# PROGNOSTIC FACTORS ASSOCIATED WITH RECURRENCE OF NASOPHARYNGEAL CARCINOMA

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Thesis
entitled

# PROGNOSTIC FACTORS ASSOCIATED WITH RECURRENCE OF NASOPHARYNGEAL CARCINOMA


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PROGNOSTIC FACTORS ASSOCIATED WITH RECURRENCE OF NASOPHARYNGEAL CARCINOMA

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ABSTRACT

This retrospective cohort study assessed the recurrence rate and factors related to recurrence of nasopharyngeal carcinoma among 366 patients admitted at Ramathibodi hospital, Bangkok, Thailand during January 1, 1996 to December 31, 2006. At least one year after finishing treatment, patient follow up ranged from 12.03 to 154.20 months, and the median follow up time was 60.20 months. There were 105 patients who had recurrence of nasopharyngeal carcinoma.

The overall incidence density of the recurrence rate of nasopharyngeal carcinoma was 5.72 per 100 person- years. The incidence density of recurrence rates in stage I+II, III, IV without metastasis and IV with metastasis were 4.02, 4.88, 7.34 and 12.82 per 100 person- years, respectively. The median recurrence time in patients with stage IV with metastasis was 62.47 months or 5 years after treatment. Results from multivariate analysis demonstrated risk of recurrence of nasopharyngeal carcinoma among patients with stage IV without metastasis was 1.96 times that of (adjusted HR= 1.96, 95% CI = 1.10-3.50, $p < 0.022$) and patients with stage IV with metastasis was 3.35 times that of patients with stage I and II nasopharyngeal carcinoma (adjusted HR= 3.35, 95% CI = 1.22-9.19, $p < 0.019$).

It is suggested that the risk group of recurrence should receive early detection and screening for recurrence, especially patients with stage IV, in order to achieve better prognosis of treatment for recurrence of nasopharyngeal carcinoma.

KEY WORDS: NASOPHARYNGEAL CARCINOMA/
RECURRENCE RATE/ PROGNOSTIC FACTORS

88 Pages

ปัจจัยที่มีความสัมพันธ์กับการกลับเป็นซ้ำของโรคมะเร็งช่องคอหลังโพรงจมูก PROGNOSTIC FACTORS ASSOCIATED WITH RECURRENCE OF NASOPHARYNGEAL CARCINOMA

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บทคัดย่อ

การศึกษานี้เป็นการศึกษาอุบัติการณ์และปัจจัยที่มีความสัมพันธ์กับการกลับเป็นซ้ำของผู้ป่วยโรคมะเร็งช่องคอหลังโพรงจมูกที่มารับการรักษาที่โรงพยาบาลรามาธิบดี ตั้งแต่ 1 มกราคม 2539 ถึง 31 ธันวาคม 2549 จำนวน 366 ราย และหลังการรักษาผู้ป่วยทุกรายได้รับการติดตามเป็นเวลาอย่างน้อย 1 ปี โดยระยะเวลาในการติดตามผลการศึกษาอยู่ระหว่าง 12.03 เดือนถึง 154.20 เดือนในผู้ป่วยทั้งหมด 366 ราย พบว่า 105 ราย มีการกลับเป็นซ้ำของโรคมะเร็งช่องคอหลังโพรงจมูกภายหลังการรักษา อุบัติการณ์การกลับเป็นซ้ำของมะเร็งช่องคอหลังโพรงจมูกเท่ากับ 5.72 ต่อ 100 คน ต่อ ปี และอุบัติการณ์การกลับเป็นซ้ำของผู้ป่วยมะเร็งช่องคอหลังโพรงจมูกที่อยู่ใน stage I+II, III, IV without metastasis และ IV with metastasis เท่ากับ 4.02, 4.88, 7.34 และ 12.82 ต่อ 100 คน ต่อปี ตามลำดับ ค่ามัธยฐานของระยะเวลาในการกลับเป็นซ้ำของผู้ป่วยโรคมะเร็งช่องคอหลังโพรงจมูกที่อยู่ใน stage IV with metastasis เท่ากับ 62.47 เดือน หรือเท่ากับ 5 ปี เมื่อวิเคราะห์ความสัมพันธ์เชิงซ้อนพบว่า ปัจจัยที่มีความสัมพันธ์กับการกลับเป็นซ้ำของโรคมะเร็งช่องคอหลังโพรงจมูก ได้แก่ overall stage grouping โดยผู้ป่วยที่อยู่ใน stage IV without metastasis มีความเสี่ยงต่อการเกิดการกลับเป็นซ้ำเป็น 1.96 เท่าของผู้ป่วยที่อยู่ใน stage I+II (adjusted HR= 1.96, 95% CI = 1.10-3.50, $p < 0.022$) และผู้ป่วยที่อยู่ใน stage IV with metastasis มีความเสี่ยงต่อการกลับเป็นซ้ำเป็น 3.35 เท่าของผู้ป่วยใน stage I+II (adjusted HR= 3.35, 95% CI = 1.22-9.19, $p < 0.019$)

จากผลการวิจัยนี้ เสนอแนะว่าผู้ป่วยที่อยู่ในกลุ่มที่มีความเสี่ยงต่อการเกิดการกลับเป็นซ้ำของโรคมะเร็งช่องคอหลังโพรงจมูกสูง โดยเฉพาะในกลุ่มที่มีระยะโรคที่รุนแรงควรได้รับการตรวจและติดตามผลการรักษาอย่างสม่ำเสมอเพื่อเป็นการคัดกรองโรคตั้งแต่ในระยะเริ่มแรกของการกลับมาเป็นซ้ำของโรค เพื่อเป็นการเพิ่มประสิทธิภาพของการรักษาการกลับเป็นซ้ำ

88 หน้า

# CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

# LIST OF FIGURES (cont.)

# CHAPTER I
# INTRODUCTION

The World Cancer Report predicted that new cases of cancer in the world will increase by fifty percent (or 15 millions) in year 2020(1). In Thailand, in 1999, the estimated age-adjusted morbidity incidence rate of cancer for all sites in Thailand was 150.4 per 100,000 for male and 123.0 for female, number of new cases of cancer was expected to be approximately 125,000 by the year 2008 compared with 81,000 case (2). During past 15 years, cancer was ranked third among causes of death in Thailand when heart disease and fatal accidents were in first and second ranked in causes of death, respectively. The death rate due to cancer increased to 50.5 per 100,000 persons 1996, as compared to 45 per 100,000 persons in 1992. In 2002, cancer became the number-one cause of death with mortality rate of 73.3 per 100,000 person, which was higher than the death rate from accidents, poisoning, hypertension and vascular disease (3).

In Thailand, nasopharyngeal carcinoma ranked fifth among other sites of cancer among Thai male with the proportion of 4.8%. Ramathibodi hospital reported that incidence rate of cancer for all sites in the year 2005 was approximately 5%, and nasopharyngeal carcinoma was in the top ten among them (4).

Among Thai male, incidence rate of nasopharyngeal carcinoma was in the fourth rank behind liver cancer, lung cancer and colorectal cancer while among women, incidence rate of nasopharyngeal carcinoma ranked seventh (5).

In the Western country, nasopharyngeal carcinoma is an uncommon type of tumor, it represented only less than 1% of all sites of cancer in the USA. The annual incidences in the USA and Europe varied between 0.22 and 0.5 per 100,000 populations. However, nasopharyngeal carcinoma was more common among people in Southern Chinese, South East Asian, Northern African and Eskimo population. The reports in incidences of nasopharyngeal carcinoma among man and woman in Hong Kong is 20-30 per 100,000 and 15-20 per 100, 000, respectively. The incidence of

nasopharyngeal carcinoma remained high among Chinese people who immigrated to Southeast Asia or North America. But the incidence was lower among Chinese people who were born in North America than who were born in Southern China (6).

Nasopharyngeal carcinoma was a dangerous disease because of its proximity to vital structure; it was invasiveness, and the difficult nature of examination for primary care physicians. It is often misdiagnosed at early because of the vagueness of presenting symptoms, and nasopharyngeal carcinoma was technically difficult to diagnosed because of its anatomical location. In addition, it is a silent tumor, the clinical symptoms of which delayed. And is mostly classified as an undifferentiated type of carcinoma, i.e. it has a rapid progression (7).

Typical problem for nasopharyngeal carcinoma was most of patients with the disease were diagnosed only when the tumor has reached an advanced stage, and patient might have return of cancer after initial treatment or called “recurrence”. The recurrence of the primary tumor is one of the major causes of death from this disease, especially with locally advanced tumors. Nasopharyngeal carcinoma recurrence were classified as local recurrence, regional recurrence and distant metastasis. Local recurrence referred to the return of cancer to the area where a patient originally had it, regional recurrence occurs in the lymph nodes and tissue locate in the original cancer, and distant recurrence or metastasis was defined as that occurring outside the radiation therapy field, including bone, lung, liver and any other distant organ away from the nasopharynx and the neck (8).

Recurrence of nasopharyngeal carcinoma can happen in years after original diagnostic or treatment. Most of recurrence occurs within 2 to 3 years after treatment and although most of recurrences occur within 5 years after diagnosis or treatment, relapse can be seen at longer intervals and more than 90% of local and distant recurrence develops within 3 year(9). Local and regional recurrence of nasopharyngeal carcinoma occurred in 9% to 40% of patients after primary radiotherapy (RT) both with and without chemotherapy, once the local and regional recurrence and distant metastasis occurred, the prognosis to survive will be worse (10). Early detection of local regional recurrence and metastasis was very important for prognosis.

Knowing potential prognostic factors, characteristics of a patient and tumor, may help physician to predict the recurrence, and plan for effective treatment. In many cases of recurrence with local and regional recurrence, it can be cured. When a cure is not possible, purposes of treatment may be to slow the growth of recurrent cancer and may help patient to live longer. A major issue in discussions of treatment of nasopharyngeal carcinoma was the management of these primary recurrent tumors. Identification of prognostic indicators that more accurately correlate with outcome would help in identifying which patient with nasopharyngeal carcinoma might benefit from adjuvant systemic therapy (11).

The aims of this study are to assess recurrence rate and to explore the prognostic factors associated with the recurrence of nasopharyngeal carcinoma among patients after receiving treatments in Bangkok. The benefits from this study were expected to be useful for effective prevention and treatment for nasopharyngeal carcinoma patients. Ramathibodi hospital in Bangkok, university hospital, which was used to be site of study because standard qualities of medical services are available.

## General Objective

To assess the recurrence rate and to assess factors related to the recurrence of nasopharyngeal carcinoma among Thai patients after receiving treatment at Ramathibodi Hospital during January 1, 1996 to December 31, 2006.

## Specific objective

1. To assess the overall recurrence rates of nasopharyngeal carcinoma.
2. To compare recurrence rates of nasopharyngeal carcinoma by demographic, pathological and treatment factors
3. To determine the associations between demographic factors (gender, age) and the recurrence of nasopharyngeal carcinoma.
4. To determine the associations between pathological factors (TNM staging, histology cell type, level of lymph node involvement, EBV IgA-VCA titer, EBV IgG-VCA titer) and the recurrence of nasopharyngeal carcinoma.
5. To determine the associations between treatment factors and the recurrence of nasopharyngeal carcinoma.

## Hypothesis

1. There were the differences in recurrence rates of nasopharyngeal carcinoma by demographic, pathological and treatment factors
2. There were the associations between demographic factor (gender, age) and recurrence of nasopharyngeal carcinoma.
3. There were the associations between histological factors (TNM stage, histology cell type, level of lymph node involvement, EBV IgA-VCA titer, EBV IgG-VCA titer) and recurrence of nasopharyngeal carcinoma.
4. There were the associations between treatment factors and recurrence of nasopharyngeal carcinoma.

