



Induction chemotherapy plus IMRT alone versus induction chemotherapy plus IMRT-based concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: a retrospective cohort study

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Abstract

Background To evaluate the value of concurrent chemotherapy after induction chemotherapy for locoregionally advanced nasopharyngeal carcinoma (NPC) in the era of intensity-modulated radiation therapy (IMRT), we performed this retrospective cohort study to compare the efficiency and toxicities of induction chemotherapy plus IMRT alone (IC + RT) versus induction chemotherapy plus IMRT-based concurrent chemoradiotherapy (IC + CCRT).

Method We analyzed data from patients with locoregionally advanced NPC (stage III–IVb) who were treated at the West China hospital between January 2008 and December 2014. Patients received docetaxel, cisplatin, and 5-fluorouracil (TPF) IC followed by IMRT alone (IC + RT group) or IMRT plus cisplatin concurrent chemotherapy (IC + CCRT group). The main endpoint was overall survival (OS), which was evaluated by the Kaplan–Meier method and log-rank test. Multivariate Cox proportional hazard analysis was used to identify potential independent prognostic factors. Treatment-associated toxicities were compared between groups using the Chi squared test.

Results A total of 78 patients treated with IC + RT and 76 with IC + CCRT were analyzed. The median follow-up time was 59 months (range: 7–108 months). There was no difference between patients treated with IC + RT and IC + CCRT in terms of 3-year OS (89.0% versus 88.0%, $p = 0.286$), progression-free survival (76.8% versus 80.0%, $p = 0.142$), locoregional recurrence-free survival (87.1% versus 90.5%, $p = 0.156$), or distant metastasis-free survival (83.6% versus 82.6%, $p = 0.567$). Treatment (IC + RT versus IC + CCRT) was not an independent prognostic factor for OS (HR 1.425, 95% CI 0.698–2.908; $p = 0.331$). IC + CCRT was associated with a higher incidence of grade 3–4 neutropenia than IC + RT during radiotherapy (11.8% versus 1.3%, $p = 0.020$).

Conclusion IC plus IMRT alone achieves similar patient survival outcomes as IC plus IMRT-based concurrent chemoradiotherapy, and has a lower incidence of toxicity.

Keywords Nasopharyngeal carcinoma · Induction chemotherapy · Concurrent chemotherapy · IMRT

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Introduction

Nasopharyngeal carcinoma (NPC) is a common squamous cell carcinoma of the nasopharyngeal epithelial tissues. NPC is ethnically specific and is widespread in East Asia, Southeast Asia, North Africa, and Alaska (Chua et al. 2016; Wei and Sham 2005). As many as 71% of newly diagnosed nasopharyngeal cancers in 2012 occurred in East Asia and Southeast Asia (Torre et al. 2015). Genetic, ethnic, and environmental factors (such as Epstein–Barr

virus infection) all play a role in the pathogenesis of NPC (Wei and Sham 2005).

The standard treatment for NPC is radiotherapy (Wei and Sham 2005). For early stage NPC, local tumor control and long-term survival can be achieved by radiotherapy alone. However, 60–70% of newly diagnosed NPC patients are locoregionally advanced cases (stage III–IVb) (Mao et al. 2009). For these patients, radiotherapy alone achieves a 5-year overall survival (OS) of only 67–77% (Yi et al. 2006). Distant metastasis remains one of the primary reasons for treatment failure. Therefore, locally advanced NPC is often treated using a combination of radiotherapy and chemotherapy.

Chemotherapy treatments that have been used to treat locally advanced NPC include cisplatin-based concurrent chemoradiotherapy (CCRT) combined with either induction chemotherapy (IC) or adjuvant chemotherapy. Many clinical studies have found that IC plus CCRT improved the survival of patients with locally advanced NPC (Hui et al. 2009; Kong et al. 2013; Sun et al. 2016). However, the optimal strategy for combining chemotherapy and IMRT is still unclear, especially since treatment with concurrent chemotherapy after IC can also increase treatment-related toxicities, leading some patients to discontinue radiotherapy. Discontinuing or prolonging treatment can reduce radiotherapy efficacy (Kwong et al. 1997).

