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ORIGINAL ARTICLE

Evaluation of overall survival of nasopharyngeal carcinoma patients treated in ten years at a single institution

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Summary

Purpose: *To evaluate the survival rates and prognostic factors of nasopharyngeal carcinoma (NPC) patients treated in Izmir Oncology Center (IOC).*

Methods: *The survival of 58 NPC patients (median age 52.5 years) treated from 1998 to 2008 were retrospectively analysed. Histological evaluation was based on WHO criteria. AJCC (1997), as well as the new proposed evaluation system by Liu (2008) for clinical staging were used. Most patients received concurrent chemoradiotherapy, some were given neoadjuvant chemotherapy (nCT). Radiotherapy (RT) was delivered by conventional technique to a total dose of 70Gy to the primary tumor and metastatic lymph nodes.*

Results: *The 5-year overall survival, disease-free survival, local failure-free survival, and distant failure-free survival rates were 55, 36, 58 and 59%, respectively. The median overall survival was 55.78 months. WHO type II disease was found in 55.2% of the patients. There was only 1 lymphoma patient. Concurrent chemoradiotherapy was given to 74.1% and nCT to 12.1% of the patients. Advanced-stage disease was determined in 81.1% of the patients; 27.6% of these had stage IV disease. Early-stage disease was infrequent (6 patients - T1N0 and T2N0) in both staging systems. No significant difference was found between disease-free survival vs. local failure-free survival, and distant failure-free survival vs. local failure-free survival for the different treatment groups (p=0.92). Male patients with WHO type II pathology had a greater risk for distant metastases.*

Conclusion: *Both staging systems yielded similar results with no significant differences in survival rates but male patients and patients with type II pathology were at greater risk of distant metastases.*

Key words: chemotherapy, nasopharyngeal carcinoma, overall survival, radiotherapy

Introduction

The causes, occurrence, diagnosis, and treatment of NPC differ significantly from other cancers of the head and neck. With few symptoms early in its course, most cases are quite advanced when first detected. NPC tends to spread widely into surrounding tissues, thus is not often treated by surgery. It has different risk factors from most oral cancers and occurs in young age groups while is not associated with smoking or alcohol abuse [1,2].

NPC is rare in some parts of the world including USA and western Europe [3]; however, it is endemic in regions such as southern China and southeast Asia, with incidence rates varying between 15 to 50 per 100,000 population [1]. The incidence reported in Turkey ranges from 15 to 20 cases per 100,000 persons [4]. The geographic pattern of the incidence of NPC suggests an interaction between genetic and environmental factors [5,6].

Consumption of foods such as salted fish and preserved foods increases the risk for NPC. High concentrations of nitrosamines in these foods can induce various types of cancer, including gastric and esophageal cancer [7-10].

Epstein-Barr virus (EBV) plays an important role in the pathogenesis of NPC, since almost all NPC cells contain EBV [11]. EBV is transmitted orally and can be detected in oropharyngeal secretions from infected individuals [12]. Although infection by EBV occurs in most individuals, it is usually asymptomatic [13]. The molecular mechanism of EBV-dependent neoplastic transformation is not well understood. More information with

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the combination of knowledge of biological processes and biological experiments is on the way to gain more insight into the molecular mechanisms of NPC [14].

Histological assessment is carried out according to WHO criteria, and NPC is classified into 3 types: type I are differentiated squamous cell carcinomas with keratin production; type II includes non-keratinizing carcinomas; and type III are described as undifferentiated carcinomas [15,16]. In the USA, NPC belongs mostly to the keratinizing type [17,18]. Most NPC cases in Turkey are of undifferentiated type, similarly to southeast Asia where NPC is more prevalent [19,20]. Studies have shown that all 3 types arise from the same cell type - the lining cell of the nasopharynx. Treatment is usually the same for all types.

