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Two-year outcome of concurrent chemoradiation with carboplatin with or without adjuvant carboplatin/fluorouracil in nasopharyngeal cancer: A multicenter randomized trial

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♆ **Authors' contributions**: IC conceived and coordinated the study, analyzed the data, and drafted the manuscript. PT performed the statistical analysis. IC, RK, TT, TA, KC, SC, and WO performed clinical data acquisition. IC, SL, WO, and PT revised the manuscript. All authors read and approved the final manuscript.

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A B S T R A C T

Background: According to the noninferiority result of chemoradiation with carboplatin in our previous nasopharyngeal carcinoma (NPC) study along with the inconclusive data on the efficacy of adjuvant chemotherapy (AC) following concurrent chemoradiotherapy (CCRT), we designed to assess the role of adjuvant carboplatin/fluorouracil following CCRT with carboplatin in locoregionally advanced NPC.
Materials and Methods: A multicenter randomized trial was conducted at 5 cancer centers in Thailand. We enrolled in stage T2N0M0-T4N2M0 (American Joint Cancer Committee 7th edition) WHO Type 2 NPC patients. N3 or metastatic disease patients were excluded. Participants were randomized into 2 groups: CCRT plus AC group vs the CCRT alone group. Patients in both groups received weekly carboplatin 100 mg/m^2 for 6 cycles concurrently with radiotherapy 69.96-70 Gy. Patients in the AC group subsequently received 3 cycles of carboplatin area under curve-5 plus 1000 mg/m^2/day of fluorouracil infusion within 96 hours every 3 weeks. We report the 2-year overall survival (OS), disease-free survival (DFS), loco-regional recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS). Treatment-related toxicities and compliance were also explored.
Results: Of 175 patients, 82 (46.9%) were assigned to the AC group, and 93 (53.1%) to the CCRT group. The compliance rate during CCRT was 90% and 86% in the AC and CCRT group, whereas 81.7% during adjuvant treatment in the AC group. With a median follow-up time of 24.4 months (interquartile range 17.9-24.4), the 2-year OS rate was 89.6% in the AC group and 81.8% in the CCRT group (P= 0.167). The 2-year DFS rate was 86.8% in the AC group and 74.6% in the CCRT group (P=0.042). The 2-year LRFS rate was 91.5% in the AC group and 88.2% in the CCRT group (P=0.443). The 2-year DMFS rate was 85.4% in the AC group and 79.6% in the CCRT group (P=0.294). The most frequent serious (grade 3/4) nonhematologic toxicity was acute mucositis, which occurred 5% in the AC group vs 4% in the CCRT group (P=0.498). For hematologic toxicity, grade 3-4 leukopenia were found 10% and 5% in the adjuvant and CCRT groups, respectively (P=0.003). Multivariate analyses determined stage N2 disease was an adverse prognostic factor associated with shorter OS, DFS, and DMFS. And the adjuvant treatment was a significant protective factor for only DFS.
Conclusions: The addition of adjuvant carboplatin/fluorouracil following CCRT with carboplatin significantly improved 2-year DFS in stage T2N0M0-T4N2M0 NPC albeit there was a nonsignificant trend in favor of a higher 2-year OS, LRFS, and DMFS. Long-term efficacy and late toxicities of AC still require exploration.

A R T I C L E I N F O

Keywords: Adjuvant; No adjuvant; Concurrent chemoradiotherapy; Nasopharyngeal cancer

Introduction

There was only 2 randomized study[1,2] comparing concurrent chemoradiotherapy (CCRT) with CCRT plus adjuvant chemotherapy (AC), both failed to show benefit of adjuvant treatment. One retrospective study[3] reported the overall survival (OS) benefit from the adding of AC to CCRT in high-risk patients only. All the studies used cisplatin during the CCRT and adjuvant regimen. Our previous study on carboplatin as a part of treatment in nasopharyngeal carcinoma (NPC) showed a better completion rate than cisplatin with no significant difference in efficacy.[4] It was important to address the issue of AC, especially with the derivative of cisplatin, carboplatin. We, therefore, carried out an open-label, randomized, phase II trial to determine both the efficacy and toxicity of adjuvant carboplatin-based after CCRT with carboplatin in stage T2N0M0-T4N2M0 NPC as per AJCC Staging (American Joint Cancer Committee) 7th edition.[5]

