A 5-Year Multicenter Clinical Experience in Local and Locally Advanced Nasopharyngeal Carcinoma from A Non-Endemic Region: A Retrospective Cohort Study

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ABSTRACT

Nasopharyngeal carcinoma is an endemic disease in certain geographic regions. This study was undertaken to identify long-term outcome data and prognostic factors for current treatment options in a non-endemic area such as Turkey. One-hundred and thirty-two patients with local and locally advanced disease treated in three distinct oncology units in Turkey between 2010 and 2019 were retrospectively evaluated. Median duration of follow-up for OS was 68.9 months, respectively. A comparison of adjuvant and induction therapy for locally advanced (Stage 3 and 4a) disease showed a 5-year DFS of 85.5% vs. 76.4%, respectively (p= 0.360). The 5-year OS for adjuvant and induction therapy were 86.4% vs. 91.7, respectively (p=0.569). When factors affecting OS were examined, visceral recurrence was significantly associated with shorter survival (HR: 0.06, 95% CI: 0.014-0.3, p< 0 .001). With regards to DFS, N2-3 status (HR: 2.33, 95% CI: 1.2-6.69, p= 0.017) and stage 3-4a disease (HR: 3.37, 95% CI: 1.01.-11.1, p= 0.047) were associated with earlier recurrence. 5-year OS and DFS outcomes of our patients with nasopharyngeal carcinoma were consistent with the published data. Our results showed that N2-3 disease was a poor prognostic indicator for DFS; on the other hand, visceral metastasis and recurrence were poor prognostic indicators for OS.

Keywords: Nasopharyngeal carcinoma, Survival, Prognosis, Clinical outcomes

INTRODUCTION

Each year nearly 129.079 patients (incidence: 0.7/100.000) are diagnosed with nasopharyngeal carcinoma and 72.987 (incidence: 0.8/100.000) patients are expected to die from this disease.[1,2] Nasopharyngeal carcinoma is endemic in Southern China and Southeast Asia. However, it is a rare malignancy in Turkey, and based on 2018 Globocan incidence data, it represents the 28th most common cancer in this country.[2,3]

Radiotherapy is the cornerstone of treatment in localized and locally advanced nasopharyngeal cancer. Intensity Modulated Radiotherapy (IMRT) has become the standard practice in many centers worldwide, as it is associated with better local control and survival rates as well as with reduced toxicity.[4,5] However, apart from stage 1 disease, concurrent cisplatin is also used as a standard practice due to the common presence of deep seated lesions and high rates of locally advanced disease at the time of diagnosis.[6,7]

The MAC-NPC meta-analysis showed that concurrent radiotherapy and chemotherapy results in better overall survival (OS) and progression free survival (PFS) and reduces local-regional recurrence, distant metastases, and nasopharyngeal cancer mortality.[8] However, 18% to 27% of the patients with local or locally advanced disease develop distant metastases despite chemoradiotherapy, which is an important consequence of insufficient treatment or treatment failure. Until now, prospective randomized studies have provided somewhat controversial results regarding the outcome of neoadjuvant and adjuvant treatments.[6,9-12]

The objective of this study was to assess 5-year survival rates and prognostic factors for localized and locally advanced nasopharyngeal cancer in Turkey, which is a non-endemic region for this condition.

PATIENTS AND METHODS

A total of 132 patients with local or locally advanced nasopharyngeal carcinoma treated and followed-up at three distinct oncology units in Turkey were included. Investigators from each oncology unit performed retrospective file reviews. Exclusion criteria were distant organ metastasis, comorbid conditions precluding standard therapy, and Eastern Cooperative Oncology Group (ECOG) performance status of 2 to 4. OS was defined as the time from diagnosis to death. DFS was defined as time from diagnosis to recurrence

Radiotherapy: IMRT was administered to all patients.Target volume delineations for IMRT were based on the ICRU 62 (International Commission on Radiation Units and Measurements Report 62) guidelines. PET-CT/MRI scans were used to delineate gross tumor volume (GTVtm) and cervical lymph-node tumor volume (GTVln). Clinical target volume consisted of the nasopharyngeal space, positive lymph node regions, as well as the GTV with a 1 to 1.5 cm margin. CTV was used to create planning target volumes (PTV) using 0.5 cm margins. The prescribed radiation doses were 69.96 Gy (2.12 Gy/F/QD) for GTV and 54-60 Gy (1.63-2 Gy/F/QD) for CTV. Other structures that were contoured by planning tomography included brain stem, spinal cord, parotid gland, eyes, optic chiasma, optic nerves, cochlea, and ears. Simultaneous integrated boost technique was used for IMRT planning.

