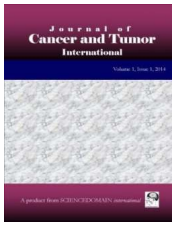

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Induction Chemotherapy Followed by Concurrent Chemo-conformal Radiation Therapy in Locally Advanced Nasopharyngeal Carcinoma

Ghada Saber Abdulmohsen[1*], Rasha Abdel Latif[1], Soumaya Eteba[1] and Enas Abd Al Halim[1]

[1]Department of Clinical Oncology and Nuclear Medicine, Mansoura University, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. Authors SE and EAAH designed the study. Author GSA performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript and managed the literature searches. Author RAL managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Background: Renewed interest in induction chemotherapy for treatment of locally advanced nasopharyngeal carcinoma has been made recently. Multiple phase III trials were going aiming to define the best candidate, and the best regimen for induction chemotherapy. We conducted this phase II study to evaluate the efficacy and safety of induction chemotherapeutic (TPF) regimen before CCRT with cisplatin weekly in locally advanced non metastatic NPC.
Methods: 36 patients diagnosed with stage III, IVA & IVB, poorly differentiated or undifferentiated carcinoma in the period between August 2014 and August 2016 were included in the study, all of them received induction chemotherapy with TPF regimen followed by cisplatin (40 mg/m^2) weekly concurrent with RT. Radiotherapy was given by 3D conformal modality where, high-risk GTVP, GTVLN & CTV was given a dose of 60 Gray / 30 fractions followed by 10-14 gray/5-7 fractions to GTVP and 6-10 Gray /3-5 fractions to GTVLN.
Results: The objective response rate was 86% (CR 12%) in the primary tumor and, 100% (CR 62%) in the cervical LN after induction chemotherapy and the corresponding rate was 100%

**Corresponding author: Email: ghadaabdulmohsen@yahoo.com, dr.ghada.saber@gmail.com;*

(CR 91%), 45-60 days after the completion of RT. No local recurrence or distant metastasis was seen during the follow-up period. The two-year DFS was 85% and the estimated two-year OS was 95%. The rate of grade 3 /4 neutropenic fever was encountered in 6% of cases during induction chemotherapy. Grade 3/4 mucositis was seen in 9 % of patients while no grade 3 or 4 skin desquamation or xerostomia were seen. There was no treatment-related death. Field in field technique gave the best coverage of the PTV without exceeding the tolerance dose of other OAR. **Conclusion:** The TPF regimen was well tolerated and had a manageable toxicity profile. 3DCRT can be tailored to reach the target of Intensity modulation modalities.

Keywords: Nasopharyngeal carcinoma; conformal radiotherapy; induction chemotherapy; TPF.

1. INTRODUCTION

Worldwide, there are about 85,000 incident cases and 55,000 deaths annually from nasopharyngeal carcinoma but with a high variation in the racial and geographical distribution with the highest prevalence in Southeast Asia and North Africa [1]. Owing to its silent, deeply seated site and vague, non-specific symptoms, its early detection is challenging as about 60–70% of cases present with locally advanced disease at diagnosis [2]. Concurrent chemo radiation is the standard treatment strategy for NPC in locally advanced stages [3-8]. However, the results of CCRT are suboptimal as over 20% of patients still experience distant metastasis after CCRT, necessitating exploration of other intensive treatment modalities for NPC as neoadjuvant chemotherapy, for improving the patients' survival rates [9]. Multiple phase II trials have described better patient tolerance and treatment tolerability as regard induction chemotherapy versus adjuvant chemotherapy as well as a high locoregional response by reducing the tumor burden and killing occult micro-metastases. Multiple chemotherapeutic regimens as (bleomycin, gemcitabine, carboplatin, and taxanes) were investigated as a neoadjuvant line in locally advanced nasopharyngeal carcinoma [10-11]. The Controversy was still around the rule of NACT in locally advanced NPC as regards its impact on the overall survival in comparison with CCRT, who is the best candidate and what is the optimal regimen. These controversial issues, makes the NCCN panel recommend NACT as category III after being class I. These controversial issues answered by these phase III and meta-analytic studies (NCT01245959, NCT00828386, NCT01536223 and NCT00201396) [12-17]. Intensity-modulated radiation therapy (IMRT) is the standard RT modality for treatment of head and neck cancer especially the NPC [18-19] but certain issues are related to IMRT, the most important are that they cannot be used universally due to unavailability of adequate equipment, organization or patient status. We initiated this study to evaluate the efficacy and tolerability of the TPF regimen followed by CCRT with 3D conformal RT modality in locally advanced NPC. We reported the two-year OS and the two-year DFS, and we have evaluated multiple fields arrangement of non-intensity modulation trying to achieve better coverage of the target and not exceeding the tolerance dose of the OAR.

