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The goal of primary therapy in non-metastatic nasopharyngeal cancer should be radiological complete response

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Abstract

Background: We aimed to investigate the effect of radiological complete response on survival outcomes in patients with non-metastatic nasopharyngeal cancer. This study is conducted as a retrospective cohort. Of the 185 patients screened, 60 were metastatic, 25 patients' data was not available, and as a result, 92 patients were included in the study. Among the complete response (CR) and incomplete response (IR) groups, overall survival (OS), distant metastasis-free survival (DMFS), and locoregional failure-free survival (LRFFS) were evaluated.

Results: Of the 92 patients, 54 (58.6%) were CR and 38 (41.4%) were IR patients. Of the whole study group, the 5-year OS, DMFS, and LRFFS rates were 75%, 78%, and 95%, respectively. A significant difference was found between the 5-year OS (90% vs. 60%, $p=0.001$) and DMFS (87% vs. 65%, $p=0.02$) rates. However, there was no significant difference in the 5-year LRFFS rate (97% vs. 92%, $p=0.16$). Complete response were determined as an independent predictor for OS (HR: 0.13, 95% CI: 0.045–0.36, $p<0.001$) and DMFS (HR: 0.26, 95% CI: 0.095–0.744, $p=0.012$).

Conclusion: As a result, the survival benefit in patients with CR after primary treatment is evident as shown in the above studies. Therefore, the aim of primary treatment should be to increase the CR rates. It is important to evaluate early tumor response to determine poor tumor regression.

Keywords: Non-metastatic nasopharyngeal cancer, Predict, Radiological complete response

Background

Nasopharyngeal cancer (NPC) is an epithelial carcinoma arising from the mucosal layer of the nasopharynx. In 2020, 133,354 new cases and 80,008 deaths were reported around the world. The etiology of NPC is multifactorial, it varies according to geographical regions. Nasopharyngeal cancer is endemic in southern China, Southeast Asia, the Arctic, and the Middle East/North Africa. It is rare in the USA and Western Europe [1, 2]. Risk in endemic populations is associated with Epstein-Barr virus (EBV) infection, environmental factors, and genetic predisposition. In the USA and Europe, the risk is associated with alcohol and smoking, similar to other head and neck tumors [3, 4]. According to the World Health Organization (WHO), there are three pathological subtypes of nasopharyngeal carcinoma: keratinized squamous cell carcinoma (sporadic), non-keratinized (differentiated and undifferentiated, associated with EBV in endemic areas), and basaloid squamous cell carcinoma (with poor prognosis) [5]. Stage I disease is treated with radiotherapy alone, locally advanced stage disease (stage II–IVa) with concomitant chemoradiotherapy (CRT) [6, 7]. Tumor response is an indicator of treatment efficacy and patient prognostic factors. There is a difference between the rate of tumor responses and the survival rate. It has been reported in the literature

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that the survival rate of cases with complete response is 75.5% and 90% [8, 9]. The number of studies investigating the relationship between tumor response and survival in NPC is limited. Also, these studies in the literature have always been reported from the endemic region.

We aimed to investigate the effect of radiological complete response on survival outcomes in patients with non-metastatic NPC.

Methods

This study is conducted as a retrospective cohort. Non-metastatic NPC patients were obtained from our Medical Oncology policlinic. A total of 185 NPC patients were determined between January 2010 and December 2020. Nasopharyngeal carcinoma patients who received induction chemotherapy (CT) followed by CRT or definitive CRT followed by adjuvant CT or radiotherapy (RT) alone were included study. Patients with distant metastases were not included in the study. Of the 185 patients screened, 60 were metastatic, 25 patients' data was not available, and as a result, 92 patients were included in the study. The Necmettin Erbakan University Meram Faculty of Medicine ethics committee approval was obtained (Approval number: 2021/3072). Clinical staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC 8) staging system. Complete response (CR) was defined as the disappearance of the target lesion (target neck pathological lymph node diameter < 10 mm, short retropharyngeal lymph node diameter < 5 mm). The incomplete response (IR) was defined as the response to stable disease (SD) (neither enough shrinkage to qualify as a partial response nor sufficient increase to qualify as progression) or a partial response (a reduction of at least 30% in the longest diameter of the lesion). Complete and incomplete response (stable and partial response) status was determined according to Response Evaluation Criteria on Solid Tumors (RECIST) criteria. The data collected were age, gender, smoking, T stage, N stage, histological type, and RT simultaneous cisplatin dose. Among the CR and IR groups, overall survival (OS), distant metastasis-free survival (DMFS), and locoregional failure-free survival (LRFFS) were evaluated.