## Limitation of study

The completely collected retrospective data from patients who came to receive diagnosis and complete treatment with the evaluation disease by standard clinical practice guideline in Ramathibodi hospital during January 1, 1996 to December 31, 2006 were used. This data included the follow up of patients until the end of study on December 31, 2007. Results from this study may not be able to imply to Thai population.

**Variable in study**

***Independent Variable:***

1. Demographic factors
   - Gender
   - Age
2. Histological factors
   - TNM stage
   - Overall stage grouping
   - Histology cell type
   - Level of lymph node involvement
   - EBV IgA -VCA titer
   - EBV IgG -VCA titer
3. Treatment factors
   - Chemotherapy (Yes/no)

***Dependent Variable***

Recurrence rate of nasopharyngeal carcinoma

## Definition of terms

**Nasopharyngeal carcinoma (NPC)**; referred a cancer originating in the nasopharynx, the upper most region of the pharynx or "throat"", where the nasal passages and auditory tube join the remainder of the upper respiratory tract (12).

**Recurrence cases of nasopharyngeal carcinoma;** referred to NPC patients had returned of cancer after treatment during follow up time over 12 months.

**Residual tumor cases**; referred to NPC patients had persistence of cancer after treatment during follow up time within 12 months.

**Local recurrence of nasopharyngeal carcinoma**; referred to recurrence is the return of cancer to the area where a patient originally or in the same place it was first found (8).

**Regional recurrence of nasopharyngeal carcinoma**; referred to recurrence occurs in the lymph nodes and tissue locate in the vicinity of original cancer (8).

**Distant recurrence of nasopharyngeal carcinoma;** referred to recurrence or metastasis is spread to other parts of the body, it commonly spreads to the lung, bones, liver and brain (8).

**Recurrence time of nasopharyngeal carcinoma**; referred to length of time or duration time from the date of first treatment up to the date of detection a recurrence of disease in patients or the date at end point.

**Age of patients**; referred to patient's age in year at time of diagnosis.

**Stage of disease**; referred to stage is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body. The stage classified of nasopharyngeal carcinoma by the American Joint Committee on Cancer (AJCC) 1997 will be used a follow (13).

**Tumor stage (T stage)** referred to stand for tumor size and far it has spread locally within the nasopharyngeal and to near by tissue.

**Lymph node stage (N stage)** referred to stand for spread to lymph nodes

**Metastasis stage (M stage)** referred for metastasis (spread to distant organ)

**Histology cell type;** referred to type of tumor cell confirmed by surgical biopsy. There were 3 types defined by World Health Organization (WHO) 1979 (14).

WHO type I: Well differentiated carcinoma

WHO type II: Poor differentiated carcinoma

WHO type III: Undifferentiated carcinoma

**Level of lymph node involvement** referred to level of lymphatic node spread from nasopharynx cancer and is the triangular region originally described in the Ho-stage classification 1978 (15).

Level I: Nodes extension to upper cervical level

Level II: Nodes between this creases and the supraclavicular fossa

Level III: Nodes extension to supraclavicular fossa

**EBV IgA –VCA titer** referred to serum level of IgA antibodies to Epstein -Barr virus capsid antigens in patients with NPC.

**EBV IgG –VCA titer** referred to serum level of IgG antibodies to Epstein -Barr virus capsid antigen in patients with NPC.

**3-year recurrence rate** referred to the percentage of patients who had recurrence of nasopharyngeal carcinoma within 3 year after primary treated.

**5-year recurrence rate** referred to the percentage of patients who had recurrence of nasopharyngeal carcinoma within 5 year after primary treated.

**Censored** referred to study population who were still have no recurrence until end of study (31 December, 2007) or who were withdrawal or loosed to follow up from the study for any reason including lost to follow up.

**Event** referred to study population who had recurrence disease within the study period (January 1, 1996– December 31, 2007).

## Conceptual framework

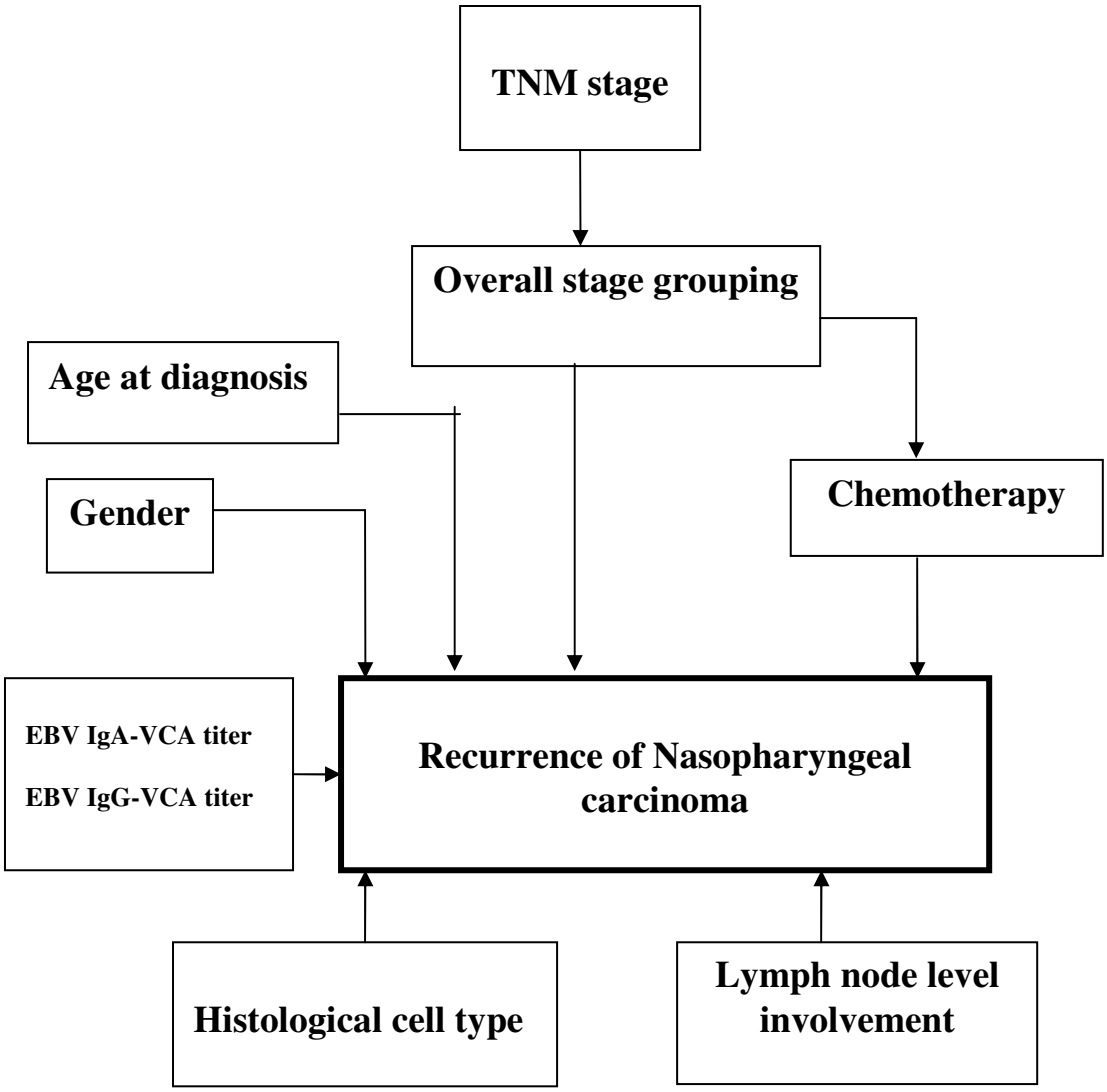


Figure 1 Conceptual framework

# CHAPTER II
# LITERATURE REVIEW

**Reviewing of the literature is divided into 4 parts as follow:**

1. Nasopharyngeal Carcinoma
2. Recurrence of nasopharyngeal carcinoma
3. Factors related to recurrence of nasopharyngeal carcinoma
4. Studies related to the etiological factors of recurrence nasopharyngeal carcinoma

## 1. Nasopharyngeal carcinoma

### 1.1 Definition

Nasopharyngeal carcinoma (NPC) is a cancer originating in the nasopharynx, the upper most region of the pharynx or "throat"", where the nasal passages and auditory tube join the remainder of the upper respiratory tract. NPC differs significantly from other cancer of the head and neck in its occurrence, causes, clinical behavior, and treatment. It is vastly more common in certain regions of East Asia and Africa than elsewhere, with viral, dietary, and genetic factors implicated in its causation (12).

### 1.2 Anatomy of Nasopharynx

The nasopharynx communicates with the nasal cavity anteriorly at the choanae and with the oropharynx inferiorly at the lower border of the soft palate. Superiorly and posteriorly, important bony landmarks include the skull base and the upper vertebral bodies. The eustachian tubes enter the nasopharynx laterally and are covered superiorly and posteriorly by cartilage known as the torus tubarius. The fossa of Rosenmuller (lateral nasopharyngeal recess) is located superior and posterior to the torus and is the most common location for nasopharyngeal carcinoma. Many of the skull base foramen that carries important neural and vascular structures is located

immediately adjacent to the nasopharynx. The nasopharynx is lined by mucosa that is covered with either stratified squamous epithelium or pseudostratified columnar epithelium. It is from this epithelium that nasopharyngeal carcinoma arises. The mucosa also contains other structures including salivary and lymphoid tissue. As mentioned above, these elements can also give rise to malignancy although much less frequently (12).

### 1.3 Natural history

Nasopharyngeal carcinoma spreads by expansion or infiltration. The primary tumor could be small and the patient's presents with enlarged neck nodes typically in the post auricular area. The most common presenting compliant of NPC is the presence of enlarged neck nodes, which occurs in over 90% of patients at diagnosis. Anterior extensions of the tumor toward the nose result in nasal stuffiness and epistaxis. Lateral extension around the Eustachian tube causes decreased hearing, pain and otitis media. Tumors can extend into the parapharyngeal space by passing laterally through the sinus of morgagni, an opening in the lateral wall of the nasopharynx through which the Eustachian tubes traverse. In the parapharyngeal space the tumor can involve the pterygoid muscles, result in trismus. The tumor then extends posteriorolaterally into the poststyloid compartment. They can also extend inferiorly into the neck. NPC can also extend inferiorly into the oropharynx and hypopharynx along the lateral and posterior pharyngeal walls. Superiorly NPC can destroy the base of skull and extend into the cavernous sinus where they can cause cranial nerve palsy of CN III, IV, and VI cranial nerves (16).

### 1.4 Epidemiology

Nasopharyngeal carcinoma is an uncommon neoplasm in most parts of the world. The age-adjusted incidence for both sexes is less than 1 per 100,000 of the population per year in many countries. The incidence varies from region to region and is high in China. Incidence also varies among different ethnic population .It is high among Greenland Eskimos and ethnic Southeastern Chinese, especially inhabitants of Guangdong province, where the reported incidence for men and women is 10 to 20 per 100,000 and 5 to 10 per 100,000 , respectively. A high frequency of NPC is also noted

in Chinese immigrants to Southeast Asia and California, as well as to other parts of the world. The findings suggest that geographic, ethnic, and environmental influences are among the etiologic factor (17).

### 1.5 Clinical of disease

Nasopharyngeal carcinoma affects relatively younger patients, compared with other malignancy of the head and neck regions. In more reports, the male to female is 3:1, with a median age of about 50 year (18). The symptoms of nasopharyngeal carcinoma are related to the location of the tumor, the degree of tumor infiltration into surrounding structure, and metastases.

