Clinical prognostic factors in locally advanced nasopharyngeal carcinoma in Moroccan population

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Abstract

Background:

Nasopharyngeal carcinoma is a distinct cancer of head and neck by its pathology, etiology, epidemiology and clinical behavior. Morocco is considered an endemic region with intermediate incidence. The aim of our report is to underline some clinical determinants of survival in locally advanced disease.

Patients and Methods:

We conducted a retrospective study from January 2003 to December 2005. All patients with undifferentiated nasopharyngeal carcinoma treated in the National Institute of Oncology of Rabat, Morocco were recorded. Classified stage II to IVB disease according to TNM classification adopted by the AJCC (American Joint Committee of Cancer) 6th edition.

Results:

The study included 339 patients, 122 women and 217 men (sex-ratio: 1.7). Mean age was 43 years old (range: 6-91years). Median duration to diagnosis was 6 months (range: 1-72) presenting symptoms at diagnosis were predominantly cervical lymph node in 79%. Forty- two patients have T1 tumors, 159 = T2 tumors, 64 = T3 tumors and 69 = T4 tumors. Sixty-five patients do not have lymph-node involvement, 49 have N1, 128 have N2 and 95 have N3. Three patients were at stage IIA, 57 patients were at stage IIB, 40 patients were at stage III, and 57 patients were at stage IVA and the remaining 96 patients were at stage IVB.

Eighty-seven percent of patients underwent sequential chemoradiation and 17% underwent concurrent chemo-radiation (CTR). Response to induction chemotherapy was assessed in 235 patients. There were 31 patients with complete response and 59 patients have partial response. Complete response to radiotherapy was reached in 235 patients. Mean overall survival (OS) was 66.2%.

Gender was a prognostic factor of OS (p=0.045) and DFS favoring women. Age wasn't a prognostic factors determining the outcome with no difference between patients aged more than 40 years old and patients younger.

Tumor size was not a determinant of survival with a non-significant p in OS and DFS (0.27 and 0.46 respectively) but T4 stage patients appear to have a worse prognosis. Lymph node involvement was significantly determining the outcome either in OS and DFS (p=0.001 and 0.009 respectively). TNM stage was also a significant prognostic factor in OS but not in DFS favoring those with early stage (p= 0, 004 and p= 0, 13 respectively)

The treatment strategy was not a significant prognostic factor with no difference between patients who underwent sequential or concurrent chemoradiation (OS p= 0, 48 and DFS p= 0, 9). In multivariate analysis, lymph-node involvement is the most significant factor.

Conclusion:

Our findings were mostly concordant with the literature data in endemic areas for TNM staging; however we are limited by the bias of retrospective studies. Prospective studies would be more accurate to define those prognostic factors in our population.

Keywords

UCNT, prognostic factors, endemic areas, lymph node involvement

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Introduction

Nasopharyngeal carcinoma is a distinct cancer of head and neck by its pathology, etiology, epidemiology and clinical behavior [1]. Pathologically it is divided into 3 histological subtypes, WHO type 1: squamous cell carcinoma that resembles to the other cancers of head and neck, WHO type 2: non keratinized squamous cell carcinoma and WHO type 3: undifferentiated nasopharyngeal carcinoma tumor (UCNT). This latter is the most frequent histological subtype in endemic areas [2]. It has no relationship with alcoholic and tobacco addiction but it is clearly associated to Epstein Bar virus infection and also to alimentary behaviors and some genetic features [3]. The geographic distribution is also one of the most important characteristic of this tumor with three frequency areas. Morocco is one of the endemic areas with intermediate incidence (8-10/100 000/year) [4]. According to Casablanca registry, it accounts to 4.3% of all cancers [5,6]. In our institution it is the fifth cancer with approximately a median of 250 new cases per year, most of them have locally advanced tumors.

Nasopharyngeal carcinoma is known to be highly sensitive to radiotherapy and chemotherapy [7,8]. Radiotherapy is the cornerstone of treatment of nasopharyngeal carcinoma but concurrent chemo-radiation platinum based is the standard of care of locally advanced tumors. [7,9,10,11,12]

Most studies about prognostic factors in nasopharyngeal carcinoma were undergone in endemic areas; they could be related to patient, tumor characteristics or to treatment modalities.

The aim of our study is to identify some clinical determinants of survival in locally advanced undifferentiated nasopharyngeal carcinoma in a Moroccan population. Secondary endpoints are to describe epidemiological and survival features.

Patients and Methods

Clinical data

With institutional scientific committee review board approval, we reviewed the medical records of all patients with locally advanced undifferentiated nasopharyngeal carcinoma treated at the National Institute of Oncology in Rabat, Morocco from January 2003 to December 2005. Patients were included if they have nasopharyngeal carcinoma WHO type III histologically proven by nasopharyngeal or cervical lymph-node biopsy, with stage II to IVB disease according to TNM classification adopted by the AJCC (American Joint Committee of Cancer) 6th edition. We excluded patients with stage I or IVC, other histological types, patients previously treated for another cancer and patients without follow up after initial diagnosis.

