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REVIEW

Management of Chemotherapy for Stage II Nasopharyngeal Carcinoma in the Intensity-Modulated Radiotherapy Era: A Review

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Peng Wu*
Yumei Zhao*
Li Xiang
Linglin Yang

Department of Oncology, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, People's Republic of China

*These authors contributed equally to this work

Abstract: Nasopharyngeal carcinoma is an endemic disease with a high prevalence in Southeast Asia, Mediterranean countries, and Northern Africa. With substantial advances in screening and diagnosis, increasingly more early-stage (stage I~II) patients are being diagnosed. The undebated treatment modality for stage I patients is radiotherapy alone. However, controversies exist for patients with stage II disease, mostly revolving around the management of chemotherapy. However, the use of intensity-modulated radiotherapy for the treatment of nasopharyngeal carcinoma has increased recently, which has drastically improved survival outcomes. Thus, many oncologists have considered omitting chemotherapy for stage II patients in the intensity-modulated radiotherapy era. Unfortunately, prospective studies comparing concurrent radio-chemotherapy with intensity-modulated radiotherapy alone are limited. Notably, stage II nasopharyngeal carcinoma consists of three subgroups, among which stage T2N1M0 disease is unique and potentially warrants additional treatment including chemotherapy. Additionally, molecular biology techniques are advancing at an incredible speed. Instead of adopting a one-size-fits-all recommendation, exploring potential predictive biomarkers to select patients who are likely to derive benefit from chemotherapy is a better choice. In this review, we summarize the data from studies and reviews regarding chemotherapy for stage II nasopharyngeal carcinoma in the intensity-modulated radiotherapy era and discuss chemotherapy utility. Eventually, we conclude that IMRT alone may be sufficient for stage II nasopharyngeal carcinoma, but this needs to be verified by prospective studies in the near future, the evidence collected thus far suggests that concurrent chemo-radiotherapy without induction or adjuvant chemotherapy is yet to be necessary for patients with stage II disease.

Keywords: stage II nasopharyngeal carcinoma, chemotherapy, intensity-modulated radiotherapy

Introduction

Arising from the nasopharynx epithelium, nasopharyngeal carcinoma (NPC) is quite different from other head and neck squamous cancers due to its biased epidemiology and unique histology. It was reported that an estimated 129,000 new cases of NPC occurred in 2018 according to the International Agency for Research on Cancer (IARC);[1] of all new cases, more than 70% were in Southern China and Southeast Asia.[2] NPC is typically treated with radiotherapy (RT) because of its unique anatomic structure and sensitivity to radiation. Currently, tumor-node-metastasis (TNM) staging is still the critical determinant of treatment strategies. National Comprehensive Cancer Network (NCCN) guidelines recommend that RT

Correspondence: Linglin Yang
Department of Oncology, The Affiliated Hospital of Southwest Medical University, 25 Taiping Road, Luzhou 646000, People's Republic of China
Tel +86 133 8828 3366
Fax +86 083 0316 5396
Email yanglinglin2003@qq.com

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alone be the standard treatment modality for stage I NPC, and concurrent chemo-radiotherapy (CCRT) followed by adjuvant chemotherapy (AC) or induction chemotherapy (IC) followed by CCRT is suggested for stage II~IVB NPC,[3] However, it remains unclear whether chemotherapy is necessary for stage II NPC. In the conventional RT era, the use of CCRT is accepted by most oncologists mainly based on a Phase III randomized clinical trial, which indicated that CCRT could provide prognostic benefits for stage II NPC.[4] However, more researchers are wondering whether chemotherapy is overused in the IMRT era.[5] In addition, three subgroups are included for stage II NPC: T2N0M0, T1N1M0, and T2N1M0. Previous studies have reported that the T2N1M0 subgroup has a greater risk of distant metastasis than the other two groups,[6,7] and additional chemotherapy or other new agents may be needed. Unfortunately, data on individual patients in this subgroup are scarce, and further studies are needed. In addition, exploring some potential molecular biomarkers, including Epstein-Barr virus (EBV), to predict clinical outcomes and guide personalized precision treatment may be helpful.