The benefits of concurrent chemotherapy with modern radiotherapy techniques such as intensity-modulated radiation therapy (IMRT) are also unclear (Sun et al. 2014; Cao et al. 2015; Xie et al. 2016). A study of 603 patients with stage III–IVb NPC treated with IMRT with or without concurrent chemotherapy found that concurrent chemotherapy increased the incidence of treatment-related toxicities without providing additional survival benefit (Sun et al. 2014). In contrast, another study in patients with stage T4/N2 NPC reported that those who were treated with concurrent chemotherapy and IMRT had a higher 5-year OS rate than patients without concurrent chemotherapy, despite also experiencing increased toxicity (Xie et al. 2016).

In this study, we aimed to evaluate the therapeutic value of IMRT alone after IC in patients with stage III–IVb NPC.

Methods

Patients

Patients with locoregionally advanced NPC who were treated at the West China hospital between January 2008 and December 2014 were retrospectively analyzed. Patients were included if they had stage III–IVb NPC, as defined

according to the 7th edition of the American Joint Committee on Cancer (AJCC) stage criteria (Edge and Compton 2010); if their diagnosis was confirmed by histopathology; and if they had received either IC plus IMRT (IC + RT) or IC combined with IMRT-based CCRT (IC + CCRT). Patients were excluded if their NPC was in stage IVc, I, or II; if they had a second primary tumor or history of malignant tumors; if they were receiving adjuvant chemotherapy or treatment against epidermal growth factor receptor (EGFR) at the time of the study; or if they did not receive IC. Written informed consent was obtained from all patients included in the study.

Chemotherapy and radiotherapy

All patients were treated with IC according to the docetaxel, cisplatin and fluorouracil (TPF) regimen. Patients were given docetaxel (75 mg/m²) and cisplatin (75 mg/m²) on day 1 and 5-fluorouracil (750 mg/m²) on days 1–5 every 3 weeks for three cycles. Patients in the IC + CCRT group were also given cisplatin (100 mg/m²) every 3 weeks. Both groups received IMRT for nasopharyngeal and cervical lymph nodes after IC using the step-and-shoot technique at an X-ray dose of 6-MV. Image-guided radiotherapy (IGRT) is not recommended routinely because positioning error of nasopharyngeal carcinoma is quite low. It was considered mainly according to the wishes of the patients.

We defined primary and nodal gross tumor volume (GTV) as all gross masses visualized on computed tomography (CT) and/or magnetic resonance imaging (MRI). The high-risk clinical tumor volume (CTV-1) was defined as the GTV plus a 5–10 mm margin, and encompassed the entire nasopharyngeal mucosa plus a 5-mm submucosal volume. The CTV-2 was designed to include regions with potential involvement as previously described (Sun et al. 2016).

A total dose of 70–74 Gy was applied to the GTV in 33 fractions (2.12–2.24 Gy/fraction), while 60 Gy was applied to CTV-1, and 54 Gy to CTV-2. Both patient groups were treated with one fraction daily, five times per week.

Follow-up

Blood cell counts and serum chemistry profiles were examined weekly during IC and radiotherapy. Therapy-related toxicities were evaluated according to the common terminology criteria for adverse events (CTCAE 4.0). All patients were followed-up every 3 months in the first 2 years after completion of treatment, then every 4–6 months until 5 years, and annually thereafter. Follow-up visits included a complete physical examination, measurement of serum chemistry profiles, Epstein–Barr viral DNA test, abdominal ultrasound, endoscopy, and MRI or CT of the head and neck as necessary.

Table 1 Baseline clinicopathological characteristics of NPC patients

Characteristic	Total (n = 154)	IC + RT (n = 78)	IC + CCRT (n = 76)	p value
Age, year				0.198
< 45	59 (38.3)	26 (33.3)	33 (43.4)	
≥ 45	95 (61.7)	52 (66.7)	43 (56.6)	
Gender				0.087
Male	112 (72.7)	52 (66.7)	60 (78.9)	
Female	42 (27.3)	26 (33.3)	16 (21.1)	
T group				0.208
T1/T2	35 (22.7)	21 (26.9)	14 (18.4)	
T3/T4	119 (77.3)	57 (73.1)	62 (81.6)	
N group				0.410
N0/N1	70 (45.5)	38 (48.7)	32 (42.1)	
N2/N3	84 (54.5)	40 (51.3)	44 (57.9)	
TNM stage				0.633
III	80 (51.9)	42 (53.8)	38 (50.0)	
IVa/IVb	74 (48.1)	36 (46.2)	38 (50.0)	
ECOG Score				0.446
0	139 (90.3)	69 (88.5)	70 (92.1)	
1	15 (9.7)	9 (11.5)	6 (7.9)	
CCI				0.474
≤ 4	137 (89.0)	68 (87.2)	69 (90.8)	
> 4	17 (11.0)	10 (12.8)	7 (9.2)	
Mean cumulative cisplatin dose ^a , mg		347 ± 38	336 ± 37	0.081