For all patients responding to inclusion criteria, epidemiological and clinical characteristics were described. Treatment modalities and follow up were also reported then survival was correlated to some characteristics to determine prognostic factors.

Treatment

Two types of treatment were used, sequential chemo-radiation with an average of 2 to 3 courses of neoadjuvant chemotherapy followed by radiotherapy alone or concurrent chemo-radiation. Platinum based regimens were mainly used for neoadjuvant chemotherapy : AP protocol with doxorubicin at 50 mg/m^2 and cisplatinum100 mg/m^2, 5FUP protocol with 5 fluorouracil 325 mg/m^2 from day 1 to 5 and platinum 100 mg/m2 on day 1, EP protocol with Epirubicin 75 mg/m^2 and cisplatinum 100 mg/m^2 , CP protocol cyclophosfamide with 750 mg/m^2 and cisplatinum 100 mg/m^2, BEP protocol for children with Bleomycin 15 mg/m^2, Epirubicin 75 mg/m^2 and cisplatinum 100 mg/m^2, MP protocol with Metothrexate weekly at 30 mg/m^2 and cisplatinum 100 mg/m^2 every 3 weeks.

For concurrent chemo-radiation, cisplatin was given weekly at the dose of 40 mg/m^2. Conventional radiotherapy with Cobalt 60 or 6MV was delivered to 250 patients and conformational one was delivered to 89 patients. A total median dose of 70 Grays was delivered to nasopharynx (initial dose of 45 to 50 Grays of photon energy then complementary dose of electron energy). A dose of 45 to 50 Grays for N0 stages and 70 Grays if there were lymph-node

involvement (complement dose with electrons after initial dose of 45 to 50 Grays with photons). Response to induction chemotherapy was assessed clinically by the measurement of lymph node involution using RECIST criteria, thus it was assessed only for patients who had positive lymph nodes while response to radiotherapy was performed radiologically by CT scan and by nasopharynx biopsy 2 to 3 months after completion of radiotherapy.

Follow up

Patients were followed up until June 2011. All patients who are not reviewed in the last consultation were contacted again by telephone. Data update was performed at 30 of June 2011.

Statistical analysis

Statistical analysis was performed using the SPSS software version 13.0. Descriptive of clinical data were expressed in percentage or median or mean ± SD (standard deviation). Overall survival (OS) was defined as the period from histological diagnosis to death from any cause. Disease free survival (DFS) was defined as the period from histological diagnosis to relapse (local or distant relapse). Survivals were calculated using the Kaplan Meier Methods and compared by the log rank test. The relationship between some parameters and outcome (DFS and OS) was assessed with Log rank test in turn using univariate and multivariate Cox's regression analysis. A p-value of < 0.05 was considered significant.

Consent and statement of ethical approval

As the treatment of each patient was decided by the medical staff of the center, oral consent was obtained from the subjects and was approved by the institutional review boards of the National Institute of Oncology in Rabat. This study was approved by the institutional review boards of National Institute of Oncology, Rabat, Morocco.

Results

Patient characteristics

The study included 339 patients with locally advanced nasopharyngeal carcinoma previously untreated. They were 122 women and 217 men (sex-ratio: 1.7), the mean age was 43 years old (range: 6-91 years). Duration time before diagnosis was long with a median of 6 months (range: 1-72) and presenting symptoms at diagnosis were predominantly cervical lymph node involvement in 268 patients (79 %), rhinologic syndrome with nasal obstruction and or epitasis in 213 patients (62%), otologic syndrome in 159 patients 49%, headache in 150 patients (44%) and neurologic syndrome including cranial nerve involvement in 59 patients (17%). Forty-two patients have T1 tumor (12%), 159 with T2 (48%), 60 with T2a and 99 with T2b, 64 with T3 (19%) and 69 with T4 tumors (20%). Sixty-five patients did not have lymph-node involvement (19%), 49 have N1 (15%), 128 have N2 (38%) and 95 have N3 (28%). Thirteen patients (13%) were stage IIA, 57 patients (22%) have stage IIB, 40 patients (15%) have stage III, 57 patients (22%) have stage IVA and the remaining 96 patients (36%) have stage IVB. Patient's characteristics are summarized in Table 1.