Treatment Patterns for Stage II NPC

IMRT Alone

It is now well accepted that CCRT remains the cornerstone of treatment for locoregionally advanced NPC.[8] With respect to stage II NPC, the NCCN guidelines are mainly based on a phase III trial performed in the conventional RT era by Chen et al.[4] In that study, 230 patients with stage II disease according to the Chinese 1992 staging system were assigned to receive either RT alone (n=114) or CCRT (n=116). The results revealed that the CCRT arm had a better 5-year overall survival (OS; 94.5% versus 85.8%; *P*=0.007), progression-free survival (PFS; 87.9% versus 77.88%; *P*=0.017), and distant metastasis-free survival (DMFS; 94.8% versus 83.9%; *P*=0.007) than the RT arm, although no statistically significant difference in locoregional relapse-free survival (LRFS; 93.0% versus 91.1%; *P*=0.29) was found between the two arms. Unfortunately, the CCRT arm experienced significantly more acute toxic effects (*P*=0.001), although the increase in the rate of late toxic effects was not statistically significant. However, it is notable that all patients in this trial underwent two-dimensional RT, which is less aggressive and may leave room for the benefits of chemotherapy. The treatment outlook has changed with the advent of intensity-modulated radiotherapy (IMRT), which delivers a conformal and high dose to the target area while restricting the dose to the surrounding organs at risk (OAR) as much as possible.[9] A wealth of studies have shown that IMRT could improve OS mainly by reducing local and regional recurrence rates compared to conventional RT, in addition to resulting in a better quality of life (QOL) and having a more acceptable toxicity for NPC patients.[10–13] Given these findings, some researchers have attempted to explore the effect of IMRT alone for stage II patients with an aim to achieve survival outcomes comparable to those obtained with CCRT but with less associated toxicity.

A retrospective study by Su et al[10] found that IMRT alone yielded very satisfactory survival outcomes for patients with stage II NPC (AJCC/UICC 6th edition), with the 5-year estimated disease-specific survival (DSS), LRFS, and DMFS rates being nearly 100% and a favorable toxicity profile. Given these findings, some clinicians argue that IMRT without concurrent chemotherapy is sufficient for stage II patients, but there is limited high-level evidence due to the lack of large-scale randomized clinical trials comparing CCRT with IMRT alone. Luckily, some researchers have tried to remedy this lack of data.

CCRT versus IMRT Alone

A multicenter Phase II study[14] including 84 stage II NPC patients (according to the AJCC 2010 staging system) demonstrated no treatment improvement after a median follow-up time of 75 months. The 5-year OS, disease-free survival (DFS), primary lesion control (PLC), regional node control (RNC), and DMFS values were 100% versus 94% (*P*=0.25), 90.4% versus 86.6% (*P*=0.72), 93.0% versus 89.3 (*P*=0.79), 97.7% versus 95.1% (*P*=0.54), and 95.2% versus 94.5% (*P*=0.77), respectively, between the IMRT alone arm and the CCRT arm. In addition, more grade 2 to 4 acute WBC toxicity was observed in the CCRT arm. However, this is the only randomized study published to date. Many retrospective studies have been conducted to compare CCRT with IMRT alone in stage II NPC, but the outcomes have been inconsistent. Su et al[15] analyzed 249 patients with stage II disease according to the 7th AJCC/UICC staging system from endemic areas. The results demonstrated that there were no survival benefits in the CCRT group compared to the IMRT alone group, with no significant differences in the 5-year OS (89.7% versus 99.0%, *P*=0.278), LRFS (94.8% versus 89.3%, *P*=0.167), and DMFS (93.4% versus 97.5%, *P*=0.349) values. Additionally, the CCRT group suffered more acute toxic effects related to mucositis (26.6% versus

15.1%, *P*=0.03) and leukopenia/neutropenia (9.1% versus 0.9%, *P*=0.005) than the IMRT alone group. Xu et al[16] retrospectively analyzed a paired cohort to evaluate concurrent chemotherapy in stage T1-2N1 NPC (according to the 6th AJCC/UICC staging system). The study also showed no significant difference in 3-year OS (*P*=0.444), PFS (*P*=0.623), relapse-free survival (RFS) (*P*=0.885), and DMFS (*P*=0.631) between the treatments.