The most important prognostic factor is stage; because how far NPC has spread locally and throughout the body is more important than its type, and this has a clear impact on treatment outcome and survival. The latest version of UICC/AJCC (1997) has confirmed its superiority over the previous UICC/AJCC versions in terms of improved prognostication and a more balanced distribution between stages [21]. A newer evaluation system has been proposed by Liu et al. in 2008 [22], since the significant difference between the T stages (T1 and T2a) in overall survival was lacking in the latest version (1997) of UICC/AJCC classification. N stage also was found to be an independent factor for overall survival and the new model involving simpler T and N stage was shown to be a better index of prognosis [22,23].

The standard therapeutic option for early stages of NPC is RT. Higher response rates were reported when RT and chemotherapy (CT) were combined in the more advanced stages [24-26].

Methods

Patients

The records of patients diagnosed with NPC who had been referred to Izmir Oncology Center (IOC) for RT between September 1998 and July 2008 were retrospectively analysed. Forty-two (72.4%) were males and 16 (27.6%) females, with a median age of 52.5 years (range 16-78). Clinical data included age, gender, and RT parameters. Histopathological evaluation was done according to WHO criteria. Four (6.9%) patients had type I, 32 (55.2%) type II, and 19 (32.8%) type III carcinoma. One patient diagnosed with lymphoma and 2 with adenocarcinoma were included in the follow-up (Table 1).

Table 1. Patient characteristics (n=58) and histopathology according to UICC/AJCC 1997

Characteristics	*Patients, n*	*%*
Sex		
Male	42	72.4
Female	16	27.6
Age (years)		
≤ 50	26	44.8
> 50	32	55.2
Histopathological type (WHO)		
I	4	6.9
II	32	55.2
III	19	32.8
Adenocarcinoma	2	3.4
Lymphoma	1	1.7

Evaluation

The primary evaluation and staging of NPC patients was done by a council with participation of radiation oncology, ENT, radiodiagnosis, pathology, and medical oncology specialists of the referring hospitals. Treatment and follow-up were carried out in IOC in cooperation with those specialists.

The primary diagnosis involved histopathological evaluation from punch biopsies, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the nasopharynx and neck. Other investigations included blood tests, X-rays, abdomen ultrasonography, and skeletal scintigraphy.

Clinical staging was first determined according the latest revision of UICC/AJCC (1997) [21]. It was repeated using the later proposed new system [22].

According to the AJCC 1997 staging system 3 patients were classified as stage I. There were no stage IIA patients, 7 patients were classified as stage IIB, 31 as stage III, 12 as stage IVA, and 4 as stage IVB. Tumor and nodal staging is shown in Table 2.

According to the new proposed staging system [22] 6 patients were classified as stage I, 7 as stage II, 32 as stage III, 9 as stage IVA, and 3 as stage IVB. Tumor and nodal staging is shown in Table 3.

Table 2. Clinical tumor and nodal staging of tumors (AJCC 1997)

	N0	*N1*	*N2*	*N3a*	*N3b*	*Total*
T1	3	1	8	0	0	12
T2a	0	1	4	0	0	5
T2b	3	2	10	1	1	17
T3	3	3	3	0	1	10
T4	3	4	5	0	1	13
Tx	0	0	1	0	0	1
Total	12	11	31	1	3	58

Table 3. Tumor and node staging according to the new (2008) proposed staging system [22]

	N0	*N1*	*N2*	*N3*	*Total*
T1	3	2	12	0	17
T2	3	2	11	1	17
T3	3	3	3	1	10
T4	3	4	5	1	13
Tx	0	0	1	0	1
Total	12	11	32	3	58

Treatment

All patients were treated with conventional RT for primary carcinomas of the nasopharynx. External-beam radiation was delivered at a mean total dose of 70 Gy (range 68-76). Co 60 or 6 MeV-X were used for the nasopharynx and cervical lymphatic area with two lateral fields and for the supraclavicular area with one frontal field. A 9-12 MeV electron boost was given to lymph nodes.

Conventional fractions were given 5 days weekly with 2 Gy/fraction (50 Gy for subclinical, 66-70 Gy for primary tumor and lymph nodes). The median RT duration was 54 days (range 30-80). Spinal cord protection was used after 44-46 Gy in all patients to avoid excessive irradiation.

