



Invited Commentary | Oncology

# Multimodality Therapy for Locoregional Nasopharyngeal Carcinoma— A Decision Tool for Treatment Optimization

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Locoregional nasopharyngeal cancer (NPC) is a heterogeneous disease with variable epidemiological, clinical, and biological characteristics. Radiotherapy (RT) has become the therapeutic backbone of this disease; however, the optimal combined modality therapeutic approach remains an area of controversy. In this setting, National Comprehensive Cancer Network guidelines offer multiple treatment options that include clinical trial enrollment, concurrent systemic therapy and RT followed by adjuvant chemotherapy, induction chemotherapy followed by systemic therapy and RT, or concurrent systemic therapy and RT without adjuvant chemotherapy.<sup>1</sup> Using a large cohort study of locoregional nasopharyngeal carcinoma, Zhang and colleagues<sup>2</sup> attempted to develop and validate a prognostic nomogram that was subsequently explored as a tool to assist with selecting an optimal combined modality therapeutic approach. The authors identified a cohort of 8093 patients with nonmetastatic NPC who were treated with RT with or without chemotherapy. This cohort was randomly allocated using a 2:1 ratio into a training cohort (n = 5398) or a validation cohort (n = 2695). Using multivariate analysis, Zhang and colleagues<sup>2</sup> identified 6 clinical prognostic markers, including T stage, N stage, Epstein-Barr virus DNA, lactate dehydrogenase level, and albumin level, and subsequently incorporated them into a prognostic nomogram for overall survival. The nomogram demonstrated excellent accuracy for overall survival and managed to outperform the eighth edition American Joint Committee on Cancer/Union for International Cancer Control TNM staging system. The authors subsequently stratified patients by quartiles based on percentile score values estimated from the established nomogram to characterize risk groups. Various multimodality treatment approaches (RT alone, chemoradiotherapy [CRT], or induction chemotherapy followed by CRT) were assessed within each risk group to suggest that a nomogram-based approach could help clinicians as a guide to optimally select a multimodal therapeutic strategy for treatment of locoregional NPC.

Multimodality therapy incorporating systemic therapy and RT for locoregional head and neck cancer has become a standard therapeutic strategy over the past several decades. Although initially demonstrated as an effective strategy for larynx cancer, subsequent meta-analyses have demonstrated a survival benefit for the addition of chemotherapy to RT alone, particularly for platinum-based therapy, which is most beneficial when given concurrently with RT.<sup>3</sup> For NPC specifically, the addition of chemotherapy to RT alone was evaluated in the Intergroup 0099 study in which CRT followed by adjuvant chemotherapy improved 3-year overall survival from 47% with RT alone to 78% with CRT followed by adjuvant chemotherapy.<sup>4</sup> A subsequent meta-analysis further supported the importance of the concurrent component with an approximately 8% improvement in 10-year overall survival with the addition of concurrent chemotherapy to RT alone.<sup>5</sup> Recently, there has been a renewed interest in the role that induction chemotherapy may play prior to CRT, especially for locoregionally advanced NPC. Three randomized phase 3 studies from China have demonstrated a survival advantage with the addition of induction chemotherapy to CRT alone, especially when incorporating highly active chemotherapeutic agents such as gemcitabine-cisplatin,<sup>6</sup> cisplatin-fluorouracil-docetaxel,<sup>7</sup> and cisplatin-fluorouracil.<sup>8</sup> Based on these data, patients eligible for an intensive treatment regimen with locoregionally advanced NPC can be treated with induction chemotherapy followed by CRT.

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For the practicing oncologist, treating with RT alone vs CRT vs induction chemotherapy followed by CRT remains a multifaceted treatment decision that considers patient characteristics, such as age and comorbidities, as well as disease characteristics, such as T stage or N stage, and anatomic factors, such as involvement of critical structures. The nomogram developed by Zhang and colleagues<sup>2</sup> for this large retrospective cohort study attempts to objectively quantify some of these disease and patient characteristics as a potential aid for oncologists to be incorporated at the bedside using readily available clinical and laboratory data. Prospective validation of the nomogram will be necessary for incorporation into clinical practice. However, this nomogram has potential to be further developed as a clinical decision tool when incorporated into the broader clinical context and judgement of the practicing oncologist in choosing a treatment strategy for a specific patient. Some limitations include the retrospective nature of this study,<sup>2</sup> which introduces an inherent selection bias, and the patient population, which includes patients treated in a region endemic for NPC which limits broader geographic application. Additional questions include the role of blood-based biomarkers, such as dynamic changes in Epstein-Barr virus DNA during and after treatment, novel genomic and other tissue-based prognostic biomarkers, and the role of immune checkpoint inhibitors in the definitive setting for NPC (NCT03734809, NCT03267498, and NCT03984357).

In conclusion, the authors should be commended for undertaking this very large cohort study of patients with nonmetastatic NPC to derive a prognostically discriminative nomogram with potential clinical application. Prospective validation and incorporation with additional novel biomarkers can further enhance the clinical application of this tool to further optimize treatment for this patient population to maximize oncologic outcomes while minimizing treatment-related toxic effects.

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#### ARTICLE INFORMATION

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