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Original Research

Ten-year outcomes of survival and toxicity for a phase III randomised trial of concurrent chemoradiotherapy versus radiotherapy alone in stage II nasopharyngeal carcinoma

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Abstract ***Purpose:*** Our previous results showed survival benefits of concurrent chemoradiotherapy (CCRT) in treating stage II nasopharyngeal carcinoma (NPC) compared with radiotherapy (RT) alone. Here, we present the updated 10-year survival results and late toxicity profile to assess the ultimate effectiveness of concurrent chemotherapy.
Methods: Patients with stage II NPC were randomly assigned to RT arm (n = 114) or to CCRT arm (n = 116) with a concurrent weekly cisplatin regimen. The primary end-point was overall survival (OS).

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Late toxicity

Results: With a median follow-up of 125 months, significant improvements in OS (83.6% vs 65.8%, P = 0.001), progression-free survival (76.7% vs 64.0%, P = 0.014), cancer-specific survival (86.2% vs 71.9%, P = 0.002), distant-metastasis free survival (94.0% vs 83.3%, P = 0.007) were observed in CCRT arm. In point of locoregional-relapse free survival, the impact of CCRT was not remarkable. The findings were in accordance with our previous report. The survival benefits earned by CCRT mainly reflected in T2N1 population. Although CCRT brought more acute toxic effects (P = 0.001), as presented in previous report, the late toxicities and treatment-associated deaths events were comparable between two arms.
Conclusions: Ten-year outcomes confirmed that CCRT could improve the OS of stage II patients without adding late toxicities compared with conventional RT.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a kind of malignancy with unique biological characteristics. Although its location makes it covert and unresectable, the property of intrinsic radiosensitivity provides a good profile of prognosis, which turns NPC to a curable cancer. Concurrent chemoradiotherapy (CCRT) is the standard treatment for patients with non-metastatic NPC, and its efficacy has been tested and verified by many phase III studies and meta-analyses. Among them, most focussed on the effect of multimodality treatment on patients with locally advanced cancer, which led to a lack of attention to stage II NPC. It is partly because of the small proportion of these patients, along with the assumption that patients with early-stage disease tend to have favourable survival outcomes. As the widespread use of Epstein–Barr virus (EBV) DNA tests and the maturity of magnetic resonance and positron-emission tomography–computed tomography make a difference in detecting NPC in early stages, the standardisation of treatment of early-stage NPC should attract more attention.

Over the years, there has always been a debate on whether patients with stage II NPC should be treated with an addition of chemotherapy. The National Comprehensive Cancer Network has recommended CCRT for all stages except stage I patients, but the efficacy of CCRT in stage II patients is weak. Our previous study [1] was the first and only randomised controlled trial (RCT) comparing CCRT with radiotherapy (RT) alone in patients with stage II NPC, and the results showed a significant improvement in 5-year overall and progression-free survival (PFS). Subsequent studies continue to explore the efficacy of chemotherapy on the basis of not only conventional RT but also intensity-modulated radiotherapy (IMRT), and the results were conflicting. Despite that the superiority of chemotherapy seems to be eclipsed by the introduction of advanced RT technique, the long-time follow-up information about stage II patients is still quite limited, let alone from prospective trials. Under this case, this report was made to fill up the blank of long-term stage II survival outcomes from RCT, as well as provide assessment about prolonged treatment-related toxicity.

2. Material and methods

2.1. Study design and participants

From October 2003 to September 2007, 230 patients, who were classified as stage II NPC by the Chinese 1992 staging system, were allocated in the trial in Sun Yat-sen University Cancer Center. The inclusion criteria were the World Health Organization types II–III nasopharyngeal carcinoma, stage II disease, good haematologic, hepatic and renal functions, aged 18–70 years and satisfactory performance status. Patients who went through previous treatment of NPC or had prior malignancy were excluded. Randomisation was performed by computer software. All patients were stratified by nodal status classification and then, were randomly assigned to either the RT arm or CCRT arm in blocks of 4 and 6.

