

# Research Progress of Immunotherapy Combined with Radiotherapy and Chemotherapy in Locally Advanced Nasopharyngeal Carcinoma

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**Abstract** Locally advanced nasopharyngeal carcinoma (NPC) suffers from unique anatomical structures and complex biological behaviors. While traditional radiotherapy and chemotherapy have controlled disease progression to some extent, the risk of recurrence and distant metastasis remains high, limiting further improvements in treatment efficacy. In recent years, the application of immunotherapy, particularly immune checkpoint inhibitors, has significantly changed the landscape of cancer treatment, bringing new hope to patients with locally advanced NPC. Current clinical research explores strategies for combining immunotherapy with radiotherapy and chemotherapy, aiming to enhance anti-tumor effects and improve patient survival through synergistic effects. This article systematically reviews the latest research progress on immunotherapy combined with radiotherapy and chemotherapy in locally advanced NPC, focusing on its mechanisms of action, clinical trial data, and potential future treatment directions. The aim is to provide theoretical support and guidance for clinical practice, promoting the development of comprehensive treatment models for locally advanced NPC.

**Keywords:** Immunotherapy; Radiotherapy and chemotherapy; Locally advanced nasopharyngeal carcinoma; Immune checkpoint inhibitors; Combination therapy; Clinical research

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## 1 Introduction

Locally advanced nasopharyngeal carcinoma (NPC) is a challenging stage in the treatment of nasopharyngeal carcinoma due to its complex biological characteristics and high risk of recurrence and metastasis, posing a significant challenge to clinical treatment. Nasopharyngeal carcinoma is a common malignant tumor in the head and neck region, with a particularly high incidence in southern China and Southeast Asia[1]. Traditional treatment methods mainly involve radiotherapy and chemotherapy, especially concurrent chemoradiotherapy (CCRT), which has become the standard treatment for locally advanced nasopharyngeal carcinoma. However, despite the continuous advancement

of radiotherapy and chemotherapy techniques, patients with locally advanced nasopharyngeal carcinoma still face the risk of treatment failure, mainly manifested as local recurrence and distant metastasis, which is closely related to tumor drug resistance and immune escape in the tumor microenvironment [2,3]. In recent years, the advancement of immunotherapy has led to significant breakthroughs in the treatment of nasopharyngeal carcinoma. In particular, immune checkpoint inhibitors (ICIs), such as PD-1/PD-L1 inhibitors, have demonstrated significant anti-tumor activity and relatively manageable safety in various solid tumors [4,5]. In nasopharyngeal carcinoma, immunotherapy not only activates the patient's own

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immune system but also effectively controls the tumor by relieving the suppression of the immune system by tumor cells. Clinical studies have shown that PD-1 inhibitors combined with chemotherapy or radiotherapy can significantly improve the treatment response rate and prolong progression-free survival, showing potential superior to traditional treatments [6, 7]. The combination strategy of immunotherapy with radiotherapy and chemotherapy is currently a hot research topic. Radiotherapy and chemotherapy not only directly kill tumor cells but also enhance antigen presentation by inducing tumor cell necrosis and releasing tumor antigens, thereby improving the immune system's ability to recognize and attack tumors. In addition, radiotherapy and chemotherapy can reshape the tumor microenvironment and promote the infiltration and activation of immune cells, which has a complementary effect with the mechanism of action of immune checkpoint inhibitors. The synergistic effect of the two is expected to overcome tumor drug resistance and improve patient prognosis [8, 9]. Studies have shown that in patients with locally advanced nasopharyngeal carcinoma, the use of PD-1 inhibitors such as toripalimab combined with chemotherapy and radiotherapy can significantly improve the treatment effect and has good safety [4, 6]. The application of molecular targeted therapy and multi-target drugs also provides more possibilities for combination strategies. Dual-targeting drugs that target EGFR and Axl have shown strong anti-tumor activity both in vitro and in vivo, suggesting that combination therapies with targeted therapies hold great promise for the future treatment of locally advanced nasopharyngeal carcinoma [1, 10]. Meanwhile, studies have also emphasized the important role of tumor molecular markers, such as HMGA2, LAG-3, and PD-L1,