Materials and Methods

This multicenter, open-label, randomized, phase II trial was conducted at 5 cancer centers in Chiang Mai, Chonburi, Lampang, Songkla, and Udon Thani, Thailand. The inclusion criteria were; age 18-70 years old, biopsy-proven WHO type 2 NPC, stage T2N0M0-T4N2M0 (AJCC 7th edition), Eastern Cooperative Oncology Group performance status 0-1, adequate bone marrow function (white blood count >3000/mL, platelet count >100,000 mL, and hemoglobin >10 g/L), and serum creatinine clearance at least 30 mL/min. Patients with N3 or metastatic disease (stage IVB and IVC) were excluded. All patients underwent nasopharyngoscopy and biopsy, complete blood count, serum chemistry profile, chest radiograph, computed tomography or magnetic resonance imaging of the head and neck, and bone scan. We did not perform a central review of histopathological diagnosis and the Epstein-Barr virus analysis in this study. Signing the written informed consent was required for all patients before entering this trial. The enrolled patients were randomized into 2 groups: CCRT followed by AC group or CCRT alone group.

Our previous chemotherapy regimen during CCRT and AC treatment were used[4]; the CCRT regimen consists of 100 mg/m^2 of carboplatin intravenous infusion within 1 hour every week concurrently with radiotherapy (RT) for a total of 6 weeks. Chemotherapy regimen during adjuvant treatment contained carboplatin with area under curve-5 plus 1000 mg/m^2/day of 5-FU intravenously infusion for 4 days every 28 days, starting at 1 month after cessation of RT for a total of 3 cycles.

We allowed all RT techniques of megavoltage photons from conventional 2-dimensional RT to intensity-modulated radiation therapy (IMRT) to be used in this protocol, depending on the treatment strategy approved by each center. Dose per fraction of 2.0-2.12Gy per fraction with 5 daily fractions per week for 6-7 weeks was prescribed. The total radiation doses were 69.96-70 Gy to the gross tumor and the involved neck node. We gave 59.4-60 Gy and 50-54 Gy to the intermediate and low-risk nodal area, respectively. The protocol RTOG 0225[6] was followed for all patients treated with IMRT in all processes (dose prescription to the target, dose constraints of normal tissues, dose optimization, and dose evaluation). The patients who received 2-dimensional RT; the RT field, technique, and dose were prescribed the same as our previous study.[4] The criteria for chemotherapy dose modification both in the concurrent and adjuvant setting were similar to our foregoing study.[4]

The patients were assessed by endoscopy every 3 months during the first 2 years, then every 6 months afterward. computed tomography or magnetic resonance imaging of the neck was performed every 6 months during the first 2 years and once a year in the following years. For the patients who had disease recurrence either local, regional, or distant, we provided the salvaging management comprising re-RT, new chemotherapeutic drugs, and surgical treatment, in compliance with the regular practice of each study center. Toxicities during the treatment and follow-up period were assessed. The chemotherapy-related toxicities were categorized according to the Common Terminology Criteria for Adverse Events (version 3.0).[7] Both Acute and Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group[8] were used to measure the RT-related side effects.

The main endpoint of the study was the 2-year OS which was counted from the date of randomizing to the date of death from any causes. The secondary endpoints were as follows: 2-year disease-free survival (DFS) which was described as the date from randomizing to the date of any disease failure or the date of death from any causes either of which event was happened first, 2-year loco-regional recurrence-free survival (LRFS) and 2-year distant metastasis-free survival (DMFS) which were identified as the date of randomizing to the date of loco-regional recurrence or distant metastasis, respectively. We censored the patients with no documentation proof of events at the date of the last follow-up. All events that happened after 2 years were also censored. The compliance rate of RT was assessed using the overall treatment time (OTT). OTT was counted from the first date until the last date of RT. Complete of all 6 cycles of chemotherapy during CCRT in both groups and 3 cycles of AC in the AC group were counted for the compliance rate of chemotherapy in this study. This study was planned to recruit totally 294 patients