The work was approved by the Clinical Research Ethics Committee in Sun Yat-sen University Cancer Center. Written informed consent were provided by all patients participated.

2.2. Treatment and follow-up

All patients allocated received 2D RT with the same demand of dose. A therapeutical accumulative dose of 68–70 Gy was given to primary tumour and 60–62 Gy to the involved neck regions. All potential metastatic lymph node drainage areas were irradiated under at least 50 Gy. The administration of cisplatin synchronised with RT. Patients in the CCRT group were given cisplatin on a weekly regimen at dose of 30 mg/m^2. Blood routine and blood biochemical results were mandatory before each cycle of chemotherapy. The delivery of cisplatin would be delayed if reaching the predetermined level of myelosuppression. There was no dose modification through the whole treatment.

Tumour response assessment was performed 3 months after the end of treatment. Follow-up visits were required every 3 months in the first 3 years and every 6 months thereafter. After a median follow-up of 60 months, we did a comprehensive evaluation and analysis to compare efficacy and safety between the two groups, and relevant details were available in our previous report [1]. We continued to follow up all participants mainly by outpatient clinic and recorded survival results and toxicities. For those who did not pay a return visit at the time of around 120 months, the survival results were obtained and toxicities evaluated through phone calls or emails. Patients undergoing treatment failure and subsequently lost to follow-up were considered dead on the day of their last follow-up. The late toxicities were graded according to the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) [2].

2.3. Statistical analysis

Statistical analyses were made based on the intention-to-treat principle. Overall survival (OS) was the primary end-point, and secondary end-points measured cancer-specific survival (CSS), PFS, locoregional relapse-free survival (LRRFS) and distant metastasis-free survival (DMFS). CSS was added to feature cancer-related events because ageing-associated disease or death was an issue for long-time follow-up analysis that may not be neglected. The definitions of end-points were in accordance with our previous report, while CSS was defined as the interval from random assignment to death caused by primary tumour, progression or protocol treatment. The assessment of late treatment toxicities was also regarded as a part of secondary end-points.

Kaplan–Meier curve was used to estimate survival between two groups, and log-rank test was used to measure the significance of difference. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs) and performed multivariable analyses with the Cox proportional hazards model. Toxicities were compared mainly using the chi-square test, and Fisher's exact test would be adopted when data could not meet the criteria of chi-square test. All tests were two sided, and the significance level was set to 0.05. All analyses were performed with SPSS 23.0 software.

3. Results

We continued to follow up the entire cohort from 17th March 2011 to 3rd December 2017. Up to then, 148 (86%) survivors were followed up for at least 10 years; 12 (5.2%) patients were lost to follow-up, and the median follow-up time was 125.0 months (range 7.2–164.7 months) for the whole cohort. Among the lost cases, nine of them (75.0%) were from the RT arm and others, from the CCRT arm; the survival results of rest 218 patients were obtained. As for the late toxicity assessment among all surviving patients, 169 (98%) were accessible. The reasons for the failure of acquiring toxicity profiles from some patients were the following: unable to communicate (n = 1), incooperative attitude (n = 1) and loss of data (n = 1).

The baseline characteristics were equally comparable between two arms (Table 1. Because all patients were originally staged according to the Chinese 1992 staging system, which was common at the time of enrolment but being replaced later, they were restaged based on the 7th American Joint Committee on Cancer (AJCC) staging system. As a consequence, 31 (13.4%) patients were reclassified as N2 and stage III. Other relevant tumour factors, compliance and results of toxic effects have been described in the previous report.

3.1. Survival

Overall, 68 (28.3%) patients experienced failure, and 58 (25.2%) died (of any cause). Compared with the 5-year OS rates, the 10-year OS has changed from 85.8% to 65.8% in the RT arm and from 94.5% to 83.6% in the CCRT arm. The superiority of chemotherapy continued to stand out in 10-year OS rate (83.6% vs 65.8%, HR = 0.40, 95% CI, 0.23–0.68, P = 0.001). Similar trends were also observed in terms of CSS (86.2% vs 71.9%, HR = 0.41, 95% CI, 0.22–0.74, P = 0.002), PFS (76.7% vs 64.0%, HR = 0.55, 95% CI, 0.34–0.89, P = 0.014) and DMFS (94.0% vs 83.3%, HR = 0.32, 95% CI, 0.13–0.76, P = 0.007); cisplatin-based CCRT possessed a significant advantage in reducing cancer/progression/metastasis-related deaths over RT alone. In point of LRRFS, the increase in survival rates brought

Table 1
Baseline characteristics.

