Induction Chemotherapy Followed by Concurrent Chemoradiotherapy in Filipinos With Locally Advanced Nasopharyngeal Carcinoma: A Cancer Institute Experience in a University Hospital

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ABSTRACT

Purpose: The objectives of this study is to report the oncologic outcomes and safety and tolerability of induction chemotherapy in locally advanced nasopharyngeal carcinoma treated at our institution – The Benavides Cancer Institute, University of Santo Tomas Hospital, Manila, Philippines

Patients and Methods: Thirty-eight patients who underwent induction chemotherapy prior to concurrent chemoradiotherapy for locally advanced nasopharyngeal carcinoma at our institution were retrospectively reviewed. Of these, 14 patients were excluded (5 patients had M1 disease at diagnosis, 5 patients received induction chemotherapy (IC) for recurrent disease, 4 patients had incomplete medical records) and 24 patients were included in the final outcomes and safety analysis.

Results: With a median follow-up of 39 months, the median overall survival (OS), progression-free survival (PFS), locoregional failure-free survival (LRFFS) and distant failure-free survival (DFFS) were not reached. The 3-year OS, PFS, LRFFS, and DFFS rates were 60.75%, 57.93%, 52.96%, and 80.67% respectively. In terms of safety, the most common adverse event reported were anemia, nausea/vomiting, and mucositis with very few reported adverse events of neutropenia (4.2% all grades) and no reported case of febrile neutropenia. In terms of tolerability, 87.5% were able to complete three or more cycles of induction chemotherapy and 70.8% completed at least two cycles of cisplatin concurrent with radiotherapy.

Conclusion: In this cohort of Filipinos with locally advanced nasopharyngeal carcinoma, induction chemotherapy strategy appears to be safe and tolerable. Oncologic outcomes were less favorable compared to the published report possibly due to very advanced disease, less use of taxane-containing regimen in this cohort, less use of advanced radiotherapy (RT) technique such as IMRT, and small sample size.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is unique compared to other head and neck cancers in terms of histology and epidemiology with the highest incidences reported in southeast Asia, Micronesia and Polynesia, eastern Asia, and northern Africa.[1] Because of its anatomical location and sensitivity to radiation, radiotherapy is the primary treatment modality for localized NPC. Most cases, as high as 70%, of newly diagnosed NPC are classified as loco-regionally advanced disease.[2]

The value of adding chemotherapy was first shown by the landmark Intergroup 0099 study, also known as Al-Sarraf protocol. The trial showed that concurrent chemoradiotherapy with adjuvant chemotherapy provided a 31% increase in 3-year OS. Since 1998, this regimen has been deemed the standard of care for advanced NPC.[3]

Since the Intergroup study, other randomized studies were conducted to confirm the role of concurrent chemoradiotherapy with adjuvant chemotherapy (CCRT + AC) of NPC in the endemic region.[4-6]. A promising strategy to further improve the treatment outcome is to alter the sequence from concurrent-adjuvant to induction-concurrent because of several potential and theoretical advantages: 1) The early use of potent combination chemotherapy drugs at full dose allows better drug delivery through a vasculature that has not been disrupted by prior RT and is effective towards eradicating micrometastases; 2) Better tolerance of induction chemotherapy compared to adjuvant chemotherapy, taking into account the poor compliance of adjuvant chemotherapy of the Al-Sarraf regimen, which is as low as 60% [7]; 3) Upfront chemotherapy can shrink the primary tumor to allow a wider margin for subsequent irradiation in patients with extensive locoregional disease near-critical neurological structures.[8]. However, in previous phase 3 studies that compared IC plus radiotherapy versus radiotherapy alone, IC did not reduce distant metastasis or prolong survival; one explanation is that a truly effective IC regimen has not yet been identified.[9-12]

Several randomized studies have reported promising results of IC with concurrent chemoradiotherapy (IC + CCRT) compared with CCRT alone. A phase II study of 65 patients in Hong Kong were randomized to IC with docetaxel and cisplatin for two cycles followed by concurrent chemoradiotherapy with weekly cisplatin versus concurrent chemoradiotherapy alone. Results showed manageable toxicity with no significant differences in the rates of acute toxicities and comparable dose intensities of concurrent cisplatin, late RT toxicities, and quality of life scores. It also showed improvement in 3-year OS (94.1% vs 67.7%).

A European phase II study was conducted by the Hellenic Cooperative Oncology Group which used cisplatin, epirubicin, and paclitaxel as induction regimen. A total of 141 patients were randomized to either IC + CCRT versus CCRT alone. The study showed similar overall response rate, 3-year PFS and OS with a manageable toxicity profile.[14]

The Hong Kong Nasopharyngeal Cancer Study Group conducted a randomized, multicenter phase 3 trial evaluating several promising strategies including changing from adjuvant to IC using cisplatin and 5FU. Induction cisplatin + 5FU (PF) did not show significant improvement in PFS and OS compared to adjuvant PF. The safety profile showed fewer neutropenia and electrolyte disturbances in the induction PF arm.

