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Treatment outcomes of Epstein-Barr virus-associated nasopharyngeal carcinoma

Authors:
Santhuri Viranna[1,2]
Hue-Tsi Wu[3]
Sameera Dalvie[1,2]

Affiliations:
[1]Department of Radiation Oncology, Faculty of Health Sciences, University of Cape Town, South Africa

[2]Department of Radiation Oncology, Faculty of Radiation Medicine, Groote Schuur Hospital, Cape Town, South Africa

[3]Department of Histopathology, Pathcare, Cape Town, South Africa

Corresponding author:
Santhuri Viranna,
santhuri.viranna@uct.ac.za

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

Aim: The aim of the study was to compare overall survival (OS) of EBV positive and EBV negative NPC patients.

Setting: Groote Schuur Hospital, South Africa.

Methods: Data were collected on all patients with histologically confirmed NPC over an 11-year period, including prevalence of EBV, OS, disease-free survival (DFS), loco-regional control (LRC), and impact of treatment interruptions on OS.

Results: There were 53 patients in total. Non-keratinising carcinoma was the primary histological subtype (86.8%). The majority of patients had EBV positive NPC (47.2%). The 2- and 5-year OS of EBV positive patients treated with curative intent were significantly higher than EBV negative patients, 84.0% versus 34.0% and 45.0% versus 17.0%, respectively (hazard ratio [HR] 0.25, 95% confidence interval [CI]: 0.10–0.63, p = 0.002). Two-year DFS was 55.0% versus 43.0% (HR: 0.59, 95% CI: 0.18–1.98, p = 0.38) and 2-year LRC were 76.2% versus 46.2% (HR: 0.40, 95% CI: 0.12–1.36, p = 0.13) for EBV positive and EBV negative patients respectively.

Conclusion: Treatment of EBV-associated NPC is associated with superior OS compared to EBV negative tumours.

Contribution: Epstein-Barr virus was found to be a significant prognostic factor associated with superior OS compared to EBV negative NPC. These findings correlate with literature from endemic and non-endemic regions.

Keywords: nasopharyngeal carcinoma; Epstein-Barr virus (EBV); prevalence; 3D-CRT; survival outcomes; prognostic factors; treatment interruptions.

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] The incidence of NPC in southern sub-Saharan Africa is low (0.57 per 100 000 people) compared to endemic regions.[3] The unbalanced global distribution of NPC may be due to race, Epstein-Barr virus (EBV) infection, diet, smoking and alcohol consumption. In South Africa, NPC is rare with a 5-year prevalence of 0.88 cases per 100 000 according to GLOBOCAN 2020 statistics.[4] The incidence of NPC is two to threefold higher in males than females, and displays a bimodal age distribution in non-endemic areas.[5]

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

(WHO type III). Epstein-Barr virus is invariably associated with the non-keratinising carcinoma subtype seen in both endemic and non-endemic regions.[11]

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.[12] Intensity modulated RT (IMRT) is the preferred radiotherapy (RT) technique for the treatment of NPC because of distinct dosimetric advantages over 3D conformal RT (3D-CRT), including superior tumour coverage and greater sparing of organs at risk.[13] 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.[14] In many developing countries, access and training to advanced techniques such as IMRT are limited and 3D-CRT 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 non-endemic NPC over a 10-year period, the rate of EBV positivity was 92%.[15] In a retrospective study from Pakistan evaluating 100 cases of NPC, 92 cases of non-keratinising carcinoma were found over a 3-year period, of which 81.5% were EBV positive.[16] Only one study evaluating EBV strain characterisation in South African patients with NPC found a strong association of 82% between EBV positivity and NPC.[17] There is a paucity of data for South Africa regarding the epidemiology, prevalence, and outcomes of EBV-associated NPC. Evaluating the distribution of EBV across various histological subtypes and stages is important to further understand the disease in our population. We aimed to compare survival outcomes between EBV positive and EBV negative NPC patients. Furthermore, we aimed to establish whether our patients have similar EBV prevalence and tumour characteristics to available international data.

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 human immunodeficiency virus (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, four patients were excluded, one patient was treated at another institution and three 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. Epstein-Barr virus staining using EBV-encoded RNA (EBER) in-situ hybridisation (ISH) was documented from pathology reports or requested from 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 imaging or clinical assessment 3 months after completion of therapy as documented in the patient's folder. Thereafter, patients were assessed clinically for recurrence and metastatic disease. Relapse was documented based on clinical examination, biopsy proven recurrence or imaging.