(147 patients per group) to have at least 80% of power to detect 15% improvement of the 3-year OS rate by the adjuvant treatment, according to 79.8% of the 3-year OS rate in AC group reported in our previous results,[4] assuming 64.8% for the CCRT group and 5% rate of early dropout or loss to follow-up. Participants were randomly assigned to one of the following groups using an allocation ratio of 1:1; the CCRT group (participants received CCRT alone) and the AC group (participants received CCRT followed by AC). The list, by blocks, was composed of running randomization numbers. Block size was not disclosed to the study site so that at no time a researcher could guess the treatment group of the next patient. Study personnel, participants, and clinical providers did not know the subjects' assignments. The AC group was not blinded as no placebo infusion given in the CCRT group. Characteristics of patients were presented as medians and interquartile ranges (IQRs) for continuous variables, and as frequencies and percentages for categorical variables. To compare the characteristics for continuous and categorical variables, the Mann-Whitney U test and Fisher's exact test were used, respectively. The proportion of acute and late toxicities was compared using Fisher's exact test. OS, DFS, LRFS, and DMFS were estimated using the Kaplan-Meier method and compared between groups using the Log-rank test. Factors associated with death from any causes, composited outcome of death or living with disease, locoregional recurrence, and distant metastasis were examined using Cox regression analysis. Also, we examined the associated factors of death from any causes using competing for risk regression analysis accounting living with the disease as competing events. All available variables were included in the multivariable analysis. *P* values of less than 0.05 were statistically significant. All *P* values described in this study are 2-sided values. We used Stata version 11 (StataCorp LP, College Station, TX) to execute all statistical analyses. The Research Ethics Committee of Faculty of Medicine, Chiang Mai University, and other 4 cancer centers approved and permitted this study.

Results

We performed a 2-year outcome report on the whole of 175 patients who were entered into this study between June 2015 and December 2018; 82 patients in the AC group and 93 patients received CCRT alone. The baseline characteristics of this study were presented in Table 1. No statistically significant difference between all variables was found in both groups.

The study flow diagram was demonstrated in Fig. 1. Thirty-nine patients did not receive allocated treatment from the protocol: 23 patients in the AC group and 16 patients in the CCRT group. One patient in the CCRT group decided not to participate in the protocol and 2 other patients discontinued their RT sessions in the first week of treatment. Besides, 15 patients in the AC group did not complete their 3 cycles of AC (1 patient did not receive any AC cycle, 8 patients received 1 cycle, and 6 patients received 2 cycles). The reason for all 15 uncompleted AC in this group was a patient refusal. The compliance rate of 3 cycles of adjuvant carboplatin/5-FU in the AC group was 81.7%. No dose modification or reduction of the number of adjuvant cycles was observed due to toxicity for the rest of the patients. However, 8 patients (10%) needed to delay their AC due to grade 3 or 4 leukopenia. Most patients in CCRT (88%) and AC (85%) group had Eastern Cooperative Oncology Group performance status 0. For the attention of the compliance rate of the total 6 cycles of weekly carboplatin during CCRT in the AC and CCRT group were 90% and 86% respectively. Eight patients in the AC group did not complete their 6 cycles of CCRT (7 patients received 5 cycles, and 1 patient received 4 cycles), while 13 patients in the CCRT group did not complete the 6 cycles. All of them received 5 cycles. The explanation of incomplete weekly carboplatin as planned for both groups were toxicities during CCRT. Nonetheless, we included all randomly assigned patients in the intent-to-treat analysis.

Table 2 summarizes the incidence of acute hematologic and nonhematologic toxicities and late toxicities of patients. The most common serious (grade 3-4) nonhematologic toxicity was acute mucositis, which occurred 5% in the AC group vs 4% in the CCRT group ($P = 0.498$). The most common severe (grade 3-4) hematologic toxicity was leukopenia, which occurred 10% in the AC group vs 5% in CCRT alone group ($P = 0.003$). We had the information of late radiation-induced toxicities in only 62 and 60 patients in the AC group and CCRT group, respectively.

Table 1
Baseline characteristics.

Characteristics n (%) or median [IQR]	CCRT + AC (n = 82)	CCRT (n = 93)	*P* value
Sex			0.340[a]
Male	32 (39%)	64 (69%)	
Female	50 (61%)	29 (31%)	
Median age (years)	52 [44-58]	49 [39-58]	0.468[b]
AJCC T stage			0.997[a]
T1	24 (29%)	26 (28%)	
T2	19 (23%)	21 (22%)	
T3	17 (21%)	20 (22%)	
T4	22 (27%)	26 (28%)	
AJCC N stage			0.775[a]
N0	9 (11%)	10 (11%)	
N1	26 (32%)	34 (36%)	
N2	47 (57%)	49 (53%)	
ECOG			0.675[a]
0	70 (85%)	82 (88%)	
1	12 (15%)	11 (12%)	
Response after treatment			0.721[a]
CR	67 (82%)	72 (77%)	
PD	1 (1%)	2 (2%)	
PR	14 (17%)	19 (21%)	
Technique			0.525[a]
2D-CRT	14 (17%)	12 (13%)	
IMRT	68 (83%)	81 (87%)	

AC, adjuvant chemotherapy; AJCC, American Joint Cancer Committee; CCRT, concurrent chemoradiotherapy; CR, complete response; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; PD, progressive disease; PR, partial response; 2D-CRT, conventional 2-dimensional radiotherapy.
[a] Fisher's exact test.
[b] Mann-Whitney U test.