In another study conducted in Singapore, the combination of gemcitabine, carboplatin, and paclitaxel was used as IC prior to CCRT. A total of 180 patients were randomized to IC + CCRT versus CCRT alone without AC. The results showed no significant difference in OS, disease-free survival, and distant metastasis-free survival. The induction arm showed higher rates of grade 3 and 4 leukopenia and neutropenia, but with comparable acute radiation toxicities and global quality of life scores.[16]

A randomized phase III study was done in China comparing neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus chemoradiotherapy alone in stage III and IVB NPC. The induction arm used cisplatin and 5FU every 3 weeks for two cycles. A total of 476 patients were randomized and results showed higher 3-year disease-free survival (DFS) of 82.0% versus 74.1% with marginal improvement in 3-year distant metastasis-free survival (DMFS) of 86.0% versus 82.0%. No improvement was seen in OS or LRRFS. The induction arm also had significantly more grade 3-4 toxicities during the CCRT.[17]

In another phase III study done in China, the docetaxel/cisplatin/5FU (TPF) regimen was investigated as an induction regimen in locally advanced NPC compared to CCRT alone. A total of 239 pa-

tients were randomly assigned to each treatment arm. The results showed that the addition of induction TPF to concurrent chemoradiotherapy significantly improved 3-year failure-free survival (80% vs 72%) with acceptable toxicity. A long-term outcome is still not reported.[18]

A retrospective study was also done in Sun Yat-sen University Cancer Center in China evaluating the long-term outcome of IC. A propensity-matched analysis was done in 318 paired patients. The 5-year OS and DFS were significantly improved with IC.[19]

Another retrospective study was done this time in Siriraj Hospital in Thailand where NAC versus AC was compared using cisplatin + 5FU/leucovorin for a maximum of three cycles. In this cohort, 79 patients received NAC while 187 patients received AC. The results showed that 3-year and 5-year OS, LLRFS, and DMFS were not improved with NAC compared to AC.[20]

A randomized trial was also done by the French group Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC) employing IC with TPF followed by CCRT versus CCRT alone. A total of 83 patients were included in the study and results showed good compliance to the induction regimen (95% received three cycles of TPF). Toxicities were comparable in both arms, while 3-year PFS and OS were significantly improved in the induction arm.

A meta-analysis of six randomized controlled trials (RCTs) and five observational studies was done showing high-quality evidence from RCTs that IC significantly improved PFS and OS but was associated with more frequent AEs. The analysis also showed no divergent results between RCTs and observational studies.[22].

In terms of local data, Dizon, *et al.* [23] reported a small phase II randomized study done at Philippine General Hospital. In this pilot study, 30 patients were randomized to receive IC (PF) followed by chemoradiotherapy versus standard Al-Sarraf protocol. Median PFS was 19.6 months (standard arm) versus 25.7 months (investigative arm). The 3-year PFS rates were 25% and 63%, respectively with hazard ratio 2.64 (p = 0.176). There was no significant difference in oncologic outcomes such as median and 3-year PFS and OS rates between the two arms. Anemia, anorexia, nausea, vomiting, and xerostomia were the most frequent grade 3 AEs reported.

The value of IC remains under investigation despite decades of research, and clear guidelines for the optimal use of IC are yet to be defined. Real-world data (RWD) and local experience are important in understanding and defining the value of IC in a specific population. There had been no published local data (retrospective or prospective) on the safety and efficacy of IC in locally advanced NPC.

This study aims to determine the oncologic outcomes as well as the safety and tolerability of IC in Filipinos with locally advanced NPC treated at the Benavides Cancer Institute from 2008 to 2018. As there is still no consensus on the role of IC in LA-NPC, RWD and local institutional experience are important in understanding the outcomes and safety of IC in a specific population.

The primary objective of this study is to determine oncologic outcomes of IC in Filipinos with locally advanced NPC treated at the Benavides Cancer Institute in terms of the OS, PFS, LRFFS, and DFFS.

The secondary objective of this study is to determine the safety and tolerability of IC in Filipinos with locally advanced NPC treated at the Benavides Cancer Institute using the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

METHODOLOGY

This is a retrospective and descriptive type of study reviewing the medical records of patients seen at the University of Santo Tomas Hospital – Benavides Cancer Institute from 2008 to 2018. The study population will include Filipino patients diagnosed with locally advanced NPC who underwent IC at the Benavides Cancer Institute at the University of Santo Tomas Hospital from 2008 to 2018. This will include patients from both private and clinical divisions.

