Translational Oncology 14 (2021) 100990

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Original Research

The effect of adding concurrent chemotherapy to radiotherapy for stage II nasopharyngeal carcinoma with undetectable pretreatment Epstein-Barr virus DNA: Retrospective analysis with a large institutional-based cohort

Ya-Nan Jin[a,1], Qing-Nan Tang[b,1], Ji-Jin Yao[c,1], Xi-Wei Xu[c], Wen-Zhuo He[a], Lei Wang[a], Ya-Fei You[a], Kun-Wei Peng[a], Chang Jiang[a,*], Liang-Ping Xia[a,*]

[a] VIP Region, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, Guangdong, China
[b] Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, Guangdong, China
[c] Department of Head and Neck Oncology, the Fifth Affiliated Hospital of Sun Yat-sen University, Guangdong Provincial Key Laboratory of Biomedical Imaging, Zhuhai 519001, Guangdong, China

ARTICLE INFO

Keyword:
Nasopharyngeal carcinoma
Epstein–Barr virus DNA
Survival
Intensity-modulated radiotherapy
Concurrent chemotherapy
Effect

ABSTRACT

Little is known about the value of adding concurrent chemotherapy (CC) to radiotherapy for stage II nasopharyngeal carcinoma (NPC) with undetectable (0 copies/mL) pretreatment Epstein-Barr Virus (EBV) DNA in the intensity-modulated radiotherapy (IMRT) era. To address this question, the present study retrospectively reviewed 514 patients with newly diagnosed stage II NPC and undetectable pretreatment EBV DNA from Sun Yat-sen University Cancer Center between March 2008 and October 2016. Clinical characteristics and survival outcomes between concurrent chemoradiotherapy (CCRT) and IMRT alone groups were compared. Propensity score matching analysis was conducted to control for confounding factors. Although CCRT group had significantly higher proportions of stage N1 disease than IMRT alone group before matching (85% vs. 61%, $p < 0.001$), no statistically significant differences were noted for OS (97.8% vs. 98.1%, $p = 0.700$), DFS (93.4% vs. 94.5%, $p = 0.846$), DMFS (96.0% vs. 96.9%, $p = 0.762$), and LRFS (97.3% vs. 98.1%, $p = 0.701$). After 1:1 propensity-score matching, 177 pairs were identified. Patients in each group were found to be well balanced in baseline characteristics and risk factors (all $P > 0.05$). The five-year OS (96.9% vs. 98.2%, $p = 0.302$), DFS (92.0% vs. 95.2%, $p = 0.777$), DMFS (95.2% vs. 97.6%, $p = 0.896$), and LRFS (97.3% vs. 97.6%, $p = 0.328$) rates remain comparable for both CCRT and RT alone groups. Additionally, subgroup analysis still failed to observe any significant survival benefit for the addition of CC to IMRT for N1 disease ($P > 0.05$ for all). Our results indicated that IMRT alone appeared to achieve comparable survival to CCRT for stage II NPC with undetectable pretreatment EBV DNA.

Introduction

A report by the International Agency for Research on Cancer (IARC) estimated that in 2018, there were 129,079 new cases of nasopharyngeal carcinoma (NPC) around the world, where 47.7% of cases were in Southern China [1]. Radiotherapy (RT) is considered the only curative starter for non-disseminated disease due to the anatomic constrains and its high degree of radio-sensitivity. Previous studies including clinical trials and systematic reviews have reported that the addition of concurrent chemotherapy (CC) to RT (CCRT) could improve survivorship for stage III-IV NPC without distant metastasis [2,3]. However, the impact of CC for stage II disease remains not well understood.

Currently, prospective clinical studies on treatment strategy for stage II NPC remain limited. In a Phase III Trial, Chen et al. observed that the inclusion of CC to RT was statistically associated with better clinical outcomes for stage II NPC [4]. However, this study was based on two-dimensional conventional RT (2D-CRT). Gradually, 2D-CRT is being replaced because of advances in radiation technology. Intensity-modulated RT (IMRT) is currently the primary means of RT due to superior locoregional control and improved long-term survival for patients with NPC [5]. Two studies in the IMRT era documented that the addition

* Corresponding authors.
E-mail addresses: jiangchang@sysucc.org.cn (C. Jiang), xialp@sysucc.org.cn (L.-P. Xia).
[1] The authors contributed equally to this work.

https://doi.org/10.1016/j.tranon.2020.100990
Received 25 July 2020; Received in revised form 6 December 2020; Accepted 7 December 2020

Table 1
Baseline characteristics in two groups before matching.

Characteristic	Total ($N = 514$)	RT alone ($N = 218$)	CCRT ($N = 296$)	*p*value
Gender				
Male	376 (73.2)	149 (68.3)	227 (76.7)	0.054
Female	138 (26.8)	69 (31.7)	69 (23.3)	
Age, year				
<50	319 (62.1)	133 (61.0)	186 (62.8)	0.726
≥50	195 (37.9)	85 (39.0)	110 (37.2)	
T stage (8th edition)				
T1	199 (38.7)	80 (36.7)	119 (40.2)	0.483
T2	315 (61.3)	138 (63.3)	177 (59.8)	
N stage (8th edition)				
N0	129 (25.1)	85 (39.0)	44 (14.86)	<0.001
N1	385 (74.9)	133 (61.0)	252 (85.14)	
Smoking history				
No	370 (72.0)	160 (73.4)	210 (70.9)	0.582
Yes	144 (28.0)	58 (26.6)	86 (29.1)	
Family of cancer				
No	328 (63.8)	132 (60.6)	196 (66.2)	0.218
Yes	186 (36.2)	86 (39.4)	100 (33.8)	
HGB, g/L				
<113	16 (3.1)	7 (3.2)	9 (3.0)	0.883
113–151	339 (65.96)	144 (66.1)	195 (65.9)	
≥151	154 (29.96)	62 (28.4)	92 (31.1)	
Unknown	5 (0.97)	5 (2.3)	0 (0)	
hs-CRP, g/mL				
<1.0	227 (44.1)	98 (45.0)	129 (43.6)	0.680
1.0–3.0	170 (33.1)	66 (30.3)	104 (35.1)	
≥3.0	97 (18.9)	41 (18.8)	56 (18.9)	
Unknown	20 (3.9)	13 (6.0)	7 (2.4)	
LDH, U/L				
<245	479 (93.2)	197 (90.4)	282 (95.3)	0.821
≥245	20 (3.9)	9 (4.1)	11 (3.7)	
Unknown	15 (2.9)	12 (5.5)	3 (1.0)	

