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Treatment Responses of Pakistani Nasopharyngeal Carcinoma Patients Treated with Induction Chemotherapy Followed by Concurrent Chemoradiotherapy

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ABSTRACT

Objective: To investigate the response of nasopharyngeal cancer patients to induction chemotherapy, followed by concurrent chemoradiation, in our patient population.
Study Design: Retrospective cohort study

Place and Duration: Institute of nucleal medicine and oncology Lahore (INMOL) and Combined Military Hospital (CMH) Rawalpindi over a period of 5 months (Between Aug 2023 to Dec 2023) on patients treated between January 2015 to Dec 2019 (5 years).

Methodology: A total of 125 patients of proven nasopharyngeal squamous cell carcinomas were treated with 3 cycles of induction chemotherapy cisplatin and 5-fluorouracil followed by concurrent chemoradiotherapy (CCRT) with weekly cisplatin to 70 Gy in 35 daily fractions over 7 weeks. Response was evaluated at 4-6 weeks of treatment completion by RECIST 1.1 criteria.

Results: Male to female ratio was 3.46:1. Mean age of the patients was 37.3 years. Majority of the patients had stage III, IVA and IVB being 36.0%, 36.0% and 20.8% respectively. Grade III (n=79, 63.2%) was commonly observed grade. There was complete response (CR) in 51.2% while 30.4% showed partial response (PR). Stable and progressive disease was observed in 8.0% and 10.4% patients respectively. A CR of 100% in stage I, 57.1% in stage II, 82.2% in stage III and 46.7% in stage IV patients. Gender wise treatment response was 53.6% CR in males and 42.9% in females (p= 0.691).

Conclusion: Induction chemotherapy followed by concurrent chemoradiation has good response rates, and can be used as treatment of choice for definitive management of advanced nasopharyngeal cancer patients.

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Introduction

Nasopharyngeal carcinomas (NPC) account for approximately 70% of all primary tumors of the Nasopharynx. Although it is rare in western countries, highest incidence is found in traditionally endemic regions such as Southern China, Southeastern Asia, and North Africa [1]. According to Globocan, there were 133354 new cases of nasopharyngeal cancers and about 80000 deaths due to this disease [2]. NPC can occur in all age groups, but there is a bimodal age distribution with small percentage of patients in late childhood and a higher number of patients presenting between 50-60 years [3]. Male to female ratio of approximately 2–3:1 so males are more commonly affected than females [4]. Pakistani population is at moderate to high risk for development of NPC, with an estimated 832 new cases and 690 deaths in 2020 [5].

Currently, radiation therapy (RT) alone is the mainstay curative treatment for patients with stage I disease, RT alone or concurrent chemoradiation (CCRT) is used for stage II disease and concurrent chemoradiation (CCRT) or induction chemotherapy followed by CCRT is standard for stage III and IV (non-metastatic) [6-8]. The 5- year disease – specific survival rate in stage I NPC is around 95% and it is 60-80% for locoregionally advanced stage patients5. The Intergroup 0099 trial introduced adjuvant chemotherapy after CCRT into the treatment of stage III-IVB NPC, and showed significantly improved 3-year PFS and OS [9]. Two phase III trials have shown benefit of induction chemotherapy in terms of failure-free survival (FFS), recurrence free survival (RFS) and overall survival (OS). The chemotherapy regimens included a combination of docetaxel, cisplatin, 5-fluorouracil (TPF) and second regimen is a combination of gemcitabine and cisplatin (GC) [10, 11]. So the current treatment recommendation for locally advanced NPC is induction chemotherapy (IC) followed by CCRT.

Considering proximity of nasopharynx to critical structures and high target radiotherapy (RT) dose, conformal RT techniques are essential. Due to large number of patients and longer waiting times for radiotherapy in past, it was not possible to start upfront chemoradiation (CCRT), so to cover gap 3 cycles of induction chemotherapy (Cisplatin/5Fu) were being used before CCRT extrapolating data from Alsarraf et al [9].

This article covers the treatment outcomes and survival rates of our patients treated by IC followed by CCRT. This will add to the pool of knowledge on induction chemotherapy and will show response of local population to this modality of treatment. Local studies on the subject are scarce. Local biology of cancer may be different. Local patients may have less tolerability of chemotherapy than the Western population. Hence this study will help to highlight response to IC and CCRT of local population.

Objective

To investigate the response of nasopharyngeal cancer patients to induction chemotherapy, followed by concurrent chemoradiation, in our patient population.

