ORIGINAL ARTICLE

Neoadjuvant Vs Concurrent Chemotherapy Addition to Radiotherapy in Locally Advanced Carcinoma Nasopharynx: Analysis of Survival & Failure Patterns

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Abstract

Locally advanced nasopharyngeal cancer necessitates the use of both chemotherapy and radiotherapy for optimal benefit. The current recommendation is to treat patients with stage IIB-IVB disease with concurrent chemoradiotherapy. The purpose of this study was to evaluate the survival outcome difference between concurrent chemoradiation and neoadjuvant chemotherapy. Between January 2000 and December 2007, 45 patients of nasopharyngeal cancer (stage IIB-IVB) were treated with curative intent in the Departmentof Radiotherapy. 23 patients receivedneoadjuvant chemotherapy followed by radical radiotherapy and 22 patients received concurrent chemoradiotherapy. The study cohort included 35 males and 10 females suffering from locally advanced carcinoma nasopharynx. Median age of the group was 52 years (range 19-76 years). 2-year failure free survival in the concurrent chemoradiotherapy arm was 62% versus 38% in the neoadjuvant group (log rank p=0.197). Statistically significant difference was not observed in terms of failure free survival between the concurrent and neoadjuvant group.

Key Words : Cancer Nasopharynx, Neoadjuvant Chemotherapy, Concurrent Chemoradiotherapy

Introduction

Radiotherapy (RT) alone is the backbone of treatment as for as early stage nasopharyngeal cancers are concerned. 10-year disease free survival (DFS) in stage I is 98% whereas it is 60% in stage II with RT alone (1). The incidence of isolated distant metastases in stage IIA is 5.7% and 14.9% in stage IIB (2). Locally advanced carcinoma nasopharynx (LA-NPC) is an altogether different clinical entity, usually associated with extensive and bilateral cervical lymphadenopathy disproportionate to the size of primary.LA-NPC comprises T2b, T3, T4 and N1-3 and M0 disease. They are associated with high failure rates and unsatisfactory long term survival rates. More than 30% patients die of distant metastases (3,4). The current standard of care for LA-NPC is concurrent chemoradiation (CRT) with or without adjuvant chemotherapy (AC). Even when treated with CRT, 3-year Progression Free Survival (PFS) is still only around 70% and overall survival (OS) at 5 years in stage III are 53-80% and 28-61% in stage IV (2,5,6,7). The rationale for adding adjuvant chemotherapy (AC) was to reduce the distant metastatic recurrences. Poor compliance and potential adverse effects of adjuvant chemotherapy limit its routine use (8). Therefore, neoadjuvant chemotherapy (NACT) followed by local treatment in the form of radiotherapy or CRT appears sensible. The NACT is based on the two simple logical assumptions: first, downstaging the disease and consequent reduction in radiation target volume should result in less toxicity and better compliance and secondly, multiagent neoadjuvant chemotherapy can take care of micrometastases in the very beginning and improve overall survival (9).The aim of this retrospective study was to compare the survival outcome of concurrent chemoradiation (CRT) with neoadjuvant chemotherapy (NACT) followed by

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radiotherapy (RT) in LA-NPC patients.

Material and Methods

Our study checked the clinical records of patients of biopsy-proven nasopharyngeal cancer, staged IIB-IVB[according to the 2002 American Joint Committee on Staging of Cancer Classification],and treated with curative intent in the Department of Radiotherapy from January 2000 to December 2007. A retrospective chart review was used to create a database of clinical and pathologic characteristics of these patients using Microsoft Excel. 23 patients received neoadjuvant cisplatin and 5-fluorouracil (5FU)based chemotherapy followed by radical RT and 22 patients received CRT. In the NACT group, chemotherapy schedule comprised of Cisplatin 80 mg/m2over 2 hours on Day1 with prehydration and post-hydration, mannitol-induced diuresis followed by 5FU 800 mg/m2 per day as a continuous intravenous infusion for 4 days on Day 2-5 every 3 weeks for a total of 3 cycles before radiotherapy. In the CRT group, weekly cisplatin 40mg/m2 was administered for 7 weeks during RT. In both groups, the radiotherapy was planned to deliver 66-70 Gy over 6.5-7 weeks to the primary tumor, 66Gy to clinically involved neck nodes and 56 Gy to the rest of the cervical lymph nodes. The fraction schedule was 2Gy/fraction using the photon beams of Cobalt-60 gamma rays. The treatment was delivered by two lateral parallel opposed fields upto44Gy/22# encompassing the sphenoid sinus, the clivus, the posterior orbits, posterior half of nasalfossae and the retropharyngeal lymph nodes and intra-cranial extension, if any followed by boost. After 44 Gy, spinal cord was excluded from the fields. The posterior neck was further treated with 6Gy for N0 and 22Gy for palpable neck nodes. The middle and inferior cervical nodes were treated with an anterior enface neck fields and dose of 50Gy/25 fractions specified at 3 cm depth. The inferior border was below the clavicular heads at the upper margin of sternum and the lateral limits at the junction of middle and lateral one-third of clavicles. All the 45patients were analyzed for outcome and toxicity.The survival was calculated by the Kaplan-Meier method and thedifferences in survival werecompared by the log rank test.