Abbreviation: HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

of CC to IMRT did not improve survival but rather elevated acute toxicity reaction prevalence among stage II NPC patients [6,7]. Besides, a recent pooled patient data meta-analysis [8] also reported no beneficial effects on survival from the addition of CC to RT was observed in stage II NPC. In contrast, Luo and his colleagues [9] reported significantly better survival for stage II (T2N1M0) disease by the addition of CC to IMRT. These inconsistences in conclusions from previous studies may partly result from the biological variability of the tumor itself. It may be more reasonable to use chemotherapy individually based on risk stratification of stage II disease. To our knowledge, pretreatment Epstein-Barr virus (EBV) DNA (pre-EBV DNA) level is strongly associated with tumor burden [10], and is useful in risk stratification to guide the treatment of NPC [11,12]. Considering the low tumor burden among patients that are stage II NPC and undetectable pre-EBV DNA, we hypothesized that addition of CC to IMRT may bring minimal benefit for these group of patients.

Hence, the present study tested this hypothesis by initiating a real-world study to evaluate the role of adding CC to IMRT for stage II NPC patients with undetectable pre-EBV DNA. To balance the effect of covariates, propensity score matching (PSM) method was utilized to decrease potential bias. Our findings will inform clinicians and patients, as well as serve as a guide for decision making on tailoring therapy among patients with stage II NPC.

Materials and methods

Patient characteristics

The study included newly diagnosed patients treated at Sun Yat-Sen University Cancer Centre (SYSUCC) between March 2008 and October 2016. Patients were included if they met the following criteria (1) pathologically diagnosed undifferentiated carcinoma of the nasopharynx (World Health Organization [WHO] type III); (2) diagnosed stage II NPC (T2N0M0; T1-2N1M0); (3) received IMRT with or without CC; (4) Karnofsky performance score (KPS) ≥70; (5) no prior diagnoses for other malignancies; and (6) presence of undetectable (0 copies/mL) pre-EBV DNA. Prior to diagnosis and treatment, an arrangement of clinical assessments was performed including physical examinations, capturing medical history, hematology and biochemistry profiles, fiberoptic nasopharyngoscopy with biopsy, abdominal sonography or computed tomography (CT), magnetic resonance imaging (MRI) of nasopharynx and neck, whole-body bone scan, and chest radiography CT. Patients included in the study were restaged based on the eighth edition of the American Joint Commission on Cancer (AJCC) staging system [13].

RT and chemotherapy

Patients included in this study received IMRT. Target volumes were delineated based on the study institution treatment protocol [14]. The institutional treatment protocol is also in agreement with the International Commission on Radiation Units and Measurements Reports 62 [15] and 83 [16]. Clinical target volumes (CTV) were separately delineated and determined by the tumor invasion pattern. Prescribed doses were (1) 66–72 Gy to the planning target volume (PTV) of the primary gross tumor volume of the primary (GTV-P); (2) 64–70 Gy to the PTV for the nodal gross tumor volume (GTV-N); (3) 60–63 Gy to the PTV of the high-risk clinical target volume (CTV1); and (4) 54–56 Gy to PTV among low-risk clinical target volume (CTV2). CTV1 comprised GTV plus the addition of 5-mm margin and involved the entire nasopharyngeal mucosa plus 5-mm submucosal volume. CTV2 protracted 5–10 mm past the margin of CTV1, comprising potentially involved regions and lymphatic regions, unless the CTV2 was adjacent to vital organs (e.g., brain stem,

Table 2
Baseline characteristics of all 177 pairs of NPC patients.

Characteristic	Total ($N = 354$)	RT alone ($N = 177$)	CCRT ($N = 177$)	*p*value
Gender				
Male	240 (67.80)	112 (63.28)	128 (72.32)	0.096
Female	114 (32.20)	65 (36.72)	49 (27.68)	
Age, year				
<50	212 (59.89)	97 (54.80)	115 (64.97)	0.073
≥50	142 (40.11)	80 (45.20)	62 (35.03)	
T stage (8th edition)				
T1	155 (43.79)	80 (45.20)	75 (42.37)	0.673
T2	199 (56.21)	97 (54.80)	102 (57.63)	
N stage (8th edition)				
N0	88 (24.86)	44 (24.86)	44 (24.86)	1.000
N1	266 (75.14)	133 (75.14)	133 (75.14)	
Smoking history				
No	265 (74.86)	134 (75.71)	131 (74.01)	0.821
Yes	89 (25.14)	43 (24.29)	46 (25.99)	
Family of cancer				
No	222 (62.71)	108 (61.02)	114 (64.41)	0.596
Yes	132 (37.29)	69 (38.98)	63 (35.59)	
HGB, g/L				
<113	10 (2.8)	6 (3.4)	4 (2.26)	0.238
113–151	243 (68.6)	126 (71.2)	117 (66.10)	
≥151	97 (27.4)	41 (23.2)	56 (31.64)	
Unknown	4 (1.1)	4 (2.3)	0 (0)	
hs-CRP, g/mL				
<1	151 (42.7)	78 (44.1)	73 (41.2)	0.551
1.0–3.0	118 (33.3)	53 (29.9)	65 (36.7)	
≥3	70 (19.8)	35 (19.8)	35 (19.8)	
Unknown	15 (4.2)	11 (6.2)	4 (2.3)	
LDH, U/L				
<245	334 (94.4)	162 (91.5)	172 (97.18)	1.000
≥245	10 (2.8)	5 (2.8)	5 (2.82)	
Unknown	10 (2.8)	10 (5.6)	0 (0)	

Abbreviation: HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

spinal cord). If CTV2 was adjacent to vital organs, the extension distance was decreased to 3–5 mm. Patients included in the study were treated with one fraction daily over 5 days per week. Concurrent chemotherapy plan included administration of cisplatin (80–100 mg/m^2, i.v.) at weeks 1, 4, and 7, or cisplatin (40 mg/m^2, i.v.) weekly, since the beginning of radiotherapy. Patients who received 5-fluorouracil or docetaxel, as well as those received targeted therapy or immunotherapy, during concurrent chemotherapy were excluded.

