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Original Research

Outcome of Elderly Nasopharyngeal Carcinoma Patients: A Single Center Study

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ABSTRACT

Objective: This study aimed to assess the efficiency of radiotherapy and evaluate its outcomes for elderly (>65 years) patients who have undergone treatment for nasopharyngeal carcinoma (NPC).

Methods: Forty-five (male, 35; female, 10) elderly patients with a diagnosis of undifferentiated NPC who were treated at our institution between 1994 and 2012 were retrospectively evaluated. The primary endpoint was the relationship between the patients' characteristics and overall survival (OS); progression-free survival (PFS), locoregional progression-free survival (LR-PFS), and toxicity analysis were the secondary endpoints.

Results: The patients had a median age of 74.2 years. At a median follow-up period of 64 months, the median OS, PFS, and LR-PFS were 45 (95% confidence interval [CI]: 5.887-84.113), 34 (95% CI: 0.0-70.504), and 45 (95% CI: 20.092-69908) months, respectively. The 2-, 3-, and 5-year OS rates were 61.5%, 53.1%, and 50.0%, respectively, and the 2-, 3-, and 5-year PFS rates were 57.6%, 46.8%, and 43.7%, respectively. Patients with T stage (T3-T4 vs.T1–T2) or N stage (N0–1 vs. N2) had significantly shorter OS ($p<0.05$), PFS ($p<0.05$), and LR-PFS ($p<0.05$) outcomes, respectively, which were also confirmed using a multivariate analysis ($p<0.05$).

Conclusion: Our results demonstrated that the established prognostic factors, including T and N stages, were important prognostic indicators of NPC in elderly patients.

Keywords: Chemoradiotherapy, elderly, nasopharyngeal carcinoma, survival

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an epithelial malignant tumor of the nasopharynx (1). However, squamous cell carcinoma is the most common histopathological type of NPC (2). The incidence rate ranges from 20 to 30 per 100.000 individuals (3). Although the early detection of NPC is important for its curability and for reducing treatment-related toxicity, majority of the patients present with symptoms of an advanced state of NPC (4).

Based on the location of the nasopharynx and due to the high radiosensitivity of the disease, radiotherapy is the standard management strategy for nonmetastatic disease (5, 6). However, the age and comorbid conditions of elderly patients with NPC pose a unique challenge for radical treatment (7). Intensity-modulated radiotherapy (IMRT), which has an advantage of more precise coverage using sharp-dose gradients, has been accepted as the gold standard radiotherapy technique that may improve tumor control and quality of life (8-10). Unfortunately, there are limited oncology centers that follow the modality of employing three-dimensional conformal radiation therapy (3D-CRT) and brachytherapy as a boost to the dose supplement.

Therefore, this study aimed to evaluate the clinical outcomes of NPC in elderly patients undergoing 3D-CRT and brachytherapy (BRT) as the treatment boost.

METHODS

A total of 45 elderly patients with NPC, treated between June 1994 and June 2012, at Hacettepe University, Department of Radiation Oncology, were retrospectively analyzed. The median follow-up duration was 32 months (range: 6-193 months). Although no defined age cutoff currently exists for patients in the field of oncology, the patients in this study were defined as elderly if they were aged ≥65 years. The patients included in this

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study were selected from 558 patients who underwent definitive radiation therapy (RT) or chemoradiation therapy (CRT).

Clinical staging was performed using head, neck, and thoracic magnetic resonance imaging (MRI), abdominal computed tomography (CT), and whole-body bone scanning. In the past decade, the clinical staging of most patients with distant metastasis was performed using 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography. All the patients were staged according to the American Joint Cancer Committee (AJCC 7th edition, 2010) TNM staging system guidelines.

Ethical Considerations

All the procedures were performed in accordance with the ethical guidelines of the institutional and/or national research committee and with the guidelines of 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the participants included in the study.

Treatments

All the patients were treated daily with doses of 1.8-2.12 Gy (median: 2 Gy). Every patient received 60-70 Gy at the primary tumor site. Patients who underwent CRT were treated with the most frequently used concurrent single agent, which was a platin-based (cisplatin or carboplatin) agent. Cisplatin (25-40 mg/week) was concomitantly admininstered for 7 weeks. Furthermore, during the course of the treatment, RT was administered using two techniques: conventional RT and 3D-CRT. BRT, in combination with external RT, was used to boost the dose supplementation in patients with locally persistent tumors. Subsequently, intracavitary BRT was administered at a total dose of 12 Gy in three fractions after external RT. BRT was performed using a high-dose rate MicroSelectron device (Netherlands), an Ir-192 source, and special single-channel applicators.

