Research Article

Neoadjuvant Chemotherapy plus Plus Volumetric-modulated Arc Therapy for the Treatment of Loco Regionally Advanced Nasopharyngeal Carcinoma: A Retrospective Study

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Abstract

Background & Purpose: Nasopharyngeal carcinoma is attributed for 33% of head and neck malignancy in Saudi Arabia. In treatment of NPC, chemoradiotherapy is used as a modality of choice. The present study aims to determine the effect of Neoadjuvant Chemotherapy (NACT) in Local Control (LC) and Overall Survival (OS) of NPC patients treated in King Faisal Hospital and Research Center (KFSHRC), Jeddah, Saudi Arabia. **Materials & Methods:** Patients treated for NPC were retrospectively studied. Demographic characteristics and chemotherapy data were gathered and analyzed. Kaplan-Meier product-survival estimates and multivariate analysis were conducted to describe and determine the effect of NACT plus CCT in LC and OS. **Results:** Seventy-seven patients with loco regional advanced NPC were studied. Majority of the patients had Stage 3 NPC (n=34, 44.2%) and had undifferentiated non-keratinizing carcinoma (Type III) (n=70, 90.9%). Fifty-three of these patients received VMAT (68.8%) as radiation treatment wherein 27 (50.9%) had NACT plus CCT, while 22 (41.5%) received CCT only. Data revealed only sixty-nine NPC patients underwent chemotherapy in which thirty-three (42.9%) received Concomitant Chemotherapy (CCT) and thirty-nine (46.8%) received NACT plus CCT. Multivariate analysis showed most CCT patients (n=32, 50.8%) did not experience relapse and incidence was slightly lower compared to the NACT plus CCT group (n=31, 49.2%). However, a significant difference was not observed between the two groups. Kaplan-Meier analysis showed incidence of relapse mostly happened in the first three years of therapy while death was observed mostly between 1 and 2.5 years after. **Conclusion:** Our study showed similar survival outcomes for CCT and NACT plus CCT. However, CCT reported a lower incidence of relapse than the group receiving NACT plus CCT.

Keywords: Nasopharyngeal carcinoma; Neoadjuvant chemotherapy; Volumetric modulated arc therapy

Highlights: Similar survival outcomes were found between NACT plus CCT and CCT

Introduction

Nasopharyngeal Carcinoma (NPC) is a head and neck malignancy and considered rare in several regions worldwide. However, incidence of NPC is common in Asia, especially in India and China. [1] NPC have been classified in various categories set by International/WHO. According to histology, NPC is classified

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alone; After chemotherapy, incidence of relapse found mostly in the first three years; After chemotherapy, death occurs between 1 and 2.5 years; NACT plus CCT lowered the incidence of relapse among NPC patients

into three distinct groups including keratinizing Squamous cell carcinoma (TYPE I), non-keratinizing carcinoma (Type II) and undifferentiated carcinoma (Type III). WHO on the other hand, classified NPC into two categories: Keratinizing squamous cell carcinoma (TYPE I), non-keratinizing carcinomas (Type II and Type III). In Saudi Arabia, NPC is attributed for one-third of head and neck cancers with incidence of 0.25% for males and 0.08% for females distributed mostly in the region of Riyadh (36%). [2]

NPC has been reported to have a very good sensitivity in different radiation treatments. [3] Radiation Therapy (RT) served as a backbone treatment for NPC. However, patients with stages 3 and 4 are at risk to suffer from recurrences and metastases after RT. However, clinical studies provide an evidence of significant improvement of progression free and overall survival when combined chemo radiotherapy was used. [4,5]

Intense-Modulated Radiation Therapy (IMRT) is considered as standard treatment for NPC because of its significant advantage in sparring of healthy organs and improved local control and survival rates. Studies showed local control rates range between 88%-97% after IMRT. [6] However, like other RT techniques, IMRT has limitations including prolonged treatment, delivery times, high usage of Monitor Units (MU) and raised doses. [7-9] The said limitations led to the proposal of Volumetric-Modulated Arc Therapy or Volumetric-Modulated Arc Therapy (VMAT) as radiation treatment for NPC. VMAT includes simultaneous modulation of dose rate, gantry rotation speed and multi-leaf collimator-leaf positions during a single 360 degrees rotation. VMAT is reported to have the ability to treat the whole target volume using arcs and superior in terms of delivery time, use of monitor units and sparing of organs at risk. [8-10]

Our study aims to determine the efficacy of NACT plus CCT in patients with loco regionally advanced NPC and to compare treatment outcomes between NACT plus CCT and CCT alone through assessment of LC and OS.