Quantification of plasma EBV DNA

We extracted and routinely measured Pre-EBV DNA levels using real-time quantitative polymerase chain reaction (PCR) as previously discussed in detail in prior publications [11,17]. Supplementary Materials (available online) describes the methodology used for detecting plasma EBV DNA. In the sample, undetectable plasma EBV DNA was set at 0 copies/mL.

Data sharing

The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit (RDD) public platform www.researchdata.org.cn, with the approval RDD number of RDDA2020001560.

Follow-up and end points

We examined patients during the first two years for a minimum of once every three months. For three to five years, we examined patients every six months, and annually thereafter. During each clinical examination follow-up visit, fiberoptic nasopharyngoscopy, and plasma EBV DNA were routinely performed. Among those with clinical suspicion of metastasis, they were recommended for MRI, whole-body bone scan, abdominal sonography, or PET/CT. Additionally, if possible, these patients were followed by confirmatory cytological biopsies. Overall survival (OS) was calculated from starting date of treatment to date of death due to any cause. Disease-free survival (DFS) was measured from the time of initial date of treatment to first relapse at any site, death from any cause, or date of last contact (last follow-up visit), whichever occurred first. Distant metastasis-free survival (DMFS) was calculated from the first date of treatment to date of distant metastasis. Finally, locoregional relapse-free survival (LRFS) was computed from date of treatment to date of first local or regional recurrent or both.

Statistical analysis

Categorical variables were determined according to clinical findings, and we transformed continuous variables into categorical variables based on previous published study findings [18]. Chi-square test (or Fisher's exact test) was used for comparing between CCRT and IMRT alone groups. To reduce selection bias because of different distributions for covariables among the two groups and mimic randomized controlled trials, PSM analysis was performed with a matching ratio of 1:1 through the nearest-neighbor method with a stringent caliper of 0.05. Using logistic regression, we computed propensity scores for each patient using presumed covariates including gender, age, T stage, and N stage. To calculate actuarial rates, Kaplan-Meier method was used and log-rank test was performed for calculating differences. Cox proportional hazards models were used to perform multivariate analyses. Additionally, Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). All reported probability values were two-sided tests, and $P < 0.05$ was determined to be statistically significant. All statistical models were performed using R 3.3.2 (The R

Table 3
Univariate analysis of prognostic factors for Stage II patients.

Characteristic	OS HR (95%CI)	*P* value	DFS HR (95%CI)	*P* value	DMFS HR (95%CI)	*P* value	LRFS HR (95%CI)	*p*value
Gender								
Male	Reference		Reference		Reference		Reference	
Female	1.03 (0.33, 3.24)	0.957	0.81 (0.39, 1.70)	0.577	0.80 (0.26, 2.42)	0.689	1.19 (0.42, 3.37)	0.749
Age, year								
<50	Reference		Reference		Reference		Reference	
≥50	3.56 (1.22, 10.44)	0.021	2.24 (1.20, 4.18)	0.012	2.20 (0.87, 5.58)	0.096	1.32 (0.50, 3.47)	0.578
T stage (8th edition)								
T1	Reference		Reference		Reference		Reference	
T2	0.88 (0.31, 2.48)	0.810	1.59 (0.79, 3.18)	0.191	1.24 (0.46, 3.30)	0.67	2.74 (0.78, 9.54)	0.114
N stage (8th edition)								
N0	Reference		Reference		Reference		Reference	
N1	1.39 (0.39, 4.94)	0.608	1.03 (0.50, 2.11)	0.933	0.86 (0.31, 2.43)	0.783	2.73 (0.62, 11.98)	0.183
Smoking history								
No	Reference		Reference		Reference		Reference	
Yes	1.74 (0.62, 4.89)	0.294	1.58 (0.83, 3.00)	0.162	2.11 (0.83, 5.35)	0.116	0.33 (0.08, 1.45)	0.144
Family of cancer								
No	Reference		Reference		Reference		Reference	
Yes	0.36 (0.10, 1.29)	0.115	0.53 (0.26, 1.07)	0.076	0.64 (0.23, 1.79)	0.394	1.53 (0.58, 4.06)	0.391
HGB, g/L								
<113	Reference		Reference		Reference		Reference	
113–151	0.00 (0.00, Inf)		1.10 (0.15, 8.14)		0.00 (0.00, Inf)		0.43 (0.05, 3.33)	
≥151	0.00 (0.00, Inf)	0.856	1.27 (0.17, 9.71)	0.899	0.00 (0.00, Inf)	0.275	0.39 (0.04, 3.36)	0.685
hs-CRP, g/mL								
<1	Reference		Reference		Reference		Reference	
1.0–3.0	7.31 (1.62, 32.99)		1.73 (0.86, 3.48)		2.05 (0.73, 5.76)		1.01 (0.35, 2.93)	
≥3	2.30 (0.32, 16.32)	0.019	1.37 (0.58, 3.28)	0.305	1.20 (0.30, 4.80)	0.366	0.93 (0.25, 3.52)	0.992
LDH, U/L								
<245	Reference		Reference		Reference		Reference	
≥245	0.00 (0.00, Inf)	0.998	0.74 (0.10, 5.38)	0.764	1.52 (0.20, 11.41)	0.685	0.00 (0.00, Inf)	0.998

Abbreviation: HR, hazard ratio; 95% CI, 95% confidence interval; OS, overall survival; DFS, disease-free survival; DMFS, distant metastasis-free survival; LRFS, locoregional relapse-free survival; HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; RT, radiotherapy; CCRT, concurrent chemoradiotherapy. P values were calculated using an adjusted Cox proportional hazards model.

Table 4
Baseline characteristics of the CCRT and RT alone groups in the N1 disease.

