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Received: 12 November 2022 | Revised: 8 February 2023 | Accepted: 14 February 2023

DOI: 10.1002/hed.27333

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ORIGINAL ARTICLE

A multicenter retrospective analysis of patients with nasopharyngeal carcinoma treated in IMRT era from a nonendemic population: Turkish Society for Radiation Oncology Head and Neck Cancer Group Study (TROD 01-001)

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Section Editor: Michael Samuels

Abstract

Background: We aimed to evaluate patients with nasopharyngeal carcinoma (NPC) in a nonendemic population.

Methods: In a national, retrospective, multicenteric study, 563 patients treated with intensity modulated radiotherapy at 22 centers between 2015 and 2020 were analyzed.

Results: Median age was 48 (9–83), age distribution was bimodal, 74.1% were male, and 78.7% were stage III-IVA. Keratinizing and undifferentiated carcinoma rates were 3.9% and 81.2%. Patients were treated with concomitant chemoradiotherapy (48.9%), or radiotherapy combined with induction chemotherapy (25%) or adjuvant chemotherapy (19.5%). After 34 (6–78) months follow-up, 8.2% locoregional and 8% distant relapse were observed. Three-year overall survival was 89.5% and was lower in patients with age ≥50, male sex, keratinizing histology, T4, N3 and advanced stage (III-IVA).

Conclusions: Patients with NPC in Turkey have mixed clinical features of both east and west. Survival outcomes are comparable to other reported series; however, the rate of distant metastases seems to be lower.

KEYWORDS

chemoradiotherapy, EBV-DNA, intensity-modulated radiotherapy, nasopharyngeal carcinoma, nonendemic

1 | INTRODUCTION

Nasopharyngeal cancer (NPC) is a rare malignancy with global age-standardized incidence rates of 2.2 per 100 000 in men and 0.8 in women.[1] It differs from other head and neck cancers in terms of epidemiological features, histopathological subtypes, treatment and prognosis. Etiology mainly includes genetic, environmental factors and Ebstein–Barr virus (EBV) infection. Plasma EBV DNA measurement has been shown to be beneficial in diagnosis, prognosis, and treatment response in NPC.[2] It has a unique geographic distribution, endemic in Southeast Asia (15–50/100 000), but less common (0.2–0.5/100 000) in Western countries. The Mediterranean region, including Turkey, represents an intermediate incidence zone (1–5/100 000) for NPC.[1] In this region, the disease shows a bimodal age distribution with the first peak starting from adolescence.[3–5] World Health Organization (WHO) has defined three main histological subtypes; keratinizing squamous cell carcinoma (WHO type 1), differentiated nonkeratinizing carcinoma (WHO type 2a), or undifferentiated nonkeratinizing carcinoma (WHO type 2b). The nonkeratinizing undifferentiated type is seen in almost all cases in endemic regions, while the keratinizing type is common in the west.[6]

Radiotherapy (RT) is the standard treatment for NPC, as it is a radiosensitive tumor and not convenient for surgical resection. In last decades, 2D and 3D conformal RT techniques have been replaced by intensity-modulated radiotherapy (IMRT), which enables better tumor dose coverage and protecting critical structures within the RT field. It has been shown that IMRT has improved local control, overall survival and patients' quality of life.[7] While radiotherapy is effective in early-stage disease, combined chemoradiotherapy is the standard treatment in locally advanced disease.[8] The Intergroup 0099 study is the first to show improved overall survival and a reduction in recurrence and distant metastasis with the addition of concomitant and adjuvant chemotherapy.[9] In recent years, satisfactory results have also been obtained with the addition of induction chemotherapy to concomitant chemoradiotherapy.[10–12]

Due to advances in diagnostic methods (MRI/PET-CT), technological progresses in RT, and the addition of systemic therapy, survival rates of patients with NPC have increased, mainly due to the impressive locoregional control. However, distant metastases, seen in up to 30% of patients, are still a major problem.[13] Recent hot topic of NPC management is the control of distant

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metastasis. It is extremely important to identify which patients are at high risk of distant failure and who may benefit from intensive systemic therapy.

The clinical approach to patients with NPC has been mainly influenced by studies in endemic areas. Data from nonendemic populations are still very limited.[14,15] Further efforts should be made to cooperate with centers from nonendemic regions and to integrate globally with the endemic area. In this study, we aimed to increase the collaboration of centers across in a nonendemic country and to evaluate the patient and tumor characteristics, treatment approaches, survival outcomes, and side effects of patients with NPC treated in the IMRT era.

2 | METHODS

TROD 01-001 study is a multicenteric retrospective evaluation of patients with NPC who received IMRT ± chemotherapy between January 2015 and December 2020. Inclusion criteria was as follows: (a) histologically confirmed nasopharyngeal carcinoma, (b) radiotherapy technique should be IMRT, (c) no evidence of distant metastases. The study protocol was approved by the ethics committee of Acıbadem University (2017-19/17).