Values are n (%)

CCI Charlson Comorbidity Index, CCRT concurrent chemoradiotherapy, ECOG Eastern Cooperative Oncology Group, IC induction chemotherapy, RT radiotherapy

^aDuring induction chemotherapy

Outcomes

The primary endpoint was overall survival (OS), calculated as the time from start of treatment until death from any cause. Secondary endpoints included progression-free survival (PFS), locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and toxicity. PFS was defined as the time from start of treatment until disease progression. LRFS was defined as the time from start of treatment until recurrence in the nasopharyngeal or neck area. DMFS was defined as the time from start of treatment until detection of distant metastasis.

Statistical analysis

Statistical analysis was performed using SPSS 24.0 software (IBM, USA), and a two-sided *p* value of < 0.05 was considered statistically significant. Baseline characteristics and the incidence of adverse events between groups were compared using the Chi squared test. The Kaplan–Meier test was used to calculate OS, PFS, LRFS and DMFS. The log-rank test was used to compare survival curves between

groups. Multivariate Cox proportional hazard analysis was used to determine the predictive value of treatment, age, gender, and tumor stage on OS.

Results

Clinical characteristics

A total of 154 eligible patients were included. Of these, 78 were treated with IC + RT and 76 were treated with IC + CCRT. The median age was 47 years (range 14–77 years). In total, 77.3% of patients were classified as T3/T4, while 22.7% were classified as T1/T2. More patients were diagnosed with N2/N3 (54.5%) than N0/N1 (45.5%). Eighty patients (51.9%) were diagnosed with stage III and 74 (48.1%) with stage IVa/IVb NPC. The IC + RT group contained 42 cases (53.8%) with stage III and 36 (46.2%) with stage IVa/IVb NPC. The IC + CCRT group contained 38 patients (50%) with stage III and 38 (50%) with stage IVa/IVb NPC. The baseline clinical characteristics of each group are shown in Table 1.

Table 2 Patient survival (%) at 1 year and 3 years after treatment

Survival outcome	IC + RT (<i>n</i> = 78)	IC + CCRT (<i>n</i> = 76)	<i>p</i> value
OS			0.286
At 1 year	98.7	97.4	
At 3 years	89.0	88.0	
PFS			0.142
At 1 year	94.8	89.4	
At 3 years	76.8	80.0	
LRFS			0.156
At 1 year	100.0	94.7	
At 3 years	87.1	90.5	
DMFS			0.567
At 1 year	94.8	90.7	
At 3 years	83.6	82.6	

CCRT concurrent chemoradiotherapy, DMFS distant metastasis-free survival, IC induction chemotherapy, LRFS locoregional recurrence-free survival, OS overall survival, PFS progression-free survival, RT radiotherapy

Treatment outcomes

Fifty-four (71.1%) patients in the IC + CCRT group and 51 (65.4%) in the IC + RT group successfully completed three cycles of IC ($p = 0.450$). The remaining patients were treated with two cycles of IC. The median cumulative dose of cisplatin in the IC + CCRT group was 240 mg/m².

The median follow-up time was 59 months (range 7–108 months). During this time, 21 patients (26.9%) died in the IC + RT group and 14 (18.4%) died in the IC + CCRT group. Patient survival at 1 and 3 years is shown in Table 2. There was no significant difference in OS between the IC + RT and IC + CCRT groups at 1 or 3 years ($p = 0.286$). In the IC + RT group, 28 cases (35.9%) experienced disease progression, and 18 cases (23.7%) developed disease in the IC + CCRT group. There was no significant difference in PFS, LRFS, or DMFS between the IC + RT and IC + CCRT groups at 3 years (Table 2). Survival curves are shown in Fig. 1.

Patient OS by age (≥ 45 years versus < 45 years), gender (male versus female), T stage (T1/T2 versus T3/T4), N stage (N0/N1 versus N2/N3) and clinical stage (III versus IVa/IVb) is shown in Table 3. We did not find any significant difference in OS between patients treated by IC + RT or IC + CCRT in each subgroup.

