Retrospective Investigation of 49 Cases of Locally Advanced Nasopharyngeal Cancer Patients who were Given Neoadjuvant Docetaxel/Cisplatin Chemotherapy and Concomitant Chemoradiotherapy

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ABSTRACT

Nasopharyngeal cancer (NPC) generally shows higher incidence in China, South-east Asia and some regions of the world. Being radio- and chemo-sensitive, NPCs have higher prevalence in middle ages and occupy a special place among head and neck tumors. The aim of this study is to investigate the results of 49 locally advanced NPC patients who were given Docetaxel/cisplatin as neoadjuvant therapy and concomitant chemoradiotherapy. Our study included 49 locally advanced NPC patients who presented to our clinic between 2004 and 2011 and received two to three cures of neoadjuvant Docetaxel/Cisplatin therapy followed by concomitant chemoradiotherapy. Neoadjuvant chemotherapy scheme was docetaxel 75 mg /m^2/day and cisplatin 75 mg/m^2/day in three weeks. Median age of the patients was 50 years, and median follow-up period was 40.4 months. After concomitant chemotherapy of the patients, complete response was obtained in 47 (95.9%) patients and partial response in 2 (4.1%) patients. Average survival was found to be 78.3 months, and 3-year and 5-year survivals were 93% and 89% respectively. 8 of 49 patients developed recurrence. Average disease-free survival (DFS) was 67.4 months and 5-year DFS rate was 84%. Neoadjuvant chemotherapy in NPC increased disease-free survival rates, but failed to increase general survival. In our study, our patients disease-free survival and 5-year overall survival is quite good, these values have been found promising for the treatment of nasopharyngeal cancer. So this treatment regimen became a promising treatment choice due to its tolerable toxicity.

Keywords: Nasopharyngeal cancer, Neoadjuvant, Docetaxel, Cisplatin, Chemoradiation

ÖZET

Lokal İleri Nazofarenks Kanserlerinde Neoadjuvan Dosetaksel/Cisplatin Kemoterapisi ve Konkomitan Kemoradyoterapi Uygulanan 49 Olgunun Retrospektif İncelenmesi

Nazofarenks kanseri genel olarak Çin, Güneydoğu Asya ve dünyanın bazı bölgelerinde yüksek insidans gösterir. Radyosensitif ve kemosensitif olan nazofarenks kanserinin, orta yaşlarda sıklığı artmakta olup baş boyun tümörleri arasında özel bir yere sahiptir. Bu çalışmanın amacı neoadjuvan Dosetaksel/Cisplatin ve konkomitan kemoradyoterapi uygulanan 49 lokal ileri nazofarenks kanseri hastanın sonuçlarını incelemektir. Çalışmamızda kliniğimize 2004-2011 yılları arasında başvuran ve tedavilerinde 2-3 kür indüksiyon Dosetaksel-Cisplatin kemoterapisi sonrası konkomitan kemoradyoterapi uygulanan 49 lokal ileri nazofarenks kanserli hasta incelendi. Neoadjuvan kemoterapi şeması olarak Dosetaksel: 75 mg/m^2 + Cisplatin: 75 mg/m^2, 3 haftada bir olarak uygulandı. Hastalarımızda ortanca yaş 50, ortanca takip süresi 40.4 aydır. Hastalarımızda konkomitan kemoradyoterapi sonrası 47 (%95.9) hastada tam yanıt, 2 (%4.1) hastada kısmi yanıt elde edilmiştir. Ortalama sağkalım 78.3 ay, 3 yıllık ve 5 yıllık sağkalım sırasıyla %93 ve %89 olarak saptanmıştır. Yine 49 hastanın 8'inde (%16.3) nüks gelişmiştir. Ortalama hastalıksız sağkalım 67.4 ay, 5 yıllık hastalıksız sağkalım %84 olarak tespit edilmiştir. Nazofarenks kanserinde neoadjuvan kemoterapi hastalıksız sağkalım oranlarını arttırmış ancak genel sağkalıma katkısı gösterilememiştir. Çalışmamızda hastalarımızın hastalıksız sağkalımı ve 5 yıllık genel sağkalımı oldukça iyidir. Bunun için bu tedavi rejimi tolere edilebilir toksisite nedeniyle umut verici bir seçenek haline gelmiştir.