Characteristic	CCRT arm (n = 116)	RT arm (n = 114)
Gender		
Male	82 (70.7%)	84 (73.7%)
Female	34 (29.3%)	30 (26.3%)
Median age (years)	42 (26–65)	43 (28–70)
Histology		
WHO II	5 (4.3%)	4 (3.5%)
WHO III	111 (95.7%)	110 (96.5%)
AJCC T stage		
T1	19 (16.4%)	21 (18.4%)
T2	97 (83.6%)	93 (81.6%)
AJCC N stage		
N0	17 (14.7%)	13 (11.4%)
N1	80 (68.9%)	89 (78.1%)
N2	19 (16.4%)	12 (10.5%)
AJCC Stage		
II	97 (83.6%)	102 (89.5%)
III	19 (16.4%)	12 (10.5%)

RT, radiotherapy; CCRT, concurrent chemoradiotherapy; AJCC, the seventh edition of the American Joint Committee on Cancer staging system.
Data are represented as n (%) or median (range).

Table 2
Comparison of survival outcomes between the CCRT arm and RT arm.

End-point	Incidence, No. (%)		HR (95% CI)	P value
	CCRT arm	RT arm		
Overall survival	19 (16.4)	39 (34.2)	0.40 (0.23–0.68)	0.001
Cancer-specific survival	16 (13.8)	32 (28.1)	0.41 (0.22–0.74)	0.002
Progression-free survival	27 (23.3)	41 (36.0)	0.55 (0.34–0.89)	0.014
Distant metastasis-free survival	7 (6.0)	19 (16.7)	0.32 (0.13–0.76)	0.007
Locoregional relapse-free survival	13 (11.2)	15 (13.2)	0.76 (0.36–1.60)	0.474

CCRT, concurrent chemoradiotherapy; RT, radiotherapy; HR, hazard ratio; CI, confidence interval.
Hazard ratios were calculated with the Cox proportional hazards model. P values were calculated with the log-rank test.

by chemotherapy was not remarkable; results were quite comparable with observation both for 5-year and for 10-year, and the impact of chemotherapy did not reach a significant level (88.8% vs 86.8%, P = 0.474).

Among 58 deaths, 41 (70.7%) (28 in the RT arm and 13 in the CCRT arm) were resulted from tumour progression and eight (13.8%) were treatment related. In patients suffering locoregional failure, 15 (of 114) and 13 (of 116) cases were from the RT arm and CCRT arm, respectively, which indicated a similar local control rate between two groups. On the other hand, the effect of chemotherapy emerged as 19 (16.7%) patients in the RT arm experienced distant progression in comparison to 7 (6.0%) distant failures developed in the CCRT arm. Twenty-three (88.5%) patients with metastasis had complete locoregional control. Four (15.4%) cases of metastases occurred after 5 years of original treatment. Seventy-eight percent (40 of 51) patients received salvage therapy, 18 received chemotherapy, while nine received chemotherapy and re-irradiation. By the time of our last assessment, the successful salvage rate was 15.0% for the whole cohort(see Tables 2–5, Figs. 1–3).

After reclassification of the stage, survival analyses were performed in AJCC 7th stage II patients. Among 199 reclassified stage II patients, 135 (67.8%) were in the T2N1 stage. Chemotherapy manifested itself in terms of OS, PFS and DMFS in T2N1 patients but did not show superiority in T1N1 and T2N0 patients. In multivariable analyses, the number of chemotherapy cycle was an independent factor for improving OS, PFS, CSS and DMFS. The classification of T stage was not predictable for all end-points, but N stage was closely related to OS, CSS and DMFS. It was noteworthy that weight loss

Table 4
Summary of multivariable analyses of prognostic factors.

