Original Article

Advanced T Stage is the Sole Determining Factor of Survival in Patients with Nasopharyngeal Carcinoma: The Outcomes of the Multi-Modality Management

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Background: Thailand is an endemic area of nasopharyngeal carcinoma (NPC). Multi-modality treatment results in significant improvement in survivals.

Objective: The overall survival (OS) of patients with early and locally-advanced (E and LA, stage I-IVa and IVb) diseases was the primary objective.

Materials and Methods: The present study was a retrospective cohort study of patients with NPC treated at Vajira Hospital between 2013 and 2016. Baseline characteristics including age, gender, histopathology, staging, modality of treatment, time to radiotherapy completion, serious adverse events, treatment responses, patterns of recurrence, and metastasis were collected.

Results: One hundred patients with mostly undifferentiated histology that presented with LA disease were included in this study. Stage III, IVa, and IVb accounted for 28%, 18%, and 22%, respectively. After median follow-up of 41.1 months, the median OS of patients E/LA diseases (stage I, II, III, IVa, and IVb) was not reached. Neither induction chemotherapy (IC) nor adjuvant chemotherapy (AC) was associated with superior disease-free survival (DFS) compared to definitive concurrent chemoradiotherapy (CRT) alone across all stage subgroups. Only T3 and T4 disease were significantly related to worse OS.

Conclusion: With the standard CCRT, patients with E and LA diseases had excellent survival outcomes compared to the results from international studies.

Keywords: Nasopharyngeal carcinoma, Multi-modality treatment, Outcomes, Real-life practice

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Nasopharyngeal carcinoma (NPC) is the most common head and neck cancer among Southeast Asian countries. According to the International Agency for Research on Cancer reported in 2018, there were about 129,000 new cases of NPC[1]. Nevertheless, more than seventy percent of new cases are in east and southeast Asia including Thailand. Thailand also had the fifth highest number of deaths from NPC behind China, Indonesia, Vietnam, and India[2]. Based on Thailand's Hospital-based Cancer Registry 2016, NPC was the twelfth most common newly diagnosed cancer[3]. The notably highest incidence of NPC in Asian countries correlates with its common risk factors, including Ebstein-Barr virus (EBV) infection, host genetics, and environmental factors[4]. The non-keratinized and undifferentiated subtypes constitute most cases in endemic areas and are predominantly associated with EBV infection[5]. Compared to non-nasopharyngeal head and neck cancer, NPC tends to have higher chances of visceral and bony metastasis, even though it has higher response to both chemotherapy and radiotherapy and longer survival[6]. Very early disease such as stage I and II, can be cured by definitive radiotherapy alone. However, more advanced diseases need the addition of systemic chemotherapy. The most widely accepted treatment for locally advanced or stage III, IVa, and IVb, NPC is definitive concurrent radiotherapy with cis-platin chemoradiotherapy (CRT). This was demonstrated by the recently updated result of MAC-NPC meta-analysis showing the consistent benefit on overall survival (OS), Furthermore, the addition of either induction chemotherapy (IC) or adjuvant

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chemotherapy (AC) with definitive radiotherapy resulted in no significant improvement in survival[7]. The Al-Sarraf's Intergroup 0099 regimen that include AC with cisplatin and fluorouracil after definitive CCRT is the most widely used paradigm in Thailand, even though there were many pitfalls in the study, especially, more patients with keratinized pathology uncommon in Asian countries and underpowered sample size[8]. A well-designed clinical study that enrolled specifically Asian patients has raised the suspicion whether AC after CRT would confer further survival benefits[9]. The standard of care among most Thai university and cancer hospitals remains the definitive CRT for patients with locally advanced disease. The present study intended to determine the outcomes of such paradigm of management.