Anahtar Kelimeler: Nazofarenks kanseri, Neoadjuvan, Dosetaksel, Cisplatin, Kemoradyoterapi

INTRODUCTION

Nasopharyngeal cancer (NPC), which shows endemic distribution, is a rare tumor in western countries with the prevalence of less than 1 out of 100,000 among all tumors. However, the prevalence in eastern countries, especially in China, increases to 20-25 in 100.000 annually. Average age of NPCs in the world is 40-50 years, with 2-3 times preference in males. The most found clinical sign in NPCs is mass in neck. Clinical involvement of cervical lymph nodes is 60-87% and nearly half shows bilateralism.[1,2]

Having a special place among head and neck cancers, NPCs are not suitable for surgery due to their anatomic localization. Radiotherapy is very effective in early stage tumors (T1-2/N0-1). However, applying only radiotherapy in locally advanced disease ends up with high recurrence rates. That is why many studies with different fractionations like neoadjuvant chemotherapy, concomitant chemoradiotherapy, adjuvant chemotherapy and radiotherapy were performed. Many studies were done to identify the effects of neoadjuvant chemotherapy on the control of locoregional tumors, the incidence of distant metastases, DFS(Disease-free survival) period and life span.[3,4]

In our study, we evaluated the results of 49 patients who presented to our clinic from 2004 to 2011 and got the neoadjuvant chemotherapy of Docetaxel/Cisplatin followed by concomitant chemoradiotherapy.

PATIENTS AND METHODS

We investigated 53 locally advanced NPC patients who presented to our clinic from 2004 to 2011 and received 3 cycles of Docetaxel/Cisplatin neoadjuvant therapy followed by concomitant chemoradiotherapy. Four patients were excluded due to the incomplete data and failure to show up for follow-up, and the rest 49 patients were included for the study.

The patients were given concomitant chemotherapy after finishing neoadjuvant chemotherapy. The applied neo-adjuvant chemotherapy scheme was docetaxel 75 mg/m2 /dayand cisplatin 75 mg/m2/day in three weeks. After applying 2-3 cures of chemotherapy, response rates were evaluated, and concomitant chemoradiotherapy was started three weeks later. Not a fixed standard therapy was used for concomitant therapy. Cisplatin 75 mg/m^2/21 day, cisplatin 40 mg/m^2/7 day or docetaxel 30 mg/m^2/7 day regimes were used.

AJCC (American Joint Committee on Cancer) 1997 TNM(Tumor Nodes Metastasis) classification method was used for staging. For this purpose, physical examinations, (ENT) Ear Nose and Throat examination, full blood count, chemistry profile, nasopharynx (MRI) Magnetic Resonance Imaging and (PET-CT) Positron Emission Tomography scanning were performed.

WHO (World Health Organization) classification was used as histological classification.

External radiotherapy planning of the patients was done in two ways.Twelve patients were performed with conventional 2-DRT(2-dimensional radiotherapy) and 41 patients were performed with (3D-CRT) 3-dimensional conformal radiotherapy. Six MV(Megavoltage) photons were used in all the treatments. In nasopharynx boost therapy, 15 MV or 18 MV photons were used. Electron energy suitable for the depth of lymph node was used in lymph node boost therapies.

In all patients, nasopharynx region, bilateral neck lymphatics and supraclavicular region were included in treatment volume. Seventy Gy of radiotherapy to nasopharynx lodge, 66 Gy to positive lymph nodes within 3 cm and 70 Gy to positive lymph nodes more than 3 cm were applied respectively.

Patients were called back for the follow-ups 1.5 months after the first radiotherapy. Follow-ups were done once in three months for the first two years, once in six months for the following three years and once per year after the fifth year. In the follow-ups, physical examination, ENT examination, Chest X-ray, full blood count and chemistry profiles were performed. The imaging of nasopharynx was done once in six months for the first three years and once a year in the following years.

In the evaluation of the response, RECIST (Response Evaluation Criteria in Solid Tumors) criteria, which are generally for the solid tumors, were used.

SPSS (Statistical Package for the Social Sciences) for Windows 7 program was used in statistical analyses in order to evaluate the data obtained from the study. Chi-squared test was used to evaluate local-regional recurrences, distant metastases and treatment response. Kaplan-Meier test was used in univariate analyses of general overall survivals and DFSs, and cox regression test in multivariate analyses. The results within 95 % confidence interval and $p< 0.05$ were assumed statistically significant.