2. PATIENTS AND METHODS

2.1 Eligibility Criteria Included

Patients with stage III, IVA & IVB NPC, age between 18 and 70 years, ECOG PS of ≤ 2 and adequate organ function. Exclusion criteria included distant metastasis, abnormal body function or ECOG 3-4, history of surgery at the tumor site or neck except for diagnostic biopsy. Other exclusion criteria included a history of RT to the H&N region or history of any malignancy, second malignancy at the time of presentation, current pregnancy or joining another clinical trial at the time of our study. We took a written consent from all patients, and the ethical committee OF Mansoura University approved our trial.

2.2 Treatment Regimens

2.2.1 Pretreatment evaluation

Pretreatment staging including clinical examination, radiological investigation (CT or MRI PNS & neck, chest CT), Bone scintigraphy and the abdominal US. Full ENT examination including endoscopy & biopsy and examination under anesthesia if needed and complete dental checkup and assurance about good oral hygiene.

2.3 Treatment Details

2.3.1 Chemotherapy

All patients were planned to receive induction chemotherapy three cycles of TPF (docetaxel 75

mg/m2 D1 3 h infusion, cisplatin 75 mg/m2 D1 2 hour infusion and 5 FU 1 g/m2 continuous IV infusion D1-D4). The cycle to be repeated every three weeks to be followed by cisplatin (40 mg/m2) weekly concurrent with RT. Growth Colony Stimulating Factor (GCSF) given when needed. Concurrent CRT with cisplatin 40 mg/m2 weekly over one-hour infusion started 2-3 weeks after finishing the 3rd cycle chemotherapy and after doing a new assessment to measure response to chemotherapy.

2.3.2 Radiotherapy

The Gross Target Volume 70 (GTV 70) consists of gross lesion seen on CT, MRI or endoscopic findings and GTV LN is any LN more than 1 cm or LN with a necrotic center. Clinical target volume 70 (CTV 70) and PTV70 encompass GTV 70 and CTV 70 + 3 -5 mm margin or less near the organs at risk (OAR) like the brainstem. Clinical Tumor Volume 59.4 (CTV59.4) include the whole NP, anterior one-third of the clivus, base of the skull, inferior portion of sphenoid sinus, cavernous sinus, pterygoid fossa, Para pharyngeal space, posterior one-fourth of the nasal cavity/maxillary sinuses, inferior portion of soft palate, retropharyngeal LN, retrostyloid space, and bilateral cervical LN from level IB to V. High-risk GTVP, GTVLN & CTV was given a radiotherapy dose of sixty Gray in thirty fractions divided into 2 phases. Phase 3 included ten to fourteen gray in five to seven sessions to GTVP and six to ten Gray in three to five fractions to GTVLN. Patients with N0 disease or lower neck (level IV and V) delivered a dose of 45-54 Gy at 1.8 Gy per fraction. Table 1. Radiation therapy was given by 3D Conformal technique and was delivered by the high energy linear accelerator (Elekta, Precise Treatment System TM), Version 5, with 6 MV and 15 MV photon energy. We tried multiple field arrangement field in field with segmentation technique was the best beam arrangement used achieving better coverage of the PTV without exceeding the tolerance dose to the OAR.