Results

The patient and tumor characteristics are summarized in Table 1. There were 35 males and 10 females. Median age was 52 years (range 19-76 years). 42 (93.3%) patients had nonkeratinizing squamous cell carcinoma. 35 (77%) patients had clinically palpabledisease in cervicallymph nodes and confirmed by FNAC. 51.1%patients had N2 or N3 disease.75.5% patients had stage III or IV disease.

Median follow up was 17 months (range 6-60months). Median follow-up was 14 months and 24 monthsin NACT and CRT group respectively. 19 patients were alive with disease (AWD)at last follow up and 26 patients were free of disease (ADF) (Table 2 and Fig. 1).There were 5 local recurrences, 9 locoregional recurrences and 10 distant metastatic failures in the whole group during the follow-up period (Table 3). Thus the local failures were seen in 11.1% patients, locoregional failures in 20% patients and distant metastases in 22.22% patients.

Median failure free survival (FFS) in the NACT group

Table 1. Patient characteristics and TNM stage

Characteristics	NACT Group n=23	CRT Group n=22	Total n=45
Sex			
Male	18	17	35
Female	5	5	10
Age			
Median	50	59	52
Range	19-75	42-76	19-76
PS			
0-1	21	19	40
2	2	3	5
Pathology			
KSCC	1	2	3
NIKSCC	22	20	42
Others	0	0	0
Stage			
IIB	1	3	4
III	12	11	23
IV	4	7	11

Table 2. Status and Response at Last Follow-up visit

	AWD	ADF
NACT (n=23)	10	13
CRT (n=22)	9	13
Total (n=45)	19	26

Table 3. Site wise pattern of treatment failure

Site of Relapse	NACT	CRT
Local only	3	2
Regional	2	2
Distant only	5	5

Table 4 Multivariate analysis of predictive factors for FFS

Variable	B	SE	Wald	df	Sig	R	Exp B
Age	–.14	.05	6.52	1	.01	–.21	.86
TNM Stg.			6.5	3	.08	.07	
Sig. IIB	–1.8	1.45	1.58	1	.207	.00	.15
Sig. III	–3.8	1.80	4.51	1	.03	–.16	.02
Sig. IV	.89	1.96	.20	1	.65	.00	2.43

Table 5. Treatment toxicity and patient's experience

Toxicity	NACT Gr3	NACT Gr4	CRT Gr3	CRT Gr4
Mucosa	7	1	10	1
Emesis	2	0	2	0
Skin	2	0	3	0
Neutropenia	3	0	2	0
Platelets	2	0	1	0

was 22 months (SE 5.44, 95% CI 11.33-32.67) vs. 60 months in the CRT arm (log rank, p=0.197). The mean FFS in the NACT group was 20.85months (SE 2.15, 95% CI 16.64-25.06) vs. 42.41 months in the CRT group (SE 5.23,95% CI 32.15-52.66).Among males, median FFS in CRT group was 29 months (SE 1.46,95%CI 26.13-31.87)vs. 19months (SE 5.79, 95% CI 7.65-30.35) in the NACT group (p=0.0143). The respective mean FFS among males undergoing CRT was 32.18 months (SE 3.67,95%CI 24.99-39.37) vs. 20.85 months (SE 2.82,95%CI 15.33-26.38) in those undergoing NACT. The 2-year FFS in the CRT group was 62% vs. 38% in NACT group (p=0.197) (Fig. 2). The 2-year FFS in the male patients receiving CRT was 78% vs. 46% (p=0.0143) in the NACT cohort (Fig. 3). Amongfemale patients, the respective 2-year FFS were 57% and 23% in the CRT and NACT arm(Fig 4).On multivariate analyses, age and stage were significant predictive factors for FFS (Table 4).The most frequent severe toxicity (Grade III/IV) in the group was mucositis: 8 (34.7%)in the NACT and