The Kolmogorov–Smirnov test was used to analyze the distribution of study data. An independent *t* test was performed for continuous variable and presented as mean ± standard deviation. Chi-square test was used to compare categorical data in study groups. OS was defined as "the time from diagnosis of NPC to death." Kaplan–Meier curves were used to calculate survival and a log-rank test was used to compare survival distribution between groups. The multivariate Cox regression model was used to estimate the hazard ratio (HR). Covariates included age, gender, T and N stage, smoking, RT concurrent cisplatin dose, and treatment response status (CR and IR). MedCalc statistical software (Version 15.2) package was used for all analyses. A p value of < 0.05 is considered as statistically significant.

Results

Of the 92 patients, 54 (58.6%) were CR and 38 (41.4%) were IR patients. The number of male patients in the CR group was 36 (66.7%), 18 (33.3%) were female, the number of male patients in the IR group was 31 (81.6%), 7 (18.4%) were female ($p = 0.11$). The mean age of the patients was 45.9 ± 14.5 in those in the CR group and 48.3 ± 11.9 in those in the IR group. Only 32 (34.8%) of the patients received induction CT. Sixteen (29.6%) of the patients with a CR and 16 (42.1%) of those with an IR had received induction CT ($p = 0.21$). There were only 4 patients who received definitive RT (two patients each in the CR and IR groups). There were 88 patients who received definitive CRT (52 patients in the CR group and 36 patients in the IR group) ($p = 0.71$). Twenty-one (38.9%) patients in the CR group and 11 (28.9%) patients in the IR group received adjuvant CT ($p = 0.58$). In the study group, 46 (54.1%) patients received 40 mg/m^2 dose of cisplatin administered weekly concurrently with RT, 39 (45.9%) patients received 100 mg/m^2 dose of cisplatin administered once every 3 weeks concurrently with RT. There was no difference between the CR and IR groups ($p = 0.16$). Also, there was no difference in gender, age, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), smoking, clinical stage, T stage and N stage at the time of diagnosis between the CR and IR groups ($p = 0.38$, $p = 0.47$, $p = 0.82$, $p = 0.74$, $p = 0.33$, $p = 0.91$, respectively). There was the most undifferentiated carcinoma histological subtype in the CR and IR groups, but was not statistically significant ($p = 0.13$). The CR and IR rates were 58.7% and 41.3%, respectively. Recurrence occurred in 24 (25.1%) of 92 patients, 9 (37.5%) patients were in the CR group and 15 (62.5%) patients were in the IR group ($p = 0.014$). Seven (7.6%) of the recurrent patients had local recurrence (3 in the CR group and 4 in the IR group), 17 (18.5%) had distant metastasis (6 in the CR group and 11 in the IR group. The most distant metastasis was the lung (8.7%). The baseline characteristics of the groups are summarized in Table 1.

Of the whole study group, the 5-year OS, DMFS, and LRFFS rates were 75%, 78%, and 95%, respectively. In univariate analysis, when CR and IR group were compared, a significant difference was found between the 5-year OS (90% vs. 60%, $p = 0.001$) and DMFS (87% vs. 65%, $p = 0.02$) rates (Fig. 1A, B). However, there was no significant difference in the 5-year LRFFS rate (97% vs. 92%, $p = 0.16$) (Fig. 1C). In the multivariate Cox regression

Table 1 Baseline characteristics of complete and incomplete response group in patients with nasopharyngeal cancer

