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Patterns of Failure and Disease Recurrence in Nasopharyngeal Cancer: A Five-Year Analysis in an EBV Endemic Population at Pakistan's Largest Cancer Center

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Abstract

This study aimed to evaluate the patterns of failure, disease recurrence, and survival outcomes in EBV-positive nasopharyngeal carcinoma (NPC) patients treated at Pakistan's largest tertiary cancer center, given the high incidence of this malignancy in endemic regions like Pakistan. We retrospectively analyzed 265 adult patients with biopsy-confirmed, locally advanced, non-metastatic NPC treated with definitive chemoradiation between January 2018 and December 2023. All patients received induction chemotherapy with Cisplatin and Gemcitabine, followed by intensity modulated radiotherapy (IMRT) combined with concurrent Cisplatin, with a median follow-up of 64 months. The cohort's median age was approximately 45 years, predominantly male, with most presenting with advanced T3/T4 (52.8%) and N2/N3 (76.6%) disease, and undifferentiated histology was common. Results showed that 69.1% of patients remained disease-free, while 30.9% experienced recurrence, mainly distant metastases involving bones, viscera, and multiple sites. Local control was satisfactory across the cohort, but distant metastasis, especially in osseous and visceral sites, was the main pattern of failure. The median overall survival was approximately 65 months, with 5-year OS of 60.9%. The five-year recurrence-free survival was 55%, and distant metastasis-free survival was 65.7%. These findings highlight that while IMRT-based treatment provides excellent locoregional control, distant metastasis remains the primary challenge to long-term survival, emphasizing the need for more effective systemic therapies and biomarker-driven strategies to reduce distant relapse in endemic NPC populations.

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Introduction

Nasopharyngeal carcinoma (NPC) is a biologically and epidemiologically distinctive head and neck malignancy which arises from nasopharyngeal mucosal lining [1]. NPC demonstrates a clear regional, racial and gender distribution, strong viral association with Epstein–Barr virus (EBV), and distinct patterns of spread and recurrence, unlike other head and neck squamous cell carcinomas [2]. Globally, NPC accounts for less than 1% of all cancers with roughly 120,000 to 135,000 new cases diagnosed annually, however, its incidence is markedly elevated in certain endemic regions, particularly Southern China, Southeast Asia, North Africa, and parts of South Asia, including Pakistan [1,3]. Age adjusted global incidence is 1.5 cases per 100,000 population but higher in high-risk areas of Asia and Africa, reaching 25 cases per 100,000 population. This geographic variation highlights the interactions of genetic susceptibilities, environmental factors, and EBV infection in NPC pathogenesis. There is higher incidence in male with a male to female ratio of 2-3:1 likely related to X chromosome susceptibility and protective role of estrogen [4,5].

EBV plays an important role in the etiology and pathogenesis of NPC in the endemic areas, particularly the undifferentiated non-keratinizing NPC where EBV infection is detected in 100% of pathology specimens [6]. However, the role of EBV in causing keratinizing NPC is less prominent. The incidence of NPC coincides with the prevalence of the EBV accounting for 95% of NPC cases and NPC related deaths. EBV integrates into the host DNA, causing latent viral gene expression specifically of LMP1 and EBNA1 proteins, and host immune evasion, thus remodeling tumor microenvironment and contributing to malignant transformation and tumor progression. Pakistan shares borders with China and India, both of which report a high incidence of EBV and its well-documented association with NPC [7]. Furthermore, regional studies indicate a high prevalence of EBV within the Pakistani population, where it is frequently linked to NPC and other malignancies [8-10].

Overall survival, and recurrences in NPC are influenced by tumor stage, EBV endemicity, treatment regimens, and radiotherapy techniques [11].

Early-stage NPC diagnosis correlates with a high 5-year overall survival rate of up to 94%, contrasting sharply with late-stage cases (stage III and IV) where the 5-year overall survival rate drops to 73.7% (12). Studies from China have showed demonstrated that high pre-treatment and post-treatment EBV DNA levels are strongly associated with increased risk of distant failure and inferior survival outcomes [13-16].

Induction chemotherapy followed by concurrent chemoradiotherapy leads to better outcomes compared to concurrent chemoradiotherapy alone [17].

Although less frequently with evolution of IMRT, locoregional recurrences continue to occur within high-dose radiation fields suggesting aggressive tumor biology. However, marginal and out-of-field recurrences reflect anatomical complexity, target delineation challenges, or suboptimal treatment delivery; issues particularly relevant in low- and middle-income countries (LMICs) like Pakistan. 5% to 30% of NPC patients experience locoregional or distant recurrence following treatment as per various studies [18-20].

Majority of recurrences (52%) predominantly occur within the first two years of treatment, 39% occurring between 2 to 5 years and the rest after 5 years of finishing treatment [21]. This retrospective study aims to identify patterns of disease recurrence and survival outcomes in NPC in EBV-positive patients in Pakistan.

