Management of Nasopharyngeal Carcinoma: Is Adjuvant Therapy Needed?

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ASSOCIATED CONTENT

See accompanying commentaries on pages 603 and 607

Abstract

Nasopharyngeal carcinoma of the undifferentiated histologic subtype is endemic and prevalent in southeast Asia. The dramatic improvement of treatment outcomes and overall prognosis during the past few decades has been attributed to advances in disease screening and diagnosis, diagnostic imaging, radiotherapy techniques, use of combination systemic therapy, and dedicated clinical and biomarker surveillance. The current practice of treating patients with advanced locoregional disease using cisplatin concurrent with conventional fractionated radiotherapy, followed by adjuvant cisplatin and fluorouracil, was established in 1998 when the landmark Intergroup-0099 Study demonstrated a survival benefit with the addition of systemic therapy.

There is little doubt regarding the need for concurrent chemotherapy, but there has been uncertainty about the magnitude of the benefit attributed to the adjuvant phase. Furthermore, instead of one-size-fits-all recommendations, it will be ideal if we can tailor adjuvant therapy to high-risk patients only to avoid unnecessary toxicities. In addition, recent evidence suggests that induction chemotherapy before concurrent chemoradiation can achieve better outcomes, especially in distant control, even in the modern era of intensity-modulated radiation therapy. This article provides a comprehensive review of key literature on the current management of locoregionally advanced nasopharyngeal carcinoma and highlights future research directions to unravel these controversies.

INTRODUCTION

According to GLOBOCAN 2012, there were 86,691 new cases of nasopharyngeal carcinoma (NPC) and 50,831 deaths worldwide.[1] This cancer shows a skewed geographic and ethnic distribution, with peculiarly high prevalence in southern China and countries in southeast Asia (annual incidence up to 30 per 100,000 persons). NPC contributes to 43.6% of the incidence of all lip, oral cavity, and pharyngeal cancers in eastern and southeast Asia.[2,3]

NPC, particularly the classical nonkeratinizing type, is notorious for its highly malignant behavior with extensive local infiltration, early lymphatic spread, and high propensity for hematogenous dissemination. Disease in the majority of patients is detected in advanced stages. Treatment is especially challenging as a result of the anatomic proximity of critical structures.

RECOMMENDATIONS ON PRIMARY MANAGEMENT OF NPC BY INTERNATIONAL GUIDELINES

The current management for diagnosis and work-up, treatment, and follow-up is largely based on the latest version of two

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major international guidelines, the 2012 European Head & Neck Society–European Society for Medical Oncology–European Society for Radiotherapy and Oncology Clinical Practice Guidelines[4] and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline (version 1.2018).[5] Table 1 summarizes the recommendations from the NCCN and European Head & Neck Society–European Society for Medical Oncology–European Society for Radiotherapy and Oncology guidelines.

CONTROVERSY ABOUT THE NEED FOR CHEMOTHERAPY IN STAGE II NPC

There is an indication for the use of concurrent adjuvant chemotherapy for patients with stage II disease in the NCCN guidelines. This is a result of the original Intergroup-0099 Study being designed for patients with stage III to IVB disease by the American Joint Committee on Cancer/Union for International Cancer Control 4th edition and among whom were patients (n = 17) categorized as stage II by the newer staging editions.[6]

Evidence for the benefit of the addition of chemotherapy is presented by a phase III trial by Chen et al to evaluate concurrent chemotherapy for stage II NPC using the Chinese 1992 system.[7] Of 230 patients studied, 90% had stage II disease and 10% stage III disease by staging criteria from the American Joint Committee on Cancer/Union for International Cancer Control system. Compared with radiotherapy alone, the chemoradiotherapy arm achieved a significant improvement in 5-year overall survival (OS; 95% *v* 86%), progression-free survival (PFS; 88% *v* 78%), and distant failure–free survival (95% vs. 84%), although no improvement in locoregional failure–free survival was achieved. The chemoradiotherapy arm had a significantly higher incidence of grade 3 and 4 acute toxicities (64% *v* 40%), but no excessive increase in late toxicity.