Materials and Methods

We retrospectively reviewed adult patients diagnosed with NPC and treated at (KFSHRC) in Jeddah, Saudi Arabia between May 2007 and December 2019. Pediatric patients were excluded in the study. The staging of the disease was stated based on the Cancer Staging Manual by the American Joint Committee on Cancer. [11]

All the patients had a confirmed histo pathologically diagnosis in our center. For assessment of radiologic staging for primary disease and to rule out metastasis, Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) was/were used. Response assessment with CT scan and/or MRI was performed one month after the completion of three cycles of Neoadjuvant Chemotherapy (NACT) and after one additional month after completion of Concomitant Chemoradiotherapy (CCT). Patients were seen before each NACT cycle and at least three times while receiving CCT. Responders were followed up with CT scans and/or MRI as per consensus guidelines, thereafter.

The patients received 2-3 cycles of 3-weelky Neoadjuvant Chemotherapy (NACT). Protocols include either cisplatin and fluorouracil (5fu), Taxane, Cisplatin and Fluorouracil (TPF), cisplatin and xeloda or cisplatin alone for three consecutive weeks. These were followed by cisplatin or cisplatin and fluorouracil as radio-sensitizer which were given concurrently, either 30-40 mg/m^2 weekly or 100 mg/m^2 every 3 weeks.

The radiation therapy oncology group atlas was followed for target volume contouring. [12] Gross primary and nodal tumors were contoured as Gross Tumor Volume (GTV) on the basis of clinical findings and CT/MRI imaging that was performed before the neoadjuvant chemotherapy. Clinical target volume consisted of computer-generated 1-cm isotropic expansion around each gross tumor volume, respecting anatomic barriers, and included all nodal groups with a greater than 10% to 15% risk of containing subclinical disease (all the neck nodes bilaterally). [13] Planning target volume was constructed by an automated 0.3 to 0.5cm expansion of the clinical target volume surfaces, to account for setup error and daily uncertainty. Patients were positioned for simulation using customized thermoplastic masks. CT scans with intravenous contrast were used for treatment planning. Both intensity-modulated RT and three-dimensional conformal RT were used for treatment techniques. Dose limits for the critical tissue structures and plan evaluation were followed as defined by the radiation therapy oncology group 0225. [14]

Demographic and clinical characteristics of patients were gathered and analyzed. Local control and overall survival were determined from the day of treatment up to the last documented clinic visit. Multivariate analysis was performed using IBM SPSS statistics software (version 23) to evaluate the effect of treatments and other variables such as pre-treatment hemoglobin level, gap in treatment, radiation dose, chemotherapy protocols and Body Surface Area (BSA) to Local Control (LC) and Overall Survival (OS). Significance was evaluated at $P<0.5$. Kaplan-Meier product-limit survival estimates were used to describe local relapse and overall survival of patients that underwent chemotherapy.

Results

In the present study, 77 patients with loco regionally advanced Nasopharyngeal Carcinoma (NPC) were evaluated. Demographic characteristics as shown in Table 1 revealed 51 patients were male (66.2%) and 26 were female (33.8%) with a mean age of 45.8 ± 14.0 years. Patients were categorized based on stages, pathology and WHO classifications. Results revealed that the majority of the patients had Stage 3 NPC (n=34, 44.2%), had undifferentiated non keratinizing carcinoma (Type III) (n=70, 90.9%) and Type 3 NPC or undifferentiated carcinoma (n=71, 92.2%), respectively.

As for radiation technique, fifty-three of the patients received VMAT (68.8%), five received IMRT (6.49%), eighteen

Table 1: Demographic characteristics of study sample.