Early symptoms are often trivial and are often ignored by the patient or misinterpreted by the physician. The most common mode of presentation of nasopharyngeal carcinoma is a painless unilateral metastasis cervical lymph node (19). Bilateral nodal involvement is not uncommon because the nasopharynx is a midline structure that has a rich bilateral lymphatic drainage. The lymph node around the digastrics muscle and upper jugular group are most frequently involved; these are often the largest nodes in the neck. These upper neck lymph nodes are nearly always affected before those of the midline and lower neck. This orderly involvement of lymph node down the neck has been shown to be prognostic significance. Computed tomography (CT) is more sensitive than clinical examination in the evaluation of cervical lymph node involvement, and a significant proportion of patient are upstaged when CT examination is used as part of the evaluation (20).

Nasal symptoms, in the form of unilateral nasal obstruction or blood-stained nasal discharge, are common when the tumor reaches a significant size and become ulcerated. Epistaxis is rarely severe and more frequently occurs as the presence of blood in the early-morning postnasal discharge. Aural symptoms include hearing loss, tinnitus, and, less frequently, otalgia. Because the tumor originates from the fossa of Rosenmuller, close to the Eustachian tube, it is not surprising that the function of the auditory tube often affected. This leads to the development of fluid in the midline ear, which is responsible for the conductive hearing loss and, occasionally, tinnius. Middle ear effusion is present in more than 40% of patients at diagnosis. For

Chinese patient, the presentation of middle ear effusion after childhood should alert the attending clinical to the possible diagnosis of nasopharyngeal carcinoma (21).

The incidence of cranial nerve involvement on presentation is about 20% and is related to direct tumor infiltration (22). Cranial nerve III, IV, and VI are involved when a tumor extend superiorly and affects the cavernous sinus. The trigeminal nerve is affects around the foramen ovale area, and cranial nerves IX to XII are affected at the paranasopharyngeal space below the base of the base of skull, where the nerves lie near the tumor. The incidence of single and multiple cranial nerve involvement is similar (23).

Other less frequent symptom, such as trismus and headache, are related to extensive tumor infiltration of the pterygoid muscles and skull base, respectively. The incidence of distant metastasis on presentation in most patients is about 5%. Radiologically, the lesions may be lytic (66%), sclerotic (21.2%), or a mixture of lytic and sclerotic (12.8%). Common sites of metastasis are the vertebrae and the femoral head. The main symptom associated with this metastasis is severe bone pain. Less frequent sites of metastasis are lung and liver. Patients with metastases to these sites may develop pulmonary symptom or altered hepatic function, respectively (24).

### 1.6 Histological cell type of nasopharyngeal carcinoma

The most widely accepted classification has been established by the World Health Organization (WHO), defined three types of nasopharyngeal carcinoma on the basis of findings on light microscopy.

**Keratinizing squamous cell carcinoma (WHO Type I)** This Keratinizing squamous cell carcinoma (WHO I) is characterized by the presence of intracellular bridges and prominent keratin formation (25). WHO Type I tumors account for approximately 25% of all nasopharyngeal carcinoma in North America only 1% of cases in endemic areas. Patients with type I disease have the worst prognosis, as the 5-year survival rate is only 35% (26).

**Nonkeratinizing squamous cell carcinoma (WHO Type II )** This tumor exhibits the maturation sequence characteristic of squamous cell carcinoma but no keratin formation (25). This is the least common of the three types, and it is often classified as type III. The 5-year survival rate is 61% (26).

**Undifferentiated carcinoma (WHO Type III)** This undifferentiated carcinoma is made up of cells of varying morphology, and it frequently contains clumps benign T cells intermixed within the tumor mass; as a result, it is also called a lymphoepithelioma (25). Type III tumors account for 95% of all cases in endemic areas and 60% of case in North America. The 5-year survival rate is 61% (26).

### 1.7 Stage of Nasopharyngeal carcinoma

The most common system used to describe the spread of nasopharyngeal carcinoma is the TNM system created by the American Joint Committee on Cancer (AJCC) 1997 (13).

T stage for tumor (its size and how far it has spread locally within the nasopharynx and to nearby tissues).

N stage for spread to lymph nodes (small bean-shaped collections of immune system cells that help the body fight infections and cancers).

M stage is for metastasis (spread to distant organs).

TNM Stage Grouping

Stage 0**:** Tis, N0, M0: The cancer is "in situ." It has not yet penetrated to a deeper layer of nasopharyngeal tissue and has not spread to lymph nodes or distant sites.

Stage I**:** T1, N0, M0: The tumor is only in the nasopharynx and has not spread to lymph nodes or distant sites.

Stage IIA**:** T2a, N0, M0 : The tumor has spread to soft tissues of the nasal cavity and/or the oropharynx but no farther and has not spread to lymph nodes or distant sites.

Stage IIB: T2b, N0 or N1, M0, T1or 2 or 2a, N1, M0: The tumor has spread to soft tissues of the nasal cavity and the oropharynx, but not into bone. It has spread to one or more single lymph nodes, not larger than 6 cm, in the same side of the neck as the original cancer. The cancer has not spread to distant sites.

Stage III: T1or 2, N2, M0, T3, N0-2, M0: The tumor has spread to soft tissues of the nasal cavity and/or the oropharynx and to lymph nodes, not larger than 6 cm, on both sides of the neck but not to distant sites. Or the tumor has spread to the

sinuses or the bones near the nasopharynx and may or may not have spread to lymph nodes but not to distant sites

Stage IVA: T4, N0-2, M0: The tumor has spread to the skull and/or cranial nerves (nerves in the head that lie near the nasopharynx and have special functions such as vision, smell, eye movement), the hypopharynx (lower part of the throat), the eye, or its nearby tissues and may or may not have spread to lymph nodes smaller than 6 cm but not to distant sites.

Stage IVB: Any T, N3, M0: The tumor is of any size but has spread to one or more lymph nodes that are larger than 6 cm and/or located above the collarbone area but not to distant sites.

Stage IVC: Any T, any N, M1: The tumor is of any size and may or may not have spread to lymph nodes but has spread to distant sites.

### 1.8 Treatment of Nasopharyngeal carcinoma

The options for treatment of nasopharyngeal cancer (NPC) are radiation therapy, chemotherapy, and occasionally surgery. In some cases, the best approach involves 2 or more of these strategies.

**1.8.1 Radiotherapy:** Radiation therapy is the standard treatment for nasopharyngeal carcinoma because most cases are the radiation-sensitive type, the non-keratinizing and undifferentiated varieties and the location of the nasopharynx its relationship to many important structures, complete surgical excision is extremely challenging. Radiation therapy uses a beam of high-energy X-rays or particles to destroy cancer cells or slow their rate of growth. Several types of radiation therapy are used to treat the main nasopharyngeal mass and nearby lymph nodes. Even if the lymph nodes are not abnormally firm or large, radiation is still used in case a few cancer cells have spread to the lymph nodes. If the lymph nodes are known to contain metastasis from NPC, higher radiation doses are used (27). External beam radiation therapy is the most common way to deliver radiation to an NPC is to carefully focus a beam of radiation from a machine outside of the body. External beam radiation therapy usually involves having treatments 5 days a week for a period of about 6 to 7

weeks. In radiotherapy a dose of 6500-7500 cGy is normally given to primary tumor and 6500- 7000 cGy to the involved neck nodes, whereas the dose for treatment a node-negative neck is 5000-6000 cGy. Many radiation oncologists are using a new form of external beam radiation therapy called intensity modulated radiation therapy (IMRT). IMRT changes the radiation beam so it is better shaped to the contours of the tumor and reduces the dose of radiation to the surrounding normal tissue.

Brachytherapy is another method of delivering radiation is to insert (implant) very thin metal rods or wires. The rods or wires contain radioactive materials and are placed in or near the cancer. This method is called internal radiation, interstitial (in the tissue) radiation, or brachytherapy. This is usually done if the cancer comes back after external beam radiation therapy (27).

**1.8.2 Chemotherapy**: is the use of special drugs for treating cancer. The drugs can be swallowed in pill form or can be injected through a needle into a vein or muscle. Chemotherapy is systemic therapy. This means that the drug enters the bloodstream and circulates throughout the body (through the whole system) to reach and destroy cancer cells. Chemotherapy can kill rapidly growing cells such as cancer cells. Some chemotherapy drugs also make cells more vulnerable to radiation. Chemotherapy often involves the use of 2 or more drugs, called combination chemotherapy. Chemotherapy is often used together with radiation therapy as the first treatment for more advanced stages of this cancer. It is also used alone for patients whose NPC has spread to distant organs such as the lungs, bones, or liver. The main drugs used in the treatment of NPC are cisplatin, 5-fluorouracil (5-FU), bleomycin, methotrexate, doxorubicin, and epirubicin. Some of the combinations used most often are cisplatin and 5-FU; cisplatin, 5-FU, and bleomycin; or cisplatin, epirubicin, and bleomycin. The most widely used cisplatin combination in these patients is the combination of cisplatin and 5-FU.5-FU is given in the form of 4 t0 5 day continuous infusion at a dose of 1000 mg/$m^2$ and cisplatin is given at a dose of 80-100 mg/$m^2$ on the first day of therapy (28). Until 1985, locally advanced nasopharyngeal cancer was treated almost exclusively with radiotherapy, but in recent years chemotherapy has assumed an important role in its management. Nasopharyngeal carcinomas are highly sensitive and responsive to chemotherapy (29).

**1.8.3 Surgery** has a limited role in the treatment of nasopharyngeal carcinoma because of the tumor's high degree of radio sensitivity and anatomic barriers to surgical access. Various surgical approaches have been described in the literature, including transpalatal, transmaxillary, middle mandibulotomy, facial degloving, infratemporal fossa and endoscopic approaches. Surgery is typically contraindicated for patients with any evidence of extension into the parapharyngeal space, skull base, paranasal sinuses, or carotid artery because of surgery's high degree of morbidity and the low probability of affecting a cure. New surgical techniques can completely remove some nasopharyngeal tumors, but this strategy is appropriate only for a relatively small number of patients. The advantages of surgical removal include the ability of the pathologist to examine the entire cancer, as well as additional tissue removed during surgery, and of the surgeon to repair/reconstruct the cancer site. As with any surgery, possible complications may develop. Nasopharyngectomy is an alternative treatment for local recurrent and residual nasopharyngeal carcinoma (7).

## 2. Recurrence of nasopharyngeal carcinoma

Recurrent of nasopharyngeal carcinoma; recurrence is defined as the return of cancer after a period of remission. Cancer recurs because undetected cancer cells can sometimes remain in the body after treatment. Over time, these undetected cells can multiply and grow large enough to be recognized and diagnosed. Depending on the type of cancer, this can happen in weeks, months, or even many years after the original cancer (or primary cancer) was treated. Cancer can recur in the same place as the original cancer or elsewhere in the body. A cancer recurrence is classified by its location where in the body it recurs, but is always referred by the name of the original or primary tumor (30).

Recurrence is divided into three categories :

Local recurrence means the cancer reappears in the same place it was first found. The cancer hasn't spread to the lymph nodes or other parts of the body.

Regional recurrence means the cancer occurs in the lymph nodes and tissue located in the vicinity of original cancer.

Distant recurrences refer to cancer that has spread (metastasis) to areas

farther away from where cancer was first located. Nasopharyngeal carcinomas had a high rate of distant metastases, more than 30% as compared to the incidence of systemic involvement from other head and neck tumor sites (30).

Nasopharyngeal carcinoma differs from other squamous cell carcinomas of head and neck in that recurrence can occur late 22 % of patients developed a recurrence 5 years after their initial treatment. Most recurrence of nasopharyngeal carcinoma occur within 2 to 3 years after cessation of treatment, and more than 90% of local and distant metastases develop within 3 years (9). However, locoregional recurrence can occur in 10-30% of patients after definitive radiotherapy and prognosis following local relapse is very poor without retreatment (31). Careful long-term follow-up of patients treated for nasopharyngeal carcinoma is necessary for early detection of recurrence. Unfortunately, no single method is consistently reliable in the diagnosis of recurrent disease.

**Treatment of recurrent of nasopharyngeal carcinoma**

There are several ways of combining chemotherapy with radiotherapy and surgery.