This trial formed the basis for the recommendation of concurrent chemoradiotherapy for patients with stage II disease; however, it should be noted that patients were treated by 2-dimensional radiotherapy and metastatic work-up by conventional scans. The exact magnitude of benefit for patients with stage II disease who were treated with a modern radiotherapy technique and staged with positron emission tomography–computed tomography remained uncertain. A retrospective study by Lee et al demonstrated that 5-year disease-specific survival of 95% could be achieved for patients with stage II disease by radiotherapy alone.[8] More recent studies in the intensity-modulated radiation therapy era further showed excellent results with radiotherapy alone. The 5-year locoregional and distant failure–free rate was almost 100%, and the only subgroup in need of additional attention is those with T2N1 disease with a 5-year distant failure–free rate of 94%.[9] Two recent meta-analyses also suggested that the addition of concurrent chemoradiation to intensity-modulated radiation therapy offered no survival benefit but increased toxicities in stage II disease.[10,11]

The remarkable improvements in the intensity-modulated radiation therapy era can be attributed to both the advancement of imaging techniques for more accurate staging and tumor delineation and the advancement of radiotherapy technologies for better radiation dose coverage and precision of delivery. Intensity-modulated radiation therapy, which uses multiple radiation beams directed to the tumor volumes, coupled with ability to modulate dose intensity within each

Table 1. Recommendations From NCCN and EHNS-ESMO-ESTRO Guidelines

Stage (8th edition)	NCCN (v 1.2018)	EHNS-ESMO-ESTRO (2012)
I	RT alone	RT alone
II	RT+C: Concurrent + adjuvant (2A), concurrent (2B), or induction + concurrent (2B)	RT+C: Concurrent (1B)
III	RT+C: Concurrent + adjuvant (2A), concurrent (2B), or induction + concurrent (2B)	RT+C: Concurrent ± adjuvant (1A)
IVA	RT+C: Concurrent + adjuvant (2A), concurrent (2B), or induction + concurrent (2B)	RT+C: Concurrent ± adjuvant (1A) or induction + concurrent (2B)
IVB	Chemotherapy or RT+C	

Abbreviations: EHNS-ESMO-ESTRO, European Head & Neck Society–European Society for Medical Oncology–European Society for Radiotherapy and Oncology; RT, radiotherapy; RT+C, radiotherapy and chemotherapy.

beam, delivers a highly conformal radiation dose to the entire tumor target compared with previous techniques. These advances thus lead to less reliance on the addition of chemotherapy to eradicate potential microscopic infiltration and micrometastases. The reported meta-analyses demonstrated that intensity-modulated radiation therapy alone could achieve locoregional relapse-free survival and distant metastasis–free survival compared with 2-dimenstional radiotherapy plus concurrent chemotherapy.[10,11]

Additional risk stratification is important. Instead of indiscriminate use of chemotherapy for patients with stage II disease, it is worth considering other prognostic factors, including pretreatment Epstein-Barr virus (EBV) DNA, gross tumor volume, and lactate dehydrogenase to select poor-risk patients for full metastatic work-up and chemotherapy. The study by Leung et al demonstrated that patients with stage I and II disease with high EBV DNA (greater than 4,000 copies) had 5-year OS similar to those with stage III and IV disease with low copies. Hence, these patients may need adjuvant chemotherapy in addition to concurrent chemotherapy, but additional studies are needed for a more definitive recommendation.[12]

VALUE OF CONCURRENT ADJUVANT CHEMOTHERAPY IN LOCOREGIONALLY ADVANCED NPC

The concurrent adjuvant sequence was established in 1998 when the landmark Intergroup 0099 trial first reported significant therapeutic benefit with this regimen. Of 147 patients who were eligible for primary analysis, the concurrent adjuvant arm produced significantly better outcomes than the radiotherapy alone arm both in terms of 3-year PFS (69% *v* 24%; $P < .001$) and OS (78% *v* 47%).[6]

Confirmatory trials from Singapore (Wee et al), Hong Kong (NPC-9901 and NPC-9902 trials by Lee et al), and mainland China (Chen et al) all consistently confirmed the efficacy of concurrent cisplatin plus adjuvant cisplatin-fluorouracil for both event-free survival and OS.[13-17] The recent update of the NPC-9901 trial, with a median follow-up of 13.7 years, further demonstrated that the addition of chemotherapy did not incur a significant excess of late toxicities or noncancer deaths.