It is worth noting that there are often systematic differences in the distribution of baseline characteristics between treated and untreated arms in retrospective studies. Thus, outcomes cannot be compared directly. Propensity score (PS) matching is an effective technique to adjust bias by creating two cohorts that are equally matched for host and tumor factors, which could mimic a randomized controlled trial.[17] Zhang et al[18] performed PS matching to analyze 448 intermediate-risk NPC patients (stage T1N1M0, T2N0-1M0 or T3N0M0 disease according to the 7th UICC/AJCC staging system), attempting to achieve more reliable results. After PS matching, they found that additional concurrent chemotherapy did not improve the survival outcomes compared to those achieved IMRT alone, with no significant difference in failure-free survival (FFS) (91.2% versus 92.8%, *P*=0.801), LR-FFS (94.4% versus 95.2%, *P*=0.755), D-FFS (96.3% versus 96.4%, *P*=0.803), or OS (98.9% versus 98.2%, *P*=0.276) values. Zhang et al[19] also acquired a similar result with PS matching.

Intriguingly, a study from a nonendemic area demonstrated a different result.[20] In that study, 69 stage I-II NPC patients were analyzed. After a median follow-up of 34 months, the CCRT group exhibited improvements in all endpoints, with significant differences in OS, LRFS, and DMFS values between the groups. Notably, the cases mainly comprised World Health Organization (WHO) type II disease (71%), and it will be important to validate the findings in endemic areas, where WHO type III disease accounts for nearly 95% of cases. In addition, Liu et al[21] performed a meta-analysis comparing CCRT with RT alone for stage II NPC patients treated with IMRT. After the endpoints were merged, no significant survival benefit was observed in terms of OS (HR=1.17, 95% CI, 0.73–1.89, *P*=0.508), PFS (HR= 0.76, 95% CI, 0.38–1.50, *P*=0.430), DMFS (HR=0.89, 95% CI, 0.33–2.41, *P*=0.816), or LRRFS (HR=1.03, 95% CI, 0.95–1.12, *P*=0.498). However, CCRT was associated with higher frequencies of grade 3–4 leukopenia (OR = 4.432, 95% CI, 2.195–8.952, *P*<0.001) than RT alone. Because randomized clinical trials comparing RT alone with CCRT in the IMRT era are thus far limited, current NCCN recommendations lack evidence-based medical evidence. Thus, more prospective studies are needed to provide persuasive evidence for clinical guidance. Several Phase II-III trials (NCT02610010, NCT02116231, and NCT02633202) aiming to evaluate the role of CCRT in stage II NPC patients treated with IMRT are ongoing.[22] The results may encourage guideline changes to the guidelines, and we are looking forward to their outcomes.

Adjuvant or Induction Chemotherapy Combined with IMRT for Stage II NPC

With the landmark Intergroup-0099[23] study finished, the regimen of CCRT with AC has become the standard of care for locoregionally advanced NPC; in this study, 17 patients were categorized as stage II by the newer AJCC staging edition, while the NCCN guidelines gave the same recommendations for stage II NPC patients as for other patients owing to a lack of evidence. Moreover, the remaining controversy surrounding AC lies in its poor compliance and uncertain efficacy for locoregionally advanced NPC;[24,25] as for stage II NPC, concurrent chemotherapy may be overused, and the management of adjuvant chemotherapy also has issues. Nevertheless, some researchers have attempted to assess the efficacy of AC in patients with stage II NPC. Pan et al[26] reviewed 251 stage II (according to the 2010 UICC/AJCC staging system) NPC patients treated with IMRT using the PS matching method. The Kaplan-Meier survival curves showed no significant difference in OS (*P*=0.200), LRFS (*P*=0.204), or DMFS (*P*=0.064) in patients treated with RT alone, CCRT, or CCRT + AC. And Chen et al[27] demonstrated a similar result.