Most of the patients were given chemotherapy concurrently with RT. nCT was given prior to RT in some patients. Chemotherapy consisted of cisplatin which was given with amifostine (ethyol), UFT, and epirubicin.

The follow-up duration of the patients was calculated from the first day of RT to the day of death or the day of the last examination. The median follow-up of the whole group was 39 months (range 1-89). Distant metastases were diagnosed by clinical symptoms, physical examination and imaging methods, including chest X-ray, bone scan, CT, and abdominal ultrasonography.

Statistical analysis

The Statistical Package for Social Sciences (SPSS), version 15.0 was used. All calculations were performed as from the first day of the treatment. Time was measured from the start of treatment to the first locoregional failure or distant failure or to the day of the last examination. Overall survival was measured from the first date of RT to the date of death or the last date the patient was known to be alive. Survival rate was computed using standard Kaplan-Meier method, and the difference in survival curves was analysed by the log-rank test. Independent prognostic factors were analysed with the Cox proportional hazards regression model. In addition, variables in the model included T staging, nodal (N) staging, and type of treatment. A two-tailed p-value < 0.05 was considered statistically significant.

Results

A total of 43 patients (74.1%) received concurrent chemoradiotherapy, 7 (12.1%) nCT, and 8 (13.8%) received RT alone. Eight patients (13.8%) received cisplatin, 28 (48.2%) cisplatin with amifostine (ethyol), and 3 (5.2%) epirubicin with cisplatin (Table 4). All but 4 (93.1%) received 66 Gy or a higher dose of RT.

The overall median follow-up time was 2.84 years (range 1 month-7 years; Figure 1). The median survival time for stage I, IIB, III, IVA, and IVB according to AJCC 1997, was 48, 60, 44.8, 24, and 64.5 months, respectively ($p > 0.05$). The median survival time for RT- only patients was the lowest (27 months), increasing to 58.6 months for RT+CT patients and 60 months for nCT patients. The overall 5-year survival was 100, 86.4, 35, 33%, and 67% for stages I, IIB, III, IVA, and IVB, respectively. Most of the patients (81.1%) were in an advanced stage on admission; 31 (53.4%) had stage III and 16 (27.6%) stage IV disease.

Patients mainly suffered from dysphagia, radiodermatitis, dry mouth, and mucositis in the early stages of RT. Ambulatory support therapies were implemented for these patients. Most of the side effects subsided within the first year except xerostomia. Partial hearing loss as late side effect was observed in 3 patients.

Distant metastasis was diagnosed in 11 patients (19%) during the 89-month follow-up period. Of those, 45.5% occurred in the first 2 years, increasing to 63.6%

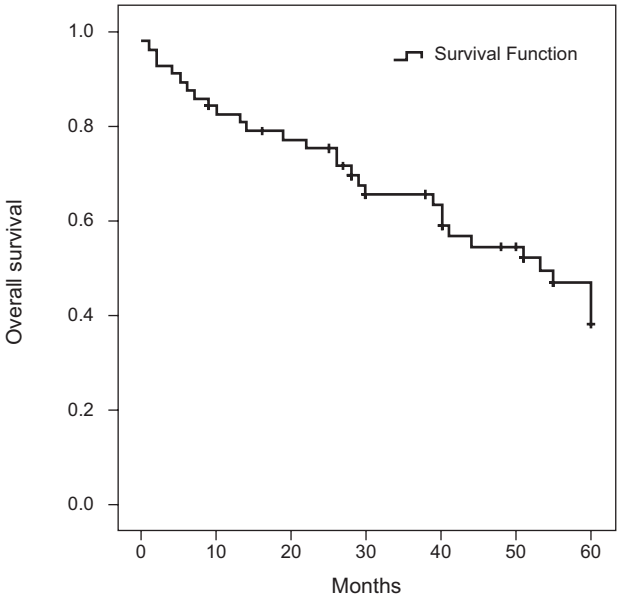

Figure 1. Overall survival of 58 patients.

