Chemoradiation in Nasopharyngeal Carcinoma: A 6-Year Experience in Tehran Cancer Institute

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Abstract- To determine the addition of value of neoadjuvant, concurrent and adjuvant chemotherapy to radiation in the treatment of nasopharyngeal carcinoma with regard to the overall survival (OS) and disease free survival (DFS) within a six year period in Tehran cancer institute. Files of all patients with nasopharyngeal carcinoma treated by radiotherapy with or without concurrent chemotherapy in a curative setting in Tehran cancer institute during the period of 1999-2005 were retrospectively reviewed.. A total of 103 patients with nasopharyngeal carcinoma had been treated during the study period with radiotherapy or chemoradiotherapy in our institute. There were 29 (28.2%) females and 74 (71.8%) males. The median age at the time of radiotherapy was 47 years old (range 9-75 years). The patients were followed 2 to 76 months with a median follow-up of 14 months. Time of first recurrence after treatment was 3-44 months with a median of 10 months.. Survival in 2 groups of patients treated with radiotherapy alone or chemoradiation did not have a significant difference (P>0.1). Two-year survival in patients treated with or without adjuvant chemotherapy and had local recurrence after treatment did not have significant difference (P>0.1). Two-year survival in patients with or without local recurrence after treatment did not have significant difference (P>0.1). A beneficial affect or a survival benefit of adjuvant/neoadjuvant chemotherapy and concurrent chemoradiation was not observed in Iranian patients.

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Introduction

Nasopharyngeal carcinoma (NPC) represents a distinct entity among head-and-neck cancers with well-defined geographic distribution, a strong relation with Epstein-Barr virus (EBV) in endemic regions, and a remarkable radiosensitivity and chemoresponsiveness. NPC is endemic in Southern China and is quite common in the Mediterranean basin. In the Middle East, NPC is very common in North African countries and in Saudi Arabia, where NPC ranks first among all head-and-neck cancers and 17th (2.3%)among all cancers (1).

In Iran, where this current study was carried out, no official data are available on NPC incidence. However, based on independent epidemiologic estimates, according to cancer research center of Tehran cancer institute approximately 1.3/100,000 cases were occurred in Tehran municipality.

Nasopharyngeal carcinoma (NPC) has three unique etiologic factors, including genetic susceptibility, chemical carcinogens, and association with Epstein-Barr virus (EBV) infection. NPC is highly radiosensitive and chemosensitive. Attempts have been made to improve treatment results by integrating radiotherapy with some form of chemotherapy (2). With no clear cause, treatment is controversial. For example, an optimal radiation regimen has not been determined, reports in the literature regarding the role of chemotherapy for advanced disease are conflicting, and treatment of local recurrences is unsettled. Still, advances in immunologic research and chemotherapy offer hope for better control of the disease (3).

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In this study we evaluated the results of radiotherapy and addition of concurrent or adjuvant/neoadjuvant chemotherapy for nasopharyngeal carcinoma in Tehran cancer institute within a six year period, during which all patients were irradiated in a hemogenous manner with an identical technique.

Patients and Methods

Files of all patients with nasopharyngeal carcinoma treated by radiotherapy with or without chemotherapy after biopsy in a curative setting in Tehran cancer institute during 1999-2005 were retrospectively reviewed.

Radiotherapy and chemotherapy

All patients received radiotherapy with or without concurrent chemotherapy. Some patients received neoadjuvant or adjuvant chemotherapy.

The RT techniques were used in a standard arrangement,.

The radiation dose was prescribed to midline. In course of treatment patients received radiation to nasopharynx (5000 to 7000) CGY with median dose of 6000CGY at 2 Gy/per fraction.

Patients also received radiation to the neck from (4800 -7000) CGY with median of 6000CGY.

All of patients were treated using 60Co photons.

Spinal cord dose was maintained at 45 Gy.

61 patients (59.2%) received concurrent chemoradiation and 42 patients were treated with radiotherapy alone.