The inclusion criteria include the following: a) Histologically confirmed locally advanced NPC who underwent IC prior to definitive concurrent chemoradiotherapy; b) Stage II to IVB based on AJCC 7th edition; and c) Age >= 18 years. Patients with incomplete hospital records were excluded from this study.

The investigators obtained the University of Santo Tomas Hospital (USTH) Institutional Research Ethics Committee (IREC) approval prior to study implementation. The investigators conducted this study in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, the

National Ethical Guidelines for Health & Health Related Research (NEGHHRR 2017), the Data Privacy Act of 2012, and the WHO Operational Guidelines 2011.

The charts of identified patients aged more than 18 years old diagnosed histologically with NPC who underwent IC from 2008 to 2018 were reviewed to obtain the following variables: a) General data: age, sex, comorbidities, province of origin, family history of cancer, smoking history, occupation, and ECOG (Eastern Cooperative Oncology Group Performance) status prior to treatment; b) Tumor data: TNM stage based on AJCC-7 and WHO histologic subtype; c) Radiotherapy data: RT-technique, dose, prescription type, fractionation, and reported side effects; d) Chemotherapy data: IC protocol, number of cycles, cisplatin dose, and reported side effects; e) Oncologic outcome: date of local recurrence, date of distant metastasis, date and cause of death, if applicable. Data analysis was done using SPSS Statistics version 24 (SPSS, Chicago, IL). Oncologic outcomes such as OS, PFS, LRRFS, and DFFS were calculated using the Kaplan-Meier method.

Definition of Terms

1. Locally advanced NPC - Stage II to IVB NPC based on AJCC 7th edition staging system.
2. Induction chemotherapy (IC) – use of chemotherapy regimen prior to definitive treatment. In the case of NPC, regimens include but not limited to combinations of platinum (cisplatin or carboplatin), 5FU, and or docetaxel. The most commonly used doublet combination is cisplatin + 5FU, while the most common triplet combination uses the TPF protocol (docetaxel + cisplatin + 5FU).
3. Concurrent chemoradiotherapy – the standard of care for locally advanced NPC. This treatment protocol makes use of high dose cisplatin @ 100 mg/m2 every 3 weeks or weekly cisplatin @ 30 mg/m2 concurrent with radiotherapy.
4. Overall survival (OS) – length of time from the date of diagnosis until death from any cause.
5. Progression-free survival (PFS) – length of time from completion of treatment up to first recurrence, progression, and/or death from any cause
6. Locoregional failure-free survival (LRFFS) – length of time from completion of treatment up to first locoregional recurrence and/or death from any cause.
7. Distant failure-free survival (DFFS) – length of time from completion of treatment up to first distant recurrence and/or death from any cause.

RESULTS

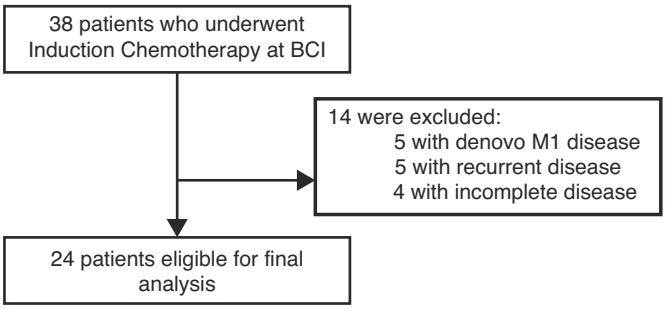

Figure 1. CONSORT diagram of patients who underwent induction chemotherapy at the Benavides Cancer Institute (BCI).

Study Population

Upon review of the hospital's cancer database, a total of 38 patients underwent IC prior to CCRT for locally advanced NPC at our institution from 2008 to 2018 and were retrospectively reviewed. Of these, 14 patients were excluded due to the following: 5 patients had M1 disease at diagnosis, 5 patients received IC for recurrent disease, 4 patients had incomplete medical records. Twenty-four patients were included in the final outcomes and safety analysis (Figure 1).

Table 1 shows the baseline characteristics of the included patients. The majority were males (66.7%) with a median age of 49, all have good performance status prior to treatment with an ECOG score of 0 or 1, and mostly non-smokers (66.7%). In terms of histology and staging, the majority are of the WHO type 3 undifferentiated type (79.2%), AJCC 7th stage IVb (62.5%), T4 (70.8%), and N3 (58.3%). Most of the patients underwent conventional radiotherapy (66.7%) rather than IMRT (33.3%). The most common IC protocol used was the PF regimen (70.8%). A taxane containing regimen (TPF or modification) was used in about 29.2%.