	Number	Percentage (%)
Sex		
– Female	122	36
– Male	217	64
Age <40 years / ≥ 40 years	132 / 207	39 /61
Presenting symptoms :		
o rhinologic syndrome	213	62
o otologic syndrome	159	49
o headache	150	44
o neurologic syndrome	59	17
o clinical lymph-node	268	79
TNM Classification :		
– T		
o T1	42	12
o T2a	60	17
o T2b	99	29
o T3	64	19
o T4	69	20
– N		
o N0	65	19
o N1	49	15
o N2	128	38
o N3	95	28
– Stage :		
o IIa	13	5
o IIb	57	22
o III	40	15
o IVA	57	22
o IVB	96	36
Traitement :		
– CTR	57	17
– SCR	282	83
Relapse	118	34
– Local	43	13
– Distant	73	21

CTR : concurrent chemoradiation SCR : sequential chemoradiation

Table 1: Patients characteristics

Treatment and outcome

An average of 2 to 3 courses of neoadjuvant chemotherapy was administered to patients. 83% of patients underwent sequential chemoradiation and 17% underwent concurrent neoadjuvant chemotherapy followed by chemo-radiation (protocols are described in (Table 2).

PROTOCOL	DRUGS	NUMBER
AP	DOXORUBICIN CISPLATINUM	238
5FUP	5 FLUOROURACIL CISPLATINUM	20
BEP	BLEOMYCIN EPIRUBICIN CISPLATINUM	10 (Childhood)
CP	CYCLOPHOSPHAMIDE CISPLATINUM	2
EP	EPIRUBICIN CISPLATINUM	20
MP	METHOTREXATE CISPALTINUM	1

Table 2. Neoadjuvant Chemotherapy Protocols

Conventional radiotherapy was delivered to 250 of patients and conformational one was delivered to 89. The median treatment radiotherapy duration was 8 weeks (range: 5.5-19 weeks). Response to induction chemotherapy was assessed in 235 patients. There were 78 patients with complete response, 133 partial response, 19 stabilizations and 5 progressions. Complete response to radiotherapy was reached in 235 patients; partial response in 39, stabilization in 3 patients and 12 patients progressed, unfortunately for 50 patients any data about response evaluation was recorded in medical files (Table3).

Mean overall survival was 66.2%. Overall survival and disease-free survival were 87.8 and 94% respectively at 1 year; 67.8 and 82 % respectively at 2 years and 60% and 53% respectively at 3 years; 53 and 21% respectively at 4 years; and 52 and 14% respectively at 5 years (Fig 1. 2).

Response	To chemotherapy	To radiotherapy
Complete response	78 (33%)	235 (81%)
Partial response	133 (56%)	39 (13%)
stabilization	19 (8%)	3 (1%)
progression	5 (2%)	12 (4%)

Table 3. Response to induction chemotherapy

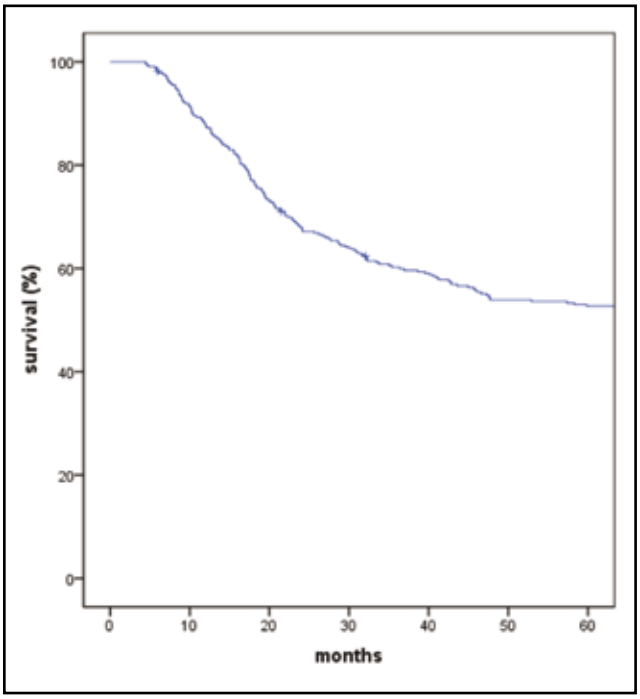

Fig. 1 Overall survival

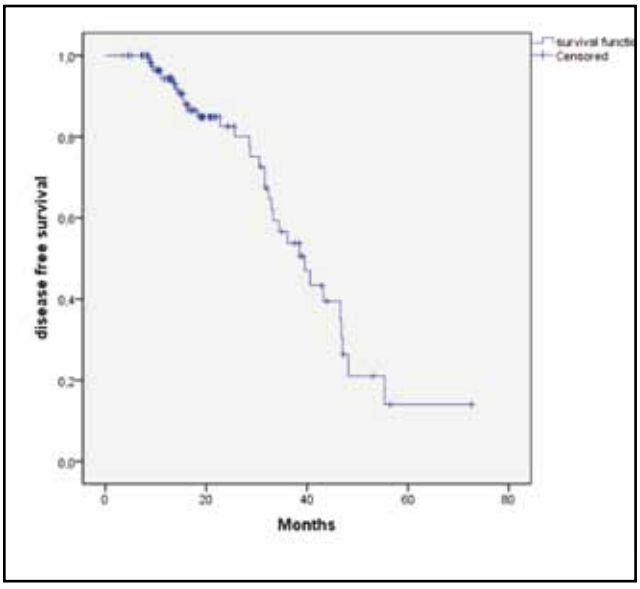

Fig. 2 Disease free survival

Among the 339 patients, 118 relapsed: 43 with locoregional relapse and 67 with distant relapse (Table 4). The median follow up duration was 48 months with a range of 5 and 82 months.