In comparison with AC, IC has several advantages. It has a better tolerance due to its moderate toxicity, which may increase its effectiveness of eradicating micrometastasis when it is combined with subsequent treatment. Moreover, IC was able to shrink tumor volumes to offer a wider field for radiation.[28] However, in the past two decades, the management of IC for locoregionally advanced NPC has been controversial owing to inconsistent outcomes in relevant studies. In a recent Phase III, multicenter, randomized controlled trial,[29] subjects randomly assigned to accept IC (based on the docetaxel, cisplatin and fluorouracil (TPF) regime) together with CCRT had a better 3-year FFS than patients who received CCRT only (HR, 0.68; 95% CI, 0.48–0.97; *P*=0.034) with acceptable and manageable toxicity. A subsequent randomized trial[30] and a pooled analysis[31] confirmed these results. Given these results, the

current NCCN guidelines added a category 2A recommendation for induction chemotherapy for the use of IC in treating locoregionally advanced NPC, whereas this had been a category 3 recommendation in the previous guidelines. However, whether patients with stage II disease could benefit from IC remains unclear, especially in the IMRT era. Recently, Li and Wang examined the efficacy of induction chemotherapy for stage II NPC patients treated with IMRT.[32,33] In the study by Li and colleagues,[32] 173 stage II NPC (according to the 7th edition guidelines) patients enrolled from two institutions were divided into two groups: the IC + CCRT group (ICRT) and the CCRT group. Univariate analyses indicated that ICRT significantly reduced 5-year OS (87.9% versus 95.5%, P=0.033), PFS (74.0% versus 86.1%, P=0.035), and LRFS (80.0% versus 91.2%, P=0.016) values compared CCRT, but no significant difference was found in 5-year DMFS (87.1% versus 94.7%, P=0.095) between the two groups. The authors explained that the unexpected results may have been due to the unbalanced baseline characteristics and additional limitations of the retrospective study. Fangzheng et al[33] found that neither CCRT nor ICRT improved the survival outcomes compared with IMRT alone; moreover, chemotherapy brought more adverse effects than the other treatments. Although the addition of IC to CCRT has yielded favorable clinical outcomes for locoregionally advanced NPC, the efficacy of induction chemotherapy before CCRT or IMRT alone is unknown in stage II NPC, and more studies including prospective clinical trials are warranted to provide support for the utility of induction chemotherapy.

T2N1M0 Subgroup

As mentioned above, three subgroups are included in stage II disease. In the conventional RT era, some studies have reported that survival outcomes are distinct between the three subgroups.[6,7] Given the great improvements in clinical outcomes achieved by IMRT, we wanted to explore whether IMRT could narrow the differences in outcomes between the subgroups. Su et al[10] indicated that stage II patients with IMRT alone exhibited good survival rates, but stage T2bN1 (T2N1 in the newer staging system) disease had a greater risk of distant metastasis than the other stages even though no significant differences were found. Subsequently, Guo et al[34] conducted a larger cohort study with a longer follow-up, and the results indicated that patients in the T2N1 subgroup had poorer survival outcomes than those in the T1N1 subgroup in terms of 5-year OS, DSS, and DMFS, but 5-year LRFS was comparable between the two groups; additionally, the T2N0 subgroup had intermediate values for the survival outcomes. Chen et al[35] also found that most locoregional recurrence (75.00%) and distant metastases (85.71%) occurred in the T2N1M0 subgroup in their study. According to the newer staging system, tumors with extension into the parapharyngeal space belong to stage T2. It is well known that involvement of cervical lymph nodes is a prognostic factor for predicting distant metastasis,[16] but it remains unclear whether parapharyngeal extension is associated with a high risk of distant metastasis in the IMRT era. Therefore, Tang et al[36] reviewed 749 nonmetastatic NPC patients treated with IMRT and found that parapharyngeal extension was a poor prognosticator for DMFS (P=0.015) according to multivariate analysis. Additionally, a significant difference (P<0.001) in DMFS rates was observed between patients with parapharyngeal extension and cervical lymph node metastasis and those with only parapharyngeal extension. Therefore, according to the interpretations above, T2N1M0 disease may be a unique subgroup, and more aggressive treatment interventions may be needed. A recent large-scale retrospective study[37] based on the National Cancer Database indicated that CCRT improved the 5-year OS rate compared with that achieved with radiation only (77.6% versus 53.9%, P=0.0240) for NPC patients with stage T2N1 disease; however, the research subjects were mainly from the United States, and it was a retrospective analysis. Therefore, we need more prospective, multicenter studies to confirm these results. When clinicians administer chemotherapy for stage II patients in the future, determining the correct subgroup should be taken into consideration; however, appropriate chemotherapy use strategies, such as the timing and which agent, are unknown. Well-designed randomized trials are warranted to determine the optimal regimen of chemotherapy for different subgroups of stage II NPC.

