Original Article / Çalışma - Araştırma

T4N0M0 nasopharyngeal carcinoma patients: do they have a distinct tumor biology?

T4N0M0 nazofarenks kanseri hastalarının farklı bir tümör biyolojisi olabilir mi?

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Objectives: To investigate the clinical manifestations and treatment outcomes of non-metastatic T4N0 nasopharyngeal cancer patients, and to compare them with other stage IVA subgroups of patients.

Patients and Methods: A retrospective analysis of 775 non-metastatic nasopharyngeal cancer patients, treated in four radiotherapy centers between 1990 and 2005, was undertaken. Among 197 stage IVA patients, 90 (11.6%) patients were staged as T4N0, 32 (4.1%) as T4N1, and 75 (9.7%) as T4N2. T4N0 patients constituted 40.8% of all T4 cases (median age 53 years; range 15 to 76 years). Cranial nerve involvement was detected in 59 (65.5%) of these cases.

Results: The median follow-up period was 38 months. There were only nine (10%) patients younger than 30 years of age with T4N0 tumors, for patients with diseases other than T4N0, 27.1% of the patients were under 30. Survival rates for five-year loco-regional progression free survival, distant failure free survival, and disease specific survival were 65.9%, 94%, and 71.4%, respectively. Distant failure free survival of T4N0 patients was more probable than for stage T4N1 (p=0.06) and T4N2 (p=0.008) patients.

Conclusion: Non-metastatic T4N0 tumors have some distinct features, including a unimodal age distribution and a better distant failure free survival than the other subgroups of stage IVA. Therefore, it may be better to include T4N0 patients in stage III instead of stage IVA.

Key Words: Nasopharyngeal cancer; recurrence patterns; stage T4N0M0.

Amaç: Tümörleri T4N0 olarak evrelenen metastatik olmayan nazofarenks kanserli hastaların tedavi ve klinik özellikleri incelendi; elde edilen sonuçlar evre IVA'nın diğer alt gruplarında yer alan hastaların sonuçları ile karşılaştırıldı.

Hastalar ve Yöntemler: Dört radyoterapi merkezinde 1990 ve 2005 yılları arasında tedavi edilmiş metastatik olmayan toplam 775 nazofarenks kanseri tanılı hasta geriye dönük incelendi. Bu hastalardan evre IVA olan 197'sinin dağılımı; 90'ı (%11.6) T4N0, 32'si (%4.1) T4N1 ve 75'i (%9.7) T4N2 şeklindeydi. T4N0 hastalar tüm T4 hastalarının %40.8'ini (ortanca yaş 53 yıl; dağılım 15-76 yıl) oluşturmaktaydı. Kraniyal sinir tutulumu bu hastalardan 59'unda (%65.5) izlendi.

Bulgular: Ortanca takip süresi 38 ay idi. T4N0 hastalardan sadece dokuzu (%10) 30 yaş altı iken diğer T4N0 alt gruplarındaki hastaların ise %27.1'i 30 yaş altında idi. Beş yıllık lokal bölgesel progresyonsuz sağkalım, uzak metastazsız sağkalım ve hastalıksız sağkalım oranları sırasıyla %65.9, %94 ve %71.4 idi. Uzak metastazsız sağkalım evre T4N0 hastalarda diğer T4N1 (p=0.06) ve T4N2 (p=0.008) evre hastalarından daha iyi idi.

Sonuç: Metastatik olmayan T4N0 tümörler, unimodal yaş dağılımları ve daha iyi uzak metastazsız sağkalım sonuçları açısından, diğer evre IVA alt gruplarından farklı özellikler göstermektedir. Bu nedenle bu hastaların evre IVA yerine evre III olarak değerlendirilmesi uygun olabilir.

Anahtar Sözcükler: Nazofarenks kanseri; nüks özellikleri; evre T4N0M0.