Variables	N=77 N (%)
Age (mean ± SD)	
Gender	45.8 ±14.0
Male	51(66.2)
Female	26 (33.8)
Stage	
1	1(1.3)
2	12(15.6)
3	34(44.2)
4a	15(19.5)
4b	11(14.3)
4c	4(5.2)
Pathology	
Keratinizing squamous cell carcinoma (Type I)	1(1.3)
Nonkeratinizing carcinoma–differentiated (Type II)	3(3.9)
Nonkeratinizing carcinoma–Undifferentiated (Type III)	70(90.9)
NK Carcinoma, undifferentiated (lymphoma like) (Type III)	2(2.6)
Basaloid squamous cell carcinoma	1(1.3)
WHO type	
1	1(1.3)
2	4(5.2)
3	71(92.2)
4	1(1.3)
Type of therapy	
Chemotherapy	69(89.6)
No chemotherapy	7(9.1)
Type of chemotherapy protocol	
Concomitent only	33(42.9)
Concomitent+Neoadjuvant	36(46.8)

Table 2: Frequency of patients and number of cycles for those who received concomitant chemotherapy only.

Chemotherapy treatment protocol	Total	Number of cycles							
		1	2	3	4	5	6	7	8	9
cisplatin weekly	20		8	1	1	3	3	4		
cis q 3 weeks	9		4	5						
Unknown	1									1
others	3	1								
Total	33	1	12	6	1	3	4	5		1

received conventional RT (23.4%) and one underwent 3D RT (1.30%). More than half of the VMAT patients (n=27, 50.9%) received both NACT and CCT while almost half (n=22, 41.5%) underwent CCT alone.

Out of these 77 study samples, 69 patients underwent chemotherapy (n=69, 89.6%). In which thirty-three (42.9%) received CCT while 36 of the patients (46.8%) underwent NACT followed by CCT. Majority (n=20/33) of CCT patients received cisplatin weekly while only nine patients received 3-weelky cisplatin CCT.

Table 2 showed the number of cycles per patient who received NACT followed by CCT. Only 14 of the patients finished three cycles of NACT while only 1 patient received a full cycle of NACT. Furthermore, the majority of patients (n=13) received cisplatin and fluorouracil (5fu) followed by 12 patients who received cisplatin and xeloda. Only 1 patient received TPF; a combination of taxane, cisplatin and fluorouracil.

After 1 to 12.5 years of follow-up, most of the patients who underwent chemotherapy experienced relapse during the first three years while most died between 1 and 2.5 years. However, no statistically significant relation was found between chemotherapy protocol with local relapse (P=0.144). Also, no statistically significant association was found between local relapse and the following factors, pretreatment hemoglobin level (p=0.919), gap in treatment (P=0.246), radiation dose (P=0.563) and BSA (P=0.868). At 0.05 significance level, patients with pretreatment hemoglobin levels greater than 12 g/dL were likely to have relapsed by 1.11 times. Patients who had gaps in their treatment were likely to have relapsed by 0.29 times. Moreover, those who had radiation doses of ≥ 7000 were less likely to have relapses by 1.94 times. Results also revealed that patients who received NACT plus CCT were more likely to have a relapse 5.16 times than those who received concomitant treatment only. Furthermore, with increased BSA, the chance of having a relapse is 1.40 times.

Table 3: Frequency of patients and number of cycles for those who received both (neoadjuvant and concomitant chemotherapy).

Neoadjuvant	Total	Number of cycle			Concomitant	Number of cycle								
		1	2	3		1	2	3	4	5	6	7	8	9
cis+5fu	13													
		1			cis q 3 weeks			1						
			6		cisplatin weekly		1				1	3	1	
			1		Others				1					
				1	cis + 5fu		1							
				4	cisplatin weekly						4			
TPF	1			1	cisplatin weekly							1		
others	9													
			4		Others		4							
				3	cisplatin weekly			1		1	1			
				2	Others						1			1
cis+xeloda	12													
			5		cisplatin weekly			1	1		3			
			4		cis q 3 weeks	2	2							
				2	cisplatin weekly						1	1		
				1	cis q 3 weeks		1							
cis q3 weeks	1													
			1		cisplatin weekly							1		
Total	36	1	21	14		2	9	3	2	1	11	6	1	1

Discussion

This retrospective study investigated the effect of Neoadjuvant Chemotherapy (NACT) on patients with locoregionally advanced NPC at (KFSHRC), Jeddah, Saudi Arabia. In treatment of NPC, a wide variety of chemotherapy drugs can be used either alone or in combination with other drugs and treatments. In this study, NACT including either cisplatin and fluorouracil (5fu), taxane, cisplatin and 5-fluorouracil (TPF) or cisplatin and xeloda was used. On the other hand, cisplatin alone was used as backbone in CCT. Literature reported that the aforementioned significantly contributed to OS and LC in patients with locally advanced NPC. [15-18] In our previous study, three cycles of NACT with taxane, platinum, and fluorouracil were given. [19]

It is noticeable in the present study that the incidence of NPC in males (n=51, 66.2%) was higher compared to female patients (n=26, 33.8%). This is comparable with the study of Alsafadi and colleagues [20] which was carried out in Saudi population as well. Moreover, patients with Stage 3 and Type III (histology, WHO type) constitute most of our study samples.

