

Original Research Article

Induction Chemotherapy followed by Concurrent Chemo-Conformal Radiation Therapy in Locally Advanced Nasopharyngeal Carcinoma

Abstract

The role of induction chemotherapy prior to CCRT in treatment of locally advanced nasopharyngeal cancer has not been determined yet. we conducted this phase II study to evaluate the efficacy and safety of induction chemotherapeutic (TPF) regimen prior to CCRT with cisplatin weekly in locally advanced non metastatic NPC. **Methods:** 36 patients diagnosed with stage III, IVa or IVb, poorly differentiated or undifferentiated carcinoma included in the study, all of them received induction chemotherapy with TPF regimen followed by cisplatin (40 mg/m²) 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 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% (CR 91%), 45-60 days after the completion of RT. No local recurrence or distant metastasis were seen during the follow up period. The 2 year DFS was 85% and the estimated 2 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 technique gave 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

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 for improving the patients' survival rates[9]. Adding taxanes to cisplatin and 5-fluorouracil (TPF regimen) prior to radiation therapy or CCRT has resulted in significantly improved treatment outcomes, including overall survival in patients with head and neck squamous cell carcinoma excluding NPC. These encouraging results provided by the TPF chemotherapeutic regimens were interesting for its use in locally advanced NPC[10-12]. Intensity modulated radiation therapy (IMRT) is the standard RT modality for treatment of head and neck cancer especially the NPC [13-14] but certain issues are related to IMRT, the most important is that they can not be used universally due to unavailability of adequate equipment, organization or patient status. Therefore we initiated this study to evaluate the efficacy and tolerability of TPF regimen followed by CCRT with 3D conformal modality in locally advanced NPC. We reported the 2 year OS and the 2 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 risky organs.

Patients and methods

Patients with non-keratinizing, poorly differentiated and undifferentiated squamous cell carcinoma of the nasopharynx of stage III, IVA&IVB were eligible to be included in our study. Other eligibility criteria included age between 18 and 70 years, ECOG PS of ≤ 2 and adequate organ function. Exclusion criteria included WHO type I NPC (keratinizing SCC), distant metastasis, abnormal organ function or ECOG 3-4, past history of surgery at the tumor site or neck except for diagnostic biopsy, past history of RT to the H&N region, past history of any malignancy, double malignancy at the time of presentation, current pregnancy or joining other clinical trial at the time of our study.

Treatment Regimens :

Pre treatment evaluation

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

Treatment details

Chemotherapy

All patients were planned to receive induction chemotherapy 3 cycles of TPF (docetaxel 75 mg/m² D1 3h infusion , cisplatin 75 mg/m² D1 2hour infusion and 5 FU 1g/m² continuous IV infusion D1-D4) to be repeated every 3 weeks to be followed by cisplatin (40 mg/m²) weekly concurrent with RT. GCSF was given when needed .Concurrent CRT with cisplatin 40mg/m² weekly .It was given over 1 hour IV infusion 2 to 4 hours before RT .

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 PTV 70 encompass GTV 70 and CTV 70 + 3 -5 mm margin or less near the risky organs 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 , parapharyngeal 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. High risk GTVP, GTVLN & CTV was given a radiotherapy dose of sixty Gray in thirty fractions divided on 2 phases. Phase 3 included ten to fourteen gray in five to seven fractions to GTVP and six to ten Gray in three to five fractions to GTVLN. A dose of 4500-5400 c Gy at 1.8 Gy per fraction was given to N0 or lower neck (level IV and V) . Radiation therapy was given by 3D Conformal technique and was delivered by high energy linear accelerator (Elekta, Precise Treatment System TM), Version 5, with 6 MV and 15 MV photon energy. Multiple field arrangement were used but field in field with segmentation technique was the best beam arrangement used achieving better coverage of the PTV without exceeding the tolerance dose of OAR .

Follow up

chemotherapy toxicities either hematological or non hematological were assessed after each cycle, while radiation toxicities were assessed weekly for acute radiation toxicity and every 3, 6 months for chronic ones. Adverse events will be evaluated according to the latest version of the National Cancer Institutes Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE).After ending CCRT , patients were followed every 3 months during the first 2 years, every 6 months for the next 2 years, and then annually .