The common late toxicities found in this study were mild to moderate grade (grade 1-2) of xerostomia. Though, we found grade 3 xerostomia in 1 and 2 patients in the AC and CCRT group, respectively. The median OTT during CCRT was 51 days (IQR 49-53) for the AC group and 50 days (IQR 49-52) for the CCRT group. There were no significant differences between both groups with regards to OTT ($P = 0.090$).

In the CCRT group, 6 months after CCRT completion, the complete response, partial response, and progressive disease rates were 72 (77%), 19 (21%), and 2 (2%), respectively. In the AC group, 3 months after 3 cycles of adjuvant treatment completion, the complete response, partial response, and progressive disease rates were 67 (82%), 14 (17%), and 1 (1%), respectively.

The median follow-up time of this study was 24.4 months (IQR 17.9-24.4). Comparing with the CCRT group, significant improvement in 2-year OS was not accomplished by adding AC (81.8% vs 89.6%, $P = 0.167$) but significantly improved in 2-year DFS (74.6% vs 86.8%, $P = 0.042$), as shown in Fig. 2a and b, respectively. The 2-year LRFS and DMFS rate was found to be increased in the AC group but did not show statistically significant differences. The 2-year LRFS rate was 91.5% in the AC group and 88.2% in the CCRT alone group ($P = 0.443$) (Fig 2c). The 2-year DMFS rate was 85.4% in the AC group and 79.6% in the CCRT alone group ($P = 0.294$) (Fig 2d).

According to multivariable analysis, stage N2 disease (adjusted sub hazard ratio = 6.32, 95% confidence interval [CI] = 1.92-20.85; $P = 0.002$) was a risk factor associated with a shorter OS (Table 3). Stage N2 (adjusted hazard ratio [aHR] = 2.93, 95% CI = 1.31-6.52; $P = 0.009$) was also a risk factor associated with a lower DFS and adjuvant treatment (aHR = 0.45, 95% CI = 0.21-0.96, $P = 0.039$) was a protective factor for DFS (Table 4). Only patients with N2 disease were associated with an increased risk of distant metastasis (aHR = 4.86, 95% CI = 1.86-12.65, $P = 0.001$). There was no significant factor related to risk of loco-regional recurrence (Supplementary Tables 1-2).

Table 2
Acute nonhematologic and hematologic toxicities and late toxicities.

Acute toxicities	CCRT + AC (n = 82)	CCRT (n = 93)	*P* value[a]
Skin			0.078
Grade 0	5 (6%)	1 (1%)	
Grade 1	60 (73%)	68 (73%)	
Grade 2	15 (18%)	24 (26%)	
Grade 3	2 (3%)	0 (0%)	
Saliva			0.136
Grade 0	0 (0%)	2 (2%)	
Grade 1	45 (55%)	41 (44%)	
Grade 2	36 (44%)	50 (54%)	
Grade 3	1 (1%)	0 (0%)	
Mucosa			0.498
Grade 0	5 (6%)	2 (2%)	
Grade 1	27 (33%)	27 (29%)	
Grade 2	46 (56%)	60 (65%)	
Grade 3	4 (5%)	4 (4%)	
Pharynx			0.253
Grade 0	3 (4%)	3 (3%)	
Grade 1	31 (38%)	25 (27%)	
Grade 2	47 (58%)	63 (68%)	
Grade 3	0 (0%)	2 (2%)	
Larynx			0.798
Grade 0	28 (74%)	25 (69%)	
Grade 1	10 (26%)	11 (31%)	
Grade 2	0 (0%)	0 (0%)	
Grade 3	0 (0%)	0 (0%)	
Anemia			0.454
Grade 0	49 (61%)	66 (72%)	
Grade 1	21 (26%)	17 (18%)	
Grade 2	10 (12%)	8 (9%)	
Grade 3	1 (1%)	1 (1%)	
Leukopenia			0.003*
Grade 0	46 (56%)	75 (82%)	
Grade 1	17 (21%)	9 (10%)	
Grade 2	11 (13%)	3 (3%)	
Grade 3	7 (9%)	5 (5%)	
Grade 4	1 (1%)	0 (0%)	
Thrombocytopenia			0.063
Grade 0	70 (87%)	88 (96%)	
Grade 1	9 (11%)	4 (4%)	
Grade 2	1 (1%)	0 (0%)	
Grade 3	0 (0%)	0 (0%)	
Grade 4	1 (1%)	0 (0%)	
Late toxicities	CCRT + AC (n = 62)	CCRT (n = 60)	*P* value[a]
Skin			0.645
Grade 0	49 (79%)	50 (83%)	
Grade 1	13 (21%)	10 (17%)	
Grade 2	0 (0%)	0 (0%)	
Grade 3	0 (0%)	0 (0%)	
Subcutaneous tissue			0.624
Grade 0	41 (66%)	40 (67%)	
Grade 1	20 (32%)	17 (28%)	
Grade 2	1 (2%)	3 (5%)	
Grade 3	0 (0%)	0 (0%)	
Saliva			0.111
Grade 0	10 (16%)	13 (22%)	
Grade 1	40 (64%)	41 (69%)	
Grade 2	11 (18%)	4 (6%)	
Grade 3	1 (2%)	2 (3%)	
Mucosa			0.584

