REVIEW ARTICLE

Recent Updates and Future Directions in Nasopharyngeal Carcinoma: A Literature Review

Ruuzeno Kuotsu[1], Neizekhotuo Brian Shunyu[2]

Received on: 18 December 2025; **Accepted on:** 20 December 2025; **Published on:** 15 December 2025

ABSTRACT

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy with distinct epidemiology, high association with Epstein Barr virus (EBV), and very high sensitivity to radiotherapy and chemotherapy. Advances in radiology, radiotherapy, systemic chemotherapy, surgical salvage techniques for early recurrent cases, incorporation of immunotherapy have all significantly improved disease control and survival outcomes, making accurate staging increasingly important. In view of increasing good prognosis, the 9th version of the AJCC/UICC staging system introduces modifications to better align with modern treatment approaches and prognostic stratification.

This review summarises highlights the recent updates in NPC staging and throw light on the advances in the management of locoregionally advanced, recurrent, and metastatic disease, with particular emphasis on immunotherapy. Emerging evidence supports plasma EBV-DNA as a useful biomarker in patients receiving anti–PD-1 therapy for prognosis and early detection of disease progression, although it is not yet incorporated into staging systems. New therapies such as antibody–drug conjugates and bispecific antibodies show promise but require further validation.

Keywords: Nasopharyngeal carcinoma, latest AJCC updates, Immunotherapy, EBV DNA biomarker for recurrent NPC.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignancy with a distinct epithelial origin, which is characterised by its unique epidemiology, distinct biological behaviour and very high sensitivity to radiotherapy and chemotherapy. With the advances in the imaging system, refined radiotherapy techniques like the intensity modulated radiotherapy (IMRT), systemic treatment, early detection of recurrence and application of appropriate surgical salvage procedures, and emerging immunotherapeutic treatment have contributed to improved disease control and survival outcomes of the patients significantly. As a result, evidence-based treatment with accurate staging has become increasingly important in the treatment outcomes of the patients.

The recent modifications by the 9th version of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) staging system have introduced revisions for improving the risk stratification, better prognostic accuracy and clinical outcomes of the patients.

Access this article online	
Website: **https:**//ajohns.net/	**Quick Response Code**
DOI: ???????	

This article reviews the recent updates in the staging, and advances in the management of Nasopharyngeal carcinoma.

Brief overview of Nasopharyngeal carcinoma

Nasopharyngeal carcinoma is a malignancy arising from the epithelial lining of the nasopharynx.[1] It has been found that the Epstein-Barr virus (EBV)-encoded RNA signal is present in all nasopharyngeal carcinoma cells.[2] Apart from EBV association, genetic predisposition, consumption of salt-preserved foods, and smoking have been linked with risk

Senior Resident[1], Professor and HOD[2]
Department of ENT-HNS[1-4]
All India Institute of Medical Science (AIIMS), Guwahati, India

Corresponding Author: Ruuzeno Kuotsu
Senior Resident, Department of ENT-HNS
All India Institute of Medical Science (AIIMS), Guwahati, India
Email ID: ruuzenokuotsu@gmail.com

Source of funding: None
Conflict of interest: None declared

How to cite this article: Kuotsu R, Brian Shunyu N. Recent Updates and Future Directions in Nasopharyngeal Carcinoma: A Literature Review. Journal of Otolaryngology and Head & Neck Surgery. 2026; 1(3):4-8

factors of NPC.[3] NPC is known to have a high tendency for regional and distant spread.

According to the World Health Organization (WHO), NPC is classified into:

- Non-keratinizing (differentiated and undifferentiated)
- Keratinizing squamous cell carcinoma
- Basaloid carcinoma

Among these, the non-keratinising undifferentiated subtype has the strongest EBV correlation and has the best prognosis.[2,4] NPC in general responds very well to Radiotherapy and Chemotherapy.