2.4 Follow-up

Chemotherapy Toxicities either hematological or non-hematological were assessed after each cycle, while radiation toxicities were evaluated weekly for acute radiation toxicity and every three, six months for chronic ones. Adverse events were estimated according to the latest version of the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE).After ending CCRT, patients were followed every three months during the first two years, every six months for the next two years, and then annually.

2.5 Statistical Analysis

Data were analyzed with SPSS version 22 and expressed as number and percentage. Kaplan–Meier method used for analysis of the survival function.

3. RESULTS

3.1 Patient Characteristics

Between August 2104 and August 2016, 36 eligible patients diagnosed with nasopharyngeal carcinoma that referred to clinical oncology and nuclear medicine department, Mansoura University Hospitals incorporated in our study after the agreement of the ethical committee of Mansoura University. The median follow-up was 23 months (Range 11-33). Males predominated; there were 25 (69%) men and 11 females (31%) with male to female ratio of about 2 to 1.The age ranged from 18 to 70 years with a median of 48 years. Most patients had a PS ECOG 1. There were 34 patients (95%) with ECOG 1 and only 2 cases (5%) with ECOG 2. Co-morbidities encountered in only five patients, and the remaining 31 (86%) patients had no associated co-morbidities. Of the 36 patients, 12 (33%) were smokers. Symptoms at presentation were different according to T and N stage. Patients with N +ve disease mainly presented by cervical lymphadenopathy while, patients with N -ve disease came with nasal or ear symptoms. Patients with T3 and T4 came mostly with cranial neuropathy. Almost all patients presented with more than one symptom. In general, the most common presenting symptoms were cervical lymphadenopathy (56%) followed by nasal symptoms (22%), cranial neuropathy (14%) and ear symptoms (9%) Patients' characteristics and staging detailed in Table 2.

3.2 Treatment Outcome

3.2.1 Response

Thirty-four patients had ended the induction phase and all of them reassessed by MRI PNS & neck and endoscope with comparison with the baseline investigation. The response assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) [20]. The objective

response rate was 86% (CR 12%) for primary tumor and 100% (CR 62%) in the cervical LN after induction chemotherapy. Out of the 34 patients that had started the CCRT, 33 patients had ended this phase and then reassessed by MRI PNS and neck, endoscopy and endoscopic biopsy if residual or suspicious residual, 45-60 days after completing radiotherapy and the corresponding rate was 100% (CR) 91%. Tables 3 and 4. The three patients who had residual disease at the primary site after CRT; one of them was offered two cycles of adjuvant chemotherapy and became free, and the other two patients were followed up regularly and did not offered adjuvant treatment as they had SD after induction chemotherapy. One of those two patients had stable disease on follow-up, and the other one had PD after ten months and was offered 1st line chemotherapy two cycles then lost follow-up before assessment.

Table 1. Suggested target volume and the prescribed doses for patients received CRT phase

Target volume	Description	Prescribed dose
High risk GTV P	Consists of all gross disease on physical examination and imaging	60 GY/ 30 ttt followed by 10-14 GY/5-7 ttt
High risk CTV P	Consists of GTV 70 + 3 mm margin or less (1 mm) around critical structures like the brainstem	60 GY /30 ttt followed by 10-14 GY/ 5-7 ttt
High risk GTV LN	Neck nodes: All nodes ≥ 1 cm or those with necrotic center	60 GY /30 ttt followed by 6-10 GY/ 3-5 ttt
CTV 59.4	Include : The whole NP , anterior one-third of the clivus ,base of the skull ,inferior portion of sphenoid sinus, cavernous sinus, pterygoid fossa ,Para pharyngeal space ,posterior one-fourth of the nasal cavity/maxillary sinuses ,inferior portion of soft palate, retropharyngeal LN ,retrostyloid space, bilateral cervical LN from level IB to V.	60 GY /30 ttt
Lower neck with LN-ve	Level IV & V LN	45-45 GY/25-28 ttt

Table2. Characteristics of the study group patients (36 locally advanced NPC cases)

