RESEARCH COMMUNICATION

Retrospective Analysis of Results of Treatment for Nasopharyngeal Carcinoma in Penang General Hospital from 2001-2005

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is one of the commonest cancers encountered in Malaysia. This study aimed to evaluate the treatment outcomes for patients with NPC treated in Penang General Hospital with specific analysis of prognostic clinicopathological features and treatment modalities. Materials and Methods: This retrospective study examined NPC patients between 1st January 2001 and 31st December 2005 in Penang General Hospital. Survival analyses were performed using the Kaplan-Meier method and comparisons between groups were made using the log-rank test. Important prognostic factors including patient demographics, tumour and treatment factors were analysed using the Cox proportional hazard model. Results: A total of 285 patients were identified with a median age of 51 years, 72.6% being males. The majority were Chinese (66%) followed by Malays (31.9%). Primary tumour stages (T stages) 3 and 4 were present in 18.6% and 34% of patients respectively, and nodal disease was present in 80.4%. On overall AJCC staging, 29.1% had stage III and 50.2% had stage IV disease. Some 39.6% of patients had WHO type 3 histology and 7.4% had WHO type 1-2 histology with the remainder having NPC with no subtype reported. Concurrent chemo-irradiation was the commonest treatment received by patients (51.9%) followed by radiotherapy alone (41.8%). The 5 year overall survival and cause specific survival were 33.3% and 42.7% respectively. Age group, T stage, N stage and WHO histological subtype were independent prognostic factors for overall survival on multivariate analysis. For cause specific survival they were T stage and N stage. Conclusion: The 5 years overall survival rate was 33.3%. This low figure is primarily due to late presentation. Efforts to detect NPC at earlier stages in Malaysia are urgently needed. These should include public education to increase awareness of the prevalence of this highly treatable disease.

Keywords: Nasopharyngeal carcinoma - treatment - late presentation - Penang, Malaysia

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Introduction

Nasopharyngeal carcinoma (NPC) is prevalent in China and the South-east Asian region with a peak incidence rate of 20 per 100,000 person-years in Hong Kong (Law and Mang, 2007). In the latest incidence report by the National Cancer Registry for Peninsular Malaysia in 2006, the incidence rate was 8.5 and 2.6 per 100,000 populations for males and females respectively. However, the incidence rate was highest amongst Chinese males with an incidence of 15.9 per 100,000 populations. NPC is also the fifth commonest malignancy in Peninsular Malaysia and it accounted for 4.5% of all malignancies reported during this period of time. The definitive treatment for NPC is with radiotherapy with or without neoadjuvant/ concurrent/adjuvant chemotherapy depending on the disease stage, presence of co-morbidities and patient's performance status. The overall worldwide 5 years survival rate ranged from 32% to 62% among series involving more than 9500 patients with all stages of NPC (Shu-Chen, 1980; Hsu et al., 1982; Al-Sarraf et al., 1990; Lee et al., 1992; Lee et al., 1993; Qin et al., 1998; Wang et al., 1998; Ali et al., 1999; Lin et al., 1999, Terence et al., 2003). As there is a paucity of data with regards to the treatment outcome in Malaysia, we report the treatment outcomes of nasopharyngeal carcinoma referred for treatment in Penang General Hospital with specific analysis on the prognostication of clinicopathological factors and treatment modalities utilized.

Materials and Methods

This study retrospectively analysed all newly diagnosed patients with NPC referred for treatment to the Oncology centre at Penang General Hospital from 2001-2005. Patients of any age and stage of disease with histologically proven diagnosis were accepted for analysis. Patients with no histological confirmation of NPC and those with recurrence or patients who were already treated prior to referral to Penang General

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Table 1. Univariate Analysis of Prognostic Factors for Overall Survival and Cause Specific Survival