Characteristic	RT alone (*N* = 133)	CCRT (*N* = 252)	*p*value
Gender			
Male	93 (69.92)	194 (76.98)	0.153
Female	40 (30.08)	58 (23.02)	
Age, year			
<50	81 (60.90)	160 (63.49)	0.675
≥50	52 (39.10)	92 (36.51)	
T stage (8th edition)			
T1	80 (60.15)	118 (46.83)	0.018
T2	53 (39.85)	134 (53.17)	
Smoking history			
No	99 (74.44)	177 (70.24)	0.425
Yes	34 (25.56)	75 (29.76)	
Family of cancer			
No	80 (60.15)	170 (67.46)	0.199
Yes	53 (39.85)	82 (32.54)	
HGB, g/L			
<113	3 (2.3)	8 (3.17)	0.888
113–151	89 (68.9)	170 (67.46)	
≥151	37 (27.8)	74 (29.37)	
Unknown	4 (3.0)	0 (0)	
hs-CRP, g/mL			
<1.0	61 (45.9)	111 (44.0)	0.416
1.0–3.0	37 (27.8)	90 (35.7)	
≥3.0	26 (19.5)	44 (17.5)	
Unknown	9 (6.8)	8 (3.2)	
LDH, U/L			
<245	120 (90.2)	239 (94.8)	0.786
≥245	4 (3.0)	10 (4.0)	
Unknown	9 (6.8)	3 (1.2)	

Abbreviation: HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

Foundation for Statistical Computing, Vienna, Austria; www.rproject.org).

Results

Baseline characteristics of the entire patient

In the present study, a total of 514 stage II NPC patients with undetectable pre-EBV DNA were included. The male-to-female ratio was 2.7:1 and median age in years was 49 (range, 23–77 years of age). For the overall cohort, median follow-up duration was 69.9 months (interquartile range, 54.9–86.6 months). During the study period, 17 patients (3.3%) exhibited locoregional relapse, 18 (3.5%) developed distant metastases, and 15 (2.9%) died. Table 1 presents the detail clinical characteristics. Overall, the fiver-year OS, DFS, DMFS, and LRFS rates were 98% (95%CI, 96%–99%), 94% (95%CI, 91%–96%), 96% (95%CI, 94%–98%), and 97% (95%CI, 96%–99%) respectively.

Survival comparison between group CCRT and RT alone

296 patients (57.6%) received CCRT, and 218 (42.4%) received RT alone. The baseline characteristics between CCRT and RT alone groups are shown in Table 1. Significant differences were observed for N stage. Those with stage N1 disease were more likely to be treated with CCRT ($p < 0.001$). No differences were observed when comparing both groups by age, gender, history of smoking, family history of cancer, HGB, CRP, LDH and T stage before propensity-score matching (P value > 0.05 for all). AS shown in Fig. 1, no statistically associated difference were observed at five-year for OS (97.8% vs. 98.1%; $p = 0.700$; Fig. 1A), DFS (93.4% vs. 94.5%; $p = 0.846$; Fig. 1B), DMFS (96% vs. 96.9%; $p = 0.762$; Fig. 1C), and LRFS (97.3% vs. 98.1%; $p = 0.701$; Fig. 1D) rates between CCRT and RT alone groups before matching

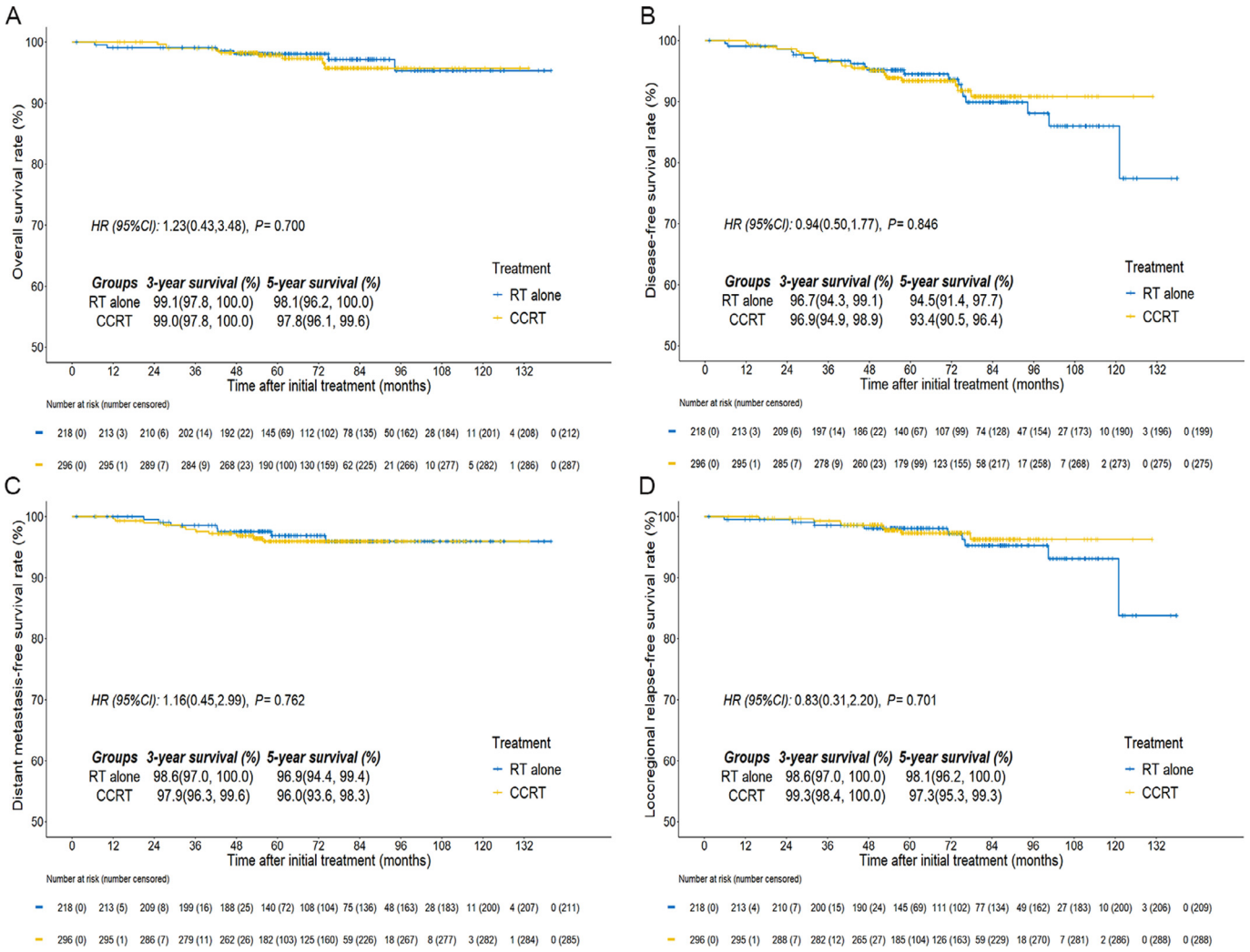

Fig. 1. Kaplan–Meier survival curves for the CCRT arm and the RT alone arm before matching. (A) Overall survival, (B) disease-free survival, (C) distant metastasis-free survival, and (D) locoregional relapse-free survival. RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