Statistical Analysis

Data were analyzed with **SPSS** version 22, and were expressed as number and percentage.kaplan–Merire was used for analysis of survival function.

RESULTS

Patient Characteristics

Between August 2104 and August 2016 , 36 eligible patients diagnosed with nasopharyngeal carcinoma who referred to clinical oncology and nuclear medicine department , Mansoura university hospitals were incorporated in our study .The median follow-up was 23 months (Range 11-33) . Patients' characteristics and staging are detailed in Tables (1)

treatmentoutcome

Response :The response to chemotherapy was assessed According to the Response Evaluation Criteria in Solid Tumors (RECIST)[15] .The objective response rate was 86% (CR 12%) for primary tumor and 100% (CR 62%) in the cervical LN after induction chemotherapy .And the corresponding rate was 100 % (CR 91%), 45-60 days after ending radiotherapy.

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 2 year DFS was 85% as shown in figure(1) .The estimated 2 year OS was 95% as shown in figure (2)

Treatment toxicity and acute adverse events

Generally, the regimen was tolerated. Only 2 patients had grade 3 toxicity after the 1st cycle and did not complete the induction phase and were excluded from the study .Thirty four patients had completed the planned

3 courses of TPF .No dose reduction was needed during the induction phase . Chemotherapy toxicity is recorded in table (2) . All patients had ended CRT phase except for 1 patient who developed grade 3 mucositis and did not complete the CRT phase . The median course of concurrent chemotherapy was 5 (1-8 courses). The number of patients who finished at least 5 courses of CT was 29 patients (85%) . No major hematological toxicities , vomiting or renal impairment were encountered during the CRT phase . Skin toxicity of grade 1 was the commonest acute effects seen in 97% of cases .table (3)

Late toxicity

After a median follow-up of 23 months , the patients showed 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. (4) .

Discussion

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 endpoint was to evaluate treatment toxicity , ,disease free survival (DFS) and over all 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 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 [16-19].Induction chemotherapy with cisplatin before radiation therapy alone , have improved treatment outcome as regard the local control and DFS in patients with locally advanced NPC with no effect on the OS.[20-22].However, 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 for NPC for improving the patients' survival rates[23] . Adding taxanes to cisplatin and 5-fluorouracil (TPF regimen) prior to radiation therapy or CCRT has resulted in significantly improved overall survival in patients with head and neck squamous cell carcinoma excluding NPC. These encouraging results provided by the TPF chemotherapeutic regimens were interesting for its use in locally advanced NPC

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 NP was 74% and in LN 38 % , SD was seen in 17% mainly in NP tumor with node –ve and no progressive disease was seen and this is coping with the results of meta analytic study done by Du and his colleagues [23] 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 copes with the design of their prognostic model in which the LN status was one of the factors that should be taken in consideration in selection of patients who will benefit from NACT however other factors in the prognostic model should be also investigated

In our study , the adverse events were acceptable as the incidence of grade 3 nausea and vomiting was only 6% and Severe neutropenia was only seen in 6 % of cases due to GCSF support .The incidence of febrile neutropenia was only 6 % . As regard hematological toxicity in those 2 studie[25-26]1.7 %& 2.3% grade 3 anemia were reported . In our study, no acute severe anemia was experienced . Generally it seemed that , the regimen of TPF was tolerable by most of the patients as only 2 patients developed GIII toxicity and did not complete the protocol. And this cope mostly with the results of studies that use TPF regimen in induction phase asin the study of Kong and his colleagues [24]

In the CRT phase ,no major 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 2 published studies on 2009 &2012 [25-26]that showed 6.4% grade 3 anemia and 26% grade 3 leucopenia ,13% neutropenic fever and 1.1 % grade 3 thrombocytoenia. As regard non hematological toxicity in the previous 2 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

Nasopharyngeal carcinoma is considered among the most difficult tumors to plan because of its complex anatomy, multiple targets with different dose prescriptions, large extension of the treatment region and the number of structures at risk. Moreover, doses up to 70 Gy with a conventional fractionation may be 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, which yield much better results than does three-dimensional conformal radiotherapy (3DCRT),

especially in 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 treatment of the most of 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 in order to improve PTV dose conformality and sparing of OAR's which were the major problems we faced. Various field arrangements were tried but the Field in field technique developed by Herassian and his colleagues [27], was the one which achieved 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 was achieved in 91% (30 patients) and PR in 9% (3 patients) in the primary tumor with an overall response rate of 100% which is better than the results of Kong and his colleagues [24] that show 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 [28] 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 regards the impact of NACT on loco-regional control were confirmed by the meta-analytic study conducted by Du and his colleagues [23].