Received / *Geliş tarihi:* November 27, 2009 Accepted / *Kabul tarihi:* February 2, 2010

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Nasopharyngeal carcinoma (NPC) is a malignant tumor with a variable range of incidence that depends on age, ethnicity, and geographic localization.[1] In Southeastern Asia, where the incidence rate is the highest in the world, there is only a single peak at about 50 years. However, these tumors show a bimodal age distribution in non-endemic countries: the first peak is seen in the second decade with a second peak later in life. While the rate of pediatric patients accounts for 6-18% of all NPC patients in non-endemic countries like Argentina, Turkey, India, Israel, Morocco, Tunisia, Algeria, and Uganda, the corresponding figure is reported to be less than 1% of all NPC's in endemic countries.[2] Nasopharyngeal carcinoma is the second most frequently treated head and neck malignancy following laryngeal carcinoma in reference hospitals with an intermediate incidence rate in our country.[2]

Nasopharyngeal carcinoma has a multifactorial etiology involving viral, environmental, and genetic components.[1,3] Distant metastases develop more often than other head and neck carcinomas.[4] Childhood and adult forms of the disease are distinguishable by their association with Epstein-Barr virus (EBV) infection, rates of undifferentiated histology, and incidence of advanced loco-regional disease.[3,5,6]

Most of the patients with NPC are diagnosed in advanced stages, and both local control and survival rates are affected by the initial stage at diagnosis.[2,4,7] Several different staging systems have been defined and the International Union Against Cancer (UICC)/American Joint Commission on Cancer (AJCC) TNM system is currently widely accepted in the world.[8] The staging system is still in progress in terms of predicting the survival, determining the loco-regional relapse patterns and the prognostic features. Therefore, continuous efforts to modify the recent system will also help to build up more precise treatment strategies for different risk groups.[8-11]

According to the 5th edition (1997) of the UICC/AJCC TNM system, a T4 tumor indicates intracranial extension, involvement of cranial nerves, hypopharynx, infratemporal fossa or orbit and any combination of these features.[12] The T4 tumors (T4N0-2M0), with the exception of N3 disease, have been staged as stage IVA. To our knowledge, there are only few studies analyzing the pattern of relapse and survival of stage IVA patients.[7,13] Therefore, we hypothesized that among stage IVA patients, T4N0 patients might have a different clinical history than T4N1 and T4N2 patients.

In this retrospective study, we investigated the characteristics of patients with stage IVA tumors and analyzed their patterns of relapse and survival in a large cohort of patients.

PATIENTS AND METHODS

Medical records of histologically proven and previously untreated non-metastatic NPC tumors from patients of four radiotherapy (RT) departments were analyzed in this study. These departments were located in the main referral university hospitals of their territories in our country. Tumor biopsies, physical and endoscopic examinations, chest radiographs, blood counts, blood chemistry, abdominal ultrasonography and bone scans were used in the staging. Radiological evaluations of contrast-enhanced computed tomography and/or magnetic resonance imaging (MRI) were used to diagnose the primary tumor extension beyond the nasopharynx and the status of cervical lymph nodes. The majority of patients were staged with MRI (85%). Clinical examination was done to detect cranial nerve involvement (CNI). Staging was uniformly done, based on the UICC/AJCC 5th edition.[12] Hence, the tumors with intracranial extension and/or involvement of the infratemporal fossa, hypopharynx or orbits and/or cranial nerve involvement without any clinical or radiological nodal and distant metastasis were confirmed as T4N0M0 tumors.

Treatment

All patients were treated with external RT using linear accelerators. Conventional treatment planning was used in all patients. In phase 1, opposing lateral fields encompassing the gross tumor, the nasopharynx, upper neck lymphatics and an anterior single field for the lower neck and supraclavicular lymphatics were used. In phase 2 of the treatment, a curative dose to the tumor and the nasopharynx was attained by using smaller parallel opposed fields. Treatment fields were modified according to the tumor extension through base of skull, brain and paranasal sinuses. All external treatments were administered in daily fractions of 180-200 cGy, 5d/wk with 6MV photons and appropriate electrons. A total dose of 6340-7600 cGy (median 6940 cGy) to primary tumors of the nasopharynx and 4400-6000 cGy (median 4900 cGy) to negative lymphatic regions were administered.

In six (6.7%) patients concomitant boost technique was used for the primary tumor. Intracavitary high dose rate (HDR) Ir-192 treatment brachytherapy was applied in 47 (52.2%) patients. A total dose of 12 Gy/3 fractions/3-5 days to 1 cm above the source of the Ir-192 was delivered.