The NPC-9901 trial, which focused on patients with N2-3 disease, is the only trial that raised caution for the fact that this regimen may not be adequate for distant control of patients with regionally advanced disease. This was largely attributed to poor tolerance in the adjuvant phase. Most of the trials showed that only approximately 60% of patients could complete three scheduled cycles during the postradiotherapy period when patients are still recovering from acute chemotherapy-radiotherapy toxicities. A combined analysis of patients from the NPC-9901 and NPC-9902 trials who were treated by conventional fractionated radiotherapy demonstrated that concurrent chemotherapy had a significant impact on locoregional control, whereas adjuvant chemotherapy, particularly the dose of fluorouracil, was important for distant control.[18] Recent updates show that patients with two or more cycles in both phases achieved the best outcomes.

ALL ABOUT TIMING: INDUCTION, ADJUVANT, AND CONCURRENT CHEMOTHERAPY

The first individual patient data meta-analysis (MAC-NPC-1) in 2006, which was composed of 1,753 patients from eight of these trials, demonstrated that the addition of chemotherapy resulted in a small but significant overall survival benefit (6% absolute improvement from 56% to 62% at 5 years; hazard ratio [HR] 0.82; 95% CI, 0.71 to 0.94; $P = .006$).[19] The trials on concurrent chemotherapy confirmed a better treatment effect than either induction or adjuvant chemotherapy (HR, 0.60; 95% CI, 0.48 to 0.76 *v* HR, 0.99; 95% CI, 0.80 to 1.21 *v* HR, 0.97; 95% CI, 0.69 to 1.38, respectively). It should be noted that the conclusions on concurrent chemotherapy in the first meta-analysis were based on heterogeneous trials, including the Intergroup 0099 trial[6] that used concurrent adjuvant chemoradiotherapy, the trial by Chan et al[20] (using concurrent chemotherapy with weekly cisplatin), and that by Kwong et al[21] (using concurrent chemotherapy with uracil-tegafur with or without adjuvant chemotherapy with cisplatin-fluorouracil alternating with vincristine-bleomycin-methotrexate). There were then no separate analyses on concurrent adjuvant trials versus concurrent alone trials. The conclusion that adjuvant chemotherapy had no significant benefit was largely based on trials that used sequential adjuvant alone chemotherapy,

The second patient data meta-analysis (MAC-NPC-2), with updated data from previous trials and the inclusion of more randomized controlled trials (RCTs), was published in 2015.[22] A total of 4,806 patients from 19 trials were included (Table 2). Median follow-up duration was 7.7 years. Trials with concurrent adjuvant chemotherapy and those with concurrent alone chemotherapy were analyzed as distinct groups in this meta-analysis compared with MAC-NPC-1. This meta-analysis demonstrated that the addition of chemotherapy to radiotherapy improved OS (6% at 5 years and 8% at 10 years; HR, 0.79; 95% CI, 0.73 to 0.86). Only the subgroup composed of trials that investigated concurrent

Table 2. Summary of Therapeutic Benefit by Addition of Chemotherapy Compared With RT Alone in the MAC-NPC Meta-Analysis

