Clinical Trial/Experimental Study

Medicine®

OPEN

Comparison of the efficacy between concurrent chemoradiotherapy with or without adjuvant chemotherapy for stage II nasopharyngeal carcinoma

Jing Chen, MD[a,b,c], Tongxin Liu, MD[a,b,c], Quanquan Sun, MD[a,b,c], Ting Jin, MD[a,b,c,*]

Abstract

Background: Although common, the use of concurrent chemoradiotherapy with adjuvant chemotherapy for stage II nasopharyngeal carcinoma (NPC) is controversial due to its undefined clinical benefits. We, therefore, conducted a retrospective cohort study to investigate whether adjuvant chemotherapy confers survival gains to stage II NPC patients.

Methods: In this study, we examined whether combining adjuvant chemotherapy (AC) and/or concurrent chemotherapy with radiotherapy (CCRT) improved survival in patients with stage II NPC. Three hundred thirty-five stage II NPC patients were retrospectively analyzed between June 2003 and June 2016 and received CCRT; some patient groups also received AC every 3 weeks for 2 to 3 cycles.

Results: The median follow-up duration was 72 months for all patients (range, 26–151 months) and the estimated 5-year locoregional relapse-free survival (LRRFS), distant metastasis-free survival (DMFS), progression-free survival (PFS), and overall survival (OS) rates were 95.1%, 97.8%, 93.5%, and 94.3%. At the last follow-up, there were no statistically significant differences among the CCRT and CCRT+AC groups in 5-year LRRFS (95.2% vs 94.9%, $P = .599$), DMFS (98.5% vs 92.4%, $P = .152$), PFS (93.8% vs 90.2%, $P = .599$), or OS (95.5% vs 93.9%, $P = .682$) rates.

Conclusion: The analyses revealed that a combined regimen was not an independent prognostic factor for any survival outcome. However, patients who received CCRT plus AC experienced more acute adverse events than those who received CCRT alone. Thus, the addition of AC to CCRT did not improve survival outcomes, but was associated with higher incidences of acute treatment-associated toxicities than CCRT alone in patients with stage II NPC.

Abbreviations: AC = adjuvant chemotherapy, CCRT = concurrent chemotherapy with radiotherapy, CRT = chemo-radiotherapy, EBV-DNA = Epstein–Barr virus Deoxyribonucleic acid, IMRT = intensity-modulated radiation therapy, MRI = magnetic resonance imaging, NPC = Nasopharyngeal carcinoma, RT = radiotherapy.

Keywords: adjuvant chemotherapy, concurrent chemoradiotherapy, intensity-modulated radiotherapy, prognosis, stage II nasopharyngeal carcinoma

1. Introduction

Nasopharyngeal carcinoma (NPC) is an endemic disease in southern China.[1] The incidence of NPC varies from 15 to 50 cases per 100,000 annually in southern China, Singapore, and Malaysia depending on age, ethnicity, and geographical region.[2] Early stage NPC is traditionally treated with radiotherapy (RT) alone which achieves high overall survival (OS) rates. However, treatment outcome after RT alone in early stage NPC is not always satisfactory in terms of locoregional control and distant metastasis. Chua et al[3] reported results of 141 early stage NPC patients treated with RT alone and found that stage II patients showed significantly poorer outcomes. Intensity-modulated radiation therapy (IMRT) has improved locoregional control, but does little to improve survival outcomes or to prevent distant failure.[4] The combination of chemo-radiotherapy (CRT) is the standard treatment for loco-regionally advanced NPC (stage II–IVb), while radiotherapy alone is regarded as the treatment of choice for stage I NPC.[5,6] However, there have been controversies regarding the treatment of stage II NPC. The question remains whether chemotherapy is essential for all the patients in stage II. With the superb outcome of NPC treated with IMRT, it is reasonable to question the additive benefit of chemotherapy used with IMRT in stage II. Significant toxicity has

Editor: Jimmy T. Efird.

The authors of this work have nothing to disclose.

The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

[a] Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, [b] Department of Radiation Oncology, Cancer Hospital of the University of Chinese Academy of Sciences, [c] Department of Radiation Oncology, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, China.

