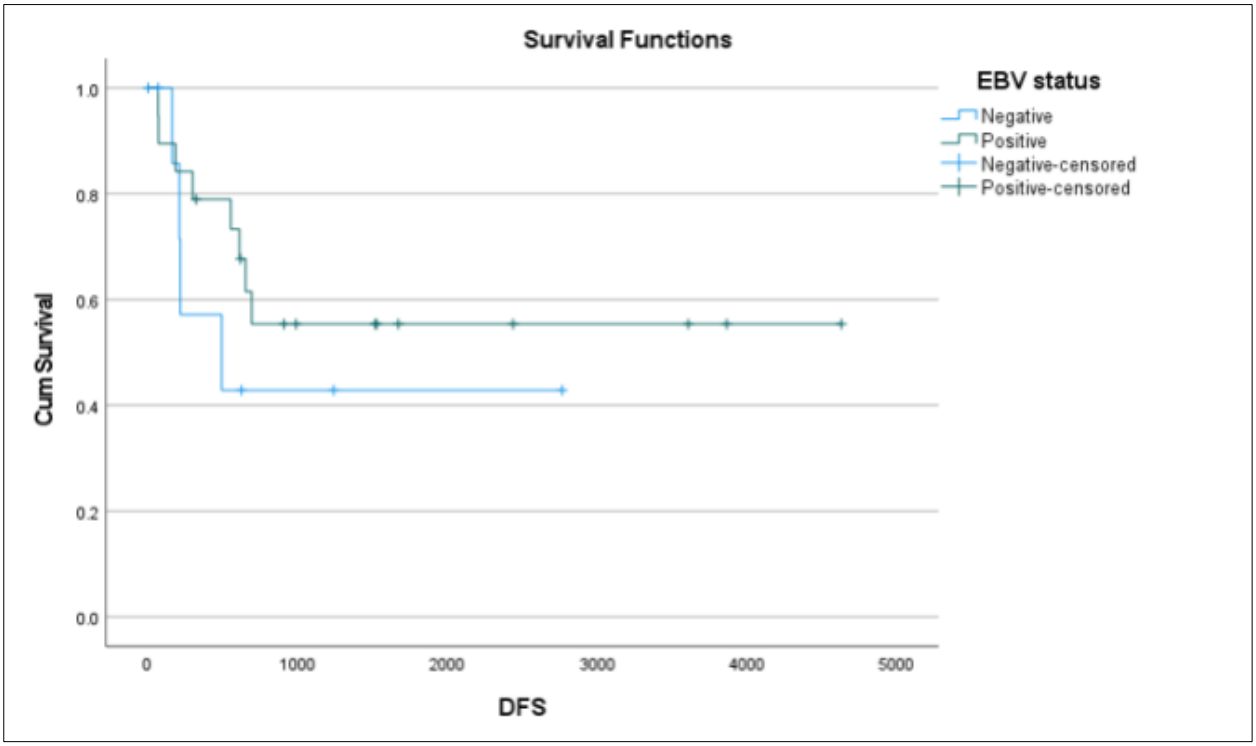


Figure 3. Kaplan-Meier survival curve for DFS in radically treated patients according to EBV status (*p*=0.38).



Two-year loco-regional control rates were 76.2% and 46.2% for EBV positive and EBV negative patients respectively but was not found to be statistically significant (*p*=0.13). The pattern of relapse between the two groups of patients were found to be similar, with EBV positive patients found to have 4% higher loco-regional relapse (LRR) and distant relapse (Table 3). The median DFS time of EBV negative patients with LRR was 219 days compared to 300 days for EBV positive radical patients. The log rank test showed that the difference in DFS in patients with LRR was not statistically significant (p=0.46) according to the EBV status. Two patients received salvage therapy after LRR. One patient with EBV associated NPC, underwent a salvage neck dissection within 4 months of completing initial treatment. The second patient, whose EBV status was unknown, was re-irradiated to 50Gy for local relapse.

Table 3. Pattern of relapse according to EBV status.