Variable		Number of patients	Overall Survival Hazard Ratio	95% Confidence Interval	p-value	Cause Specific Survival Hazard Ratio	95% Confidence Interval	p-value
Age Group	Up to 50	142	1	-	-	-	-	-
	51-69	117	1.16	0.86-1.56	0.334	0.81	0.58-1.14	0.231
	70 and above	26	2.25	1.41-3.59	0.001*	1.19	0.64-2.24	0.583
Sex	Male	207	1	-	-	1	-	-
	Female	78	0.86	0.63-1.18	0.354	0.9	0.63-1.29	0.581
Race	Malay	91	1	-	-	1	-	-
	Chinese	188	0.6	0.44-0.80	0.001*	0.64	0.46-0.89	0.008*
	Indian	4	0.42	0.10-1.72	0.229	0.56	0.13-2.31	0.425
	Others	2	NR	NR	NR	NR	NR	NR
T Stage	T1	46	1	-	-	1	-	-
	T2	89	0.76	0.48-1.20	0.241	0.65	0.38-1.11	0.114
	T3	53	1.15	0.71-1.86	0.571	1.18	0.68-2.04	0.558
	T4	97	1.75	1.15-2.66	0.009*	1.94	1.21-3.12	0.006*
N Stage	N0	56	1	-	-	1	-	-
	N1	47	1.34	0.81-2.24	0.26	1.19	0.66-2.15	0.568
	N2	113	1.84	1.22-2.87	0.004*	1.78	1.10-2.89	0.019*
	N3	69	2.8	1.79-4.40	0.000*	3.01	1.82-4.96	0.000*
M Stage	M0	275	1	-	-	1	-	-
	M1	10	2.06	1.05-4.04	0.036*	2.37	1.16-4.96	0.018*
WHO Type	III	113	1	-	-	1	-	-
	Unknown	151	1.25	0.93-1.69	0.145	1.21	0.86-1.70	0.272
	I-II	21	1.86	1.10-3.17	0.022*	1.66	0.89-3.11	0.111
Treatment	RT only	119	1	-	-	1	-	-
	CCRT	148	1.11	0.83-1.49	0.485	1.08	0.78-1.51	0.638
	Others	18	1.33	0.75-2.35	0.329	1.06	0.53-2.14	0.87

The first strata for each variable acted as the reference group with a hazard ratio of 1.0 for which other groups were compared against; * p-value <0.05; NR, not recordable

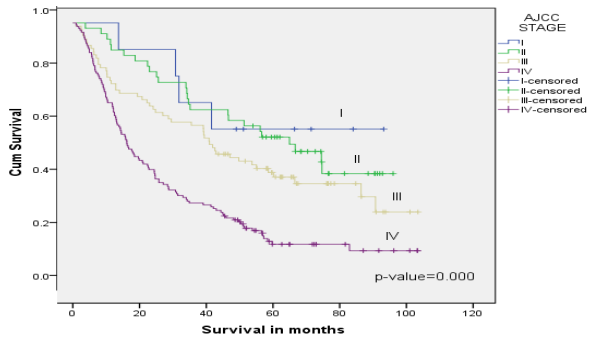

Figure 1. Overall Survival According to AJCC Stage

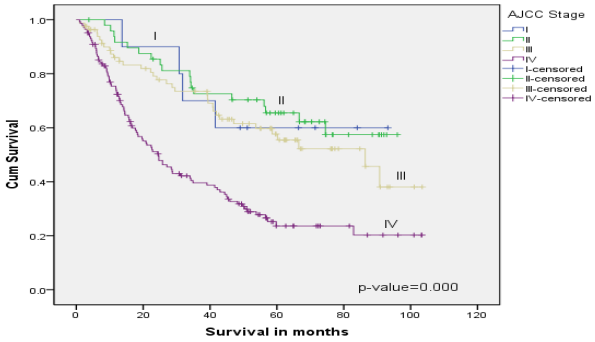

Figure 2. Cause Specific Survival According to AJCC Stage

Hospital were excluded. Information collected included patient demographics, clinical stage based on TNM and AJCC staging for NPC, treatment received including any neoadjuvant, concurrent or adjuvant chemotherapy and the treatment outcome. Patients lost to follow-up were contacted via phone to determine their current status and if any of these patients were not contactable, their latest status was determined by contacting the National Registration Department. Statistical analysis was performed using the SPSS software. Kaplan-Meier method was used for survival analysis and differences in survival according to AJCC stage was compared using the log-rank test. Important prognostic factors on treatment outcome including patient, tumour and treatment factors were analysed using the Cox proportional hazard model.