ONCOLOGIC OUTCOMES

Figure 2 shows the Kaplan-Meier estimate of the OS of patients who underwent IC prior to CCRT. With a median follow-up of 39 months (range 5 to 129 months), the median OS is not reached. The 1-year,

Table 1. Baseline demographic and clinical characteristics of patients who underwent induction chemotherapy

Characteristics	Induction Chemotherapy Group (n = 24)
Median Age (range) – years	46 (19 – 61)
Sex – no. (%)	
Male	16 (66.7%)
Female	8 (33.3%)
ECOG – no. (%)	
0	10 (41.7%)
1	14 (58.3%)
Smoking History – no. (%)	
Non-smoker	16 (66.7%)
Light smoker	3 (12.5%)
Heavy smoker	5 (20.8%)
WHO histologic subtype – no. (%)	
Type 1 - Differentiated keratinizing	2 (8.3%)
Type 2 - Differentiated non-keratinizing	3 (12.5%)
Type 3 - Undifferentiated	19 (79.2%)
AJCC 7th Stage	
Stage III	3 (12.5%)
Stage IVa	6 (25.0%)
Stage IVb	15 (62.5%)
T Stage – no. (%)	
T2	3 (12.5%)
T3	4 (16.7%)
T4	17 (70.8%)
N Stage – no. (%)	
N1	1 (4.2%)
N2	9 (37.5%)
N3a	6 (25.0%)
N3b	8 (33.3%)
RT technique – no. (%)	
Conventional	16 (66.7%)
IMRT	8 (33.3%)
Induction chemotherapy protocol – no. (%)	
PF	17 (70.8%)
TPF or modified TPF	7 (29.2%)

2-year, and 3-year OS rates are 91.67%, 74.77%, and 60.75%, respectively.

Figure 3 shows the Kaplan-Meier estimate of PFS of patients who underwent IC followed by CCRT. The median PFS is not reached with a 1-year, 2-year, and

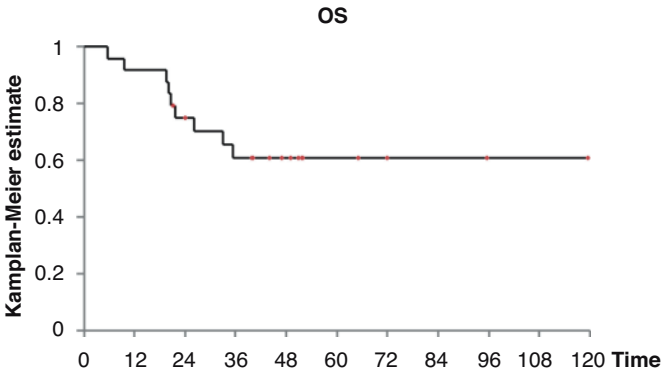

Figure 2. Kaplan-Meier OS curve of patients who underwent induction chemotherapy

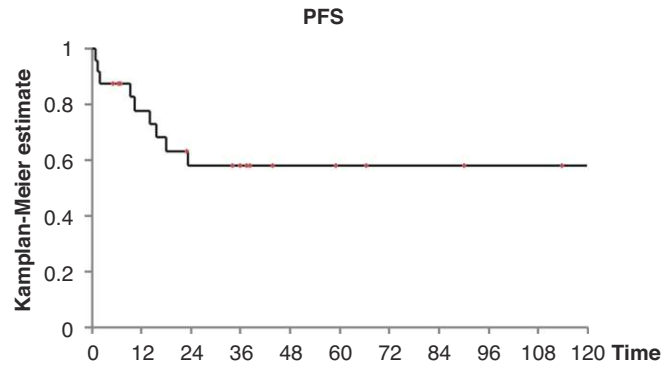

Figure 3. Kaplan-Meier PFS curve of patients who underwent induction chemotherapy

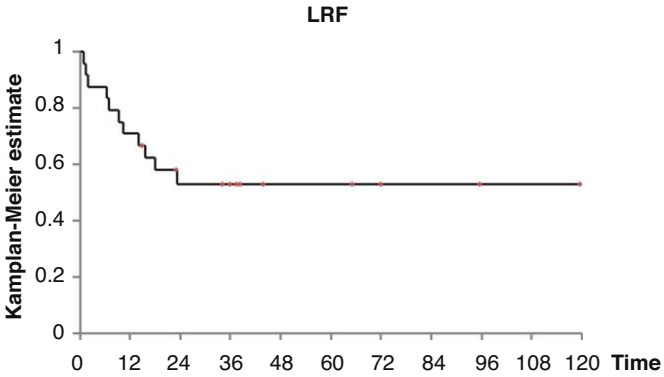

Figure 4. Kaplan-Meier LRFFS curve of patients who underwent induction chemotherapy

3-year PFS rates of 77.78%, 57.93%, and 57.93%, respectively.