Table 1. Characteristics of the patients

Characteristics	Number of patients	%
Age (years)		
<30	6	12.2
30-60	34	69.3
>60	9	18.5
Gender		
Female	13	26.5
Male	36	73.5
ECOG		
0	16	32.7
1	27	55.1
2	6	12.2
WHO		
1-2	17	34.7
3	32	65.3
T		
1-2	35	71.4
3-4	14	28.6
N		
0-1	15	30.6
2	27	55.1
3	7	14.3
Stage		
2	11	22.4
3	26	53.1
4	12	24.5

RESULTS

In sex distribution of the patients, 36 males (73.5%) and 13 females (26.5%) were present. Male to female ratio was 2.76. Median age was 50 years (15-75). Most of the patients' performance status were ECOG (Eastern Cooperative Oncology Group) 0-1 (n= 43, 87.8%) and only 6 patients (12.2%) were ECOG 2. Histopathologically, all the patients had epithelial tumors, most of them having indifferentiated tumors (n= 32, 65.3%). Other patient characteristics are described in the table (Table 1).

Table 2. Failure of the Treatment

Place of Failure	Number of Patients	%
Nasopharynx	4	8.2
Neck	2	4.1
Nasopharynx + Metastasis	2	4.1
Metastasis	3	6.15

Treatment Outcomes

Patients were examined with MRI-CT imagings 2-3 weeks after neoadjuvant chemotherapy. Hundred percent of the patients responded well after neoadjuvant chemotherapy. Complete response was obtained in 21 out of 49 patients (42.8%) and partial response in 28 patients (57.2%). Large portion of the patients who obtained complete response had undifferentiated carcinoma histologically. Among 21 patients with comlete response, 18 had WHO type 3 while 3 had WHO type 2.

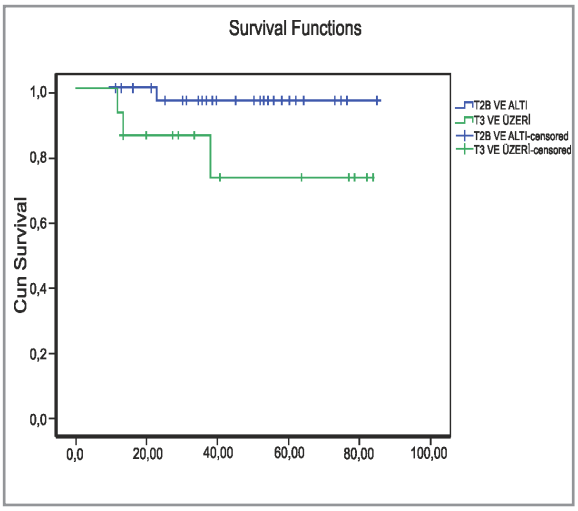
After concomitant chemoradiotherapy, 47 patients (95.9%) obtained comlete response and 2 patients (4.1%) got partial response. Patients were followed up for the average of 40.4 months (10.9-85). Recurrence developed in 8 patients (16.3%). Failure of the treatment regions are described in the table (Table 2).

N stage and performance status were found to be significant in term of recurrence. All the eight patients who developed recurrence, had stage at or above N2 (p= 0.04). Among 6 patients with ECOG 2 or above, developed recurrence in three of them (p= 0.04).

Making a pause in radiotherapy is found to increase recurrence risk, which, although not statistically sig-

Table 3. Parameters which increase the recurrence risk of the patients

		Recurrence absent	Recurrence present	P
Pause to radiotherapy	Absent	19 (95%)	1 (5%)	0.07
	Present	21 (75%)	7 (25%)	
Stage	2 and lower	11 (100%)	0	0.1
	3 and above	30 (78.9%)	8 (21.1%)	
T Stage	T2b and lower	31 (88.6%)	4 (11.4%)	0.1
	T3 and above	10 (71.4%)	4 (28.6%)	
Performance	ECOG 0-1	38 (88.4%)	5 (11.6%)	0.04
	ECOG 2	3 (50%)	3 (50%)	
N Stage	N1 and lower	15 (100%)	0	0.04
	N2 and above	26 (76.5%)	8 (23.5%)	