Incidence of Nasopharyngeal carcinoma

Nasopharyngeal carcinoma ranks 23rd among all the common cancers worldwide.[5] whereas around one in nine men and one in 12 women die from it. Lung cancer was the most frequently diagnosed cancer in 2022, responsible for almost 2.5 million new cases, or one in eight cancers worldwide (12.4% of all cancers globally The incidence of Nasopharyngeal carcinoma (NPC) is highly uneven in distribution, with high incidence only in certain parts of the world, like Eastern Asia (China) and Southeast Asia,[6,7] dominating the global burden up to 83.3% cases, with a higher proportion of cases in males.[8] The Northeastern part of India has a surprisingly high rate of incidence and has a significant impact on global burden.[9] Bengaluru, and the Tata Memorial Centre, Mumbai, India, were utilised. The 37 PBCRs were divided into six regions including central, east, north, northeast, west and south. The age-standardised incidence rate of HNC was 25.9 (95% CI 25.7-26.1 In India, Nagaland ranks among the highest with incidence of 19.4/100,000 population.[10] The second and third in rank among the northeast India are Manipur and Mizoram.[11]

Importance of the topic

NPC has a rather specific geographic distribution with high incidence in Southern China, Southeast Asia, Northeast part of India. And even though it is relatively rare if we look at it globally, NPC is no doubt a major burden in the endemic regions. Therefore, updated management strategies are critical for improving outcomes. And advances in the NPC management, including evolution in the radiation technique, emergence of immunotherapy and targeted therapy and integration of biomarkers like plasma EBV-DNA for risk stratification all will directly improve the prognosis for the large at-risk populations.

Objectives of the review

1. To outline the updates by the 9th version of the AJCC/UICC staging system, which helps in refining the prognosis and redistribution of the staging.
2. To review the intensification and treatment modalities for locoregionally advanced cases.
3. To review whether EBV DNA titres are associated with the outcomes of patients with recurrent or metastatic NPC (R/M-NPC) in patients who are receiving anti- PD1 therapy.
4. To identify the emerging therapies and evaluate the clinical impact on the patients.

Early foundational studies

Radiotherapy has been the primary mainstay of treatment for NPC because of its anatomic location and radiosensitivity. And as time progressed the technique of radiotherapy became more precise and Intensity modulated radiotherapy (IMRT) has been used as it gave better results in tumour control and less toxicity to normal tissue. For the locoregionally advanced NPC (LA-NPC), concurrent chemoradiotherapy (CCRT) has been the treatment modality, with the mechanism that chemotherapy acts as a radiosensitiser and targets occult distant metastasis.[12] However, it has been found that patients with LA-NPC has a higher chance of distant metastases, so the introduction of induction chemotherapy (IC) along with CCRT has increased the overall survival rate.[13]

It has been concluded that NPC is a clinically heterogeneous disease and treatment recommendations can be stratified and individualised based on the on-treatment responses after IC or midway through radiotherapy or CCRT.[10] Nasopharyngeal carcinoma is a distinct malignancy with unique epidemiology and high sensitivity to radiotherapy and chemotherapy. Advances in imaging, IMRT, systemic therapy, and immunotherapy have significantly improved disease control and survival outcomes. The 9th version AJCC/UICC staging system refines anatomical classification and prognostic accuracy, aligning staging with modern treatment approaches. However, the lack of integration of biological markers such as EBV-DNA and limited global representation in clinical trials remain important limitations. Emerging therapies show promise, but further research is needed to validate long-term efficacy, address treatment resistance, and support biomarker-driven personalized management.[14]

Management of recurrent and metastatic disease

Similarly, for patients with recurrent or metastatic NPC (R/M-NPC), treatment can be individualised basing on the volume of disease and the site of involvement.[15,16] For limited Primary site recurrence (rT1,rT2) with or without nodal disease, endoscopic salvage nasopharyngectomy with or without neck dissection basing on the nodal involvement, followed by adjuvant platinum-doublet chemotherapy[17] and good survival outcome has been obtained.[18] For patients with oligometastatic NPC platinum -doublet chemotherapy was given which was followed by consolidation radiotherapy to the primary with or without metastases directed therapy.[19]

For polymetastatic disease, the new standard of care as introduced in 2025 is the combination of platinum-doublet chemotherapy with immune checkpoint inhibitors that is anti-programmed cell Death-1 (Anti PD-1) like Camrelizumab, Tislelizumab and Toripalimab which is supported by phase III randomised control trials, namely Rationale-309, Captain-1st and Jupiter-02.[20–22]

Association of EBV DNA titres with outcomes in R/M-NPC patients receiving Anti-PD-1 Therapy:

EBV DNA titre has long been associated with NPC.[23] It has already been used as an established marker for evaluating treatment response or relapse after radiotherapy and chemotherapy.[24–26] There is not much study on the use of EBV DNA biomarker in patients with Recurrent or metastatic NPC who are on treatment with Anti-PD-1 immunotherapy. Among the few studies, one large study by Xu et al, analysed data from the prospective POLARIS-02 clinical trial to correlate the role of EBV DNA with disease progression monitoring and prognosis prediction in NPC patients receiving immunotherapy. The results showed that patients with higher baseline EBV DNA titres, as well as those whose 4th week baseline titre ratio higher than 0.5, were significantly associated with poorer outcomes, including shorter overall and progression-free survival and a lower rate of durable clinical benefit. Notably, plasma EBV DNA levels were found to be elevated 2.6 months before disease progression was detected on imaging, suggesting that it acts as an early indicator of relapse and a useful tool for closer monitoring during anti-PD-1 therapy.[27,28]

Updates in the latest 9th version of AJCC/UICC on Nasopharyngeal Carcinoma:

Earlier usage of the term "edition" has been replaced by the term version in the updated 9th version of AJCC/UICC staging system of NPC.

The new TNM staging system for NPC has done refinement in the T staging, has added changes in the N category and redefinition of stage groupings.[29]

Refinement in the T category:

- Unequivocal involvement of bone will be considered as T3
- Involvement of the surrounding structures like the orbit, cranial nerves, parotid gland or anything beyond the lateral surface of the lateral pterygoid muscle will be considered as T4

Changes in the N category:

- Advanced extra-nodal extension is considered as N3

Subdivision in M category:

- The M1 has been divided into M1a and M1b; M1a being ≤ 3 metastatic lesions and M1b >3 metastatic lesions

Redefinition of stage groupings:

Stage1 has been expanded and subdivided into stage 1a and stage 1b. Stage 1a being (T1-2, N0, M0) and Stage 1b being (T1-2, N1, M0).

Non metastatic disease (M0) is now grouped into stage (1-III), M0 will not be considered as stage IV, earlier T3/T4 with N3 M0 was considered as stage IV.

Now stage IV will be reserved for metastatic disease with Stage IVa being M1a (<3 metastatic lesions) and Stage IVb being M1b (>3 metastatic lesions).

Recent developments

Newer therapeutic combinations apart from chemotherapy and anti PD-1 antibody are in the pipeline and clinical trials including antibody-drug conjugates (ADCs) and bispecific antibodies (BsAb).[30] They represent the new generation of antibodies, wherein they use specific tumour antigens to destroy the cancer cells. ADCs are antibodies which have cytotoxic agents which are bound via a linker, and thus allow specific delivery of chemotherapeutic agents to the antigen-expressing tumour cells, leading to a decrease in systemic toxicity.[30] In the contrary, a BsAb will bind to two distinct epitopes of the same antigen or two different antigens at the same time, allowing targeted immune effector T-cell engagement with cancer cells.[30] They show promising results for recurrent and metastatic NPC but until now they're in phase -1 trial. Future research still needs to be done.

Critical Analysis

The management of Nasopharyngeal carcinoma (NPC) through various literature shows rapid evolution, with refined staging and incorporation of immunotherapy, but critical gaps do exist in personalization and long-term toxicity data. The 9th AJCC/UICC TNM staging, effective since January 2025, increases the prognostic accuracy yet it still demands validation in diverse populations.[31] where the endemic subtype is strongly associated with Epstein-Barr virus (EBV The new AJCC 9th version still depends mainly on anatomical landmarks and it has overlooked the EBV-DNA biomarkers which has a high chance of future studies. Most of the study data of phase III trials are from Asia, favoring selection bias, leading to global disparities in access and ethnicity adjusted outcomes.

There is a lot of data on the response rates of immunotherapy however, the data showing resistance to immunotherapy is very limited. More meta-analysis on this is required to understand its true effectiveness.

Research Gaps

Even though, advances have been made in the staging and management of nasopharyngeal carcinoma, key research gaps

remain. The current AJCC/UICC 9th edition staging system relies mainly on anatomical factors and does not incorporate EBV-DNA biomarkers, leading to limiting the precise risk stratification. There are many studies on the use of EBV DNA correlation with disease progression or relapse in patients who have taken chemotherapy and radiotherapy, but there are very less studies on the use of EBV DNA titre for checking disease progression and relapse on recurrent or metastatic NPC patients undergoing immunotherapy. Most of the trials and studies are from Asian populations, leading to reduced global generalizability. Although immunotherapy shows promising responses, data on resistance to the drug, long-term outcomes, and real-world effectiveness are still limited, and the emerging ADCs and BsAb therapies are still in early-phase trials.