Results

Between 1st January 2000 and 31st December 2005, 299 patients with newly diagnosed NPC were referred to the Penang General Hospital for treatment. Case notes were traceable in 285 patients giving a retrieval rate of 95.3%. Analysis was therefore performed on these 285 patients..

The 5 years overall survival (OS) rate was 33.3% with a median follow up of 34 months. The 5 years OS according to AJCC stages were 60% for stage I, 57% for stage II, 43.6% for stage III and 16.6% for stage IV. The prognostic association of AJCC stage with OS was statistically significant (p-value=0.000) (Figure 1). Univariate analysis revealed age group, race, tumour stage (T stage), nodal stage (N stage), presence of metastasis (M stage) and WHO histological subtype to be of prognostic significance (Table 1). Parameters which retained independent prognostic significance on multivariate Cox's regression analysis were age group, T stage, N stage and WHO histological subtype (Table 2).

The 5 years cause specific survival (CSS) was 42.7%

Table 2. Multivariate Analysis of Prognostic Factors for Overall Survival and Cause Specific Survival

Variable		Number of patients	Overall Survival			Cause Specific Survival		
			Hazard Ratio	95% Confidence Interval	p-value	Hazard Ratio	95% Confidence Interval	p-value
Age Group	Up to 50	142	1	-	-	NR	NR	NR
	51-69	117	1.31	0.96-1.79	0.084	NR	NR	NR
	70 and above	26	3.18	1.91-5.30	0.000*	NR	NR	NR
Race	Malay	91	1	-	-	1	-	-
	Chinese	188	0.81	0.59-1.11	0.196	0.84	0.59-1.20	0.329
	Indian	4	0.71	0.17-2.98	0.64	0.66	0.16-2.73	0.561
	Others	2	NR	NR	NR	NR	NR	NR
T Stage	T1	46	1	-	-	1	-	-
	T2	89	0.74	0.46-1.17	0.194	0.67	0.39-1.15	0.149
	T3	53	1.04	0.63-1.71	0.884	1.12	0.64-1.95	0.689
	T4	97	1.81	1.16-2.82	0.009*	1.85	1.13-3.03	0.014*
N Stage	N0	56	1	-	-	1	-	-
	N1	47	1.37	0.81-2.31	0.239	1.35	0.74-2.46	0.335
	N2	113	1.83	1.19-2.82	0.006*	1.67	1.02-2.72	0.041*
	N3	69	2.82	1.78-4.48	0.000*	2.8	1.69-4.64	0.000*
M Stage	M0	275	1	-	-	1	-	-
	M1	10	1.24	0.62-2.48	0.553	1.46	0.70-3.02	0.312
WHO Type	III	113	1	-	-	NR	NR	NR
	Unknown	151	1.29	0.95-1.75	0.11	NR	NR	NR
	I-II	21	1.97	1.15-3.39	0.014*	NR	NR	NR

The first strata for each variable acted as the reference group with a hazard ratio of 1.0 for which other groups were compared against; * p-value <0.05; NR, not recordable

with a median follow up of 46 months. The 5 years CSS according to AJCC stage were 60% for stage I, 65.5% for stage II, 57.7% for stage III and 23.6% for stage IV. The prognostic association of AJCC stage with CSS was statistically significant (p-value=0.000) (Figure 2). Univariate analysis showed race, T stage, N stage and M stage to be of prognostic significance (Table1). Parameters which retained independent prognostic significance on multivariate Cox's regression analysis were T stage and N stage (Table 2). The discrepancy between the 5 years OS and the CSS was due to deaths of other causes. This accounted for 42 deaths (21.5%) of the total of 195 deaths and the commonest cause was listed as old age which occurred in 28 patients (14.4%). It was not possible to ascertain if these deaths were indeed due to old age or as a direct consequence of NPC which would then mean the actual 5 years CSS would be closer to the 5 years OS of 33.3%. Other causes of death were neutropaenic sepsis (4), pneumonia (2), second malignancy (2), suicide (2), stroke (1), accident (1), renal failure (1) and sepsis (1).