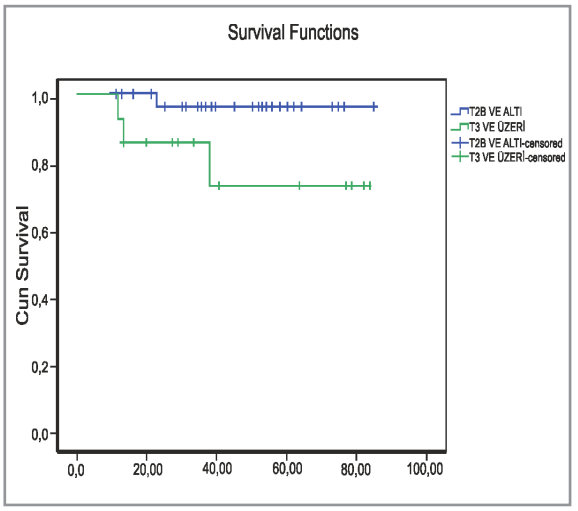


Figure 1. Curves of median survival and disease-free survival

nificant, has value near to significance. Only 1 out of 20 patients who did not give a pause to radiotherapy, developed recurrence (5%) while 7 out of 28 patients (25%) developed recurrence without a pause to radiotherapy (p= 0.07). Likewise, other patient parameters which increased recurrence are described in the table (Table 3).

Survival

Follow-up period of the patients was 40.4 months (10.9-85). Median survival was found to be 78.36±3.16 months (95% CI: 72.15-84.57); 5-year survival was 89% respectively. Four out of 49 patients (8.1%) died of the disease. Eight out of 49 patients (16.3%) developed recurrence. Median DFS was 67.41±3.79 months and 5-year DFS was 84% (Figure 1). Median survival in univariate analysis was significant only in T stage. Death occurred only in 1 out of 35 patients with T2B and lower while in T3 and above patients, death occurred in 3 out of 14 patients. Median survival in T2B and lower patients was 82.84±2.11 months (95% CI: 78.7-86.99) while it was 67.78±7.96 months (95% CI: 52.16-83.4) in T3 and above patients (p= 0.037). T stage was found to be significant in multivariate survival analyses (p= 0.04) (Figure 2). In univariate analysis, DFS was significant in patient performance and N stage. Recur-