CONCLUSION

Nasopharyngeal carcinoma is a malignancy with unique epidemiology and geographic distribution and is highly sensitive to radiotherapy and chemotherapy. Advances in imaging, radiation techniques (IMRT), systemic chemotherapy, and immunotherapy have significantly improved disease control and survival outcomes. The 9th version AJCC/UICC staging system has redefined the anatomical classification and prognostic accuracy. It has modified the staging system as well so that it can align with the modern treatment approaches. However, the lack of integration of biological markers such as EBV-DNA and very limited representation in clinical trials remain important limitations. Upcoming immunotherapy and antibodies therapies show good promise, but further research is needed to validate long-term efficacy, and look for resistance to treatment and to include biomarker for checking the prognosis and response to the treatment and early detection of relapse.

REFERENCES

1. Brennan B. Nasopharyngeal carcinoma. Orphanet J Rare Dis. 2006 Dec;1(1):23.
2. Wei WI, Sham JS. Nasopharyngeal carcinoma. The Lancet. 2005 Jun;365(9476):2041–54.
3. Jicman (Stan) D, Niculet E, Lungu M, Onisor C, Rebegea L, Vesa D, et al. Nasopharyngeal carcinoma: A new synthesis of literature data (Review). Exp Ther Med. 2021 Dec 13;23(2):136.
4. Chan JK. Virus-associated neoplasms of the nasopharynx and sinonasal tract: diagnostic problems. Mod Pathol. 2017 Jan;30:S68–83.
5. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2024 May [cited 2025 Dec 15];74(3):229–63. Available from: https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21834
6. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. The Lancet. 2019 Jul;394(10192):64–80.
7. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209–49.
8. Zhang Y, Rumgay H, Li M, Cao S, Chen W. Nasopharyngeal Cancer Incidence and Mortality in 185 Countries in 2020 and the Projected Burden in 2040: Population-Based Global Epidemiological Profiling. JMIR Public Health Surveill [Internet]. 2023 Sep 20 [cited 2025 Dec 15];9:e49968. Available from: https://publichealth.jmir.org/2023/1/e49968
9. Bagal S, Budukh A, Thakur JS, Dora T, Qayyumi B, Khanna D, et al. Head and neck cancer burden in India: an analysis from published data of 37 population-based cancer registries. Ecancermedicalscience. 2023;17:1603.
10. Kataki AC, Simons MJ, Das AK, Sharma K, Mehra NK. Nasopharyngeal carcinoma in the Northeastern states of India. Chin J Cancer. 2011 Feb;30(2):106–13.
11. Kataki AC, Simons MJ, Das AK, Sharma K, Mehra NK. Nasopharyngeal carcinoma in the Northeastern states of India. Chin J Cancer. 2011 Feb 5;30(2):106–13.
12. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol. 1998 Apr;16(4):1310–7.
13. Petit C, Lee A, Ma J, Lacas B, Ng WT, Chan ATC, et al. Role of chemotherapy in patients with nasopharynx carcinoma treated with radiotherapy (MAC-NPC): an updated individual patient data network meta-analysis. Lancet Oncol. 2023 Jun;24(6):611–23.
14. Lv J, Xu LX, Li ZX, Lin L, Wu CF, Quan TQ, et al. Longitudinal on-treatment circulating tumor DNA as a biomarker for real-time dynamic risk monitoring in cancer patients: The EP-SEASON study. Cancer Cell. 2024 Aug;42(8):1401-1414.e4.
15. Zou X, You R, Liu H, He YX, Xie GF, Xie ZH, et al. Establishment and validation of M1 stage subdivisions for de novo metastatic nasopharyngeal carcinoma to better predict prognosis and guide treatment. Eur J Cancer. 2017 May;77:117–26.
16. Liu Y, Zuo ZC, Zeng XY, Ma J, Ma CX, Chen RZ, et al. Establishing subdivisions of M1 stage nasopharyngeal carcinoma based on decision tree classification: A multicenter retrospective study. Oral Oncol. 2024 Jun;153:106834.
17. Shunyu NB, Lynrah Z, Medhi J, Aktar H, Syiemlieh J, Lyngdoh N. Salvage Endoscopic Nasopharyngectomy for Locally Recurrent T1 and T2 Nasopharyngeal Carcinoma. Indian J Otolaryngol Head Neck Surg. 2023 Sep;75(3):2688–93.
18. Fee, Jr WE, Moir MS, Choi EC, Goffinet D. Nasopharyngectomy for Recurrent Nasopharyngeal Cancer: A 2- to 17-Year Follow-up. Arch Otolaryngol Neck Surg. 2002 Mar 1;128(3):280.
19. You R, Liu YP, Huang PY, Zou X, Sun R, He YX, et al. Efficacy and Safety of Locoregional Radiotherapy With Chemotherapy vs Chemotherapy Alone in De Novo Metastatic Nasopharyngeal Carcinoma: A Multicenter Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020 Sep 1;6(9):1345.