in predicting treatment response and prognosis, laying the foundation for personalized precision medicine [2, 4]. In summary, the treatment of locally advanced nasopharyngeal carcinoma is shifting from traditional chemoradiotherapy to immunotherapy and its combination therapy. Immunotherapy, especially immune checkpoint inhibitors, has shown significant synergistic effects when combined with chemoradiotherapy, and is expected to overcome the limitations of traditional treatments, improving patient response rates and quality of life. This article aims to systematically summarize the latest research progress in immunotherapy combined with chemoradiotherapy for locally advanced nasopharyngeal carcinoma, focusing on its mechanism of action, clinical trial data, and future development directions. It provides a theoretical basis and guidance for clinical practice.

## **2 Mechanism of action of immunotherapy in locally advanced nasopharyngeal carcinoma**

### *2.1. Immune escape mechanism and its manifestation in nasopharyngeal carcinoma*

Nasopharyngeal carcinoma (NPC) is a malignant tumor closely related to the EB virus. Its tumor microenvironment has a complex immunosuppressive mechanism, which enables tumor cells to escape the surveillance of the immune system, thereby promoting tumor progression and drug resistance. The surface of tumor cells and surrounding vascular endothelial cells generally highly express programmed death ligand 1 (PD-L1). This phenomenon has been confirmed to be common in NPC patients, and high expression of PD-L1 is closely related to poor prognosis. Tumor-associated vascular endothelial cells bind to PD-1 on T cells through PD-L1, thereby inhibiting the killing function of T cells and facilitating immune escape

[11]. The infiltration of regulatory T cells (Tregs) in the tumor microenvironment is significantly increased. These Tregs exhibit high proliferative activity and express activating and immunosuppressive molecules such as FOXP3, CD38, HLA-DR, CD39 and PD-1. The abundance of Ki67+ proliferating Tregs is positively correlated with the risk of relapse after treatment, suggesting their key role in immune escape in NPC [12]. Meanwhile, tumor cells can further exacerbate immunosuppression by secreting various immunosuppressive cytokines, such as kynurenine produced by IDO1, which promotes CD8+ T cell exhaustion and Treg differentiation [13]. Tumor-associated fibroblasts (CAFs) also accumulate in relapsed NPC, promoting radiotherapy resistance and inhibiting T cell infiltration through the collagen IV pathway, thus enhancing immune escape [14]. NPC cells enhance the expression of the immune checkpoint molecule CD276 (B7-H3) through epigenetic regulatory mechanisms such as the PBK/MSL1 axis, exacerbating the immunosuppressive environment [15]. The high PD-L1 expression, active regulatory T cell infiltration, and secretion of immunosuppressive cytokines in the NPC tumor microenvironment collectively form a complex immune escape network, making it a key target for immunotherapy.

### 2.2 Mechanism of Action of Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) mainly restore the anti-tumor activity of T cells by blocking inhibitory signals on the surface of tumor cells or immune cells. In NPC, blocking the PD-1/PD-L1 axis is currently the most mature and widely used immunotherapy strategy. PD-1 inhibitors such as toripalimab, nivolumab, and pembrolizumab can relieve T cell immunosuppression and activate the patient's own immune system to attack tumor cells. Numerous clinical studies have confirmed that the expression level of

PD-L1 is closely related to the response to immunotherapy, and patients with high PD-L1 expression tend to respond better to ICIs [16]. In locally advanced NPC, the treatment regimen of immune checkpoint inhibitors combined with radiotherapy and chemotherapy significantly improved the objective response rate and progression-free survival. A randomized clinical trial of toripalimab combined with induction chemotherapy and concurrent chemoradiotherapy showed that the 3-year progression-free survival rate was significantly improved compared with the placebo group (92% vs 74%), and the safety profile was manageable [17]. Additionally, immunotherapy can promote the increase of PD-1+CD8+ T cells in the peripheral blood. These cells exhibit high expression of killer-related molecules, such as IFN- $\gamma$  and Granzyme B, and have been shown to be effective against anti-EBV-positive NPC cells [18]. However, the efficacy of immune checkpoint inhibitors is also heterogeneous. Some patients may not respond well due to the complex immunosuppressive mechanism of the tumor microenvironment or immune tolerance. Therefore, combination therapy strategies and biomarker screening have become research hotspots [19].