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 et al [24] 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.

The researchers have concluded that there is significant improvement in OS for patients who received induction TPF in comparison with CCRT. [24, 26, 29, 30, 31] The findings from our trials confirm the encouraging results mentioned above where the 2 year OS reached 95% and the 2 year DFS reached 85%.

Conclusion

The TPF regimen was well tolerated and had a manageable toxicity profile. The addition of TPF prior to 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 best coverage of the PTV without exceeding the tolerance dose to the OAR .

TABLE (1) PATIENT CHARACTERISTICS

Characteristic		No.(36)	%
Sex	Male	25	69
	Female	11	30
Age Range(18-70) Median (48)	18-40	14	39
	41-70	22	61
ECOG P.S	0	23	64
	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
	Cervical lymphadenopathy	20	56
	Nasal symptoms	8	22

Symptoms	Cranial neuropathy	5	14
	Ear symptoms	3	9

TABLE (2) Chemotherapy TOXICITY

	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						
Nausea and Vomiting	20	55	14	39	2	6
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 (3) acute radiation toxicity

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(
Throbocytopenia	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)

Late Radiation toxicity Table (4)

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

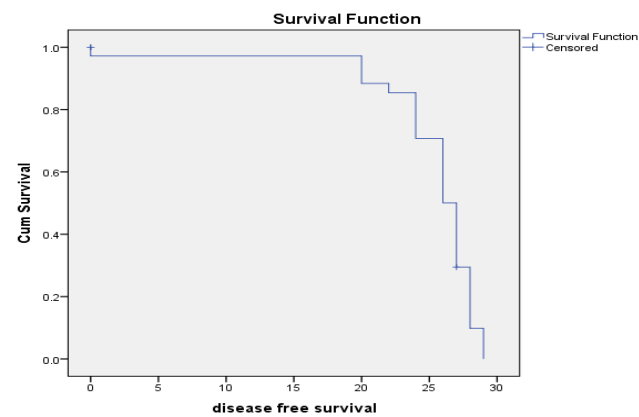


Figure1: 2- year DFS among all studied cases

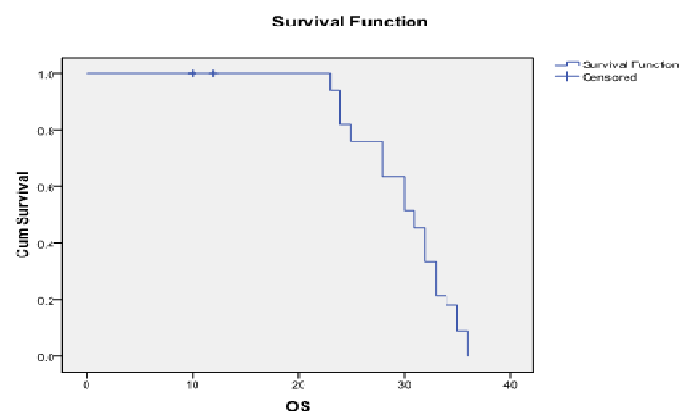


Figure 2 : 2- y OS among all studied cases

References :

- 1.Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136:E359.
- 2.Chen, L. et al.The seventh edition of the UICC/AJCC staging system for nasopharyngeal carcinoma is prognostically useful for patients treated with intensity-modulated radiotherapy from an endemic
- 3.Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J ClinOncol.* 1998;16:1310-1317.
4. Lin JC, Jan JS, Hsu CY, et al. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival.
J ClinOncol. 2003;21:631-637.
5. Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst.* 2005;97:536-539.
6. Zhang L, Zhao C, Peng PJ, et al. Phase III study comparing standard radiotherapy with or without weekly oxaliplatin in treatment of locoregionally advanced nasopharyngeal carcinoma: preliminary
results. *J ClinOncol.* 2005;23:8461-8468.
7. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemo-radiotherapy 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. *J ClinOncol.* 2005;23:6730-6738.
8. Lee AW, Lau WH, Tung SY, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally advanced nasopharyngeal carcinoma: NPC-9901 trial bythe Hong Kong Nasopharyngeal Cancer Study Group. *J ClinOncol.* 2005;23:6966-6975.
- 9.Wu, F. *et al.* Concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: treatment outcomes of a prospective, multicentric clinical study. *Radiother Oncol.*2014; 112(1) ;106–111 .