Data were collected via online patient forms. A total of 701 patient data were submitted from 22 radiotherapy centers in Turkey, primarily from Istanbul (41%). After excluding patients who were treated with non-IMRT radiotherapy methods, with less than 6 months of follow-up and who were oligometastatic at the time of diagnosis, 563 patients were included in the final analysis. Data were collected from 13 university, 6 public, and 3 private hospitals. The median number of patients included per center was 25 (10–57). All patients were staged according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. The Common Terminology Criteria for Adverse Events (CTCAE) v4.0 was used for grading acute side effects.

2.1 | Statistical analysis

Data analysis was performed using the Statistics Package for Social Science (SPSS 23.0; IBM, New York, NY). Patient characteristics were reported as *n* (percent) or median (minimum–maximum) for categorical and continuous variables, respectively. Overall survival (OS), disease-free survival (DFS), locoregional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS) times were calculated from diagnosis to last follow-up or death, to last follow-up or to any event, to last follow-up or locoregional recurrence and, to last follow-up or to distant metastasis, respectively. Kaplan–Meier curves for overall survival, disease free survival, local recurrence, and metastasis were plotted. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for each prognostic factor. Risk factors were identified by univariate and multivariate analysis using the cox regression model. Factors that were statistically significant in the univariate model were included in the multivariate model. The *p*-value was set at <0.05 for statistical significance.

3 | RESULTS

The median age of the patients was 48 (9–83) years. Thirty one (5.5%) were younger than 18 years old. The age–incidence curve revealed a bimodal age distribution with a threshold value of 27. The first and second peaks were observed at the ages of 16–20 and 46–54, respectively (Figure 1). Tumoral EBV-encoded small RNA

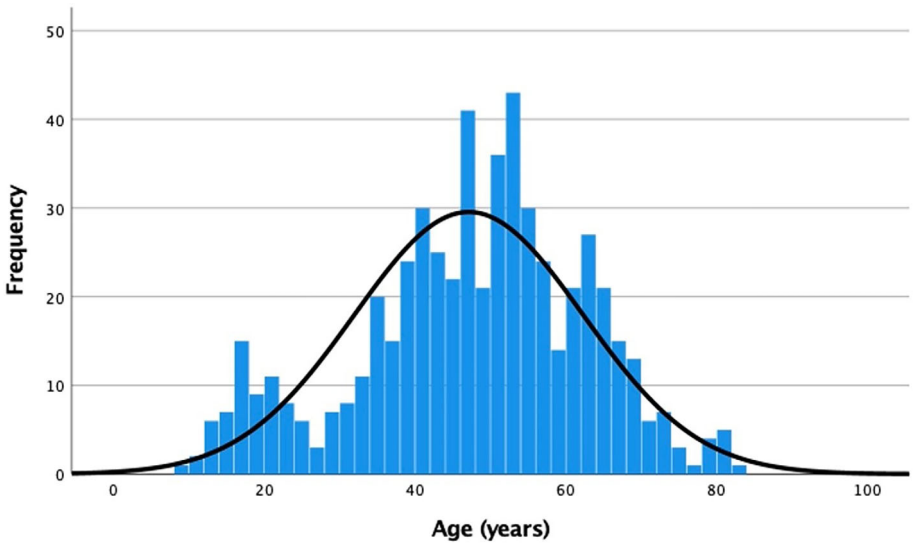


FIGURE 1 Histogram of age distribution [Color figure can be viewed at wileyonlinelibrary.com]

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TABLE 1 Patient and disease characteristics

	n (%)
Age (years)	
<50	292 (51.9)
≥50	271 (48.1)
Sex	
Female	146 (25.9)
Male	417 (74.1)
ECOG performance status	
0–1	491 (87.2)
2–3	14 (2.5)
Unknown	58 (10.3)
Smoking status	
≥10 pack/years	192 (34.1)
<10 pack/years	79 (14.0)
Nonsmoker	227 (40.3)
Unknown	65 (11.5)
Alcohol consumption	
Regular	28 (5.0)
Social	71 (12.6)
Never	379 (67.4)
Unknown	84 (14.9)
Histology	
Keratinizing	22 (3.9)
Nonkeratinizing-differentiated	68 (12.1)
Nonkeratinizing-undifferentiated	457 (81.2)
Unknown	16 (2.8)
EBV-DNA (copy/ml)	
<4000	125 (22.2)
≥4000	48 (8.5)
Unknown	390 (69.3)
T stage	
T1	126 (22.4)
T2	217 (38.5)
T3	112 (19.9)
T4	108 (19.2)
N stage	
N0	77 (13.7)
N1	109 (19.4)
N2	290 (51.5)
N3	87 (15.5)
AJCC 8th staging	
1	16 (2.8)
2	104 (18.5)
3	260 (46.2)
4A	183 (32.5)

(EBER), human papilloma virus (HPV), and baseline plasma EBV-DNA were assessed in 28.6%, 11%, and 30.7% of the patients, with positive rates of 86.3%, 7%, and 63.6%, respectively. The median value of baseline plasma EBV-DNA was 2.439 (53-195.791) copy/ml. Plasma EBV-DNA level was correlated with overall stage ($p = 0.029$) and N stage ($p = 0.010$), but not T stage ($p = 0.166$). The majority of the study population was in locally advanced stages (78.7%). Staging was mostly done with PET-CT (91%) and MRI (90%). A total of 58 cranial nerve palsies observed in 47 (8.3%) patients at presentation. The abducens nerve was the most common affected nerve (29.3%). Patients and disease characteristics are summarized in Table 1.