Variables	HR	95% CI for HR	P value
Overall survival			
Gender	1.49	0·80–2.80	0.21
Age	2.18	1.22–3.88	<0.01
T stage	1.30	0.64–2.64	0.48
N stage	1.84	1.06–3.19	0.03
No. of chemotherapy cycles	0.87	0·79–0.96	<0.01
Weight loss	2.17	1.19–3.95	0.01
Cancer-specific survival			
Gender	1.33	0.65–2.70	0.44
Age	2.09	1.11–3.93	0.02
T stage	1.39	0.62–3.10	0.42
N stage	2.08	1.14–3.80	0.02
No. of chemotherapy cycles	0.88	0.79–0.98	0.02
Weight loss	2.56	1.34–4.88	<0.01
Progression-free survival			
Gender	1.21	0·67–2.18	0.54
Age	1.73	1·02–2.94	0.04
T stage	1.21	0.64–2.32	0.56
N stage	1.62	0.97–2.70	0.07
No. of chemotherapy cycles	0.91	0·83–1.00	0.04
Weight loss	1.71	0.98–3.01	0.06
Distant metastasis-free survival			
Gender	0.84	0·33–2.17	0.72
Age	1.34	0.60–3.00	0.48
T stage	2.83	0.67–11.98	0.16
N stage	2.60	1.18–5.69	0.02
No. of chemotherapy cycles	0.85	0.74–0.99	0.04
Weight loss	1.56	0.66–3.66	0.31
Locoregional relapse-free survival			
Gender	1.52	0.62–3.76	0.36
Age	0.97	0.41–2.30	0.95
T stage	0.82	0.33–2.01	0.66
N stage	1.83	0.81–4.12	0.14
No. of chemotherapy cycles	0.94	0·82–1.08	0.37
Weight loss	2.06	0.85–5.02	0.11

HR, hazard ratio; CI, confidence interval.
Categorical variables were gender (male vs. female), age (≤45 vs. >45), readjusted T stage (T1 vs. T2), readjusted N stage (N0, N1, N2), No. of chemotherapy cycles (0–8) and weight loss during treatment (≤10% vs. >10%).
P values were calculated with the two-sided Wald test in the Cox proportional hazard model.
All HRs presented in the table are adjusted for other covariates.

Table 3
Subgroup analysis in reclassified stage II patients between the CCRT arm and RT arm.

End-point	Restaged T2N1 patients (N = 135)			Restaged T1N1 and T2N0 patients (N = 64)		
	Incidence (%)	HR (95% CI)	P value	Incidence (%)	HR (95% CI)	P value
OS	15.4 vs. 31.4	0.39 (0.18–0.82)	0.010	12.5 vs. 31.3	0.36 (0.11–1.16)	0.075
CSS	15.4 vs. 24.3	0.51 (0.23–1.11)	0.083	3.1 vs. 28.1	0.10 (0.01–0.79)	0.007
PFS	20.0 vs. 34.3	0.48 (0.25–0.95)	0.032	25.0 vs. 31.3	0.73 (0.29–1.86)	0.513
DMFS	4.6 vs. 17.2	0.23 (0.07–0.82)	0.013	3.1 vs. 9.4	0.31 (0.03–2.98)	0.284
LRRFS	10.8 vs. 8.6	1.13 (0.38–3.37)	0.825	15.6 vs. 9.4	0.54 (0.13–2.28)	0.398

CCRT, concurrent chemoradiotherapy; RT, radiotherapy; OS, overall survival; PFS, progression-free survival; CSS, cancer-specific survival; DMFS, distant metastasis-free survival; LRRFS, locoregional relapse-free survival; HR, hazard ratio; CI, confidence interval.
Hazard ratios were calculated with the Cox proportional hazards model. P values were calculated with the log-rank test.

Table 5
Major late adverse events.

