

## RESEARCH ARTICLE

# Five-Year Survival and Median Survival Time of Nasopharyngeal Carcinoma in Hospital Universiti Sains Malaysia

Ab Hamid Siti-Azrin\*, Bachok Norsa'adah, Nyi Nyi Naing

## Abstract

**Background:** Nasopharyngeal carcinoma (NPC) is the fourth most common cancer in Malaysia. The objective of this study was to determine the five-year survival rate and median survival time of NPC patients in Hospital Universiti Sains Malaysia (USM). **Methods:** One hundred and thirty four NPC cases confirmed by histopathology in Hospital USM between 1<sup>st</sup> January 1998 and 31<sup>st</sup> December 2007 that fulfilled the inclusion and exclusion criteria were retrospectively reviewed. Survival time of NPC patients were estimated by Kaplan-Meier survival analysis. Log-rank tests were performed to compare survival of cases among presenting symptoms, WHO type, TNM classification and treatment modalities. **Results:** The overall five-year survival rate of NPC patients was 38.0% (95% confidence interval (CI): 29.1, 46.9). The overall median survival time of NPC patients was 31.30 months (95% CI: 23.76, 38.84). The significant factors that altered the survival rate and time were age ( $p=0.041$ ), cranial nerve involvement ( $p=0.012$ ), stage ( $p=0.002$ ), metastases ( $p=0.008$ ) and treatment ( $p<0.001$ ). **Conclusion:** The median survival of NPC patients is significantly longer for age  $\leq 50$  years, no cranial nerve involvement, and early stage and is dependent on treatment modalities.

**Keywords:** Nasopharyngeal carcinoma - five-year survival rate - median survival time - Malaysia

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## Introduction

Cancer was the third common cause of deaths in the Ministry of Health Malaysia Hospitals after heart diseases and diseases of pulmonary circulation and septicaemia in 2007. A total of 18,219 new cancer cases were diagnosed in 2007 and registered at the National Cancer Registry (Zainal and Nor, 2007). In Malaysia, NPC is the fourth most common cancer among population and the third most common cancer among males (Abdullah et al., 2009).

NPC showed a distinct racial and geographical distribution NPC (Xie et al., 2013). It was rare cancer in most populations but a leading form of cancer in a few well-defined populations, including natives of Southern China, Southeast Asia, the Arctic, and the Middle East/North Africa (Pua et al., 2008). The highest risk areas were South East Asia and Southern China.

Cancer survival rates can be used to understand about cancer prognosis, the chances of cancer will be cured. There are many factors that influence the survival. The five-year survival rates are used to compare the effectiveness of treatment. It can help to understand the potential benefits and risks of each treatment we are considered. Thus, the risk can be predicted closely. Different studies reported variation of significant factors that influence the survival of NPC patients (Heng et al., 2008; Liu et al., 2008). Differences in the survival

may be explained the marked variation in geographical distribution with changes in staging system and treatment modalities.

Although many studies had been done in other countries to determine that influence the survival of NPC patients, a few had been done in Malaysia. There is no well-documented study on the survival in Malaysia. Therefore, this problem needs further investigation with regard to the factors so that the findings may improve the survival of NPC patients. This study was conducted to determine the five-year survival rate and the median survival time of NPC patients in Hospital USM. Hopefully the result from this study could help in management of NPC patients and reference for future studies.

## Materials and Methods

The study design was a retrospective cohort which patients' medical records were reviewed retrospectively and important information on variables of interest and patients' survival status was extracted and recorded. The enrolment duration of the study participants was between 1<sup>st</sup> January 1998 and 31<sup>st</sup> December 2007 with an additional follow up of 12 months.

The sampling frame of this study was patients diagnosed with NPC in Hospital USM between 1<sup>st</sup> January 1998 and 31<sup>st</sup> December 2007. Study participants were

NPC patients who fulfilled the inclusion and exclusion criteria. Inclusion criteria were those patients who were newly diagnosed with NPC and confirmed with histopathology. Patients who presented with incomplete data more than 30% were excluded.

A priori calculation of sample size by using PS software showed that the required cases was 158 with significance level 0.05 (two tailed), power 0.8 and additional 20% was added.

A total of 159 patients were subsequently identified. After applying the inclusion and exclusion criteria, only 134 patients were eligible for this study. No probability sampling method was applied for this study. All data were extracted and recorded in the data extraction sheet. A single researcher retrieved the required information.

A follow up after recruitment phase was conducted to increase the chance of determining the patient's survival status especially to patients who were included at the end of the recruitment phase, to allow for any lag in updating records. The exact date and cause of death were obtained from medical records for patients who died at Hospital USM. Survival status of patients that were not recorded in medical records was obtained from the National Registration Department.