In terms of locoregional failure, 11 out of 24 patients had a locoregional failure (45.83%). Figure 4 shows the Kaplan-Meier estimate of LRFFS. The median LRFS is not reached with a 1-year, 2-year, and 3-year LRFFS rates of 70.83%, 52.96%, and 52.96%, respectively.

In terms of distant failure, only 4 out of 24 had a distant failure (16.67%). Figure 5 shows the Kaplan-Meier estimate of the DFFS of the cohort.

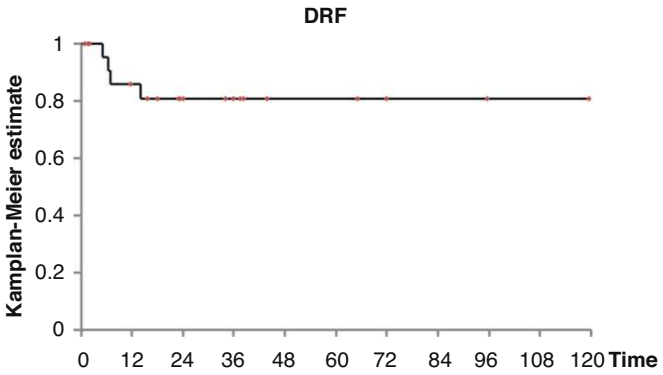

Figure 5. Kaplan-Meier DFFS curve of patients who underwent induction chemotherapy

The estimated median DFFS is not reached with 1-year, 2-year, and 3-year DFFS rates of 85.71%, 80.67%, and 80.67%, respectively. Table 3 shows the summary of oncologic outcomes for the entire cohort.

Safety and Tolerability

Table 3 showed the most common AEs that were reported during the induction phase and CCRT phase. The most common AEs are as follows: Anemia (62.5% all grades, 4.2% grade 3 or higher); nausea/vomiting (45.8% all grades, 0% grade 3 or higher); and mucositis (33.3% all grades, 12.5% grade 3 or higher). An increase in creatinine was reported in 16.7%, all grade 1 or 2. Other electrolyte abnormalities reported were hyponatremia (12.5%), hypokalemia (8.3%), and hypomagnesemia (4.2%); all were grade 1 or 2. There were very few reported AEs of neutropenia (4.2% all grades) and there was no reported case of febrile neutropenia.

In terms of tolerability, Table 4 shows the median number of completed cycles and mean total cisplatin dose received during the IC and CCRT phases. A majority of patients were able to complete three or more cycles of IC (21 out of 24 or 87.5%) with a

Table 3. Reported adverse events of patients who underwent induction chemotherapy using the common terminology criteria for adverse events (CTCAE) version 5.

Variable	Induction Chemotherapy Group (n = 24)	
	All Grades	Grades >= 3
	number of patients (percent)	
Anemia	15 (62.5%)	1 (4.2%)
Neutropenia	1 (4.2%)	0 (0%)
Platelet decreased	1 (4.2%)	0 (0%)
Creatinine increased	4 (16.7%)	0 (0%)
Hyponatremia	3 (12.5%)	0 (0%)
Hypokalemia	2 (8.3%)	0 (0%)
Hypomagnesemia	1 (4.2%)	0 (0%)
Nausea and vomiting	11 (45.8%)	0 (0%)
Diarrhea	1 (4.2%)	0 (0%)
Constipation	1 (4.2%)	0 (0%)
Weight loss	4 (16.7%)	0 (%)
Headache	1 (4.2%)	0 (0%)
Anorexia	2 (8.3%)	0 (0%)
Mucositis	8 (33.3%)	3 (12.5%)
Esophagitis	2 (8.3%)	1 (4.2%)
Thrush	1 (4.2%)	0 (0%)
Dysphagia	2 (8.3%)	1 (4.2%)
Dermatitis	4 (16.7%)	1 (4.2%)

Table 4. Median number of completed cycles during induction chemotherapy and concurrent chemoradiotherapy

	Induction Chemotherapy Group (n = 24)	
	Induction chemotherapy	Concurrent chemoradiotherapy
Median number of completed cycles – no. cycles (range)	3 (1 – 4)	3 (0-3)
Mean total cisplatin dose received – mg/m2	250.8 mg/m2	239.2 mg/m2

Table 2. Summary of oncologic outcomes of patients who underwent induction chemotherapy

	Induction Chemotherapy Group (n = 24)			
	Median (months)	1-year rate (%)	2-year rate (%)	3-year rate (%)
Overall Survival	NR	91.67%	74.77%	60.75%
Progression-Free Survival	NR	77.78%	57.93%	57.93%
Locoregional-Free Survival	NR	70.83%	52.96%	52.96%
Distant Metastasis-Free Survival	NR	85.71%	80.67%	80.67%.