20. Yang Y, Qu S, Li J, Hu C, Xu M, Li W, et al. Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2021 Aug;22(8):1162–74.

21. Yang Y, Pan J, Wang H, Zhao Y, Qu S, Chen N, et al. Tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer: A multicenter phase 3 trial (RATIONALE-309). Cancer Cell. 2023 Jun;41(6):1061-1072. e4.

22. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, et al. Toripalimab Plus Chemotherapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: The JUPITER-02 Randomized Clinical Trial. JAMA. 2023 Nov 28;330(20):1961.

23. Chua MLK, Wee JTS, Hui EP, Chan ATC. Nasopharyngeal carcinoma. The Lancet [Internet]. 2016 Mar [cited 2025 Dec 17];387(10022):1012–24. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673615000550

24. Wang W, Twu C, Chen H, Jiang R, Wu C, Liang K, et al. Long□term survival analysis of nasopharyngeal carcinoma by plasma Epstein□Barr virus DNA levels. Cancer [Internet]. 2013 Mar [cited 2025 Dec 17];119(5):963–70. Available from: https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.27853

25. Lai L, Chen X, Zhang C, Chen X, Chen L, Tian G, et al. Pretreatment Plasma EBV-DNA Load Guides Induction Chemotherapy Followed by Concurrent Chemoradiotherapy in Locoregionally Advanced Nasopharyngeal Cancer: A Meta-Analysis. Front Oncol [Internet]. 2021 Feb 16 [cited 2025 Dec 17];10:610787. Available from: https://www.frontiersin.org/articles/10.3389/fonc.2020.610787/full

26. Chan ATC, Hui EP, Ngan RKC, Tung SY, Cheng ACK, Ng WT, et al. Analysis of Plasma Epstein-Barr Virus DNA in Nasopharyngeal Cancer After Chemoradiation to Identify High-Risk Patients for Adjuvant Chemotherapy: A Randomized Controlled Trial. J Clin Oncol [Internet]. 2018 Nov 1 [cited 2025 Dec 17];36(31):3091–100. Available from: https://ascopubs.org/doi/10.1200/JCO.2018.77.7847

27. Xu JY, Wei XL, Ren C, Zhang Y, Hu YF, Li JY, et al. Association of Plasma Epstein-Barr Virus DNA With Outcomes for Patients With Recurrent or Metastatic Nasopharyngeal Carcinoma Receiving Anti–Programmed Cell Death 1 Immunotherapy. JAMA Netw Open [Internet]. 2022 Mar 1 [cited 2025 Dec 17];5(3):e220587. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2789514

28. Wang FH, Wei XL, Feng J, Li Q, Xu N, Hu XC, et al. Efficacy, Safety, and Correlative Biomarkers of Toripalimab in Previously Treated Recurrent or Metastatic Nasopharyngeal Carcinoma: A Phase II Clinical Trial (POLARIS-02). J Clin Oncol [Internet]. 2021 Mar 1 [cited 2025 Dec 17];39(7):704–12. Available from: https://ascopubs.org/doi/10.1200/JCO.20.02712

29. Pan JJ, Mai HQ, Ng WT, Hu CS, Li JG, Chen XZ, et al. Ninth Version of the AJCC and UICC Nasopharyngeal Cancer TNM Staging Classification. JAMA Oncol. 2024 Dec 1;10(12):1627.

30. Jiménez-Labaig P, Rullan A, Hernando-Calvo A, Llop S, Bhide S, O'Leary B, et al. A systematic review of antibody-drug conjugates and bispecific antibodies in head and neck squamous cell carcinoma and nasopharyngeal carcinoma: Charting the course of future therapies. Cancer Treat Rev. 2024 Jul;128:102772.

31. Chua MLK, Zhang X, Wong KCW, Marret G, Spreafico A, Ma B. Updates on Treatments and Management of Nasopharyngeal Carcinoma. Am Soc Clin Oncol Educ Book. 2025 Jun;45(3):e472460.