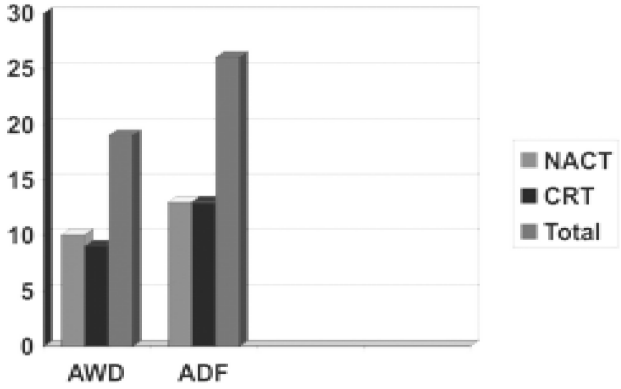

Fig 1. Status and Response at last Follow-up Visit

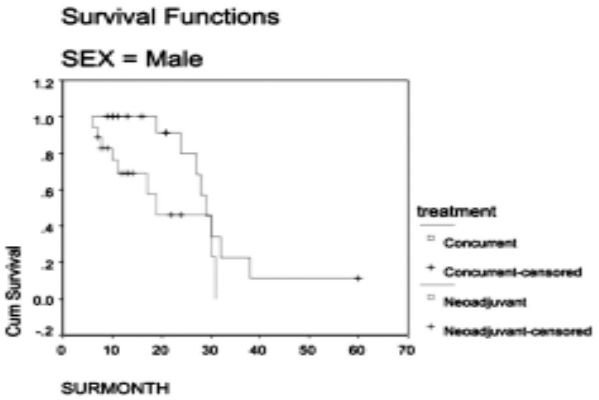

Fig 2. Kaplan-Meier curve depicting comparison of FFS-NACT vs. CRT

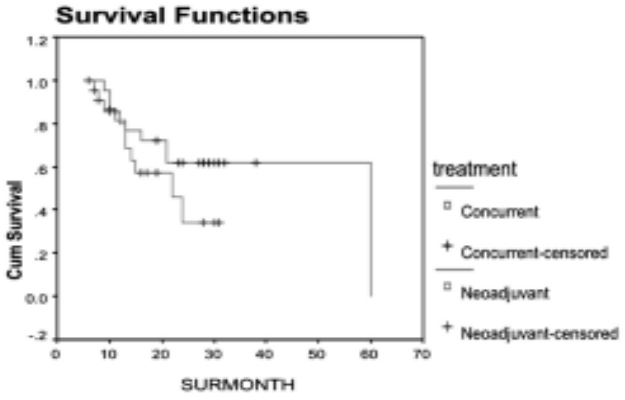

Fig 3. Kaplan-Meier curve depicting comparison of FFS in male patients- NACT vs. CRT.

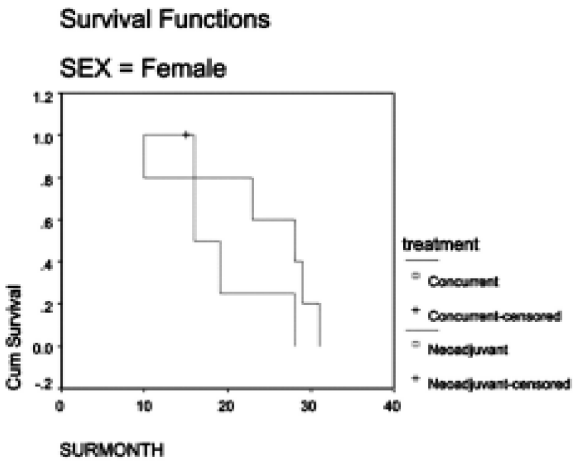

Figure 4: Kaplan-Meier curve depicting comparison of FFS in female patients- NACT vs. CRT.

11(50%) in the CRT group (*Table 5*).

Discussion

LA-NPC necessitates the use of both chemotherapy and radiotherapy for optimal benefit. In this retrospective cohort study, our aim was to analyze survival outcomes of LA-NPC patients treated with CRT or NACT followed by RT. This study found that LA-NPC patients treated with CRT had mean survival of 42.41 months whereas it was 20.85 months in NACT group. The difference was not statistically significant. However when adjusted for gender, median FFS of 29 months among male patients receiving CRT was significantly better than median FFS of 19 months in male patients of NACT group. The 2-year FFS rate of 62% in CRT group as a whole and 78% in males receiving CRT is similar to that reported by Intergroup 0099 study (EFS 69% at 3-years in CRT arm) (5).