Trial	Stage	RT Technique	Experimental Regimen	Timepoint, Years	EFS Rate, %	*P*	OS Rate, %	*P*
Concurrent								
PWHQEH-94	II-IV (AJCC/UICC 1997)	2D	Concurrent	5	60.2 (PFS)	.06	70.3	.049
QMH-95Conc	II-IV (AJCC/UICC 1997)	2D	Concurrent and adjuvant	3	69.3 (FFS)	.14	86.5	.06
VUMCA-95 (unpublished)	III-IV (AJCC/UICC < 1997)	2D	Induction and concurrent	NA	NA	NA	NA	NA
Guangzhou 2001	III-IV (AJCC/UICC 1997)	2D	Concurrent	5	74.7 (MFS)	.027	73.2	.028
Guangzhou 2002-02	III-IV (Chinese 1992)	2D	Induction and concurrent	5	61.9 (FFS)	.992	70.3	.734
Guangzhou 2003	II-III (AJCC/UICC 2009)	2D	Concurrent	5	87.9 (PFS)	.017	94.5	.007
Concurrent adjuvant								
INT-0099	II-IV (AJCC/UICC < 1997)	2D	Concurrent and adjuvant	3	69 (PFS)	< .001	78	.005
SQNP01	II-IV (AJCC/UICC 1997)	2D	Concurrent and adjuvant	3	72 (DFS)	.0093	80	.0061
NPC-9901	III-IV (AJCC/UICC 1997)	2D, 3D, and IMRT	Concurrent and adjuvant	5	62 (PFS)	.035	68	.22
NPC-9902CF	III-IV (AJCC/UICC 1997)	2D, 3D, and IMRT	Concurrent and adjuvant	3	73 (PFS)	.69	87	.84
NPC-9902AF	III-IV (AJCC/UICC 1997)	2D, 3D, and IMRT	Concurrent and adjuvant	3	88 (PFS)	.061	88	.65
QMH-95Conc^{+}	II-IV (AJCC/UICC 1997)	2D	Concurrent and adjuvant	3	69.9 (FFS)	NA	89	NA
Guangzhou 2002-01	III-IV (AJCC/UICC 1997)	2D	Concurrent and adjuvant	5	72 (FFS)	.02	72	.043
Induction alone								
PWH-88	II-IV (Ho)	2D	Induction and adjuvant	2	68 (DFS)	NS	80	NS
AOCOA	II-IV (AJCC/UICC < 1997)	2D	Induction	3	48 (RFS)	.45	78	.57
VUMCA-89	II-IV (AJCC/UICC < 1997)	2D	Induction	5	NA	< .01	NA	NS
Japan-91	I-IV (AJCC/UICC < 1997)	2D	Induction	5	55 (PFS)	NS	60	NS
NPC008	III-IV (AJCC/UICC 1997)	2D	Induction and concurrent	3	88.2 (PFS)	.12	94.1	.012
HeCOG	II-IV (AJCC/UICC 2002)	3D	Induction and concurrent	3	64.5 (PFS)	.708	66.6	.652
Adjuvant alone								
TCOG-94	III-IV (AJCC/UICC < 1997)	2D	Adjuvant	5	54.4 (RFS)	.38	54.5	.5
QMH-95Adj	II-IV (AJCC/UICC 1997)	2D	Concurrent and adjuvant	3	62.5 (FFS)	.83	80.4	.69
Guangzhou 2006	II-IV (AJCC/UICC 2002)	2D, 3D, and IMRT	Concurrent and adjuvant	5	75 (FFS)	.45	83	.35

Abbreviations: 2D, 2-dimensional; 3D, 3-dimensional; AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer Control; DFS, disease-free survival; EFS, event-free survival; FFS, failure-free survival; IMRT, intensity-modulated radiation therapy; MFS, metastasis-free survival; NA, not available; NS, not significant; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

alone chemotherapy and the subgroup composed of trials on concurrent adjuvant chemotherapy showed significant improvement in both OS and PFS. OS benefit at 5 years was 2.5% (95% CI, −4.2% to 9.2%) by induction chemotherapy, 3.3% (95% CI, −3.8% to 10.4%) by adjuvant chemotherapy, 5.3% (95% CI, 0.8% to 9.8%) by concurrent alone chemotherapy,

and 12.4% (95% CI, 7.0% to 17.8%) by concurrent adjuvant chemotherapy.

As highlighted by the authors, there are major limitations that pertain to MAC-NPC-2, including the heterogeneity of trial designs and chemotherapy regimens, as well as the use of old 2-dimensional radiotherapy techniques in more than three quarters of the study patients. This meta-analysis was also unable to perform a detailed analysis of long-term toxicities because of the data quality and low event rates. The dose-response relationship of cisplatin and treatment outcomes also could not be further evaluated.