Table 4. Treatment characteristics (n=58)

Treatment	*Patients, n*	*(%)*	*Number of chemotherapy cycles; average (range)*
Radiotherapy only	8	13.8	
Chemotherapy (with radiotherapy)	43	74.1	
cisplatin (40 mg/m^2/week)	8	13.8	3.75 (2-6)
cisplatin (40 mg/m^2/week) + amifostine (500 mg/day)	28	48.2	3.68 (1-6)
cisplatin (70 mg/m^2/3 weeks) + epirubicin (90 mg/m^2/3 weeks)	3	5.2	4.33 (4-5)
cisplatin (40 mg/m^2/week) + UFT (300 mg/m^2/day)	3	5.2	2.66 (2-4)
UFT	1	1.7	2 (2)
Neoadjuvant chemotherapy	7	12.1	2.99 (2-3)
cisplatin (40 mg/m^2/week)	1	1.7	3 (3)
cisplatin (70 mg/m^2/3 weeks)+ epirubicin (90 mg/m^2/3 weeks)	3	5.2	3.66 (2-3)
cisplatin (40 mg/m^2/week)+ amifostine (500 mg/day)	3	5.2	3.66 (2-3)
Radiotherapy (Gy)			
<70	4	6.9	
≥70	54	93.1	

in the first 3 years. The first metastatic locations were in the bones and lungs, with later involvement of multiple organs. Four of the patients with distant metastases received RT and concurrent with CT. Five patients received in addition supportive therapy concurrently with the RT+CT.

Of the whole group of 58 patients followed-up 61% were alive and disease-free for more than 5 years. The median overall survival was 55.78 months (Figure 1). Median disease-free survival, local failure-free survival and distant failure-free survival were 37.43, 61.57, and 62.25 months, respectively (Table 5). The 5-year overall survival, disease-free survival, local failure-free survival, and distant failure-free survival rates were 47, 25, 52 and 53%, respectively.

Factors affecting survival

Overall survival

RT dose and additional CT were independent prognostic factors for overall survival (Figure 2). The 5-year overall survival for patients that received CT and nCT was 49 and 82%, respectively (p=0.01; Table 6). nCT patients were more likely to have had a longer time to death from the start of chemotherapy (p=0.05, HR=7.865, 95% CI=1.002-61.762). There was no significant difference between groups concerning sex, age, histopathology, stage, and stage groups on overall sur-

Table 5. Cumulative proportion of survival during 6 years in 12-month intervals (%)

Months Survival	*12*	*24*	*36*	*48*	*60*	*72*
Overall	83	75	66	55	47	32
Disease-free	81	67	52	36	25	15
Local failure-free	81	73	64	58	52	35
Distant failure-free	83	81	73	59	53	39

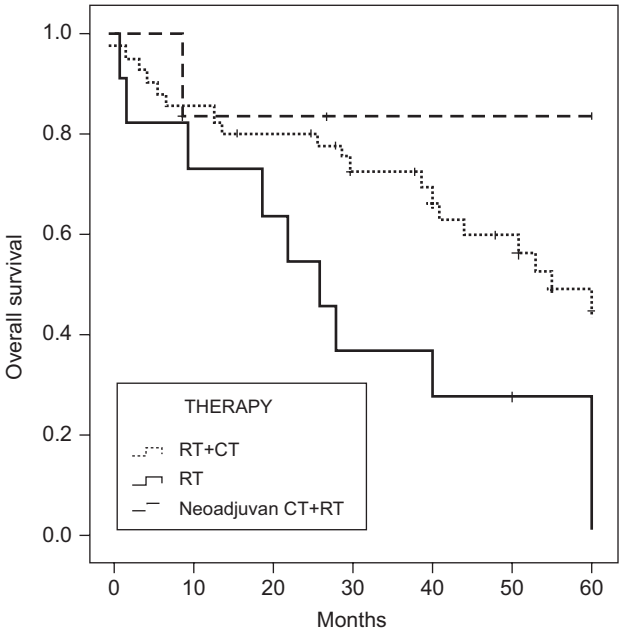

Figure 2. Overall survival for different treatment groups. RT: radiotherapy only, RT+CT: radiotherapy and chemotherapy, nCT: neoadjuvant chemotherapy. Pooled overall log rank comparison p=0.010; RT vs. RT+CT p=0.024; RT vs. nCT p=0.009.