With the use of PSM (1:1), 177 patients who underwent RT alone were matched with 177 patients who underwent CCRT. After matching, both groups had highly balanced characteristics in host and tumor factors (all $P>0.05$; Table 2). Compared with CCRT group, RT alone group did not have a significant reduction in the five-year actuarial incidence of OS (96.9% vs. 98.2%; $p=0.302$; Fig. 2A), DFS (92% vs. 95.2%; $p=0.777$; Fig. 2B), DMFS (95.2% vs. 97.6%; $p=0.400$; Fig. 2C), and LRFS (97.3% vs. 97.6%; $p=0.328$; Fig. 2D).

Prognostic factors and subgroup analysis

Table 3. presents the value for potential prognostic factors including gender, smoking history, age, family history of cancer, T stage, N stage, HGB, CRP, and LDH. In the univariate analysis, we observed that patients aged ≥ 50 years were statistically associated with poorer OS (HR, 3.56; 95% CI, 1.22–10.44; $p=0.021$) and DFS (HR, 2.24; 95% CI, 1.20–4.18; $p=0.012$) rates in comparison with those < 50 years of age, but not associated with DMFS (HR, 2.20; 95% CI, 0.87–5.58; $p=0.096$) and LRFS (HR, 1.32; 95% CI, 0.50–3.47; $p=0.578$). We did not conduct multivariate analyses since very limited predictors were identified as significant in the univariate analyses.

To examine the efficacy of CC among stage N1 disease patients, we further performed subgroup analysis. A total of 385 N1 patients were enrolled, including 133 (34.5%) receiving RT alone and 252 patients (65.5%) receiving CCRT. Table 4 presents the clinical characteristics of patients in two groups. Patients with stage T2 disease were more likely to be treated with CCRT ($p=0.018$). The Kaplan–Meier curves showed that CCRT was still not statistically associated with improvement at five-year OS (97.4% vs. 98.4%; $p=0.397$; Fig. 3A), DFS (93.2% vs. 96.0%; $p=0.821$; Fig. 3B), DMFS (96.2% vs. 97.5%; $p=0.781$; Fig. 3C), and LRFS (96.8% vs. 97.6%; $p=0.621$; Fig. 3D) in comparison with RT alone.

Discussion

According to the National Comprehensive Cancer Network (NCCN) guideline, CCRT with or without sequential chemotherapy (e.g. induction, or adjuvant chemotherapy) is the current standard treatment modality for stage III-IV NPC [19]. However, the role of CC in stage II NPC remains controversial due to absence of phase III randomized trials in IMRT era. In the present study, IMRT with or without CC was compared to assess the influence of CC in stage II NPC with undetectable pre-EBV DNA. Our results showed that IMRT alone appeared to achieve comparable survival to CCRT for stage II NPC and undetectable pretreatment EBV DNA. Further subgroup analysis also obtained similar results for N1 disease.

Several retrospective studies have examined in IMRT settings the efficacy of CC. For instance, a study by Luo et al. investigated and compared clinical outcomes among 69 patients in the CCRT and IMRT group.