The median time for RT completion was 52 days (range 34 to 83 days). Fifty (55.5%) patients received induction chemotherapy (CT) while 71 (78.8%) patients received adjuvant CT. Platinum-based concurrent CT was administered in 46 (51.1%) patients. Two patients were re-irradiated due to a local recurrence in the nasopharynx. One patient was treated with a linear accelerator and another received 12 Gy/single fraction (to the 50% isodose line) stereotactically with a Gamma Knife Unit.

Follow-up and clinical end points

Clinical and radiological evaluations were done every three months during the first two years, every four months in the third year and every six months thereafter. A comprehensive physical examination, in addition to routine complete blood counts, serum biochemical analyses, contrast-enhanced computed tomography or magnetic resonance scans of the nasopharynx and neck were performed in every follow-up visit. A chest radiograph was done every six months and abdominal ultrasonography or computed tomography and/or bone scintigraphy were done when necessary.

All survival end-points were calculated from the day of histopathological diagnosis to death or last follow-up. Loco-regional progression free survival (LRPFS) was defined as the time period from histopathological diagnosis to the loco-regional tumor progression. Distant failure free survival (DFFS) was defined as the time period from histopathological diagnosis to distant metastasis. Disease free survival (DFS) was defined as the time period from histopathological diagnosis to any type of disease progression. Disease specific survival (DSS) was defined as the time period from the date of diagnosis to the date of death due to nasopharyngeal cancer. Overall survival (OS) was defined as the time period from diagnosis to death from any cause. Tumor recurrence was defined as any local relapse after radiological complete or partial response.

Statistical analyses

All survival rates were calculated using the Kaplan-Meier product limit method.[14] The differences between the curves were compared using the log-rank test. A p-value of less than 0.05 was considered statistically significant. Different prognostic factors were included in the univariate analysis, such as gender, median age, histopathology, CNI, cumulative dose to nasopharynx, administration of chemotherapy in neoadjuvant, concurrent or adjuvant settings. A Cox regression analysis was performed for each end point of LRRFS, DFFS, DFS, DSS and OS in order to evaluate the independent significant prognostic factors.[15]

RESULTS

Patient characteristics and distribution among decades

A total of 775 non-metastatic NPC white Caucasian patients were treated between 1990 and 2005 in four major radiotherapy centers in Turkey. Among these 775 patients 197 (25.4%) patients were staged as IVA patients. Among the 197 patients, 90 (11.6%) patients were staged as T4N0, 32 (4.1%) were staged as T4N1 and 75 (9.7%) staged as T4N2 disease. T4N0 patients constituted 40.8% of all T4 and 45.6% of stage IVA cases. Patient distributions according to stages are given in Table 1.

Sixty-three (70%) patients of T4N0 tumors were male and 27 (30%) were female, giving a male/female ratio of 2.3:1. Undifferentiated [WHO: World Health Organization (WHO) type 3] carcinoma

Table 1. T and N stage distribution in non-metastatic nasopharyngeal carcinoma patients according to UICC/AJCC TNM 1997 staging system

Stage	T1		T2		T3		T4		*Total*	
	n	%	n	%	n	%	n	%	n	%
N0	40	5.1	38	4.9	37	4.8	90	11.6	205	26.4
N1	52	6.7	44	5.7	19	2.5	32	4.1	147	19
N2	65	8.4	66	8.5	77	9.9	75	9.7	283	36.5
N3	40	5.1	47	6.1	30	3.9	23	3.0	140	18.1
Total	197	25.3	195	25.2	163	21.1	220	28.4	775	100

was the most common histological finding (n=64, 71.1%), while 20 (22.2%) patients had non-keratinizing (WHO type 2) squamous cell carcinoma (SCC) and only six (6.7%) had keratinizing SCC (WHO type 1). Cranial nerve involvement was detected in 49 (54.4%) patients. The median age was 53 years and the range was 15 to 76 years. The most frequent age of involvement was in the 5th decade (28%) and the proportion of patients younger than 20 years was 4.4%. Patient distribution among decades for all stage IVA patient subgroups is shown in Table 2.