3.1 | Radiotherapy

All patients were treated with IMRT. Half of the patients (50.4%) were treated with volumetric modulated arc therapy (VMAT), and the rest with dynamic IMRT. Simultaneous integrated boost (SIB) was used in 465 (82.6%). The median volume of primary gross tumor volume (GTV-p) and nodal gross tumor volume (GTV-n) were 22.8 cc (1.2–250) and 22 cc (0.7–269), respectively. The median dose prescribed to GTV-p was 70 Gy (60–70.2) and the median dose prescribed to GTV-n was 70 Gy (54–70.2). The median dose for intermediate lymphatic risk regions was 60 Gy (54–66). Low-risk lymphatic region was treated with a median dose of 54 Gy (45–60). Some patients' radiotherapy doses were reduced based on age, response to chemotherapy, and tumor volume due to toxicity concerns. In most pediatric patients, GTV-p and GTV-n were reduced to 60–66 Gy depending on the chemotherapy response. GTV-n was reduced to 54 and 56 Gy in only two patients. In adult patients, GTV-p was reduced to 66 Gy in only a few patients, and GTV-n was reduced to 66 Gy in some patients due to bulk volume. Similarly, doses of 54–60 Gy and 45–54 Gy were prescribed to intermediate and low-risk lymphatic regions in some pediatric patients. Adaptive radiotherapy was performed in 86 (15.3%) patients. Reasons for re-planning were weight loss in 33 (38.4%), tumor shrinkage in 15 (17.4%), and both in 28 (32.6%) patients. The median radiotherapy fraction time for adaptive planning was 22 (9–28). IGRT was executed using daily/weekly CBCT (19.4%), kV-kV (6%), and both (41.2%). MV portal image was used in remaining patients. Treatment characteristics are given in Table 2.

3.2 | Chemotherapy

The majority (85%) of the patients had concomitant chemotherapy with 30–40 mg/m^2 cisplatin weekly or 75–

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TABLE 2 Treatment characteristics

	n (%)
Treatment	
RT	29 (5.2)
CRT	275 (48.9)
IC + RT/CRT	141 (25.0)
CRT + AC	110 (19.5)
IC + RT/CRT + AC	8 (1.4)
Type of IMRT	
Conventional IMRT	199 (35.4)
VMAT	284 (50.4)
Tomotherapy	61 (10.8)
Hybrid	19 (3.4)
Adaptive planning	
Absent	477 (84.7)
Present	86 (15.3)
Concomitant chemotherapy agent	
Cisplatin	479 (96.0)
Other	20 (4.0)
Concomitant chemotherapy timing	
Weekly	310 (61.9)
3 weekly	191 (38.1)
Cumulative dose of concomitant cisplatin (mg/m^2)	
≥200	228 (53.5)
<200	198 (46.5)

Abbreviations: AC, adjuvant chemotherapy; CRT, chemoradiotherapy; RT, radiotherapy; IC, induction chemotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy.

100 mg/m^2 cisplatin every 3 weeks starting on the first day of RT. Cumulative cisplatin dose was ≥200 mg/m^2 in 228 (53.5%) of these (Table 2). Nearly half of the patients (46%) received induction and/or adjuvant chemotherapy. The most common regimen for induction chemotherapy was TPF (75 mg/m^2 docetaxel and 75 mg/m^2 cisplatin on Day 1 and 750 mg/m^2 5-Fluorouracil on Days 1–5 every 3 weeks) and PF (80 mg/m^2 cisplatin on Day 1 and 800–1000 mg/m^2 5-Fluorouracil from Day 1 to Days 4–5) for adjuvant chemotherapy. Majority of the patients (>70%) had 3 cycles of induction or adjuvant chemotherapy (Table 3).

3.3 | Follow-up

The patients were followed-up according to the protocols of the institution where they were treated. The follow-up period was ended on 1 July 2021. The median follow-up time was 34 (6–78) months. After completion of treatment, patients were re-evaluated with MRI at 1.5–3 months and/or PET-CT at 3–4 months, 94% had a complete/near complete response. Plasma EBV-DNA levels was re-assessed in 96 (17.1%) patients. Among 96, 86 (90%) were negative and 10 (10%) were positive at the end of radiotherapy. In addition to physical examination, 511 (90.8%) patients were followed-up with MRI, 394 (70%) patients with endoscopic examination, and 15 (2.7%) patients with computerized tomography. PET-CT was also used for response assessment in 457 (81.2%) of them. While histological confirmation was performed for locoregional failures, radiological finding was considered sufficient for distant metastasis.