**A. Treatment of recurrent tumor in the nasopharynx** (Local recurrence)

Recurrent tumor in the nasopharynx can be managed with a second course of radical external radiotherapy. The recommended radiation dose must exceed 6,000 cGy if the eradication of those tumor cells that survived the initial irradiation is to be achieved. Especially if limited to the primary site, without intracranial extension, should be considered for re-treatment with radiotherapy (30).

Nasopharyngectomy or surgical resection, if the residual or recurrence tumor in the nasopharynx is too extensive for brachytherapy or extended to the paranasopharyngeal space, or when the tumor has recurred after brachytherapy, the only chance of salvage without excessive risk of complications from a third course of radiotherapy is surgical resection. The problems associated with surgical salvage of NPC lie in the fact that the nasopharynx is located in the center of the head, which makes it difficult to approach; it s also difficult to obtain adequate exposure of the region for a safe oncologic procedure (32). In summary, the difficulty in achieving local tumor control for patients who have recurrent NPC after radiotherapy is the

inability to identify local recurrence early. If recurrences can be diagnosed when they are localized to the mucosa, interstitial brachytherapy offers a good chance that the tumor will be eradicated, with low morbidity. Larger tumors that are still localized to the nasopharynx and the paranasopharyngeal space are best managed with surgical resection (30).

**B. Treatment of regional recurrence disease (lymph node)**

Both sides of the neck are routinely included in the radiation field even if there are no palpable lymph modes. Despite this, 9.2% to 12% of patients develop recurrence in the cervical lymph nodes. Recurrence tumor in the neck after radiotherapy is notoriously difficult to confirm because in some lymph node only clusters of tumor cell are present. Aggressive treatment for recurrence nasopharyngeal carcinoma is warranted (30).

Radical neck dissection the main of the classical radical neck dissection as the treatment of choice for these patients is whether such an extensive operation is necessary to achieve control of the neck disease. First, examination of the resected specimen following radical neck dissection sometimes revealed no tumor in any of the lymph nodes removed. Second, in some patients, the cervical metastasis presented clinically as a solitary node, and it is thought that is necessary. Neck dissections are an important part of treating many types of head and neck cancer that have spread or have a high chance of spreading into the neck. This procedure, however, is not often used for NPC. Most cases of NPC are sensitive to radiation, so neck dissection is usually recommended only if the cancer has persisted after radiation treatment or has come back after a period of time (a recurrence) (33).

**C. Treatment of distant metastases**

Compared with other cancers of the head and neck region, nasopharyngeal carcinoma has a high propensity to develop distant metastases. The most common sites of distant spread are liver, bones, and lungs. In some case, the surgical treatment of metastasis to the bone is appropriate. Generally, however, palliative radiochemotherapy is the treatment of choice. The quality of life of these patients should be the objective of each treatment strategy performed for the purpose of

palliation. Sufficient pain control therapy is of great importance. At the same time, vital functions such as respiration and nutrition must be ensured and, if necessary, elective tracheotomy or percutaneous gastronomy should be performed. Due to the fact that it is almost impossible for the families of these patients to care for them adequately, the support of nursing services or institutions should be discussed with relatives or concerned persons (34).

**3. Factors related to recurrence of nasopharyngeal carcinoma**

There have been inconsistent finding about what were the significant factor influencing. Analyzing the prognostic factor for nasopharyngeal carcinoma, Perez et al. (35) demonstrated that the most significant prognostic factor in nasopharyngeal carcinoma were patient age, stage of disease, presence of cervical lymphadenopathy and certain technical factor of irradiation. Likewise, Sanguinetti et al. (36) suggested that T-stage, N-stage and dose to the primary site were prognostic indicators for local and regional recurrence. Furthermore, Cheng et al. (37) study of 149 patients with nasopharyngeal carcinoma revealed that WHO type II histology, T4 stage and parapharyngeal extension were poor prognostic factor for locoregional recurrence; T4, N3 stage, serum LDH level > 410 U/I, parapharyngeal extension and infiltration of clivus were significantly associated with poor prognosis for distant metastasis.

Stage of disease**:** A large variation of tumor volume is present in T stage of different staging system, and primary tumor volume represents an independent prognostic factor of local control and is more predictive with the AJCC/UICC staging system than with Ho's T stage classification. Based on the difference in recurrence pattern, different prognostic categories can be defined across stages (6).

(1) T1-2 N0-1 ; relatively good treatment outcome

(2) T3-4 N0-1 ; mainly local recurrence

(3) T1-2 N2-3 ; mainly regional recurrence and metastasis

(4) T3-4 N2-3 ; local, regional recurrence and distant metastases

Histological cell type: The 5-year survival rate of non keratinizing (WHO II) and undifferentiated nasopharyngeal carcinomas (WHO III), with appropriate treatment, is about 65% overall. Cure is highly possible, even when disease has spread to the regional lymph nodes. Rate of distant metastasis are higher in patients with type II or III tumors. On the other hand, type II and III tumors are more easily controlled, their greater degree of radiosensitivity, and therefore patients with type II or III disease have a better prognosis (7).

Primary tumor size: Validity of tumor volume has been confirmed in patients with T3 and T4 tumors, and there is an estimated 1% increase in risk of local recurrence for every 1 cm. increase in primary tumor volume (7).

Involvement lesions: Moderately advanced lesions without clinical evidence of spread to cervical lymph nodes are often curable and have shown survival rates of 50% to 70%. Tumors invading into skull base and those cranial nerve palsies have a poor prognosis. Level of lymph node involvement, extension to the upper lymph node involvement have a better prognosis than extension to lower lymph node involvement (15).

Major prognostic factors adversely influencing outcome of treatment include large size of the tumor, higher N stage, and the presence of involved neck nodes. Other factors linked to diminished survival that were present in some, but not all, studies include age, nonlymphoepithelial histology, long interval between biopsy and initiation of radiation therapy, diminished immune function at diagnosis, incomplete excision of involved neck nodes, pregnancy during treatment and certain EBV antibody titer patterns (36). These prognostic grouping will have important implications for the selection of appropriate treatment strategies and the design of future clinical trials to address different failure patterns. There is early evidence that for advanced disease, adding chemotherapy to radiotherapy will improve treatment outcome, both in terms of locoregional recurrence and distant metastases.

**4. Studies related to the etiological factors of recurrence of nasopharyngeal carcinoma**

Those which have been report included the following

**Age at diagnosis**

Age was generally accepted as risk factor the development of cancer. From study in 2004, performed a retrospective analysis of 35 patients with nasopharyngeal carcinoma between March 1994 and November 2002.The median age at diagnosis was 43 year and median recurrence time of 28 months( rang, 11-158). Multivariate analysis using the Cox model analysis for recurrence rate of nasopharyngeal carcinoma showed that older age at diagnosis had more than recurrence rate and had a statistically significant. (HR= 1.057, p value<0.02) (38). Similarly studies of Ma J. et al. showed that age was positively associated with recurrence rate of nasopharyngeal carcinoma, In multivariate analysis, it was found that age < 40 year was a significant independent positive predictor for local recurrence (HR = 1.02, 95% CI = 1.01-1.04, p=0.0385) (39).

**Gender**

As a result, reported that recurrence rate of nasopharyngeal carcinoma of being male patients was significantly higher than that of being female patients (HR = 1.17, 95% CI = 1.10 – 1.82, p = 0.033) (40).

**Stage of disease**

The most report found that stage of disease had associated for recurrence of nasopharyngeal carcinoma. Some researchers believed that distant metastases rate of nasopharyngeal carcinoma were influenced by N stage in TNM classification (41, 42), whereas primary local recurrence rate correlated well to T stage (43). Other investigators believed that N3 stage in TNM classification and Ho's advancing lymph node involvement significantly associated with distant metastatic rate while locoregional recurrence rate was affected by both T stage and N stage (44).

From study to evaluate of 83 patients with nasopharyngeal carcinoma in the Department of Clinical Oncology at the Tyen Mun Hospital, 1070 patients with nasopharyngeal carcinoma were treated with radical radiotherapy, they found that T

stage of disease was a significant predictor of recurrence favoring those with early-stage (T1+T2)(p=0.04) and (T1+T2) stage had a 3 -years recurrence rates of nasopharyngeal carcinoma were 32% versus T3+T4, with a 3 -year recurrence rates were 51%, respectively (45). Selek U et al., evaluate the outcome of patients with non-metastatic nasopharyngeal carcinoma. The study reported that the 5 -year recurrence rates were 41% for patients with N3 stage and 18% for N0, N1, N2 stage (p= 0.08), respectively and two of the three local recurrence occurred within 2 years after the initiation of treatment (46).

Many studies reported that TNM stage had association with recurrence of nasopharyngeal carcinoma, example study in Taiwan evaluated to 149 patients with newly diagnosed and histological proven nasopharyngeal carcinoma were prospectively treated with concomitant chemotherapy and radiotherapy (CCRT) followed by adjuvant chemotherapy. Multivariate analysis by Cox proportional hazards model showed that T4 stage as the most important for locoregional recurrence with a relative risk for recurrence of 5.97 (adjusted HR = 5.97, p=0.02) and T4, N3 classification were the two factors that independently predict distant metastasis of nasopharyngeal carcinoma; the hazard ratio were 3.99 (adjusted HR = 3.99, p=0.02 and 3.39, p=0.01), respectively (37). Similarly from this study that reviews tumor control data of 496 patients with nasopharyngeal carcinoma to whom a radical course of radiotherapy with or without induction chemotherapy was given and result showed that T- stage were independent predictors for local recurrence rate of nasopharyngeal carcinoma, whereas N stage were major determinants for regional recurrence rate of nasopharyngeal carcinoma in lymph node positive patients. Pattern of recurrence seems to vary with nodal status and locoregional recurrence rates between node negative and node positive patients were similar: 24.2% vs. 19.7%. Distant metastases rate for node negative patients was only 4.2% but this rate increased up to 23.7% for node positive patients, which is consistent with the findings from other series that node positive patients develop distant metastases more often than node negative patients (47).

**Histological cell type**

Reviewed the records of 74 patients with recurrence of nasopharyngeal carcinoma treated at the University of California, San Francisco. Result showed that 5-years recurrence rates were significantly higher in the undifferentiated carcinoma group (WHO III) than the non-keratinizing (WHO II) and squamous cell carcinoma group (61% vs. 32% vs. 0%, respectively, p=0.035) (48).

Histological cell type was an independent prognostic factor recurrence as well as survival. As result, showed that patient with poor differentiated carcinoma (WHO Type II) as compared to with undifferentiated carcinoma (WHO Type III) had a greater risk of recurrence of nasopharyngeal carcinoma (adjusted HR = 3.55, p = 0.054) (37).

**Involvement of cancer factor.**

Feng A. et al., study to evaluate the prevalence and prognostic significance of prevertebral muscle involvement in patients with nasopharyngeal carcinoma between July 1990 and December 2001. In multivariate analysis accounting for all previously know prognostic factor, prevertebral muscle invasion was associated with an increased risk for any recurrence (adjusted HR = 2.01, $p < 0.001$), locoregional recurrence (adjusted HR =2.69, $p < 0.001$), and distant metastasis (adjusted HR = 2.25, $p < 0.001$). So prevertebral muscle involvement was independent prognostic factor for recurrence of nasopharyngeal carcinoma and prevertebral muscle involvement was significantly associated with an increased probability of any recurrence ($p < 0.001$). The probability of 5-years recurrence rates of nasopharyngeal carcinoma was 26.4% in patients with prevertebral muscle involvement vs. 17.4% in patients without prevertebral muscle involvement. ($p < 0.001$) (8).