n		Study group		
		Incomplete response group (%)	***Complete response group (%)***	***p***
Age (mean ± St.D.)		45.9 ± 14.5	48.3 ± 11.9	0.38
Gender (*n*)	Female	31 (33.7)	36 (39.2)	0.52
	Male	7 (7.6)	18 (19.5)	
T stage (*n*)	T1	16 (17.4)	20 (21.7)	0.33
	T2	8 (8.7)	24 (26.1)	
	T3/T4	14 (15.2)	10 (10.9)	
N stage (*n*)	N0	5 (5.4)	7 (7.6)	0.91
	N1	10 (10.9)	12 (13)	
	N2	20 (21.7)	32 (34.8)	
	N3	3 (3.3)	3 (3.3)	
Clinical stage (*n*)	Stage 1	3 (3.3)	2 (2.2)	0.74
	Stage 2	6 (6.5)	11 (12)	
	Stage 3	25 (27.2)	37 (40.2)	
	Stage 4a	4 (4.3)	4 (4.3)	
Histological type (*n*)	Keratinizing SCC	13 (14.1)	8 (8.7)	0.06
	Non- Keratinizing differentiated carcinoma	13 (14.1)	19 (20.7)	
	Non- Keratinizing differentiated carcinoma	12 (13)	27 (29.3)	
Smoking (*n*)	No	22 (23.9)	30 (32.6)	0.82
	Yes	16 (17.4)	24 (26.1)	
ECOG-PS (*n*)	0	2 (2.2)	5 (5.4)	0.47
	1	36 (39.1)	49 (53.3)	
Induction chemotherapy (*n*)	No	22 (23.9)	38 (41.3)	0.21
	Yes	16 (17.4)	16 (17.4)	
Definitive RT/CRT (*n*)	RT	2 (2.2)	2 (2.2)	0.71
	CRT	36 (39.1)	52 (56.5)	
Adjuvant chemotherapy (*n*)	No	26 (28.3)	34 (37)	0.58
	Yes	12 (13)	20 (21.7)	
Cisplatin dose with RT (*n*)	40 mg/m^2 weekly	21 (24.7)	25 (29.4)	0.16
	100 mg/m^2 once every 3 weeks	12 (14.1)	27 (31.8)	
Recurrence/metastasis (*n*)	Yes	15 (16.3)	9 (9.8)	**0.014**
	No	23 (25)	45 (48.9)	

SCC squamous cell carcinoma, *RT* radiotherapy, *CRT* concurrently radiotherapy

analysis, CR were determined as an independent predictor for OS (HR: 0.13, 95% Cl: 0.045–0.36, $p < 0.001$) and DMFS (HR: 0.26, 95% CI: 0.095–0.744, $p = 0.012$). The confounder variables were age, gender, T stage. ECOG-PS, smoking, N stage, and cisplatin dose in concurrent CRT variables were used only for OS in multivariate analysis (Table 2).

Discussion

In this study, it was found that the radiological CR obtained after primary treatment of NPC is an independent predictor for OS and DMFS. The presence of the CR was associated with better OS and DMFS, but had no significant effect on LRFFS. Five-year OS and DMFS rates in those with CR, 90% and 87%, respectively. The 5-year OS and DMFS differences due to CR were approximately 30% and 22%, respectively.

The prognostic factors of NPC can be divided into patient-related (age, gender, and ethnicity), disease-related (histology type, TNM staging), and treatment-related factors [10]. The primary treatment response is one of the treatment-related factors. There are few studies investigating the prognostic significance of primary treatment response. CR is a term used for patients who have no residual disease. Primary tumor regression rate after primary treatment in NPC patients was found to