TABLE 3 Induction and adjuvant chemotherapy regimens and cycles

	Induction CT, *n* (%)	Adjuvant CT, *n* (%)
CT regimen		
TPF	80 (53.7)	14 (11.9)
PF	17 (11.4)	81 (68.6)
TP	17 (11.4)	
GP	16 (10.7)	4 (3.4)
Other	19 (12.7)	19 (16.1)
Number of cycles		
1	2 (1.3)	6 (5.1)
2	22 (14.8)	16 (13.6)
3	105 (70.5)	87 (73.7)
>3	20 (13.4)	9 (7.6)

Abbreviations: CT, chemotherapy; F, fluorouracil; G, gemcitabine; P, cisplatin; T, taxane.

3.4 | Outcomes

Overall disease progression was observed in 81 (14.4%) patients, including 46 (8.2%) locoregional recurrence and 45 (8%) distant metastases. Locoregional recurrences were observed in the primary site in 24 (4.3%), in the nodal regions in 10 (1.8%), and both in 12 (2.1%) patients. 43.5% of locoregional recurrences occurred after 2 years, particularly in the 4th year (26.1%). Majority of the distant metastases (84.4%) were seen within 2 years. Fifty nine (10.5%) patients expired, 37 (6.6%) were due to disease progression, and 22 (3.9%) were due to other causes. Three years of OS, DFS, LRRFS, and DMFS were found; 89.5%, 85.6%, 92.8%, and 90.8%, respectively (Figure 2).

In univariate analysis; older age (≥50) and keratinizing histology were significantly associated with inferior

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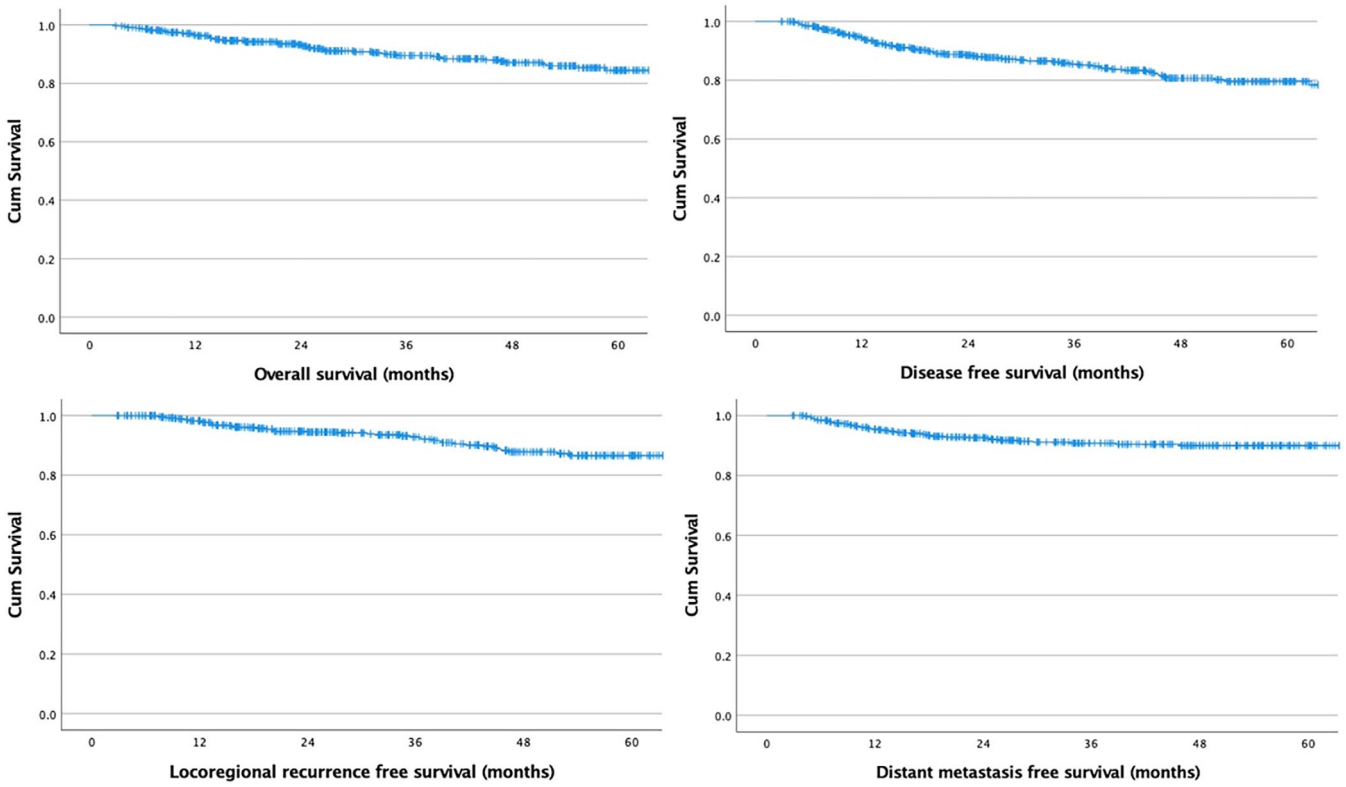


FIGURE 2 Overall, disease-free, locoregional recurrence-free, and distant metastasis-free survival curves [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Acute and late side effects