**Level of lymph node involvement factor**

Based on a study by Lee A. et al, the levels of lymph node involvement (upper-mid vs. lower neck) were found to be significant factors for distant metastasis of nasopharyngeal carcinoma (49). According to a similar many studies, that level lymph node involvement was an independent prognostic factor governing and distant metastases. This study found that patient with lower lymph node involvement had a

higher risk of recurrence of nasopharyngeal carcinoma than those with upper-mid lymph node involvement. (adjusted HR = 1.67, 95% CI= 1.25-1.84, p < 0.0001) (39).

In addition, resulted of the multivariate analysis of various clinical endpoints were discussed that levels of lymph node involvement were significant factor of recurrence rates of nasopharyngeal carcinoma (p=0.0275) (45).

**Treatment factor**

Wolden S. et al.(50) reported on the result of accelerated concurrent boost radiotherapy a cisplatin for two courses in 50 patients with advanced (stage II-IV) nasopharyngeal carcinoma. Adjuvant chemotherapy of cisplatin and 5-FU infusion for three courses was given to 37 patients. These patients were compared to 51 patients treated with standard fractionation radiotherapy without chemotherapy. They reported significant improvement with 3-years recurrence rate of nasopharyngeal carcinoma in patients given chemoradiotherapy and patients given radiotherapy alone (11% vs. 26%). The encouraging results obtain with concurrent cisplatin and radiotherapy led to a prospective randomized phase III Intergroup trial conducted in North America by the RTOG and ECOG (51). In this study, 193 patients were registered and 185 patients were randomized and stratified to receive radiation therapy alone (92) to a total dose of 70 Gy versus a combination of chemotherapy and radiotherapy (93), they found that adjuvant chemotherapy was given to decrease locoregional recurrence and systemic metastases. This important trial demonstrated a highly significant difference in 5 – years recurrence rate of nasopharyngeal carcinoma (71% for RT group vs. 42% for CT-RT group, p< 0.001). This consists of initial concurrent cisplatin and radiotherapy to produce the best locoregional control, followed by adjuvant chemotherapy of cisplatin and 5-FU infusion for three courses to consolidate this control and to reduce the incidence of systemic metastases. This study demonstrates clearly that chemoradiotherapy is highly effective in the treatment of locally advanced nasopharyngeal carcinoma and is now considered as the standard of care in treatment of patients.

Ma J. al. (52), compare induction chemotherapy with cisplatin, 5-FU infusion, and belomycin follow by radiotherapy to patients who received radiation treatment only, result showed that significant improvement in 5 –years recurrence rats of nasopharyngeal carcinoma were 41% vs. 51%, p < 0.05). Farias T. et al. (53)

reported that the use of combination chemotherapy – radiotherapy has been investigated, with a view to decreasing the rate of distant metastasis and recurrence of nasopharyngeal carcinoma, which were similarly to several results reported in the literature (54).

# CHAPTER III
# MATERIAL AND METHODS

## Study design

Retrospective cohort study which all the data was retrieved from medical records at cancer clinic, Ramathibodi hospital, Bangkok, Thailand.

## Reference population and study population

The study population included all patients who had been diagnosed of nasopharyngeal carcinoma with histological confirmed and received treatment at Ramathibodi hospital during January 1, 1996 to December 31, 2006.

## Inclusion criteria

1. Who had been diagnosed with histological confirmed of primary nasopharyngeal carcinoma.

2. Who already received completely treatment for nasopharyngeal carcinoma at Ramathibodi hospital during January 1, 1996 to December 31, 2006.

3. Who finished treatment for nasopharyngeal carcinoma at Ramathibodi hospital during January 1, 1996 to December 31, 2006 for more than 12 months.

## Exclusion criteria

1. Who had cancer of nearby sites such as pharyngeal cancer, larynx cancer, oral cavity cancer, tongue cancer, hypopharynx cancer.

2. Who had incomplete information for the analysis.

**Sample size and sampling techniques**

Total patients who meet the inclusion criteria were included in the analysis of this study.

Calculated of formula (event rate)

$$\text{Hazard ratio} = \Delta = \left(\frac{\lambda t}{\lambda c}\right) = \left(\frac{\ln \pi_t}{\ln \pi c}\right)$$

$$E = \left(\frac{(Z_{\alpha/2} + Z_\beta)(1+\Delta)}{1-\Delta}\right)^2$$

$$n = \frac{2E}{2-\pi_t-\pi_c}$$

$$n = \frac{2\left(\frac{(Z_{\alpha/2} + Z_\beta)(1+\Delta)}{1-\Delta}\right)^2}{2-\pi_t-\pi_c}$$

n = minimum sample size

E = Event cases

(1-α) = Alpha error, $\alpha = 0.05$, $Z_{\alpha/2} = 1.96$

(1-β) = 90% power of test, $\beta = 0.10$, $Z_\beta = 1.28$

$\pi_t$ = Recurrence rate of nasopharyngeal carcinoma of patients with negative lymph node involvement at five years = 0.24

$\pi_c$ = Recurrence rate of nasopharyngeal carcinoma of patient with positive lymph node involvement at five years = 0.47

$\Delta$ = Hazard ratio between two groups = 2.3

Previous study by Vendelbo Johansen et al. (55) looked at the recurrence rate associated with clinical significance of lymph node involvement in nasopharyngeal carcinoma. They reported that patients with negative lymph node involvement had a recurrence rate of nasopharyngeal carcinoma were 24% at five years when compare to 47% with positive lymph node involvement. After controlling

for significant prognostic factors, patients with positive lymph node involvement increased the risk of recurrence of nasopharyngeal carcinoma than patients with negative lymph node involvement. (HR=2.3, 95% CI=1.2 – 4.4, p=0.02)

Computation of sample size;

$$n = \frac{2\left(\frac{(1.96+1.28)(1+2.3)}{1-2.3}\right)^2}{2-0.24-0.47}$$

$$n = 105 \text{ cases per groups}$$

There for, the minimum number of sample size for these studies were 210 cases. The total number of patients include in this study were 366 cases.

**Materials**

Data collection form was performed by research was used for retrieving data from hospital records. It composed of 4 parts of information as follow;

Part I General information; name of patients, age of patients, gender, part of history of disease, family history of having cancer, smoking and alcohol consumption status.

Part II Nasopharyngeal carcinoma information; date of diagnostic, histological cell type, stage of disease, location of primary tumor (T), regional lymph node involvement (N), site of distance metastasis (M), EBV IgG-VCA titer, EBV IgA-VCA titer.

Part III Treatment information; first date at treatment , last date at treatment and type of treatment received which were single and combination treatments of radiotherapy, chemotherapy, adjuvant therapy, having fibrosis which is the complication of treatment.

Part IV Patient's last status or outcome of study which were date of last follow up, types of last status: having recurrence, loss to follow up, date of diagnosis of having recurrence, location of recurrence.

**Methods of data collection**

1. Research protocol was reviewed by the Ethical committee of Mahidol University and by the Ethical committee of the Faculty of medicine, Ramathibodi hospital, Mahidol University.

2. Data were retrieved from hospital and medical record of nasopharyngeal carcinoma patients at the Department of medical record.

**Statistical analysis**

1. Descriptive statistics was used to descriptive characteristics of patients by frequency, percent, mean, standard deviation to describe characteristic of study population.

2. Analytic statistics

Kaplan-Meier was used to estimate the recurrence rate of nasopharyngeal carcinoma among independent variables. The log- rank test was used to demonstrate significant differences of recurrence rate of nasopharyngeal carcinoma among independent variables.

Cox's regression was used to determine crude and adjusted association factors with recurrence nasopharyngeal carcinoma by hazard ratio (HR) with 95% confident interval of HR and p-value.

510 patients with the diagnosis of nasopharyngeal carcinoma by pathological confirmation. They received treatment in Ramathibodi hospital.

- 71 patients were excluded because they received treatment before year 1996.
- The remaining was 439 patients.

- Total 439 patients were followed up till the end of the study in December 31, 2007.
- 73 patients were excluded because follow up time was less than 12 months, and they were residual cases not recurred cases.

- Total 366 patients were included in the analysis. There were
  - 105 with recurrence
  - 261 with no recurrence

**Figure 2** Study diagram

# CHAPTER IV
# RESULTS

This retrospective cohort study aims to assess the recurrence rate, the recurrence times and prognosis factors related to recurrence of the nasopharyngeal carcinoma among patients at Ramathibodi hospital. The data was collected from the medical hospital records of patients who admitted during January 1, 1996 to December 31, 2006. After receiving treatment, each of patients was then followed up until the end of study on December 31, 2007. Among total 439 patients with the follow up time ranged from 1 to 154 months, there were 42 cases with residual and 105 cases with recurrence. Total number of 366 patients with 105 patients had recurrence of nasopharyngeal carcinoma had followed up times ranged from 12.03 to 154.20 months (median follow up time was 60.20 months) was included in the analysis. The results were presented as follows:

4.1 The characteristic of total study population and pathological characteristic of study population with recurrence

4.2 Incidence density of recurrence rates of nasopharyngeal carcinoma patients by prognostic factors

4.3 Survival curves and log rank test of recurrence rate of nasopharyngeal carcinoma patients by prognostic factors.

4.4 Crude analysis of the association between prognostic factors and recurrence rate of nasopharyngeal carcinoma

4.5 Multivariate analysis of the association between prognostic factors and recurrence rate of nasopharyngeal carcinoma

## 4.1 The characteristic of the study population.

### 4.11 The general characteristic of study population

With the total patients of 366, 52.73% of them were 45 years old and older, and 47.27% were under 45 years old. The mean age was 46.13 years (SD=12.15). There were 233 (63.66%) male and 133 (36.34%) females. Majority of patients with 59.84% were from Central region, 13.35% from Northeastern region, 11.75% from Southern region, 9.02% from Eastern region, 4.37% from Western region and 1.64% from Northern region of Thailand. One hundred-eleven (30.33%) of patients had a history of tobacco consumption and 102 cases (27.87%) had a history of alcohol consumption at the time of diagnosis of having nasopharyngeal carcinoma before the recurrence. (Table 1)

**Table 1 General characteristic of study population**

| Variable | Number (n=366) | Percentage |
|---|---|---|
| **Gender** | | |
| Male | 233 | 63.66 |
| Female | 133 | 36.34 |
| **Age** | | |
| < 45 | 173 | 47.27 |
| ≥ 45 | 193 | 52.73 |
| Mean (SD) = 46.13(12.15) | | |
| **Place of residence** | | |
| Northern | 6 | 1.64 |
| Central | 219 | 59.84 |
| Eastern | 33 | 9.02 |
| Western | 16 | 4.37 |
| Northeastern | 49 | 13.35 |
| Southern | 43 | 11.75 |
| **Cigarette Smoking** | | |
| No | 171 | 46.72 |
| Yes | 111 | 30.33 |
| Unknown | 84 | 22.95 |
| **Alcohol drinking** | | |
| No | 180 | 49.18 |
| Yes | 102 | 27.87 |
| Unknown | 84 | 22.95 |

**The pathological characteristics of the study population**

By the histological cell type of nasopharyngeal carcinoma, there were 18 cases (4.92%) with well differentiated carcinoma, 213 cases (58.020%) with poor differentiated carcinoma, 131 cases (35.79%) with undifferentiated carcinoma and 4 cases (1.05%) with other type nasopharyngeal carcinomas or unknown.

With the 1997 AJCC system or TNM staging system ( tumor, node and metastasis), the proportion of patients with tumor staging or T staging as T1, T2, T3 and T4 were 15.85%, 29.51%, 27.32% and 37.32% respectively. The proportion of patients by lymph node involvement as N0, N1, N2, and N3 were 18.58%, 18.58%, 46.17% and 16.67% respectively. The proportion of patients by status of metastasis as no metastasis (M0) was 97.27% and having metastasis (M1) was 2.73%. For the overall stage grouping, there were 16 cases (4.37%) in stage I, 68 cases (18.58%) in stage II, 128 cases (34.97%) in stage III, 144 cases (39.34%) in stage IV without metastasis and 10 cases (2.73%) in stage IV with metastasis.