[*] Correspondence: Ting Jin, Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, Department of Radiation Oncology, Cancer Hospital of the University of Chinese Academy of Sciences, Department of Radiation Oncology, Zhejiang Cancer Hospital, No. 1 East Banshan Road, Hangzhou 310022, Zhejiang Province, China (e-mail: jinjin_2019@163.com).

How to cite this article: Chen J, Liu T, Sun Q, Jin T. Comparison of the efficacy between concurrent chemoradiotherapy with or without adjuvant chemotherapy for stage II nasopharyngeal carcinoma. Medicine 2020;99:29(e20443).

Received: 30 June 2019 / Received in final form: 27 March 2020 / Accepted: 26 April 2020

http://dx.doi.org/10.1097/MD.0000000000020443

been observed in patients who receive adjuvant chemotherapy after concurrent CRT. Several multicenter trials reported that only around 60% to 70% of patients could tolerate the entire adjuvant chemotherapy regimen.[7,8] Therefore, many have questioned the contribution of adjuvant chemotherapy and advocated concurrent CRT alone. Because adjuvant chemotherapy is mostly for microscopic disseminated disease, in a phase II prospective study, these patients were treated with concurrent CRT only and still achieved >90% of 5-year distant metastasis-free survival (DMFS).[9] In this retrospective study, we compared the efficacy between concurrent chemoradiotherapy with or without adjuvant chemotherapy for stage II NPC.

2. Materials and methods

2.1. Patients

Between June 2003 and June 2016, the patients were enrolled in this study in the Department of Radiation Oncology, Zhejiang Cancer Hospital. The study was approved by the ethics committee of Zhejiang Cancer Hospital. All patients provided informed consent. Eligible patients met the following criteria:

1. newly diagnosed NPC;
2. stage II;
3. Eastern Cooperative Oncology Group performance status $\leq$1;
4. treated with CCRT or CCRT+AC;
5. no previous anti-cancer treatment.

Pretreatment evaluation included a complete medical history, physical examination, fiber-optic endoscopic examination, MRI of the head and neck, chest and upper abdomen CT, bone scintigraphy, complete blood counts, and serum chemical evaluation. All patients underwent nasopharyngeal biopsy to determine the pathology. All patients were staged according to the 2010 American Joint Committee on Cancer staging system. Tumor histology was classified per the World Health Organization classification.

2.2. Treatment method

All patients received CCRT. Radiation technique before 2010 was 2D conformal radiotherapy and was gradually shifted to intensity-modulated radiotherapy (IMRT) in the middle of 2010. The details of 2D conformal RT have been reported before. The IMRT protocol included the following.

The doses for planning gross primary tumor and retropharyngeal lymph node volume (PGTVnx+rn), high-risk planning tumor volume (PTV1), low-risk planning tumor volume (PTV2), and gross tumor volume of neck lymph nodes (GTVnd) were 6000 to 7600, 5400 to 6600, 5000 to 6000, and 6000 to 6996 cGy, respectively. The dose of important functional organs and endanger organs was limited. The Dmax (maximum dose) brain stem was $\leq$54 Gy, spinal cord was $\leq$40 Gy, optic nerve and the optic chiasm was $\leq$54 Gy, crystal was <8 Gy, the temporal lobe was $\leq$54 to 60 Gy, mandible was $\leq$60 Gy, temporomandibular joint was $\leq$50 Gy, and 50% volume parotid was $\leq$30 Gy. The Pinnacle 7.6 planning system was used to design the plans through synchronous integrated technology (SMART boost), and the physician outlined the target areas and normal tissues and set the prescription dose and endanger organ dose. The physical therapist established and optimized the IMRT plan. The evaluation of treatment plan included the target region, endanger organ dose volume histogram, and layer evaluation of each equal section. The doctors first confirmed the treatment plan, and then, dosimetric verification was performed. Finally, RT was carried out.