Methodology

It is a retrospective cohort study performed at Institute of nucleal medicine and oncology Lahore (INMOL) and Department of oncology at Combined Military Hospital (CMH) Rawalpindi. Due to early adoption of modern techniques, these hospitals are referral centers of all complex cases like nasopharyngeal cancers in upper and central Pakistan. This study was performed between 01 Aug 2023 to 30 Dec 2023, on patients treated between 01 January 2015 to 31 Dec 2019 (5 years). Institutional review board (IRB) permission was sought via reference number "Onc-01-23" of INMOL Lahore. This study included a total of 125 patients. The sample size was calculated by statistician by using WHO sample size calculator where the confidence level was kept at 88%, alpha value was taken at 5%. Estimated locoregional control of 84.8% was used for sample size calculation, as was seen in a study by Fang et al. where 3-year locoregional control was measured [12]. Calculated sample size was 125. The sampling technique employed was a consecutive convenience sampling. Informed consent was attained from all the partakers of the study. Short history was taken before enrolment into study. Five year data i.e. 2015-19 of the patients registered with histologically proven NPC at these hospitals was retrospectively reviewed.

Inclusion Criteria

We included patients of both genders with any stage and grade, between 15 to 80 years of age, having diagnosed and histopathologically proven nasopharyngeal cancer, and undergone radiotherapy or concurrent chemoradiotherapy by 3-D conformal or intensity modulated radiotherapy (IMRT) technique.

Exclusion Criteria

All patients with age<15 years or >80 years were excluded. We also excluded patients receiving <70 Gy or equivalent dose. Patients of other head and neck carcinomas subsites except nasopharynx were not included.

All patients of stage II-IV (non-metastatic) were treated with 3 cycles of induction chemotherapy cisplatin 80 mg/m2 on Day-1 and 5-fluorouracil (5-FU) 1000 mg/m2 / day for four days (Day 1- Day 4) followed by concurrent chemoradiotherapy (CCRT) with weekly cisplatin 40 mg/m2. Using 3DCRT, a cone down technique was used. 70 Gy was given to high risk planning target volume (HR-PTV) in 35 daily fractions (Fx) with 2 Gy/Fx and 60 Gy was given to intermediate risk target volume (IR-PTV) with 2 Gy/Fx, 50 Gy to uninvolved nodal levels. While using IMRT, dose delivered to the HR-PTV was 69.96 Gy with 2.12Gy/Fx and to IR-PTV was 59.4 Gy with 1.8Gy/Fx. Linear accelerator (LINAC) machines with 6 MV (mega volt) energy was used for radiation delivery. Patients with stage I disease were treated with radiotherapy alone.

Treatment response for all study participants were measured in terms of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Treatment response for all study participants were also measured in terms of objective response rate (ORR), defined as the proportion of patients with a complete response or partial response to treatment according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) [13].

SPSS v.20.0 was used for statistical analysis. Age was determined in mean with standard deviation. Gender was age at presentation was calculated with mean and standard deviation. Categorical variables i.e. gender, grade, stage and treatment response were described as frequencies and percentages. Difference of mean was determined by applying analysis of variance (ANOVA). P-values < 0.05 were considered significant.

Results

Study cohort comprised 125 patients with male (n=97) to female (n=28) ratio being 3.46:1. Mean age of the patient population was 37.3 + 19.9 (Range: 17.0-80.0) years. Females presented at a comparatively younger age i.e. 35.7 + 15.0 years as compared to men while males had mean age of 37.8 + 21.1 years at presentation as shown in table-1. The difference was however statistically insignificant (P = 0.633).

Stage wise distribution of the patients in our study population reveals that majority of the patients had stage III, IVA and IVB being 45 (36.0%), 45 (36.0%) and 26 (20.8%) respectively (Table 1). Grade III (n=79, 63.2%) was commonly observed grade (Table 1). Baseline characteristics of the study population are tabulated (Table 1).

Table 1: Patient Characteristics

Variable	Frequency	Percentage
Gender		
Male	97	77.6
Female	28	22.4
Stage		
Stage I	2	1.6
Stage II	7	5.6
Stage III	45	36.0
Stage IVA	45	36.0
Stage IVB	26	20.8
Grade		
Grade I	16	12.8
Grade II	30	24.0
Grade III	79	63.2

Tumor (T), node (N) and metastasis (M) stage distribution is tabulated in Table 2. Majority of the patients (n= 99, 79.2%) had non metastatic disease at presentation. Metastatic disease (M1) at presentation was seen in 26 (20.8%) of patients.

Table 2: TNM Stage

Variable	Frequency	Percentage
T Stage		
T1	13	10.4
T2	21	16.8
T3	35	28.0
T4	52	41.6
Tx	4	3.2
N Stag		
N0	19	15.2
N1	17	13.6
N2	67	53.6
N3	21	16.8
Nx	1	0.8
M Stage		
M0	99	79.2
M1	26	20.8

Out of total 125 patients, objective response rate (ORR) turned out to be in 102 patients (81.6%). While 23 (18.4%) didn't respond to treatment as shown in figure-1.