Acute side effects	Grade 1–2, *n* (%)	Grade 3–4, *n* (%)
Mucositis	337 (59.9)	109 (19.4)
Dysphagia	336 (59.7)	93 (16.5)
Dermatitis	355 (63.1)	27 (4.8)
Xerostomia	242 (43.0)	23 (4.1)
Nausea	174 (30.9)	26 (4.6)
Hematologic	127 (22.6)	25 (4.4)
Late side effects		***n* (%)**
Xerostomia		225 (40.0)
Ototoxicity		135 (24.0)
Caries		36 (6.4)
Neck fibrosis		29 (5.2)
Dysphagia		25 (4.4)
Chronic sinusitis		20 (3.6)
Endocrinologic		18 (3.2)
Trismus		7 (1.2)
Temporal lobe necrosis		5 (0.9)
Cranial nerve damage		4 (0.7)

OS and LRRFS. Male sex was also found to be a prognostic factor for lower OS. Patients with stages 3 and 4a had inferior OS and DMFS than patients with stage 1. Patients with stage T4 had inferior OS, LRRFS and DMFS than patients with stage T1, whereas patients with stage N3 have lower rates of OS and DMFS than patients with stage N0 (Table 4). Three-year LRRFS for patients with stage T1–T4 was 92.8%, 96%, 95.4%, and 82.7% (p:0.007). Three-year DMFS for patients with stage N0–N3 was 97.9%, 94.4%, 90.8%, and 80.2% ($p < 0.001$), respectively (Figure 3). Patients treated with induction and/or adjuvant chemotherapy had worse DMFS rates than others (3 year; 87.3% vs. 93.6%, $p = 0.034$). However, the ratio of locally advanced stage patients was higher in patients who received induction and/or adjuvant chemotherapy (91.1% vs. 68.1%, $p < 0.001$).

In multivariate cox regression analysis, advanced age was associated with inferior OS (HR: 2.4 (1.4–4.1), $p = 0.003$) and locoregional disease control (HR: 2.1 (1–3, 9), $p = 0.019$). T stage was found to be a risk factor for locoregional disease control (T4 vs. T1, HR: 2.4 (1.0–5.4), $p = 0.039$).

3.5 | Treatment at locoregional recurrence

Of the 24 patients with relapse only in the nasopharynx, 16 received full-dose (60 Gy) re-irradiation, two underwent nasopharyngectomy, and the remainder

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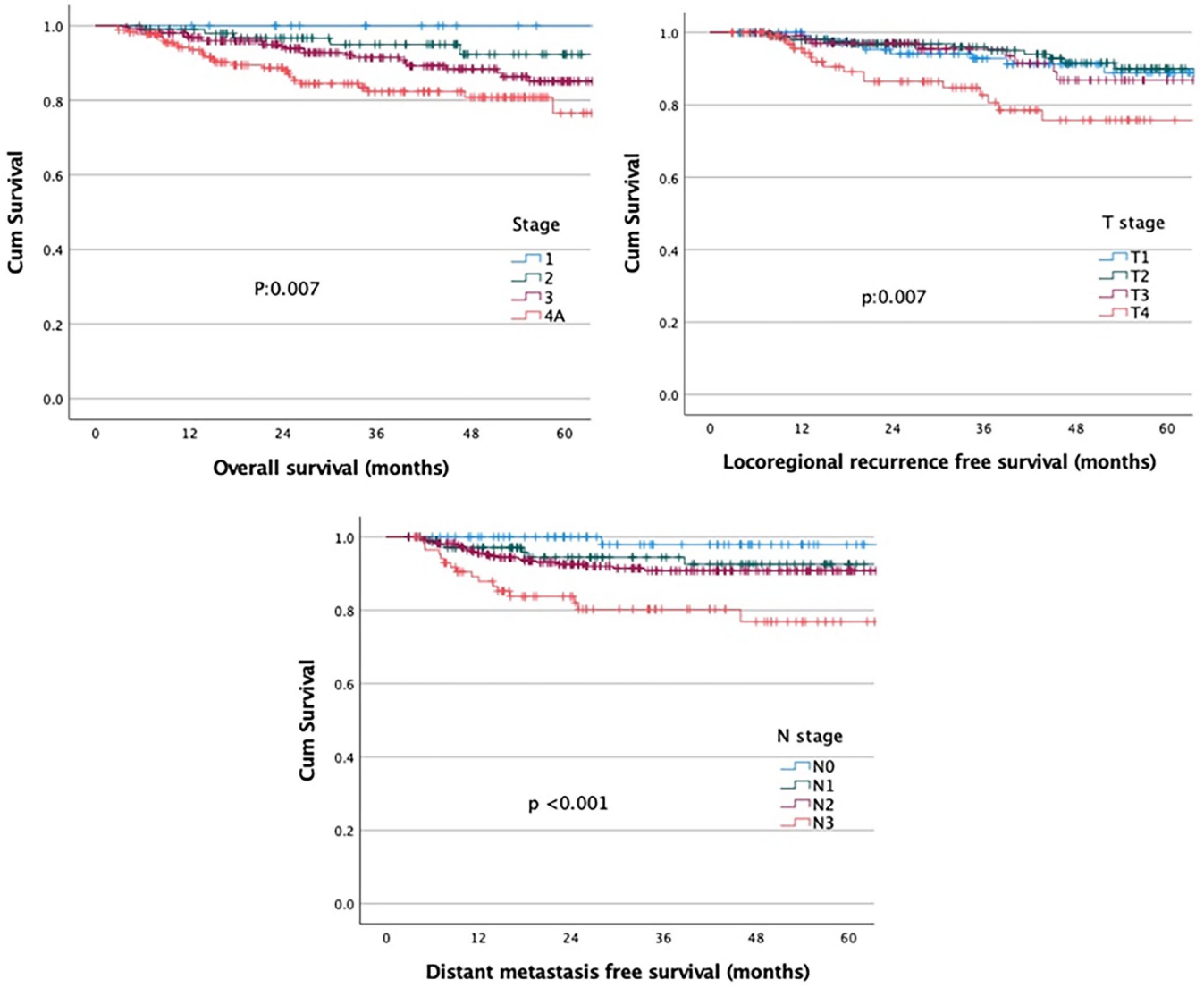