Concurrent chemotherapy based NDP or DPP 80 mg/m^2 d1 to d3 every 21 days during radiotherapy. Adjuvant chemotherapy was performed about 1 month after CCRT. We chose platinum-based 2 to 3 cycles adjuvant chemotherapy. PF: comprised nedaplatin (NDP) 75 mg/m^2 on days 1 to 3, tegafur 1 g on days 1 to 3, or 5-Fu 300 to 500 mg/m^2 via continuous intravenous injection (CIV) 72 to 120 h for 21 days/cycle. Meanwhile, TP comprised docetaxel 75 mg/m^2 on day 1, DDP 75 mg/m^2 on days 1 to 3 for 21 days/cycle.

2.3. Observation and follow-up during treatment

Biochemical and routine blood tests were carried out every week during treatment. Tumor regression was assessed using the nasopharyngofiberoscope or via indirect nasopharyngoscopy every 7 to 10 days. The acute responses of patients to radiotherapy and chemotherapy were recorded. Acute toxicity and late adverse reaction evaluation criteria referred to LENT SOMA and Common Terminology Criteria for Adverse Events version 3.0 (CTCAE3.0) grade evaluation criteria. Nasopharyngofiberoscope was used and magnetic resonance imaging (MRI), chest radiography, blood test, and B-ultrasonography were conducted to assess the local control rate. Moreover, the side effects of radiotherapy were recorded. We can evaluate the control rate and identify the side effects of radiotherapy by reexamining the MRI, rhinitis fiberscopy, chest radiography, B-ultrasonography, and blood test results 1 month after the treatment to review the cases once every 3 months within 1 year, every 6 months in 3 years, and every 1 year after 5 years later. The patients should be comprehensively evaluated by assessing for thirst, neck fibrosis, and sight and hearing loss. According to the National Cancer Center of Common Toxicity Criteria version 3.0, the main adverse reactions during chemotherapy were decreased levels of granulocytes, thrombocytes, and hemoglobin. Decreased serum albumin and elevated aminotransferase levels commonly indicate liver and kidney damage. Cardiovascular abnormalities consisted of abnormal heart rhythm, electric conduction abnormalities, and cardiac insufficiency. None of the patients died during treatment.

2.4. Statistical analysis

The survival time was calculated from the diagnosed time to the end of the follow-up. The Kaplan–Meier test and log-rank test of SPSS 17.0 statistic software (SPSS, Shanghai, China) package were used to calculate survival rate, compare, and analyze the survival rates of each group. Cox model was used to analyzing the prognosis factors. The prognosis was evaluated from gender, age, pathological type, T stage and chemotherapy in Log-rank test.

3. Results

3.1. Patient characteristics

Clinical data for newly diagnosed NPC patients who received IMRT at Zhejiang Cancer Hospital between June 2003 and June 2016 were retrospectively reviewed. A total of 335 patients with stage II were enrolled. Basic patient characteristics are summarized in Table 1. The median age was 46.6 years (range 21–74 years), and the male to female ratio was 2.68:1 (244:91). There were no statistically significant differences in age, gender,

Table 1

Basic characteristics for 335 stage II NPC patients treated with IMRT plus AC and/or CC.

Characteristic	CCRT	CCRT+AC	P
Sex			.591
Male	184	60	
Female	66	25	
Age (years)			.192
<50	163	41	
≥50	87	44	
T stage			.09
T1	93	23	
T2	157	62	
N stage			.877
N0	46	15	
N1	204	70	
Clinical stage			.751
T1N1	93	23	
T2N0	46	15	
T2N1	111	47	
Radiotherapy			.549
IMRT	93	45	
2D-CRT	157	40	

AC= adjuvant chemotherapy, CCRT= concurrent chemotherapy with radiotherapy, CRT= chemo-radiotherapy, IMRT=intensity-modulated radiation therapy.

T category, N category, or clinical subgroup among the two treatment regimens.