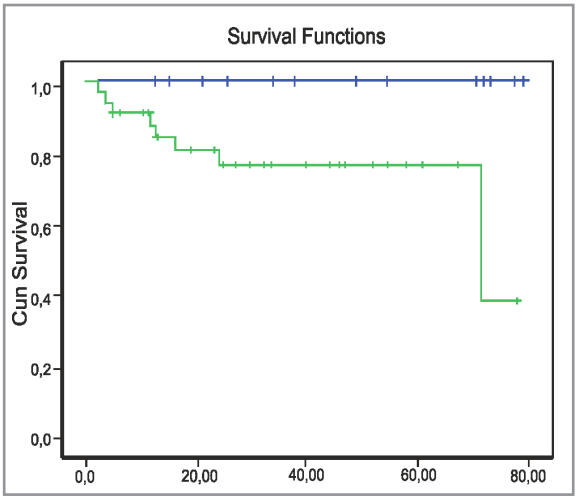


Figure 2. Distribution of survival according to T stage

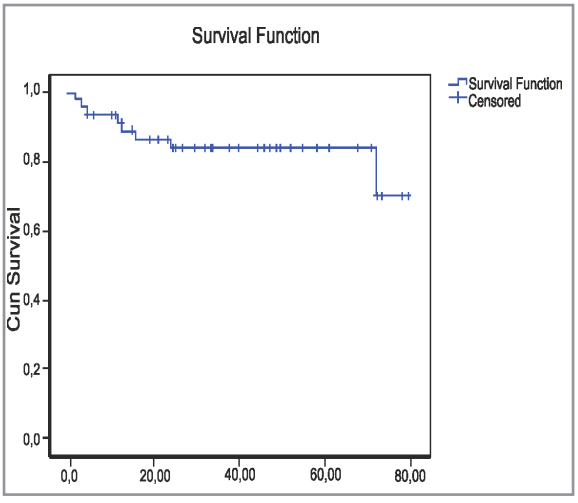


Figure 3. Effect of patient performance on disease-free survival

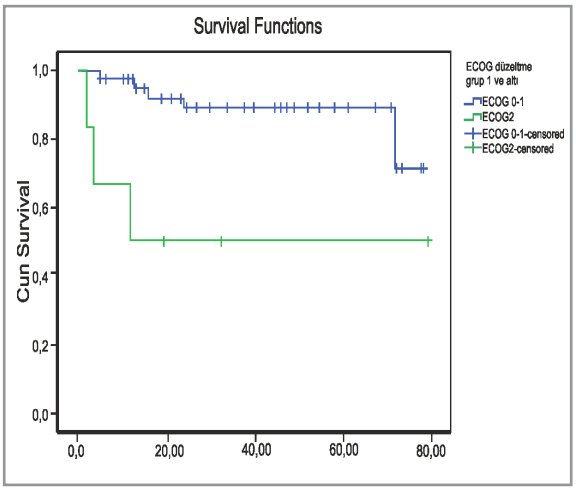


Figure 4. Effect of N stage on disease-free survival

Table 4. Results of the univariate analysis of the factors affecting overall survival and disease-free survival

Factors that affect prognosis	Overall survival (p)	Disease-free survival (p)
Stage	0.1	0.1
T Stage	0.03	0.1
N Stage	0.2	0.02
ECOG	0.1	0.009
Giving a pause to radiotherapy	0.1	0.07

rence occurred in 5 out of 43 patients with ECOG performance of 0-1 whereas 3 patients with ECOG of 2 and above experienced recurrence. DFS in ECOG of 0-1 was 70.02±3.33 months (95% CI: 63.48-76.55) and 42.4±15.07 (95% CI: 12.85-71.94) in patients with ECOG of 2 and above (p=0.009) (Figure 3). No recurrence was found in patients with DFS of N1 while all the recurrences (8 patients) occurred in N2 and higher. These values were significant in term of DFS (p= 0.02) (Figure 4).

Giving a pause to radiotherapy was not significant in term of DFS, but p value was almost significant. Recurrence occurred in 7 out of 28 patients who gave a pause to radiotherapy while only 1 recurrence occurred in 20 patients without a pause. Average DFS was 61.79±5.73 months (95% CI: 50.55-73.04) in patients with a pause whereas it was 70.17±2.99 months (95% CI: 64.31-76.04) (p= 0.07) (Table 4).

DISCUSSION

Nasopharyngeal carcinoma is usually seen among males. The rate of female/male is 2.2. It is reported that the peak incidence of patients is 5 decades, the histopathology is 90% epidermoid and undifferentiated carsinoma. It is informed that the average age in China is 45, 50-55 in less risky regions. Nasopharyngeal carcinoma is usually seen in endemic regions and the most often seen histopathological type is WHO 3 which is between 63-80%. Type WHO 2 is seen around 12% and Type WHO 1 is around 10%. In our series, a patient is of type WHO 1(2%), 16 patients of are type 2 (32.7) and 32 patients are type of WHO 3(65.3%) and these show similarity in literature. Nasopharyngeal carcinoma is a radio-responsive tumor. The researches have been made nowadays show that nasopharyngeal carcinoma is sensitive at the same time to chemotherapy. In many centres, thanks to the neoadjuvant chemotherapy which is applied with combinations especially including Cisplatin, it is determined that in local advenced stage tumors in comparision to the patients who are only applied radiotherapy are found to a lesser extent locoregional recurrence and distant metastasis.[5]

Kuten et al. got replies on the rate of 88 % about the neodjuvant chemotherapy which is applied in their retrospective study and informed that neodjuvant chemotherapy gives promising. Gu etal. applied 3 cure neodjuvant Cisplatin and 5-FU chemotherapy to a patient of advanced stage nasopharyngeal carcinoma. After that these patients were applied radiotherapy and 58 patients were only applied radiotherapy as a control group. As a result of the research, replies were achieved on the arm of chemotherapy an the rate of 89%. But in our series, after neoadjuvant chemotherapy, we achieved complete response from 21 of 49 patients (42.8%) and partial response from 28 of 49 patients (57.2%) after concomitant chemoradiotherapy, we achieved response 100% of our patients. We achieved complete response from 47 (95.5%), and partial response from 2 (4.5%).