Prognostic analysis

Multivariate Cox proportional hazard analysis was performed to evaluate the potential effects of treatment group, patient age and sex, and tumor stage on OS. None of the tested factors (including treatment regimen) were found to

be prognostic for OS (Table 4). There were also no significant correlations between the tested factors and PFS, LRFS, or DMFS (Table 5).

Adverse events

The most frequently observed grade 3–4 hematologic toxicity during IC was neutropenia, which occurred in 12 patients (15.8%) in the IC + CCRT group and 20 patients (25.6%) in the IC + RT group (Table 6). There was no difference in the incidence of adverse events during IC between the two treatment groups. However, the incidence of grade 3–4 neutropenia was higher during radiotherapy in the IC + CCRT group (11.8%) than the IC + RT group (1.3%, $p = 0.020$). There was no difference in the incidence of thrombocytopenia during radiotherapy between the two groups. No patients suffered grade 3–4 liver damage during radiotherapy. Among non-hematological toxicities, patients in the IC + CCRT group had a higher incidence of grade 3–4 nausea or vomiting than patients in the IC + RT group (17.1% versus 5.1%, $p = 0.018$).

Discussion

In this study, we investigated the effect of combining IC with IMRT alone in the treatment of advanced NPC. We found that IC plus IMRT alone offered similar survival benefit over IC plus IMRT-based concurrent chemoradiotherapy in our cohort.

A previous trial reported that adding chemotherapy to radiotherapy increased 3 year PFS by 45% and 3-year OS by 31% in patients with stage III/IV NPC (Al-Sarraf et al. 1998). This finding has been supported by several studies, and chemotherapy has since become an integral part of the treatment regimen for NPC. Chemotherapy provides better local and regional control by increasing radio-sensitivity, and improves survival by eliminating subclinical metastatic sites. Nevertheless, the most effective way to combine chemotherapy with radiotherapy remains controversial (Blanchard et al. 2015; Wang et al. 2015; Ribassin-Majed et al. 2017; Zhang et al. 2010).

IC is considered to be more effective than adjuvant chemotherapy which can be associated with poor patient compliance (Chua et al. 2016). A prospective, randomized, multicenter, phase 3 trial reported that patients with locoregionally advanced NPC treated with IC plus concurrent chemoradiotherapy had significantly longer 3 year DFS, OS, and DMFS than those treated with concurrent chemoradiotherapy alone (Sun et al. 2016). The incidence of grade 3–4 neutropenia was also much higher in patients treated with IC plus concurrent chemoradiotherapy group (42%) than in patients treated with