FIGURE 3 Overall survival for AJCC 8th stage, locoregional recurrence-free survival for T stage, distant metastasis-free survival for N stage [Color figure can be viewed at wileyonlinelibrary.com]

underwent palliative chemotherapy and/or RT. Neck dissection was performed in 6 of 10 patients with relapses in regional lymphatics only, and palliative chemotherapy and/or RT in 4 patients. Seven of 12 patients with both local and regional relapses were treated with palliative content, while 3 and 2 patients underwent re-irradiation and neck dissection, respectively.

3.6 | Side effects

Grade ≥3 acute oral and pharyngeal mucositis were seen 19.4% and 16.5%, respectively. Any grade of xerostomia and hearing loss/serous otitis were comprising 64% of late toxicity (Table 5).

4 | DISCUSSION

Nasopharyngeal carcinoma incidence in Turkey between 2014 and 2017 was 1.2/100 000 in men and 0.4/100 000 in women.[16] The availability of high-tech radiotherapy facilities in the country has increased significantly over the past decade, and IMRT has become the most widely used technique in radiotherapy centers nationwide.[17] This multicentric retrospective study is the most comprehensive case series of nasopharyngeal carcinoma treated with IMRT to date in Turkey.

The age distribution of our study population shows a bimodal characteristic. Data from population-based cancer registries also showed a first peak in 15–24 years, followed by a second peak at 65–79 years in low-risk geographic areas. The first peak was explained by a major

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TABLE 5 Univariate Cox proportional hazards regression analyses

	OS		DFS		LRFS		DMFS	
Characteristic	**HR (95%CI)**	***p*-value**	**HR (95%CI)**	***p*-value**	**HR (95%CI)**	***p*-value**	**HR (95%CI)**	***p*-value**
Age								
<50	Ref.		Ref.		Ref.		Ref.	
≥50	**2.4 (1.4–4.1)**	**0.001**	1.4 (0.9–2.2)	0.117	**2.3 (1.3–4.3)**	**0.006**	1.2 (0.7–2.2)	0.534
Sex								
Female	Ref.		Ref.		Ref.		Ref.	
Male	**2.0 (1.0–3.9)**	**0.050**	1.5 (0.9–2.6)	0.129	1.2 (0.6–2.3)	0.638	1.8 (0.8–3.8)	0.140
AJCC stage 8th								
1	Ref.		Ref.		Ref.		Ref.	
2	1.1 (0.7–3.3)	0.969	1.0 (0.1–8.3)	0.997	0.6 (0.1–5.7)	0.691	1.1 (0.9–2.7)	0.973
3	**1.8 (1.1–3.1)**	**0.008**	2.1 (0.3–15.4)	0.462	1.3 (0.2–9.4)	0.824	**2.7 (1.4–5.0)**	**0.002**
4A	**3.6 (1.4–9.3)**	**0.027**	4.8 (0.7–35.2)	0.119	2.3 (0.3–17.2)	0.413	**5.6 (1.7–18.5)**	**0.005**
T stage								
T1	Ref.		Ref.		Ref.		Ref.	
T2	1.1 (0.5–2.3)	0.755	1.2 (0.6–2.2)	0.563	0.9 (0.4–2.1)	0.781	1.7 (0.7–4.0)	0.245
T3	0.9 (0.4–2.3)	0.950	0.9 (0.4–2.0)	0.909	1.1 (0.4–2.8)	0.866	1.0 (0.3–3.0)	0.989
T4	**2.5 (1.2–5.2)**	**0.018**	**2.5 (1.3–4.7)**	**0.005**	**2.7 (1.2–6.1)**	**0.017**	**2.6 (1.0–6.5)**	**0.043**
N stage								
N0	Ref.		Ref.		Ref.		Ref.	
N1	2.7 (0.7–9.5)	0.135	0.6 (0.2–1.4)	0.240	0.4 (0.1–1.1)	0.086	4.6 (0.5–38.2)	0.158
N2	2.8 (0.9–9.1)	0.089	0.9 (0.5–1.9)	0.959	0.6 (0.3–1.2)	0.158	6.2 (0.8–45.8)	0.075
N3	**4.2 (1.2–14.9)**	**0.024**	1.9 (0.9–4.0)	0.070	0.7 (0.3–1.8)	0.410	**16.2 (2.2–122.4)**	**0.007**
Treatment								
RT/CRT	Ref.		Ref.		Ref.		Ref.	
CRT + Ind/Adj	1.0 (0.6–1.7)	0.922	1.4 (0.9–2.2)	0.120	1.1 (0.6–2.0)	0.682	**1.9 (1.0–3.4)**	**0.037**
Histology								
Nonkeratinizing	Ref.		Ref.		Ref.		Ref.	
Keratinizing	**4.4 (2.0–9.8)**	**<0.001**	2.1 (0.8–5.2)	0.113	**4.6 (1.8–11.9)**	**0.001**	0.6 (0.1–4.3)	0.606
EBV-DNA (copy/ml)								
<4000	Ref.		Ref.		Ref.		Ref.	
≥4000	1.2 (0.4–3.5)	0.700	1.2 (0.5–2.8)	0.740	0.6 (0.1–2.6)	0.475	1.8 (0.7–5.2)	0.247
Concurrent cisplatin dose (mg/m^2)								
≥200	Ref.		Ref.		Ref.		Ref.	
<200	1.0 (0.6–1.9)	0.875	0.8 (0.5–1.2)	0.280	0.6 (0.3–1.2)	0.175	0.7 (0.4–1.3)	0.253
GTV primary (cc)	1.01 (1.0–1.02)	0.093	1.01 (1.0–1.02)	0.105	1.01 (1.0–1.02)	0.080	1.01 (1.0–1.02)	0.478
GTV nodal (cc)	1.01 (1.0–1.02)	0.139	1.01 (1.0–1.02)	0.095	1.01 (1.0–1.02)	0.296	1.01 (1.0–1.02)	0.193
RT time (day)	0.99 (0.95–1.03)	0.680	0.99 (0.96–1.03)	0.765	1.01 (0.97–1.05)	0.669	1.01 (0.98–1.05)	0.468