Site of relapse					
EBV status			Frequency	Percent	Valid Percent
Negative	Valid	Local and regional	2	15.4	50.0
		Distant	2	15.4	50.0
		Total	4	30.8	100.0
	Missing	System	9	69.2	
	Total		13	100.0	
Positive	Valid	Local and regional	4	19.0	50.0
		Distant	4	19.0	50.0
		Total	8	38.1	100.0
	Missing	System	13	61.9	
	Total		21	100.0	

EBV negative patients: Two EBV negative patients' site of relapse were locoregional and two were distant (15,4% of EBV negative patients respectively)
EBV positive patients: Four EBV positive patients' site of relapse were locoregional and four were distant (19,0% of EBV positive patients respectively)

Missing patients refers to patients who did not relapse/ deceased/ lost to follow up.

Predictive factors for OS

On univariate analysis in radically treated patients, statistically significant predictive factors for OS included EBV status, histological subtype, smoking status, and HIV status (Table 4).

The mean OS of radically treated patients with treatment interruptions was lower (1249 days) compared to patients without treatment interruptions (1440 days). The impact of treatment interruptions on overall survival, however, was not found to be statistically significant (p=1.28).

Patients with non-keratinizing carcinomas had the longest OS compared to other histological subtypes (Figure 4). Patients that were smokers at presentation had significantly inferior OS compared to non-smokers (p=0.003). The 2-year OS for smokers versus non-smokers was 62% and 91% respectively (Figure 5).

HIV positive patients had significantly higher OS compared to HIV negative patients (Figure 5). Of the seven HIV positive patients, four (57.1%) were treated with radical intent. Most of the HIV positive patients had non-keratinizing histology (85.7%) and were EBV associated.

In terms of 2-year survival according to stage of disease, patients with stage II disease had the highest rates of survival (80%). Stage IVA patients had the lowest survival (40.6%) overall. Stage I, III and IVB had equivalent survival rates of 50%. Two patients had stage 1 disease at

presentation. One patient demised from pneumonia while on treatment, while the other patient had a complete response to treatment.

Table 4. Predictive factors of overall survival

Log Rank (Mantel-Cox)	Chi-Square	Significance (p value)
Test of equality of survival distributions for the different levels of **EBV status**.	9.831	**0.002**
Test of equality of survival distributions for the different levels of **Histology**.	13.5	**0.004**
Test of equality of survival distributions for the different levels of **Stage.**	3.233	0.521
Test of equality of survival distributions for the different levels of **Age at diagnosis.**	1.089	0.78
Test of equality of survival distributions for the different levels of **HIV status.**	4.397	**0.036**
Test of equality of survival distributions for the different levels of **Gender.**	0.004	0.949
Test of equality of survival distributions for the different levels of **Smoking status.**	8.684	**0.003**
Test of equality of survival distributions for the different levels of **Treatment interruption.**	2.32	1.28

Figure 4. Kaplan-Meier survival curve for OS according to histological subtype (*p*=0.004).