Although the benefit of concurrent and adjuvant chemotherapy for all survival outcomes was greatest compared with other treatment modalities, differences in study design between trials on concurrent chemotherapy and those on concurrent adjuvant chemotherapy precluded a dedicated and unbiased comparison of these two chemotherapy schedules. Therefore, this meta-analysis could not conclude with certainty whether there is an advantage in adding adjuvant chemotherapy after concurrent chemotherapy compared with concurrent chemotherapy alone.

On the basis of the updated data from the individual trials, we note that, whereas the trials in the concurrent adjuvant groups demonstrated consistent significant benefit in both PFS and OS, results among the trials that were included in the concurrent alone groups are far less consistent. Only the trial by Chen et al—using cisplatin for stage II disease—and that by Wu et al—using oxaliplatin for stage III and IV disease—achieved significant benefit, the commonly used regimen of cisplatin 40 mg/m^2 per week did not reach statistical significance.[7,23]

The only trial that tried to evaluate the benefit of the adjuvant phase was that by Chen et al which compared concurrent adjuvant chemotherapy-radiotherapy with concurrent alone chemotherapy-radiotherapy. The authors concluded that the adjuvant phase was not needed as the concurrent adjuvant chemotherapy-radiotherapy arm failed to achieve a survival benefit[24,25]; however, it should be noted that 18% of patients did not proceed to receive adjuvant chemotherapy and only 63% completed all cycles of adjuvant chemotherapy. In addition, 69% and 49% of patients who received adjuvant chemotherapy had treatment interruption and subsequent dose reduction, respectively.

A different conclusion was drawn by an individual patient data network meta-analysis, which aimed to answer the question of whether there were survival differences with different timings of chemotherapy.[26] A total of 20 trials until the end of 2010 that were composed of 5,144 patients were included. Concurrent adjuvant chemotherapy achieved the highest effect on OS, with P scores—a higher score meaning a higher probability of being the best treatment—of 96%. This was followed by concurrent alone and induction concurrent treatment schedules with respective P scores of 70% and 63%. Concurrent adjuvant chemotherapy was also ranked as best for PFS, followed by induction concurrent and concurrent alone treatment, with respective P scores of 94%, 79%, and 52%. Concurrent adjuvant chemotherapy achieved significantly better PFS compared with concurrent alone chemotherapy (HR, 0.81; 95% CI, 0.66 to 0.98). Of interest, results suggested that induction-concurrent treatment would be the best treatment of distant control (HR, 0.44; 95% CI, 0.27 to 0.71). However, additional chemotherapy also resulted in more toxicity, as reflected by the highest P scores for mucositis/hearing loss and neutropenia/weight loss after treatment with concurrent adjuvant chemotherapy.

SELECTIVE ADJUVANT CHEMOTHERAPY FOR HIGH-RISK GROUPS

Instead of adding adjuvant chemotherapy to all patients with stage III and IVA disease after radical concurrent chemoradiation, it would be ideal if this is used only in patients with a high risk of failure after concurrent alone chemotherapy. Post–chemotherapy-radiotherapy plasma EBV DNA is most promising marker, and multiple studies have demonstrated that patients with persistent detectable EBV-DNA copies had poor outcomes. Twu et al demonstrated that the addition of adjuvant oral tegafur-uracil for 1 year significantly improved distant control and OS in patients with persistently detectable plasma EBV DNA taken 1 week after the completion of radiotherapy[27]; however, the NPC-0502 Trial showed contrary results. Although post-treatment plasma EBV-DNA was a significant prognostic factor for relapse-free survival and OS, outcomes of patients with detectable plasma EBV DNA at 6 weeks after concurrent chemotherapy-radiotherapy who were randomly assigned to adjuvant chemotherapy with gemcitabine and cisplatin for six cycles was not better than observation alone.[28,29] There are some postulations for the failure of this study. First, repeating the plasma EBV DNA measurement at 6 weeks after treatment may not be the optimal time, and a more discriminating cutoff value may be needed to distinguish high- and low-risk patients. A prospective observational study by Lee et al[30] showed that some