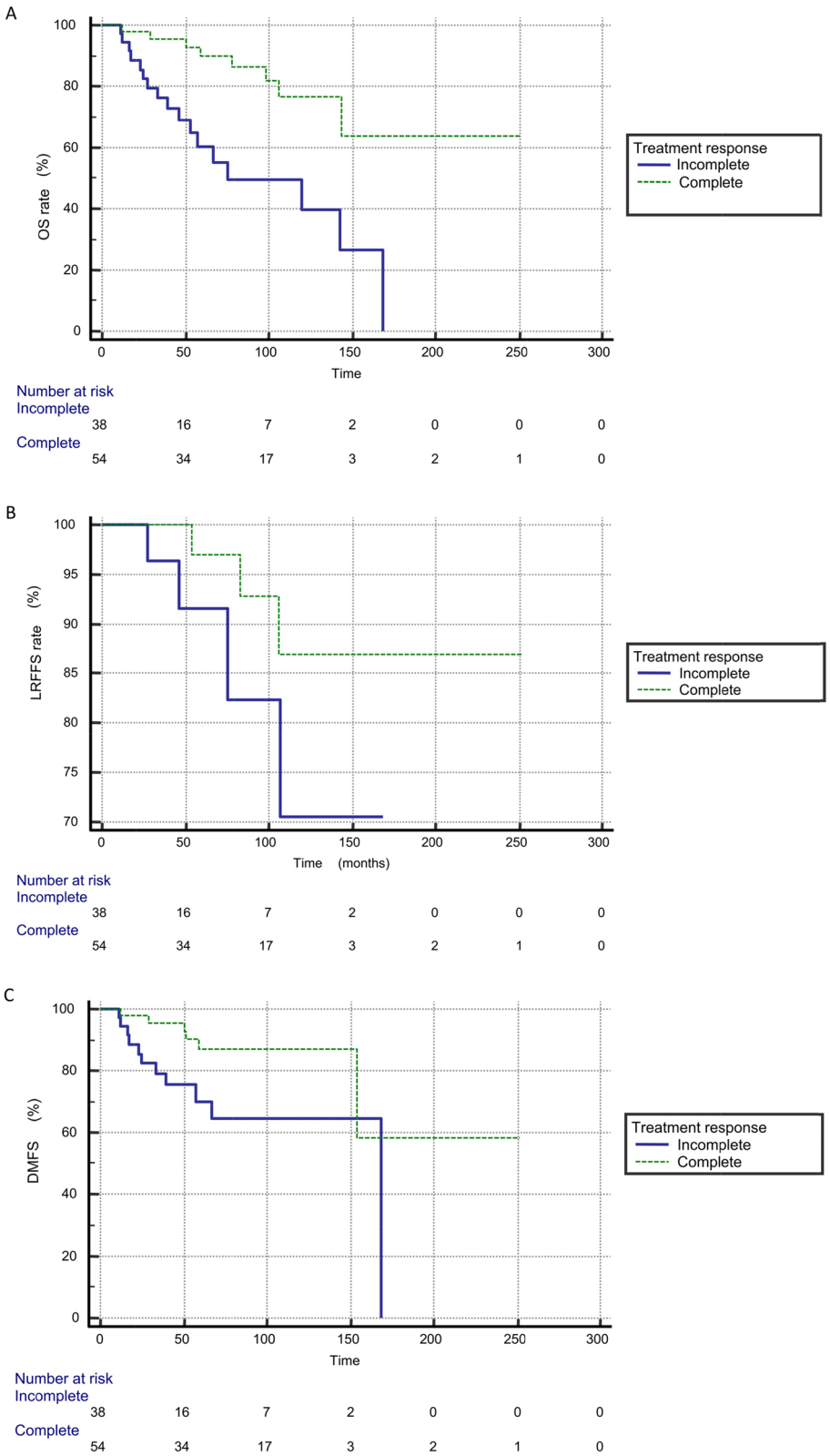

Fig. 1 Kaplan–Meier curve for patients with nasopharyngeal carcinoma with an incomplete response and complete response after treatment. (**A**) Overall survival (OS). (**B**) Distance metastasis free survival (DMFS). (**C**) Locoregional failure free survival (LRFFS)

Table 2 Multivariate analyses of prognostic factors for nasopharyngeal carcinoma

		5-year OS			5-year DMFS			5-year LRFFS		
		Hazard ratio	**95% CI**	***p***	**Hazard ratio**	**95% CI**	***p***	**Hazard ratio**	**95% CI**	***p***
CR vs IR		0.13	0.045–0.036	**< 0.001**	0.26	0.095–0.744	**0.012**	0.78	0.34–1.24	0.18
Age		1.016	0.974–1,059	0.47	0.97	0.90–1.024	0.32	1.083	0.998–1.175	0.05
Gender (F/M)		0.99	0.2683.661	0.98	0.51	0.106–2.52	0.41	0.60	0.049–7.47	0.69
T stage (T1–2/T3–4a)		0.84	0.298–2.395	0.75	0.56	0.158–2.03	0.38	0.50	0.055–4.659	0.54
N stage	N0	Reference	Reference	0.46	-	-	-	-	-	-
	N1	3.32	0.363–30.45	0.28	-	-	-	-	-	-
	N2	3.95	0.479–32.65	0.20	-	-	-	-	-	-
	N3	8.13	0.597–110.86	0.11	-	-	-	-	-	-
ECOG-PS		2.15	0.212–21.85	0.51	-	-	-	-	-	-
Smoking		2.11	0.668–6.698	0.2	-	-	-	-	-	-
Cisplatin dose with CRT (40 mg/m^2 vs 100 mg/m^2)		2.12	0.734–6.132	0.16	-	-	-	-	-	-

be independent prognostic factors for OS, LRFFS, and DMFS [9, 11].