Statistical Analysis

The primary focus was to investigate the effect of potential prognostic factors associated with OS, while the secondary focus was to evaluate the associations between the prognostic factors, PFS, and LR-PFS. Descriptive statistics and the Kaplan-Meier survival test were performed to evaluate the population frequencies and estimate the overall survival (OS), respectively. OS was defined as the interval between the diagnosis date and death/last follow-up date. The interval between the first day of concomitant CRT and progression/recurrence at the nasopharynx and/or ipsi-/contralateral neck or death/last follow-up date (for LR-PFS), and any disease progression or death/last follow-up date (for PFS), respectively, were estimated. The data were analyzed using Statistical Package for the Social Sciences version 22.0 for Windows (IBM SPSS Corp., Armonk, NY, USA). Categorical variables were expressed as frequency, whereas numerical variables were expressed as descriptives. $P<0.05$ was considered significant.

Main Points:

- The normal diameter of the main portal vein measured on CT examination is different from the commonly accepted normal value of 13 mm.
- The mean diameter of the main portal vein measured using contrast-enhanced CT was larger than that measured using non-contrast-enhanced CT.
- Considering that the mean diameter of the main portal vein on CT is 15.5 mm in healthy subjects, the normal upper limit will be higher than this value.

RESULTS

The median age of the patients was 74.2 years (range: 65-82 years). Of the 45 patients in total, 35 (77.7%) were males and 10 (22.3%) were females. The distribution of the patients who were treated according to the AJCC 2010 staging system during the diagnosis is as follows: T1 (n=14; 31.2%), T2 (n=8; 17.6%), T3 (n=14; 31.2%), T4 (n=9; 20%), N0 (n=20; 44; 5%), N1 (n=14; 31.1%), and N2 (n=11; 24.4%). A diagnosis analysis showed that 7 patients (15.6%) had stage I, 8 (17.6%) had stage II, 21 (46.8%) had stage III, and 9 (20%) had stage IVA NPC.

All the patients were treated with doses of 1.8–2.12 Gy (median: 2 Gy) per day. The primary tumor site received a dose of 60–70 Gy (median: 70 Gy). The following treatments were administered: RT alone, n=16 (35.5%); concurrent CRT, n=12 (26.7%); CRT+adjuvant chemotherapy (CT), n=3 (6.7%); neoadjuvant CT+CRT, n=8 (17.7%); and neoadjuvant CT+RT, n=6 (13.4%). The median RT duration was 52 days (range: 30–73 days). Of all the patients, 26 (57.7%) received BRT as a treatment boost. The patient characteristics and treatment details are listed in Table 1.

The last follow-up visit indicated that 17 (37.7%) patients survived with no evidence of the disease, 2 (4.5%) survived with local recurrence (LR), and 1 (2.2%) survived with distant metastasis. Furthermore, 25 (55.6%) patients died, of which 20 (43.5%) deaths were caused by disease recurrence, 2 (4.4%) by treatment-related toxicity, and 3 (6.6%) by nontumor-related causes. The 2-, 3-, and 5-year OS rates were 61.5%, 53.1%, and 50.0%, respectively, and the median OS time was 45 months (95% CI 5.887–84.113). The evaluation of the patient survival rates was performed using a univariate analysis based on the T stage (1–2 vs. 3–4), N stage (0–1 vs. 2), sex, treatment modality, BRT boost, and age groups (<70 years vs. ≥70 years). The estimated OS for the T stage 1–2- and 3–4-group was 95 and 22 months, respectively, which was statistically significant (p=0.003). However, the other potential prognostic factors (age, treatment modality, and BRT boost) did not show any effect on OS. The results of the univariate analysis revealed that a lower T stage (1–2 vs. 3–4) and N stage (0–1 vs. 2) was associated with a significantly improved OS rate (Figure 1). However, in the multivariate analysis, these factors remained independent of the OS rate.