Correlation of prognostic factors to survival

Sex, age, T-classification, N-classification, TNM staging, parapharyngeal space involvement and treatment modalities were evaluated as

Side of metastasis	Number of patients
bone	31
liver	6
lung	6
spine	3
Cerebral	7
Bone and liver	4
Bone and lung	2
Liver and lung	1
Local and distant failure:	8
Local and bone	6
Local and liver	1
Local and lung	1

Table 4. Treatment failure

prognostic factors for survival.

Gender was a prognostic factor for OS (p=0.045) and DFS favoring women but not determinant of DFS (p=0.14) (fig 3. 4)

Age was not a prognostic factor determining the outcome with no difference between patients aged more than 40 years old and younger patients neither in OS (p=0.46) nor in DFS (p=0.14). (Fig. 5, 6)

Tumor size was not a determinant of survival with a non significant p in OS and DFS (0.27 and 0.46 respectively) but T4 stage appears to have a worse prognosis (Fig.7, 8). Also the parapharyngeal space involvement in T2 tumors (T2a and T2b) wasn't significant for DFS and OS (p=0, 13 and p=0,25 respectively)

Lymph node involvement was significantly determinant of the outcome either in OS and DFS (p=0.001 and 0.009 respectively) (Fig. 9, 10)

TNM stage was also a significant prognostic factor for OS but not for DFS favoring those with early stage (p= 0, 004 and p= 0, 13 respectively) (Fig.11, 12)

The treatment strategy was not a significant prognostic factor with no difference between patients who underwent sequential or concurrent chemoradiation (OS p= 0, 48 and DFS p= 0, 9) (Fig. 13. 14)

In multivariate analysis, lymph-node involvement is the most significant factors (Table 5).