Among patients with lymph node involvement, it was found that, there were 126 cases (34.43%) had upper lymph node level involvement, 70 cases (19.13%) had mid lymph node level involvement and 19 cases (5.19%) had lower lymph node level involvement. There were 98 cases (26.78%) of nasopharyngeal carcinoma patients had EBV IgG-VCA titer $\geq$ 160 and 21 cases (5.74%) for patients had EBV IgG-VCA titer < 160. There were 70 cases (19.13%) of nasopharyngeal carcinoma patients had EBV IgA-VCA titer $\geq$ 40 and 97 cases (26.50%) for patients had EBV IgA-VCA titer < 40. There were 237 cases (64.75%) of nasopharyngeal carcinoma patients had neck fibrosis after receiving treatment, while 69 cases (18.85%) had no neck fibrosis and 280 cases (76.50%) received chemotherapy treatment which were 86 cases (23.50%) no received chemotherapy. For the last status at end study, there were 105 cases (28.69%) had recurrent and 261 or 77.311% had no recurrent and loss to follow up. (Table 2)

**Table 2 Pathological characteristic of the study population**

| Variable | Number (n=366) | Percentage |
|---|---|---|
| **Tumor stage (T stage)** | | |
| T1 | 58 | 15.85 |
| T2 | 108 | 29.51 |
| T3 | 100 | 27.32 |
| T4 | 100 | 27.32 |
| **Lymph node stage (N stage)** | | |
| N0 | 68 | 18.58 |
| N1 | 68 | 18.58 |
| N2 | 169 | 46.17 |
| N3 | 61 | 16.67 |
| **Metastasis stage ( M stage)** | | |
| Without metastasis | 356 | 97.27 |
| With metastasis | 10 | 2.73 |
| **Overall stage grouping** | | |
| Stage I | 16 | 4.37 |
| Stage II | 68 | 18.58 |
| Stage III | 128 | 34.97 |
| Stage IV without metastasis | 144 | 39.34 |
| Stage IV with metastasis | 10 | 2.73 |
| **Histology cell type** | | |
| Well differentiate carcinoma (WHO I) | 18 | 4.92 |
| Poor differentiate carcinoma (WHO II) | 213 | 58.20 |
| Undifferentiated carcinoma( WHO III) | 131 | 35.79 |
| Other or unknown | 4 | 1.05 |

**Table 2 Pathological characteristic of the study population (continued)**

| Variable | Number (n=366) | Percentage |
|---|---|---|
| **Lymph node level involvement** | | |
| No involvement | 58 | 15.85 |
| Upper lymph node level | 126 | 34.43 |
| Mid lymph node level | 70 | 19.13 |
| Lower lymph node level | 19 | 5.19 |
| Unknown | 93 | 25.41 |
| **Neck fibrosis** | | |
| No | 69 | 18.85 |
| Yes | 237 | 64.75 |
| Unknown | 60 | 16.39 |
| **Chemotherapy received** | | |
| No | 86 | 23.50 |
| Yes | 280 | 76.50 |
| **EBV IgG-VCA titer** | | |
| < 160 | 21 | 5.74 |
| ≥ 160 | 98 | 26.78 |
| Unknown | 247 | 67.48 |
| **EBV IgA-VCA titer** | | |
| < 40 | 97 | 26.50 |
| ≥ 40 | 70 | 19.13 |
| Unknown | 199 | 54.37 |
| **Status at end of study** | | |
| No recurrence | 261 | 77.31 |
| Having recurrence | 105 | 28.69 |

**Pathological characteristic of nasopharyngeal carcinoma patients with recurrence**

At the end of the study, there were 105 cases had recurrent after primary treatment. The highest percentages by types of recurrence were 39.05% from distant metastasis alone, 28.57% from local recurrence alone and 7.62% from regional recurrence alone. There were 12 cases (11.42%) had local plus metastasis recurrence, 8 cases (7.61%) had regional plus metastasis recurrence , 5 cases (4.76%) had local plus regional recurrence and 1 cases had local plus regional plus metastasis recurrence. ( Table 3)

**Table 3 Pathological characteristic of nasopharyngeal carcinoma patients by types of recurrence**

| Variable | n = 105 | Percentage |
|---|---|---|
| **Type of recurrence** | | |
| Local recurrence alone | 30 | 28.57 |
| Regional recurrence alone | 8 | 7.62 |
| Metastasis alone | 41 | 39.05 |
| Local plus regional recurrence | 5 | 4.76 |
| Local plus metastasis recurrence | 12 | 11.42 |
| Regional plus metastasis recurrence | 8 | 7.61 |
| Local plus regional plus metastasis recurrence | 1 | 0.95 |

**Table 4 Number and percentage of nasopharyngeal carcinoma patient with recurrent by follow up time after treatment**

| Follow up time after treatment (years) | Total of patient | Number of recurrence | Percent of recurrence |
|---|---|---|---|
| Within 1 year (residual tumor) | 73 | 42 | 28.57 |
| >1 – 3 years | 139 | 62 | 42.18 |
| >3 - 5 years | 57 | 19 | 12.93 |
| >5 – 8 years | 91 | 18 | 12.24 |
| > 8 years | 79 | 6 | 4.08 |

With the total patients of 439, there were 42 cases (28.57%) had recurrent after primary treatment within 1 year which were classified as residual tumor**,** The highest percentages of patients with recurrent were 42.18% found in follow up time during 1 - 3 years, 12.93% in follow up time 3 – 5 years, 12.24% in follow up time 5 – 8 years, and 4.08% in follow up time over 8 years after treatment.

**4.2 Incidence density of recurrence rates of nasopharyngeal carcinoma patients by prognostic factors.**

Total person -years of observation was 1,836 years of 366 patients. Overall incidence density of recurrence rate of nasopharyngeal carcinoma was 5.72 per 100 person- years. Incidence density of recurrence rates of nasopharyngeal carcinoma among female was higher than in those among male (6.24 vs. 5.42 per 100 person-years). By age group, incidence density of recurrence rates of nasopharyngeal carcinoma was 5.83 per 100 person–years in patients with age ≥ 45 years which was higher than patients with age < 45 years. It was found that incidence density of recurrence rates of patients who used to smoking was higher than those who never smoking (5.76 vs. 5.49 per 100 person- years). The incidence density of recurrence rates of nasopharyngeal carcinoma patients who had never consumed alcohol was 5.72 per 100 person–years which was higher than who consumed alcohol in 5.37 per 100 person –years. (Table5)

By TNM system, the incidence density of recurrence rates of nasopharyngeal carcinoma patients with T1, T2, T3 and T4 were 5.68, 5.27, 6.45 and 5.48 per 100 person -years respectively. Incidence density of recurrence rates of nasopharyngeal carcinoma patients with lymph node involvement in stage N0, N1, N2 and N3 were 4.02, 6.28, 5.35 and 8.48 per 100 person -years, respectively. It was found that incidence density of recurrence rates of nasopharyngeal carcinoma patients without metastasis stage was 5.56 per 100 person- years while among patients with metastasis was 12.82 per 100 person-years. Patients with stage IV with metastasis had the highest incidence density of recurrence rates was 12.82 per 100 person-years and patients with stage IV without metastasis had incidence density of recurrence of nasopharyngeal carcinoma of 7.34 per 100 person-years. The patients with stage I+II and III had incidence density of 4.02 and 64.88 per 100 person–years, respectively. For cell types, the incidence density of recurrence rates of nasopharyngeal carcinoma were 3.49 and 5.27 and 7.10 per 100 person-years for well differentiate, poor differentiate and undifferentiated carcinoma cell type, respectively.

The incidence density of recurrence rates of nasopharyngeal carcinoma among patients with no lymph node involvement, with upper lymph node level involvement, mid lymph node level involvement and lower lymph level involvement were 4.13, 5.32, 5.98 and 11.86 per 100 person- years, respectively. It found that patients with lower lymph node level involvement had the highest incidence density of recurrence rates of nasopharyngeal carcinoma, 11.86 per 100 person- years. It was found that incidence density of recurrence rates of nasopharyngeal carcinoma patients who had present neck fibrosis were lower than those patient with no neck fibrosis (4.51 vs. 10.47 per 100 person- years). The incidence density of recurrence rates of nasopharyngeal carcinoma patients had EBV IgG-VCA titer ≥ 160 and patients had EBV IgG-VCA titer < 160 were 3.32 and 3.21 per 100 person- years, respectively. The incidence density of recurrence rates of nasopharyngeal carcinoma patients had EBV IgA-VCA titer ≥ 40 and patients had EBV IgA-VCA titer < 40 were 4.93 and 5.82 per 100 person- years, respectively.

The incidence density of recurrence rates of nasopharyngeal carcinoma patients with received chemotherapy and no received chemotherapy were 5.89 and 5.27 per 100 person- years, respectively. (Table5)

**Table 5 Incidence density of recurrence rates of nasopharyngeal carcinoma patients by prognostic factors**

| Variables | Total | Number of recurrence | Person – years observation | Incidence density (per 100 person-years) |
|---|---|---|---|---|
| **Overall** | 366 | 105 | 1,836 | 5.72 |
| **Gender** | | | | |
| Male | 233 | 63 | 1,162 | 5.42 |
| Female | 133 | 42 | 673 | 6.24 |
| **Age at diagnosis (years)** | | | | |
| < 45 | 173 | 50 | 891 | 5.61 |
| ≥ 45 | 193 | 55 | 944 | 5.83 |
| **Cigarette Smoking** | | | | |
| No | 171 | 49 | 891 | 5.49 |
| Yes | 111 | 31 | 538 | 5.76 |
| **Alcohol drinking** | | | | |
| No | 180 | 53 | 926 | 5.72 |
| Yes | 102 | 27 | 503 | 5.37 |
| **By TNM system** | | | | |
| **Tumor stage (T stage)** | | | | |
| T1 | 58 | 17 | 299 | 5.68 |
| T2 | 108 | 28 | 531 | 5.27 |
| T3 | 100 | 33 | 511 | 6.45 |
| T4 | 100 | 27 | 493 | 5.48 |

**Table 5 Incidence density of recurrence rates of nasopharyngeal carcinoma patients by prognostic factors (continued)**

| Variables | Total | Number of recurrence | Person – years observation | Incidence density (per 100 person-years) |
|---|---|---|---|---|
| **Lymph node stage (N stage)** | | | | |
| N0 | 68 | 16 | 398 | 4.02 |
| N1 | 68 | 22 | 350 | 6.28 |
| N2 | 169 | 43 | 803 | 5.35 |
| N3 | 61 | 24 | 283 | 8.48 |
| **Metastasis stage (M stage)** | | | | |
| Without metastasis | 356 | 100 | 1,796 | 5.56 |
| With metastasis | 10 | 5 | 39 | 12.82 |
| **Overall stage grouping** | | | | |
| Stage I+II | 84 | 19 | 472 | 4.02 |
| Stage III | 128 | 32 | 655 | 4.88 |
| Stage IV without metastasis | 144 | 49 | 668 | 7.34 |
| Stage IV with metastasis | 10 | 5 | 39 | 12.82 |
| **Histological cell type** | | | | |
| Well differentiate carcinoma | 18 | 3 | 86 | 3.49 |
| Poor differentiate carcinoma | 213 | 63 | 1,196 | 5.27 |
| Undifferentiated carcinoma | 131 | 38 | 535 | 7.10 |