The chemosensitivity of locoregional recurrence is

clear as seen in the researches. But there is a need of prospective randomized researches with approriate schema and appropriate medication which determine it. The rates of locoregional recurrence are informed between 15-54 % in many press. Basically, influencing factor of local recurrence are T stage , histopathology, radio therapy technique, topical dose rate and treatment's exceed of optimal time. On the followings of our patients ; with local recurrence is developed with 8 patients (16.3%) and distant metastatis with 5 patients (10.2%).

Local failure was observed on the rate of 16.3% and is the biggest reason of failure. In terms of local control rates, it is determined a significant difference on age, sex and histopathological groups.[6,7]

In nasopharyngeal cancers, there is a strong relationship with N stage and local recurrence. In Sanguineti's study, N stage and tumor histology was significant in term of recurrence. In this study, median recurrence time was 8.2 months in local cases and 13 months in regional ones. Kajanti et al. reported regional control rates as 96%, 76%, 61% and 63% for N0, N1, N2 and N3 respectively. The higher the N stage, the less the local control rate. Recurrence rate in neck of our patients was 4.1%. In our patients, loco-regional recurrence rate becomes significant with the increase of N stage. 8 out of 34 patients in our study (23.5%) with N2 and higher developed recurrence (p= 0.043). In most of our patients with locally advanced stage, local recurrence developed within one year, similar to the literature. This shows the importance of the follow-up, especially within 1-2 years.[8,9,10,11,12]

In a study of 110 patients carried out by Abdullah Al-Amro et al., chemoradiotherapy was given concomitantly after neoadjuvant chemotherapy. They applied two cures of Cisplatin (100 mg/m^2/21 days) and Epirubicin (70 mg/m^2/21 days), followed by concomitant chemoradiotherapy of Cisplatin (100 mg/m^2/21 days). After the follow-up of 37 months, rates for stage IIb, III, IVa and IVb were found to be as follow: 89%, 71%, 68% and 70% for general survival; 78%, 70%, 49% and 45% for recurrence-free survival; 88%, 89%, 61% and 60% for local regional control; and 89%, 74%, 77% and 69% for survival without distant metastases.[13]

Docetaxel has started to be used as neoadjuvant chemotherapy in recent years. Hui et al. performed a randomized phase II study with 65 locally advanced NPCpatients, comparing concomitant only chemoradiotherapy (Cisplatin 40 mg/m^2/2 weeks) with concomitant chemoradiotherapy (Cisplatin 40 mg/m^2/2 weeks) after 2 cure doses of neoadjuvant Docetaxel (75 mg/m^2/21 days) and Cisplatin (75 mg/m^2/21 days). As a result of the study, 3-year general survival was 94% in neoadjuvant chemotherapy group in contrast to 68% only in concomitant group. 3-year DFS was similar though. In term of toxicity during the neoadjuvant chemotherapy, 97% of the patients developed grade 3 neutropenia and 12% febrile neutropenia. There was no difference in the two groups in term of acute side effect during concomitant therapy. Concomitant chemotherapy after Docetaxel-based neoadjuvant chemotherapy was well tolerated and caused no compliant problems. Moreover, with preresults, significant difference was obtained in general survival in neoadjuvant group. Hence the need to perform more extended phase III randomized study was emphasized. Our study protocol was similar to this study.[14]

In a Phase II study of 33 locally advanced NPCpatients carried out by Bae et al., they applied 3 cures of TPF (Docetaxel 70 mg/m^2 and Cisplatin 75 mg/m^2 on 1st day and 5-FU 1000 mg/m^2 infusion throughout 1st to 4th day), followed by concomitant chemoradiotherapy (Cisplatin 100 mg/m^2/day in three weeks). As a result, 3-year disease-free and general survival was 76% and 86% respectively. As side effects, neutropenia developed in 72% of the patients and febrile neutropenia and nausea in 9%. This is the first study which applies TPF neoadjuvant chemotherapy in locally advanced nasopharyngeal patients. The authors emphasized that neoadjuvant chemotherapy in locally advanced patients is a promising treatment choice with tolerable toxicity. They also stated that Phase III GORTEC (Oncology and Radiotherapy Group for Head and Neck Cancer), which compares concomitant chemoradiotherapy and neoadjuvant TPF chemotherapy after concomitant chemoradiotherapy in locally advanced nasopharyngeal patients, can answer many questions on the affectivity of this treatment modality. Likewise, our patients tolerated concomitant chemoradiotherapy after neoadjuvant chemotherapy very well; and there were no patient who could not complete the treatment course.[15]