NR - not reached

mean total cisplatin dose received of 250.8 mg/m2. Also, a majority of patients received at least two cycles of cisplatin concurrent with radiotherapy (17 out of 24 or 70.8%)

DISCUSSION

Based on this data set, IC as the initial treatment strategy for locally advanced NPC is associated with less favorable oncologic outcomes as compared with historical control. In the landmark Intergroup Study 0099, the median OS of the chemoradiotherapy group was not reached while the 3-year OS rate was 76%. The median PFS in the intergroup study was also not reached in the chemoradiotherapy group while the 3-year PFS rate was 69%.[3] In the updated MAC-NPC meta-analysis (Blanchard, *et al., Lancet Oncology* 2015), the reported outcomes in the standard concurrent chemoradiotherapy with adjuvant chemotherapy showed OS rates at 2-year, 5-year, and 10-year of 86.6%, 70.5%, and 57.0% respectively. The meta-analysis also reported PFS rates at 2-year, 5-year, and 10-year of 77.7%, 62.2%, and 53.2%, respectively.

Table 5. Comparison of oncologic outcomes with previously published studies on induction chemotherapy

Study/ Country	No. of Patients	Study Design	Induction Protocol	OS	PFS/DFS/ FFS	Locoregional failure-free survival	Distant failure-free survival
Current study (2019) Philippines	19	Retrospective	Multiple protocols	3-year OS: 60.75%	3-year OS: 57.93%	3-year LRFFS: 52.96%	3-year DFFS: 80.67%
Sun Y, *et al.*[18] (2016) China	480 (2 arms)	Phase III, randomized	TPF (Docetaxel, Cisplatin, 5FU)	3-year OS: 92%	3-year FFS: 80%	3-year LRFFS: 92%	3-year DFFS: 90%
Hui EP, [13] (2016) Hong Kong	65 (2 arms)	Phase II, randomized	TP (Docetaxel, Cisplatin)	3-year OS: 94.1%	3-year PFS: 88.2%	NR	NR
Fountzilas G, *et al.* [14] (2011) Greece	141 (2 arms)	Phase II, randomized	CEP (Cisplatin, Epirubicin, Paclitaxel)	3-year OS: 66.6%	3-year PFS: 64.5%	NR	NR
Lee AW, *et al.*[15] (2014) Hong Kong	706 (6 arms)	Phase III, randomized	PF (Cisplatin, 5FU)	3-year OS: 85%	3-year PFS: 79%	NR	NR
Tan T, *et al,*[16] (2015) Singapore	172 (2 arms)	Phase II/III, randomized	GCP (Gemcitabine, Carboplatin, Paclitaxel)	3-year OS: 94.3%	3-year DFS: 74.9%	NR	3-year DFFS: 83.8%
Cao SM, *et al.*[17] (2017) China	478 (2 arms)	Phase III, randomized	PF (Cisplatin, 5FU)	3-year OS: 88.2%	3-year DFS: 82.0%	3-year LRFFS: 88.2%	3-year DFFS: 86.0%
Peng, H, *et al.*[19] (2017) China	318 (matched pairs)	Retrospective	Multiple protocols	5-year OS: 87.2%	5-year DFS: 80.7%	5-year LFFS: 92.1%	5-year DFFS: 88.1%
SetakornnukulJ, *et al.*[20] (2018) Thailand	266	Retrospective	Multiple protocols	3-year OS: 72% 5-year OS: 62%	NR	3-year LFFS: 70%	3-year DFFS: 79%
Frikha M, *et al.*[21] (2018) France and Tunisia	83 (2 arms)	Randomized, Phase III	TPF (Docetaxel, Cisplatin, 5FU)	3-year OS: 86.3%	3-year PFS: 73.9%	NR	NR
Dizon D, *et al.* (2011) [24] Philippines	30 (2 arms)	Phase II, randomized	PF (Cisplatin, 5FU)	3-year OS: 25.4%	3-year PFS: 63.0%	NR	NR

OS - overall survival, PFS - progression free survival, DFS - disease free survival, FFS - failure free survival, LRFFS - locoregional failure-free survival, DFFS - distant failure-free survival, NR - not reached

Comparing our results with published IC studies also showed less favorable oncologic outcomes. In the study of Ying Sun, *et al.* in which they enrolled only stage III and IV locally advanced NPCA,[18] they reported a 3-year failure-free survival was 80% 3-year OS of 92% in the IC group using the TPF protocol. However, our result showed more favorable oncologic outcomes if we compare it with the only published local data by Dizon, *et al.*[24]. In that study, the median OS and PFS were 21.5 and 25.7 months, respectively while the 3-year OS and PFS rates were 25.4% and 63%, respectively. Table 5 shows the oncologic outcomes of previously published studies on IC and as compared to the current study.