EBV DNA: A Potential Biomarker for the Selection of Chemotherapy in Stage II NPC

Advances in new technology and the advent of novel therapies are driving the transformation of treatment strategies to precision medicine, but authoritative guidelines, including NCCN guidelines, are still based on TNM staging, which is anatomy-based. Therefore, there is still a long way to go before personalized therapy can be fully realized. Exploring

potential prognostic biomarkers for NPC has been a hot study topic in recent years, and among the markers, EBV DNA detected in cell-free plasma is the most important.[38] In endemic areas, EBV is highly related to NPC, and many studies have demonstrated that EBV is a critical factor in the pathogenesis of the nonkeratinizing subtype, which accounts for nearly 95% of all patients with NPC cases.[2] In addition, multiple previous studies have revealed that plasma EBV DNA is an available biomarker for population screening,[39] prognostication, prediction of treatment response, and disease surveillance.[40,41] The majority of researchers have focused on the role of EBV DNA in the prognostication of NPC. An early study carried out by Leung et al[42] demonstrated that early-stage NPC patients (stage I~II) with a plasma EBV DNA load above 4,000 copies/mL had a worse 5-year OS than those with an EBV DNA load below the cut-off (64% versus 91%, $P = 0.0003$). Furthermore, a prospective study[43] conducted in Hong Kong indicated that posttreatment (patients subjected to RT or CCRT) EBV DNA was a better prognostic biomarker for NPC. Survival analysis showed that 3-year RFS and OS rates were 48.6% and 69.9% for EBV DVA-positive patients and 85.8% and 94.5% for EBV DVA-negative patients, respectively ($P<0.0001$ for both RFS and OS). Intriguingly, some researchers are attempting to use EBV DNA as a biomarker to select patients who are mostly like to benefit from additive chemotherapy. Most recently, the Hong Kong 0502 trial[44] made a novel attempt. In that study, 789 patients with histologically confirmed NPC underwent EBV DNA screening after curative radiotherapy or chemo-radiotherapy. Patients (n=104) with detectable plasma EBV DNA were randomly assigned to receive AC with cisplatin and gemcitabine (arm 1) or undergo only observation (arm 2). The results showed that there was no significant difference in the 5-year relapse-free survival (RFS) rate between the two arms (49.3% versus 54.7%; $P=0.75$; hazard ratio for relapse or death, 1.09; 95% CI, 0.63 to 1.89) after a median follow-up of 6.6 years, but the study has the potential to influence future research. This is the first study to analyze the use of chemotherapy in high-risk patients with NPC as identified by EBV DNA after curative RT or CCRT. Two other clinical trials (NCT02135042 and NCT02363400) utilizing post-RT EBV DNA levels to guide AC for high-risk advanced NPC patients are ongoing.[28] The results of these trials may help us to demonstrate that post-RT EBV DNA levels can be used to determine the risks of advanced NPC patients for personalized treatments, ultimately potentially leading to a methodology that is the same as that used for early-stage NPC. Unfortunately, there is a lack of evidence, and much work needs to be done.

Conclusion

NPC is not common compared with other cancers, while its incidence rate in southern China and Southeast Asia is pretty high. Nowadays, treatment strategies of NPC are mainly dependent on TNM staging system, RT alone is standard treatment for stage I disease, while chemo-radiation based treatment pattern is recommended and widely accepted for loco-regionally advanced NPC. Currently, a consensus has yet to be reached regarding treatment decisions for NPC patients with stage II disease, and the main debate surrounds the utility of chemotherapy. It is likely that additional concurrent chemotherapy with IMRT does not induce a survival benefit but does lead to an increased amount of adverse effects and decreased QOL. Notably, the results in this review were mainly from retrospective studies, which highlights the necessity for more prospective studies. Even fewer relevant studies have been performed on AC and IC, and their enhanced toxicities compared with that of IMRT and their uncertain efficacy may further limit their use. Stage T2N1M0 disease might be a unique subgroup due to its poor survival outcomes; and more aggressive treatment interventions may be administered, however, large-scale studies are needed to confirm this strategy. In addition, the prognostic value of the post-RT EBV DNA level in early-stage NPC is unclear and worthy of further research.

Disclosure

The authors report no conflicts of interest in this work.

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