Chemotherapy: Concurrent chemotherapy protocol included cisplatin 40 mg/m^2 weekly for 5-7 weeks depending on the toxicity. Induction and adjuvant therapy included 2 or 3 courses of DCF (docetaxel 60 mg/m^2 + cisplatin 60 mg/m2 + 5-fluorouracil 600 mg/m^2 once every 21 days) or CF (cisplatin 80 mg/m^2 + 5-fluorouracil 4000 mg/m^2, once every 21 days).

Ethics committee approval was obtained from SBU Dr. Abdurrahman Yurtaslan Oncology training and research hospital (Date and number: 26.08.2020, 2020-08/765). The study was conducted in accordance with the principles of the Helsinki Declaration.

Statistical Analyses

Categorical variables were compared using Chi-square and Fisher's exact tests. The survival curves and rates were determined using log-rank test and Kaplan-Meier analysis. For hazard ratios, Cox proportional hazards model was used with 95% confidence intervals. Univariate analyses were based on Cox proportional hazards model. A p value of less than 0.05 was considered statistically significant.

RESULTS

The median age was 49 years (range: 17-90 years), and 68.2% of the patients were male. The most common presenting symptoms included swelling in the neck (40.9%, n= 58), impaired hearing (22.7%, n= 30), nasal obstruction (21.9%, n=29), and fullness sensation in the ear (9%, n= 12).

Histopathological examination showed non-keratinized, undifferentiated, and keratinized carcinoma in 42.4% (56), 54.5% (72), and 3% (4) of the cases, respectively (Table 1). The disease stage at the time of presentation was 1 in 3.8% (5), 2 in 22.7% (30), 3 in 50.8% (67), and 4a in 22.7% (30).

Recurrence occurred in 21.8% (28) of the patients. The most common sites of recurrence included bone in 35.7% (10), lung in 28.5% (8), liver in 21.4% (6), local sites in 21.4% (6), and brain in 10.7% (3) (Table 1).

Table 1. General features

		N:132
Age-Median	49 (Range: 17-90)	
Gender	Female	42 (31.8%)
	Male	90 (68.2%)
Symptom	Swelling in the neck	54 (40.9%)
	Hearing problems	30 (22.7%)
	Stuffy Nose	29 (21.9%)
	Fullnes in the ear	12 (9%)
	Headache	3 (2.2%)
	Epistaxis	3 (2.2%)
	Vision problems	2 (1.5%)
	Neurological symptoms	3 (2.2%)
	Dyspnea	1 (0.8%)
	Dysphagia	1 (0.8%)
Smoke	Yes	78 (59.1%)
	No	54 (40.9%)
Histologic subtypes		
Keratinizing squamous cell carcinoma (WHO type 1)		56 (42.4%)
Nonkeratinizing-differentiated (WHO type 2)		4 (3%)
Nonkeratinizing-undifferentiated (WHO type 3)		72 (54.5%)
T	T1	12 (9.1%)
	T2	78 (54.5%)
	T3	28 (21.2%)
	T4	20 (15.2%)
N	N0	28 (21.2%)
	N1	30 (22.7%)
	N2	62 (47%)
	N3	12 (9.1%)
Stage	Stage 1	5 (3.8%)
	Stage 2	30 (22.7%)
	Stage 3	67 (50.85)
	Stage 4a	30 (22.7%)
Recurrence	Yes	28 (21.2%)
	No	104 (78.8%)
Recurrence area	Bone	10 (35.7%)
	Lung	8 (28.5%)
	Local	6 (21.4%)
	Liver	6 (21.4%)
	Brain	3 (10.7%)
	Axillary lap	1 (0.3%)
Exitus	Yes	17 (12.9%)
	No	115 (87.1%)