Multiple factors may contribute to these inferior oncologic outcomes. In the current study cohort, all included patients are at least stage III and 87.5% are stage IV, which makes this a cohort of very advanced disease and therefore poorer oncologic outcome is expected. Furthermore, only 29.2% used a taxane containing IC regimen in the current cohort. As seen in the study by Sun Y, *et al.*, the use of taxane containing IC regimen resulted in improved failure-free survival compared to non-taxane containing chemotherapy protocol.[18]

Another possible factor that could contribute to the less favorable oncologic outcomes is the infrequent use of more advanced radiotherapy techniques such as IMRT. In this cohort, the majority used conventional RT (70.8%) and only 29.2% used IMRT. Although the advantage of IMRT is its improved safety and less toxicity compared to conventional RT, some studies showed improved oncologic outcomes with IMRT use, specifically in locally advanced NPC. A Korean study showed improved survival (OS and PFS) in NPC using 3D and IMRT techniques compared to 2D techniques, particularly in T3 and T4 tumors.[24]

In terms of patterns of failure, our results were consistent with most studies showing very few distant failures with the use of IC strategy. In this data set, only 4 out of 24 patients had distant failure (16.67%) while 11 out of 24 patients had locoregional failure (45.83%). In the Chinese study by Sun Y, *et al.*,[18] IC significantly improved DFFS (90% vs 83% at 3-years, p = 0.031) but not LRFFS.

In terms of safety, the IC strategy appears to be safe as shown by very few reported AEs in all grades and most especially in grade 3 or higher. In the current study, the increase in creatinine is only observed in 16.7%, all of which were grade 1 or 2. Also, there are very few reported events of neutropenia (4.2%) and no documented report of febrile neutropenia. It is important to note that this being a retrospective study is prone to recall bias and under-reporting of AEs. In the study of Sun Y, *et al.*,[18] 43% had grade 3 or 4 AEs, the majority of which were hematologic such as neutropenia and leukopenia.

Tolerability of IC was also appreciated in terms of the number of completed cycles both in the induction phase and concurrent chemoradiotherapy phase. The majority of patients were able to complete three or more cycles of IC (21 out of 24 or 87.5%) and the majority completed at least two cycles of cisplatin concurrent with radiotherapy (17 out of 24 or 70.8%). In the original Al-Sarraf study,[3] only 63% of patients received the three courses of concurrent chemoradiotherapy and only 55% received all three courses of adjuvant chemotherapy. In the study of Sun Y, *et al.*,[18] 88% completed three cycles of induction TPF while only 30% completed three cycles of concurrent chemoradiotherapy.