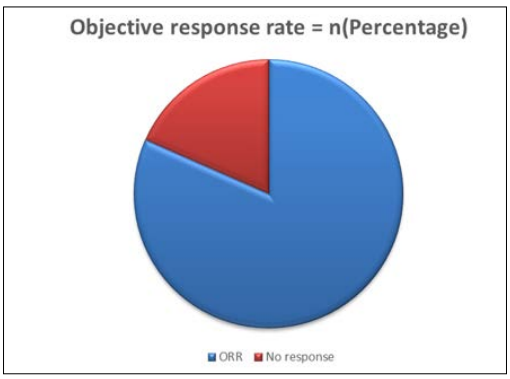

Figure 1: Objective Response Rate (ORR)

Response as per RECIST criteria version 1.1 is shown in Table-3. It showed that complete response (CR) was obtained by 64 (51.2%) while 38 (30.4%) showed partial response (PR). Stable and progressive disease was observed in 10 (8.0%) and 13 (10.4%) patients respectively

Response to treatment	Frequency (n)	Percent
PD	13	10.4
SD	10	8
PR	38	30.4
CR	64	51.2
Total	125	100

Stage wise response rates were CR of 100% in stage I (n=2). In stage II, seven patients were registered. Complete response was 4 out of 7 (57.1%) and 3 out of 5 (42.9%) had partial response. No patient in both stage I & II had either stable or progressive disease. In stage III, 45 patients were followed. Thirty seven out of 45 (82.2%) had CR while PR was 5 (11.1%), SD remained 3 (6.7%) while no PD was seen. In stage IVA (n=45), there was CR in 21(46.7%), PR in 13(28.9%), SD in 7(15.6%) and PD was observed in 4(8.9%). In stage IVB (metastatic patients), 9(34.6%) had PD and PR was 17(65.4%).

Treatment response was comparable in both males and females (P = 0.691). Amongst 97 male patients, 52 (53.6%) had CR, 27(27.8%) had PR, 8(8.2%) had SD and PD remained 10(10.3%). While amongst females (n=28), CR was 12(42.9%), PR remained 11(39.3%), SD was 2(7.1%) and PD 3(10.7%).

Discussion

Nasopharyngeal cancer is one of the success stories of oncology. Primary treatment with curative intent does not need invasive and disfiguring surgeries. Out 125 patients, 97 (77.6%) with male to female ratio of 3.46:1 Female ratio of 3.46:1 which was 2.5:1 in Malaysia while in India it was 3:1 [14, 15]. Stage I patients comprised of 1.6% cases, stage II were 5.6%, stage III represented 36.0%, stage IVa were 36.0% and stage IVb were 20.8% in our population. Which means advanced stage patients were 82.8% while in Malaysia 85% presented in advanced stages (Stage III and IV) [16]. which is roughly similar. So many advanced stage patients indicates the early nodal spread of the NPC which upstages the disease.

An objective response rate (ORR) of 81.6% was seen in our patients, while 18.4% didn't respond to treatment. It was almost similar to the ORR quoted in a study where ORR was 83% in induction chemotherapy followed by CCRT arm [17]. Induction chemotherapy was better as compared to concurrent chemoradiation alone with hazard ratio for objective response of 0.60 (P=0.0002), showing CCRT to be a better modality [18]. Many studies have used the induction chemotherapy followed by concurrent chemoradiation as a treatment option. These studies have used different regimens for induction [19-21]. In our study treatment response was comparable in both males and females (P = 0.691). Male patients had CR in 53.6%, PR in 27.8%, SD in 8.2% and PD in 10.3%. While amongst females, CR was 42.9%, PR in 39.3%, SD 7.1% and PD in 10.7%. So response to treatment was not gender dependent. Chemoradiation has many side effects which can be debilitating during the treatment (acute effects) or latter in life (Long term effects) [22]. These side effects are mitigated by the use of highly focused radiation like intensity modulated radiotherapy or volumetric arc therapy techniques.

A collaboration is suggested to learn from the experience of high incidence countries and apply to the areas with low incidence [23]. In this way, the outcomes will improve, leading to better response rates and survivals. This study can be a milestone in therapeutic approach for local nasopharyngeal cancer patients, as no such study has been conducted on local population. Further investigations, prospective trials and larger study populations are necessary to authenticate these findings and provide more convincing evidence.

Conclusions

This study sheds light on the response of our population to the induction chemotherapy followed by concurrent chemoradiation. Response to treatment in our patient population is almost similar to the response quoted in international published literature. Further prospective research is also warranted in our population, to

substantiate these findings and reconnoiter clinical implications for optimizing treatment strategies and enhancing patient outcomes.

Conflict of Interest
There was no conflict of interest amongst authors.

Limitations of the Study
This study was done one smaller sample size and at two cities. Multicentric studies on different populations/ ethnicities of Pakistan and more number of patients are suggested, to truly represent the whole nation.

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Authors Contributions
Following authors have made substantial contributions to the manuscript as under

SS & AZ
Conception of study, Supervision of data collection, IRB approval, final approval and reference writing.

MSN & RNM
Synopsis, compilation of data, conception of study, table making and final approval.

MSN & RNM
Synopsis, compilation of data, conception of study, table making and final approval.

AS & IF
Collection of data, making tables, analysis of data and final approval.
Authors agree to be accountable for all facets of the work in guaranteeing that questions related to the accurateness or integrity of any part of the work are appropriately investigated and resolved.

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