patients took longer time for EBV-DNA to become totally undetectable, the detectable rate decreased to 11.5% between 8 and 16 weeks after radical treatment, and the optimal balance between unnecessary overtreatment versus undesirable delay in the commencement of adjuvant chemotherapy has yet to be defined. Second, the inclusion of stage IIB disease—constituting approximately 24% of the whole study population—may dilute the impact of chemotherapy as these patients may have better prognosis. Third, the unknown and imbalanced distribution of intensity-modulated radiation therapy in the control and experimental arms could also be a contributing factor in the negative result. Finally, the adjuvant phase remains difficult to tolerate.

The combined phase II and III NRG-HN001 trial (ClinicalTrials.gov identifier: NCT02135042) to test the feasibility of using plasma EBV DNA after intensity-modulated radiation therapy to personalize the treatment regimen is now ongoing. The goal for patients with undetectable EBV-DNA 1 week after the completion of concurrent chemotherapy-radiotherapy is to assess whether the adjuvant phase of cisplatin and fluorouracil can be safely omitted, whereas the goal for those with detectable EBV-DNA is to test whether adjuvant chemotherapy can achieve better outcome using gemcitabine and paclitaxel compared with standard cisplatin and fluorouracil. Results are keenly awaited to resolve the current controversy regarding adjuvant chemotherapy.[31]

EMERGING EVIDENCE FOR INDUCTION CONCURRENT SEQUENCE

Induction strategy has theoretical advantages. Induction chemotherapy will be better tolerated, and upfront systemic treatment with potent combination will potentially be more effective in eradicating micrometastasis. Furthermore, this could shrink both the primary tumor and neck nodes to give a wider margin for irradiation, an advantage that is particularly needed for patients with extensive locoregional infiltration that abuts critical neurologic structures.

Despite encouraging results from many phase II studies, the early randomized phase II studies demonstrated conflicting results. The study by Hui et al[32] using cisplatin and docetaxel achieved significantly better 3-year OS but no increase in EFS. Both the study by Fountzilas et al[33] using cisplatin and epirubicin and that by Tan et al[34] using carboplatin, gemcitabine, and paclitaxel were negative compared with concurrent alone treatment.

Recent reports from randomized phase III trials that compared induction concurrent with concurrent alone chemotherapy-radiotherapy showed significant benefit. The trial by Sun et al[35] using modified docetaxel-cisplatin-fluorouracil—with doses at 60, 60, and 600 mg/m^2, respectively—plus concurrent cisplatin achieved significantly better PFS (80% *v* 72% at 3 years) compared with concurrent cisplatin. The trial by Cao et al[36] using induction cisplatin-fluorouracil plus concurrent cisplatin achieved a similar benefit for PFS (82% *v* 74% at 3 years). The GORTEC 2006-01 trial, which used classical docetaxel, cisplatin and fluorouracil—with doses at 70, 70, and 750 mg/m^2, respectively—plus concurrent cisplatin also showed improvement (74% *v* 57% at 3 years).[37]

The Hong Kong NPC-0501 study was the only phase III RCT that directly compared induction chemotherapy with adjuvant chemotherapy in the context of concurrent chemoradiation and conventional/accelerated radiotherapy fractionation.[38] A total of 803 patients were accrued in this six-arm trial to explore the therapeutic benefit of changing the chemotherapy sequence, radiotherapy fractionation, and substitution of fluorouracil with capecitabine. Preliminary 3-year results show that changing radiotherapy fractionation from conventional to accelerated did not provide any benefit but resulted in greater toxicity. Reversing the timing of cisplatin-fluorouracil (PF) from an adjuvant to an induction sequence did not achieve any survival benefit. Of interest, induction cisplatin-capecitabine (PX) demonstrated a favorable PFS compared with adjuvant PF among patients who were irradiated with conventional fractionation (81% *v* 75% at 3 years; $P = .045$). Moreover, induction PX produced fewer acute toxicities—neutropenia and electrolyte disturbance—than did induction PF. The feasibility of induction PX followed by concurrent cisplatin warrants additional validation, and 5-year results will soon be released.