Patterns of treatment failure and complications

The median follow-up period was 38 months (range 6-130 months). At the time of analysis 54 (60%) patients were alive and 47 (52.2%) had no evidence of disease, whereas seven patients were alive with disease, five with local progression and two with distant metastases. Local relapse was detected in 27 (30%) patients and two of these patients also had distant metastases to lung and bone. A total of six (6.6%) patients developed distant metastases. One of the patients with a lung metastasis also had regional recurrence in the neck. No other neck recurrences were observed. For local recurrent patients, nine were re-irradiated either externally (n=7) or stereotactically (n=2) and the rest of the patients received palliative CT.

During the follow-up period 36 patients died; 17 (47.2%) of these deaths were due to uncontrolled local disease and three (8.3%) to loco-regional progression and distant metastases. Seven patients died without any disease progression, but they had either a general state disorder within months of treatment (n=4), brain necrosis (n=2) or radiation myelopathy (n=1). Seven patients died due to an intercurrent disease, one patient died for an unknown reason and, one patient died due to secondary cancer in the lung.

At the time of analysis, four patients had developed brain necrosis, three had hearing loss, three had optic neuropathy, one had trismus and one had hypothalamo-hypophyseal insufficency.

Table 2. Number of patients in subgroups of stage IVA among ages

	Age (years)					
	0-29		30-79		*Total*	
Stage	n	%	n	%	n	%
T4N0	10.0	9	90	81	100	90
T4N1	28.1	9	71.9	23	100	32
T4N2	26.6	20	73.4	55	100	75

Survival analysis

For stage T4N0 patients five-year LRPFS, DFFS, DFS, DSS and, OS rates were 65.9, 94, 56.6, 71.4 and, 59.5%, respectively. For stage T4N1 patients LRPFS, DFFS and OS rates were 63.3, 76.5 and 66.2% and for stage T4N2 patients they were 67.3, 74.8 and 57.7%, respectively. There were no statistically significant differences between the subgroups of stage IVA for LRPFS and OS. However, the DFFS was significantly better for T4N0 patients compared to T4N0 patients (p=0.008), and there was a trend for a better DFFS for T4N0 patients compared to T4N1 patients (p=0.06; Figure 1).

Analysis of prognostic factors

Univariate analysis for the T4N0 patients revealed an older age (≥53 years) as an unfavorable prognostic factor for OS (p=0.02), CNI as an unfavorable prognostic factor for DFS (p=0.03), WHO type 1 histopathology as an unfavorable prognostic factor for LRPFS, DFS, OS (p<0.0001) and for DSS (p<0.01; Table 3).

By Cox multivariate analysis, a WHO type 1 histopathology was an unfavorable prognostic factor for LRPFS, DFS, DSS and OS. Cranial nerve involvement was an unfavorable prognostic factor for DFS. Patients who were younger (median <53 years) and

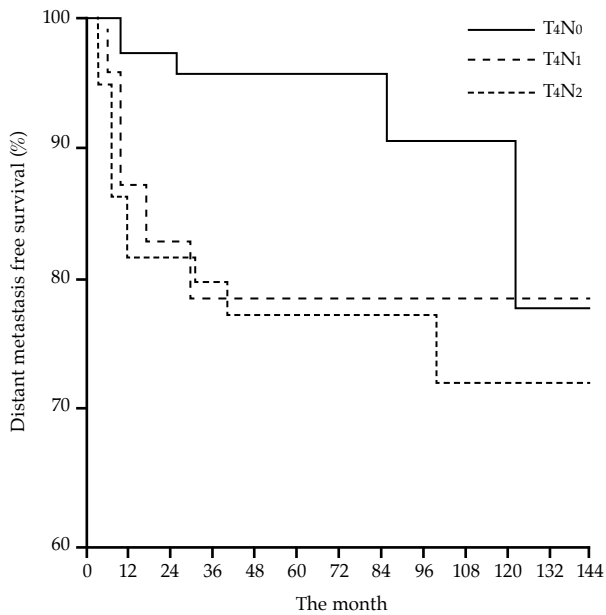

Figure 1. *Distant failure free survival plots for patients of stage IVA subgroups (p=0.06) for T4N1 and (p=0.008) for T4N2 in favor of T4N0.*