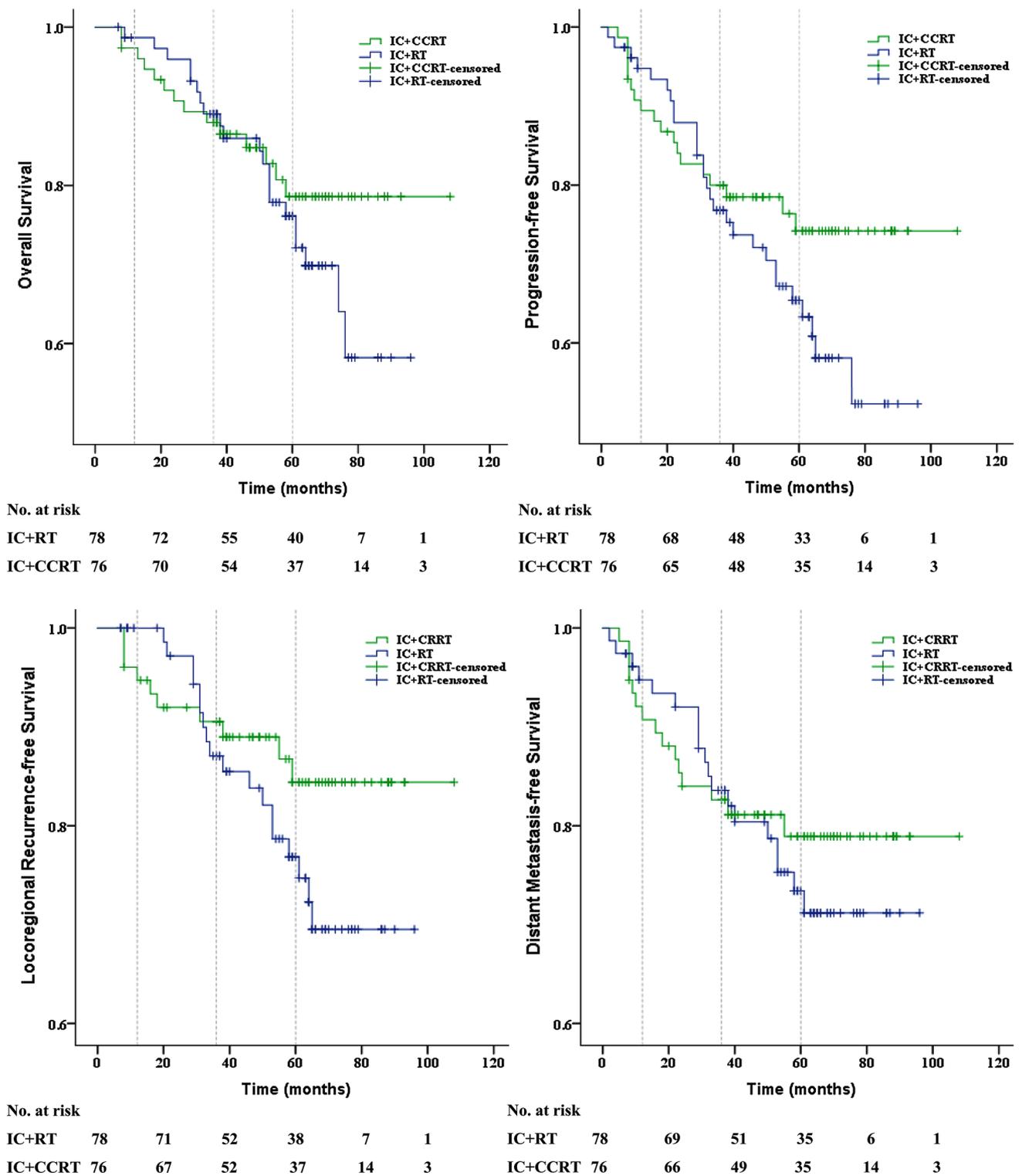


Fig. 1 Kaplan–Meier curves of overall survival, progression-free survival, locoregional recurrence-free survival, and distant metastasis-free survival in NPC patients treated with IC + RT or IC + CCRT

concurrent chemoradiotherapy alone (7%), suggesting increased toxicity.

Several studies report that combining concurrent chemotherapy and radiotherapy increases the risk of treatment-associated complications. Patient intolerance to these

Table 3 Overall survival in NPC patients treated with IC + RT or IC + CCRT, stratified by age, sex, or tumor stage

Subgroup	IC+RT	IC+CCRT	Hazard ratio (95 %CI)	p-value	Forest plot
Total	78	76	1.442 (0.732-2.839)	0.290	
Age					
≥ 45y	52	43	1.749 (0.759-4.031)	0.189	
< 45y	26	33	0.661 (0.164-2.653)	0.559	
Gender					
Male	52	60	2.142 (0.980-4.680)	0.056	
Female	26	16	0.422 (0.103-1.727)	0.230	
T group					
T1/T2	21	14	1.414 (0.258-7.758)	0.690	
T3/T4	57	62	1.580 (0.749-3.330)	0.229	
N group					
N0/N1	38	32	2.825 (0.910-8.772)	0.072	
N2/N3	40	44	0.877 (0.355-2.165)	0.776	
TNM stage					
III	42	38	1.769 (0.441-7.094)	0.421	
IVa/IVb	36	38	1.355 (0.622-2.950)	0.445	

CI confidence interval, CCRT concurrent chemoradiotherapy, IC induction chemotherapy, RT radiotherapy

Table 4 Multivariate analysis of the associations between overall survival and clinicodemographic variables

Variable	Hazard ratio	95% CI	p value
Age (< 45 versus ≥ 45 years)	0.589	0.273–1.274	0.179
Gender (female versus male)	0.838	0.369–1.903	0.673
T group (T1/T2 versus T3/T4)	0.724	0.275–1.909	0.514
N group (N0/N1 versus N2/N3)	0.967	0.459–2.038	0.929
Treatment (IC + RT versus IC + CCRT)	1.425	0.698–2.908	0.331

CI confidence interval, CCRT concurrent chemoradiotherapy, IC induction chemotherapy, RT radiotherapy

Table 5 Multivariate analysis of associations of PFS, LRFS, or DMFS with clinicodemographic variables