(*continued on next page*)

Table 2 (*continued*)

Acute toxicities	CCRT + AC (n = 82)	CCRT (n = 93)	*P* value[a]
Grade 0	53 (85%)	54 (90%)	
Grade 1	9 (15%)	6 (10%)	
Grade 2	0 (0%)	0 (0%)	
Grade 3	0 (0%)	0 (0%)	
Trismus			0.492
Grade 0	62 (100%)	59 (98%)	
Grade 1	0 (0%)	1 (2%)	
Grade 2	0 (0%)	0 (0%)	
Grade 3	0 (0%)	0 (0%)	
Pharynx			0.492
Grade 0	62 (100%)	59 (98%)	
Grade 1	0 (0%)	1 (2%)	
Grade 2	0 (0%)	0 (0%)	
Grade 3	0 (0%)	0 (0%)	

AC, adjuvant chemotherapy; CCRT, concurrent chemoradiotherapy.
[a] Fisher's exact test.
* Statistical significance at level of 0.05.

Discussion

In our present study, the focus was on the importance of AC in NPC patients who had only nonmetastatic stage T2N0M0-T4N2M0 according to the 7th edition AJCC/UICC staging system. We excluded both N3a and N3b patients due to their high risk of distant metastasis and AC is required.

There are several network meta-analysis studies[9-11] attempting to summarize the contribution of adding chemotherapy in this disease and the sequence of treatment with RT. The first study[9] did not demonstrate the significant differences in the effectiveness of addition chemotherapy either neoadjuvant or adjuvant setting compared to CCRT only, except for the marginally better distant metastasis control in the neoadjuvant approach. The second study[10] demonstrated the best survival outcome and improved locoregional control/distant metastasis

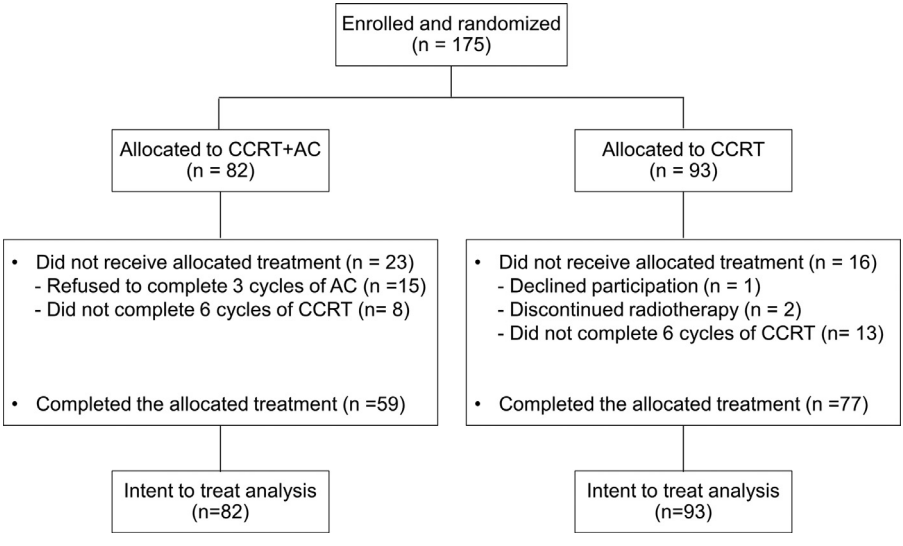

Fig. 1. Consort diagram.