Table 6. Relationship between 5-year survival rates and prognostic factors according to AJCC1997. Univariate analysis

	Overall survival (p-value)	*Disease-free survival (p-value)*	*Local failure-free survival (p-value)*	*Distant failure-free survival (p-value)*
Sex	0.07	0.114	0.120	0.128
Male				
Female				
Age (years)	0.17	0.035	0.119	0.132
≤ 50				
> 50				
Histopathology (WHO)	0.23	0.12	0.17	0.198
Type I				
Type II				
Type III				
Adenocarcinoma				
Lymphoma				
T stage	0.62	0.46	0.63	0.42
T1				
T2a				
T2b				
T3				
T4				
N stage	0.48	0.79	0.36	0.78
N0				
N1				
N2				
N3a				
N3b				
Stage grouping AJCC 1997	0.198	0.59	0.24	0.49
I				
IIA				
IIB				
III				
IVA				
IVB				
IVC				
Treatment	0.01	0.001	0.007	0.003
RT+CT				
RT				
nCT				
Radiotherapy dose (Gy)	0.019	0.045	0.009	0.011
<70				
≥70				

For abbreviations see text

vival. Only advanced-stage patients (stage III and IV, AJCC 1997) lived less than early-stage (stage I and II, AJCC 1997) patients (p=0.047). Also, advanced-stage (AJCC 1997) patients who received RT alone were found to have shorter time to death compared to patients who received nCT (p=0.033). Similar results were obtained for the new proposed staging system (p=0.035).

The 5-year overall survival for males and females was 61% (standard error/SD ±9), and 42% (SE ±7), respectively (p=0.07); for patients aged >50 and ≤50 years it was 40% (SE ±10), and 58% (SE ±10%), respectively (p=0.17).

Disease-free survival

Disease-free survival was significantly and independently related to the RT dose (p=0.045), type of treatment (p=0.001), and age (p=0.035) (Table 6). Multivariate analysis affecting disease-free survival showed that sex (p=0.037; HR=0.13; 95% CI=0.021-0.890) and histology (p=0.009; HR=2.92; 95% CI=1.307-6.512) had similar impact on disease-free survival. None of the other prognostic factors showed any significant effect on disease-free survival.

Local failure-free survival

There was no difference for local failure-free survival for most of the prognostic factors. The only significant factor found was the type of the treatment given (p=0.007; Table 6). Male patients who received RT with concurrent CT lived longer (p=0.41; HR=3.05; 95% CI=1.50-3.473). Otherwise, sex (p=0.015; HR=0.245; 95% CI=0.079-0.759) and histology (p=0.009; HR=2.0; 95% CI=1.188-3.378), were found to contribute equally to local failure-free survival. The 5-year freedom from local failure on multivariate analysis of sex and age was not significant (p=0.79; HR=1.669; 95% CI=0.033-84.444).

Distant failure-free survival

Being male and having type II pathology was found to be an important risk factor for distant metastasis. Males were more likely to have distant failure than females (p=0.037; HR=4.132; 95% CI=1.09-15.66). It was also found that regardless of sex, histology was an important risk factor for distant failure (p=0.046; HR=0.061; 95% CI=0.004-0.952). None of the other prognostic factors displayed any significant effect on distant failure-free survival. No significant difference was found for pairwise comparisons of different stages according to AJCC1997 for distant failure-free survival.

Stage grouping according to AJCC 1997 and the new proposed system were found to have no significant effect on distant failure-free survival (p=0.49 and p=0.39, respectively) (Tables 6 and 7).

Discussion

This retrospective study evaluated the data of NPC patients who had been treated in IOC. The patient num-

Table 7. Five-year survival rates using the T, N and group staging according to the new (2008) proposed staging system [22]. Univariate analysis

	Overall survival (p-value)	*Disease-free survival (p-value)*	*Local failure-free survival (p-value)*	*Distant failure-free survival (p-value)*
T stage	0.53	0.63	0.55	0.58
T1				
T2				
T3				
T4				
Tx				
N stage	0.58	0.86	0.43	0.89
N0				
N1				
N2				
N3				
Stage grouping	0.24	0.45	0.24	0.39
I				
II				
III				
IVA				
IVB				
IVC				

bers were low due to the low incidence of NPC in Turkey.