It was the first trial that showed significant survival benefit in LA-NPC with the use of concurrent chemoradiotherapy (CRT) and adjuvant chemotherapy vs. radiotherapy alone. Al Sarraf M, *et al* reported 3-year event free survival (EFS) was 69% vs. 24% (p<.001) and 5—year overall survival (OS) 67% vs. 37% in favorof CRT. They reported median PFS of 15 months and median survival time of 34 months in RT arm. Subsequent trial of CRT by Lin et al using concurrent cisplatin and 5FU, confirmed significant benefit in both EFS and OS (72% vs. 54% with survival gain 18%) (6).The distant metastases were reduced by 17% in the CRT arm vs. RT alone.

Our retrospective study calculated 2-year FFS of 62% in the CRT group vs. 38% in NACT group (p=0.197). These figures are in consonance with those reported in MAC-NPC analysis (10,11) and National Cancer Database Analysis by Tam M et al. (3-year OS of 70% in CRT and 66% in NACT, p=0.54) (12).Meta-analysis by Baujat et al. published in 2006 with updated patient data of 1753 patients from 8 accepted trials, showed a small but significant benefit by adding chemotherapy: the absolute gain for 5-year EFS was 10% (52% vs. 42%) and for OS it was 6% (62% vs. 56%). The reduction in the pooled HR of death was significant (0.82; 95% CI 0.71-0.94; p=0.006). The survival benefit was essentially confined to the CRT subset rather than NACT or adjuvant ones10. An update of MAC-NPC meta-analysis published in 2015 incorporating 19 trials and 4806 patients with median follow-up of 7.7 years showed absolute survival advantage of 6.3% with addition of chemotherapy to radiation and improved OS (HR 0.79, p<.0001). MAC-NPC meta-analysis showed improvement in all the end points of progression free survival (HR 0.75), locoregional control (HR 0.73), distant control (HR 0.67) and cancer mortality (HR 0.76) with CRT with or without adjuvant chemotherapy, but no benefit of NACT (11).

Tam M *et al.* identified 1731 patients of locoregionally advanced cancer nasopharynx patients from 2004 to 2014. 504 (27%) patients received neoadjuvant chemotherapy (12). After a median follow-up of 36.6 months, patients had a 3-year OS of 66% in the NACTgroup compared with 70% withCRT (log rank, p=0.24). On multivariate analysis, there was no significant survival difference associated with induction chemotherapy (adjusted HR 1.05,p=0.54). Hui EP et al. reported 3-year OS rate of 67.7% with cisplatin-based CRT(13). Sun Y et al. also reported 3-year FFS of 72% in CRT arm (14).

Distant metastases occurred in 5 patients in NACT group and 5 patients in the CRT group in our study cohort. Our results showing distant metastases recurrence in 22.22% patients is similar to the figure of 25% reported by Intergroup 0099 and others (5,6). Qiu WZ et al. have reported the distant metastases rate of 18.8% with NACT and 21.1%with CRT (15).The locoregionalrecurrence rate of 20% reported in our study is similar to the rate of 19% in the NACT arm and 12% in the CRT arm by Komatsu *et al.*(16) and 14% reported by Jeraporn Setapornnukul et al. from Thailand (17). A retrospective study by Wu SY *et al.* reported that NACT followed by RT alone delivered poorer locoregional control (18).No significant

difference was detected by us in locoregional recurrences in the two groups under study.The studies using IMRT have reported locoregional recurrence rates of 9.4% and 9.8% with NACT and CRT respectively (15).

On multivariate analyses for prognostic factors done in this study, age and overall stage were significant independent predictive factors for FFS; and it is a well-known fact and corroborated in other studies as well (15,19,20).

We do not use adjuvant chemotherapy as a routine after CRT in our group of patients as it merely adds to morbidity and has not been shown to impact efficacy. The role of adjuvant chemotherapy with CRT is limited as has been shown by Lin JC *et al*.(6) and Chen *et al* (21). Lin JC *et al*. reported that adjuvant chemotherapy benefit may be limited to high risk patients: nodal size>6 cm, supraclavicular lymphadenopathy, multiple neck node metastases withone lymph node > 4 cm, stage T4N2 (1992 AJCC).Chen et al. updated the results of a phase III trial to explore the addition of AC to standard CRT. No significant survival benefit detected for adjuvant cisplatin and 5FU after CRT in LA-NPC after a median follow up of 68.4months. 5-year FFS rate was 75% in CRT+AC vs. 71% in CRT arm (HR 0.88, p=0.45) (21).