3.2. Survival

For all patients, the median follow-up period was 72 months (range 26–151 months) and the estimated 5-year locoregional relapse-free survival (LRRFS), DMFS, progression-free survival (PFS), and OS rates were 95.1%, 97.8%, 93.5%, and 94.3%, respectively (Fig. 1). As shown in Figure 2, there were no statistically significant differences among the CCRT and CCRT +AC groups in 5-year LRRFS (95.2% vs 94.9%, $P=.599$), DMFS (98.5% vs 92.4%, $P=.152$), PFS (93.8% vs 90.2%, $P=.599$), or OS (95.5% vs 93.9%, $P=.682$) rates.

3.3. Toxicity of radiotherapy and chemotherapy

The concurrent CRT was well tolerated by all 335 patients. Comparison of adverse events was performed using χ^2 statistic for nominal variables as appropriate. The most severe side effects (stage 3 or more) during treatment were stomatitis/mucositis (56.4%), pharyngitis (14.8%), and nausea/ vomiting (10.1%). The most commonly observed complications included hematologic and non-hematologic side effects. During the period of treatment (Table 2), incidences of grade 3 to 4 leukocytopenia

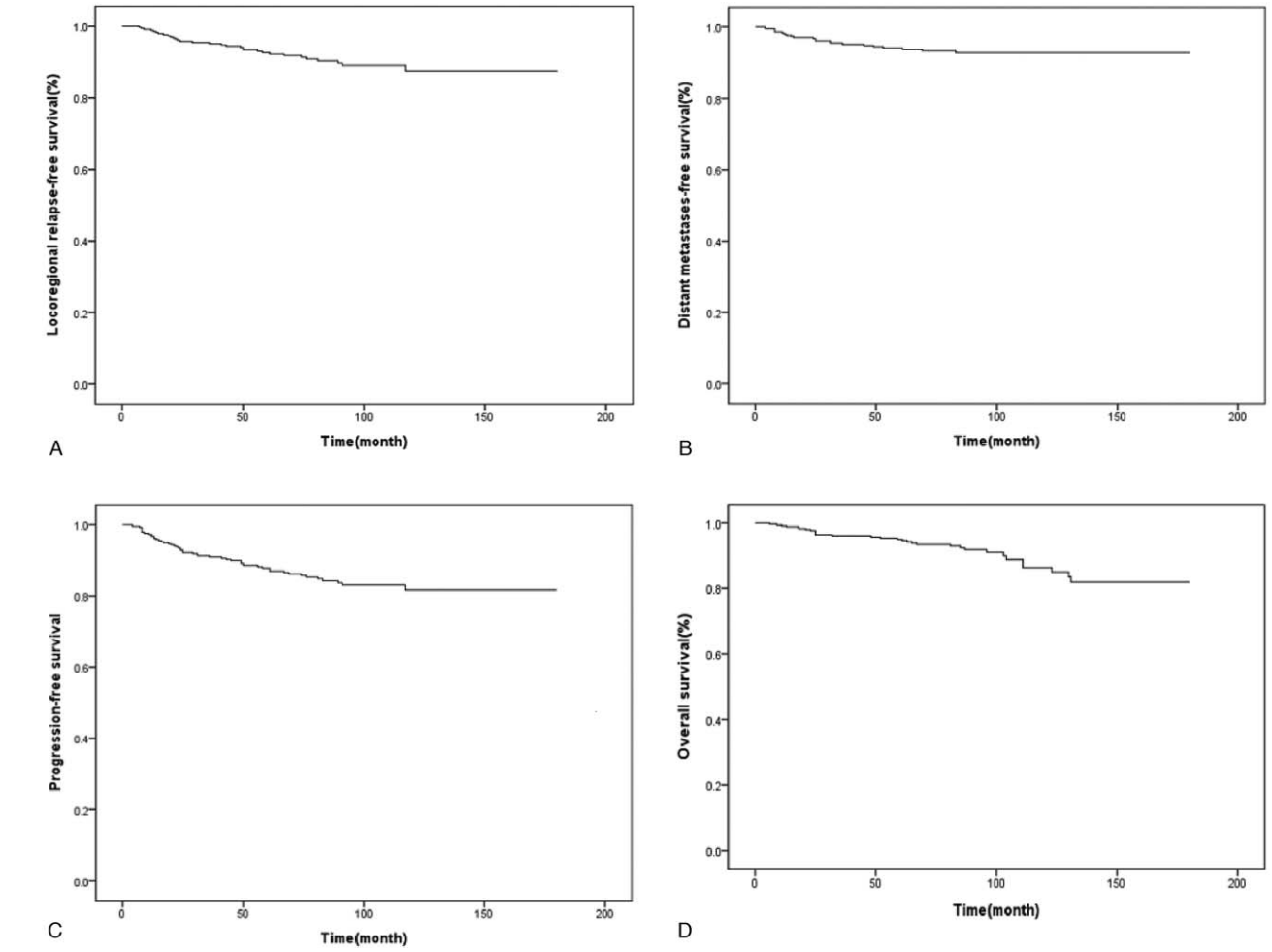

Figure 1. (A–D) The estimated 5-year locoregional relapse-free survival (LRRFS), distant metastasis-free survival (DMFS), progression-free survival (PFS), and overall survival (OS).