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-CRT. All patients were setup and immobilised in a custom-made thermoplastic mask. The radiotherapy prescription ranged between 60 Gy and 70 Gy to the gross tumour and 50 Gy 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 monthly 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 Gy and 36 Gy using hypo-fractionated regimens.

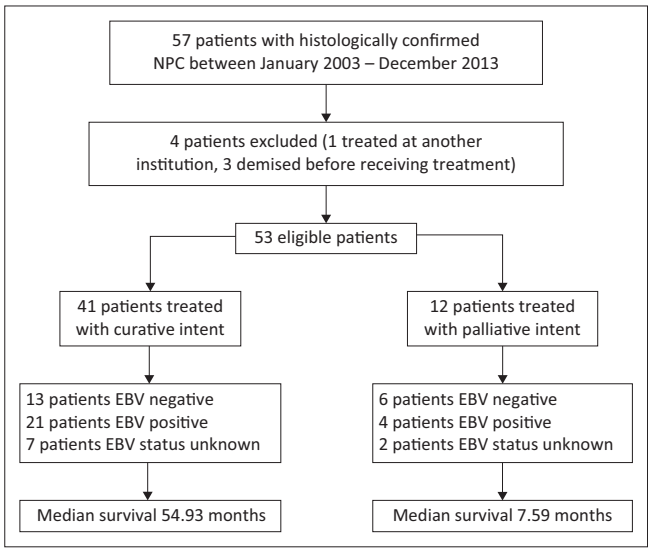
Statistical analysis

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 were stored in the REDCap (Research Electronic Data Capture) database and was used to analyse variables relevant to the study. Statistical Package for the Social Sciences (SPSS) version 27 (SPSS, Chicago, Illinois, United States) software was used for descriptive and inferential statistics to analyse 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 Cox regression model was used to determine hazard ratios (HRs). The Chi-square test was used to determine the association between 2-year local control and EBV status. Only univariate analysis was performed because of small number of subjects.

Ethical considerations

The Human Research Ethics Committee of the University of Cape Town approved the proposed study with reference number 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.



NPC, nasopharyngeal carcinoma; EBV, Epstein-Barr virus.

FIGURE 1: Flowchart of study profile.

Results

Patient characteristics

A total number of 53 patients were eligible for the study (Figure 1). The demographic data of the study population is included in Table 1. Forty-one (77.4%) patients were treated with curative intent and 12 (22.6%) 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 years and 59 years, which accounts for 41.5% of cases. Twelve (22.6%) patients

TABLE 1: Demographic data of the study population.

Variable	*n*	%
Treatment intent		
Curative	41	77.4
Palliative	12	22.6
Gender		
Male	42	79.2
Female	11	20.8
Age (in 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	66.0
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		
Keratinising carcinoma	6	11.3
Non-keratinising carcinoma	46	86.8
Basaloid carcinoma	1	1.9
EBV status		
Negative	19	25.8
Positive	25	47.2
Unknown	9	17.0

HIV, human immunodeficiency virus; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group.

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 1. 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 three were treated palliatively. Only one patient that was HIV-positive had metastatic disease at presentation.

Non-keratinising carcinoma was the predominant histological subtype in 46 patients (86.8%). Keratinising 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%) who were EBV negative. Non-keratinising carcinomas had the highest rate of EBV positivity (92%) compared to other histological subtypes as displayed in Table 2.

Treatment

At presentation, the most common imaging modalities used included CT (94.3%) and bone scan (54.7%). Magnetic resonance imaging 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 because of defaulting treatment. Most patients (39 patients, 95.1%) received between one and 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 mg/m² – 100 mg/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 2. The most common reasons for radiotherapy interruptions were treatment toxicity (37.5%) followed by linear accelerator (LINAC) related issues (33.3%). The average dose of radical RT received was 59.4 Gy (range 6.3 Gy – 70 Gy). The reasons for patients receiving a lower RT dose than prescribed included treatment interruptions because of 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, nine patients experienced treatment toxicity. Neutropenia was the most common reason chemotherapy was delayed.

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, 20 Gy in 5 fractions (42.9%), 30 Gy in 10 fractions (28.6%), and 36 Gy in 12 fractions (28.6%). Seven patients received palliative chemotherapy using a platinum agent with 5FU.