Materials and Methods

We retrospectively reviewed all the patients diagnosed with nasopharyngeal carcinoma after obtaining approval from the Institutional Review Board. A total of 265 adult patients with biopsy-proven, locally advanced, non-metastatic NPC who completed definitive treatment between January 2018 and December 2023 and had at least one followed up visit with imaging were included. These patients were treated at the Clinical and Radiation Oncology Department of Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore with induction chemother-

apy followed by definitive chemoradiotherapy using intensity-modulated radiotherapy (IMRT) per institutional practice. Patients with metastatic disease at presentation, treated in palliative intent, or with no follow up data were excluded from the study.

Patients were evaluated and staged at the in-house facilities using a standard approach of basic clinical history, physical examination including fiberoptic nasopharyngoscopy, serum chemistries, imaging with MRI of the face and neck, chest radiograph and a whole-body bone scan using single-photon emission computed tomography (SPECT). Pathology and histology were reviewed for keratinizing vs differentiated non-keratinizing vs undifferentiated non-keratinizing tumor subtypes. Imaging reports were reviewed for tumor size and staging.

All patients were reviewed in multidisciplinary head and neck tumor board. After completion of staging workup, patients received induction chemotherapy with 2-3 cycles of Cisplatin 75mg/2 and Gemcitabine 1000mg/m2 followed by concurrent chemoradiotherapy 70 Gy in 33 to 35 fractions with concurrent three weekly Cisplatin 75mg/2 (day 1, 22 and 43). There were exceptions to induction chemotherapy, type of chemotherapy and radiation dose and fractionation as mentioned in the results section.

Patients were treated with 6 MV photon external beam radiotherapy delivered via a linear accelerator, with treatment planning based on computed tomography (CT) imaging. The radiotherapy technique employed was IMRT (static or dynamic), with treatments administered daily from Monday to Friday in 2–2.12 Gy fractions. Following completion of radical treatment, an MRI head and neck and whole-body PET scan was obtained at 3 months to assess response to the treatment.

Patient's demographics including age and gender, TNM stage (2017 AJCC Cancer Staging Manual), histology, chemotherapy mode and type, response to the treatment and disease relapses with patterns of failure were collected for all the patients [22].

Overall survival (OS) defined by time from start of induction chemotherapy to death or last follow up, recurrence-free survival (RFS) defined by time from start of induction chemotherapy to any recurrence or last follow up, local relapse-free survival (LRFS) defined by time from start of induction chemotherapy to local recurrence in the primary area and/or neck or last follow up, and distant relapse-free survival (DRFS) defined by time from start of induction chemotherapy to distant recurrence other than primary and/or regional nodes recurrence, or last follow up were also collected. Statistical analyses were performed using SPSS version 16.0 (SPSS, Chicago, IL, USA). The actuarial rates were estimated using the Kaplan–Meier method, and the survival curves were compared using the log-rank test.

Results

A total of 265 patients were included in the study with a median age of 44.76 years at presentation. 190 were males and 75 females. Histopathological evaluation showed that one hundred and ninety (71.7%) patients had undifferentiated keratinizing carcinoma, thirty (11.3%) had poorly differentiated carcinoma and only four (0.16%) keratinizing carcinoma, while further characterization of histology was not available in 41 (15.5%) of cases. Tumor staging revealed primary tumor status of T1 (n=50), T2 (n=62), T3 (n=43), T4 (n=97), and Tx (n=13). Nodal staging identified N0 disease in 17 patients, N1 in 45, N2 in 101, and N3 in 102 patients. Metastatic disease evaluation demonstrated M0 in 251 patients and M1 in one patient, with 13 cases recorded as indeterminate (Mx). The patient with M1 disease-initiated treatment with definitive intent, however, because metastatic disease was found during the course of treatment and the original treatment plan was continued. Table 1 shows baseline demographics, histology, staging, and treatment regimens. 260 (98.1%) patients received induction chemotherapy with Cisplatin/Gemcitabine, and 5 patients did not receive induction chemotherapy for low performance status. All 265 patients received radiation therapy 70 Gy in 33-35 fractions using IMRT, 248 (95.5) with concurrent chemotherapy (cisplatin, n=248; carboplatin, n=5) and 12 (4.5%) received radiation alone.