CONCLUSION AND RECOMMENDATION

In this cohort of Filipinos with locally advanced NPC, IC strategy appears to be safe and tolerable. Oncologic outcomes were less favorable compared to the published report possibly due to very advanced disease, less use of taxane containing regimen in this cohort, less use of advanced RT technique such as IMRT, and small sample size. Nevertheless, this report of our experience is an important step in determining the applicability of IC strategy in the local setting and in Filipinos in general. Due to the small sample size of this cohort, it is recommended to combine this data with other institutions or a national database. Furthermore, a prospective trial is recommended to better understand the role of IC in our local setting.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA: a cancer journal for clinicians*. 2015 Mar;65(2):87-108.
2. Mao YP, Xie FY, Liu LZ, Sun Y, Li L, Tang LL, et al. Re-evaluation of 6th edition of AJCC staging system for nasopharyngeal carcinoma and proposed improvement based on magnetic resonance imaging. *International Journal of Radiation Oncology Biology Physics*. 2009 Apr 1;73(5):1326-34.
3. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *Journal of Clinical Oncology*. 1998 Apr;16(4):1310-7.
4. Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *Journal of Clinical Oncology*. 2005 Sep 20;23(27):6730-8.
5. Lee AW, Tung SY, Ngan RK, Chappell R, Chua DT, Lu TX, et al. Factors contributing to the efficacy of concurrent–adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: combined analyses of NPC-9901 and NPC-9902 trials. *European Journal of Cancer*. 2011 Mar 1;47(5):656-66.
6. Chen Y, Sun Y, Liang SB, Zong JF, Li WF, Chen M, et al. Progress report of a randomized trial comparing long-term survival and late toxicity of concurrent chemoradiotherapy with adjuvant chemotherapy versus radiotherapy alone in patients with stage III to IVB nasopharyngeal carcinoma from endemic regions of China. *Cancer*. 2013 Jun 15;119(12):2230-8.
7. Chen L, Hu CS, Chen XZ, Hu GQ, Cheng ZB, Sun Y, 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. *The Lancet Oncology*. 2012 Feb 1;13(2):163-71.
8. Ng WT, Chang AT, Lee SW, Sze HC, Lee AW. Chemotherapy for nasopharyngeal cancer: neoadjuvant, concomitant, and/or adjuvant. *Current Treatment Options in Oncology*. 2015 Sep 1;16(9):44.
9. VUMCA I, International Nasopharynx Cancer Study Group. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV (> or= N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. *International Journal of Radiation Oncology, Biology, Physics*. 1996 Jun 1;35(3):463.
10. Chua DT, Sham JS, Choy D, Lorvidhaya V, Sumitsawan Y, Thongprasert S, et al. Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 1998 Dec 1;83(11):2270-83.
11. Ma J, Mai HQ, Hong MH, Min HQ, Mao ZD, Cui NJ, et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. *Journal of Clinical Oncology*. 2001 Mar 1;19(5):1350-7.
12. Hareyama M, Sakata KI, Shirato H, Nishioka T, Nishio M, Suzuki K, et al. A prospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. *Cancer*. 2002 Apr 15;94(8):2217-23.
13. Hui EP, Ma BB, Leung SF, King AD, Mo F, Kam MK, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *Journal of Clinical Oncology*. 2009 Jan 10;27(2):242-9.
14. Fountzilas G, Ciuleanu E, Bobos M, Kalogera-Fountzila A, Eleftheraki AG, Karayannopoulou G, et al. Induction chemotherapy followed by concomitant radiotherapy and weekly cisplatin versus the same concomitant chemoradiotherapy in patients with nasopharyngeal carcinoma: a randomized phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG) with biomarker evaluation. *Annals of Oncology*. 2011 Apr 27;23(2):427-35.
15. Lee AW, Ngan RK, Tung SY, Cheng A, Kwong DL, Lu TX, et al. Preliminary results of trial NPC-0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer*. 2015 Apr 15;121(8):1328-38.
16. Tan T, Lim WT, Fong KW, Cheah SL, Soong YL, Ang MK, et al. Concurrent chemo-radiation with or without induction gemcitabine, carboplatin, and paclitaxel: a randomized, phase 2/3 trial in locally advanced nasopharyngeal carcinoma. *International Journal of Radiation Oncology Biology Physics*. 2015 Apr 1;91(5):952-60.
17. Cao SM, Yang Q, Guo L, Mai HQ, Mo HY, Cao KJ, et al. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase III multicentre randomised controlled trial. *European Journal of Cancer*. 2017 Apr 1;75:14-23.
18. Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. *The Lancet Oncology*. 2016 Nov 1;17(11):1509-20.
19. Peng H, Chen L, Zhang J, Li WF, Mao YP, Zhang Y, et al. Induction chemotherapy improved long-term outcomes of patients with locoregionally advanced nasopharyngeal carcinoma: a propensity matched analysis of 5-year survival outcomes in the era of intensity-modulated radiotherapy. *Journal of Cancer*. 2017;8(3):371.
20. Setakornnukul J, Thephamongkhol K. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in locally advanced nasopharyngeal carcinoma. *BMC Cancer*. 2018 Dec;18(1):329.
21. Frikha M, Auperin A, Tao Y, Elloumi F, Toumi N, Blanchard P, et al. A randomized trial of induction docetaxel–cisplatin–5FU followed by concomitant cisplatin-RT versus concomitant cisplatin-RT in nasopharyngeal carcinoma (GORTEC 2006-02). *Annals of Oncology*. 2017 Dec 11;29(3):731-6.

22. Tan TH, Soon YY, Cheo T, Ho F, Wong LC, Tey J, et al. Induction chemotherapy for locally advanced nasopharyngeal carcinoma treated with concurrent chemoradiation: A systematic review and meta-analysis. *Radiotherapy and Oncology*. 2018 Oct 1;129(1):10-7.
23. Dizon DS, Fragante E, Ramirez F, Ruste SA, Sagpao C, Beatrice T. Induction chemotherapy followed by concurrent chemoradiotherapy vs concurrent chemoradiotherapy followed by chemotherapy in the treatment of patients with advanced nasopharyngeal carcinoma. *Philippine Journal of Internal Medicine*. 2011 Jan 1;49(1):1-7.
24. Moon SH, Cho KH, Lee CG, Keum KC, Kim YS, Wu HG, et al. IMRT vs. 2D-radiotherapy or 3D-conformal radiotherapy of nasopharyngeal carcinoma. *Strahlentherapie und Onkologie*. 2016 Jun 1;192(6):377-85.