Table 3
Risk factors of overall survival.

Factors	n/N (%)	Death[a]				Death accounting for competing risk of living with disease[b]			
		Univariable analysis		Multivariable analysis[c]		Univariable analysis		Multivariable analysis[c]	
		HR (95% CI)	*P* value	aHR (95% CI)	*P* value	SHR (95% CI)	*P* value	aSHR (95% CI)	*P* value
Sex			0.740				0.673		
Female	9/61 (15%)	1.00				1.00			
Male	14/114 (12%)	0.87 (0.36-2.01)				0.84 (0.36-1.92)			
Age			0.708				0.682		
≤50 years	11/91 (12%)	1.00				1.00			
>50 years	12/84 (14%)	1.17 (0.52-2.65)				1.19 (0.52-2.68)			
AJCC T stage			0.299				0.292		
T1	9/50 (18%)	1.00				1.00			
T2	7/40 (18%)	0.99 (0.37-2.67)	0.990			0.98 (0.37-2.58)	0.960		
T3	2/37 (5%)	0.27 (0.06-1.27)	0.098			0.27 (0.06-1.25)	0.094		
T4	5/48 (10%)	0.56 (0.19-1.68)	0.303			0.56 (0.19-1.67)	0.296		
AJCC N stage			0.003*		0.003*		0.002*		0.002*
N0-N1	3/79 (4%)	1.00		1.00		1.00		1.00	
N2	20/96 (21%)	6.29 (1.87-21.17)		6.29 (1.87-21.17)		6.32 (1.92-20.85)		6.32 (1.92-20.85)	
ECOG			0.511				0.507		
0	21/152 (14%)	1.00				1.00			
1	2/23 (9%)	0.61 (0.14-2.62)				0.61 (0.14-2.66)			
Treatment			0.174				0.205		
CCRT	15/93 (16%)	1.00				1.00			
CCRT + AC	8/82 (10%)	0.55 (0.23-1.30)				0.58 (0.25-1.35)			
Technique			0.175				0.152		
2D-CRT	6/26 (23%)	1.00				1.00			
IMRT	17/149 (11%)	0.52 (0.21-1.33)				0.51 (0.21-1.28)			

AC, adjuvant chemotherapy; aHR, adjusted hazard ratio; AJCC, American Joint Cancer Committee; aSHR, adjusted sub hazards ratio; CCRT, concurrent chemoradiotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; SHR, subhazard ratio; 2D-CRT, conventional 2-dimensional radiotherapy.

[a] Cox regression.

[b] Competing risk regression.

[c] All variables were included in the multivariable analysis.

* Statistical significance at level of 0.05.

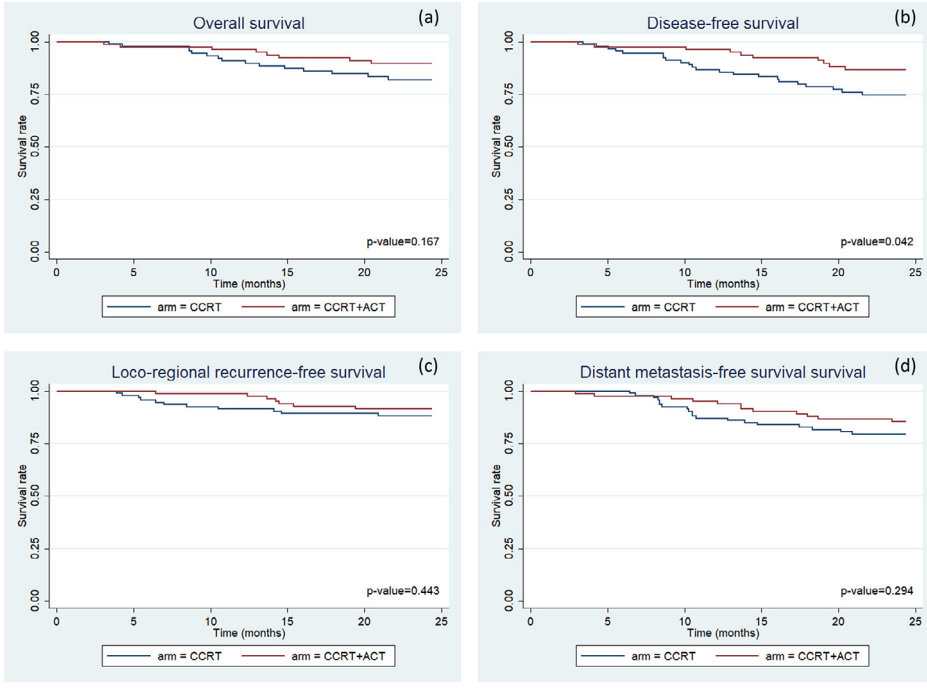

Fig. 2. Survival rate: (a) 2-year overall survival (OS), (b) 2-year disease-free survival (DFS), (c) 2-year loco-regional recurrence-free survival (LRFS), (d) 2-year distant metastasis-free survival (DMFS).