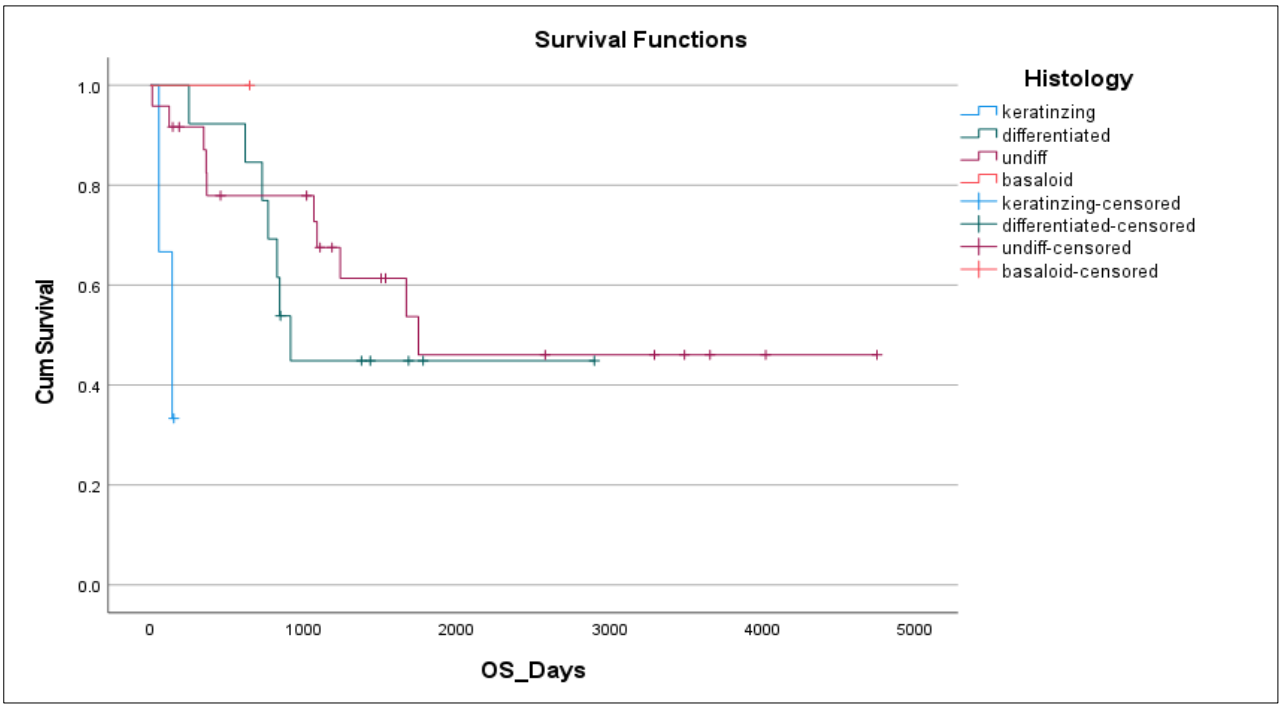
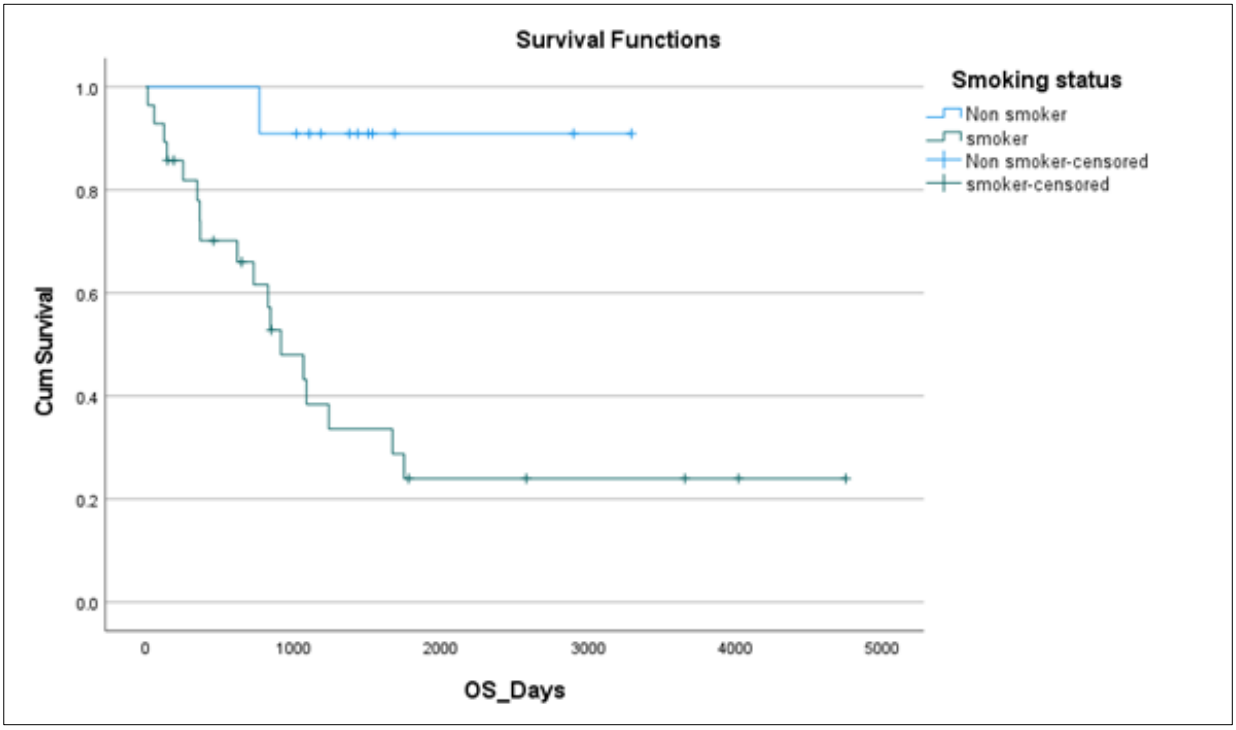