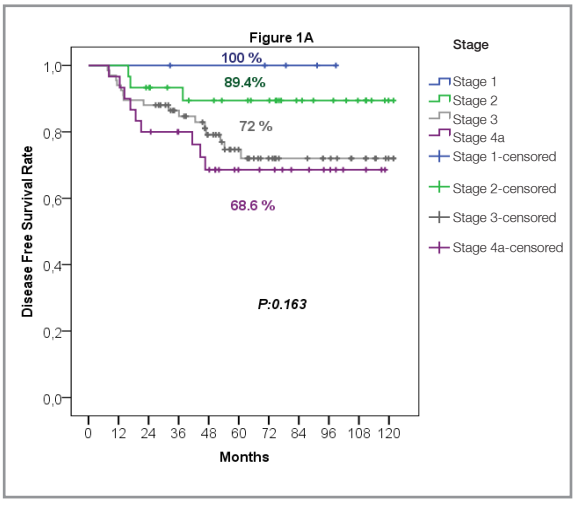

Figure 1A. Five-years Kaplan-Meier DFS analysis

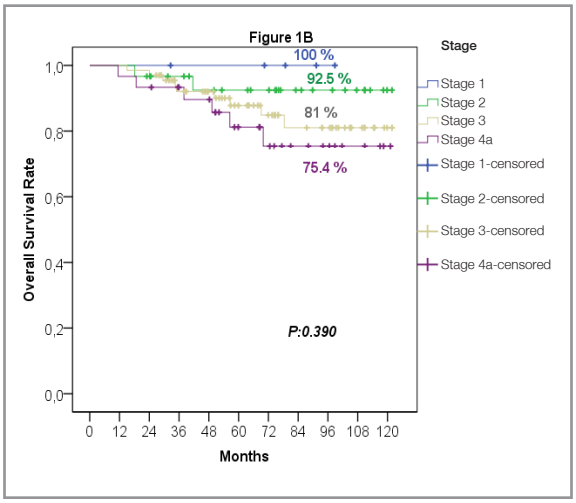

Figure 1B. Five-years Kaplan-Meier OS analysis

Except for stage 1 patients, who received radiotherapy only, all other subjects with local or locally advanced disease received IMRT together with chemotherapy. While induction chemotherapy was given in 14.2% (n= 19), 50.4% (n= 67) of the patients received adjuvant chemotherapy. Adjuvant and induction therapy were mainly preferred for stage 3 and 4a disease. Among those who received adjuvant chemotherapy, CF was administered in 3 courses in 65.6% (n= 44), and 2 courses in 34.3% (n= 23). For induction chemotherapy, 73.6% of the patients (n= 14) received 3 courses of DCF, 15.7% (n= 3) received 2 courses of DCF, and 10.5% (n= 2) received 2 courses of CF. The median duration of follow-up for OS was 68.9 months (range: 11.4-121.7 months).

5-year OS for stage 1, 2, 3, and 4a disease was 100%, 92.5%, 81%, and 75.4% (p= 0.39). The corresponding 5-year DFS was 100%, 89.4%, 72%, and 68.6% (p= 0.163). In the overall patient group, the 5-year OS was 87.8% and DFS was 76.6% (Figures 1A-B).