There are several treatment-related factors that can affect CR rates. One of these may be that patients receive induction CT. It is known from neoadjuvant treatment studies of some cancers that the better the response to the first treatment in non-metastatic diseases, the better the survival will be. Several studies have shown that the overall tumor response after induction CT is an independent prognostic factor for disease-free survival (DFS), OS, and LRFFS. In studies conducted, the CR, PR, and SD rates after induction CT were ranged from 8 to 27%, 55% to 64%, and 11% to 17.6%, respectively [12, 13]. In the study of Dwijayanti F. et al. investigating the tumor response to CRT after induction CT in patients with NPC, 5-year survival rates in the CR, PR, and progressive disease (PD) group were 71%, 30.4%, and 10.6%, respectively. Tumor response has been reported to be an independent prognostic factor. [11] In our study, the rates of induction CT were the same in the CR and IR groups (17.4%). Therefore, we think that induction CT does not contribute to our CR rates. Peng H. et al. reported that 4-year DFS, OS, DMFS, and LRFFS rates for the entire cohort, including CR, PR, and SD, were 79.9%, 88.9%, 87.4%, and 90.1%, respectively. Satisfactory tumor response to induction CT has been associated with significantly improved DFS, OS, and LRFFS for patients with NPC. In terms of the overall response after IC, the 4-year DFS, OS, DMFS and LRFFS rates for patients with CR was 85.5% vs. 92.3% vs. 90.5% vs. 97.7%, for patients with PR was 79.1% vs. 89.2% vs. 85.7% vs. 94.2%, and for patients with SD was 70.7% vs. 80.6% vs. 85.9% vs. 88.5%, respectively [9].

In another study comparing survival rates in the CR and IR groups, a significant difference was found between the 5-year OS (85.6% vs. 71.5%) and LRFFS (96.6% vs. 87.3%) rates. However, there was no significant difference in the 5-year DMFS rate (86% vs. 84.2%) [14]. Similar to our data, longer survival results were obtained in complete responders in all studies analyzing survival by response status in the literature.

Adjuvant CT is another treatment-related factor that may affect the CR rate. The landmark Intergroup-0099 study showed that CRT plus adjuvant CT for radiotherapy alone increased 3-year OS by 31% and PFS by 45%. This is the first study to show the efficacy of adjuvant therapy in NPC [15]. After this study, it has been included in the adjuvant CT guidelines. In the meta-analysis conducted by the MAC-NPC collaborative group, they reported that the use of CT is beneficial in increasing survival endpoints. Also, they reported that this benefit varied with the timing of CT and that the best outcome was from the CRT plus adjuvant CT arm compared to CRT only, induction CT only, and adjuvant CT only arm [7]. In the study investigating the efficacy of adjuvant CT combined with RT in the treatment of patients with advanced NPC, the CR and IR rates were 46% and 52% in those receiving adjuvant therapy. The 1-, 3- and 5-year OS rates in the adjuvant CT group were 87%, 80%, and 76%, and those in the only RT group were 74%, 64%, and 51%, respectively ($p < 0.05$) [16]. In contrast, Yang S et al. evaluated the prognostic value of adjuvant CT in NPC patients with residual disease after CRT and showed that adjuvant CT did not significantly improve 3-year OS, LRFFS, failure-free survival (FFS), and DMFS rates [17]. Generally, CRT plus adjuvant CT has been shown to improve CR, OS, DMFS, and DFS rates in patients with stage III-IVa NPC [18]. In our study, the rate of adjuvant CT

was higher in the CR group compared to the IR group, although it was not significant. Therefore, we think that adjuvant CT contributes to the increase of our CR rates.

Conclusions

The survival benefit in patients with CR after primary treatment is evident as shown in the above studies. Therefore, the aim of primary treatment should be to increase the CR rates. Although the benefit of adjuvant CT after CRT in NPC is controversial, the rate of adjuvant CT in our patients with CR was higher. Therefore, adjuvant CT may be recommended to increase CR rates in patients with poor tumor regression after primary treatment. It is important to evaluate early tumor response to determine poor tumor regression.

The limitations of our study were the retrospective design at a single center and the small sample size.

Abbreviations

AJCC: American Joint Committee on Cancer; CR: Complete response; CRT : Chemoradiotherapy; CT: Chemotherapy; DMFS: Distant metastasis-free survival; EBV: Epstein-Barr virus; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FFS: Failure-free survival; HR: Hazard ratio; IR: Incomplete response; LRFFS: Locoregional failure-free survival; NPC: Nasopharyngeal cancer; OS: Overall survival; PD: Progressive disease; RECIST: Response Evaluation Criteria on Solid Tumors; RT: Radiotherapy; SD: Stable disease; WHO: World Health Organization.

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No.

Authors' contributions

MK: Written, literature review, data collecting, design. MKE: Data collecting, Controller, design. MZK: Data collecting, English editing. AD: Data collecting. MK: Data collecting, English editing. MA: Controller. All authors have read and approved the article.

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There are no financial interests.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Necmettin Erbakan University Meram Faculty of Medicine ethics committee approval was obtained (Approval number: 2021/3072). Written informed consent was not obtained from the patients because this study was conducted on retrospective file data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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