Characteristic		No. (36)	%
Sex	Male	25	69
	Female	11	30
Age			
Range(18-70)	18-40	14	39
Median (48)	41-70	22	61
ECOG	0	23	64
P.S	1	11	31
	2	2	5
Special habits	No	29	81
	Smoking	6	16
Co morbidities	DM	2	6
	HTN	1	4
	Cardiac	2	6
Pathology	Undifferentiated carcinoma	36	100
T stage	T1	13	37
	T2	11	31
	T3	10	27
	T4	2	5
N stage	N0	10	28
	N1	6	17
	N2	19	53
	N3	1	2
Symptoms	Cervical lymphadenopathy	20	56
	Nasal symptoms	8	22
	Cranial neuropathy	5	14
	Ear symptoms	3	9

Table 3. Summary of the results of induction chemotherapy phase

Patients	Patients finishing induction CTH	Response to induction CTH					
		NP (34)			LN+(26)		
		CR	PR	CR+PR	CR	PR	CR+PR
36 (100%)	34 (94%)	4 (12%)	25 (74%)	86%	16(62%)	10(38%)	100%

Table 4. Summary of results of CCRT phase

Patients finishing CRT	Response to CRT		Follow -Up failure	
			Local	Distant
NO (33)	(30) CR	(3) PR in NP	0	0
% (100)	91% CR	9% PR	0	0

CR (Complete response)-PR (Partial response)-SD (stationary disease)-NP (nasopharynx)-LN (lymph node)

3.2.2 Survival rate

All of the 30 patients who achieved complete response remain disease free, no local recurrence, no bone or visceral metastases. Using the Kaplan-Meier method, the two-year DFS was 85% as shown in Fig. 1. The estimated two-year OS was 95% as shown in Fig. 2.

3.3 Treatment Toxicity and Acute Adverse Events

The TPF regimen was tolerable. Only two patients (6%) out of the 36 developed grade III febrile neutropenia and one of them (3%) developed grade III mucositis, diarrhea and grade III hepatic and renal impairment and did not complete the induction phase and excluded from the study. Thirty four patients had completed the planned three courses of TPF .No dose reduction needed during the induction phase. Chemotherapy toxicity recorded in the Table 5. Out of the 34 patients who entered the CRT phase, three patients (9%) had grade III mucositis, 2 of them had treatment interruption, but they completed the CRT phase and only one of them lost to follow-up and dropped out this phase. The median course of concurrent chemotherapy was 5 (1-8 courses). The number of patients who finished at least five courses of CT was 29 patients (85%). No significant hematological toxicities, vomiting or renal impairment encountered during the CRT phase. Skin toxicity of grade 1 was the commonest acute effects seen in 97% of cases Table 6.

3.4 Late Toxicity

After a median follow-up of 23 months, the patients showed a low incidence of severe late complication. Of the 33 patients who completed the concurrent CRT phase, no one developed G3 toxicity. The most common late radiation effect was xerostomia with G 1 seen in 76% of patients and G 2 in 24% of patients Table 7.

Table 5. Hematological and non-hematological toxicities encountered in the study group during the induction phase

Hematological	G1		G2		G3	
	N	%	N	%	N	%
Anemia	3	8	1	3	0	0
leucopenia	6	17	2	6	1	3
Neutropenia	4	11	2	6	2	6
Neutropenic fever	0	0	0	0	2	6
Thrombocytopenia	4	11	1	3	1	3
Non hematological	20	55	14	39	2	6
Nausea and Vomiting						
Diarrhea	28	77	2	6	1	3
Hair loss	0	0	34	100	_	_
Mucositis	15	42	6	17	1	3
Liver impairment	1	3	2	6	1	3
Renal impairment	2	6	0	0	1	3
Peripheral neuropathy	9	25	2	6	0	0

Table 6. Acute radiation toxicities encountered in the study group during the CRT phase

Toxicity	Grade 1	Grade 2	Grade 3
Anemia	6 (18%)	1 (3%)	0 (0)
Leucopenia	2 (6%)	1 (3%)	0 (0)
Neutropenia	2 (6%)	1 (3%)	0 (0)
Neutropenic fever	0 (0)	0 (0)	0 (0)
Thrombocytopenia	2 (6%)	0 (0)	0 (0)
Nausea and vomiting	4 (11%)	2 (6%)	0 (0)
Liver impairment	1 (3%)	1 (3%)	0 (0)
Renal impairment	5 (15%)	2 (6%)	0 (0)
Mucositis	5 (14%)	26 (77%)	3 (9%)
Skin toxicity	33 (97%)	1 (3%)	0 (0)