when adding the AC to CCRT. The third meta-analysis[11] reported the most promising strategy is neoadjuvant chemotherapy plus CCRT. They could not demonstrate the significant difference in survival outcomes and all the endpoints between AC in addition to CCRT against CCRT alone. Furthermore, most of the studies in these meta-analyses had cisplatin in their concurrent and adjuvant regimen. As we are aware that the compliance rate of chemotherapy during the treatment is important for the treatment outcome. The compliance rate of cisplatin ranged from 43-71% during CCRT and 15-76% during adjuvant treatment.[1,3,12-16] The derivative of cisplatin; carboplatin has been applied in the chemotherapy regimen for advanced NPC to resolve this problem. Songthong et al.[17] and our previous study[4] reported the compliance rate of carboplatin 68.5 and 77% during CCRT and 69.8 and 72% during adjuvant treatment. Dechapunkul et al.[18] also had the outstanding compliance rate at 98% for all planned 5 cycles of carboplatin throughout the treatment which was less than other studies for 1 adjuvant cycle. In this present study, we still demonstrated a satisfactory compliance rate with 90% during CCRT and 81.7% in the adjuvant setting. CCRT-related adverse events were the reason for incomplete 6 cycles of carboplatin in both groups, whereas the cause of incomplete 3 cycles of AC was a patient refusal. The median OTT of RT in our current study is in line with many CCRT studies.[2,13,17]

Only 2 prospective studies explored the influence role of AC addition to CCRT.[1,2] The latest update from Chen et al.[1] still concluded that AC were unsuccessful to show the survival advantage over CCRT alone. The problem of low compliance rate of chemotherapy during CCRT and adjuvant treatment was mentioned in their study. Although they used a weekly cisplatin during CCRT, the compliance rate was still low at 45%. Consequently, severe side effects during CCRT reduced the number of patients to complete all cycles of AC. They found that 63% of patients received all 3 cycles of AC. This could be the reason of how adding AC to CCRT failed to be a part of the treatment of this disease. A factorial study from Kwong et al.[2] did not prove the usefulness of AC after RT alone or CCRT. They also reported the high rate of severe side effects

Table 4
Risk factors of disease-free survival.

Factors	n/N (%)	Death or living with disease[a]			
		Univariable analysis		Multivariable analysis[b]	
		HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Sex			0.583		
Female	10/61 (16%)	1.00			
Male	22/114 (19%)	1.23 (0.58-2.60)			
Age			0.598		
≤50 years	15/91 (16%)	1.00			
>50 years	17/84 (20%)	1.21 (0.60-2.41)			
AJCC T stage			0.302		
T1	10/50 (20%)	1.00			
T2	10/40 (25%)	1.29 (0.54-3.10)	0.571		
T3	3/37 (8%)	0.37 (0.10-1.34)	0.130		
T4	9/48 (19%)	0.91 (0.37-2.24)	0.840		
AJCC N stage			0.010*		0.009*
N0-N1	8/79 (10%)	1.00		1.00	
N2	24/96 (25%)	2.85 (1.28-6.35)		2.93 (1.31-6.52)	
ECOG			0.496		
0	29/152 (19%)	1.00			
1	3/23 (13%)	0.66 (0.20-2.17)			
Treatment group			0.047*		0.039*
CCRT	22/93 (24%)	1.00		1.00	
CCRT + AC	10/82 (12%)	0.47 (0.22-0.99)		0.45 (0.21-0.96)	
Technique			0.338		
2D	7/26 (27%)	1.00			
IMRT	25/149 (17%)	0.66 (0.29-1.53)			

AC, adjuvant chemotherapy; aHR, adjusted hazard ratio; CCRT, concurrent chemoradiotherapy; CI, confidence interval; HR, hazard ratio.
[a] Cox regression.
[b] All variables were included in the multivariable analysis.
* Statistical significance at level of 0.05.

of AC with 57.3% grade 3-4 leukopenia. However, they remarked about the ineffectiveness of their AC regimen using cisplatin plus fluorouracil alternating with vincristine, bleomycin, and methotrexate.