Toxicity, No. (%)	CCRT arm (N = 91)			RT arm (N = 78)			P value
	Grades I	Grade II	Grade III-IV	Grades I	Grade II	Grade III-IV	
Hearing impairment/otitis	15 (16.5)	18 (19.8)	14 (15.4)	11 (14.1)	16 (20.5)	10 (12.8)	0.92
Dry mouth	23 (25.3)	52 (57.1)	0 (0)	15 (19.2)	46 (59.0)	0 (0)	0.37
Skin fibrosis[a]	23 (25.3)	15 (16.5)	3 (3.3)	18 (23.1%)	11 (14.1)	4 (5.1)	0.89
Trismus[a]	19 (20.9)	18 (19.8)	2 (2.2)	21 (26.9)	11 (14.1)	1 (1.3)	0.65
Temporal lobe injury	14 (15.4)	11 (12.1)	9 (9.9)	12 (15.4)	13 (16.7)	5 (6.4)	0.75
Endocrine dysfunction[a]	0	1 (1.1)	0	1 (1.3)	1 (1.3)	0	0.73
Eye damage[a]	0	0	1 (1.1)	0	0	1 (1.3)	1.00
Cranial neuropathy[a]	2 (2.2)	4 (4.4)	10 (11.0)	2 (2.6)	6 (7.7)	9 (11.5)	0.85
V[a]	1 (1.1)	3 (3.3)	0	2 (2.6)	2 (2.6)	0	0.86
VI[a]	0	0	1 (1.1)	0	0	1 (1.3)	1.00
IX[a]	0	0	4 (4.4)	0	1 (1.3)	4 (5.1)	0.72
XII[a]	1 (1.1)	1 (1.1)	5 (5.5)	0	3 (3.8)	4 (5.1)	0·63
Second malignancy[a]	0	0	1 (1.1)	0	0	0	1.00

CCRT, concurrent chemoradiotherapy; RT, radiotherapy.
P values were calculated across toxicity grades (grade 0, I, II, III–IV) with the chi-square test or Fisher's exact test.
Second malignancy refers to radiation-induced malignancy: soft tissue sarcoma over the irradiated area (n = 1).
[a] These items were calculated with Fisher's exact test.

>10% during treatment was a significant prognostic factor for 10-year OS (HR, 2.17; 95% CI, 1.19–3.95, P = 0.01) and CSS (HR, 2.56; 95% CI, 1.34–4.88, P < 0.01). The prognostic significance of weight loss, which is usually associated with anorexia, energy depletion, sarcopenia and inflammation, should be valued.

3.2. Toxicities

Among all late radiation-related toxicities, xerostomia and concomitant dental caries were the most common chief complaint in patients' routine follow-up visits. By the time of last follow-up, 80.5% (136 of 169) patients were bothered by xerostomia and loss of teeth. In the RT and CCRT arm, 46 (59.0%) and 52 (57.0%) survivors, respectively, were evaluated as grade II xerostomia with significant oral intake alteration. With regard to hearing impairment, skin fibrosis, trismus and neurological damage, the incidence rates in the CCRT arm were parallel with those in the RT arm. Altogether, there were 40 (34.5%) occurrences of grade III or IV late toxicities in the CCRT arm compared with 30 (26.3%) in the RT arm. Chemotherapy did not increase or magnify relevant late adverse events to RT. Only one patient developed radiation-induced second malignancy. Concerning treatment-associated deaths, four (50.0%) died of temporal lobe necrosis, one because of intracranial infection and one because of malnutrition brought by hypoglossal nerve damage.

4. Discussion

In this study, the 10-year survival results were proved to be in accordance with those at 5 years, and the disparity between the two arms maintained over time. As the only RCT focussing on stage II patients, the current update verified the survival benefits gained by CCRT in conventional RT settings. In the meantime, late complications did not increase with the use of chemotherapy. Similar results were observed in the study by Chua *et al.*'s [3], as combined chemotherapy improved OS and DMFS significantly. However, in a retrospective study by Xu *et al.* [4], CCRT significantly improved the 5-year relapse-free survival in T2N1 patients (91.5% vs. 77.3%, P = 0.008), instead of reducing chance of distant metastasis. The potential explanation might be that patients in the CCRT group exhibited more biopsy-proven lymph node metastasis than the RT group (P = 0.02), who were inclined to develop later tumour progression.