Discussion

The result of this series of patients with NPC lies in the lower range of previously published 5 years OS. A major contributing factor is the fact that many patients in this series presented with advanced disease. A total of 79.3% of patients presented with either AJCC stage III or IV disease. Multivariate analysis clearly demonstrated the hazardous effect of late stage disease with regards to survival. T4 disease was associated with a hazard ratio of 1.85 as compared to T1 disease. N3 and N2 diseases were associated with hazard ratios of 2.80 and 1.67 respectively when compared to N0 disease. Late presentation in this part of the region cannot be underestimated. Possible factors in the late presentation of NPC include a delay in seeking medical advice, confusing nature of presenting symptoms which can be misleading to the clinician, the difficult nature of a clinical examination of the nasopharynx and the spread of a silent submucosal lesion with a normal appearance during examination of the nasopharynx (Abdullah et al., 2009). A study conducted in Sarawak involving 216 patients on late presentation showed a mean delay of 176 days from duration of presenting symptoms to seeking professional attention (Tiong and Subramaniam, 2007). The three major reasons found in this series for this phenomenon were patients being unaware of NPC and the seriousness of NPC (72%), patients having no pain(30%) and patients seeking traditional treatment first(24%). In a separate study done involving 100 patients in the University Hospital Kuala Lumpur whereby late presentation in stage III and IV disease accounted for 94% of patients, it was found that the median delay on the part of the doctors to confirm the diagnosis of NPC was 127 days as compared to the median delay of 2.5 days on the part of the patients in consulting a doctor (Prasad and Pua, 2000). The delay was particularly acute when the patients presented with ear symptoms (266 days) followed by those with neck swelling (94 days). The authors suggested for increased awareness with regards to the diagnosis of NPC amongst the general practitioners as 82% of the patients first consulted the general practitioners. In this present study it is unclear what the contributing factors were for the late presentation. However, it is clear that public education to all is required including the general public and general practitioners to improve the pickup rate during earlier stages of the disease. NPC is a highly radiosensitive disease when treated in its early stages with radical radiotherapy which can achieve a high cure rate. Sham and Choy (1990) reported a study involving

759 patients treated in the Queen Mary Hospital in Hong Kong whereby the survival rates at 5 years for patients with stage I and II diseases were 80.8% and 71.5% respectively. A more recent study done in China reported by Yi and colleagues (2006) showed 5 years OS rate of 95.5% and 87% for stage I and II disease respectively treated by radiotherapy alone. It is imperative for the health authorities to focus our efforts on earlier diagnosis to improve the survival rate in this region. A recent publication involving six major tertiary referral centres in Malaysia which recruited all confirmed NPC patients, in its preliminary analysis for cases reported from July 2007 to February 2008 showed a similar trend of late presentation whereby 75% of the patients presented with either stage III or IV disease (Pua et al., 2008).

The other significant independent prognostic factor on multivariate analysis for overall survival in this series was the WHO histological type. The WHO type 1-2 had a hazard ratio of 1.86 as compared to the much commoner WHO type 3 disease. Due to the low number of patients (7.4%) with the poorer prognosis WHO type 1-2 in this series, it is unlikely to have much impact on the relatively low 5 years OS observed. However, this issue is far from certain as there were a large number of patients (53%) for which is was not possible to ascertain which histological subtype they belonged to. This group though did not show any significant difference on multivariate analysis when compared to the WHO type 3 disease.

A very important endpoint in the outcome of NPC is the rate of locoregional recurrence. This is not reported in this series as it was not possible to obtain the relevant information due to several factors. The Penang General Hospital receives referrals from other states for radiotherapy treatment including the states of Perlis, Kedah and northern Perak. Many of the patients in this series were subsequently followed up in the states where they lived. Efforts to obtain information by telephone to these patients were also hampered by a change in the telephone numbering system from 7 digits to 8 digits. Visits to the referring hospitals to check the records of these patients also showed many patients were missing their follow-up. As such it was not possible to obtain accurate information for locoregional recurrence. Information on OS and CSS were possible by enlisting the assistance of the National Registration Department to check the living/mortality status of these patients. To overcome this shortcoming a prospective study is required whereby follow-up of these patients can be closely monitored to obtain the relevant information. The long term side effects of radiotherapy can also be obtained.

In summary this series showed a 5 years OS of 33.3% with a high percentage of patients presenting in late stages of the disease. Efforts to improve early diagnosis must be instituted. It is vital to provide public education and increase the awareness of the prevalence of this highly

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