The latest AJCC staging system (1997) and the new 2008 staging system were used to investigate the prognosis and risk factors [21,22]. Most (81.1%) of the patients had advanced-stage disease. Early-stage patients (6 patients - T1N0 and T2N0) were too few using both staging systems. The median survival time for stage IVB patients was surprisingly high (64.5 months, AJCC 1997) which might be attributed to the very few patients (n= 4). As expected, advanced-stage patients were found to live less than early-stage patients. Thirty-six patients were found to have N0 disease using both staging systems. Unlike other reported series from Turkey, the number of non-keratinizing type 2 tumors (55.2%) exceeded the number of undifferentiated type 3 tumors (32.8%).

The findings of this study confirm that systemic treatment in addition to RT is advisable for early-stage NPC, due to the high incidence of late development of distant metastases and poor long-term survival after RT alone [27]. The addition of CT improved survival and reduced the risk of distant metastases in early-stage NPC patients. More prospective studies to evaluate the benefits of adjunctive CT in early-stage NPC are needed.

According to the University of Texas M. D. Anderson Cancer Center (MDACC) study [28], 5-year local control rates for T stages (1992 AJCC staging system) were 93, 79, 68 and 53%, respectively. This series showed that RT is successful only in the very early stages without inclusion of CT, and CT is necessary for advanced-stage lesions.

We found that the survival rates (both overall and disease-free) were improved significantly with combined therapy. In another reported randomized trial [29] comparing RT with or without concurrent CT, local control for 3 years was 70% with combined therapy (RT with cisplatin and 5-FU), and 44% with RT only (p=0.01). The International Nasopharynx Study Group [30] also found significantly improved disease-free survival rates when patients were treated with combined treatment. No statistical significance was obtained for overall survival, which is possibly related to deaths as a result of CT side effects.

The overall and disease-free survival rates were similar in another study conducted in Izmir [19], but the local failure-free and distant failure-free survival rates were lower. Otherwise, no significant difference was found between disease-free vs. local failure-free survival and distant failure-free vs. local failure-free survival for different treatment groups (p=0.92).

Combination CT, as part of the standard therapy for all cases, increased the efficiency of both treatment and survival. Patients starting later nCT were more likely to have a shorter time to death than the RT and RT+CT patients. Advanced-stage (AJCC 1997) patients who received RT alone had shorter time to death than patients who received nCT and then RT.

RT dose was a factor improving survival rates, but this difference could be due to the small patient numbers who received <70 Gy.

Both staging systems, AJCC 1997 and the new 2008 system showed no significant differences in survival rates, but male patients and patients with type II pathology were under greater risk for distant metastases when using the new system.

The present study suggests indirectly a low incidence of NPC in the greater Izmir area. Diet and genetic factors are important factors in NPC. Studies revealed that there is a relationship between diet and cancer. Frequent intake of vegetable and fruits decrease the risk of oral and pharyngeal cancer [9]. The risk was found to increase with red meat, pork and processed meat. Mediterranean diet, mainly consumed in the Aegean coast of Turkey, is cooked with olive oil. It is very well known that olive oil is protective against cancer with its antioxidant properties [31-33]. This may be a reason for the low prevalence of NPC in Turkey along with genetic factors.

In conclusion, early diagnosis seems an important factor for successful treatment of this disease. Combined treatment with CT and RT from the beginning gave the most favorable results and is recommended. Both the UICC 1997 system and the new proposed system for staging gave similar findings in this series and it seems to be little advantage in using the new proposed

system. This, however, may be due to the low numbers in this study.

The complexity of staging and its prognostic significance will cease when the interaction of tumor cell and patient's immune system are better understood. Research into biological processes, mostly virus-host interactions, gene expression, and immune response, are future targets for improved biological staging systems and possibly more effective treatments.

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