The 2-, 3-, and 5-year PFS rates were 57.6%, 46.8%, and 43.7%, respectively, and the median PFS time was 34 months (95% CI: 0.0–70.504). The estimated PFS for the T stage 1–2- and 3–4-group was 83 and 18 months, respectively, which was statistically significant (p=0.002). Furthermore, the estimated PFS for the N stage 0–1- and 2-group was 34 and 11 months, respectively, which was statistically significant (p=0.009). However, the other potential prognostic factors showed no effect on PFS. The

Table 1. Patients characteristics and treatment details in patients with elderly NPC

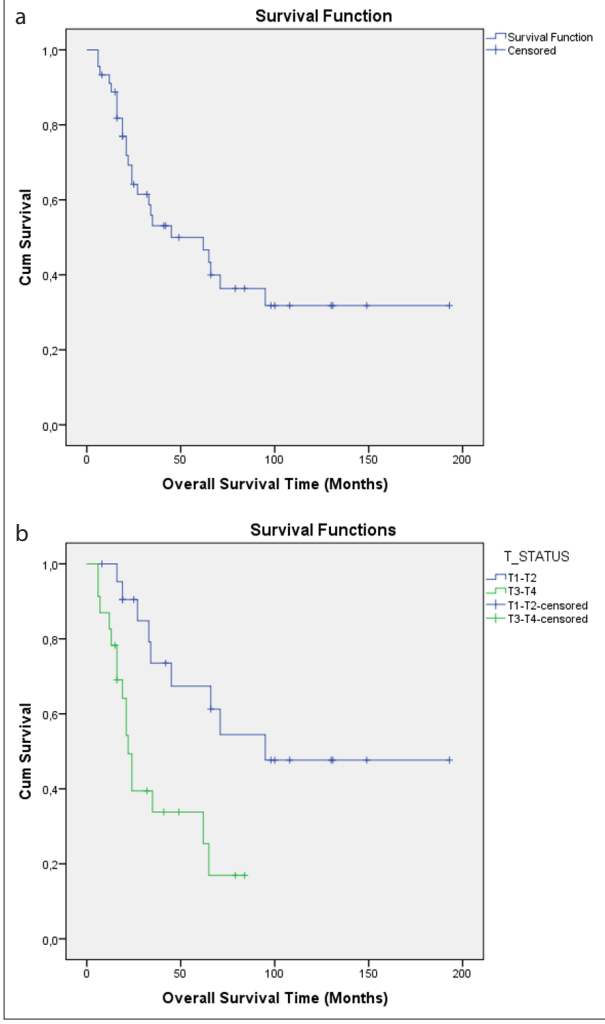
Characteristics	Patients	
	Number	%
Gender		
Male	35	77.7
Female	10	22.3
Age (year)		
<70	21	46.7
≥70	24	53.3
Brachytherapy boost		
Present	26	57.7
Absent	19	42.3
WHO morphology		
Type I (keratinizing)	3	6.7
Type II (non–keratinizing)	25	55.5
Type III (undifferentiated)	17	37.8
External radiotherapy dose		
<6500 cGy	6	13.3
≥6500 cGy	39	86.7
T stage (2010 AJCC 7th)		
T1	14	31.2
T2	8	17.6
T3	14	31.2
T4	9	20.0
N stage (2010 AJCC 7th)		
N0	20	44.5
N1	14	31.1
N2	11	24.4
TNM stage (2010 AJCC 7th)		
I	7	15.6
II	8	17.6
III	21	46.8
IV a	9	20.0
Treatment modality		
RT	16	35.5
CRT	12	26.7
CRT+Adjuvant CT	3	6.7
Neoadjuvant CT+ CRT	8	17.8
Neoadjuvant CT+RT	6	13.3
CT		
Yes	17	37.8
No	28	62.2
Concomitant CRT		
Yes	23	51.1
No	22	48.9

AJCC: American Joint Cancer Committee; RT: radiotherapy; CRT: Cchemo–radiotherapy; CT: chemotherapy; WHO: World Health Organization; TNM: Tumor, Node and Metastasis

outcomes of the univariate analysis revealed that a lower T stage (1–2 vs. 3–4) and N stage (0–1 vs. 2) was significantly associated with better PFS outcomes (Figure 2). However, the results of the multivariate analysis revealed that these factors remained independent of the PFS rate.