### 2.3 The Regulatory Effects of Radiotherapy and Chemotherapy on the Immune System

Radiotherapy and chemotherapy, as traditional treatments for NPC, can not only directly kill tumor cells but also activate the body's anti-tumor immune response by inducing immunogenic cell death to release tumor-associated antigens. Immunogenic cell death activates antigen-presenting cells (such as dendritic cells), promotes the presentation of tumor antigens and the activation of effector T cells, thereby enhancing the immune system's ability to recognize and eliminate tumors [20]. Radiotherapy and chemotherapy can regulate the

immunotherapy combined with radiotherapy and chemotherapy in locally advanced NPC tumor microenvironment, inhibit the activity of immunosuppressive cells such as tumor-associated macrophages and regulatory T cells, and improve the functional status of tumor-infiltrating lymphocytes [21]. Low-dose radiotherapy can also enhance the treatment effect by stimulating the anti-tumor immune response, and when combined with immunotherapy, it exhibits a synergistic effect [22]. Clinical studies have shown that the treatment regimen of radiotherapy and chemotherapy combined with immune checkpoint inhibitors can not only improve the local control rate but also help prolong progression-free survival and overall survival. After induction chemotherapy combined with immunotherapy, the complete remission rate of patients is significantly improved, and immunotherapy enhances the anti-tumor effect of radiotherapy and chemotherapy [6, 23]. However, radiotherapy and chemotherapy may also lead to immune-related side effects, and it is necessary to reasonably assess patient tolerance and manage risks [24]. Radiotherapy and chemotherapy significantly enhance the effect of immunotherapy by inducing immunogenic cell death and remodeling the tumor microenvironment, providing a theoretical basis and clinical support for the comprehensive treatment of locally advanced NPC.

### **3 Clinical Research Progress of Immunotherapy Combined with Radiotherapy and Chemotherapy**

#### *3.1 Early Clinical Trial Results*

Several phase I/II clinical trials have preliminarily confirmed that immune checkpoint inhibitors (ICIs) combined with radiotherapy and chemotherapy have shown high response rates and manageable safety in the treatment of locally advanced nasopharyngeal carcinoma (NPC). Although the objective response rate of ICI monotherapy is

limited, the immunomodulatory effect of radiotherapy and chemotherapy can enhance the immunogenicity of tumors and significantly improve the treatment effect. PD-1 inhibitors combined with cisplatin-based radiotherapy and chemotherapy have been reported to significantly improve the progression-free survival (PFS) of patients, which is attributed to the remodeling of the tumor microenvironment and activation of the immune status by radiotherapy and chemotherapy [25, 26]. In addition, the synergistic effect of immunotherapy and radiotherapy and chemotherapy is also reflected in enhancing the function of natural killer cells (NK) and T cell-mediated anti-tumor responses. Some nanoparticle technologies have also been explored to improve the targeting and synergistic effect of drugs [27]. In head and neck squamous cell carcinoma (HNSCC), similar combination therapy strategies have also shown the potential for immune activation and lesion shrinkage, suggesting their application prospects in NPC [28]. Despite encouraging early trial results, more data are needed to clarify the optimal combination therapy regimen and patient selection criteria.

#### *3.2 Large-scale randomized controlled trials*

Currently, several phase III randomized controlled trials are evaluating the long-term efficacy and safety of immunotherapy combined with chemoradiotherapy in locally advanced NPC. These trials typically use overall survival (OS), disease-free survival (DFS), and quality of life as primary endpoints to verify whether combination therapy can significantly improve patient prognosis. A recent systematic review that included several phase III trials found that immune checkpoint inhibitors combined with standard chemotherapy improved PFS and OS in relapsed/metastatic NPC, and high-grade adverse events were manageable [29]. Some studies have demonstrated

the economic advantages of sintilimab combined with chemoradiotherapy in the management of NPC through cost-benefit analysis [26]. In addition, similar strategies have demonstrated good efficacy in other tumor types, such as lung cancer and non-small cell lung cancer (NSCLC), suggesting that integrating chemoradiotherapy and immunotherapy may become a new direction for treating various locally advanced tumors [30, 31]. Nevertheless, the optimal timing, dosage, and patient selection for immunotherapy combined with chemoradiotherapy still need to be optimized through more high-quality randomized controlled trials.