In a study of Itami et al. which studied T stages, recurrence-free survival was 80% and 43% in T1-2 and T4 patients respectively. In the multivariate analysis of this study, T stage was found to be significant as

a prognostic factor in term of local recurrence-free survival. Also in our study, only T stage was found to be significant in the univariate analysis of median survival. Death occurred only one out of 35 patients with T2B and lower while 3 death events occurred in 14 patients with T3 and above. Median survival was 82.84±2.11 months (95% CI: 78.7-86.99) in T2B and lower patients and 67.78±7.96 months (95% CI: 52.16-83.4) (p= 0.037). T stage in multivariate analysis was found to be significant (p= 0.04).[16-18]

In a study by Lee et al. 3250 patients with positive lymph node were examined and prognostic factors were defined in multivariate analysis. They found that nodal involvement in central neck region was not worse than that confined to upper neck region although the prognosis of nodal involvement extended to lower neck region was significantly bad. Especially, the prognosis of large lymph node of more than 6 cm and bilateral involvement was found to be bad. Kaasa et al. studied nodal involvements in their study and found that relative death risk in N 2-3 stage was 2.1 times higher than that in N 0-1 stage, and hence asserted that N stage was a strong prognostic factor in term of survival. In our patients DFS was significant in N stage. No one in 15 N1 patients developed recurrence while all the recurrences were found to be in N2 and above patients (8 patients). These values were significant in term of DFS (p= 0.02).[19,20]

A study by Vikram et al. reported that local control rates of 67% in radiotherapy group without any pause in contrast to 34% in patients with a pause of 21 days or longer. Luo et al asserted that treatment without a pause is superior especially in stage II-IV patients than split course treatment, which gives interval of 21 days or more to the course. However, they also found that lengthening the treatment to 45 days in stage I-II patients does not affect the local control rate. In our study, a pause to the radiotherapy was not significant in term of DFS and yet p value was almost significant (p= 0.07). 7 out of 28 patients who gave a pause to the radiotherapy developed recurrence while only one out of 20 patients developed recurrence who did not give a pause.[21,22]

In a study by Kong L et al. 52 eligible patients with stage III NPC and 64 eligible patients with nonmetastatic stage IV NPC were evaluated. The authors studied the efficacy of neoadjuvant chemotherapy, consisting of a taxane, cisplatin, and 5-fluorouracil (5-FU) (the TPF regimen) followed by concurrent chemoradiation, in 2 separately designed and synchronously executed phase 2 trials for stage III and IVA/IVB NPC(NPC). With a median follow-up of 32.9 months, the 3-year overall survival rates were 94.8% (95% confidence interval [CI], 87.6%-100%) and 90.2% (95% CI, 81.8%-98.6%) for the stage III NPC group and the IVA/IVB NPC group.[23]

In another sudy, a total of 338 patients with biopsy-proven NPC were randomly assigned to receive neoadjuvant chemotherapy followed by radical radiotherapy then adjuvant chemotherapy or concurrent chemoradiotherapy followed by adjuvant chemotherapy. With a median follow-up 60 months, results demonstrated no significant survival benefit of concurrent chemoradiotherapy over neoadjuvant chemotherapy in patients with locoregionally advanced NPC. Concurrent chemoradiotherapy only showed significant metastasis-free survival efficacy in T3-4N0-1 populations.[24]

In a meta-analysis, OuYang PY et al. Demonstrated the efficacies of neoadjuvant chemotherapy and adjuvant chemotherapy for (NPC) patients based on randomized, controlled trials. Neoadjuvant chemotherapy can effectively enhance overall survival and reduce distant metastasis rate, not locoregional reccurence rate in NPC. And adjuvant chemotherapy only helps to better control locoregional recurrence of NPC.[25]

Nowadays, it is well known that in several studies done in many centers, especially with cisplatin-including combinations, neoadjuvant chemotherapy followed by radiotherapy relatively decreases locoregional recurrence and distant metastasis, and it promisingly increases DFS and life span. Besides tumoricidal effects, chemotherapeutic agents have radio-sensitizing effects too. As a result, neoadjuvant Docetaxel/cisplatin chemotherapy followed by concurrent chemoradiation was well tolerated and produced encouraging outcomes in patients with locally advanced NPC in this hypothesis-generating study.

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