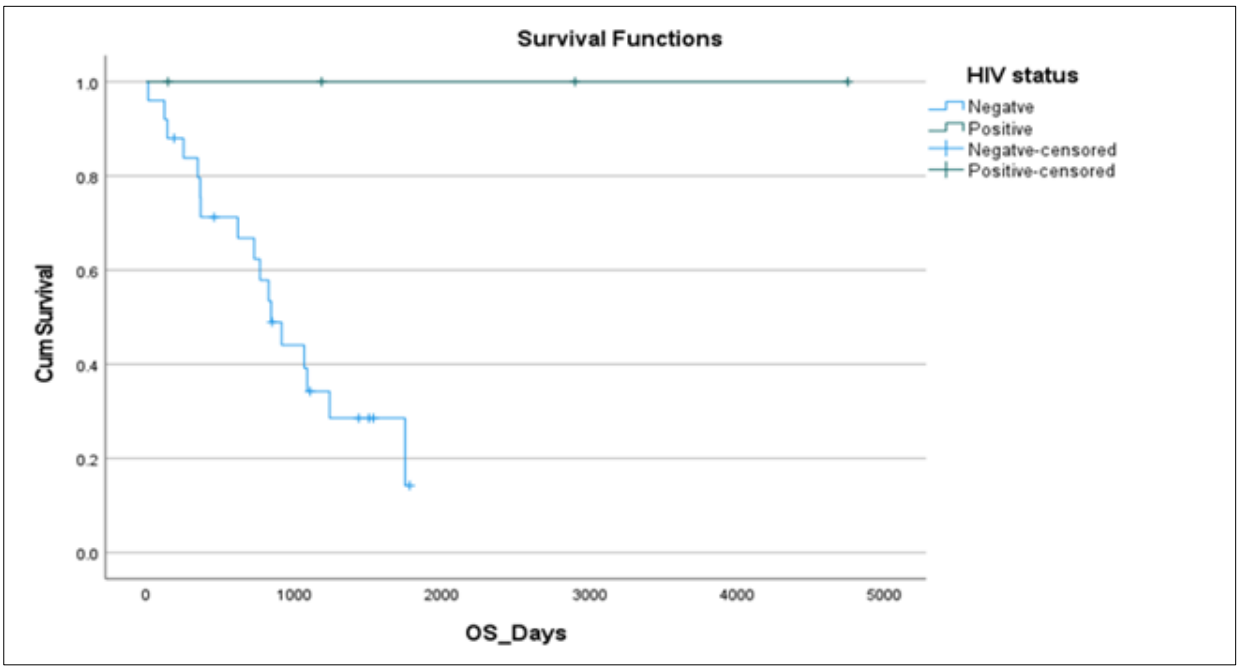