**Table 5 Incidence density of recurrence rates of nasopharyngeal carcinoma patients by prognostic factors (continued)**

| Variables | Total | Number of recurrence | Person - years observation | Incidence density (per 100 person-years) |
|---|---|---|---|---|
| **Lymph node level involvement** | | | | |
| No involvement | 58 | 15 | 363 | 4.13 |
| Upper lymph node level | 126 | 29 | 545 | 5.32 |
| Mid lymph node level | 70 | 20 | 334 | 5.98 |
| Lower lymph node level | 19 | 7 | 59 | 11.86 |
| **Neck fibrosis** | | | | |
| No | 69 | 31 | 296 | 10.47 |
| Yes | 237 | 56 | 1,240 | 4.51 |
| **Chemotherapy received** | | | | |
| No | 86 | 27 | 512 | 5.27 |
| Yes | 280 | 78 | 1,323 | 5.89 |
| **EBV IgG-VCA titer** | | | | |
| < 160 | 21 | 5 | 156 | 3.21 |
| ≥ 160 | 98 | 18 | 541 | 3.32 |
| **EBV IgA-VCA titer** | | | | |
| < 40 | 97 | 28 | 481 | 5.82 |
| ≥ 40 | 70 | 17 | 345 | 4.93 |

**4.3 Survival curves of recurrence rates of nasopharyngeal carcinoma patients by prognostic factors.**

**Overall recurrence rate**

Of 366 nasopharyngeal carcinoma patients, 105 patients had recurrence after treatment. The overall 2, 3 and 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients were 12.16 %, 18.80%, and 26.11%, respectively. (Table6)

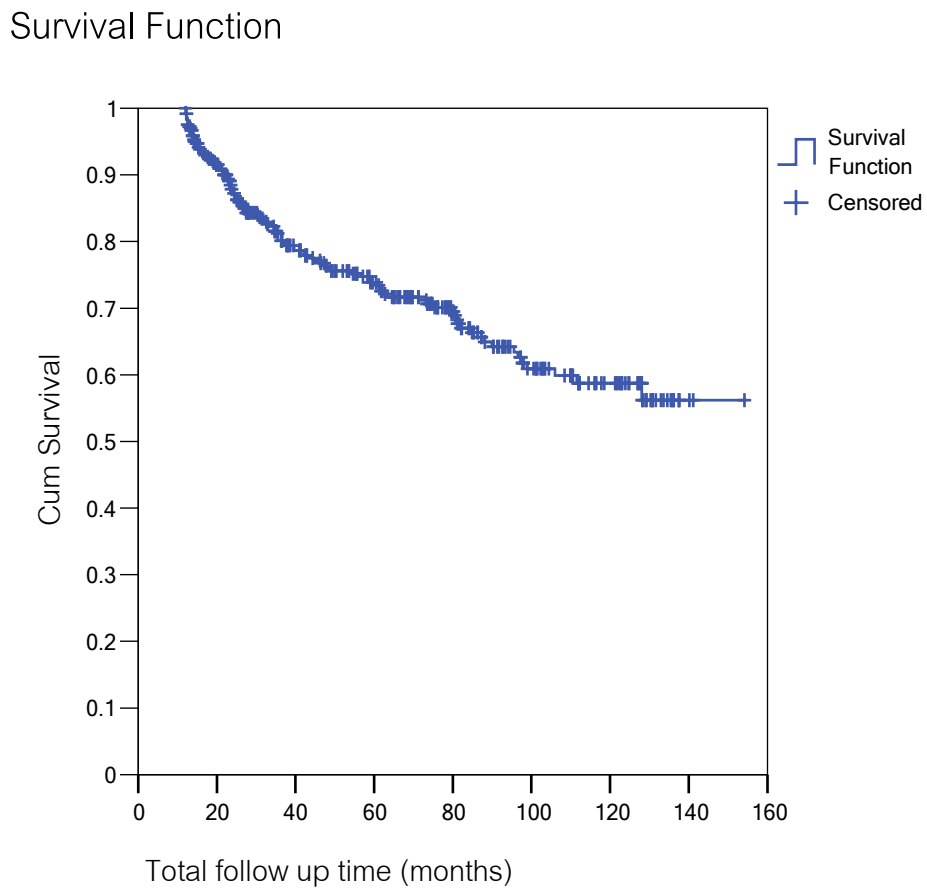


**Figure 3** The overall survival curve of recurrence rate of nasopharyngeal carcinoma patients

**Gender**

The 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients were 25.83% for male and 26.61 % for female patients, respectively. The median recurrence time among female patients was 111.53 months. There were no significant difference in the survival curves of recurrences rates of patients by gender (p=0.532). (Table6)

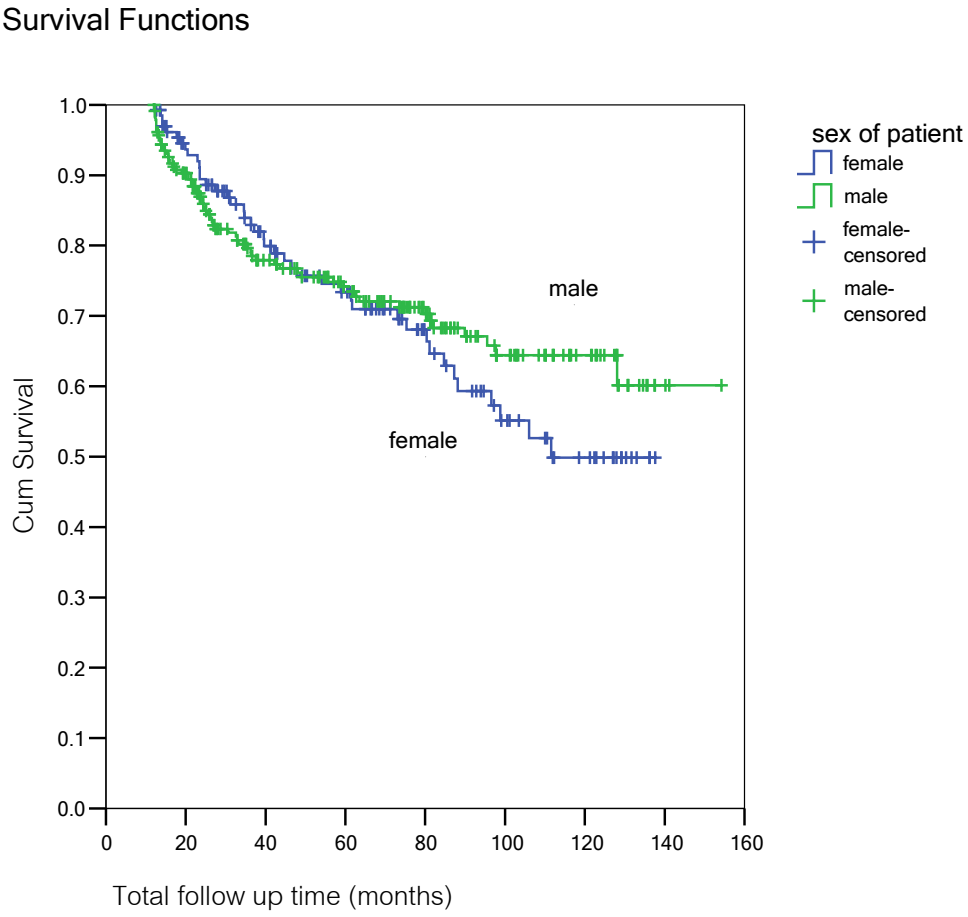


**Figure 4** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by gender. (p = 0.532)

**Age at diagnostic**

The 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients were 28.53% for the age group less 45 years and 23.90 % for the age group 45 year and over, but no significant difference in the survival curves of recurrences rates of patients by age group (p=0.913). (Table6)

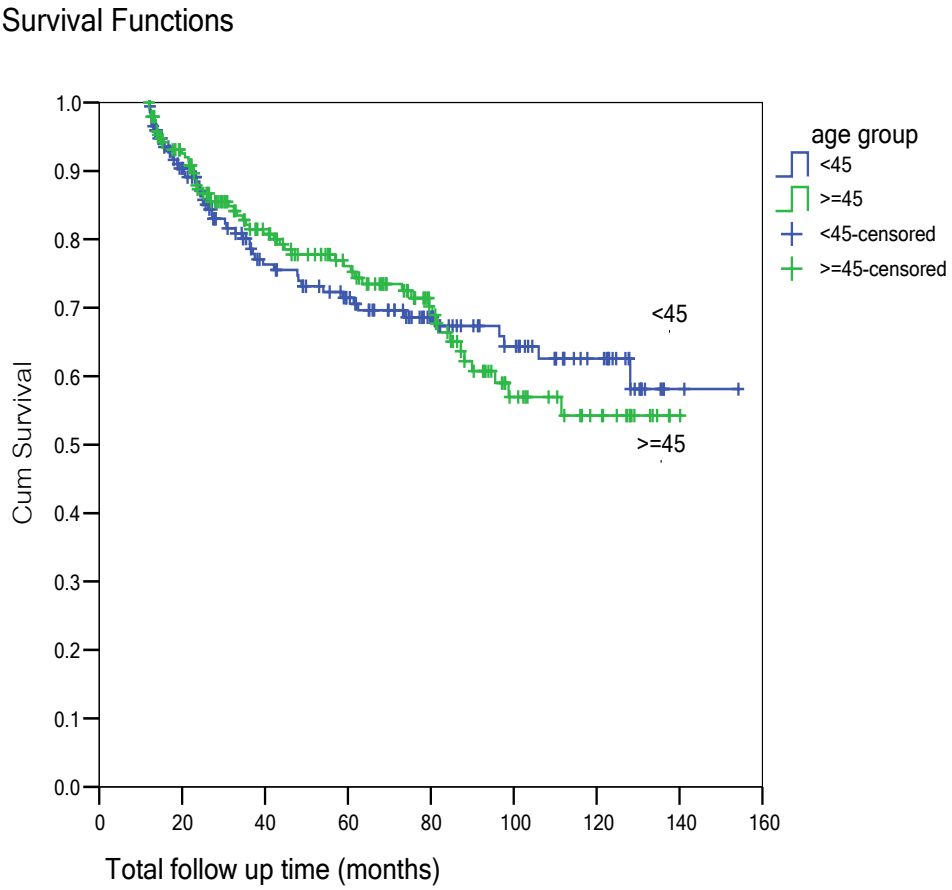


**Figure 5** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by age group. (p = 0.913)

**Cigarette Smoking**

The 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients were 25.12% for non-smoker and 26.86% for smokers, but no significant difference in survival curves of the recurrences rates of nasopharyngeal carcinoma patient by status of smoking (p=0.851). (Table6)