Over the years, IMRT has gradually taken over from conventional 2D or 3D RT for its better conformity of tumour coverage and the sparing of organs at risks. The superiority of chemotherapy over conventional RT has been challenged after the application of IMRT. Su *et al.* [5] has reported satisfactory 5-year DSS, LRFS and DMFS rates of 97.3%, 97.7% and 97.8%, respectively, in patients with early-stage NPC undergoing IMRT alone. Several studies explored the efficacy of concurrent chemotherapy in IMRT settings, and their results were inconsistent. Luo *et al.* [6] compared the clinical outcomes in the IMRT and CRT group in 69 patients and found significantly poorer OS, LRFS and DMFS in the IMRT alone group in T2N1 patients. However, there were another three studies [7–9] reporting comparable outcomes between the CCRT group and IMRT group. Meanwhile, the significant survival benefits gained from only LRRFS were observed in studies by Guo et al. [10] and Kang et al. [11]. The incompatible results among different studies made the impact of IMRT less clear, which also indicated the heterogenous nature of each study. The variation partly lied in the differences in

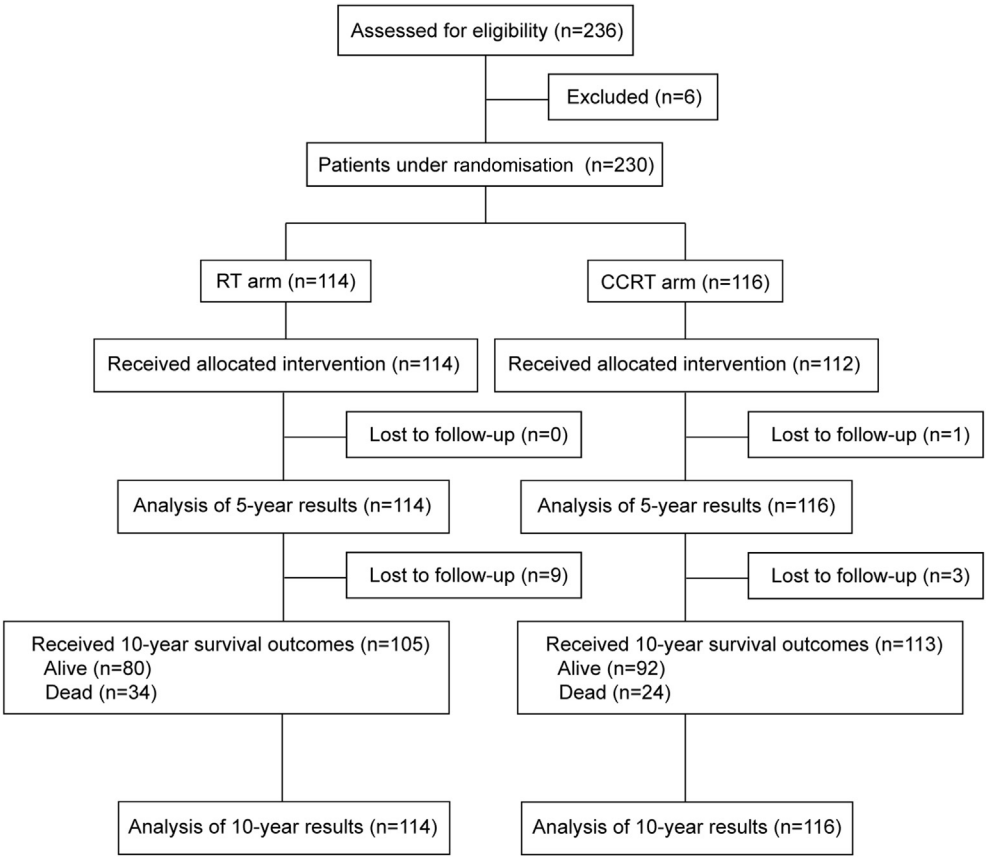

Fig. 1. Flow diagram. CCRT, concurrent chemoradiotherapy; RT, radiotherapy.