Materials and Methods

After being approved by the Committee of Medical Research Ethics of Navamindradhiraj University (COA 149/2561), the investigators retrieved the information from the electronic and written databases. The participants included NPC patients aged 18 years or older who attended the Vajira Hospital between January 1, 2013 and December 31, 2016, and had full-detailed medical records including full results of otolaryngology examination, histopathology, imaging studies, and treatments. Only patients with complete details of treatments and regular follow-ups, no matter whether they completed the course of multi-modality treatment or not were included in the analyses. Participants were followed from the date of diagnosis as indicated in the official pathological report to the date of death. The exact date of cancer recurrence or metastasis was the date indicated on the official radiological report of recurrence or metastasis. If not available, the date indicated first on the medical record confirming recurrence or metastasis was used. The investigators collected the baseline characteristics of patients including age at diagnosis, gender, histopathology classification based on the World Health Organization (WHO) 1978[10], composite TNM stage (based on The American Joint Committee on Cancer (AJCC) Seventh edition[11]), tumor stage (T), nodal stage (N), modality of primary definitive treatment, including definitive radiotherapy only (RT), definitive chemoradiotherapy only (CRT), definitive chemoradiotherapy and adjuvant chemotherapy (CRT→AC) and induction chemotherapy, and then definitive chemoradiotherapy (IC→CRT). All the patients indicated for RT received conventionally fractionated radiotherapy. External RT was applied with conventional 2-D technique. To define treatment fields, facial or cervical radiograms were taken using a computed tomography (CT) simulator. Nasopharynx, metastatic lymph nodes, and adjacent tissues were treated with 70.2 Gy and the uninvolved neck with 59.4 to 64.8 Gy (1.8 Gy daily fractions, five fractions per week), using a shrinking lateral opposed field technique, with exclusion of the spinal cord after 39.6 to 43.2 Gy. The lower neck was treated with 50 to 54 Gy through a single anterior field with midline shielding. Whether an adjuvant boost of 5 Gy (in two fractions) was given to stage I-IIB patients was under discretion of a radiation oncologist. Neither intensity-modulated radiotherapy (IMRT) nor intensity-guided radiotherapy (IGRT) was performed. Definitive CRT was the standard of care for patients with stage III, IVa, and IVb diseases, and some patients with bulky or symptomatic stage II disease. RT was administered concomitant with either bolus cisplatin at 75 to 100 mg/m² on days 1, 22, and 43, or weekly cisplatin at 40 mg/m² weekly until completing RT session. The regimen consisting of carboplatin at AUC 5 mg/minute/mL, and 5-fluorouracil (5-FU), which is 1,000 mg/m²/day on days 1 to 4, was routinely replaced by bolus cisplatin in patients with impaired renal function, which is creatinine clearance of 40 mL/minute or less. According to the institute's routine practice, IC was recommended in patients with bulky lymph node metastasis, stage IVa and IVb diseases and those presented with intractable epistaxis. The IC regimen consisted of cisplatin 80 mg/m² on day 1 and 5-FU 1,000 mg/m²/day was administered on day 1 to 4 every three to four weeks up to three courses prior to definitive RT, otherwise, whether AC with the same regimen given, was under the discretion of the medical oncologist. The investigators also included the duration of RT session and response to primary definitive treatment as the potential prognostic variable. Delayed time to complete RT course was defined as the time to complete RT session that was delayed for more than two weeks as expected date of completion. Either CT or MRI scans of the nasopharynx and the whole neck with contrast enhancement were obtained prior to starting the treatment and within two to three months after finishing definitive treatment to determine the treatment response. Either chest roentgenography with ultrasonography of upper abdomen or CT of chest including upper abdomen in combination with bone scintigraphy were obtained to exclude the distant metastasis. Positron emission tomography (PET)-CT scan was not compulsory. The treatment response

was assessed with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1[12]. The response after IC was determined clinically by a medical oncologist, but the response after finishing RT was assessed using imaging study. Treatment-related toxicities during multi-disciplinary management including hematologic and nephrogenic toxicities, electrolyte imbalances and oral mucositis were documented and systemically graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 2.0[13]. The data were censored on December 31, 2019. Dates of death were confirmed with the Ministry of Internal Affair Census Database.