#### Statistical analysis

Data analysis was conducted using SPSS version 20 (IBM Corp, 2011) and STATA software, version 11 (Stata Corp, 2009). Statistical analysis was performed in this study was survival analysis. The outcome factor in this study was survival time that can be defined as the time to death of patients due to NPC or its complications. This study considered the observation was censored when patients survived beyond the end of study period, untraceable or loss to follow up. The significance of censored data being considered in the analysis was to avoid underestimation of survival time.

The survival probability of patients with NPC was estimated using the Kaplan Meier product limit method. The survivorship function or the Kaplan Meier survival

curve was used to estimate the 50th percentile (the median) of survival time and to compare survival distributions of two or more groups. Survival rate indicates the percentage of people in a study group who alive for a given period of time after diagnosis. The five-year survival rate is simply the cumulative proportion surviving at the end of the fifth year.

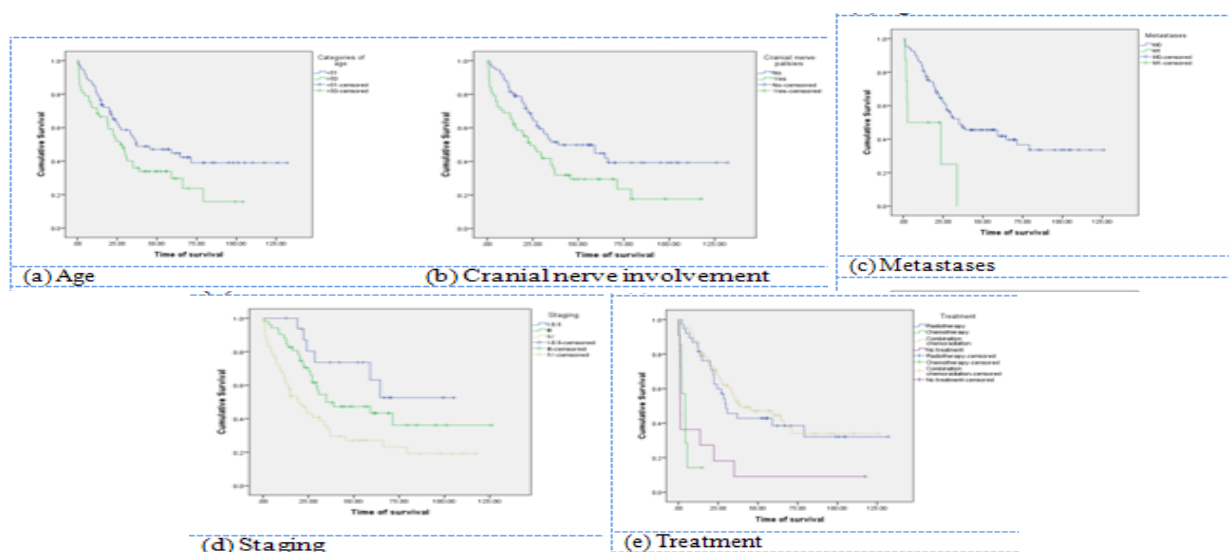
The survival curves of groups were compared using log rank test. For independent variables that have more than two groups, multiple pair wise comparisons produced cumulative type I error. Bonferroni correction was applied to  $\alpha$  where the value was divided by number of pair compared ( $\alpha/\text{number of pair compared}$ ). The p value obtained was compared to the corrected  $\alpha$  to determine for the significance level.

Ethical approval was obtained from the Human Research Ethics Committee of USM. Permission to access patient's folder or record was obtained from the Director of Hospital USM. Confidential code was used in the data extraction sheet to represent each patient. This code was kept separately with a confidential safe guard.

## Results

The mean age at diagnosis was 48.12 years (15.88). More than two-thirds 102 (76.1%) of the cases were males. Malay was the largest group compared to Chinese and other ethnicity (81.3%, 17.9% and 0.7%) respectively. Only 24.6% of patients had co-morbidities at the time of diagnosis. Table 1 shows the presenting symptoms of NPC patients in Hospital USM.

WHO type III constituted about 69.9% of all histological type. Most of the patients presented with T4 (48.1%), N3 (32.3%) and no metastases (82.7%). There were 3.0%, 9.8%, 39.1% and 40.6% patients diagnosed at stage I, II, III and IV respectively. There were 10 patients with missing data for staging. Majority of the patients, 86.5% received radiotherapy followed by 63.9% patients treated with chemotherapy.