Table 1: Demographics, Clinicopathologic features and treatment regimens for patients with nasopharyngeal carcinoma

Variables		Frequency	Percentage
Age	(Mean)	44.76	
Gender	Male	190	71.7
Histology	Female	75	28.3
	Keratinizing (Type I)	4	0.16
	Undifferentiated Keratinizing (Type II/III)	190	71.7
	Poorly Differentiated (Type II/III)	30	11.3
	Not Defined	41	15.5
T Stage	Tx	13	4.9
	T1	50	18.9
	T2	62	23.4
	T3	43	16.2
	T4	97	36.6
N Stage	No	17	6.4
	N1	45	17
	N2	101	38.1
	N3	102	38.5
M stage	Mx	13	4.9
	M0	251	94.7
	M1	1	0.4
Induction Chemotherapy	Received	260	98.1
	Not Received	5	1.9
Concurrent Chemoradiotherapy		253	95.5
Radiotherapy		12	4.5
Concurrent Chemotherapy Agent	Cisplatin	248	93.6
	Carboplatin	5	1.8

One hundred and eighty-three (69.1%) patients did not develop recurrence (local or distant) and showed great treatment response. Eighty-two (30.9%) patients experienced disease recurrence. Twenty-six (9.8%) of all patients developed local recurrence, of which twenty (76.9%) recurred in primary nasopharynx area, 5 (19.2%) in the lymph nodes of the neck and 1 (3.9%) recurred in both locations. Sixty-one (23.01%) of all patients developed distant recurrence. Among patients with distant failure, sites of metastasis were osseous (n=14), visceral (n=11), node only (n=1), combined visceral and osseous (n=16), combined visceral and nodal (n=3), and multiple sites in 14 patients. These results indicate that while local control was satisfactory, distant metastases, particularly in the osseous and visceral regions, remained the predominant pattern of failure. The details of patterns of failure are summarized in Table 2.

Table 2: Frequency Distribution of Events in Patients

Events		Frequency	Percentage
Relapse		82	30.9
Local Relapse		26	9.8
Local Relapse sites	Primary Area	20	76.9
Regional Relapse	Nodes	5	19.2
	Both primary and nodes	1	3.9
Distant Relapse		61	23.01
Distant Relapse Site	Visceral	11	18.0
	Nodal	1	1.6
	Osseous	14	23.0
	Visceral and Osseous	16	26.2
	Multiple sites	14	23.0
	Visceral and Nodal	3	4.9
	Osseous and Nodal	2	3.3
Death		64	24.2

Median OS was 64.8 months, with a 5-year OS of 60.9% (95% confidence interval [CI], 52.3%–71.1%). Median RFS was 68 months, and the 5-year RFS rate was 55.0% (95% CI, 47.5%–64.8%). With respect to patterns of disease control, the estimated mean LRFS was 63.0 months (median not reached) and 5–year LRFS of 82.5% (95% CI, 76.2%–89.3%), indicating favorable long-term locoregional disease control. In contrast, DRFS demonstrated lower durability, with an estimated mean of 68.1 months (median not reached) and a 5-year DRFS of 65.7% (95% CI, 57.4%–75.2%), highlighting distant metastasis as a predominant mode of failure. Figure 1 shows the estimated mean, median, and 5-year OS, RFS, LRFS, and DRFS.