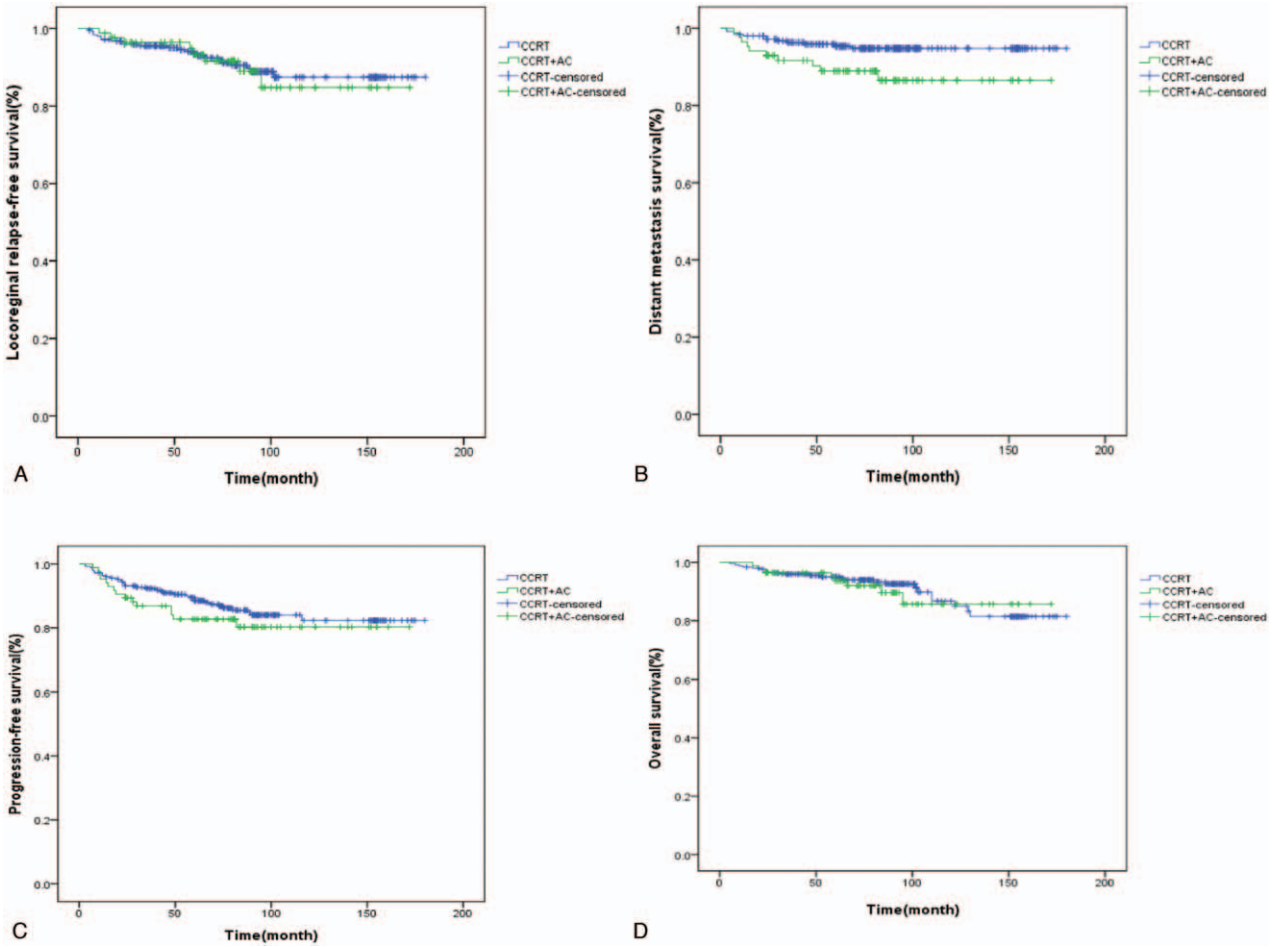

Figure 2. (A–D) CCRT and CCRT+AC groups in 5-year LRRFS, DMFS, PFS, and OS.

and neutropenia were higher in patients treated with CCRT+AC compared to those treated with CCRT alone ($P = .029$ and $P = .038$). In addition, incidence of grade 3 to 4 stomatitis/mucositis was higher in patients treated with CCRT+AC than in those treated with CCRT alone ($P = .017$). There were no other significant differences in treatment toxicity among the groups ().

4. Discussion

The strength of our single-center study is uniform staging, treatment, and long follow-up (72 months). The study spanned a long period and involved changes in radiotherapy and chemotherapy protocol. Our study confirms that patients with

Table 2

Toxicity of radiotherapy and chemotherapy.

	CCRT		CCRT+AC		
Adverse events	**0–2**	**3–4**	**0–2**	**3–4**	***P***
Hematologic					
Leukocytopenia	64	0	42	2	.029
Neutropenia	59	0	40	2	.038
Anemia	62	0	32	0	.577
Thrombocytopenia	65	2	31	1	.641
Liver function	20	0	9	0	.854
Renal function	7	0	3	0	.596
Non-hematologic					
Stomatitis/mucositis	93	12	77	7	.017
Pharyngitis	35	3	10	1	.235
CCRT+AC	8	0	3	0	.652
Nausea/vomiting	27	0	6	1	.351

AC = adjuvant chemotherapy, CCRT = concurrent chemotherapy with radiotherapy.

Table 3

Univariate and multivariate analysis of prognostic factors.

	P							
	Univariate analysis				Multivariate analysis			