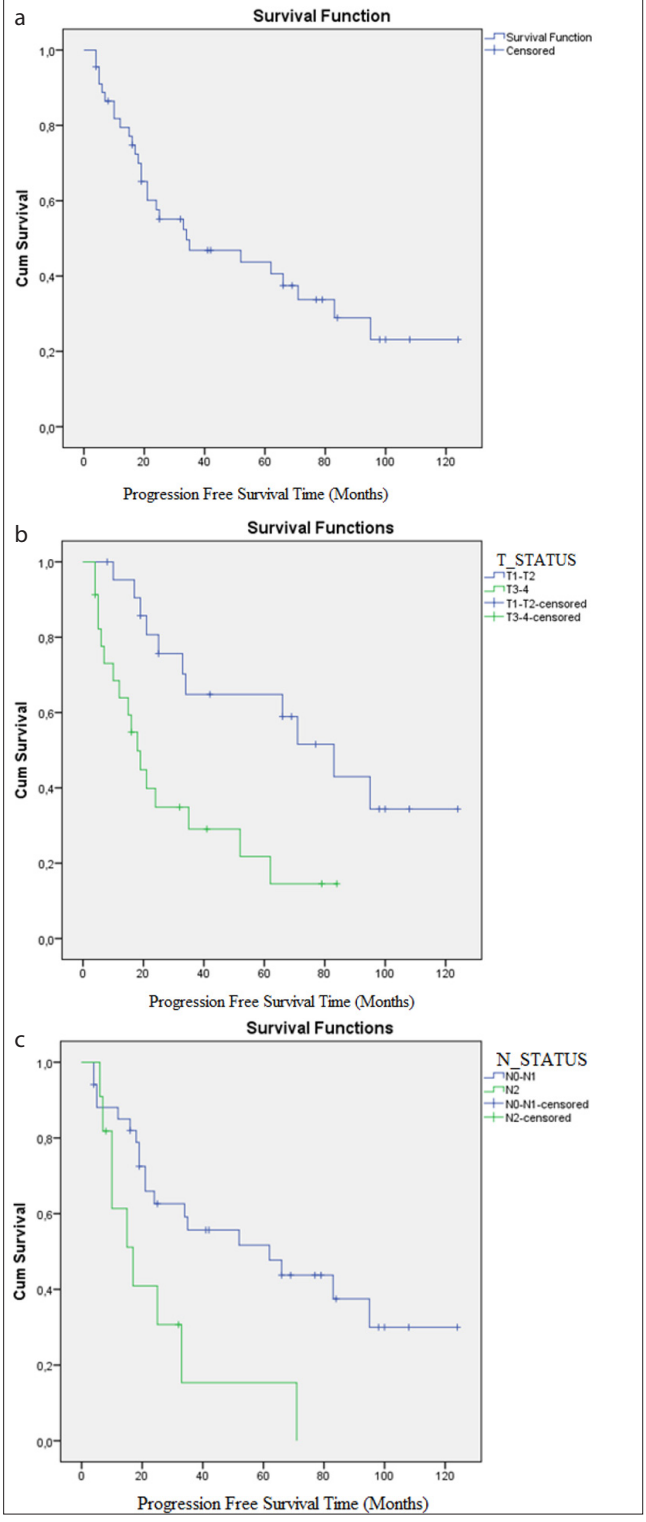
During the follow-up period, 10 (22.3%) patients experienced recurrences, of which 7, 2, and 1 experienced local, regional, and locoregional recurrences, respectively. The 2-, 3-, and 5-year LR-PFS rates were 67.5%, 53.1%, and 50.0%, respectively. The median LR-PFS time was 45 months (95% CI: 20.092–69908). The estimated LR-PFS for the T stage 1–2- and 3–4-group was 83 and 18 months, respectively, which was statistically significant (p=0.001). Additionally, the estimated LR-PFS and for the N stage 0–1- and 2-group was 62 and 25 months, respectively, which was statistically significant (p=0.034). The results of the univariate analysis revealed that a lower T stage (1–2 vs. 3–4) and N stage (0–1 vs. 2) were significantly associated with an improved LR-PFS (Figure 3). The results of the univariate analysis are summarized in Table 2. In contrast, the multivariate analysis

Figure 1. a, b. Overall Survival curve in 45 elderly patients with NPC. (a) OS curve. (b) Log-Rank curve of OS estimation for T status (p=0.003)



showed that these factors remained independent of the LR-PFS rate; the results of the multivariate analysis are summarized in Table 3.