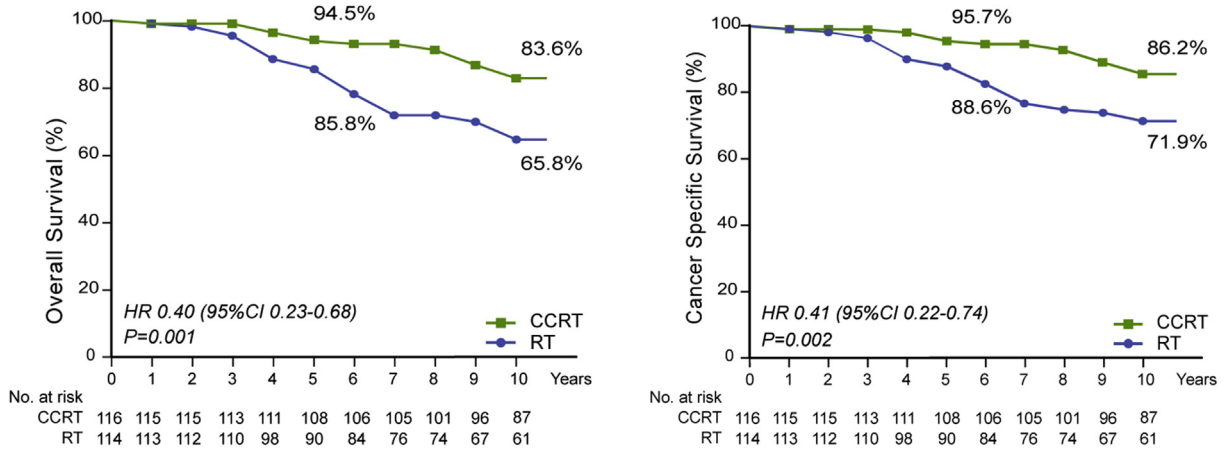

Fig. 2. Kaplan–Meier survival curves for the CCRT arm and RT arm (A) Overall survival (B) Cancer-specific survival. CCRT, concurrent chemoradiotherapy; RT, radiotherapy; HR, hazard ratio; CI, confidence interval. P values were calculated with the unadjusted log-rank test. P values were calculated with the unadjusted log-rank test.

subgroup proportions among the trials. As T2N1 patients were observed to have higher probability of distant metastases and poorer outcomes compared with other groups [5,6,10,12], a smaller proportion of T2N1 [10,11] may tend to a favourable overall outcome, thus overshadow the efficacy of chemotherapy. Besides, the survival end-points for stage II were small probability events, so it is difficult for cohorts with a small sample size to detect significant difference. Moreover, because all studies aforementioned were retrospective, selection bias may exist in treating high-risk stage II patients. The role of EBV as an etiologic agent and a prognostic factor has been demonstrated by many studies [13–15]; stage II patients with high EBV DNA levels [16] were also observed to easily develop distant metastasis, and other factors including extensive parapharyngeal