Variate	OS	LRRFS	DMFS	PFS	OS	LRRFS	DMFS	PFS
Age	0.792	0.836	0.520	0.205	0.731	0.866	0.654	0.188
Sex	0.370	0.537	0.899	0.367	0.744	0.335	0.787	0.258
T stage	0.565	0.453	0.477	0.674	0.865	0.416	0.354	0.653
N stage	0.962	0.538	0.466	0.281	0.384	0.572	0.142	0.854
Clinical stage	0.443	0.577	0.668	0.974	0.126	0.885	0.552	0.642
Treatment	0.732	0.814	0.382	0.532	0.795	0.714	0.362	0.237

DMFS = distant metastasis-free survival, LRRFS = locoregional relapse-free survival, OS = overall survival, PFS = progression-free survival.

stage II NPC (T1-T2 N0–2 except T1N0) can be managed with CCRT without adjuvant chemotherapy. The estimated 5-year LRRFS), DMFS, PFS, and OS were 95.1%, 97.8%, 93.5%, and 94.3%. At the last follow-up, there were no statistically significant differences among the CCRT and CCRT+AC groups in 5-year LRRFS (95.2% vs 94.9%, $P = .599$), DMFS (98.5% vs 92.4%, $P = .152$), PFS (93.8% vs 90.2%, $P = .599$), or OS (95.5% vs 93.9%, $P = .682$) rates. There was no statistical difference between the two groups. The patients who received CCRT plus adjuvant chemotherapy experienced more acute adverse events than those who received CCRT alone. Thus, the addition of AC to CCRT did not improve survival outcomes, but was associated with higher incidences of acute treatment-associated toxicities than CCRT alone in patients with stage II NPC.