Multivariate analysis revealed that the combination of NACT and CCT (n=5, 83.3%) resulted in a higher incidence of relapse than CCT alone (n=1, 16.7%). However, statistical significance was not achieved. Nevertheless, the majority of the patients experienced no relapse for both treatment groups. This implies treatments could be used to improve LC and OS of NPC patients. Product-limit survival estimate showed that the majority of the patients experienced relapse in the first three years while death occurrence was found between 1 and 2.5 years after chemotherapy. Our results are similar to other studies involving VMAT and IMRT treatments. In the study of Franzese and colleagues, improvements in terms of acute toxicity were better in patients who received VMAT compared to CCT. However, no significant effect was found on LC and OS in VMAT patients. [21] Guo et al. reported high loco regional control and survival outcomes after VMAT. [22] Meta-analysis of Blanchard et al. revealed that the combination of CCT and RT significantly improved the PFS, locoregional and distant controls and cancer mortality of patients. [22] Huang and colleagues reported 100% loco regional control with CCT-RT. [23] Study of Hadadi et al. showed good survival outcomes in terms of relapse free survival local control (76.8%) and overall survival (84.8%) using VMAT plus NACT. [24] Al-Amro et al. reported in their retrospective study that the combination of NACT and CCT is a safe and efficient treatment for NPC. [3] Furthermore, Maklad and colleagues revealed that the combination of NACT and IMRT alone or with chemotherapy contributed to improvement of OS of Saudi patients with NPC. [25]

Majority of the study samples used VMAT as a radiation technique for NPC. VMAT is an arc-based or rotational therapy in which a radiation source is continuously rotated making the dose distribution to be precise and highly conformal. [10] Previous studies reported advantages of VMAT in NPC treatment. In the comparative study of Verbakel, VMAT was better in terms of dose conformity and number of monitor units (lower) than IMRT. [26] Chen et al. found that VMAT showed better treatment delivery time although not superior in terms of PTV coverage and OAR sparing. [27]

We assessed other predictive factors for LC and OS. Analysis showed that pretreatment hemoglobin levels, gap in treatment, radiation dose and BSA were important variables in predicting relapses among patients. However, no significant difference was seen between sub-variables of each factor. Nevertheless, the result in pretreatment hemoglobin is to some extent similar to the following IMRT series. Guo et al. concluded in their study that hemoglobin level is an essential prognostic factor in NPC patients treated with IMRT. [28] Topkan and colleagues study lead into the conclusion that pre-CCRT hemoglobin level that is less

than 11.0 g/dL is a strong prognostic factor in regards to PFS, OS and Loco Regional Progressive-Free Survival (LRPFS). [29] Fareed et al. retrospectively studied the effect of IMRT with SMART plus CCRT as treatment for NPC and determined significant prognostic factors for locoregional recurrence. Results showed that combination of IMRT with SMART and CCRT is effective as a clinical response while Epstein-Barr Virus (EBV), node involvement and histopathology were found to be important prognostic variables. [30] Cao and colleagues reported poor outcomes in NPC patients with tumor PD-L1 expression and BRAF mutation. Nevertheless, PD-L1 is a significant prognostic factor in determining survival outcomes. [31]

One limitation of this study is its retrospective nature. Patients came from a single center; thus it may not represent the general population of NPC patients treated with NACT and CCT. Nevertheless, the large sample size of this study gave conclusive results. Second, the study samples were composed mostly of stage 3 and Type III patients that could affect the overall assessment of variables used in this study. Regardless of that, findings could be used as a reference for studies involving stage 3 and Type III NPC patients.

Conclusion

The current study found out that addition of NACT followed by CCT lowered the incidence of relapse among patients with loco regionally advanced NPC. However, no statistically significant difference in relapse was found between the two treatment groups. Thus, NACT followed by CCT produces similar overall survival as CCT alone.

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