Figure 5. Kaplan-Meier survival curves for OS according to smoking status (p=0.003) (A) and HIV status (p=0.036) (B).

A.



B.



Discussion

The majority of data regarding treatment outcomes of NPC comes from regions where the disease is endemic, including Southern China and Hong Kong(2). Literature from non-endemic regions is mainly limited to retrospective studies from single institutions. The aim of this study focused on determining treatment outcomes and prevalence of EBV associated NPC at GSH. 3DCRT was the treatment technique used to treat all radical patients in this study. To date, no similar studies have been carried out in South Africa comparing OS of EBV associated NPC with EBV negative tumours.

From our study, the median OS after radical treatment was approximately 2.5 years longer in EBV positive patients compared to EBV negative patients (1582 days vs 661 days). Two and five-year OS was approximately 40% higher in this group of patients (p=0.002), irrespective of treatment intent. In addition to a significant OS benefit, a trend, although non-significant was observed for improved 2-year DFS and LRCR compared to EBV negative tumours. Firm conclusions cannot be drawn from this observation because of the study's limited numbers and inconsistent methods used for following up patients, but these differences may have been significant with a larger patient cohort. Despite this, we found that EBV associated patients had higher rates of loco-regional control and distant relapses compared to EBV negative patients, which is in keeping with other studies(7,17). These findings are extremely valuable in a resource constrained environment and suggest that EBV associated tumours should be prioritized in terms of resource allocation in view of superior outcomes.

Treatment delays in radiation and chemotherapy are known to have an adverse impact on survival(18). Most patients in our study experienced treatment interruptions (78%), mainly due to treatment toxicity, resulting in a lower average dose of RT than intended. Overall survival was found to be lower in patients with treatment interruptions compared to those without, despite not being statistically significant in this study. The use of IMRT has been shown to have distinct dosimetric advantages over 3DCRT, including superior tumour coverage and greater sparing of organs at risk(12). Two retrospective studies comparing IMRT and 3D-CRT in NPC did not show any differences in tumour control however, a third study by Kuang et al demonstrated that IMRT was associated with a better prognosis and less toxicity(19–21). Results of a recent meta-analysis of 13 studies, containing only 1 randomised controlled trial and 1 prospective study, indicated that IMRT is associated with improved oncological outcomes compared to conformal RT(13). The findings from this study support the use of volumetric modulated arc therapy (VMAT) in the treatment of NPC as a potential way to reduce treatment toxicity, allow dose escalation and improve outcomes in the future.

The rate of EBV positivity in this study (47.2%) was lower compared to other retrospective studies from non-endemic regions, which ranged from 62-92%(14,22). The EBV status in nine patients (17%) were not confirmed in this study and could account for the lower prevalence. Despite this, EBV associated NPC contributed to a significant proportion of patients in this study and further studies relating to the prevalence of EBV associated NPC in South Africa should be carried out on a larger scale.

The causal relationship between non-keratinizing carcinomas and EBV is well established(9). Nonkeratinizing carcinomas was the most common histological subtype, accounting for 92% of EBV positive cases in our study, which is comparable to other endemic and non-endemic countries(14,15).

The study found a bimodal age distribution similar to other low and intermediate risk populations(4). Two peaks were noted, in patients between 40-59 years and in those under 25 years of age. A male predominance (79.2%) was observed similar to other studies from non-endemic developing countries, such as Pakistan and Tanzania(15,23,24).

Most patients in this study presented with locally advanced stage III and IV disease (86.8%). This is similar to the 86.2% of patients with advanced disease from an Ethiopian study(25), and 80% of patients found to have stage IV disease in a study from Tanzania(23). In a middle-income country such as South Africa, late presentation and advanced disease is common due to poor socio-economic status and limited access to health care. Data from two retrospective studies conducted at Charlotte Maxeke Academic hospital in Johannesburg revealed enlarged neck nodes as the most common presenting symptom, with 80% of patients having T4 disease and bone metastases being the most common site of distant metastases(26,27). Advanced disease at presentation is a known adverse prognostic factor in NPC(28). This is in keeping with this study, with patients presenting with stage IVA disease having the lowest 2-year survival rates of 40.6%. The survival data shows that is reasonable to use induction chemotherapy to reduce bulk of disease, and as a temporising measure in low- and middle-income countries (LMIC) to improve throughput. The effect of smoking was investigated and found to be a significant adverse prognostic factor in this study, with 2-year OS in non-smokers being 91% vs 62% in smokers. These findings are in keeping with the known unfavourable outcomes associated with tobacco smoking during radiotherapy in head and neck cancer(29).