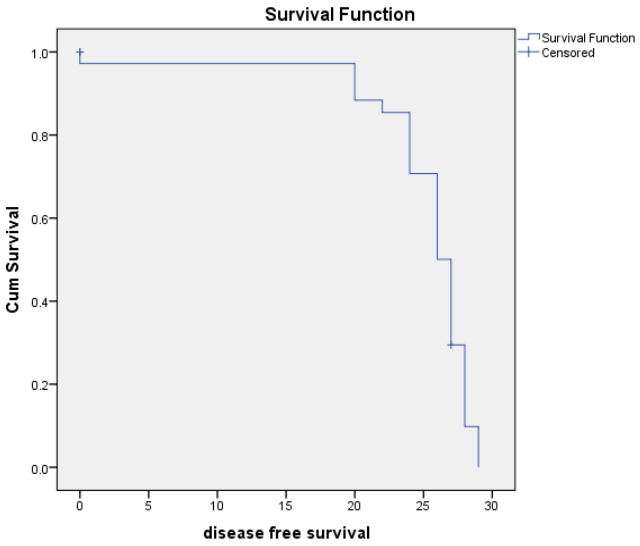

Fig. 1. 2- year DFS among all studied cases

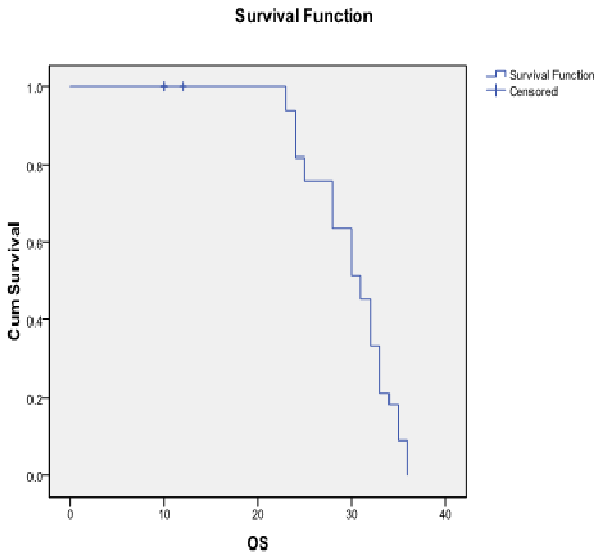

Fig. 2. 2-year OS among all studied pla

Table 7. Late Radiation toxicities encountered in the study group who finished the CRT phase

Toxicity	G1	%	G2	%	G3	%	G4	%
Xerostomia	25	76	8	24	0	0	0	0
Dysphagia	2	6	0	0	0	0	0	0
Trismus	2	9	0	0	0	0	0	0
Subcutaneous fibrosis	2	6	0	0	0	0	0	0
Hearing deficit	1	3	0	0	0	0	0	0

4. DISCUSSION

Renewed interest in the role of neoadjuvant chemotherapy was made recently in managing locally advanced NPC. The NCCN panel recommends it as being category III after being category I while ESMO guidelines still recommend it as class I. Multiple trials were going aiming to define the best candidate and the best regimen for neoadjuvant chemotherapy in locally advanced NPC and to confirm whether NACT affects the OS in comparison with CCRT [12-17].

The main aim of our study was the evaluation of the efficacy and safety of neoadjuvant chemotherapeutic TPF regimen followed by CCRT for advanced non metastatic NPC. The primary endpoint was the response rate, and the secondary endpoints were to evaluate treatment toxicity, disease-free survival (DFS) and overall survival (OS) and if we can achieve better coverage to the PTV without exceeding the tolerance dose to the OAR with non-modulation RT techniques.