Statistical analysis

Based on the study by Kong et al[14], the number of participants required for survival outcome were more than 100. The primary objective was to determine the 5-year OS of patients with early and locally advanced diseases (stage I-IVa and IVb). The secondary objectives were to explore the 5-year disease-free survival (DFS), the independent prognostic factors of DFS and OS among patients without distant metastasis at presentation (stage I, II, III, IVa, and IVb), the effect of IC and AC upon CRT and OS among patients with distant metastatic (stage IVc). The 5-year OS and DFS were the percentage of patients who survived and those without recurrence or metastasis or death five years after diagnosis, whichever occurred first after diagnosis, respectively. The DFS was analyzed and measured from the date of initial diagnosis to the date of recurrence (local, loco-regional, or distant) or death whatever occurred first. The descriptive variables were reported as median and IQR. Comparing the demographic data among different groups of interest, used either chi-square or t test as appropriated. Kaplan-Meier method was used to estimate the survival outcomes. The 5-year DFS and OS were calculated using log rank test and reported as percent and 95% confidence interval (CI). Hazard ratio (HR) of DFS, and OS between different groups of interest were calculated using Cox proportional hazard model. Factors associated with adverse DFS in univariate analysis as considered by p-value of less than 0.05 were later analyzed in multivariate analysis using Cox regression analysis to determine the independent factors. All the statistical data were evaluated using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA).

Results

One hundred forty-eight patients with nasopharyngeal cancer were treated at Vajira Hospital, however, only 100 patients had complete detailed medical information and regular follow-up visits. Thirty-six patients had been treated during the multi-modality management period and sent back to their primary hospitals while 12 patients were lost follow-up visits. The baseline patient characteristics are shown in Table 1.

IC→CRT (44%) was the most commonly-used modality of treatment. Cisplatin (78%) was most commonly used during concurrent with RT, while regimen including carboplatin with or without 5-FU was less commonly used and limited to patients with impaired renal function. Definitive RT alone (4%) was applied in a small group of patients with small-volume stage I and slightly symptomatic stage II diseases. Eighty of the ninety-nine patients (80%) who received radiation with curative intent with or without chemotherapy had objective response. Patients with metastatic disease at presentation were treated with chemotherapy alone in one patient, the rest were treated with both palliative chemotherapy and RT later. Around half of the patients (52%) received and finished RT session on time as defined as not being later than two weeks after the expected date of completion. Serious adverse events during treatment occurred in one-fifth of the patients (20 patients). Severe oral mucositis occurred most (80% of all severe adverse events). Renal impairment and electrolyte imbalances were the less frequent ones, however, such serious toxicities usually appeared simultaneously with oral mucositis. They always happened during CRT with cisplatin and after at least two cycles of bolus cisplatin or after four weeks of daily doses of cisplatin. Sepsis and febrile neutropenia rarely occurred. IC did not result in more toxicities during subsequent CRT.

Interestingly, disease recurrence usually appeared within the first three years after diagnosis (Figure 1B). Loco-regional recurrence, at tumor site or regional lymph nodes, in 19 of the 36 patients, (52.8%), was more common than bone and visceral metastases with 11 patients (30.6%) and 10 patients (27.8%), respectively. Palliative chemotherapy was most commonly used for patients with recurrent locoregional and metastatic (LRM) diseases. Combination platinum-based chemotherapy of cisplatin or carboplatin plus 5-FU, paclitaxel, or gemcitabine, was the preferred first-line regimen. However, the response in patients with recurrent LRM diseases was less satisfactory. Twelve of 29 evaluable patients (41.4%) had objective response.