There is limited data regarding the impact of HIV status in NPC in the literature. In this study we observed that an HIV positive status was a significant favourable prognostic factor for OS. Most of the HIV positive patients had EBV associated non-keratinizing carcinomas which are known to have superior survival. No conclusions can be made regarding the prognostic value of HIV status from this study however further research on this topic should be encouraged.

The limitations of this study include its retrospective nature and small sample size limited to a single institution with resource constraints. Only 83% of patients had histologically confirmed EBV statuses which could impact the outcomes of the study due to limited numbers. In terms of long term follow up, 17% and 34% of patients were lost to follow up at 2 and 5 years respectively, resulting in less accurate survival data. The reasons for poor attendance are not always clear and coupled with insufficient record keeping, these factors limit detailed long term follow up. Only univariate survival analysis was done and therefore groups were not normalised for different prognostic factors as would take place in a multi-variate analysis. Patients were also assessed clinically for recurrence with limited routine radiological investigations done. The study also does not report on long term toxicity such as xerostomia, hearing loss and endocrine dysfunction. Further research on treatment toxicity and outcomes should be conducted on a larger scale, possibly a multicentre study with larger number of subjects.

Conclusion

Nasopharyngeal carcinoma is a rare cancer, and its unique pathogenesis is influenced by multiple aetiological factors including EBV infection. Evaluating treatment outcomes from non-endemic regions is essential to optimise tumour treatment and minimise toxicity in the successful the management of NPC. In our local setting, EBV associated NPC was found to be a significant prognostic factor associated with superior OS compared to EBV negative NPC. There was a non-significant trend for EBV associated patients to have improved DFS and LRCR. This correlates with literature from endemic and non-endemic regions. Additionally, this study provides treatment outcomes from the 3DCRT era, which is still the main modality used in many LMIC and can be used to compare outcomes from these regions. According to this study, a significant proportion of patients have EBV associated NPC and the findings are considered hypotheses generating. Further research should be conducted on a larger scale to improve the body of knowledge on EBV associated NPC in South Africa.

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PART C: APPENDICES

Data collection instrument

Patient details

Record ID	_____
Patient number	_____
Hospital number	_____
Date of registration	_____
Radiation number	_____

Demographics

Record ID	_____
Age at diagnosis	_____
Smoking status	◯ Smoker ◯ Non-smoker ◯ Unknown
HIV status	◯ Positive ◯ Negative ◯ Unknown
Performance status	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ unknown
Sex	◯ Male ◯ Female

Tumour characteristics

Record ID	_____
Histology	◯ Keratinizing ◯ Differentiated non-keratinizing ◯ Undifferentiated non-keratinizing ◯ Basaloid
Histology date	_____
EBV status	◯ Positive ◯ Negative ◯ Unknown
Primary Tumour (T)	◯ Tx ◯ T0 ◯ T1 ◯ T2 ◯ T3 ◯ T4
Regional lymph nodes (N)	◯ NX ◯ N0 ◯ N1 ◯ N2 ◯ N3
Distant metastasis (M)	◯ M0 ◯ M1
Stage	◯ 0 ◯ I ◯ II ◯ III ◯ IVA ◯ IVB

Imaging

Record ID	_____
CT scan	◯ Yes ◯ No ◯ Unknown
MRI	◯ Yes ◯ No ◯ Unknown
PET-CT	◯ Yes ◯ No ◯ Unknown
Bone scan	◯ Yes ◯ No ◯ Unknown