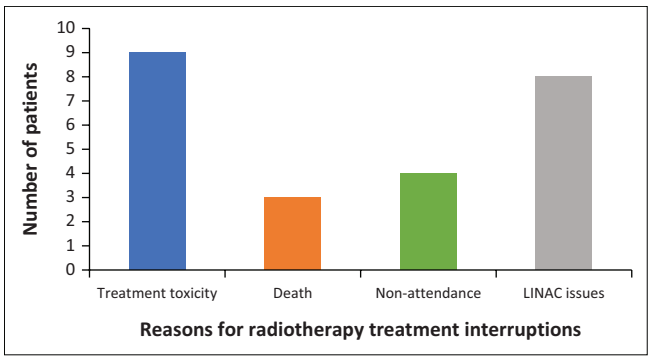
Treatment outcomes

In terms of the primary endpoint, 2-and 5-year OS after curative treatment of EBV positive and EBV negative patients were 84% versus 34% and 45% versus 17%, respectively (HR: 0.25, 95% confidence interval [CI]: 0.10–0.63, $p = 0.002$). The mean OS of radically treated EBV positive patients was 1582 days compared to 661 days in EBV negative patients (Figure 3). 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% (HR: 0.25, 95% CI: 0.11–0.55, $p < 0.001$) for EBV positive and EBV negative patients, respectively.

TABLE 2: Histological subtypes according to Epstein-Barr virus status.

Histology	EBV positive		EBV negative		EBV unknown	
	n	%	*n*	%	*n*	%
Non-keratinising carcinoma	23	92.0	16	84.2	7	77.8
Keratinising carcinoma	2	8.0	3	15.8	1	11.1
Basaloid carcinoma	0	-	0	-	1	11.1

EBV, Epstein-Barr virus.



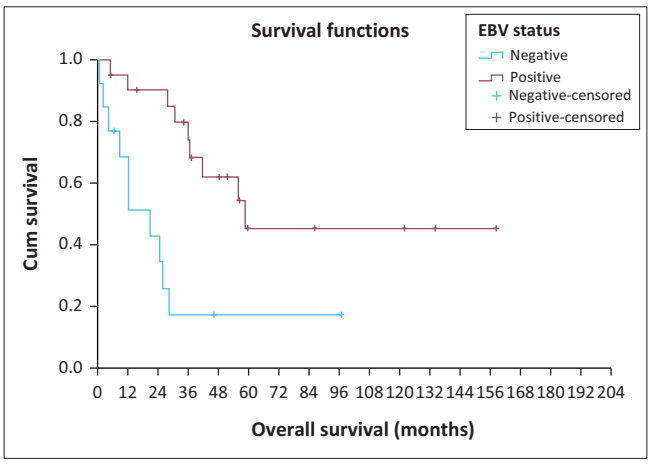
LINAC, linear accelerator.

FIGURE 2: Bar chart showing reasons for radiotherapy treatment interruptions in radical patients.

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 2 years after treatment was 63% and 37% at 5 years. The median survival time of radically treated patients was 1671 days compared to 231 days for palliative patients.

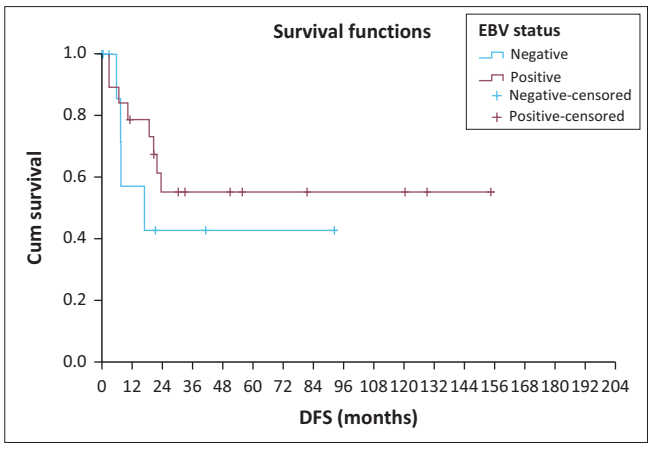
The cumulative 2- and 5-year DFS of EBV-associated NPC compared to EBV negative cases was 55% and 43%, respectively (Figure 4). Disease-free survival of EBV positive patients was 12% higher than EBV negative patients, but was not found to be statistically significant (HR: 0.59, 95% CI: 0.18–1.98, $p = 0.38$).