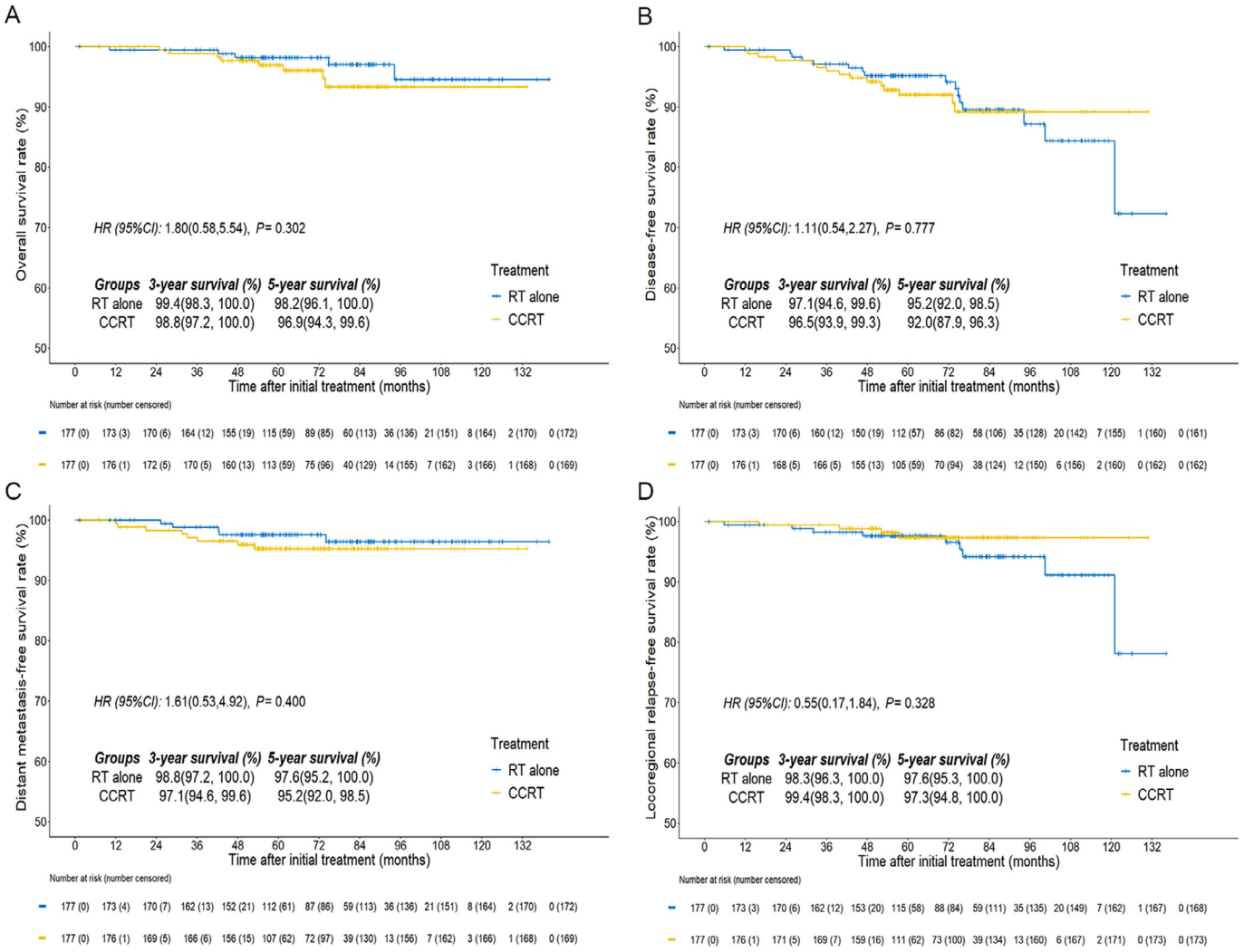

Fig. 2. Kaplan–Meier survival curves for the CCRT and the RT alone arm in the propensity-matched cohort of 354 patients. (A) Overall survival, (B) disease-free survival, (C) distant metastasis-free survival, and (D) locoregional relapse-free survival. RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

The study did observe an association for poorer LRFS, DMFS, and OS in the RT alone group for stage II (T2N1M0) NPC [9]. However, three other studies [6-8] observed similar outcomes between CCRT and RT alone groups. Su et al. [7] carried out a study among 249 patients to compare CCRT with RT alone and indicated that the five-year DMFS and OS all had no associated differences between two groups. Similar findings were obtained in another recent retrospective study [7] and meta-analysis [8]. However, inconsistences in findings may partly result from the small sample size and heterogeneity of population in these studies. For example, suppose two NPC patients with T2N1M0 disease come to the clinic, one patient had only retropharyngeal lymph node involvement, and another had both retropharyngeal lymph node and unilateral cervical lymph node involvement. If they were both to receive RT alone, their prognosis may be completely different. We suggest that the application of traditional staging systems solely for treatment decision-making may not be reasonable enough for stage II NPC, and the application of chemotherapy should be individualized according to the risk stratification of this disease.

Literature have reported that NPC is an EBV-associated cancer [20]. Prior studies have established that patients with higher pre-EBV DNA levels could be at greater risk of developing disease failure [21 22]. In recent years, pre-EBV DNA levels were considered to be strongly associated with tumor burden [10], which could be a supplement to the TNM staging system to enhance its accuracy and guide individualized treatment strategies [11,23-24]. In this study, all recruited patients had undetectable plasma EBV DNA, which was defined as low-risk disease failure. Our results demonstrated that adding CC to RT could not improve survival in this population. However, other studies demonstrated that stage N1 is the greatest risk factor in predicting DMFS and OS among stage II disease [4,9]. Therefore, further stratified analysis based on N1 category was conducted in the current study. In the current analysis, we still failed to observe any significant survival benefit over CC in this group of patients. The possible reasons behind these findings can be as follows. First, the development of current RT technology has allowed for “tailoring” dose distribution, resulting in significantly improving clinical outcome and reducing the incidence of toxicities in organs at risk (OARs) [25-27]. Second, pre-EBV DNA was correlated with tumor burden, and those with undetectable pre-EBV DNA had a relatively low tumor burden. Therefore, the potential survival benefits gained from the addition of CC for T1–2N1 disease may be weakened in the IMRT era. To the best of our knowledge, our study is the first to compare both CCRT with RT alone for stage II NPC with undetectable pre-EBV DNA.

For patients with stage II NPC, Luo et al. [9] reported patients with stage N0 had significantly superior survival than patients with stage N1. However, in the current study, clinical outcomes did not differ significantly between N0 and N1 disease, with corresponding five-year DFS rates of 93.8% and 93.5%. This inconsistency is potentially contributed to differences between patients included in the study by Luo et al.

