RESEARCH COMMUNICATION

Prognostic Factors in Patients with Nasopharyngeal Carcinoma Treated in Hospital Kuala Lumpur

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Abstract

Background: Nasopharyngeal carcinoma is the third most common cancer among men in Peninsular Malaysia. However, no information is available about the prognostic factors. The objective of this study was to identify factors with an influence on outcome in patients treated in Hospital Kuala Lumpur. Methods: A total of 159 patients with non-metastatic nasopharyngeal carcinoma treated during 2002-2003 in Hospital Kuala Lumpur were included in this study. All received radiotherapy. Fifty three patients were treated with radiotherapy alone, while 106 patients received combination chemotherapy. Overall survival and local recurrence-free survival were analyzed using the Kaplan-Meier method and univariate analysis was performed using the log-rank test. Results: This study found out that 5-year overall survival and 5-year local recurrence-free survival rates were 58.6% and 54.2% respectively. The stage specific 5-year overall survival rates were: Stage I, 100%; Stage II; 93.3%, Stage III, 62.7%; Stage IVA, 42.2%; and Stage IVB, 40.6%. On univariate analysis, gender (p<0.05), T-classification (p< 0.001), N-classification (p<0.05), stage (p<0.05) and cranial nerve involvement (p< 0.001) were found to be significant prognostic factors for 5-year overall survival, while gender (p<0.05) and N-classification (p<0.05) were significant prognostic factors for 5-year local recurrence-free survival. Conclusion: The overall survival rate of patients for this study was low. The patient factor that significantly affected 5-year overall survival was gender, while disease factors were stage, T-classification, N-classification and cranial nerve involvement.

Keywords: Nasopharyngeal carcinoma - prognostic factors - overall survival

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Introduction

Nasopharyngeal carcinoma (NPC) is a carcinoma arising in the nasopharyngeal mucosa that shows light microscopic or ultrastructural evidence of squamous cell carcinoma (Barnes et al., 2005). NPC is the most common type of nasopharyngeal tumour, showing a distinct racial and geographical distribution (Boyle et al., 2008). According to World Cancer Report 2008, NPC is a rare malignancy in high-resource nations, in which the incidence is less than 1 per 100,000 populations per year for both males and females. However, the cancer has relatively high rate in Asia where age standardized incidence in males is 20 per 100,000 population.

In Peninsular Malaysia, NPC was the third most common cancer among men. According to Malaysian Cancer Statistics- Data and Figure Peninsular Malaysia 2006, there were 981 cases of nasopharyngeal cancer registered with National Cancer Registry in 2006. Age-standardized incidence (ASR) for nasopharyngeal cancer was 8.5 and 2.6 per 100,000 population for males and females, respectively (Zainal et al., 2006). Prevalence rate of the cancer in males is higher than in females, with a male to female ratio of 2.3 to 1. In most of the populations, age is a risk factor but the prevalence rate of the cancer is high in adolescence in low to moderate risk populations such as in North Africa, United States blacks and whites, Malaysian Kadazans, and Indians (Parkin et al, 2005; Yu et al., 2002).

Many studies have been done to find out the prognostic factors in NPC patients (Heng et al., 1999; Liu et al., 2003; Kalogera-Fountzila et al., 2006; liu et al., 2008). Prognostic factors commonly used were patient factors and disease factors. The patient factors included age, race and gender, while disease factors included TNM classification, stage of the cancer and WHO histopathological subtypes. Although many studies had been done in other countries to determine the prognostic factors of NPC, none had been done in Malaysia. Thus the objective of this study was to identify the prognostic factors in nasopharyngeal carcinoma patients who were treated in Kuala Lumpur Hospital.

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Materials and Methods

Patient characteristics

This was a cross-sectional study which included patients who were diagnosed with non-metastatic (M0) NPC. The study population was patients who were newly diagnosed with NPC and received treatment at the Department of Radiotherapy and Oncology of Hospital Kuala Lumpur (HKL) from January 2002 to December 2003. Sampling method was universal sampling. Data was collected from the medical files of patients. There were a total of 190 cases traceable for the study. However, 11 patients with distant metastasis, 12 patients who refused or defaulted treatment and 8 cases in which the information was not complete were excluded. Therefore 159 patients were included in this study.

Treatment

All patients included in this study were treated with radiotherapy. Fifty three patients (33%) were treated with radiotherapy alone, while 106 patients (67%) were treated with radiotherapy in combination with chemotherapy. Forty six patients (29%) had concurrent chemoradiation therapy with or without neoadjuvant or adjuvant chemotherapy, while 60 (38%) had neoadjuvant chemotherapy. The regimens that were mostly used in chemotherapy were cisplatin and 5-fluorouracil as adjuvant or neoadjuvant, while cisplatin alone was used as a radiosensitizer to radiotherapy.