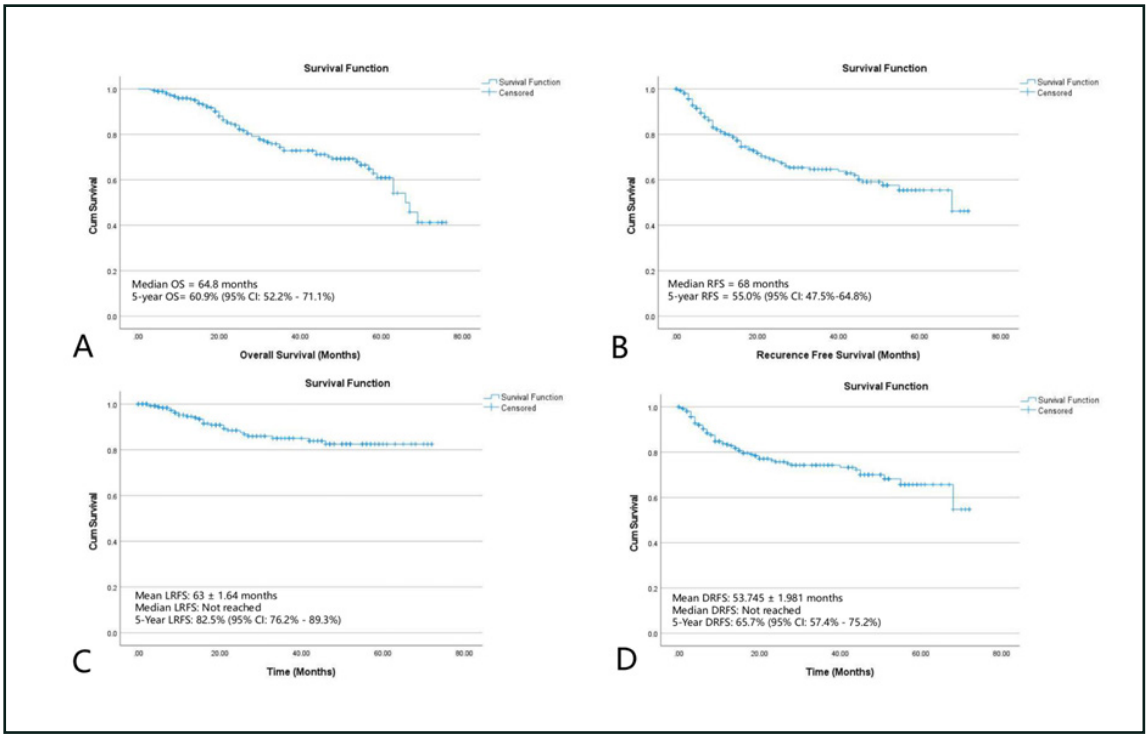

Figure 1: Estimated and actuarial 5-year Overall Survival (A), Recurrence Free Survival (B), Local Relapse Free Survival (C), and Distant Relapse Free Survival (D).

Discussion

NPC continues to pose a significant health burden in endemic regions, particularly where EBV infection is highly prevalent. In our study of EBV-positive NPC patients treated with standard protocols, the observed 5-year overall survival (OS) rate of 60.9% is consistent with figures reported in similarly affected areas such as Taiwan and Hong Kong, underscoring common regional challenges in disease control and survivorship [23,24].

EBV plays a central role in the pathogenesis of endemic NPC, with nearly all cases demonstrating a viral association (25). High circulating EBV DNA levels have been strongly linked to poor prognosis and increased recurrence, making viral load a compelling candidate for prognostication. A meta-analysis of 26 studies by Alami et al. confirmed that elevated EBV DNA levels are significantly associated with reduced OS, suggesting that routine measurement of viral DNA may enhance risk stratification and monitoring [26,27].

In addition to viral factors, host genetic susceptibility contributes to disease development and progression. Certain human leukocyte antigen (HLA) alleles and genetic polymorphisms have been associated with increased risk of NPC and may modulate host immune responses to EBV infection [25,28]. These gene–virus interactions are particularly relevant in endemic populations, where they may influence disease aggressiveness and treatment outcomes.

Comparatively, EBV-negative NPC—more frequently encountered in non-endemic regions—typically presents with keratinizing histology and is more often linked to environmental carcinogens such as tobacco and alcohol. These tumors are generally less responsive to radiotherapy and carry a worse prognosis relative to EBV-positive NPC. The treatment paradigm is also different in non-endemic regions like the UK and USA where definitive (chemo)radiation is usually employed with only a small percentage of patients receiving induction chemotherapy [29]. While EBV-positive tumors are more radiosensitive and exhibit improved locoregional control, they are more prone to distant metastasis, necessitating ongoing post-treatment surveillance [25].

While our results were comparable to other studies in endemic regions, they were in contrast with a retrospective cohort study by Mao et al. conducted in South

China, where the 5-year OS and LRFS rates were reported as 82.0% and 94.6%, respectively (30). In our cohort, these figures were lower at 60.2% and 82.5%. The differences may reflect disparities in healthcare infrastructure, access to specialized oncology services, health literacy, cultural barriers and technology under development; all of which can influence treatment efficacy and outcomes [31].

While the T stage remained a significant predictor of OS, our analysis revealed limited differences in survival between adjacent T categories. This finding suggests a diminished prognostic utility of the T classification in the current treatment era. Recent literature has proposed condensing the T staging system from four to three groups, reflecting improved local control rates and reduced heterogeneity in survival outcomes [32, 33].

Similarly, no statistically significant associations were observed between N or M stages and overall survival, calling into question the adequacy of the current TNM system in EBV-associated NPC.

Despite therapeutic advances, the relatively high recurrence rate and modest long-term survival observed in our cohort highlight the need for a more nuanced approach to risk stratification and treatment planning. The limited predictive power of traditional staging metrics underscores the need to incorporate molecular and virological markers into routine clinical practice.

Conclusion

This study provides valuable insights into the outcomes and recurrence patterns of EBV-positive NPC in an endemic Southeast Asian population. Compared to EBV-negative disease, EBV-positive NPC demonstrates superior radiosensitivity and locoregional control but carries a persistent risk of distant metastasis. Traditional TNM staging shows limited prognostic discrimination in this setting, emphasizing the need for updated models that integrate EBV DNA load, host genetic markers, and tumor biology.

Future research should focus on unraveling the molecular mechanisms of EBV-driven oncogenesis and developing biomarker-guided therapeutic strategies. Incorporating genomic profiling, immunological parameters, and viral dynamics into treatment algorithms may enhance personalization of care, leading to improved long-term survival in this complex disease.

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