Two-year LRCR 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 50 Gy for local relapse.



OS, overall survival; EBV, Epstein-Barr virus.

FIGURE 3: Kaplan-Meier survival curve for overall survival in radically treated patients according to Epstein-Barr virus status ($p = 0.002$).



DFS, disease-free survival; EBV, Epstein-Barr virus.

FIGURE 4: Kaplan-Meier survival curve for disease-free survival in radically treated patients according to Epstein-Barr virus status ($p = 0.38$).

Predictive factors for overall survival

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 OS, however, was not found to be statistically significant ($p = 1.28$).

Patients with non-keratinising carcinomas had the longest OS compared to other histological subtypes (Figure 5). 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 6).

Human immunodeficiency virus-positive patients had significantly higher OS compared to HIV negative patients (Figure 7). Of the seven HIV-positive patients, four (57.1%) were treated with radical intent. Most of the HIV-positive patients had non-keratinising histology (85.7%) and were EBV associated.

TABLE 3: Pattern of relapse according to Epstein-Barr virus status.

EBV status	Site of relapse	Frequency (*n*)	Percentage (%)
Negative	Loco-regional	2	15.4
	Distant	2	15.4
	Relapse free	9	69.2
Positive	Loco-regional	4	19.0
	Distant	4	19.0
	Relapse free	13	61.9

EBV, Epstein-Barr virus.

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**.	13.500	**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	0.780
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.**	2.320	1.280

Note: Bold values are statistically significant.

HIV, human immunodeficiency virus; EBV, Epstein-Barr virus.

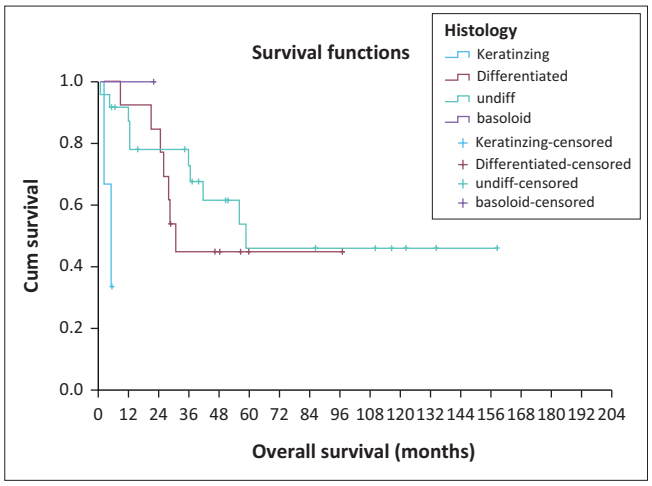


FIGURE 5: Kaplan-Meier survival curve for overall survival according to histological subtype ($p = 0.004$).

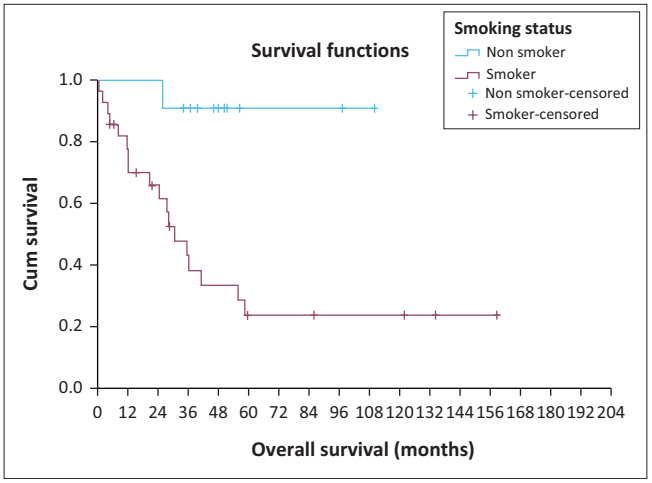


FIGURE 6: Kaplan-Meier survival curves for overall survival according to smoking status ($p = 0.003$).

