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A retrospective analysis of 32 locally advanced nasopharyngeal carcinoma patients treated with chemotherapy and radiotherapy

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To analyze the impact of neoadjuvant chemotherapy on the treatment of locoregionally advanced nasopharyngeal carcinoma and to assess the outcomes of patients receiving such treatment, we analyzed 32 cases that have been treated with neoadjuvant chemotherapy followed by radiotherapy and adjuvant chemotherapy retrospectively at GATA Military Medical School between 1996-2000. Out of 32 cases, 27 were male, 5 were female (sex ratio 5.4:1 respectively). Median age was 25 (19-64). 15.62% of the cases were Stage III and 84.37% were stage IVA-B. 20 cases had undifferentiated carcinoma, 9 cases had squamous cell carcinoma (SCC), 2 cases had anaplastic carcinoma and one case had lymphoepithelioma as histopathologic diagnosis. All cases were given one of the following chemotherapy regimes for 2-3 cycles; Cisplatin + 5-fluorouracil + Bleomycin, Cisplatin + Ifosfamide + Mesna + Bleomycin and Cisplatin + Adriamycin + Bleomycin. Following chemotherapy 66–70 Gy radiotherapy was delivered to every patient using Co-60 teleradiotherapy machine. After the radiotherapy, patients had received 3 to 4 cycles of chemotherapy. The objective response rate was 96.87%, complete response rate was 40.62%, partial response rate was 56.25% and no-response rate was 3.12%. Three-year overall cumulative survival rate was 48.11% while disease free survival rate was 43.75%. Complication rates due to chemotherapy were mucositis (grade I 6.25%, grade II 6.25%, grade III 3.12%), myelosuppression (grade II 21.87%, grade III 3.12%, grade IV 6.25%) and nausea (grade I 3.12%) whilst radiotherapy–related complication rates were; mucositis (grade I 6.25%, grade II 15.62%, grade III 6.25%), dysphagia (grade I 6.25%, grade II 6.25%), nausea (grade I 3.12%) and fibrosis of skin (grade II 6.25%). While not providing conclusive evidence, historical data of our institution suggest that addition of chemotherapy to

standard radiotherapy improves survival despite increasing the toxicity of the treatment. [Turk J Cancer 2001;31(3):106-113]

Key words: Nasopharyngeal carcinoma, radiotherapy, chemotherapy

Nasopharyngeal cancer represents 0.1% of all cancers and of cancer deaths. Although rare in Western Europe, nasopharyngeal cancer is very common in the Far East. The strongest evidence for a causative agent is the presence of antibodies to a virus (Epstein–Barr) in serum of nasopharyngeal carcinoma patients and there is evidence that this virus can persist as a latent infection in nasopharyngeal epithelium. Smoking and curing of salty fish, a common practice in the Far East, have been postulated as sources of chemical carcinogens. The disease is commoner in men (sex ratio 3:1) and commonest between the ages of 40 and 60 (1).

Symptoms and signs at presentation include painless, enlarged lymph nodes in the neck (present in approximately 75% of patients and often bilateral and posterior), nasal obstruction, epistaxis, diminished hearing, tinnitus, recurrent otitis media, cranial nerve dysfunction (usually II-VI or IX-XII), sore throat, and headache. Magnetic resonance imaging (MRI) is more informative than computerized tomography (CT) for radiological diagnosis and clinical staging (2). Definitive diagnosis is made via biopsy of the nasopharyngeal and/or neck mass. Most frequent distant metastasis site is bone, followed by lung and liver. Major prognostic factors adversely influencing outcome of treatment include large size of the tumor, higher T stage, and the presence of involved neck nodes (3). Other factors linked to diminished survival in some, but not all, studies include age, non-lymphoepithelial histology, long interval between biopsy and initiation of radiation therapy, diminished immune function at diagnosis, incomplete excision of involved neck nodes, pregnancy during treatment, loco-regional relapse, and certain EBV antibody titer patterns.

Although a wide variety of malignant tumors may arise in the nasopharynx, squamous cell carcinoma is the most common histopathological type. Subdivisions of squamous cell carcinoma in this site include lymphoepithelioma (Schminke tumor); transitional cell tumors, well to poorly differentiated grade; and keratinizing or nonkeratinizing variety (4).