Nasopharyngeal carcinoma with primary tumor extended beyond the nasopharynx and neck lymph node enlargement has long been considered as "advanced"-stage for its poor prognosis after radiotherapy alone.[3] Five randomized studies from an NPC endemic Asia-Pacific region using similar enrollment criteria to the US intergroup 0099 study showed that the addition of chemotherapy to radiotherapy improved survival for advanced NPC.[10,11] Our findings can be explained by tumor biology and anatomy. NPC usually has an orderly lymphatic spread from the upper to the lower neck. Concurrent CRT can effectively control the disease unless there is an extension of the tumor to the lower neck or bulky disease, regardless of unilateral or bilateral cervical lymphadenopathy (N1 or N2). In contrast, if the tumor locally invades highly vascular regions, such as the parapharyngeal space or prevertebral fascia, there will be a greater chance for cancer cells to spread to distant sites via the bloodstream. The CCRT alone is sufficient in early NPC, more chemotherapy is required for advanced nasopharyngeal cancer. Therefore, our study shows a good prognosis with CCRT alone in stage II NPC.

A multicenter phase III randomized controlled trial from China compared CCRT (weekly cisplatin 40 mg/m^2) plus adjuvant chemotherapy (cisplatin 80 mg/m^2 day 1 and fluorouracil 800 mg/m^2 day 1–5) vs CCRT alone in patients with AJCC stages III to IV (excluding T3–4N0) NPC.[8] At a median follow-up of 37.8 months, estimated 2-year failure-free survival, OS, distant failure-free survival, or locoregional failure-free survival did not differ significantly between the 2 groups. It also proves that there is no need to add AC to CCRT in stage II NPC patients. In summary, some low-risk patients with AJCC 1997 stage II and III (AJCC 2010 T1N1–2) NPC have a very low risk of distant metastasis and excellent survival with CCRT alone. We can avoid giving adjuvant chemotherapy and exposing these patients to unnecessary side effects and risks.

In addition, there are some different opinions on the treatment in stage II NPC. Lee et al[12] from Hong Kong demonstrated excellent treatment outcomes of NPC patients treated by three-dimensional conformal radiotherapy (3D-CRT)/IMRT alone. In their series, the 5-year DSS and disease free survival (DFS) for stage II were 95% and 90%, respectively. In contrast, Luo et al[13] showed that T2N1 disease (2002 AJCC) was a unique subgroup with higher risk of distant metastasis and the addition of chemotherapy is necessary to improve the treatment outcomes. We do agree that applying a uniform treatment strategy to all the patients in stage II is inappropriate. The main point to debate now is whether it is necessary to deliver chemotherapy to all patients in stage II, and how to find out the unique subset that would benefit from the addition of chemotherapy and how chemotherapy should be given to different subgroups in stage II. With further research into other predicting factors of NPC, such as tumor volume,[14] serum lactate dehydrogenase,[15] comorbidity,[16] and Epstein–Barr virus deoxyribonucleic acid (EBV-DNA)[17,18] and other molecular prognostic markers, it is likely that these will be taken in conjunction with stage classification in grouping patients into different prognostic groups, each with different recommended treatment.

Several limitations should be addressed in our series. First, the retrospective nature of the study certainly served as an inherited and fundamental pitfall; prospective randomized control clinical trials should be conducted. Secondly, the chemotherapy was not protocolized and used at discretion of the attending physician of individual cases, in terms of the indications, timing of chemotherapy and chemotherapy agents to use. This limited our ability to perform any meaningful and scientific analysis, and further well-designed prospective study by multicenter collaboration is warranted.

In summary, concurrent chemotherapy significantly improved LRRFS and PFS in stage II NPC, whereas adjuvant chemotherapy did not. These findings need to be confirmed by a randomized clinical trial. Furthermore, since distant metastasis occurred in 13% of patients and was not reduced by adding chemotherapy, more effective novel agents are required.