Table 3. Five year loco-regional progression free survival, distant failure free survival, disease free survival, disease specific survival and overall survival according to the prognostic factors for stage T4N0 patients

Prognostic factors	LRPFS		DFFS		DFS		DSS		OS	
	%	p	%	p	%	p	%	p	%	p
Gender										
Female	61.1		95.5		48.7		58.1		59.3	
Male	68.2	0.5	93.2	0.75	60.5	0.34	67.4	0.19	59.5	0.61
Age										
<53	72.05		97.2		64.9		73.1		70.5	
≥53	59.5	0.48	90.6	0.32	48.6	0.34	70.9	0.43	49.1	0.02
Cranial nerve involvement										
(+)	60.5		87.3		48.4		63.6		56.8	
(–)	72.2	0.2	100	0.09	66.4	0.03	80.2	0.12	61.2	0.19
Histopathology										
WHO type 1	0		100		0		33.3		22.2	
WHO type 2	66.8		100		62.4		71.3		63.6	
WHO type 3	71.8	<0.0001	91.8	0.24	59.6	<0.0001	74.7	0.01	61.7	<0.0001
Radiation dose										
≤70Gy	63.0		94.2		54.3		67.9		57.3	
>70Gy	81.8	0.60	100	0.93	71.6	0.44	90.9	0.30	71.6	0.44
Neoadjuvant chemotherapy										
(+)	73.7		96.9		58.1		75.8		71.6	
(–)	65.4	0.62	91.9	0.30	55.9	0.83	70.2	0.40	54.7	0.12
Concomittant chemotherapy										
(+)	65.1		94.6		55.9		71.9		69	
(–)	66.5	0.82	95	0.18	58.1	0.39	71.3	0.88	54.9	0.37
Adjuvant chemotherapy										
(+)	55.7		100		52		55.4		59.6	
(–)	68.3	0.41	92.7	0.20	57.8	0.66	74.0	0.37	60	0.87

LRPFS: Loco-regional progression free survival; DFFS: Distant failure free survival; DFS: Disease free survival; DSS: Disease specific survival; OS: Overall survival; p: Probability value; WHO: World Health Organization.

received induction CT before RT tended to have a better OS (Table 4).

DISCUSSION

Although NPC is a relatively less common cancer in the Mediterranean region, the bimodal age distribution is an intriguing characteristic for this region. On the other hand, a retrospective analysis from Tunisia, Maalej et al.[16] mentioned that almost all patients with non-metastatic T4N0 disease were over the age of 30. In their series, distant metastases represented 13% of cases, which is lower than expected, whereas the main failure of treatment was a local recurrence. They therefore concluded that the unimodal age distribution and the low rate of distant metastases were probably distinctly different entities concerning T4N0 patients. Another group of scientists from Tunisia previously showed that p53 accumulation is much rarer in patients below 30 years.[17] The same group recently showed that the Bcl-2 score was much lower for younger patients than older patients.[18] These observations suggest that distinct oncologic mechanisms may exist for the two age groups.

Our study showed two peculiar findings for stage T4N0 tumors compared to other subgroups. First, there was the difference between T4N0 and other IVA subgroups with respect to their failure pattern and second, there was the unimodal age distribution with the lack of an adolescent peak in contrast to the distinct bimodal characteristic for all stages of NPC.

The survival analyses and their comparisons for stage IVA subgroups showed that the curves

Table 4. Multivariate Cox proportional Hazards analysis of loco-regional progression free survival, disease free survival, disease specific survival and overall survival