The small lesions of the nasopharynx are quite curable, which have a survival rate of 80-90%. The survival rate is 50-70% for partially advanced lesions without cervical lymph node involvement (5). The standard therapy for patients with stage-I and II nasopharyngeal cancer is high-dose radiation therapy to the primary tumor site and prophylactic radiation therapy to the nodal drainage (6-8). For Stage III and stage IVA-B lesions the standard treatment choices include chemoradiotherapy, high-dose or hyperfractionated radiation therapy to the primary tumor site and bilateral neck nodes that are clinically positive, neck dissection may be indicated for persistent or recurrent nodes if the primary tumor site is controlled (8-14). For stage IVC cases systemic chemotherapy is applied (8,13).

Materials and Methods

Thirty-two cases that have been treated with neoadjuvant chemotherapy followed by radiotherapy and then again chemotherapy were analyzed retrospectively. All patients were Stage III (T1-2 N2, T3 N0-2), stage IVA (T4 N0-2) and stage IVB (any T N3) on the basis of AJCC (15). All cases were given one of the following chemotherapy regimes for 2-3 cycles as neoadjuvant setting; Cisplatin + 5-Fluorouracil + Bleomycin, Cisplatin + Ifosfamid + Mesna + Bleomycin and Cisplatin + Adriamycin + Bleomycin. After the chemotherapy, all patients received radiotherapy. Following the radiotherapy chemotherapy has been resumed and completed to six cycles (Figure 1).

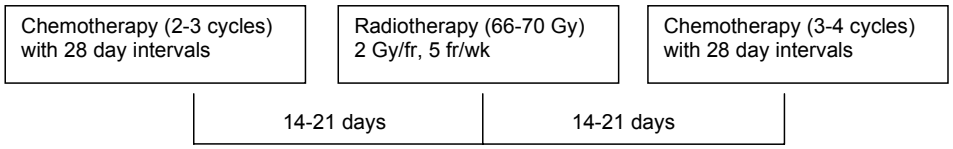

Fig 1. Schedule of nasopharyngeal cancer treatment

Radiotherapy was delivered using Co-60 teletherapy machine in conventional fractions (2 Gy/fr) with a total dose of 66-70 Gy to the primary site and 50 Gy to the cervical lymph nodes. A large, lateral opposed pair of field encompass the primary tumor and the nodes of the upper neck. The field encompasses the nasopharynx, the base of skull, the parapharyngeal space and any tumor extending into the nasal cavity or the oropharynx. Once, a maximum safe dose to the spinal cord has been reached (46 Gy in 23 daily fractions), the volume is reduced from the posterior margin of the field to the front of the spinal cord. The lower neck is treated by a direct anterior field with midline shielding of the larynx and spinal cord.

Results

Of the 32 cases, 27 were male and 5 were female (sex ratio 5.4:1). Age distribution was 19-64 and median age was 25 (Table 1).

Table 1
The number of cases according to age

Age	Number of cases (%)
<30	19 (59.37%)
31-40	2 (6.25%)
41-50	5 (15.62%)
51-60	5 (15.62%)
>60	1 (3.12%)

Among pathology findings, undifferentiated carcinoma was determined in 20 cases (62.5%), squamous cell carcinoma in 9 (28.8%), anaplastic carcinoma in 2 (6.25%) and lymphoepithelioma was seen in one case (3.12%) (Table 2).

Table 2
The number of cases according to histopathology

Histopathology	Number of cases (%)
Undifferentiated carcinoma	20 (62.5%)
Squamous cell carcinoma	9 (28.8%)
Anaplastic carcinoma	2 (6.25%)
Lymphoepithelioma	1 (3.12%)

Most frequent symptom at the time of diagnosis was neck mass in 11 patients (34.3%). Other symptoms were pain in 8 patients (25%), hearing loss in 4 patients (12.5%), nasal bleeding in 3 patients (9.3%), nasal congestion in 2 patients (6.25%), weight loss in one patient (3.12%) and cranial nerve palsy in one case (3.12%).

All of the patients that received chemotherapy were stage III and stage IVA-B. Five cases were stage III (15.62%), 27 cases were stage IVA-B (84.37%). T and N stage distribution are given in table 3.