### *3.3 Adverse Reactions and Management*

While immunotherapy combined with chemoradiotherapy improves efficacy, it also presents challenges related to immune-related adverse events (irAEs). Common immune-related adverse events (irAEs) include rash, abnormal liver function, and immune-related pneumonia. Chemoradiotherapy itself can also cause adverse reactions such as myelosuppression, radiation-induced pneumonia, and mucositis [32, 33]. Although most irAEs caused by combined therapy are manageable, some patients, especially younger patients, those with a high neutrophil/lymphocyte ratio (NLR), or those receiving three-drug chemotherapy regimens, have an increased risk of severe radiation-induced oral mucositis [34]. Therefore, early identification and standardized management of adverse reactions are crucial for ensuring treatment safety. Establishing risk prediction models and developing individualized treatment plans are of great significance [35]. For severe side effects such as immune-related pneumonia, timely discontinuation of medication, application of glucocorticoids, and multidisciplinary collaborative management are currently the main strategies.

Studies have shown that combined therapy with immune checkpoint inhibitors and chemoradiotherapy may induce complex immune phenomena such as pseudoprogression and immune tolerance, requiring clinicians to have sufficient understanding and coping abilities [28, 36]. While immunotherapy combined with radiotherapy and chemotherapy has improved the treatment prospects for locally advanced NPC, safety management remains a key focus and challenge in clinical application.

## **4 Challenges and Future Development Directions of Combination Therapy**

### *4.1 Screening of Biomarkers and Precision Treatment*

Immunotherapy has shown significant therapeutic potential in locally advanced nasopharyngeal carcinoma (NPC), but its response heterogeneity is substantial, resulting in substantial differences in efficacy among patients. Therefore, it is urgent to screen effective predictive biomarkers to achieve precision treatment. Studies have shown that PD-L1 expression level is an important indicator for assessing the efficacy of immune checkpoint inhibitors (ICIs), but PD-L1 expression alone is insufficient to fully predict the patient's response to immunotherapy [37, 38]. Tumor mutation burden (TMB), a representative of tumor genomic instability, has also been used as a potential biomarker for predicting immunotherapy response; however, its application in NPC still requires further validation [37]. It is worth noting that NPC is closely related to EBV infection, and the level of EBV DNA in peripheral blood has been studied for monitoring disease burden and prognosis, with some value in predicting immunotherapy response [26]. Due to the limited predictive power of single biomarkers, the current research trend is to combine multi-omics data, including genomic,

immunotherapy combined with radiotherapy and chemotherapy in locally advanced NPC transcriptomic, proteomic, and metabolomic information, to construct multidimensional predictive models and achieve a higher level of treatment personalization [39, 40]. This multi-omics integration strategy not only helps to accurately identify immunotherapy-sensitive patients but also reveals immune escape mechanisms and guides the design of combination therapy regimens. In addition, the application of machine learning technology provides a powerful tool for screening and integrating complex biomarkers, further promoting the development of precision immunotherapy [41]. Biomarker screening and precision treatment are key issues that urgently need to be addressed in the current field of combined immunotherapy and radiotherapy/chemotherapy. In the future, by leveraging multi-omics data and artificial intelligence technology, it is possible to develop efficient and accurate predictive models, thereby improving the efficacy and safety of combined immunotherapy and enhancing the guidance of clinical decision-making.

#### *4.2 Optimization of Combination Regimens*

Although the combined application of immunotherapy and radiotherapy/chemotherapy has yielded certain clinical benefits, optimizing combination regimens still presents numerous challenges. First, the combination strategies of different immunotherapeutic drugs, such as CTLA-4 inhibitors and tumor vaccines, with radiotherapy and chemotherapy are still in the exploratory stage. Current clinical practice is mainly based on the combination of PD-1/PD-L1 inhibitors with radiotherapy and chemotherapy [42, 43]. CTLA-4 inhibitors have shown synergistic effects in some solid tumors and are expected to improve efficacy when combined with radiotherapy and chemotherapy in the future, but their toxic side effects and dosing sequence need to be carefully evaluated [44]. As an