Drugs for chemotherapy were cisplatin (52 patients 50.5%) and cisplatin +5-fu in 8 patients (7.8%).

36 patients received Neoadjuvant chemotherapy and 33 patients (32%) received adjuvant chemotherapy.

The decision to deliver of neoadjuvant or adjuvant chemotherapy depended on the managing physician.

Follow-up

All patients were evaluated for locoregional control, complications, distant metastases, and survival by a multidisciplinary team of physicians at 3-month intervals for the first 2 years, at 6-month intervals for the 3rd–5th year, and at 1-year intervals thereafter.

Follow-up examination of the primary tumor was initially assessed by fiberoptic endoscopy and CT-SCAN imaging three months after completion of radiotherapy. Fiberoptic endoscopy was then performed on every return visit subsequently.

The period of follow –up was calculated from the start of radiotherapy (RT) to the date of last follow-up visit or death. Local relapse was defined as the appearance of cancer in nasopharynx in nasopharyngoscopy or regional lymph nodes confirmed by pathology. All other relapse locations were assumed to be distant metastases.

Follow-up duration was 2-76 months with a median of 14 months.

Time of first recurrence after treatment was 2-44 months with a median of 10 months.

Results

A total of 103 patients with nasopharyngeal carcinoma had been treated with radiotherapy or chemoradiotherapy during the study period in our institute.

There were 29 (28.2%) females and 74 (71.8%) males (Table 1).

The median age at that time of radiotherapy was 47 years (range 9-75 years).

Distribution of age in radiotherapy or chemoradiation group was similar and there was no significant difference (P>0.1).

Pathology was squamous cell carcinoma in 14 (13.6%) patients, poorly differentiated carcinoma in 11 (10.7%) and undifferentiated carcinoma in 77 (74.8%) patients. Surprisingly we have not any lymphoepithelioma in these patients. Immunohistochemistery test was done for only 9 patients (8.7%), the result of which was undifferentiated carcinoma in all. Neck lymphadenopathy was present in 65(63%) patients. Size of the patients' tumors according to the AJCC 1997 staging system is shown in table (2).

In assessing lymph nodes of neck according to the AJCC 1997 staging system data are in table (3) .

And 5 patients were in stage 1(4.9)%, 14 patients in stage 2(13.6%), 24 patients in stage 3(23.3%) and 37 patients in stage 4(35.9%). Distribution of stage in two groups was similar and there was no difference in two groups (P=0.143). 10 patients had local recurrence (9.7%) and distant metestases appeared in 18 patients. (17.5%) which was: bone metestases in 9 patient (8.7%), brain metestasis in 3 patient (2.9%),liver metestasis in 3 patients (8.7%) and axillary lymph nodes in 1 patient (1%.). One patient had lung and liver metestasis and one patient bone, lung and liver metestases at the same time.

Patients conditions at the end of our follow up from 103 patients were: 77(74.8%) patients were good, 11 (10.7%) patients were died and 15(14.6%) patients

received treatment because of local recurrence or distant metastasis. Time of death was 2 -46 months after treatment with a median of 46 months. The mean of overall survival was 63 months (±4) and Two-year overall survival was 91.7+/_3.06%. Survival in 2 groups of patients treated with radiotherapy alone or chemoradiation did not have a significant difference (*P*>0.1). Two-year survival in 2 groups of patients treated with radiotherapy alone or chemoradiation after recurrence did not have a significant difference (*P*> 0.1).

Two-year survival in patients with or without distant metestases did not have a significant difference (*P*>0.1).

Distant Metestases was 14.2% in patients treated with radiotherapy alone and 20% in chemoradiation group. There was no significant difference in two groups (*P*>0.1). Distant metestases was 14.7% in patients without lymph node metestases and 18.7% in patients with lymph node metestases and there was no significant difference in two groups (*chi*-square test) (*P*>0.1).