Table 3
The number of cases according to TNM stage

Stage	Number of cases (%)
T stage	
T1	6 (18.7%)
T2	7 (21.8%)
T3	8 (25%)
T4	11 (34.3%)
N stage	
N1	1 (3.1%)
N2	8 (25%)
N3	12 (37.5%)
N4	11 (34.3%)

Among the 32 nasopharyngeal cancer cases, primary site was bilateral wall in 50%, lateral wall and Rosenmüller fossa in 43.7% and anterior wall in 6.2%. Cervical lymph node involvement was 68.7% and cranial nerve involvement was 12.5%.

In 32 cases that received chemotherapy and radiotherapy median survival was found to be 26 months (6-108), median follow-up times by N and T stages were given in table 4.

Table 4
Median follow-up time according to TNM stage

Stage	Median follow-up time (months)
T stage	
T1	40
T2	30
T3	24
T4	31
N stage	
N1	43
N2	24
N3	21
N4	30

For stage III cases, median follow-up time was 18 months (7-34 months) while for stage IV cases it was 30 months (6-108 months).

When the survival rates were observed, 2-year overall survival was found to be 80.19% (SE: 7.96) and 3-year overall survival was 48.11% (SE: 10.62). Median survival time was 33 months. 43.75% of our cases were alive with no evidence of disease, 4 patients (12.5%) were alive with disease while 14 patients (43.75%) were lost due to locoregional recurrence and/or distant metastasis. Cases with over three years of follow-up period with no evidence of disease constituted 8 patients (25%). When the response rates were analyzed, partial response was seen in 56.25% (18 pts) and complete response was seen in 40.62% (13 pts), overall response rate was 96.87% (31 pts) and 3.12% (1 pt) of the cases had no response.

The most frequent complication due to chemotherapy was grade II myelosuppression (21.8%) while the most frequent complication due to radiotherapy was grade II mucositis (15.6%) (Table 5). Among our cases, other than the loco-regional recurrences, the most frequent site of metastasis was bone (Table 6).

Discussion

Due to their anatomical location, having borders with the cranium base, widespread infiltration characteristics and early metastases, the surgical treatment of nasopharyngeal cancer is quite limited. Therefore the primary treatment of nasopharyngeal cancer is radiotherapy (14). On the other hand, chemotherapy can be used as adjuvant or neoadjuvant therapy in locally advanced stages in order to decrease the rate of distant metastases and control the rate of locoregional failure (16). In our cases 2-3 cycles of neoadjuvant chemotherapy followed by radiotherapy and 3-4 more cycles of chemotherapy, totally 6 cycles of systemic chemotherapy, were performed. Overall response rate was 96.87% (31 pts) while rate of no response was 3.12% (1 pt). The case with no response was stage IV and histopathologic grade was diagnosed as anaplastic carcinoma. In our study it was observed that as the T and N stages increased, survival times shortened. The survival time was found to be shorter in the case with anaplastic carcinoma. Two-year overall survival rate of the

patients in our study (80.19%) is consistent with the literature results of nasopharyngeal cancer patients treated with neoadjuvant chemotherapy+radiotherapy+chemotherapy setting (17).

The most frequent site of distant metastasis was bone and lung. Bone metastasis was mostly observed in our cases with anaplastic carcinoma. Our local failure rate was 28.12% and similar to the experience of Fu (18) and Wang (19,20).

Although neoadjuvant chemotherapy is still investigated in clinical trials for patients with stage III and IVA-B nasopharyngeal cancer, in phase III clinical trial performed by Al-Sarraf et al. (9) neoadjuvant chemotherapy was shown to increase disease-free survival.

Table 5
Various complications due to chemotherapy and radiotherapy modalities

Complications	Chemotherapy	Radiotherapy
Mucositis		
Grade I	6.25%	6.25%
Grade II	6.25%	15.62%
Grade III	3.12%	6.25%
Myelosuppression		
Grade II	21.87%	-
Grade III	3.12%	-
Grade IV	6.25%	-
Nausea		
Grade I	-	3.12%
Grade III	3.12%	-
Dysphagia		
Grade I	-	6.25%
Grade II	-	6.25%
Skin Fibrosis		
Grade II	-	6.25%

Table 6
The number of cases according to metastasis region

Metastasis region	Number of cases (%)
Loco-regional recurrence	9 (28.12%)
Bone metastasis	6 (18.75%)
Lung metastasis	4 (12.5%)
Lung+bone metastasis	1 (3.12%)
Axillary lymph node metastasis	1 (3.12%)

Although our tumor control rates were improving, further optimization is obviously needed. The present paper gives an overall picture of this malignancy, but proper design of future trials demands more detailed analyses of the different treatment aspects.