Note: Bold values are statistically significant ($p < 0.05$).

Abbreviations: AC, adjuvant chemotherapy; CRT, chemoradiotherapy; GTV, gross tumor volume; IC, induction chemotherapy; RT, radiotherapy.

genetic susceptibility and exposure to EBV during adolescence, while the second peak was thought to be due to cigarette/alcohol consumption and environmental/occupational carcinogens in addition to minor genetic

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predisposition. In regions with a high incidence, latent EBV infection and other environmental carcinogens have been accused in individuals with minor genetic susceptibility.[18] The prevalance and latency period of EBV differ between countries and EBV-related tumors. Therefore, the time to malignant transformation and peak ages may be different.[19] We observed the first peak at ages 16–20 as in nonendemic populations, and the second peak at ages 46–54, similar to endemic areas. This may be because our patient population has similar genetic predisposition to nonendemic areas and environmental factors/EBV latent period similar to endemic areas. This mixed epidemiological features postulation may also explain the histologic distribution as well. While type WHO 1 incidence (3.9%) was lower than western countries (21–25%), undifferentiated type (81%) was lower than endemic areas (>94%).[9,13,20] Similar to the literature, local control (3 year; 72.5% vs. 93.2% and 94.0%, $p = 0.002$) and OS (3 year; 71.9% vs. 93.2% and 90.2%, $p < 0.001$) were lower in keratinizing subtype versus differentiated and undifferentiated carcinomas.[21] A report from nonendemic part of China reported that the differentiated type was more common in northwest China and had a lower LRRFS (86.6%) and DMFS (85.7%) than the undifferentiated type.[22] However, we did not find any survival difference between differentiated and undifferentiated carcinomas. There is also finding about the impact of race in certain histologic types of NPC. Asian patients have found to be superior survival than white patients among patients with keratinizing and differentiated nonkeratinizing histology, while similar survival rates were observed in all patients with nonkeratinizing undifferentiated histology.[23] Recent data from genome-wide association studies in China estimated the heritability of NPC is around 10%.[24] Family history of our cohort is very low (0.9%) in contrast to Southeast Asia (10%).[13]

Tumoral EBER and plasma EBV-DNA were assessed in one third of our patients with a positivity rates of 86.3% and 63.6%, which was lower than reported in endemic areas. Despite the fact that plasma EBV-DNA level is a validated prognostic factor for NPC, a recent review by Lee AW reported that 12%–29% of patients may have undetectable plasma EBV-DNA levels at presentation.[25] Negativity rates of 10%–52% have also been described in nonendemic countries.[26] Two recent studies from the Mediterranean area found plasma EBV-DNA levels to be prognostic for OS. A study conducted in Casablanca reported a median viral load of 7710 IU/ml with a positivity of 90.9%.[27] Another from Milan reported a median viral load of 554 copy/ml with 79.2% positivity ratio.[28] We found a median viral load of 2439 copy/ml and correlated with overall stage and N stage. Although real-time quantitative PCR assays in this study were performed in experienced and accredited laboratories, there may be interlaboratory variations without harmonization.[29] The results of plasma EBV-DNA measurements in the study should be interpreted in caution. Proposals have also been made in the literature to integrate EBV-DNA levels into NPC staging.[30] Ongoing studies exploring individualized treatment strategies based on post-treatment EBV-DNA level will demonstrate the utility of this biomarker.[31] In our cohort, only 17% of patients assessed after treatment with a positivity rate of 10%. We were unable to perform detailed analysis due to inadequate numbers, however, we found a lower propensity for DFS ($p = 0.065$) in patients with proceeding plasma EBV-DNA level. It would be beneficial to increase the pre/post treatment evaluation rates of plasma EBV-DNA across the country.