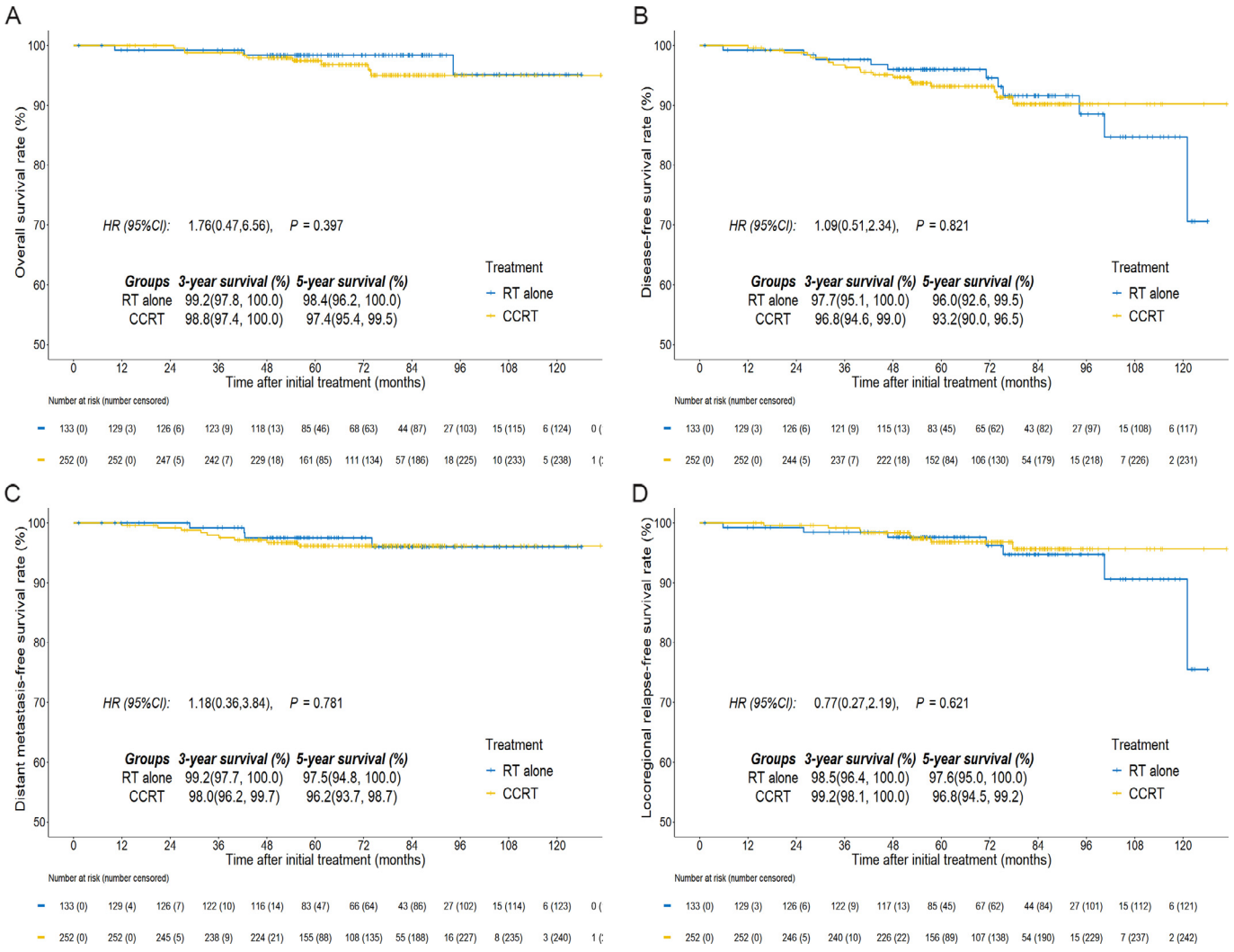

Fig. 3. Kaplan–Meier survival curves for the CCRT arm and the RT alone arm in the subgroup stratified by N1 disease. (A) Overall survival, (B) disease-free survival, (C) distant metastasis-free survival, and (D) locoregional relapse-free survival. RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

[9] and the study by Luo et al. [9] did not consider pre-EBV DNA status, which may include more patients with higher malignancy of stage N1 disease in the study. However, only undetectable pre-EBV DNA patients that were diagnosed stage II NPC were included in this study. In addition, for this group of patients, the five-year DFS rate was up to 94%, and only 21 patients (21/385; 5%) suffered disease failure. Considering the excellent survival of patients with stage II and undetectable pre-EBV DNA, the prognostic impact of N category may be narrow for this group.

The present study has several strengths that must be noted. First, we conducted a head-to-head comparison between patients given RT with or without CC through PSM. This method allowed for addressing both divergent confounders and potential selection bias as a result of the retrospective analysis [28]. Second, the study population we selected had stage II NPC with undetectable pre-EBV DNA, potentially reducing heterogeneity of tumors. However, some limitations must be noted. First, data used in this study were obtained entirely from one center in an endemic area, and external validation could not be performed as a result of deficiency in available per-patient data from other hospitals. For this reason, the generalizability of our findings to other populations needs to be validated. Second, treatment-related toxicities were lacking in the current study. Second, it should be pointed out, patients who had detectable pre-EBV DNA were excluded in this study, and all recruited patients had undetectable pre-EBV DNA at initial diagnose. Because pre-EBV DNA level is strongly associated with tumor burden, the study population included in our study may be a low-risk group of stage II NPC. Hence, randomized clinical trial is still needed to confirm whether our conclusion is applicable to all of stage II NPC patients.

In conclusion, the present study confirmed that RT alone contributes to excellent survival for stage II NPC and undetectable pre-EBV DNA patients. Additionally, the addition of CC to RT failed to improve significant survival outcomes. Taking into account cost and inconvenience of CC, RT alone may be a feasible treatment strategy for those with stage II NPC and undetectable pre-EBV DNA in the IMRT era. Our analysis provided references for optimizing individualized treatment among patients with stage II NPC. Relative randomized clinical trial is still needed to confirm our findings.

Author contributions statement

Ya-Nan Jin, Qing-Nan Tang & Ji-Jin Yao: the acquisition of data, analysis of data, and drafting the article;

Xi-Wei Xu & Wen-Zhuo He: the analysis of data and interpretation of data;

Ya-Fei You, Kun-Wei Peng & Lei Wang: the acquisition of data, the conception of the study;

Chang Jiang: the conception and design of the study, revising the article critically for important intellectual content;

Liang-Ping Xia: final approval of the version to be submitted.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by grants from the Natural Science Foundation of Guangdong, China (2015A030313010), Science and Tech-nology Program of Guangzhou, China (1563000305), the Guangdong Innovative and Entrepreneurial Research Team Program (2016ZT06S638), the Science and Technology project of Guangdong Province (2017A020215031) and National Natural Science Foundation of China (81901699, 81773051 and 81572409).

Ethics Statement

Ethical approval for this research was given by the institutional review board and ethics committee of Sun Yat-sen University Cancer Center. All of the participants provided written informed consent.