	RR	95% CI	*p*
Loco-regional progression free survival			
Histopathology (WHO)			
III	1		
II	1.24	0.47-3.30	0.65
I	13.91	3.91-49.37	<0.0001
Disease free survival			
Cranial nerve involvement			
(–)	1		
(+)	2.61	1.25-5.56	0.01
Histopathology (WHO)			
III	1		
II	0.88	0.37-2.13	0.79
I	7.5	2.31-24.39	0.01
Disease specific survival			
Histopathology (WHO)			
III	1		
II	0.96	0.33-2.81	0.94
I	12.17	1.80-82.15	0.01
Overall survival			
Age			
≥53	1		
<53	0.46	0.21-1.02	0.05
Histopathology (WHO)			
III	1		
II	1.06	0.45-2.51	0.88
I	16.33	4.15-64.27	<0.0001
Neoadjuvant chemotherapy			
(+)	1		
(–)	2.88	0.98-8.43	0.05

RR: Relative risk; CI: 95% confidence interval; p: Probability value; WHO: World Health Organization.

for LRPFS and DSS were almost the same, whereas the curve for the DFFS was better in the T4N0 subgroup than in the others. In the literature, only a few articles report the stage IVA and IVB outcomes separately.[7,13]

We know that the T category is the most important unfavorable prognostic factor for local control. Local relapse rates increase with an advanced T stage.[19] Another important aspect is the rapid and early metastasis potential of NPC, unlike other head and neck squamous cell carcinomas.[3,4] Yet in our cohort of T4N0 patients, we observed only six (6.7%) patients with distant failure. These locally advanced tumors have a direct infiltration into the rich vascular network at the base of the skull and despite that, rarely show systemic metastasis. Distant failure is significantly correlated with lymphatic involvement.[20] It may be argued that these tumors had different molecular aspects and that their biological behaviors, like the lymphatic and vascular invasion, are correlated. Therefore, this phenomenon needs further research to define the probable molecular markers and pathways.

Since local progression is more prominent for T4 tumors, we think that more aggressive local treatment strategies may increase tumor control. However, in our study we did not observe any increase in local control with increasing radiation

doses to more than 70 Gy with conventional RT. The addition of CT may have a benefit that the comes mainly from the concomitant usage, rather than from the induction or adjuvant CT.[21] However, induction CT may shrink the primary tumor before the RT. In our study patients who had received induction CT tended to have a better OS rates.

Because of the anatomic proximity to critical structures at the base of the skull it is difficult to reach the curative doses for T4 tumors without risk of complications. Moreover, all patients in our study were irradiated with conventional techniques and we observed a high incidence of toxicity. Thus, modern techniques like intensity modulated radiotherapy are required to improve the tumor control with less normal tissue toxicity.

Our second consideration regarding T4N0 patients was the age distribution of the patients. It has been reported that the age distribution for non-keratinizing NPC is bimodal in North American populations and in the Mediterranean region, with an early peak at 10-20 years and a second peak at 40-60 years.[6] However, we did not find the early peak in T4N0 patients. Moreover, other reports from our country rarely reported this entity,[2,6] and in our data only 4.4% of patients were younger than 20 years. Meanwhile, 45% of our patients were in the 40 to 60 year age group which has been described as a peak incidence for high-risk areas,[6] and in this study the commonest decade was the 5th decade (n=25, 27.7%). Nevertheless, it is not clear whether the prognosis differs significantly between the young and relatively older age groups. In some studies age and gender were reported as having prognostic importance, with a better prognosis for younger and female patients for all stages.[10,22] In our study we observed a slightly better result for OS in patients younger than the median age of 53, but we did not observe any better outcome according to gender.

Nasopharyngeal carcinoma tumors with non-keratinizing and undifferentiated histological characteristics had higher control rates for primary tumors and involvement of neck nodes whereas a keratinizing histology had better distant control rates.[23] In our study most of the patients showed undifferentiated histological features and keratinizing tumors showed a worse prognosis for surviving parameters. However, we did not observe any difference between histological subgroups in terms of DFFS.

T4N0M0 disease of NPC may have characteristic biological and etiological factors. Although the combination of RT and CT treatments produces a high rate of success, it seems that the intracranial component of the tumors requires higher doses than conventional doses. Modern RT techniques are essential for obtaining these doses. Taking into consideration the favorable survival features of T4N0M0 tumors compared to other stage IVA subgroups, these patients may be grouped with stage III in the stage category. Further data are required to support our findings.

Acknowledgement

We thank to Prof Ray Guillery for his contribution of English editing on our manuscript.

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