Table 1. Baseline characteristics of participants (n=100)

Characteristics	Patients; n (%)
Sex	
Male	74 (74)
Female	26 (26)
Age (years); median (IQR)	50 (43.5 to 59.0)
WHO classification	
Type 1 (keratinized squamous cell carcinoma)	4 (4)
Type 2 (non-keratinized squamous cell carcinoma)	14 (14)
Type 3 (undifferentiated)	80 (80)
Not defined	2 (2)
T stage	
1	36 (36)
2	17 (17)
3	21 (21)
4	26 (26)
N stage	
0	14 (14)
1	35 (35)
2	25 (25)
3	26 (26)
Composite stages (AJCC 7th edition)	
Stage I	5 (5)
Stage II	24 (24)
Stage III	28 (28)
Stage IVa	18 (18)
Stage IVb	22 (22)
Stage IVc (with distant metastasis)	3 (3)
Planned definitive treatment (n=97)	
Definitive RT	4 (4.12)
Definitive CCRT	34 (35.05)
Definitive CCRT + adjuvant chemotherapy	15 (15.46)
Induction chemotherapy + definitive CCRT	44 (45.36)
Induction chemotherapy (IC)	
No	56 (56)
CDDP or CBDCA + FU	44 (44)
Number of cycles of IC (n=44)	
1 cycle	3 (6.81)
2 cycles	10 (22.72)
3 cycles	30 (68.18)
6 cycles	1 (2.27)
Response after induction chemotherapy (n=44)	
SD	3 (6.8)
CR/PR	40 (90.1)
PD	1 (2.3)

Characteristics	Patients; n (%)
Time to RT completion (n=99)	
Not completed/not received	10 (10)
Delayed	37 (37)
On time	52 (52)
Serious AEs (CTCAE grade 3 or more or required hospitalization) during RT or CCRT (n=20)	
Oral mucositis	16 (80)
Severe electrolyte imbalances	8 (40)
Presumed concomitant infection or febrile neutropenia	5 (25)
Responses after RT/CCRT (n=99)	
PD	11 (11.1)
SD	8 (8)
CR/PR	80 (80.8)
Adjuvant chemotherapy (AC)	
No	82 (84.53)
Yes	15 (15.46)
Number of cycles of AC	
1 cycle	2 (13.33)
2 cycles	1 (6.67)
3 cycles	12 (80)
Recurrence (n=36)	
Locoregional (tumor bed and/or regional lymph nodes)	19 (52.8)
Distant metastasis	18 (50)
• Bones	11 (30.6)
• Viscera	10 (27.8)
Both locoregional and distance metastasis	1 (2.8)
Subsequent treatment (n=36)	
Re-irradiation	10 (27.8)
Surgery	1 (2.8)
Chemotherapy	29 (80.6)
Palliative care only	5 (13.9)
First line palliative chemotherapy (n=29)	
CDDP/CBDCA + FU	12 (41.3)
CDDP/CBDCA + Paclitaxel	3 (10.3)
CDDP/CBDCA + Gemcitabine	12 (41.4)
Others	2 (6.9)
Response to first-line chemotherapy	
PD	12 (41.4)
SD	5 (17)
CR/PR	12 (41.4)
Status at the time of censored data	
Alive	70 (70)
Dead	30 (30)

WHO=World Health Organization; AJCC=American Joint Committee on Cancer; RT=radiotherapy; CCRT=concurrent chemoradiotherapy; CDDP=cisplatin; CBDCA=carboplatin; FU=fluorouracil; SD=stable disease; CR=complete response; PR=partial response; PD=progressive disease; AEs=adverse events; CTCAE=Common Terminology Criteria for Adverse Events; IQR=interquartile range