Two-year survival in patients with or without local recurrence did not have a significant difference (*P*>0.1).

Local recurrence was 14.2% in patients treated with radiotherapy alone and 6.55% in chemoradiation group and there was no significant difference in two groups (*P*>0.1). Local recurrence was 8.8% in patients without lymph node metestases and 9.3% in patients with lymph node metestases and there was no significant difference in two groups (*P*>0.1).

Two-year survival in patients with or without adjuvant chemotherapy did not have a significant difference (*P*>0.1).

Two-year survival in patients with or without neoadjuvant chemotherapy did not have a significant difference (*P*>0.1).

Two-year survival in patients treated with or without neoadjuvant chemotherapy who had local recurrence did not have significant difference (*P*>0.1).

Two-year survival in patients treated with or without adjuvant chemotherapy who had local recurrence did not have significant difference (*P*>0.1).

Overall Survival in the stage 1&2 based on Kaplan – meier test was not detectable because of inadequate number of cases in two groups (Figure 1). The difference in overall Survival in stage 3 & 4 in two groups of radiotherapy and chemoradiation was not significant (*P*>0.1) (Figures 2&3)

Table 1. Sex distribution

	Frequency	Percent
male	74	71.8
female	29	28.2

Table 2. T staging

T	Frequency	Percent
1	11	10.7
2	24	23.3
3	13	12.6
4	24	23.3

Table 3. N staging

N	Frequency	Percent
0	34	33
1	20	19.4
2	24	23.3
3	20	19.4

Table 4. Chemotherapy

Drug	Frequency	Percent
Cisplatin	52	50.5
Cisplatin+5-fu	8	7.8
total	60	58.3

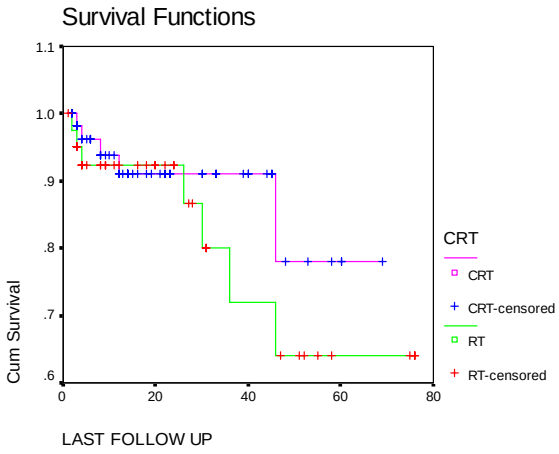

Figure 1. Survival function in stage1&2

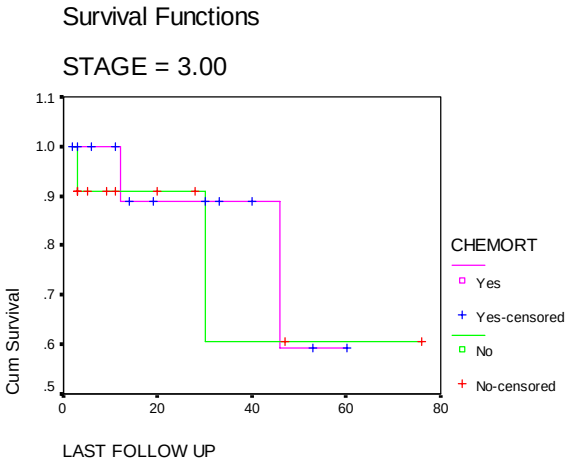

Figure 2. Survival function in stage 3

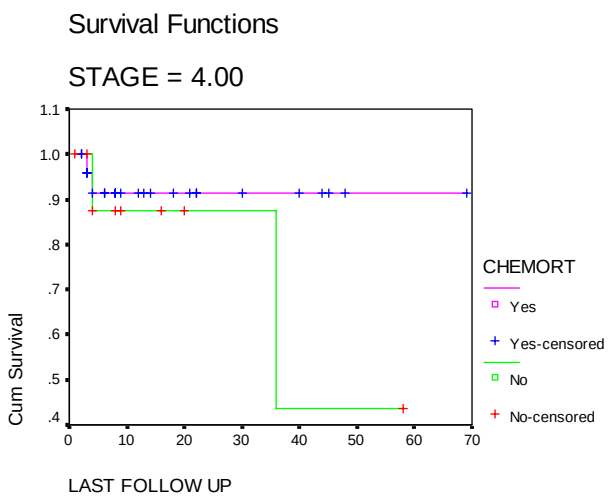

Figure 3. Survival function in stage 4

Discussion

In this study, we report the results of definitive RT with or without additive chemotherapy for a series of patients treated at the Tehran cancer institute.

Radiation therapy for cancer is a critical medical procedure that occurs in a complex environment involving numerous health professionals, hardware, software and equipment.

Uncertainities and potential incidents can lead to inappropriate administration of radiation to patients, with consequences such as increased complication rate and/or appreciably impaired quality of life (4).

Thus optimization of radiotherapy techniques at least within each radiation oncology center is very important .one of positive points of this report is the homogenized radiation treatment all the patients had received , which makes interpretation easier ,simpler and more reliable. The incidence of NPC in different countries of the Middle East is not well documented. In countries in which proper cancer registries are available, such as Saudi Arabia, this incidence is about 1.7/100,000 inhabitants, almost three times greater than that observed in Western countries(5).