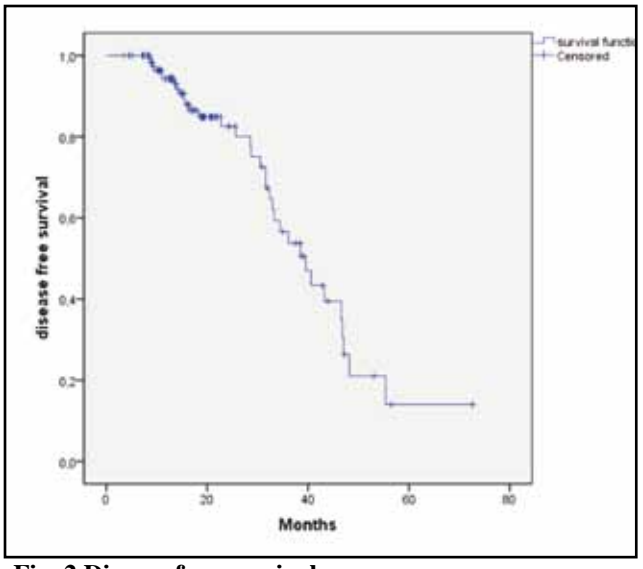

Fig. 2 Disease free survival

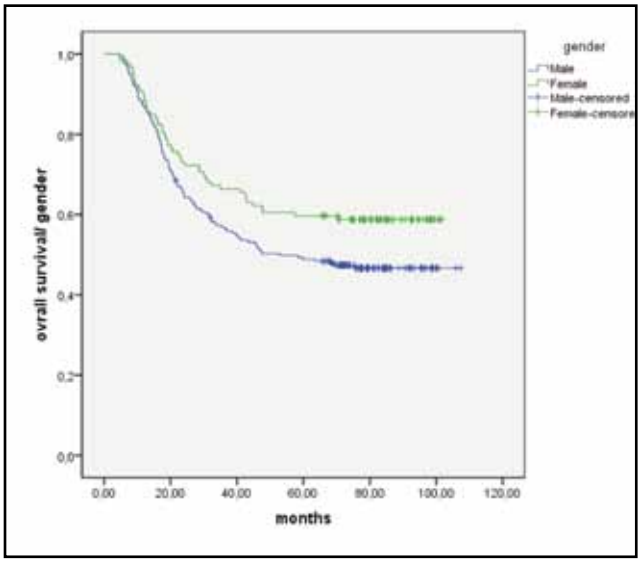

Fig 3. Gender/ OS

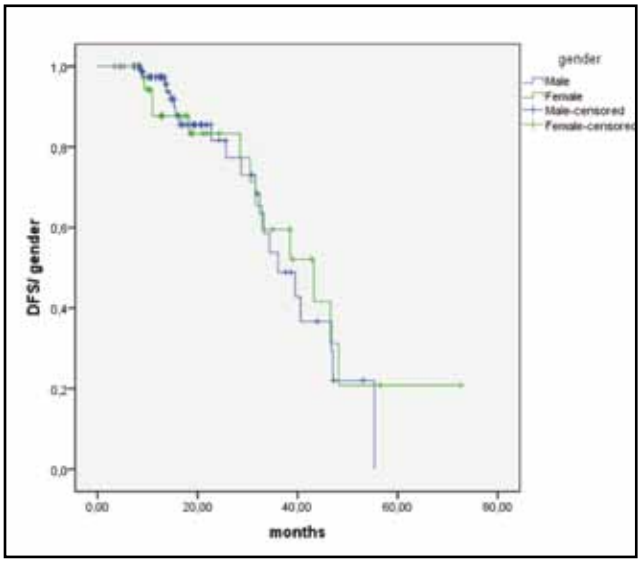

Fig 4. Gender/ DFS

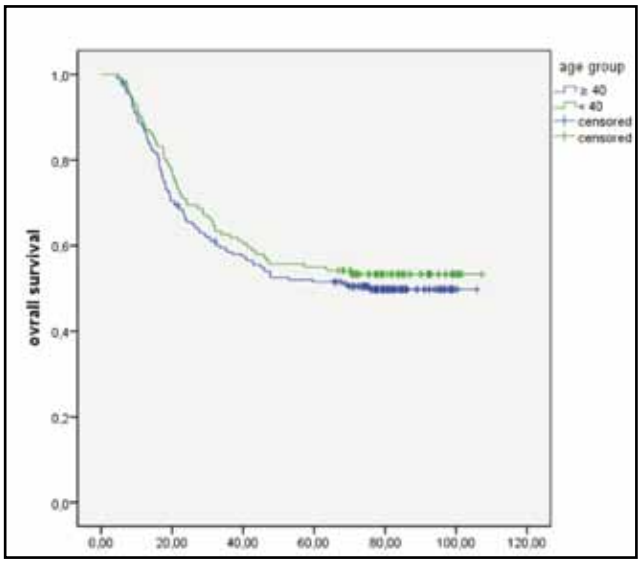

Fig 5. Age/ OS

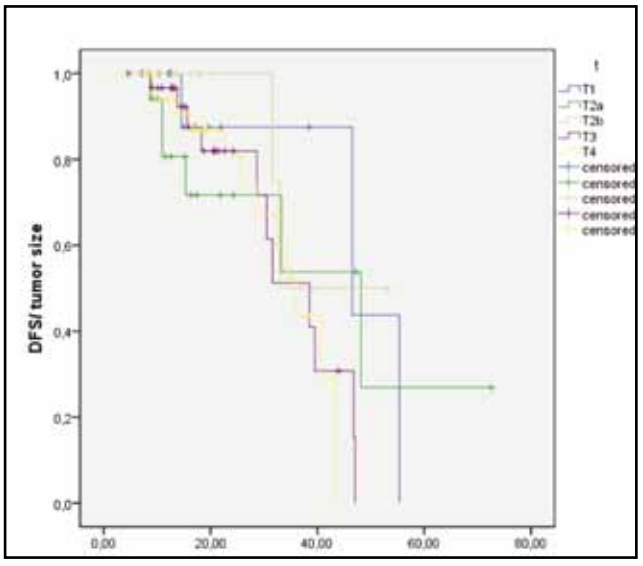

Fig 8. T stage / DFS

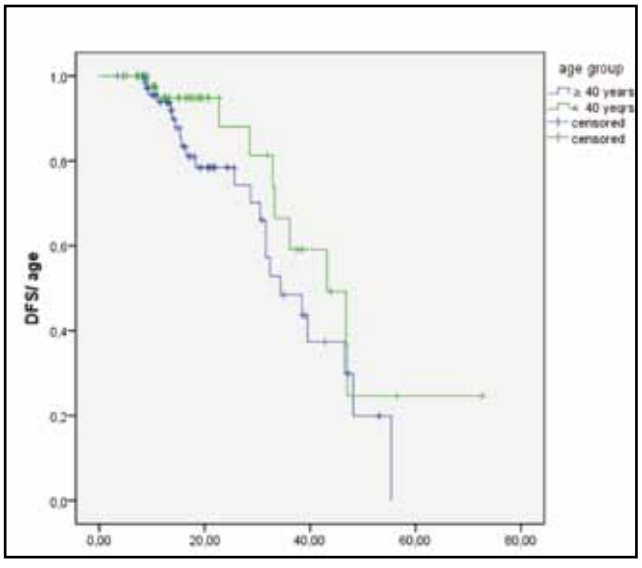

Fig 6. Age/ DFS

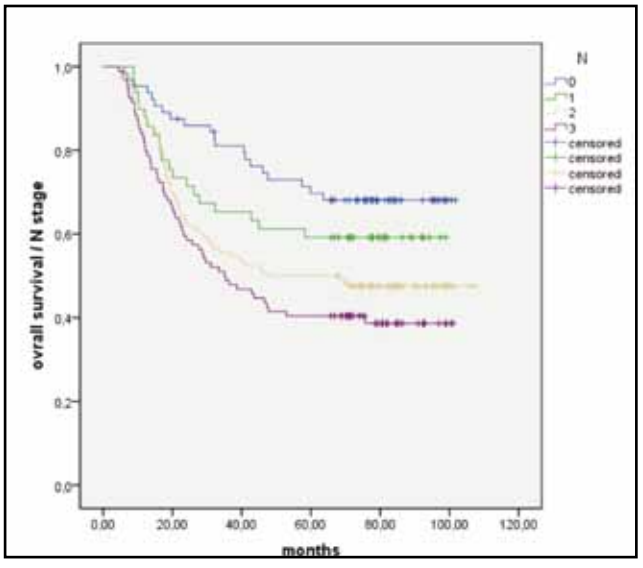

Fig 9. N stage / OS

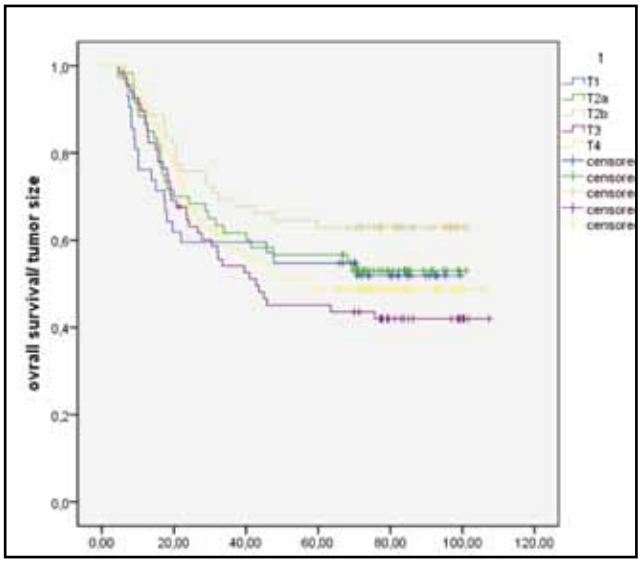

Fig 7. T stage / OS

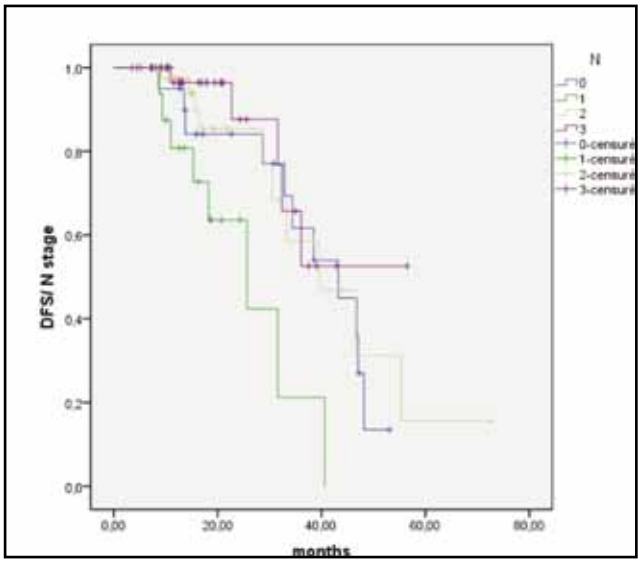