References

1. Bomford CK, Kunkler IH, Sherriff SB. Nasophpharynx. In: Walter and Miller's Textbook of Radiotherapy. 5th ed. London: Churchill Livingstone, 1993; 326-8.
2. Perez CA. Nasopharynx. In: Perez CA, Brady LW, editors. Principles and Practice of Radiation Oncology. U.S.A.: Lippincott-Raven, 1998; 897-939.
3. Sanguineti G, Geara FB, Garden AS, et al. Carcinoma of the nasopharynx treated by radiotherapy alone; determinant of local and regional control. Int J Radiat Oncol Biol Phys 1997;37:985-96.
4. Ensley J, Crissman J, Kish J, et al. The impact of conventional morphologic analysis on response rates and survival in patients with advanced head and neck cancers treated initially with cisplatin-containing combination chemotherapy. Cancer 1986;57:711-7.
5. Bailet JW, Mark RJ, Abemayor E, et al. Nasopharyngeal carcinoma; treatment results with primary radiation therapy. Laryngoscope 1992;102:965-72.
6. Mesic JB, Fletcher GH, Goepfert H. Megavoltage irradiation of epithelial tumors of the nasopharynx. Int J Radiat Oncol Biol Phys 1981;7:447-53.
7. Hoppe RT, Goffinet DR, Bagshaw MA. Carcinoma of the nasopharynx: eighteen years' experience with megavoltage radiation therapy. Cancer 1976;37:2605-12.
8. Schantz SP, Harrison LB, Forastiere AA. Tumors of the nasal cavity and paranasal sinuses, nasopharynx, oral cavity, and oropharynx. In: DeVita VT Jr, Hellman S, Rosenberg SA, editors. Cancer: Principles and Practice of Oncology. 5th ed. Philadelphia: Lippincott-Raven Publishers, 1997; 741-801.
9. 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 Clin Oncol 1998;16:1310-7.
10. Teo PM, Chan AT, Lee WY, et al. Enhancement of local control in locally advanced node-positive nasopharyngeal carcinoma by adjunctive chemotherapy. Int J Radiat Oncol Biol Phys 1999;43:261-71.
11. Mesic JB, Fletcher GH, Goepfert H. Megavoltage irradiation of epithelial tumors of the nasopharynx. Int J Radiat Oncol Biol Phys 1981;7:447-53.
12. Hoppe RT, Goffinet DR, Bagshaw MA. Carcinoma of the nasopharynx: eighteen years' experience with megavoltage radiation therapy. Cancer 1976;37:2605-12.
13. Johnson CR, Schmidt-Ullrich RK, Wazer DE. Concomitant boost technique using accelerated superfractionated radiation therapy for advanced squamous cell carcinoma of the head and neck. Cancer 1992;69:2749-54.
14. Rubbe C, Grevers G, Grimminger H, et al. Primary radiotherapy of nasopharyngeal carcinoma. Laryngo Rhino Otolog 1995;72:103-7.
15. American Joint Committee on Cancer Staging Manual. 5th ed. 1997; 35.

16. Forastiere AA. Cisplatin and radiotherapy in the management of locally advanced head and neck cancer. Int J Radiat Oncol Biol Phys 1993;27:465-70.
17. 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. Asian-Oceanian Clinical Oncology Association Nasopharynx Cancer Study Group. Cancer 1998;83:2270-83.
18. Fu KK, Newman H, Philips TL. Treatment of locally recurrent carcinoma of the nasopharynx. Radiology 1975;117:425-31.
19. Wang CC. Carcinoma of the nasopharynx. In: Wang CC, editor. Radiation Therapy for Head and Neck Neoplasms: Indications, Techniques, and Results. 2nd ed. Chicago, London: Yearbook Medical Publishers, Inc., 1990; 261-83.
20. Wang CC. Re-irradiation of recurrent nasopharyngeal carcinoma – treatment techniques and results. Int J Radiat Oncol Biol Phys 1987;13:953-6.