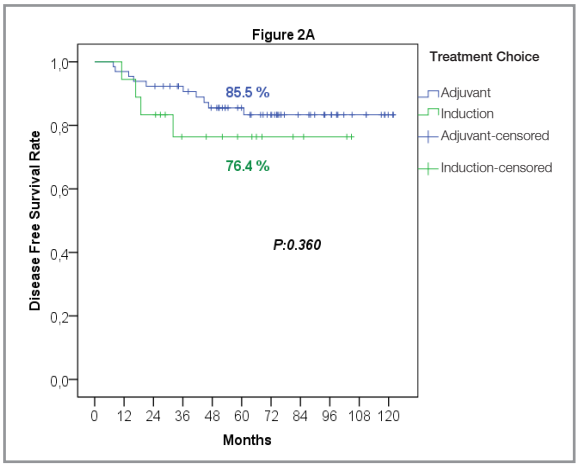

Figure 2A. Five-years Kaplan-Meier DFS analysis according to treatment choice

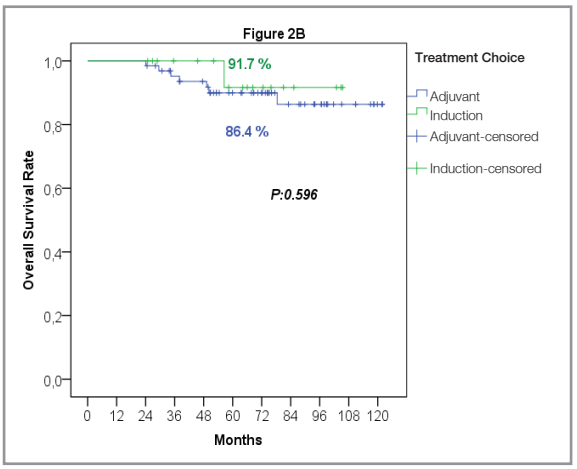

Figure 2B. Five-years Kaplan -Meier OS analysis according to treatment choice

Comparison of adjuvant or induction therapy for locally advanced disease (stage 3 and 4a) revealed 5-year DFS of 85.5% vs. 76.4%, respectively (p= 0.360). The corresponding 5-year OS were 86.4% vs. 91.7% (p= 0.596). Despite numerical differences in 5-year DFS and OS, these did not reach statistical significance (Figure 2A, B).

Based on the univariate analyses, visceral recurrence was associated with significantly shorter OS (HR: 0.06, 95% Confidence Interval (CI); 0.014-0.3, p < 0.001) (Table 2)

Again, when prognostic factors for DFS were examined with univariate analyses, N2-3 disease (HR: 2.33, 95% CI; 1.2-6.69, p= 0.017) and stage 3-4a disease (HR: 3.37, 95% CI: 1.01.-11.1, P= 0.047) were found to be associated with earlier recurrence (Table 3).

DISCUSSION

Nasopharyngeal cancer is a malignancy of the head and neck that exhibits significant geographical variations, with relatively lower incidence rates in non-endemic areas. The present study is one the largest studies of localized nasopharyngeal cancer from our region.

Presenting symptoms of nasopharyngeal cancer vary according to local and regional spread of the disease.[10,13] In the current study the most common presenting symptoms included swelling in the neck (40.9%), impaired hearing (22.7%), nasal obstruction (21.9%), and fullness sensation in the ear (9%).

In a previous large and retrospective cohort from an endemic region, the most common tumor histology was WHO (World Health Organization) Type 3 in 94.4% of the patients.[14] In another study from a non-endemic region, the reported histology was Type 1, 2, and 3 in 18.7%, 6.7%, and 74.7% of the subjects.[15] On the other hand, in our study from an non-endemic region, Type 1, 2, and 3 histological categories comprised 42.4%, 3%, and 54.5% of the cases, respectively.

In a large-scale study from Hong Kong, the disease stage at the time of diagnosis was Stage 1, 2, 3, 4a, and 4b in 7.7%, 17.7%, 47.7%, 16.1%, and 10.8% of the patients.[3] Again, the corresponding figures were 4.8%, 26.2%, 45.4%, 18.4%, and 5.2% in another report.[14] Similarly, among our patients 3.8%, 22.7%, 50.8%, and 22.7% had Stage 1, 2, 3, or 4a disease at the time of diagnosis.

In one comprehensive study from an endemic region, the 5-year OS was 81.1%, DFS was 82.6%, local recurrence free survival (RFS) was 95.4, and regional RFS was 92.9% after a median follow up of 58 months. Five-year DFS based on disease stage were 97.2%, 90.6%, 82.9%, 68%, and 69% for stage 1, 2, 3, 4a, and 4b, respectively. Despite numerical differences in OS, statistical significance was not reached.[14]

Table 2. OS univariate analysis

		N	Event	Hazard Ratio	95 % Confidence Interval (CI)	P value
Age		–	–	1.008	0.97-1.044	0.669
Gender	Male	90	13	1.381	0.78-2.42	0.261
	Female	42	4			
Histology	WHO type 1	50	6	1.277	0.47-3.45	0.630
	WHO type 2	4				
	WHO type 3	61	11			
Recurrence	*Non- viscerall*	*12*	*2*	*0.06*	*0.014-0.3*	*< 0.001*
	Visceral	*15*	*15*			
Smoke	Yes	78	11	0.712	0.26-1.92	0.505
	No	54	6			
T	T1-2	76	8	1.951	0.75-5.06	0.169
	T3-4	39	9			
N	N0-1	58	5	2.24	0.78-6.4	0.129
	N2-3	74	12			
Stage	Stage 1-2	35	2	2.92	0.66-12.8	0.154
	Stage 3-4	97	15			