Fig 10. N stage / DFS

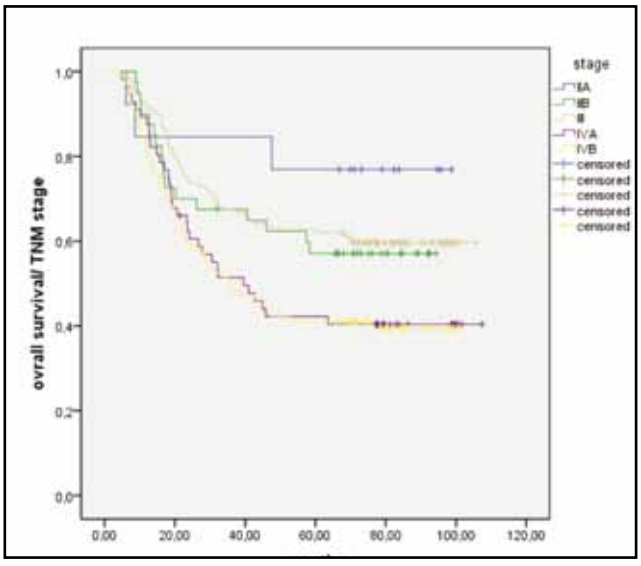

Fig 11. TNM stage / OS

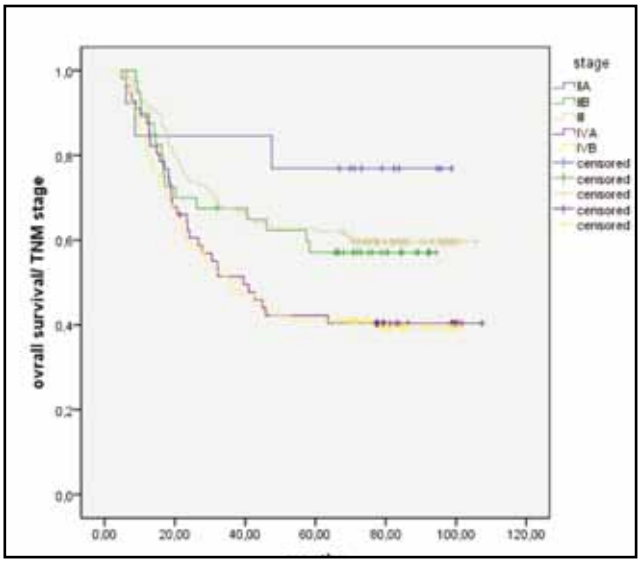

Fig 12. TNM stage / DFS

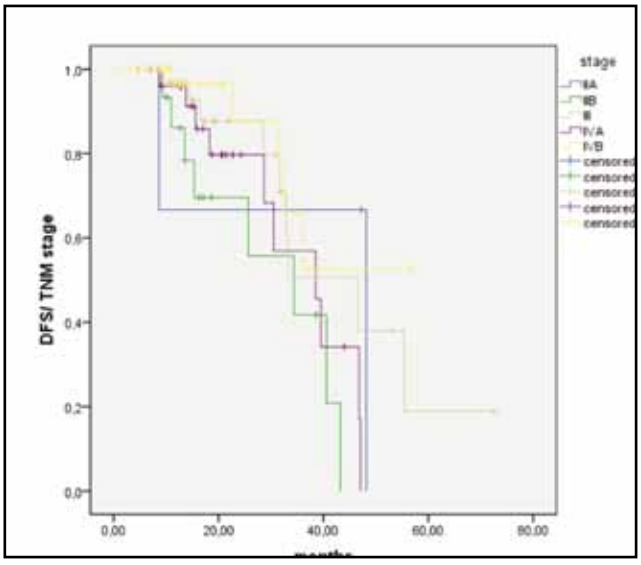

Fig 13. Treatment strategy / OS

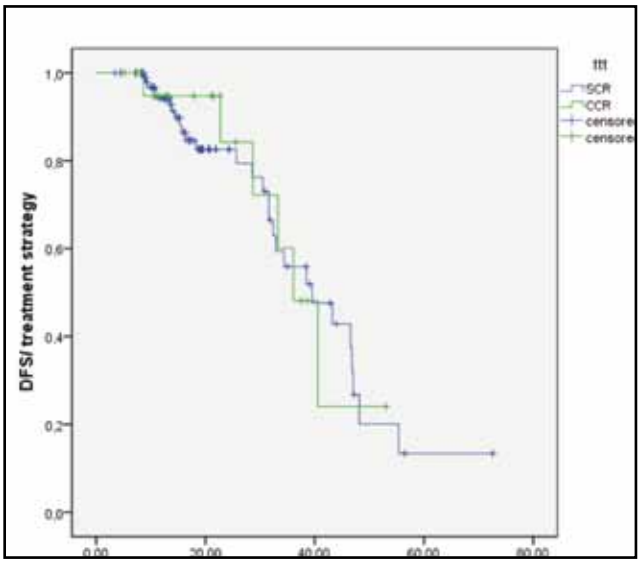

Fig 14. Treatment strategy/ DFS

	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
T stage						
T1	0.85	0.50-1.46	0.56	0.71	0.41-1.24	0.23
T2a	0.77	0.47-1.24	0.28	0.70	0.43-1.15	0.16
T2b	0.56	0.33-0.94	0.027	0.61	0.36-1.02	0.059
T3	1			1		
T4	0.83	0.55-1.26	0.38	0.67	0.45-1.06	0.09
N stage						
N0	0.39	0.23-0.65	<0.001	0.39	0.23-0.6	0.001
N1	0.57	0.34-0.95	0.031	0.54	0.31-0.92	0.024
N2	0.99	0.56-1.13	0.20	0.77	0.53-1.13	0.18
N3	1			1		
TNM						
IIA	0.30	0.09-0.94	0.039			
IIB	0.62	0.36-1.07	0.83			
III	0.55	0.38-0.80	0.002			
IVA	0.95	0.62-1.47	0.83			
IVB	1					
Age group						
<40 years	1			1		
≥40 years	1.13	0.82-1.55	0.47	1.16	0.84-1.61	0.38
sex						
Female	1			1		
Male	1.41	1.01-1.97	0.046	1.30	0.92-1.84	0.14
Treatment						
CCR	1.15	0.78-1.71	0.48	1.03	0.71-1.62	0.75
SCR	1			1		