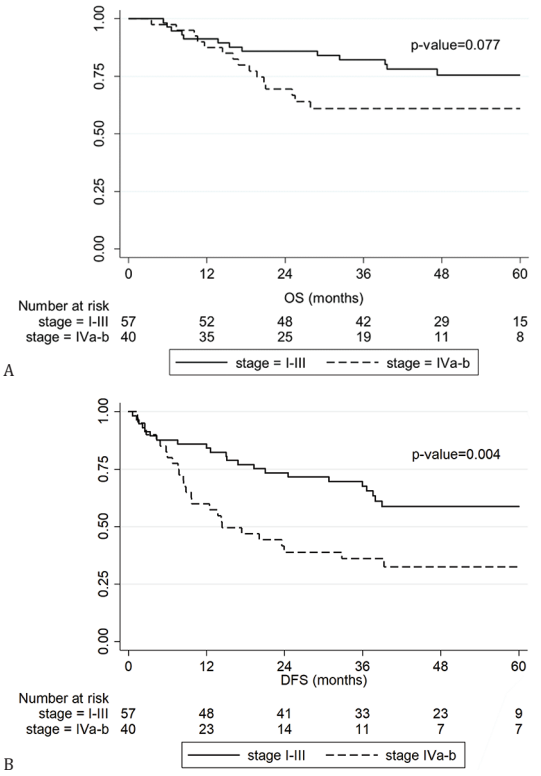

Figure 1. Kaplan-Meier curves of OS (A) and DFS (B) among patients with non-metastatic diseases (stage I-IVa and IVb).

Re-irradiation was possible in only a minority of such patients. Surgery was rarely done and indicated only in a patient with regional lymph node recurrence amenable to radical neck dissection.

After median follow-up of 41.1 months (IQR 22.75 to 58.80), the median OS of patients E/LA diseases (stage I, II, III, IVa, and IVb) was not reached (Figure 1). The 5-year OS of patients E/LA diseases was 68.13% (95% CI 57.46 to 76.66) and patients with distant metastatic disease (IVc) was only 33.3% (95% CI 0.9 to 77.41). There was no significant OS difference among patients with stage I, II, III compared with patients with very locally advanced (stage IVa and IVb) (Figure 1A). However, there was statistical differences among 5-year DFS of patients with stage I, II, III [58.84% (95% CI 44.24 to 70.83)] compared with patients with very locally advanced (stage IVa and IVb), [32.56% (95% CI 18.21 to 47.74)]. Only advanced T stage (T3/4) and composite stage (IVa and IVb) were independently associated with shorter DFS. Response to primary treatment (CRT or IC→CRT or CRT→AC) was not included in the analysis because treatment responses were confounded by different time points of response assessment, i.e., follow-up imaging studies for those who received IC or AC tended to be obtained two to three months later than patients who received CRT alone. Age, gender, histology, nodal stage, delayed RT completion were not the predictors (Table 2). To determine the outcomes among patients who were strongly indicated for definitive CCRT, stage III and IVa and IVb, the investigators found that both 5-year DFS and 5-year OS among these groups were 38.23% (95% CI 26.14 to 50.20) and 64.12% (95% CI 50.83 to 74.68), respectively. Neither IC nor AC was associated with superior DFS compared to CRT alone in this subgroup and across all stage subgroup (Table 3). Excluding the subgroup with distant metastatic disease (stage IVc) at presentation, univariate analyses of factors associated with shorter OS included T3/4, N3 and composite stage IVa and IVb at diagnosis, however, only T3/4 disease was independently related to worse survival in multivariate analysis (Table 4).

Discussion

NPC is the most common head and neck cancer in Thailand and endemic in Eastern and South-eastern Asian countries due to the association with Ebstein-Bar virus. Since the progress of treatment with definitive concurrent CRT, the survival outcomes have improved. The investigators performed a retrospective cohort study on patients with NPC treated with conventional 2-D technique and concurrent chemoradiation as the backbone of management and revealed the excellent outcomes among patients with early and locally advanced (E/LA) diseases (stage I, II, III, IVa and IVb). The median OS stratified by staging at diagnosis did not reach. The 5-year OS of patients E/LA diseases was 68.13% and patients with distant metastatic disease was only 33.33%. The present study survival outcome was comparable to the results reported in both the Western and Asian countries. Based on the USA SEER database, the 5-year survival among patients with localized disease and with distant metastasis treated between 2009 and 2015 was 82% and 48%, respectively[15]. The 5-year OS reported in clinical studies conducted in Asian countries were between 70% and 73%[16-20]. Such the excellent results are contributable to the adoption of the standard treatment proven in clinical studies.