Follow-up

The median follow-up period was 14 months (range, 2-87 months). The duration was calculated from the date of diagnosis to either date of death or the date of the last follow-up.

Statistical Analysis

The end points used in the statistical analysis were the actuarial rates of overall survival (OS) and freedom from local recurrence (LRFS). OS was defined as the time from diagnosis to death resulting from any cause. Patients who were alive were censored at time of last follow-up visit. LRFS was defined as the time from diagnosis to time of local recurrence. Patients who were alive without local recurrence were censored at time of last follow-up visit. Using the Statistical Package for Social Sciences, version 16.0, we performed univariate analysis using Kaplan-Meier method (Kaplan & Meier 1958) and the differences were compared with the log-rank test. Level of significance was 0.05.

Results

There were 159 patients in this study. Of the 159 cases of NPC patients, 124 (78%) were males and 35 (22%) were females. Both median and mean age were 48 years (range, 14-78 years). Histopathologically, 53 patients (33%) had World Health Organization (WHO) type II, and 106 (67%) had WHO type III. On the basis of sixth edition of American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system, 14 patients (9%) had T1, 61 (38%) had T2, 22 (14%) had T3, and 62 (39%) had T4 tumors. Eight patients (5%) had N0, 30 (19%) had N1, 69 (43%) had N2, and 52 (33%) had N3 lymph nodes. Three patients (2%) had Stage I, 19 (12%) had Stage II, 49 (31%) had Stage III, and 88 (55%) had Stage IVA-B. Details are shown in Table 1.

Table 1. Clinical and Pathologic Characteristics of the 356 CRC Cases in this Study

Characteristics		Cases (n)	Percentage (%)
Gender	Male	124	78
	Female	35	22
Age	≤ 48 years	81	51
	> 48 years	78	49
Race	Malay	78	49
	Chinese	70	44
	Indian	4	3
	Other	7	4
Histopathology	WHO type II	53	33
	WHO type III	106	67
T-classification	T1	14	9
	T2	61	38
	T3	22	14
	T4	62	39
N-classification	N0	8	5
	N1	30	19
	N2	69	43
	N3	52	33
Stage	I	3	2
	II	19	12
	III	49	31
	IVA-B	88	55

In this study, the most common signs and symptoms of the patients were neck swelling (72%), nasal presentations (56%) and aural presentations (25%). Nasal presentations included nasal blockage, bloody nasal discharge and epistaxis, while aural presentations included tinnitus, hearing loss, deafness and serous otitis media. Other signs and symptoms included cranial nerve palsies (opthalmoplegia, visual changes and numbness), hoarseness of voice and headache. The mean time for first presentation to diagnosis was 6.4 months, with the range of 0.25-72 months.

In the period of follow up, there were 36 deaths (22.6%) and 29 (18.2%) recurrences. Five-year OS and 5-year LRFS were 58.6% and 54.2%, respectively. Gender, age, race, WHO histopathological subtypes, T-classification, N-classification, cranial nerve involvement, stage and treatment were analyzed as prognostic factors for survival outcome.

In univariate analysis, gender ($p<0.05$), T-classification ($p<0.001$), N-classification ($p<0.05$), stage ($p<0.05$) and cranial nerve involvement ($p<0.001$) were found to be the significant prognostic factors for 5-year OS. However, patient related factors such as age ($p=0.307$) and race ($p=0.430$) were found to be not statistically significant. Besides that, disease related factors such as WHO histopathological subtype ($p=0.566$) were not significant. In addition, the type of treatment ($p=0.236$) was also found to be not statistically significant for 5-year OS.

Stage of NPC was a significant prognostic factor for 5-year OS (Figure 1a). Early stage had better survival