References

[1] Y.P. Chen, A.T.C. Chan, Q.T. Le, et al., Nasopharyngeal carcinoma, Lancet 394 (10192) (2019) 64–80.
[2] A.W. Lee, S.Y. Tung, D.T. Chua, et al., Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma, J. Natl. Cancer Inst. 102 (15) (2010) 1188–1198.
[3] P. Blanchard, A. Lee, S. Marguet, et al., Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis, Lancet Oncol. 16 (2015) 645–655.
[4] Q.Y. Chen, et al., Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial, J. Natl. Cancer Inst. 103 (2011) 1761–1770.
[5] G. Peng, T. Wang, K.Y. Yang, S. Zhang, T. Zhang, Q. Li, et al., A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radio- therapy for the treatment of nasopharyngeal carcinoma, Radiother. Oncol.: J. Eu ropean Soc. Therap. Radiol. Oncol. 104 (3) (2012) 286–293 PMID: 22995588, doi:10.1016/j.radonc.2012.08.013.
[6] Z. Su, Y.P. Mao, J. Tang, et al., Long-term outcomes of concurrent chemoradiotherapy versus radiotherapy alone in stage II nasopharyngeal carcinoma treated with IMRT: a retrospective study, Tumour Biol. 37 (4) (2016) 4429–4438.
[7] F. Zhang, Y. Zhang, W.F. Li, et al., Efficacy of concurrent chemotherapy for intermediate risk NPC in the intensity-modulated radiotherapy era: a propensity-matched analysis, Sci. Rep. 5 (2015) 173–178.
[8] S. Wang, S. Li, L Shen, Combined chemoradiation vs radiation therapy alone in stage-II nasopharyngeal carcinoma: a meta-analysis of the published literature, Curr Prob Cancer 42 (3) (2018) 302–318.
[9] S. Luo, L. Zhao, J. Wang, et al., Clinical outcomes for early-stage nasopharyngeal carcinoma with pre-dominantly WHO II histology treated by intensity-modulated radiation therapy with or without chemotherapy in nonendemic region of China, Head Neck 36 (6) (2014) 841e7.
[10] J.Y. Shao, Y.H. Li, H.Y. Gao, et al., Comparison of plasma Epstein-Barr virus (EBV) DNA levels and serum EBV immunoglobulin A/virus capsid antigen antibody titers in patients with nasopharyngeal carcinoma, Cancer 100 (2004) 1162–1170.
[11] L.T. Liu, Q.Y. Chen, L.Q. Tang, et al., Neoadjuvant or adjuvant chemotherapy plus concurrent CRT Versus Concurrent CRT alone in the treatment of nasopharyngeal carcinoma: a study based on EBV DNA, J. Natl. Compr. Canc. Netw. 17 (6) (2019) 703–710.
[12] H. Liang, X. Lv, L. Wang, et al., The plasma Epstein-Barr virus DNA level guides precision treatment for nasopharyngeal carcinoma in the intensity-modulated radiotherapy era: a large population-based cohort study from an endemic area, Ther. Adv. Med. Oncol. 10 (2018) 1758835918782331.
[13] M. Amin, American joint committee on cancer, AJCC Cancer Staging Manual, Springer, New York, 2016.
[14] W.F. Li, Y. Sun, M. Chen, et al., Locoregional extension patterns of nasopharyngeal carcinoma and suggestions for clinical target volume delineation, Chin. J. Cancer 31 (12) (2012) 579–587.
[15] ICRU reportVol. 62: Prescribing, recording, and Reporting Photon Beam Therapy, International Commission on Radiation Units and Measurements, Maryland, 1999.
[16] ICRU ReportVol. 83: Prescribing, Recording, and Reporting Photon-Beam Intensity–Modulated Radiation Therapy (IMRT), International Commission on Radiation Units and Measurements, Maryland, 2010.
[17] X. An, F.H. Wang, P.R. Ding, et al., Plasma Epstein-Barr virus DNA level strongly predicts survival in metastatic/recurrent nasopharyngeal carcinoma treated with palliative chemotherapy, Cancer 117 (2011) 3750–3757.
[18] L.Q. Tang, C.F. Li, J. Li, W.H. Chen, Q.Y. Chen, L.X. Yuan, et al., Establishment and Validation of Prognostic Nomograms for Endemic Nasopharyngeal Carcinoma, J. Natl. Cancer Inst. 108 (1) (2015).
[19] Pfister D.G., Spencer S., Adelstein D., et al. NCCN clinical practice guidelines in oncology: head and neck cancers. Version 1.2019. Accessed April 29, 2019. To view the most recent version, visit NCCN.org.
[20] A.T.C. Chan, E.P. Hui, R.K.C. Ngan, et al., Analysis of plasma Epstein-Barr virus DNA in nasopharyngeal cancer after chemoradiation to identify high-risk patients for adjuvant chemotherapy: a randomized controlled trial, J. Clin. Oncol. (2018) JCO2018777847.
[21] R. Guo, L.L. Tang, Y.P. Mao, et al., Proposed modifications and incorporation of plasma Epstein- Barr virus DNA improve the TNM staging system for Epstein-Barr virus-related nasopharyngeal carcinoma, Cancer 125 (2019) 79–89.
[22] C.W. Twu, W.Y. Wang, W.M. Liang, et al., Comparison of the prognostic impact of serum anti-EBV antibody and plasma EBV DNA assays in nasopharyngeal carcinoma, Int. J. Radiat. Oncol. Biol. Phys. 67 (1) (2007) 130–137.
[23] S.F. Leung, K.C. Chan, B.B. Ma, et al., Plasma Epstein-Barr viral DNA load at midpoint of radiotherapy course predicts outcome in advanced-stage nasopharyngeal carcinoma, Ann. Oncol. 25 (2014) 1204–1208.
[24] V.H.F. Lee, D.L.W. Kwong, T.W. Leung, et al., The addition of pretreatment plasma Epstein-Barr virus DNA into the 8th edition of nasopharyngeal cancer TNM stage classification, Int. J. Cancer 144 (2018) 1713–1722.
[25] M. Zhang, J. Li, G. Shen, et al., Intensity-modulated radiotherapy prolongs the survival of patients with nasopharyngeal carcinoma compared with conventional two-dimensional radiotherapy: a 10-year experience with a large cohort and long follow-up, Eur. J. Cancer 51 (2015) 2587–2595.
[26] S. Lai, W. Li, L. Chen, et al., How does intensity-modulated radio- therapy versus conventional two-dimensional radiotherapy influ- ence the treatment results in nasopharyngeal carcinoma patients? Int J Radiat Oncol Biol Phys. 80 (2011) 661–668.
[27] X. Sun, S. Su, C. Chen, et al., Long-term outcomes of intensity-modulated radiotherapy for 868 patients with nasopharyngeal carcinoma: an analysis of survival and treatment toxicities, Radiother. Oncol. 110 (2014) 398–403.
[28] P.C. Austin, The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies, Med. Decis. Mak. 29 (2009) 661–677.