Regarding the prognostic factors, the investigators demonstrated that advanced T stage (T3/4) and composite stage (IVa and IVb) were associated with shorter DFS, and only advanced T stage was related

Table 2. Univariate and multivariate Cox regression analyses of factors associated with adverse disease-free survival among patients with non-metastatic diseases (stage I to IVa and IVb)

	Univariate		Multi-variate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)				
<50	Reference	1		
≥50	1.3 (0.74 to 2.3)	0.364		
Sex				
Female	Reference	1		
Male	0.81 (0.44 to 1.49)	0.504		
T stage				
T1-T2	Reference	1	Reference	1
T3-T4	2.89 (1.61 to 5.2)	<0.001*	2.42 (1.3 to 4.51)	0.005*
N stage				
N0-N2	Reference	1		
N3	1.36 (0.73 to 2.54)	0.333		
Staging				
Stage I-III	Reference	1	Reference	1
Stage IVa-IVb	2.29 (1.29 to 4.06)	0.005*	1.7 (0.92 to 3.12)	0.090
Planned definitive treatment				
Definitive RT or definitive CCRT	Reference	1		
Definitive CCRT + AC or IC + definite CCRT	1.33 (0.74 to 2.39)	0.341		
Chemotherapy only	0 (0 to 1)	0.975		
Time to RT completion				
On time	Reference	1		
Delayed or Not completed	1.28 (0.73 to 2.26)	0.393		
WHO classification				
Type 2, type 3, undefined	Reference	1		
Type 1	1.09 (0.26 to 4.47)	0.91		

RT=radiotherapy; CCRT=concurrent chemoradiotherapy; AC=adjuvant chemotherapy; IC=induction chemotherapy; WHO=World Health Organization; HR=hazard ratio; CI=confidence interval

Table 3. Univariate analysis of addition of chemotherapy on definitive chemo-radiotherapy across disease stages

	HR (95% CI)	p-value
DFS stage I		
IC>CCRT	Reference	1
RT alone	0.7 (0.06 to 7.92)	0.775
DFS stage II		
CCRT	Reference	1
IC>CCRT and CCRT>AC	0.49 (0.05 to 4.39)	0.521
DFS stage III		
CCRT	Reference	1
IC>CCRT and CCRT>AC	0.68 (0.23 to 2.05)	0.498
DFS stage IVa and IVb		
CCRT	Reference	1
CCRT>AC or IC>CCRT	0.51 (0.2 to 1.3)	0.156

DFS=disease-free survival; IC=induction chemotherapy; RT=radiotherapy; CCRT=concurrent chemoradiotherapy; AC=adjuvant chemotherapy; HR=hazard ratio; CI=confidence interval

to shorter OS. In comparison to other studies, these findings were not surprisingly different to the real-world data. Kong et al[14] performed a retrospective cohort analysis of Chinese patients treated with conventional RT technique and revealed that tumor stage, RT dose, and RT regularity were the independent prognostic factors. Ameri et al[21] conducted a retrospective cohort study in a single institution in Iran also reported that advanced tumor stage (T3/4) and distant metastasis at presentation were the independent risk of adverse survival outcome. The T3 and T4 diseases consist of tumor with extension to base of skull and paranasal sinuses. Conventional RT cannot eradicate such the difficult lesions completely and probably leave the residual foci to later recur or disseminate. Newer RT techniques like IMRT and proton therapy would be more promising. A meta-analysis by Zhang et al proved that IMRT led to better 5-year locoregional control and OS

Table 4. Univariate and multivariate Cox regression analyses of factors associated with adverse overall survival among patients with non-metastatic diseases (stage I to IVa and IVb)