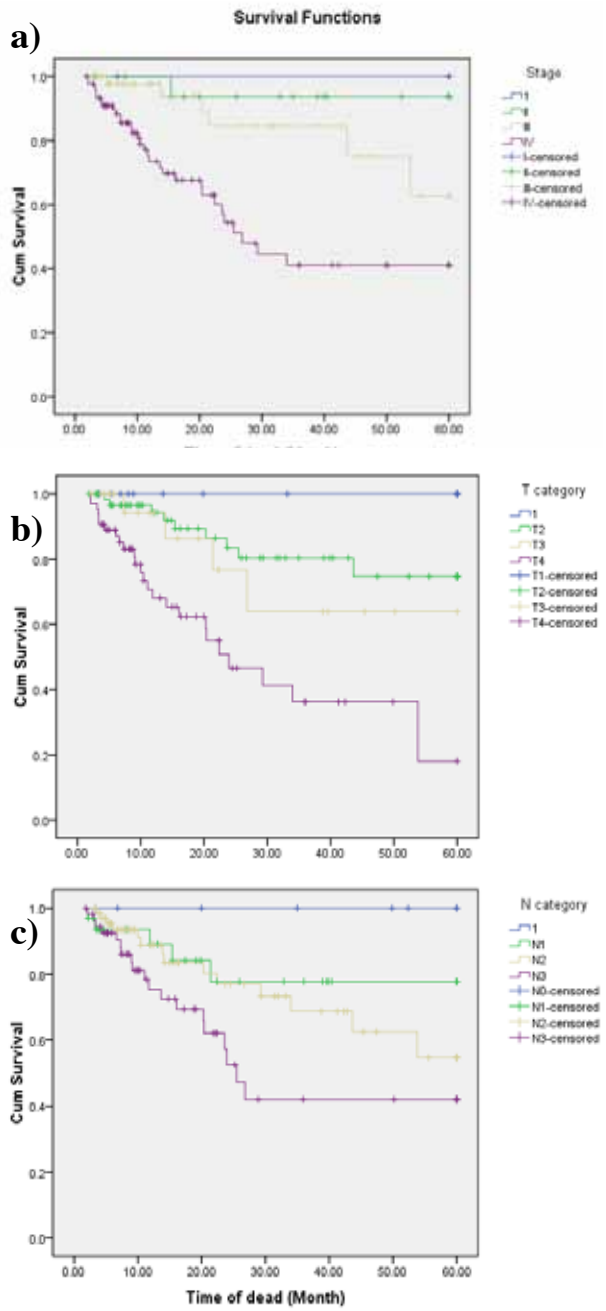

Figure 1. Five-year Overall Survival Curves. a) By stage; b) by T-classification; c) by N-classification

outcome compared to advanced stage. Five-year OS for stage IVA and IVB were 42.2% and 40.6% respectively. Besides, patients with advanced T-classification had a worse 5-year OS, with T4 patients having 5-year OS of 18.7%, while T3, T2 and T1 had OS of 63.9%, 74.1% and 100% respectively (Figure 1b).

Patients with advanced N-classification also had poor 5-year OS, with N3 patients having 5-year OS of 41.1%, while N2, N1 and N0 had OS of 54.9%, 76.9% and 100%, respectively (Figure 1c). Furthermore, males had a poor 5-year OS compared to females, in which 5-year OS for males and females were 47.4% and 80.8% respectively. In addition, patients with cranial nerve palsy had poor survival outcome compared to patients who had no cranial nerve involvement. Five-year OS for patients with cranial nerve involvement and patients without cranial nerve involvement were 18.2% and 67.9% respectively.

For 5-year LRFS, univariate analysis showed that gender ($p<0.05$) and N-classification ($p<0.05$) were significant prognostic factors. However, patients related factors such as age ($p=0.226$) and race ($p=0.716$) were found to be statistically not significant. Furthermore, disease related factors such as WHO histopathological subtype ($p=0.161$), T-classification ($p=0.091$), stage of cancer ($p=0.721$) and cranial nerve involvement ($p=0.273$) were found to be not significant. In addition, type of treatment ($p=0.113$) was also not a significant prognostic factor for LRFS.

Males had poor 5-year LRFS compared to females. The 5-year LRFS for males and females were 33.3% and 92.5% respectively. Patients with N1 had poor 5-year LRFS followed by patients with N2 and N3. Five-year LRFS for N1 patients was 35.0%.

Discussion

Our study found that 86% of the NPC patients were diagnosed with advanced stages (stages III-IV). This may be explained by the fact that nasopharyngeal tumors may initially grow without producing signs and symptoms due to location and anatomical structure of the nasopharynx (Licitra et al, 2003). Similarly, in an earlier study most patients presented with stage III (Lee et al., 1998).

Five-year OS for the patients in this study was 58.6%. This finding was similar with the results of a study carried out in Singapore in which 5-year OS for the patients was 56.6% (Heng et al., 1999) However, some studies showed 5-year OS of 65-75% (Lee et al., 2005; Liu et al., 2008) The lower Five-year OS in our study is because most of the patients (86%) presented with advanced stage. While, there were 53-61.1% of patients presented with advanced stage in the stated studies.