**Figure 1. Kaplan-Meier Estimate for Survival Time of NPC Patients in Hospital USM Based on Age, Cranial Nerve Involvement, Metastases, Staging and Treatment (n=134)**

**Table 1. Symptoms of patients with NPC in Hospital USM (n=134)**

Symptoms	Died	Censored	Total
Neck swelling	63 (64.3)	35 (35.7)	98 (73.1)
Nasal presentation	49 (60.5)	32 (39.5)	81 (60.4)
Nasal blockage	30 (56.6)	23 (43.4)	53 (39.6)
Nasal discharge	7 (46.7)	8 (53.3)	15 (11.2)
Epistaxis	33 (56.9)	25 (43.1)	58 (43.3)
Aural presentation	38 (64.4)	21 (35.6)	59 (44.0)
Tinnitus	16 (57.1)	12 (42.9)	28 (20.9)
Hearing loss	30 (63.8)	17 (36.7)	47 (35.1)
Deafness	2 (100)	0 (0.0)	2 (1.5)
Serous otitis	2 (25.0)	6 (75.0)	8 (6.0)
Cranial nerve palsies	41 (70.7)	17 (29.3)	58 (43.3)
Ophthalmalgia	8 (61.5)	5 (38.5)	13 (9.7)
Visual changes	20 (66.7)	10 (33.3)	30 (22.4)
Numbness	5 (50.0)	5 (50.0)	10 (7.5)
Hoarseness of voice	4 (57.1)	3 (42.9)	7 (5.2)
Headache	25 (61.0)	16 (39.0)	41 (30.6)

### *Five-Year Survival Rate and Median Survival Time between Groups*

The overall five-year survival of NPC patients in Hospital USM obtained was 38.0% (95%CI: 29.06, 46.92). The overall median survival time obtained in this study was 31.30 months (95%CI: 23.76, 38.84).

Figure 1 illustrates the five-year survival rate and median survival time of NPC in Hospital USM based on factors. Log-rank test used for comparing the survival showed a significant difference in the following variables; age ( $p=0.041$ ), cranial nerve palsies ( $p=0.012$ ) and metastases ( $p=0.008$ ). Stage I & II with IV ( $p=0.004$ ), stage III with IV ( $p=0.011$ ), radiotherapy with chemotherapy ( $p<0.001$ ), radiotherapy with no treatment ( $p=0.001$ ), chemotherapy with combination therapy ( $p<0.001$ ) and combination therapy with no treatment ( $p<0.001$ ) after Bonferroni correction.

## **Discussion**

The mean age at diagnosis of NPC patients in this study was 48.12 years old (SD 15.88). The age ranged from 11 to 93 years old. This was similar as reported by El-Sherbieny et al., (2011). A study by Prasad and Rampal (1992) in Peninsular Malaysia showed that the mean of 365 newly diagnosed patients was 46.8 years old (SD 12.2). While a study in Hong Kong during the period 1983 till 2008 reported that incidence of NPC increased with age until peaking at ages 55 to 59 years old and showed a decline thereafter (Xie et al., 2013).

More than two-thirds (77.2%) of the patients were males. Similarly, other study by Pua et al. (2008) reported that the male: female ratio was 3: 1. Our study was different compared to Prasad and Rampal (1992) that reported that the male/female ratio was 2.8:1. It almost same as reported by National Cancer Registry in 2007 where the incidence was more than 2 folds higher among males when compared to females. Chee Ee Phua et al., (2013) in their study also showed similar ratio of 2.3:1.0. Although the male to female ratio among studies were different, it still showed that NPC was more common in male patients than female patients.

Malay was the largest group compared to Chinese

and other ethnicity (81.3% versus 17.9% versus 0.7%). This was different with study reported by Chee Ee Phua et al. (2013) where most of cancer patients were Chinese patients. This can be explained that our study conducted in Kelantan that have predominantly Malay population.

Most of the patients in our study presented with WHO type III which was constituted about 69.1% of all histological type. It was almost similar to the study by Chee Ee Phua et al. (2013) which about 70.5% of the patient presented with WHO type III. Most of the patients in this study presented with T4 (48.1%), N3 (32.3%) and no metastases (82.7%). Study by El-Sherbieny et al., (2011) showed similar trend except that the study did not include the distant metastases patients.

In our study, 79.7% patients were diagnosed at advanced stage III and IV which was supported by Chee Ee Phua et al. (2013). Many patients with NPC present with an advanced stage of the disease as NPC usually grow without producing signs and symptoms due to location and anatomical structure of the nasopharynx (Licitra et al., 2003). Abdullah et al. (2009) reported the possible factors of late presentation of NPC include delay in seeking medical advice, confusing nature of presenting symptoms, difficult nature of clinical examination and silent spread of submucosal lesion with normal nasopharynx.

Majority of the patients, (86.5%) received radiotherapy followed by (63.9%) patients treated with chemotherapy. It was different from study reported by Chee Ee Phua et al. (2013) where 69.3% treated with radiotherapy in combination with chemotherapy. Sixteen point five percent had concurrent chemo-radiation therapy, while 14.8% had neoadjuvant chemotherapy.