The 5-year OS reported after chemoradiotherapy and/or induction, adjuvant therapy in different studies ranged between 68% and 94, while the reported PFS was between 58% and 74%.[16]

In our patient group, the 5-year OS for stage 1, 2, 3, and 4a disease was 100%, 92.5%, 81%, and 75.4%, respectively, while the respective 5-year DFS in the same groups was 100%, 89.4%, 72%, and 68.6%. In the overall patient group, the 5-year OS was 87.8% and 5-year DFS was 76.6%. Despite numerical these differences in OS and DFS between different stages, these were not significant , due to the small number of patients.

In our study, the most frequent sites of recurrence included the bone in 35.7%, lungs in 28.5%, liver in 21.4%, and local sites in 21.4%.

EBV infections are closely linked with nasopharyngeal carcinoma, with previous studies reporting higher rates of distant relapse and mortality in subjects with high levels of EBV DNA. A risk classification based on EBV DNA and disease stage was performed with the assumption that high risk patients would benefit more from neoadjuvant and adjuvant therapy.[9]

In one Phase 3 randomized study evaluating the induction therapy, although increased local control was associated with reduced distant metastasis, it did not appear to affect short term survival rate.[17] Again, in another Phase 3 randomized study, adjuvant treatment arm had a 5-year failure free survival (FFS) of 75%, which was not statistically different from that in the controls.[18]

In our study, 5-year DFS for adjuvant vs. induction therapy in locally advanced disease (Stage 3 and 4a) was 85.5% and 76.4%, respectively, while the corresponding figures for 5-year OS were 86.4% vs. 91.7%. However, differences were numerical, rather than being statistically significant.

In a multivariate analysis from an endemic region, skull base infiltration, gender, age, and T and N staging were reported to predict mortality as well as distant organ metastasis.[14] In another report involving patients with Stage 2 nasopharyngeal cancer, the single most important determinant of local-regional recurrence and survival was the lymph node (N) status.[19]

In a study assessing the long-term outcomes of induction chemotherapy, N3 and stage 4 disease were found to be associated with local failure and

Table 3. DFS, Univariate analysis

		N	Event	Hazard Ratio	95% Confidence Interval (CI)	P value
Age		-	-	0.993	0.96-1.02	0.610
Gender	Male	90	23	1.6	0.98-2.56	0.056
	Female	42	5	1		
Histology	WHO type 1	56	7	0.445	0.18-1.053	0.066
	WHO type 3	72	20	1		
Smoke	Yes	78	17	0.906	0.42-1.93	0.799
	No	54	11	1		
T	T1-2	84	17	1.11	0.52-2.37	0.786
	T3-4	48	11	1		
N	N0-1	58	7	1		
	N2-3	74	21	2.83	1.2-6.69	0.017
Stage 1-2		35	3	1		
Stage 3-4a		97	25	3.37	1.01-11.17	0.047

distant metastasis.[15] In our study, univariate analysis examining the factors that have an impact on OS suggested that visceral recurrence was significantly associated with shorter survival.

Again, a similar analysis for DFS showed that N2-3 and stage 3-4a disease were associated with earlier recurrence and distant metastasis. Despite the numerical associations of male gender as well as type 3 histology (undifferentiated carcinoma) with poor prognosis, the differences did not reach statistical significance.

Limitations

Limitations of our study include its retrospective design, relatively small sample size and low number of participating centers, and absence of EBV testing. Lack of treatment toxicities was one of the limitations of our study.

Conclusion

Previously large scale studies have been reported from endemic regions for nasopharyngeal carcinoma. In this regard, we believe that our retrospective study may represent a significant source of information from a non-endemic region, where this malignancy is relatively scarce; thus, reflecting real-life data. Local or locally advanced nasopharyngeal cancer is generally associated with a favorable survival. In the current study, the observed 5-year OS and DFS results based on current therapeutic modalities are similar to those reported in some previously published studies. Visceral recurrence was associated with poorer OS. In addition, N2-3 and stage 3-4a disease were associated with poorer DFS.

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