active immunization method, tumor vaccines can induce specific T cell responses, and their combination with radiotherapy and chemotherapy may enhance anti-tumor immunity, but relevant clinical data are still limited [45]. Second, the optimization of dosing sequence and dosage is crucial to the combined efficacy and safety. Some studies have shown that the simultaneous administration of immunotherapy and radiotherapy, as well as chemotherapy, is more effective than sequential treatment, which can maximize the activation of the immune system. However, simultaneous treatment may increase immune-related side effects [46, 47]. Adjustments to radiotherapy and chemotherapy dosage also impact immunogenic cell death and the degree of immune activation. Reasonable dosage design helps to improve efficacy and reduce toxicity [48]. Future clinical trials should focus on exploring various combinations of immunotherapeutic drugs, radiotherapy, and chemotherapy dosing regimens, while balancing efficacy and safety, to further optimize combined treatment regimens. Finally, the management of toxic side effects is an important part of optimizing combination therapy regimens. Immunotherapy and radiotherapy/chemotherapy can both cause immune-related adverse events and radiation damage. When used in combination, the toxicity may be superimposed or amplified, requiring the establishment of a sound monitoring and intervention mechanism [49, 50]. Optimizing medication strategies and individualizing adjustments to reduce toxic side effects and improve patients' quality of life are key directions for future optimization of combination therapy regimens.

#### *4.3 Exploration of Novel Immunotherapy Strategies*

With the continuous development of the field of immunotherapy, the application potential of novel

immunotherapy strategies such as cell therapy, bispecific antibodies, and immunomodulatory small molecule drugs in nasopharyngeal carcinoma is gradually emerging. Chimeric antigen receptor T-cell therapy (CAR-T) has made significant breakthroughs in hematological malignancies; however, its efficacy in solid tumors is limited by the inhibition of the tumor immune microenvironment [51]. To overcome this bottleneck, the combined use of CAR-T cells and immune checkpoint inhibitors has been proposed, which can synergistically enhance the anti-tumor effect and improve the treatment effect of solid tumors [52]. Bispecific antibodies, which simultaneously target tumor antigens and T cells, are expected to achieve precise killing of tumor cells, and related clinical trials are currently underway [53]. Immunomodulatory small molecule drugs, as regulators of small molecule targets, can modulate the tumor microenvironment to achieve immune activation or inhibition, and have become an emerging immunotherapy strategy [48]. Their combined use with radiotherapy and chemotherapy can enhance the anti-tumor response through multimodal mechanisms, promoting innovation in treatment models. Multimodal treatment plans integrate radiotherapy and chemotherapy with novel immunotherapy, aiming to overcome tumor immune escape and enhance treatment efficacy through comprehensive, multi-target, and multi-mechanism effects [54]. In the future, with in-depth research in molecular biology and immunology, novel immunotherapy strategies are expected to play a greater role in the treatment of nasopharyngeal carcinoma. Multimodal treatment plans combined with radiotherapy and chemotherapy will lead to innovation in the treatment model of nasopharyngeal carcinoma, improve patient survival rate and quality of life. Clinical translational

research and large-scale clinical trials will be key links in promoting the development of these strategies.

## 5 Conclusion

In summary, immunotherapy combined with radiotherapy and chemotherapy has shown significant clinical value in the treatment of locally advanced nasopharyngeal carcinoma, becoming an important means to break through the bottleneck of traditional treatment. Immunotherapy activates the body's immune system, enhancing its anti-tumor capabilities, while radiotherapy and chemotherapy directly target tumor cells. The two exhibit a synergistic effect in their mechanisms, and this revelation of their immunological basis provides solid theoretical support for clinical applications. However, despite the encouraging results of current research, limitations cannot be ignored. Most clinical trials have limited sample sizes, lacking sufficiently large randomized controlled trials to comprehensively evaluate the long-term effects and potential risks of this combination therapy. Therefore, future research requires further multi-center, large sample randomized controlled trials to validate and solidify existing findings and improve the level of evidence. Through multifaceted efforts, it is hoped that patients with locally advanced nasopharyngeal carcinoma can achieve long-term survival and a better quality of life, ultimately benefiting more patients in the future.

## Conflict of Interest

None.

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None.

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