In Iran, where this current study was carried out, no official data are available on NPC incidence. However, based on independent epidemiologic estimates, according to cancer research center of Tehran cancer institute approximately 1.3/100,000 cases were occurred in Tehran municipality. In addition the relative absence of Lymphoepithelioma in our patient population has been nearly comparable to that reported in Western studies and not as high as that of endemic regions. This feature has been commonly found to be of prognostic significance in Western, but not Asian, studies (5).

A beneficial affect of adjunctive chemotherapy was not truly observed in this retrospective study and In our study ,concurrent and adjuvant/neoadjuvant chemotherapy did not provide a survival benefit. This could be related to many confounding factors in this retrospective study, primarily the absence of the more chemoresponsive Lympho Epithelioma tumors in groups , thus putting chemotherapy group at a disadvantage. The role of adjunctive chemotherapy in NPC has been intensely debated in academic circles during the past decade.

Although emerging evidence from Western trials has confirmed the positive impact of neoadjuvant and concurrent cisplatin-based chemotherapy in NPC , trials from endemic regions have consistently showed marginal or no role for systemic chemotherapy (5).

Arguments about proper patient selection, use of aggressive RT, and suboptimal doses and drugs of chemotherapy have been advanced to explain these differences, but none of these has been powerful enough to reconcile this discrepancy.

In the West , concurrent chemotherapy has proven effective in advanced-stage NPC patients, and cisplatin-based chemotherapy has become standard adjunctive therapy. There was no advantage of chemoradiation for NPC in the current report.

In our series, local recurrence and distant metestasis were not reduced. As a result, survival was not improved, illustrating the importance of distant failure in determining short-term survival in loco regionally advanced NPC. It is may be because of our study was limited by the small sample size and use of retrospective analysis.

Despite these limitations, our results do suggest that concomitant chemoradiation alone is probably ineffective in reducing distant metastasis and locoregional failure. According to the litreatures concomitant CRT improves locoregional control in Chinese patients with locoregionally advanced NPC (6), but our analysis failed to detect any impact on distant failure and survival.

Our findings suggest that caution should be exercised in extrapolating the findings of the Intergroup study to Iranian patients, and confirmatory results from prospective randomized studies in the endemic population are needed. In conclusion, the relative role of concurrent and adjuvant chemotherapy remains uncertain , at least in our Iranian patients.

Future studies should address the relative contributions of chemoradiation and adjuvant chemotherapy, as well as define patient subgroups that may benefit most from CRT.

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