The overall five-year survival of NPC patients in Hospital USM slight higher compared to study by Pua et al. (2011) on 285 patients treated from 2001 until 2005 at Penang General Hospital (38.0% vs 33.3%). The reason for low survival rate was due to late presentation. Both results were lower compared to study by El-Sherbieny et al. (2011) in Hospital Kuala Lumpur with the overall survival of 58.6%. The difference might be due to exclusion of metastases patients in the previous study. A study by Chee Ee Phua et al. (2013) had shown higher overall survival of 51.6%, which might be due to all patients, received radiotherapy. In our study, not all patients received treatment. It is well known that radiotherapy is an effective treatment for NPC that may prolong survival time (Zhang et al., 2013).

Our study showed difference in the five-year survival between age group. Patients aged 50 years and below had higher five-year survival. A study by Kalogera-Fountzila et al. (2006) also found that younger patients had significantly better survival compared to older patients. In contrast to a study by Liu et al. (2003) which had similar age classification reported that the five-year survival difference was not statistically significant due to a very small patients in the younger age group.

Metastasis was a significance factor that influenced the five-year survival of NPC patients in our study. Teo et al., (1996) also found that metastases had the influence on the NPC patient's survival. In that study, the authors compared patients who had metastases at diagnosed to those who

had metastases after receiving primary radiotherapy. There were other factors that were considered such as age and site of metastases. The study also mentioned about the age of patients when diagnosed with metastases (hepatic and neck swelling). Older patients had shorter survival time than younger patients (Teo et al., 1996). In our study, most of the patients who had distant metastases were in older age and presented with neck swelling.

The five-year survivals in our study according to stage I, II, III, IV were 50.0%, 66.0 %, 41.8% and 28.0% respectively. This finding was similar to other studies (Chee Ee Phua et al., 2013) where the survival decreased as the stage of disease increased. The study by Chee Ee Phua et al. (2013) found that the survival according to stage was 81.8% for stage I, 77.9% for stage II, 47.4% for stage III and 25.9% for stage IV. Higher survival was observed in patients diagnosed at all stage except for stage IV (Chee Ee Phua et al., 2013). The survival was higher compared to our study. This might be due to the higher number of patients in the study received concurrent chemo-radiation compared to our study (69.3% versus 58.2%).

In our study, significantly higher five-year survival rate could be observed in patients treated with combination radiotherapy and chemotherapy compared to those with radiotherapy alone as a primary treatment. Other studies also found that patients who underwent concurrent chemo-radiation treatment had better survival compared to those who received radiotherapy (Chan et al., 2005; Lee et al., 2005b; Zhang et al., 2005). Zhang et al. (2005) showed that the five-year survival rate of NPC patients were almost 100% while Chan et al., (2005) reported 70%. Those who received chemo-radiation were diagnosed at early stage and hence had longer survival. The utilization of radiotherapy is particularly valuable in patients with NPC because the nasopharynx areas is complex and surrounded by a number of critical normal structures and thus permit the irradiation of patients with complex-shaped tumours in locations which are difficult to access (Ji et al., 2013).

There were several limitation of our study. Several patients' record could not found and discarded because patients did not turn up for follow in a long period of time. This led to less number of patients eligible to enter the study.

In addition, some information in the record was not complete or lost such as blood results, histopathology and computerised tomography scan reports. Some reports were not clear and confusing since different doctors reporting in different ways. About 24 of NPC patients with incomplete data on many factors were excluded from the analysis. The cases in the excluded group might have different survival time, resulted in an under or over estimation of our outcome.

Due to the limited number of patients who completed treatment, the effect of treatment modalities might be bias. Forty four percent of the patients did not come for the follow-up appointment. In addition, cause of death was verified through state registry which inclined to state the old age as the cause of death, rather than possible NPC related death.

One of the possible reasons for the lower overall

median and five-year survival of our study was late stage at diagnosis. It is believed that early detection will reduce mortality caused by NPC. People should be educated on symptoms and signs of NPC and they should have early consultation when having any symptoms of NPC.

All the missing, unavailable, incomplete and ambiguous data can be avoided if the information is recorded properly by following standard criteria. Important information such as family history, smoking and result of investigations should be reported clearly. Further study with a larger sample size is needed to identify more significant factors that influence the survival of NPC patients. Expanding the research setting to a multi-centre research may accommodate a larger sample size, span of coverage and guarantee of validity of study. Larger sample size can be achievable and more factors can be study related to NPC. Prospective cohort or interview studies can be one of study design to study on NPC patients. This study designs have advantage of least missing data or incomplete data.

In conclusion, the median survival time and five-year survival rates of NPC patients in Hospital USM were lower compared to other studies. The median survivals of NPC patients were influenced by severity of symptoms, TNM classification and different treatment modalities.

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- Five-Year Survival and Median Survival Time of Nasopharyngeal Carcinoma in Hospital Universiti Sains Malaysia*
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