	Univariate analysis		Multi-variate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)				
<50	Reference	1		
≥50	0.98 (0.48 to 2.01)	0.955		
Sex				
Female	Reference	1		
Male	0.99 (0.43 to 2.22)	0.974		
T stage				
T1 to T2	Reference	1	Reference	1
T3 to T4	2.8 (1.31 to 6.01)	0.008*	3.02 (1.3 to 7.01)	0.010*
N stage				
N0 to N2	Reference	1	Reference	1
N3	2.12 (1.02 to 4.41)	0.044*	2.39 (0.92 to 6.18)	0.073
Staging				
Stage I-III	Reference	1		
Stage IVa, IVb	1.94 (0.92 to 4.09)	0.083		
Planned definitive treatment				
Definitive RT or definitive CCRT	Reference	1		
Definitive CCRT + AC or IC + definitive CCRT	0.92 (0.45 to 1.89)	0.819		
Chemotherapy only	0 (0 to 1)	0.982		
Time to RT completion				
On time	Reference	1		
Delayed or not completed	1.11 (0.54 to 2.27)	0.779		
WHO classification				
Type 2, type 3, undefined	Reference	1		
Type 1	0.82 (0.11 to 6.01)	0.843		

RT=radiotherapy; CCRT=concurrent chemoradiotherapy; AC=adjuvant chemotherapy; IC=induction chemotherapy; WHO=World Health Organization; HR=hazard ratio; CI=confidence interval

compared with 2D- or 3D- radiotherapy, as well as significant reduction of radiation-induced toxicities such as temporal lobe neuropathy, late xerostomia, and trismus[22]. Due to the retrospective study design, long-term toxicities such as xerostomia, hearing loss, and dental caries and jaw necrosis were not thoroughly documented. In accordance with many reports, the investigators did not demonstrate the nodal status as a prognostic role. It would be postulated that even bulky lymph node metastasis could be eliminated solely by CCRT. The investigators did not include the role of cumulative cisplatin dose during definitive treatment as a candidate prognostic factor. Most of the patients in the present cohort received cumulative cisplatin dose more than 160 mg/m², including during both IC and CRT. Based on the literature review, the threshold for optimal efficacy without IC would be 200 mg/m²[23] and 160 mg/m² cisplatin when receiving additional IC[24]. The investigators did not show the addition of either IC or AC translated into longer DFS, even among patients with bulky or locally advanced diseases (stage III to IVa and IVb). However, due to the retrospective design of the present cohort study, the investigators suggest that the addition of IC is suggested in some high-risk locally advanced disease at least to downsize the tumor and relieve the local symptoms. Zhang et al recently published the phase 3 study that demonstrated the role of induction cisplatin and gemcitabine upon the current standard definitive CRT with cisplatin alone in patients with locally advanced disease[25]. Such regimen is about to be a new standard.

According to the Thailand's national practice, plasma EBV DNA is still a novel assay. Tang et al proposed a nomogram combining pre-treatment plasma EBV DNA and clinicopathological variables would lead to more precise prognostic factor for patients with NPC[26]. However, the role of plasma

EBV DNA as a predictive factor to determine the necessity of AC is still doubtful[27]. The investigators found that the recurrence or metastasis usually happened within the first three years after the diagnosis. Until the plasma EBV DNA assay is validated, harmonized, and incorporated into routine clinical practice to monitor post-treatment relapse[28], the investigators suggest the surveillance protocol including history taking and physical examination every three to four months during the first three years after definitive treatment. The imaging studies is recommended only whenever clinically indicated.

Conclusion

The investigators demonstrated that the survival outcomes of multi-modality management of NPC were excellent and comparable to the international data. Definitive concurrent CRT is the backbone of the treatment. IC is suggested especially for high-risk locally advanced disease, to downsize the tumor and immediately relieve the local symptoms and potentially improve survival. The T3/4 disease is associated with adverse DFS and OS outcomes, therefore, more sophisticated multi-modality management is suggested.

What is already known on this topic?

NPC is a potential curable cancer, even among the patients with very locally advanced disease. Definitive concurrent chemoradiotherapy with or without induction chemotherapy leads to excellent clinical outcomes.

What this study adds?

Advanced T stages (T3 and T4) is the prognostic factor of both shorter disease-free survival and overall survivals. The investigators suggest that such patients deserve more sophisticated multi-modality management.

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Conflicts of interest

The authors declare no conflict of interest.

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