Table 5. Univariate and multivariate analysis for prognostic factors affecting overall survival

Discussion

We report one of the largest studies in the literature examining clinical prognostic factors of undifferentiated nasopharyngeal carcinoma in an endemic area and showing that lymph-node involvement is the most important determinant of survival. Those factors have been studied in many reports from endemic areas. They could be related to patient, disease characteristics or treatment modalities.

Concerning epidemiologic features, the influence of age at diagnosis is controversial [13]. Young people seem to have better prognosis in a

large series reported by Haldum [14]. Also women are known to have better outcome according to many series [14, 15]. In our series neither age has an impact to the prognosis but women have better OS.

There are many classifications of T-stage in nasopharyngeal carcinoma, thus comparison of literature data is difficult [16]. HO classification is the most used in Asia and southern east countries [17]. In Europe and North America, TNM classification adopted by AJCC recently modified is the reference [18]. This TNM staging remains a strong prognostic indicator with two independent prognostic factors: tumor size or volume (T) and lymph node involvement (N). Haldum reported in a large series that in a WHO type 3 nasopharyngeal carcinoma representing 76% of the tumors, T staging is determinant for overall survival and disease free survival[14]. The same findings were reported by Ching Chih and Cheng [19, 20]. In our report T-staging wasn't significant for survival however T3 and T4 tumors seem to have poor prognosis. In fact tumor volume calculated by multiplying the sum of all areas by the image reconstruction interval (summation of area technique) is more accurate to describe the tumor size. It is the most studied parameter for prognosis and highly significant in determining outcome [20, 21, 22, 23]. Unfortunately in our series, the evaluation of tumor volume for prediction of outcome wasn't possible due to the non-availability of computed imaging database in our institute. Other interesting parameters are parapharyngeal space and pre-vertebral involvement. The parapharyngeal space (PPS) involvement graded by Sham and Choy from 0 to 3 is largely discussed in the literature with controversial finding [24]. In some reports this feature affects local, distant control and overall survival [25, 26]. Other authors and from our own study, the parapharyngeal space involvement is not determinant to the outcome [27, 28, 29]. This difference in findings could be due to differences in the definition and incidence of PPS in published series with different imaging modalities (computed tomography or MRI) [28]. The role of pre-vertebral space involvement as a prognostic factor is also controversial. However, most authors suggest that it is determinant for distant recurrence [23, 26]. We could not evaluate the pre-vertebral space involvement for our patients because MRI was rarely performed.

The stronger predictive factor for overall and disease free survival remains lymph-node involvement with concordant results in the literature data. N3 patients have worse prognosis

All previous authors that studied tumor volume and lymph-node involvement confirm the potency of TNM staging in predicting the outcome. That was concordant with our findings.

Treatment modalities are also a strong prognostic factor. The introduction of chemotherapy to treatment strategies has prolonged a patient's survival while concurrent chemoradiation is the standard of care of locally advanced tumors [30]. We think that the lack of benefit of the concurrent strategy in our series is due to the non-balanced arms. During the study period in our institution, a vast majority of patients received sequential chemoradiation and there were more advanced stages in patients who received CTR. The dose of radiotherapy and treatment duration were the focus of many reports that demonstrated the benefit of high dose in advanced stages for local control [26, 31, 32] and a loss of local control in prolonging radiotherapy[33, 34, 35, 36].

Biological features are also studied as Epstein Barr Virus (EBV) serology, lactic- dehydrogenase serum level, with discordant findings in the literature [37, 38, 39, 40]. The decrease of hemoglobin level during radiotherapy is a predictive factor of response to treatment [41, 42, 43]. In our practice the EBV serology, hemoglobin decrease and LDH level were not dosed routinely at the time of study period. More recently molecular markers are being evaluated for prognosis as the over-expression of phosphatase of regenerating liver-3 (PRL-3), eukaryotic translation initiation factor 4 gamma 1 (EIF4G1), Latent membrane protein 1(LMP1) and many others. In our context molecular markers are not available.

Conclusion

Our findings were mostly concordant with the literature data in endemic areas for TNM staging, but we did not find a benefit for a standard

treatment which CTR over sequential chemo-radiotherapy probably due to the large amount of patients receiving the latter treatment. However we are limited by the bias of retrospective studies. Prospective studies would be more accurate to define those prognostic factors in our population.

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