In conjunction with the meta-analysis from Ribassin-Majed et al.,[10] our current study demonstrated that the addition of AC to CCRT could significantly increase DFS. Although the results in this study did not prove the significant OS benefit, given the trend to favor of adding AC after CCRT for this treatment outcome (89.6% vs 81.8%) and others, eg, LRFS (91.5% vs 88.2%), DMFS (85.4% vs 79.6%). Comparing the CCRT plus AC group in other studies, our treatment outcomes are consistent with their results as shown in SupplementaryTable 3, except our previous study. One explanation for the higher PFS and OS rate in our current study[4] comparing to our previous one[4] even though using the same chemotherapy regimen during CCRT and adjuvant treatment is the difference in the criteria of inclusion and exclusion between the 2 studies. The earlier study[4] enrolled more advanced NPC than the recent one. While we excluded the patients with lymph node size more than 6 cm or supraclavicular lymph node metastasis out from this study, on the contrary, the previous study enrolled this group of patients for 60% of the trial. Another reason for the satisfactory treatment outcome in our present study is the high percentage of using IMRT (83%) whereas 100% of conventional RT in our former study. Although we had a combination of conventional RT and IMRT techniques in our patient population, both groups were well balanced. It should be noted that the IMRT technique was not a significant protective prognostic factor in every outcome (LRFS, DMFFS, DFS, and OS) in our multivariate analysis. Songthong et al.[17] had only 11% of N3 patients in their trial and treated with IMRT 100% to the patients, the survival outcome was consistent with our existing study. The multivariate analysis was con-

firmed the benefit of AC as the protective factors for death and patient with N 2 disease had a higher risk for death. This is in line with the retrospective study from Taiwan[19] revealed that advanced stage NPC and suboptimal of AC cycle (no AC or receiving only 1 cycle) were the poor risk factors for the survival endpoints from their multivariate analysis. Consistent with the study from Liang et al.,[3] they reported that only high-risk group patients showed improvement in survival outcome as a result of combining AC to CCRT. The latest prognostic index for the OS of NPC patients was proposed by Liang et al.[20] (T stage, N stage, age, and pretreatment serum alkaline phosphatase) and patients with high risk achieved survival benefits from AC, whereas only the N stage has been presented to be the only poor risk factor in our study. Another retrospective study investigating the role of AC adding to CCRT with the IMRT technique[16] demonstrated a marginally increasing OS (P value = 0.055) in the adjuvant treatment for stage III-IV patients.

We preferred to compare the toxicities with all studies using carboplatin including our previous one.[4,17-18] We did not find any severe dermatitis in this study, whereas 10% in our previous one.[4] This could be the effect of the IMRT technique used in this study. However, late grade 3 xerostomia is still the most common severe late toxicity in this study (1.2%) as in the previous one (3%). Grade 3-4 leukopenia was found in 10% in the AC group and 5% in the CCRT group in this study. In agreement with Songthong et al.[17] which had 6.8% of severe leukopenia. Late severe ototoxicity was not revealed in this study, also not reported in other carboplatin studies. In contrast with other studies with a cisplatin regimen, they reported severe ear toxicity 13-21% of the patients.[1,13] However, the period of follow-up time is still short in this study with a median of 24.4 months (IQR 17.9-24.4). With the limitation mentioned, additional extended time of follow-up may provide the accurate incidence of late radiation-induced toxicities and the long-term benefit of AC after CCRT. Another limitation is that we did not have documentation in some chemotherapy-related toxicities, ie, nausea/vomiting, diarrhea, renal failure, etc.

This is the first reported exploration of the role of adding AC to CCRT using carboplatin instead of cisplatin. Moreover, the treatment outcomes of our AC group are comparable to many cisplatin studies.[1,3,12-16] This study has failed to meet the primary endpoint of OS but demonstrated a benefit of DFS. We decided to discontinue enrolling more patients into this study. As a consequence of our findings, it should be encouraged to use this regimen both in CCRT and AC for this group of patients.

Conclusion

Adjuvant carboplatin and fluorouracil significantly improved DFS following CCRT with carboplatin in stage T2N0M0-T4N2M0 NPC patients with very few severe treatment-related side effects. However, extended follow-up time is still warranted for the long-term efficacy and late radiation-induced toxicity assessment.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2020.100620.

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