This study showed that the stage at diagnosis was a statistically significant prognostic factor in predicting OS of the NPC patients as early stages (stage I and II) had better outcome compared to advanced stages (stage III and IV). Five-year OS for stage I, II, III, IVA and IVB were 100%, 93.3%, 62.7%, 42.2% and 40.6%, respectively. The usefulness of the AJCC/UICC staging system in predicting the prognosis had been demonstrated repeatedly by several earlier studies (Heng et al., 1999; Liu et al., 2003; Liu et al., 2008; Cooper et al., 1998; Mao et al., 2009). On the basis of Sixth Edition AJCC/UICC staging system, 5-year OS for stage I and II that we found was similar with studies such as (Liu et al., 2008; Mao et al. 2009). The 5-year OS for stage III and IV that we found was higher than that by (Liu et al., 2008), but lower than that by (Mao et al., 2009).

This study also showed that T classification was significant prognostic factor in predicting 5-year OS of the NPC patients. T4 had significantly worse OS compared to other T-classification. Few studies had also confirmed the importance of T-classification as a prognostic factor (Heng et al., 1999; Liu et al., 2008; Lu et al., 2006; Ng et al., 2008). On comparing our findings with an earlier study which also used Sixth Edition AJCC/UICC staging system, we found that 5-year OS for T1-3 was higher than in (Liu et al., 2008). However, 5-year OS for T4 was lower

than in the stated study.

Moreover, this study also proved that N classification was a statistically significant prognostic factor for OS. Patients with N1-3 had poor outcome compared to N0. This finding was similar to earlier findings (Heng et al., 1999; Liu et al.2008; Ng et al., 2008).

This study found that gender was a significant prognostic factor which predicts 5-year OS of the patients. Female gender was significantly more favourable prognostic factor for OS compared to male gender. Five-year OS for females and males were 80.8% and 47.4%, respectively. Other studies also showed gender to be a prognostic factor (Teo et al., 1996; Ng et al., 2008). However, this finding was contradictory to studies which found that there was no significant difference between genders in terms of OS (Ho et al., 2008; Lee et al, 2008). It is not known why males had worse prognosis compared to females. However, males had higher risk of distant failure and local recurrence (Lee et al, 2005; Liu et al, 2008).

Apart from that, we also found out that cranial nerve involvement was a significant prognostic factor affecting 5-year OS. This finding was similar to other studies (Heng et al., 1999; Teo et al., 1996). Cranial nerve palsy has a poor survival outcome, as it is associated with advanced spread of the primary tumor.

In addition, we found out that WHO histopathological subtypes were not significantly predicting 5-year OS. In this study, no patients presented with WHO type I carcinoma. This was because WHO type II and III were common in Asians, while WHO type I was common in non-Asians (Marks et al., 1998). The result obtained in this study was similar with studies which also only compared OS of patients with WHO type II and WHO type III carcinoma (Teo et al., 1996; Chan et al., 2009) Similarly, an earlier study found that patients with WHO type II and type III carcinoma had significantly higher survival rate than those with WHO type I carcinoma, while 5 years survival rates for WHO type II and type III carcinoma did not differ significantly (Reddy et al., 1995). This was because both WHO type II and type III carcinoma were non-keratinizing types, more responsive and more likely to be cured by ionizing radiation than keratinizing WHO type I. Similar survival outcome for both WHO type II and III carcinoma was due to similar response to ionizing radiation.

We also found that older patients (> 48 years) had poorer survival outcome compared to younger patients (≤ 48 years) but the difference was non-significant. This was similar with a study which showed that age (≤ 50 years old or > 50 years old) had a non-significant effect on OS of the patients (Liu et al., 2003). This contradicted studies which found that younger patients had significantly better survival outcome compared to older patients (Kalogera-Fountzika et al., 2006; Liu et al., 2008; Teo et al., 1996).

We found that race was not statistically significant factor in predicting 5-year OS although Malays had worse survival outcome compared to other races. In a study which was conducted in United States, it was found that those original groups with the highest proportion of WHO type II and type III carcinomas had the best survival whereas original groups with the highest proportion of keratinizing carcinomas (WHO type I) had the lowest survival rate (Marks et al., 1998). Race was not a significant factor in our study because all patients presented with WHO type II and type III carcinomas.

In conclusion, the patient factor that significantly affected 5-year OS was gender, while disease factors that significantly affected 5-year OS were stage of the cancer, T-classification, N-classification as well as cranial nerve involvement. Also, the patient factor that significantly affected 5-year LRFS was gender, while the disease factor that significantly affected 5-year LRFS was N-classification.

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