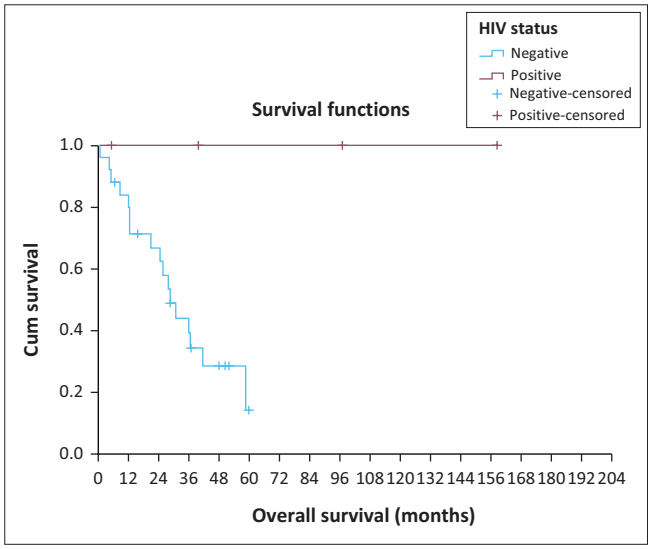


FIGURE 7: Kaplan-Meier survival curves for overall survival according to HIV status ($p = 0.003$).

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.

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 focussed on determining treatment outcomes and prevalence of EBV-associated NPC at GSH. 3D conformal RT (3D-CRT) 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-year and 5-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 for improved 2-year DFS ad LRCR was observed for EBV positive tumours, although not statistically significant. 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.[8,18] These findings are extremely valuable in a resource constrained environment and suggest that EBV associated tumours should be prioritised 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.[19] Most patients in our study experienced treatment interruptions (78%), mainly because of 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 3D-CRT, including superior tumour coverage and greater sparing of organs at risk.[13] 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.[20,21,22] Results of a recent meta-analysis of 13 studies, containing only one randomised controlled trial and one prospective study, indicated that IMRT is associated with improved oncological outcomes compared to conformal RT.[14] The findings from this meta-analysis 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% to 92%.[15,23] The EBV status of 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-keratinising carcinomas and EBV is well established.[10] Non-keratinising 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.[15,16]

The study found a bimodal age distribution similar to other low and intermediate risk populations.[5] Two peaks were noted, in patients between 40 years and 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.[16,24,25]

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,[26] and 80% of patients found to have stage IV disease in a study from Tanzania.[24] In a middle-income country such as South Africa, late presentation and advanced disease are common because of poor socio-economic status and limited access to healthcare. 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.[27,28] Advanced disease at presentation is a known adverse prognostic factor in NPC.[29] 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 it is reasonable to use induction chemotherapy to reduce bulk of disease, and as a temporising measure in low- and middle-income countries (LMICs) 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% versus 62% in smokers. These findings are in keeping with the known unfavourable outcomes associated with tobacco smoking during radiotherapy in head and neck cancer.[30]

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-keratinising carcinomas which are known to have superior survival.[7,8] 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 because of limited numbers. In terms of long term follow up, 17% and 34% of patients were lost to follow up at 2 years 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 multivariate analysis. A univariate approach was taken to look at each variable individually and to determine the more important predictor, being EBV status in this study. Patients were also assessed clinically for recurrence with limited routine radiological investigations done. The study 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.

The findings from this study highlight the prognostic value of EBV status in NPC. Epstein-Barr virus status does not change management according to current treatment guidelines; however, EBV testing should be considered.[31] Major issues in our local setting in the management of NPC include late presentation with advanced disease at diagnosis, budget restrictions, and access to imaging. In view of the significantly shorter survival of EBV negative patients found in this study, palliative interventions should be implemented early in locally advanced and metastatic disease. In patients with EBV positive NPC, resources such as PET imaging and aggressive salvage treatments should be prioritised in the setting of relapsed disease, given the significantly better survival outcomes in these patients. These recommendations can be applied to other settings with similar resource limitations. Epstein-Barr virus plasma DNA is an emerging biomarker that is currently being extensively researched.[32] Developing a sensitive and accurate biomarker is important for cost effective treatment stratification and post-treatment surveillance, particularly in LMICs which face unique challenges in delivering adequate patient care.

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 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 3D-CRT era, which is still the main modality used in many LMICs, 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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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

Data collection, analysis and manuscript composition were carried out by S.V. Testing of extra pathology specimens was carried out by H.-T.W. Review, expert consultation and final documentation approval were carried out by S.D.

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Data availability

Data supporting the findings of this study are available from the corresponding author, S.V., on request.

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