Nasopharyngeal carcinoma is radio and chemo-sensitive. Combined chemo-radiotherapy with or without adjuvant chemotherapy underwent extensive studies and proved to be the standard treatment line for advanced non metastatic NPC [3-6]. Various phase 3 and meta-analytic studies have confirmed that adjuvant chemotherapy gave no significant improvement in patients' survival and was found to be poorly tolerated and has limited compliance because patients suffer substantial toxicities from CCRT and may be unfit to receive further chemotherapy [21-24]. Despite being the standard treatment, most of the results of CCRT are suboptimal as over 20% of patients still experience distant metastasis after CCRT, necessitating exploration of other intensive treatment modalities as neo-adjuvant chemotherapy for improving the patients survival rates [25].The reported studies clearly illustrate that, with neoadjuvant chemotherapy, tolerance and compliance are substantially better, and nearly 100% of patients can tolerate at least two cycles. However, induction chemotherapy using cisplatin or its combination, such as combined cisplatin, epirubicin and paclitaxel failed to improve the OS according to the results from several randomized clinical trials [26-28].

Docetaxel has demonstrated significant efficacy as a single agent or in combination with platinum in head and neck squamous cell carcinoma (HNSCC).Compared with paclitaxel, it has less neurotoxicity, which supports its combined use with cisplatin. Its efficacy in the treatment of HNSCC has been demonstrated in randomized clinical trials. The results from the TAX 3238 and TAX 3249 studies revealed that, when used with CCRT or RT, the addition of docetaxel to cisplatin and 5-FU (TPF) reduced the risk of death by nearly 30% [29-31]. Such encouraging results obtained by the TPF chemotherapeutic regimens in HNSCC were impressive for its use in locally advanced NPC. Further phase II and phase III trials have evaluated and confirmed the efficacy and tolerability of TPF regimen in locally advanced NPC and recently, recommend it as the optimal neoadjuvant regimen [12,15,32].

In our study, Initial assessment after the induction phase showed that CR in the NP was achieved in 12% and 62% in the LN while PR in the NP was 74% and in the LN 38%. Stationary disease was seen in 17% mainly in the primary tumor with node -ve disease and no progressive disease was seen. Our results cope with the results of the meta-analytic study done by Du and his colleagues [25] that showed that neoadjuvant chemotherapy was a significant factor predicting good response rate for all patients with node-positive NPC (N2&N3) (P value 0.006). Also the high incidence of CR that occurred mainly in the LN after the induction phase in our study comes with the design of their prognostic model in which the LN status was one of the factors that should be taken into consideration in selection of patients who will benefit from NACT, however, other factors in the prognostic model should be also investigated.

The opinion of Kong and his colleagues [32] supporting the role of induction chemotherapy in locally advanced NPC through its ability to shrink

the GTV and so decreasing the dose to critical structures as brainstem and optic chiasma not achieved in the current study. Two of our cases were T4 No disease, one of them did not complete the induction phase and the other when assessed after the 3rd cycle revealed stationary course and on giving the CRT phase, the PTV was accepted to be covered by only 90% in order not to exceed the tolerance dose of the OAR. However, this is needed to be confirmed by much more cases.

The most commonly recorded severe acute toxicity (≥ grade 3) in the most representative studies of NACT in NPC [10,33] were nausea/ vomiting (25.6%), followed by neutropenia (17.3%). In the current study, the incidence of grade 3 nausea and vomiting was only 6%, and this is probably due to more potent antiemetic used .Severe neutropenia was only seen in 6% of cases due to GCSF support.

Regarding diarrhea and mucositis associated with induction chemotherapy, grade 3 seen in only one patient (3%), however, it was not observed in [10,33]. This difference between results may probably due to the use of 5-fluorouracil in the TPF regimen while the regimens used in the previous 2 studies were taxanes and cisplatin only.

Acute severe liver dysfunction and renal dysfunction were seen in only one patient (3%) while they were not experienced in [10,32,33] and this may be explained by the associated co-morbidities in the patients included in our trial. It seemed that the regimen of TPF was tolerable by most of the patients as only two patients developed GIII toxicity and did not complete the protocol. These results cope mostly with the results of the studies utilizing TPF regimen in induction phase as in [12,15,32].