Most of the patients in the above mentioned trials were treated with 2D or 3D conformal radiotherapy. There is no published data from randomized control trials to address the role of CRT with IMRT for LA-NPC but retrospective studies are galore (7). Zhang MX *et al* compared the results of IMRT with 2-D RT in a large cohort of 7081 non-metastatic NPC patients and found that the patients administered IMRT had significantly higher LRFS, LRRFS, PFS and OS (95.6%, 92.5%, 82.1% and 87.4% respectively) than those administered 2D RT (90.8%,88.5%,76.7% and 84.5%respectively, p<0.001) (22). Chen X *et al*.comparedNACT+IMRT vs. NACT+IMRT+CRT in LA-NPC patients and reported 3-year OS, LRFS, DMFS and PFS rates of 89.4%,91.7%,83.3%,77.8% respectively vs. 88.5%,94.4%,82%,76.4% (p=0.114,0.124,0.668,0.475 respectively). The locoregional recurrences were recorded in 8(6.4%) and distant metastases in 19(15.2%) patients (23).

We are using weekly cisplatin regime for CRT rather than 3-weeklycisplatin, and a phase III multicenter randomized control trial has just concluded that weekly regimen of cisplatin as CRT shows similar treatment efficacy with somewhat increased toxic effect of leucopenia and thrombocytopenia compared with 3-week schedule in LA-NPC. 2-year FFS was92% vs. 88.3% (24).

Several studies have compared NACT followed by RT vs. RT alone. Although a reduction in relapse-free and disease-specific survival was observed with NACT in some studies, no differences in OS or treatment failure pattern were observed (25,26). International nasopharynx Cancer Study Group using cisplatin, epirubicin, bleomycin achieved significant improvement in event free survival (58% vs. 35% at 3 years;p<.01) but no improvement in OS at 5 years with treatment related mortality 8% vs. 1%. A meta-analysis of two phase III trials of NACT published by Chua DT in 2005 concluded that addition of NACT to RT was associated with a decrease in relapse by 14.3% and cancer-related deaths by 12.9% at 5-years (9). The 5-year RFS was 50.9% and 42.7% in the NACT and RT arm, respectively (p=0.014). 5-year DSS 63.5% and 58.1% (p=.029). The 5-year OS was 61.9% and 58.1% (p=0.092). The incidence of locoregional failure and distant metastases was reduced by 18.3% and 13.3% (9). Another meta-analysis by Ou Yang PY *et al* demonstrated that NACT combined with RT or CRT resulted in OS gain of 5.13% and reduced the distant metastases rate at 3 years without improving locoregional recurrences (27).

The focus of latest ongoing trials has shifted to use of both the modalities of NACT and CRT together for maximum efficacy.In a phase II trial, Hui et al. reported that in the NACT+CRT group patients, 3—year OS rate of 94.1% was significantly higher than CRT (67.7%) (13). NACT has shown benefit in survival only when triple drug regimen of TPF is added to CRTin node positive stage III-IVB14. 3 year FFS is improved from 72% to 80% (HR 0.68, p= 0.034) and OS - 86% to 92% (p=0.029). Another positive trial GORTEC trial showed NACT with TPF regime to improve 3-year PFS from 57.2% to 73.9% (HR=0.44, p=0.042) and 3-year OS 68.9% to 86.3% (HR 0.40, p= 0.05) (28).A meta-analysis by Tan et al included six RCT and five observational studies involving 2802 patients showed that NACT+CRT improves PFS (HR 0.69,p=.0003) and OS (HR 0.77, p=0.03)(29). NACT+CRTapproach seems appealing with this data.The addition of NACT to CRT has been put to test with the rationale of improving distant control but at the exorbitant cost of increased risk of toxicity. NACT+CRThave a few practical pitfalls. First, overall response rate by the TPF chemotherapy is expected to

be 75%, still significant proportion of the patients do not achieve favorable response following NACT,who subsequently may have lower chance of cure than upfront CRT because of the delay. Second, NACT can deteriorate the patient's general condition, which often adversely affects the subsequent treatment schedule. Third, thetarget volume delineation can be hampered bydifficulty in interpreting post-NACT imagingbecause of non-concentric shrinkage of tumor.Knowing fully well the pros and cons of NACT, it may be advisable to add NACT in a peculiar clinical situation where the tumor is very bulky and located just adjacent to critical organ like brain, brainstem or the optic apparatus. Other than the proven advantage of CRT over RT alone, there is no concrete evidence in favor of routine addition of NACT to CRT (30).

Conclusions

No statistically significant difference was observed in terms of failure free survival between the concurrent and neoadjuvant group in this study. When adjusted for gender, the 2-year failure free survival in the male patients in concurrent arm was significantly superior to that of male patients in the neoadjuvant group. Failure free survival was strongly related to age and stage on multivariate analysis.

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