NEW POTENTIAL OPTIONS FOR ADJUVANT THERAPY

The use of targeted therapy against epidermal growth factor receptor and vascular endothelial growth factor and its receptor has also been explored; however, most studies were either retrospective or phase II, and some of the targeted agents used are only available in People's Republic of China[39-43] (Table 3).

The development of immunotherapy brings new exciting opportunities. Hsu et al[44] revealed in their phase Ib multicohort study, KEYNOTE-028, that pembrolizumab, a

Table 3. Selected Studies on the Use of Targeted Therapy as Adjuvant Treatment in Combination With Intensity-Modulated Radiation Therapy for Nasopharyngeal Carcinoma

Trial	Year	Selection	No.	Dose, Gy	No. of Fractions	Chemotherapy, %			Targeted Therapy	3-Year LFFS, %	3-Year RFFS, %	3-Year DMFS, %	3-Year DFS/ PFS/RFS, %	3-Year OS, %
						Concurrent	Induction	Adjuvant						
Lee et al[39]	2012	IIB-IVB	46	70	33	100	No	100	Bevacizumab	83.7 (locoregional; 2 years)		90.8 (2 years)	74.7 (2 years)	90.9 (2 years)
Niu et al[40]	2013	II-IVB	33	66-70.4	30-35	63.6	54.5	18.2	Weekly cetuximab	86.3	83.4	83.6	70.5	90.9
He et al[41]	2013	III-IVB	21	69.75-78	31-38	90	100	33.3	Weekly cetuximab	100 (local control)	100 (regional control)	95.2 (distant control)	NR	NR
Kong et al[42]	2014	I-IVB	364	66-70.4	30-32	25.3	84.1	65.9	Cetuximab (3.6%); nimotuzumab (8.5%)	97.6 (2 years)	96.8 (2 years)	89.1 (2 years)	NR	93.5 (2 years)
Cao et al[43]	2015	T4N0-N3	335	70-76	33	71.3	11.3	6.9	Cetuximab (5.4%); nimotuzumab (20.6%)	84.1 (5 years)	92.2 (3 years and 5 years)	74.1 (5 years)	NR	63.0 (5 years)

Abbreviations: DFS, disease-free survival; DMFS, distant metastasis–free survival; LFFS, local failure-free survival; NR, not reported; OS, overall survival; PFS, progression-free survival; RFFS, regional failure-free survival; RFS, relapse-free survival.

monoclonal antibody against programmed death 1, produced an objective response rate of 25.9% in patients with locally advanced or metastatic NPC. Another multinational phase II study also demonstrated a similar response rate of 20.5% with nivolumab in patients with pretreated recurrent or metastatic NPC.[45] A phase III multicenter RCT that compared pembrolizumab with standard chemotherapy as second- or third-line treatment after experiencing failure with platinum compound in metastatic NPC has just completed patient accrual (KEYNOTE-122; ClinicalTrials.gov identifier: NCT02611960).

In the concurrent with or without adjuvant setting, there are at least two clinical trials on immune checkpoint inhibitors for locoregionally advanced disease. The first is a phase II single-arm study using nivolumab in combination with concurrent chemoradiation with or without adjuvant nivolumab for up to 3 months at different dose schedules (ClinicalTrials.gov identifier: NCT03267498). A phase III multicenter RCT in People's Republic of China on the use of a locally manufactured programmed death 1 monoclonal antibody (SHR-1210) every 4 weeks for 12 cycles starting 4 to 6 weeks after concurrent