5. Conclusions

Adding adjuvant chemotherapy to CCRT led to no survival benefit and increased acute toxicity reactions for stage II NPC. In the treatment of patients with stage II NPC, there were no statistically significant differences among the CCRT and CCRT+AC groups in 5-year LRRFS, DMFS, PFS, or OS rates.

Author contributions

Conceptualization: Jing Chen, Quanquan Sun, Ting Jin.
Data curation: Tongxin Liu.
Formal analysis: Tongxin Liu.
Supervision: Ting Jin.
Writing – original draft: Quanquan Sun, Ting Jin.
Writing – review & editing: Quanquan Sun, Ting Jin.

References

[1] Wei WI, Sham JS. Nasopharyngeal carcinoma [J]. Lancet (London, England) 2005;365:2041–54.
[2] Tang LLCW, Xue WQ, et al. Global trends in incidence and mortality of nasopharyngeal carcinoma [J]. Cancer Lett 2016;374:22–30.
[3] Chua DT, Sham JS, Kwong DL, et al. Treatment outcome after radiotherapy alone for patients with stage i-ii nasopharyngeal carcinoma [J]. Cancer 2003;98:74–80.
[4] JW. Nasopharyngeal carcinoma: a promising future [J]. Lancet Oncol 2012;13:116–8.
[5] Lai SZLW, Chen L, et al. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? [J]. Int J Radiat Oncol Biol Phys 2011;80:661–8.
[6] Chan ATGV, Lefebvre JL, et al. Nasopharyngeal cancer: Ehns-esmo-estro clinical practice guidelines for diagnosis, treatment and follow-up [J]. Ann Oncol 2012;23(Suppl 7):vii83–85.
[7] Blanchard P, Lee A, Marguet S, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the mac-npc meta-analysis [J]. Lancet Oncol 2015;16:645–55.
[8] Chen L, Hu C, Chen XZ, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: A phase 3 multicentre randomised controlled trial [J]. Lancet Oncol 2012;13:163–71.
[9] Wu JS, Tsai YC, Jian JJ, et al. Survival without adjuvant chemotherapy for selected patients with stage ii and iii nasopharyngeal carcinoma after concurrent chemoradiotherapy alone [J]. Head Neck 2018;40:2070–7.
[10] Chan AT, Leung SF, Ngan RKC, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma [J]. J Natl Cancer Inst 2005;97:536–9.
[11] Chen Y, Liu M-Z, Liang S-B, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of China [J]. Int J Radiat Oncol Biol Phys 2008;71:1356–64.
[12] Lee AWM, Ng WT, Chan LK, et al. The strength/weakness of the AJCC/UICC staging system (7th edition) for nasopharyngeal cancer and suggestions for future improvement [J]. Oral Oncol 2012;48:1007–13.
[13] Luo S, Zhao L, Wang J, et al. Clinical outcomes for early-stage nasopharyngeal carcinoma with predominantly who ii histology treated by intensity modulated radiation therapy with or without chemotherapy in nonendemic region of China [J]. Head Neck 2014;36:841–7.
[14] Chen C, Fei Z, Pan J, et al. Significance of primary tumor volume and t-stage on prognosis in nasopharyngeal carcinoma treated with intensity-modulated radiation therapy [J]. Jpn J Clin Oncol 2011;41:537–42.
[15] Turen S, Ozyar E, Altundag K, et al. Serum lactate dehydrogenase level is a prognostic factor in patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy [J]. Cancer Invest 2007;25:315–21.
[16] Guo R, Chen X-Z, Chen L, et al. Comorbidity predicts poor prognosis in nasopharyngeal carcinoma: development and validation of a predictive score model [J]. Radiother Oncol 2015;114:249–56.
[17] Leung SF, Zee B, Ma BB, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma [J]. J Clin Oncol 2006;24:5414–8.
[18] Leung SF, Chan ATC, Zee B, et al. Pretherapy quantitative measurement of circulating Epstein-Barr virus DNA is predictive of posttherapy distant failure in patients with early-stage nasopharyngeal carcinoma of undifferentiated type [J]. Cancer 2003;98:288–91.