Interestingly, both locoregional recurrence and distant metastasis rates were 8% in our study. Similar low metastasis rate (4%) was reported from Canada over 15 years period.[14] Most studies reported the common failure pattern of distant metastasis up to 30%. It is not clear why our patients have lower rates of distant metastasis. Most of the patients (90%) received concomitant chemotherapy, half of the patients received induction and/or adjuvant chemotherapy with a compliance rate of 70% for all 3 cycles. A recent multicentric cohort study from nonendemic areas found that intensive treatment, such as induction or adjuvant chemotherapy in addition to chemoradiotherapy yielded better DFS in EBER+ NPC patients, but not in EBER− ones.[15] Although we could not demonstrate any statistically significant benefit of intensive chemotherapy in addition to backbone of chemoradiotherapy, intensive chemotherapy may have lowered the possible distant metastasis rates. Second, the use of MRI and PET-CT at high rates (>90%) for staging can detect microscopic distant disease at the time of diagnosis, which we excluded in this study. In addition, advanced imaging technology can result accurate radiation therapy planning which can implement higher doses to even smaller involved lymph nodes. Finally, a median follow-up of 3 years may not be sufficient to detect distant metastasis and longer follow-up may be required. However, most of the distant metastases in this study occurred within the first year. On the other hand, a significant proportion of regional recurrences (43.5%) were observed after the second year. We could not find any prognostic factors for late locoregional recurrences. Tumor biology could be the possible reason for late recurrences. A similar observation of late local relapses was reported from Memorial Sloan-Kettering Cancer Center in New York. Close follow-up as they have mentioned may be useful till 5th year.[32]

In our study AJCC 8th staging predicted OS outcomes fairly well. However, the differences between T1–T3 and N1–N2 are not clear. Advances in NPC treatment, have reduced the importance of T and N staging, particularly

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in lower stages. Lee et al. proposed a simplified T and N staging with merging T2 and T1, and merging all cervical/retropharyngeal nodes <6 cm above the supraclavicular fossa as N1, regardless of their laterality. Their data showed that these patient subgroups had high disease control rates, and it was also possible to omit chemotherapy.[33] By supporting this, a big data from Hong Kong in the modern era revealed that, IMRT yields excellent 8 year local control rates of >87% in T1–T3 tumors but lowered for T4 tumors (71.6%). Also excellent regional control rates of more than 90% were reported for N0–N2 tumors, dropping to 76.4 and 81.8% for N3a-b according to AJCC 7th.[34] Poor survival outcomes of stage N3 were also noted in a large nonendemic data.[35] A recent validation study reported better predictive models with 8th staging, although T2 and T3 survival curves were similar.[36] In parallel, a nonendemic cohort from China was reported to have better prognostic separation for 8th classification in global stage and N stage, but not T stage.[37] As the success of NPC treatment increases, possible improvements in staging may be made in the future.

The most common acute side effects in our study population were grade 1–2 oral/pharyngeal mucositis and dermatitis, which is similar to other reports.[22,38] Grade 3–4 oral/pharyngeal mucositis was also seen in the range of 16%–19%. It would be beneficial to conduct preventive researches on this subject. For late side effects, any grade of xerostomia and ototoxicity were observed 40% and 24%, respectively. Longer follow-up is needed to find exact rates of late toxicities.

4.1 | Limitations

Due to the retrospective nature of the study, we cannot rule out treatment bias. In addition, one-third of the patients were followed for less than 2 years. Updated results will be useful in future. Lastly, the absence of plasma EBV-DNA level in two-thirds of the patients and the absence of central laboratory plasma EBV-DNA assessment do not allow a clear interpretation. More data is needed on this subject. However, the study addresses the epidemiological patterns and treatment characteristic of patients with NPC in a nonendemic population.

5 | CONCLUSION

Patients with NPC in Turkey have mixed epidemiological features of the east and west. T4 stage is a major challenge for locoregional control. Overall survival and locoregional failure rates are comparable to other series reported, but the rate of distant metastases is lower than other series. Further follow-up is required for interpretation.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The study protocol was approved by the ethics committee of Acıbadem University (2017-19/17).

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How to cite this article: Yildirim HC, Kupik GE, Mustafayev TZ, et al. A multicenter retrospective analysis of patients with nasopharyngeal carcinoma treated in IMRT era from a nonendemic population: Turkish Society for Radiation Oncology Head and Neck Cancer Group Study (TROD 01-001). *Head & Neck*. 2023;1-12. doi:10.1002/hed.27333

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