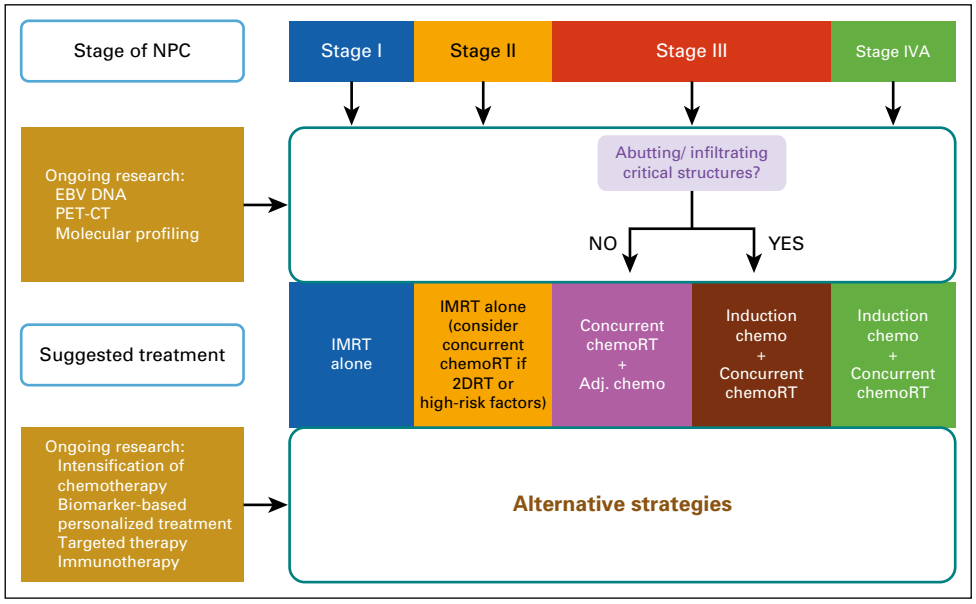

Fig 1. Adjuvant treatment algorithm for nasopharyngeal carcinoma (NPC) modified from European Head & Neck Society–European Society for Medical Oncology–European Society for Radiotherapy and Oncology Clinical Practice Guidelines (2012) and the NCCN Clinical Practice Guideline (version 1.2018). 2DRT, 2-dimensional radiation therapy; chemoRT, chemoradiation; EBV, Epstein-Barr virus; IMRT, intensity-modulated radiation therapy; PET-CT, positron emission tomography–computed tomography.

chemoradiation for stage III and IVA NPC versus no adjuvant therapy is ongoing (ClinicalTrials.gov identifier: NCT03427827).

Until now, there have not been reliable potential predictive and prognostic biomarkers with which to select patients with a higher chance of response to immunotherapy. The expression level of programmed death ligand 1 as a predictive/prognostic marker after treatment with nivolumab in metastatic head and neck squamous cell carcinoma cannot be directly extrapolated to NPC.[46]

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

With current evidence, the addition of concurrent cisplatin plus adjuvant PF to conventional fractionated radiotherapy remains the regimen with level 1 evidence for patients with locoregionally advanced NPC; however, poor tolerance of the adjuvant phase remains a concern and this affects the impact of the regimen, especially for distant control. Induction concurrent chemotherapy is an effective option (level 2A evidence), but whether this is superior to concurrent adjuvant chemotherapy has not yet been determined. The algorithm for clinical approaches for different stages is shown in Figure 1.

It will be ideal to avoid the indiscriminate addition of the adjuvant phase by using prognostic markers, such as EBV-DNA, but more studies are needed to define the optimal timing of the test, the best cutoff value, and the most potent and tolerable systemic therapy. With encouraging results from the addition of immunotherapy in the adjuvant phase for non–small-cell carcinoma and melanoma, trials specific for NPC are keenly awaited. However, the search for an accurate predictive marker is fundamental, and the indiscriminate use of immunotherapy is even more undesirable as the response rate is probably less than 30%.

Furthermore, it is crucial to work toward personalized precision treatment with more accurate risk stratification. In addition to anatomic TNM staging and parameters available in the clinic, including primary tumor volume,[47] serum lactate dehydrogenase,[48] and plasma EBV-DNA, exploration of additional novel nonanatomic factors, including comprehensive genomic profiling, radiomic, and other biomarkers, are ongoing. In addition, basic improvement in radiotherapy by consistent use of the standardized international guideline on target volume delineation is fundamental for future development.[49] Close collaboration between clinicians and scientists in continued efforts to explore more potent and/or less toxic therapy tailored for the individual patient is always in demand. JOP

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Nasopharyngeal Carcinoma: Is Adjuvant Therapy Needed?

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