Variable	PFS	LRFS	DMFS
Age (< 45 versus ≥ 45 years)	0.539	0.883	0.331
Gender (male versus female)	0.947	0.663	0.775
T group (T1/T2 versus T3/T4)	0.765	0.197	0.757
N group (N0/N1 versus N2/N3)	0.450	0.775	0.960
Treatment (IC + CCRT versus IC + RT)	0.220	0.164	0.728

All results are p values

CCRT concurrent chemoradiotherapy, DMFS distant metastasis-free survival, IC induction chemotherapy, LRFS locoregional recurrence-free survival, PFS progression-free survival, RT radiotherapy

adverse effects limits the usefulness of concurrent chemoradiation. Retrospective studies investigating the benefits of using concurrent chemotherapy during IMRT have yielded

varying results, with some studies reporting no survival benefit for patients with stage III/IVa–b NPC, (Sun et al. 2014), while others reported that the addition of concurrent chemotherapy to IMRT improved treatment outcomes in patients with T4 and N2 NPC (Xie et al. 2016).

The benefits of combining IC with IMRT are also unclear. A retrospective study in 370 patients with locoregionally advanced NPC reported that IC + CCRT did not improve 3-year local/regional control, DFS, and OS compared to IC + IMRT alone (Lin et al. 2010). However, it should be noted that the IC regimen was not uniformly applied in that study. And another small retrospective study also found no difference in 3-year OS, DMFS, LRFS, or PFS between patients treated with IC + IMRT and those treated with IC + CCRT (Zhang et al. 2015).

Table 6 Frequency of treatment-related grade 3–4 adverse events during induction chemotherapy and radiotherapy in NPC patients

Adverse event	Total (n = 154)	IC + RT (n = 78)	IC + CCRT (n = 76)	p value
During induction chemotherapy				
Neutropenia	32 (20.8)	20 (25.6)	12 (15.8)	0.132
Thrombocytopenia	4 (2.6)	4 (5.1)	0 (0.0)	0.135
Liver dysfunction	2 (1.3)	2 (2.6)	0 (0.0)	0.497
During radiotherapy				
Neutropenia	10 (6.5)	1 (1.3)	9 (11.8)	0.020*
Thrombocytopenia	4 (2.6)	1 (1.3)	3 (3.9)	0.594
Liver dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	–
Xerostomia	49 (31.8)	26 (33.3)	24 (31.6)	0.816
Nausea/vomiting	17 (11.0)	4 (5.1)	13 (17.1)	0.018*
Stomatitis/mucositis	61 (39.6)	27 (34.6)	34 (44.7)	0.199
Dermatitis	9 (5.8)	5 (6.4)	4 (5.3)	0.762
Esophagitis	0 (0.0)	0 (0.0)	0 (0.0)	–
Discontinuation of radiotherapy ^a	47 (30.5)	25 (32.1)	22 (28.9)	0.676

Values are n (%)

CCRT concurrent chemoradiotherapy, IC induction chemotherapy, RT radiotherapy

* $p < 0.05$

^aBecause of treatment-related toxicity

Our study shows that adding concurrent chemotherapy to IMRT after IC did not improve OS, PFS, LRFS, or DMFS in NPC patients. These results are consistent with those of previous studies (Lin et al. 2010; Zhang et al. 2015). Subgroup analysis further showed no survival difference between patient groups, regardless of age, sex, or tumor stage.

IMRT is known to improve local and regional control compared with conventional two-dimensional radiation therapy (Chua et al. 2016). Despite this, IMRT may be ineffective at reducing distant metastasis in locally advanced NPC (Kam et al. 2004; Tham et al. 2009). In our study, the main cause of patient death was metastasis: 3-year DMFS was lower than LRFS in both treatment groups. New strategies combining different treatment modalities should be explored to improve control of distant metastasis.

The main limitation of our study is the retrospective design. Another limitation is that all patients in this study were from a single center, and the sample was small; thus the results of this study may not be representative of all NPC patients. Last, our study did not include an analysis of patient treatment response, which is also an important factor in choosing treatment.

Conclusion

IC plus IMRT alone appears to provide similar survival benefit over IMRT-based chemoradiotherapy combined with IC in patients with locally advanced NPC. At the same time, IMRT alone combined with IC may be associated with lower

incidence of treatment-related adverse events. These results need to be validated and extended in prospective studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics statement All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the West China Hospital Human Research Ethics Committee.

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