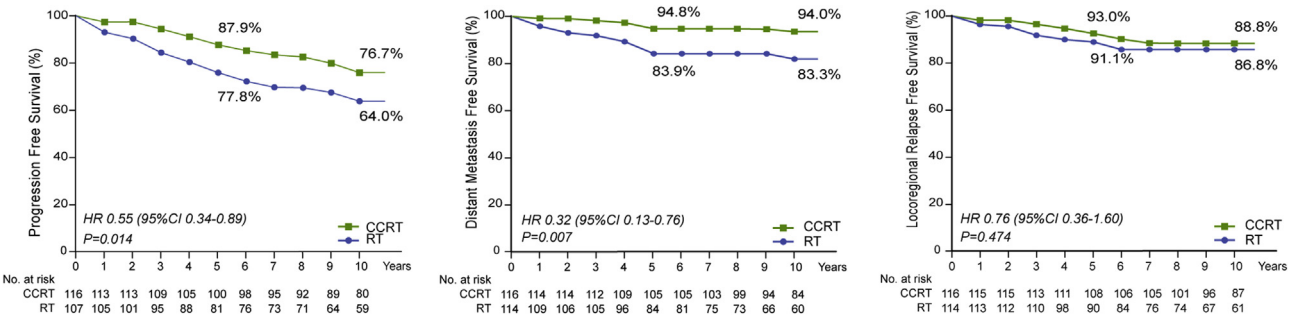

Fig. 3. Kaplan–Meier survival curves for the CCRT arm and RT arm (A) Progression-free survival (B) distant metastasis-free survival and (C) locoregional relapse-free survival. HR, hazard ratio; CI, confidence interval; CCRT, concurrent chemoradiotherapy. P values were calculated with the unadjusted log-rank test.

involvement and bulky unilateral lymph node invasion [16] were usually considered as high-risk variables that led to positive systemic intervention. Therefore, further investigations on selecting high-risk stage II patients and giving individualised treatment on the basis of IMRT are needed. So far, an ongoing clinical trial (NCT01187238) exploring the effect of chemotherapy with IMRT on stage II patients has finished recruitment. Another promising prospect on the efficacy of cetuximab or nimotuzumab in early-stage NPC is also worth exploration.

In multivariate analysis, the item of weight loss was introduced to predict survival and manifest importance of providing nutrition support to patients with NPC. The disparity in survival between different weight loss levels was also reported by many studies in patients with head and neck cancer [17–19]. The maintenance of the well nutritional status and sufficient nutrition support are highly suggested. Concerning the treatment-related toxicities, xerostomia was the most debilitating symptom that compromised the quality of life most with the highest incident rates among all late toxicities. In addition to xerostomia, the incidences of temporal lobe injuries, hearing impairment/otitis, skin fibrosis and trismus were all comparable between the two groups. Concurrent chemotherapy did not increase the numbers and severity of late complications on the basis of 2D CRT.

There are several limitations to this study. All patients were allocated based on the Chinese 1992 staging system, which did not completely tally with the AJCC staging system. Even though patients were restaged, the survival results of the whole cohort cannot represent stage II population for 31 were reclassified as stage III. As all patients underwent conventional RT in this study, which was gradually replaced by IMRT, the actual function of chemotherapy in IMRT setting still remains to be explored. EBV DNA tests were not mandatory before treatment, the baseline EBV DNA levels for the whole cohort were incomplete; therefore, the analysis on whether EBV DNA levels also serve as a prognostic factor in stage II patients was vacant. The late toxicity assessments of 28 patients were made through phone calls; physician bias and patient bias may exist in the process of asking and answer.

5. Conclusions

To our knowledge, survival results of stage II patients were quite limited, and our study was the first and the only RCT to fill the vacancy of long-term survivals of this stage. Results showed that CCRT significantly improved 10-year OS, PFS, CSS and DMFS compared with receiving RT alone without adding more late toxicities in stage II patients. However, further studies are still needed to verify the effectiveness of concurrent chemotherapy in IMRT settings and to select high-risk stage II patients to receive multimodality treatment.

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Author contributions

Hai-Qiang Mai and Lin-Quan Tang contributed to study concepts and quality control of data and algorithms. Lin-Quan Tang, Xiao-yun Li and Xue-Song Sun contributed to the study design. Yu-Jing Liang, Jin-Jie Yan, Shan−Shan Guo, Li-Ting Liu and Qing-Nan Tang helped in data acquisition. Xue-Song Sun and Sai-Lan Liu participated in data analysis and interpretation. Qiu-Yan Chen and Xiao-yun Li helped in manuscript preparation and statistical analysis. Xue-Song Sun, Sai-Lan Liu and Yue-feng Wen helped in editing the manuscript. Hai-Qiang Mai, Lin-Quan Tang, Ling Guo, Hao-Yuan Mo, Ming-Yuan Chen, Ying Sun and Jun Ma reviewed the manuscript.

Conflict of interest statement

The authors declare that they have no competing interests.

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