Figure 2. a-c. Progression Free Survival in 45 elderly patients with NPC. (a) PFS curve. (b) Log-Rank curve of PFS estimation for T status (p=0.002). (c) Log-Rank curve of PFS estimation for N status (p=0.009)



Toxicity

Xerostomia (Grade≤2) was the most frequent treatment-related complication that was reported in 31 (68.9%) patients. During

Figure 3. a-c. Locoregional -Progression Free Survival in 45 elderly patients with NPC. (a) LR-PFS curve. (b) Log-Rank curve of LR-PFS estimation for T status (p=0.001). (c). Log-Rank curve of LR-PFS estimation for N status (p=0.034)

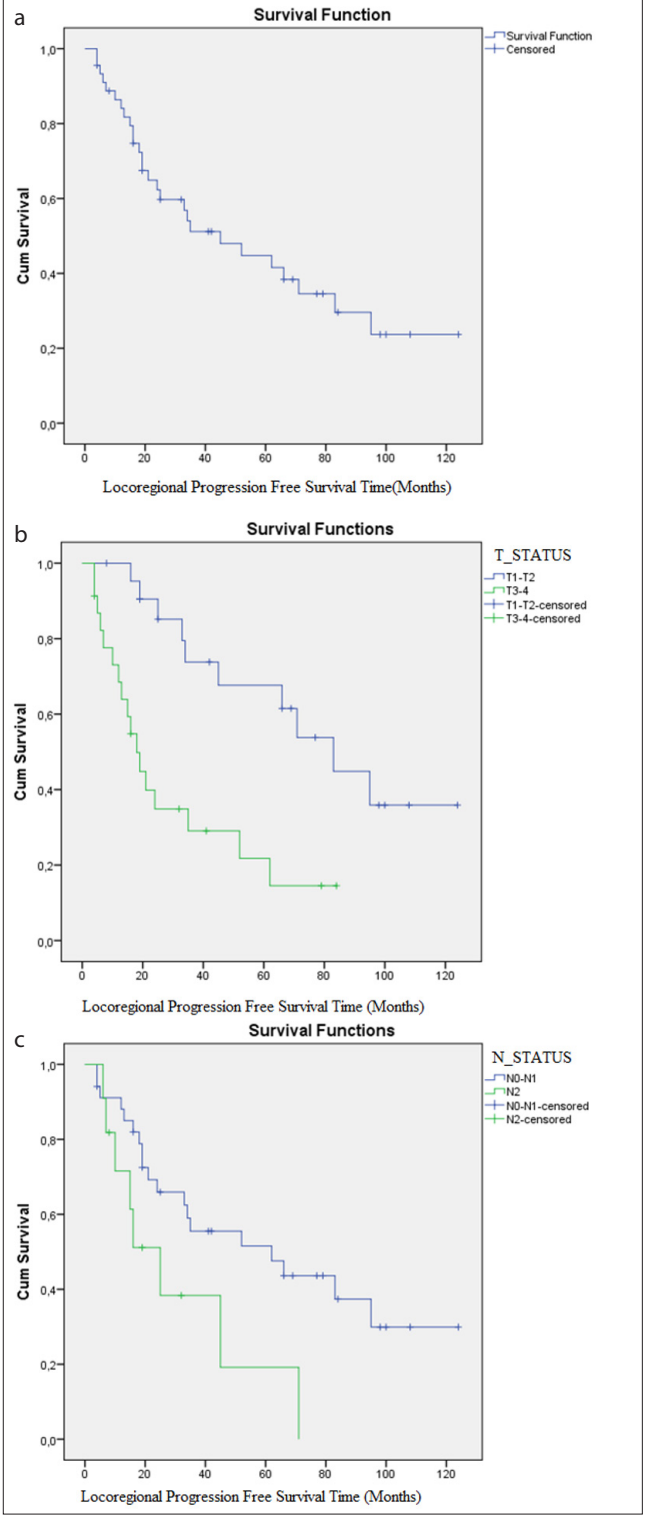


Table 2. Univariate analysis with Kaplan–Meier for prognostic factors in patients with elderly NPC