Treatment

Record ID	_____
Treatment intent	◯ Radical ◯ Palliative
Modality of treatment	◯ Induction chemotherapy + chemo-RT ◯ Chemo-RT ◯ RT alone ◯ Chemotherapy alone
Treatment start date	_____
RT technique	◯ 2D ◯ 3DCRT ◯ IMRT
RT site	◯ Primary site ◯ Metastasis ◯ Not applicable
RT Dose	_____
RT start date	_____
RT last date	_____
Completed RT	◯ Yes ◯ No ◯ Unknown
Concurrent chemotherapy	◯ Yes ◯ No ◯ Unknown
Chemotherapy regimen	_____
Number of chemotherapy cycles	_____
Chemotherapy start date	_____
Last date of chemotherapy	_____

Treatment interruptions

Record ID	_____
Treatment interruption RT	◯ Yes ◯ No ◯ Not applicable
Reason for RT interruption	◯ Social ◯ Transport ◯ Treatment toxicity ◯ RT machine service/ problem ◯ Patient defaulted ◯ Not applicable
Length of RT interruption	_____
Treatment interruption chemotherapy	◯ Yes ◯ No ◯ Not applicable
Reason for chemotherapy interruption	◯ Social ◯ Transport ◯ Treatment toxicity ◯ Pharmacy problem ◯ Patient defaulted ◯ Not applicable
Length of chemotherapy interruption	_____

2-Year assessment post treatment

Record ID	_____
Date of assessment	_____
Assessment of response	◯ Clinical ◯ Radiology ◯ Clinical and radiology ◯ Not applicable
Response to initial treatment	◯ Complete response ◯ Partial response ◯ Disease progression ◯ Stable disease ◯ Deceased ◯ Lost to follow up
Date of local control	_____
Relapse	◯ Yes ◯ No ◯ Not applicable
Date of relapse	_____
Time of relapse	◯ < 1 year ◯ 1-2 years ◯ >2 years
Site of relapse	◯ Local ◯ Regional ◯ Distant

Overall survival

Record ID	_____
Start date of treatment	_____
Date of death	_____
Date last seen	_____
Time till death	_____

Ethical Approval

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 October 2018

HREC REF: 671/2018

Dr Sameera Dalvie
Radiation Oncology
LE32

Dear Dr Dalvie

PROJECT TITLE: NASOPHARYNGEAL CARCINOMA: A RETROSPECTIVE ANALYSIS OF TREATMENT OUTCOMES AT GROOTE SCHUUR HOSPITAL, CAPE TOWN, SOUTH AFRICA (MMed Candidate - Dr S. Viranna)

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

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 October 2019.

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/humanethicslforms)

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.

The HREC acknowledge that the student, Dr Santhuri Viranna will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

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 / santhuriviranna@hotmail.com

Dear Dr Dalvie

RESEARCH PROJECT: Treatment Outcomes Of Nasopharyngeal Carcinoma Patients Treated at Groote Schuur Hospital: A Retrospective Review.

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 April 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: 23 June 2021

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

Departmental Approval

Radiation Oncology

Professor Jeannette Parkes
Head of Division

Groote Schuur Hospital, Observatory, 7925, South Africa

Tel: +27 (0) 21 404 4263/5, +27 (0) 21 406 6801 Fax: +27 (0) 21. 404 5259
E-mail: Jeannette.parkes@uct.ac.za

17 May 2021

Dear Dr S Dalvie and Dr S Viranna

Permission is hereby granted for the following study to be conducted in the Department of Radiation Oncology:

HREC REF: 671/2018

Protocol Name: Nasopharyngeal carcinoma: A retrospective analysis of treatment outcomes at Groote Schuur Hospital, Cape Town, South Africa (MMED Candidate - Dr S Viranna)

Please note that permission is also required from Dr Eick through Lionel Naidoo's institutional research committee and from Ethics committee before the trial may commence.

Kind regards

Professor Jeanette Parkes
HOD Radiation Oncology Division

cc. Dr S Viranna

South African Journal of Oncology Criteria for submission

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