- Hitt R, Lopez-Pousa A, Martinez-Trufero J, et al. Phase III study10.Hitt R, Lopez-Pousa A, Martinez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J ClinOncol.* 2005;23:8636-8645.
11. Vermorken JB, Remenar E, van Herpen C, et al. EORTC 24971=TAX 323 Study Group. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med.* 2007;357: 1695-1704
12. Posner MR, Hershock DM, Blajman CR, et al; TAX 324 Study Group.Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med.* 2007;357:1705-1715.
- 13.Wee J. Nasopharyngeal cancer: a promising future. *Lancet Oncol.*2012; 13: 116-8.
14. Lai SZ, Li WF, Chen L, Luo W, Chen YY, Liu LZ, et al. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? *International journal of radiation oncology, biology, physics.* 2011; 80: 661-8.
- 15.Eisenhauer EA ,Therasse P, Arbuck SG , et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst.* 2008;92:205-216.
- 16-Chen L, Hu CS, Chen XZ, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentrerandomised controlled trial. *Lancet Oncol.* 2012;13:163-171.
17. Chi KH, Chang YC, Guo WY, et al. A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients.*IntRadiatOncolBiol Phys.* 2002;52:1238-1244.
18. Rossi A, Molinari R, Boracchi P, et al. Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. *J ClinOncol.* 1988;6:1401-1410. 19. Langendijk JA, Leemans CR, Buter J, et al. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. *J ClinOncol.* 2004;22:4604-4612.
- 20.Chua DT, Sham JS, Choy D, 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*. 1998;83:2255-2258.

21. Ma J, Mai HQ, Hong MH, et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. *J Clin Oncol*. 2001;19:1350-1357.

22. Chua DT, Ma J, Sham JS, et al. Long-term survival after cisplatin based induction chemotherapy and radiotherapy for nasopharyngeal carcinoma: a pooled data analysis of 2 phase III trials. *J Clin Oncol* 2005;23:1118-1124.

23. Du X-J, Tang LL, Chen L, et al. Neoadjuvant chemotherapy in locally advanced nasopharyngeal carcinoma: Defining high-risk patients who may benefit before concurrent chemotherapy combined with intensity modulated radiotherapy. *WWW.nature.com/scientific reports*. last retrieved on 13 November 2015.

24. Kong L, Hu C, Niu X, et al. Neoadjuvant Chemotherapy Followed by Concurrent Chemoradiation for Locoregionally Advanced Nasopharyngeal Carcinoma. *Cancer* 2013;119:4111-8.

25. 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. *J Clin Oncol* 2009; 27: 242-9.

26. 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. *Ann Oncol*. 2012; 23: 427-35.

27. Herrassi M, Bentayeb F, Malisna M, et al. Comparative study of four advanced 3d-conformal radiation therapy treatment planning techniques for head and neck cancer. *Journal of Medical Physics* .2013 ;38(2): 9828.

28. Bae, W. K. *et al*. Phase II study of docetaxel, cisplatin, and 5-FU induction chemotherapy followed by chemoradiotherapy in locoregionally advanced nasopharyngeal cancer. *Cancer Chemother Pharmacol*. 2010 .65, 589–595 .

29.Ekenel M, Kestin S, Basaran M, et al. Induction chemotherapy with docetaxel and cisplatin is highly effective for locally advanced nasopharyngeal carcinoma. *Oral Oncol.* 2011;47:660-664.

30.Li W-F , Chen L , Sun Y, et al. "Induction chemotherapy for locoregionally advanced nasopharyngeal carcinoma .*Chinese Journal of Cancer* **2016** ;**35**(1): 94.

31.Peng H , Chen L ,Zhang J, 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.