Analysis data	OS			PFS			LR–PFS		
	Survival Rates			Survival Rates			Survival Rates		
Variant	3–5 years (%)	Months (Median)	p	3–5 years (%)	Months (Median)	p	3–5 years (%)	Months (Months)	p
T stage(AJCC)									
T1–T2	73.5– 67.4	95	0.003	64.8–58.9	83	0.002	73.8–67.7	83	0.001
T3–T4	49.3–33.8	22		29.1–21.8	18		29.1–21.8	18	
N stage(AJCC)									
N0–N1	66.5–56.6	65	0.065	55.7–51.7	34	0.009	55.5–51.5	62	0.034
N2	42.1–21.0	27		40.9–15.3	11		51.1–19.2	25	
Age (years)									
<70	39.0–31.2	34	0.346	37.3–29.8	24	0.545	43.3–29.7	24	0.388
≥70	64.2–58.8	66		64.7–55.0	62		63.2–57.5	66	

OS: Overall Survival; PFS: Progression Free Survival; LR–PFS: Locoregional Progression Free Survival; AJCC: American Joint Cancer Committee

Table 3. Multivariate analysis with Cox Regression for prognostic factors in patients with elderly NPC

	OS			PFS			LR–PFS		
Variant	p	SE	p	p	SE	p	p	SE	p
T status (AJCC) (T1–T2 vs. T3–T4)	0.002	0.453	0.001	0.002	0.416	0.00	0.00	0.434	0.00
N status (AJCC) (N0–N1 vs. N2)	0.028	0.472		0.004	0.439		0.009	0.459	

OS: Overall Survival; PFS: Progression Free Survival; LR–PFS: Locoregional Progression Free Survival; SE: Standard Error; AJCC: American Joint Cancer Committee

Table 4. Late toxicities of subsequent radiotherapy

Complication	Number of patients	%
Xerostomia	31	68.9
Hearing loss	5	11.1
Optic neuropathy	4	8.9
Neck Fibrosis	1	2.3
Lhermitte's sign	1	2.3
Brain Necrosis	1	2.3
Bleeding	1	2.3
Total	44	98.1

the follow-up, late severe complications were observed in 9 (20%) patients, of which 5 (11.1%) had hearing loss and 4 (8.9%) had optic neuropathy. Other toxicities observed in the patients included neck fibrosis (2.2%), Lhermitte's sign (2.2%), brain necrosis (2.2%), and bleeding (2.2%); the details of these complications are summarized in Table 4.

DISCUSSION

In this study, the poor OS, PFS, and LR-PFS outcomes in elderly patients with advanced T and N stages of NPC clearly indicate that these established parameters are important prognostic indicators in elderly patients.

A study conducted by Xiao et al. (11) on patients with early-stage NPC demonstrated that although the 5-year OS rates in T1N0, T2N0, and T1N1 were reported to be comparable, unfavorable OS outcomes were reported in patients with T2N1 when compared to patients in other groups. Moreover, our results, which are in line with the results of this study, reveal that elderly patients with higher T (T3–4 vs. T1–2) and N (N2 vs. N1–0) stages of NPC have lower OS (p=0.002), PFS (p=0.002), and LR-PFS (p<0.001) rates.

Based on the fact that older patients with NPC (>70 years) are usually excluded from clinical trials, the current management strategy for this group was performed according to guidelines for adult and/or studies including patients aged 60–65 years (12-14). However, patients with NPC, aged >70 years, are more likely to have various comorbidities and a poor performance status, limiting the efficacy of radiotherapy and chemotherapy and subsequently resulting in more unfavorable outcomes (7, 15-18). In an IMRT study including patients with NPC, aged >70 years, approximately 30% of the deaths were caused by internal medical problems that were not associated with the cancer. Furthermore, the 5-year OS rate has been shown to be significantly higher in patients with a good performance status (18). Therefore, future

investigations should include more homogenous populations comprising older patients, which may help to update the current literature.

In contrast, no advantage of the multimodal treatment was observed in the elderly patients. Moreover, radiotherapy treatment might be a better option to avoid toxicity. Therefore, an improvement in radiotherapy and chemotherapy is thought to lead to the reduction of acute and late toxicity, thereby improving the quality of life of the patients.

Our study has several limitations. The first and major limitation of this study is its retrospective nature. Moreover, some patients were examined by CT scan of the nasopharynx and neck post 2010, rather than by MRI. Therefore, the patient staging may have been inaccurate. In this regard, additional prospective randomized clinical trials are needed to clearly determine the optimal treatment in elderly patients with NPC.

CONCLUSION

The present findings demonstrate the prognostic value of the established T and N stages in elderly patients with NPC.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013)

Informed Consent: Written informed consent was obtained from participants who participated in this study.

Peer-review: Externally peer-reviewed.

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