In the CRT phase, no significant hematological, gastrointestinal, renal toxicities or skin toxicities were noticed. For hematological toxicities, no grade III toxicities were seen in our study. Our results are better than the results of the two published studies on 2009 & 2012 [10,33] that showed 6.4% grade 3 anemia and 26% grade 3 leucopenia, 13% neutropenic fever and 1.1% grade 3 thrombocytopenia. As regard non-hematological toxicity in the previous two studies, G3 nausea and vomiting was reported in 16.8% of cases, renal impairment in 6%, skin toxicity in 8.4% and 28% had grade 3 mucositis. In our study no grade III non hematological toxicities were experienced except for 9% G3 mucositis and this is explained by the potent antiemetic measures used during CCRT, conformal RT techniques sparing the parotid gland and buccal mucosa in comparison with the conventional ones.

Nasopharyngeal carcinoma is considered among the most difficult tumors to plan because of its complex anatomy, multiple targets with different dose prescriptions, a significant extension of the treatment region and the number of structures at risk. Moreover, doses up to 70Gy with a conventional fractionation are prescribed. To overcome planning difficulties, highly sophisticated techniques such as intensity-modulated radiation therapy (IMRT), intensity-modulated arc therapy, or volumetric modulated arc therapy (VMAT) have been developed. These modern techniques gave much better results than does three-dimensional conformal radiotherapy (3DCRT), especially in the differentiation of dose distribution towards treatment targets and sparing of the OARs. However, these techniques cannot be universally used, due to unavailability of adequate equipment, organization or patient status, and this gives the 3DCRT the upper hand in the treatment of the most of the cancers including Head and Neck cancers. In our study, CRT phase was given utilizing 3D conformal technique due to unavailability of IMRT which was tailored to improve the PTV dose conformality and sparing of the OAR's which were the biggest problems we faced. Various fields arrangement were tried but Field in field technique developed by Herassi and his colleagues [34], was the one which achieves our target.

In the current study that was ended by 33 patients, final assessment after CRT revealed that CR in the primary site and neck achieved in 91% (30 patients) and PR in 9% (3 patients) in the primary tumor. The overall response rate is 100% which is better than the results of Kong and his colleagues [32] that show an overall response of 94.9% with induction TPF followed by CCRT. The results of our study were comparable with the results of Bae and his colleagues [35] that reported an ORR of 98%. As regards the local control rate which reached 91% in our study, it was found comparable to the previous study.

These encouraging results as regard the impact of NACT on loco-regional control were confirmed by these recently published phase III and meta-analytic studies [12-17,25].

In our study and after a median follow-up period of 23 months, the incidence of local recurrence and distant metastases in patients who reach complete response (30 patients) was 0%, and these are better results than those of Kong and his colleagues [32] that showed 21 failures observed during follow-up. This difference in the incidence of loco-regional recurrence and distant metastases between our study and the previous one may be contributed to the larger number of patients and longer follow-up period in Kong et al than those of our study.

Recently, the researchers have concluded that there is a significant improvement in the OS for locally advanced NPC patients who received induction chemotherapy in comparison with CCRT. [12-17] and the TPF regimen has been recommended to be the optimal neoadjuvant regimen [12,15]. The findings from our trial confirm these encouraging results where the 2-year OS reached 95%, and the 2-year DFS reached 85%. However, our study lacks the comparative arm.

5. CONCLUSION

Neoadjuvant chemotherapy is an important line in treating advanced NPC as it has been confirmed to improve the OS compared with CCRT but the optimal candidate and the best regimen are needed to be defined. Extensive N stage (N2&N3) is one of the parameters to be put into consideration in the selection of the patient for NACT. The TPF regimen was well tolerated and had a manageable toxicity profile. The addition of TPF before CCRT significantly increased failure-free survival, OS and distant failure-free survival rates; however, long-term follow-up is required. The standard technique in advanced NPC is IMRT; however, if not available, 3D conformal techniques can be tailored to achieve the best coverage of the PTV without exceeding the tolerance dose to the OAR.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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