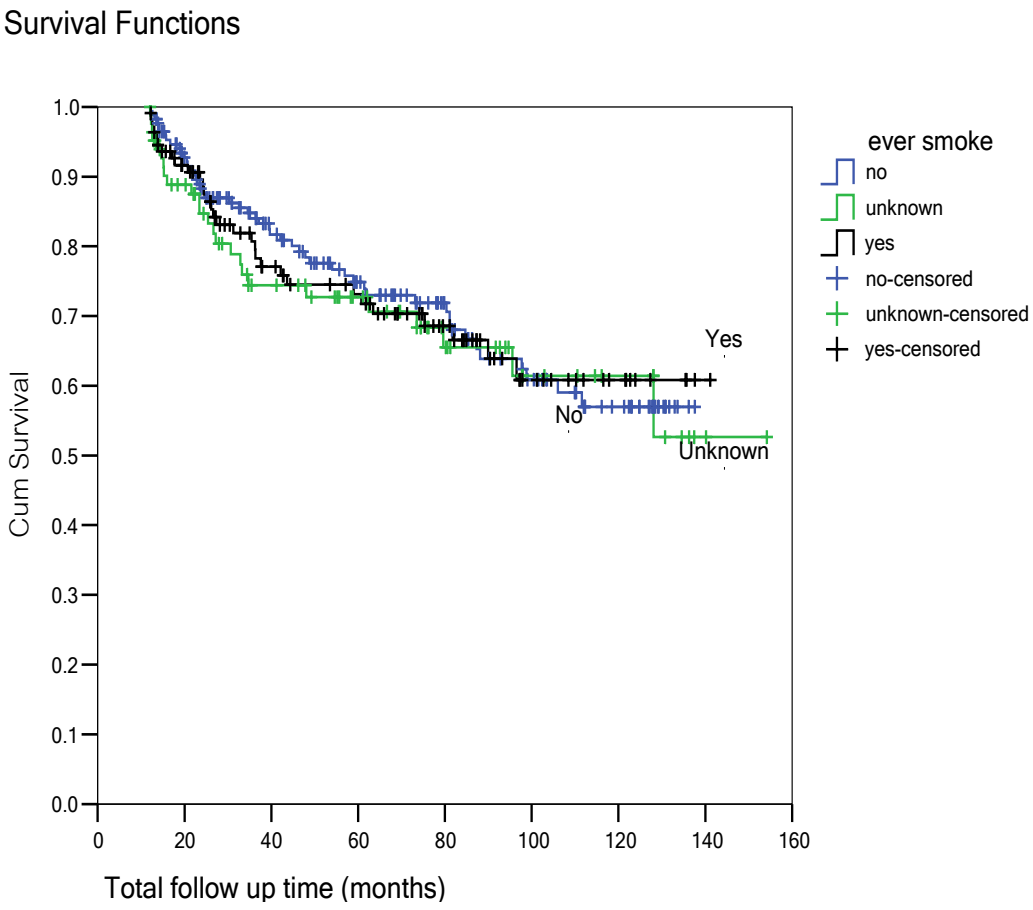


**Figure 6** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by smoking status. (p = 0.851)

**Alcohol drinking**

The 5-years cumulative recurrence rates of nasopharyngeal carcinoma in patients who had never consumed were 25.85% and 25.49% for those who used drink alcohol. There were no significant difference in survival curves of recurrence rates of nasopharyngeal carcinoma patients by status of alcohol drinking status (p=0.845). (Table6)

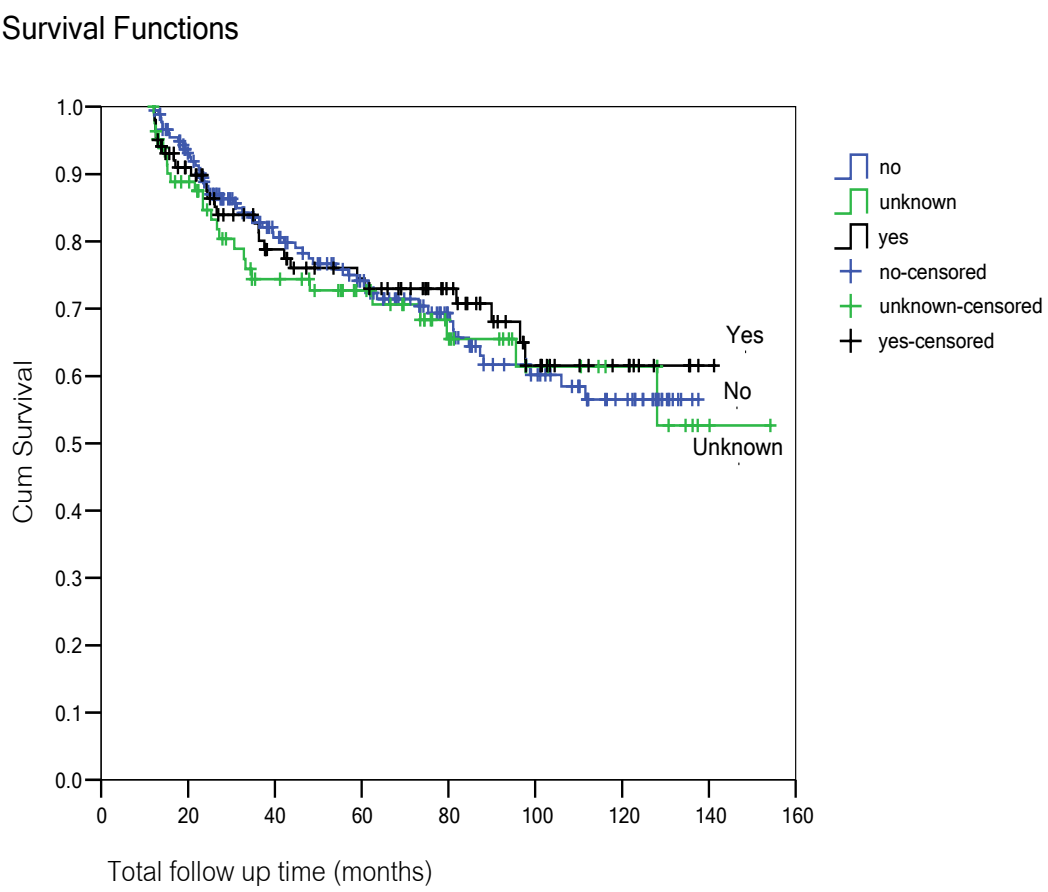


**Figure 7** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by alcohol drinking status. (p =0.845)

**Tumor stage (T stage)**

The 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients with T stage T1, T2, T3, and T4 were 28.82%, 21.02%, 27.82% and 27.90%, respectively, according to the 1997 AJCC classification. The median recurrence time among patients with T3 stage was 128.10 months. There had been no significant difference in survival curves of recurrence rates of nasopharyngeal carcinoma patients with different T stage (p=0.875). (Table6)

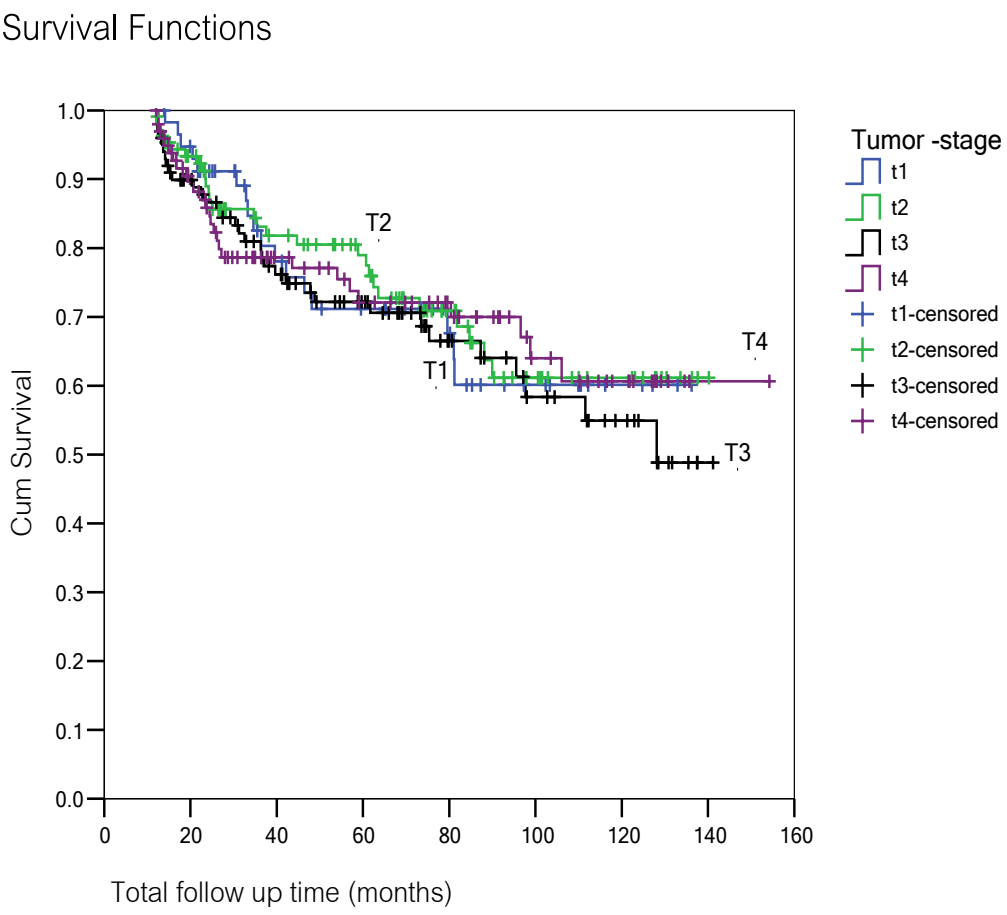


**Figure 8** Comparison of survival curves of recurrence rates of nasopharyngeal carcinoma patients by T stage. (p =0.875)

**Lymph node stage (N stage)**

The 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients with N stage N0, N1, N2, and N3 were 14.77%, 29.26%, 25.02% and 38.25%, respectively, according to the 1997 AJCC classification. There had been no significant difference in survival curves of recurrence rates of nasopharyngeal carcinoma patients with different N stage (p=0.098). (Table6)

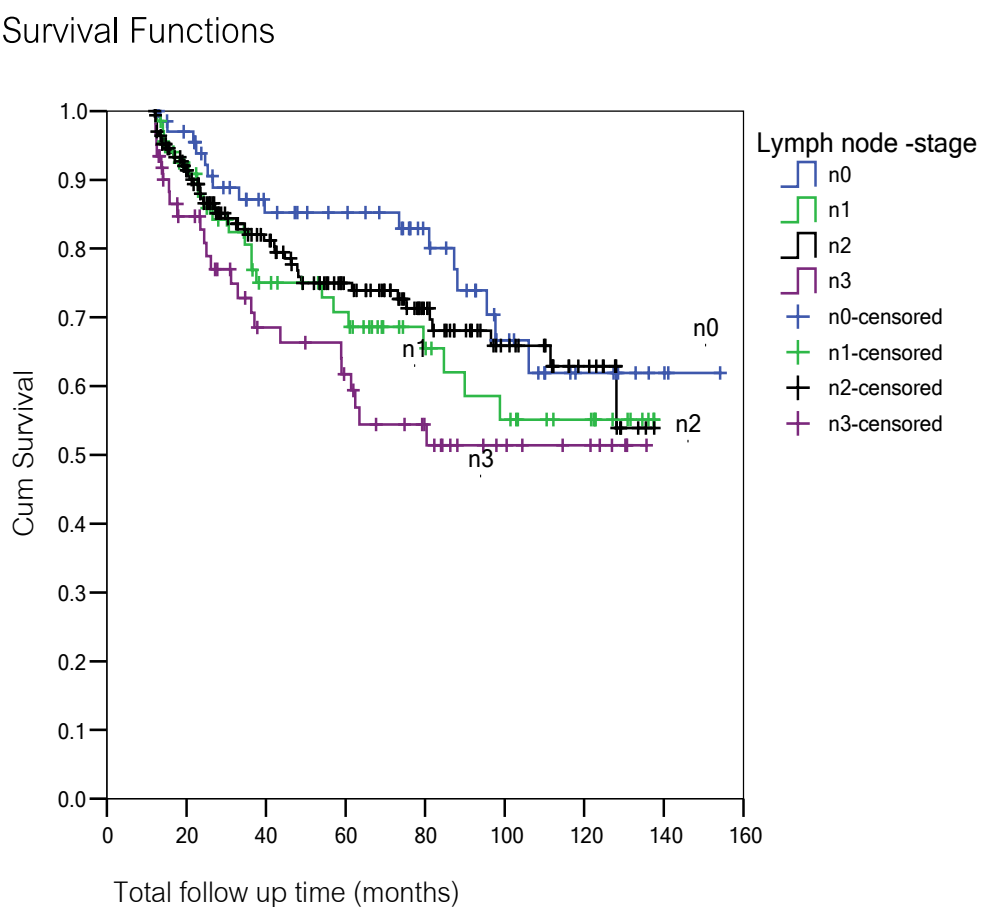


**Figure 9** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by N stage. (p =0.098)

**Metastasis stage (M stage)**

The 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients was 25.44% for patients without metastasis and was 48.57% for the patients with metastasis. The median recurrence time among patients with metastasis was 62.47 months. Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients with and without metastasis by log rank test showed no significant difference (p=0.077). (Table6)

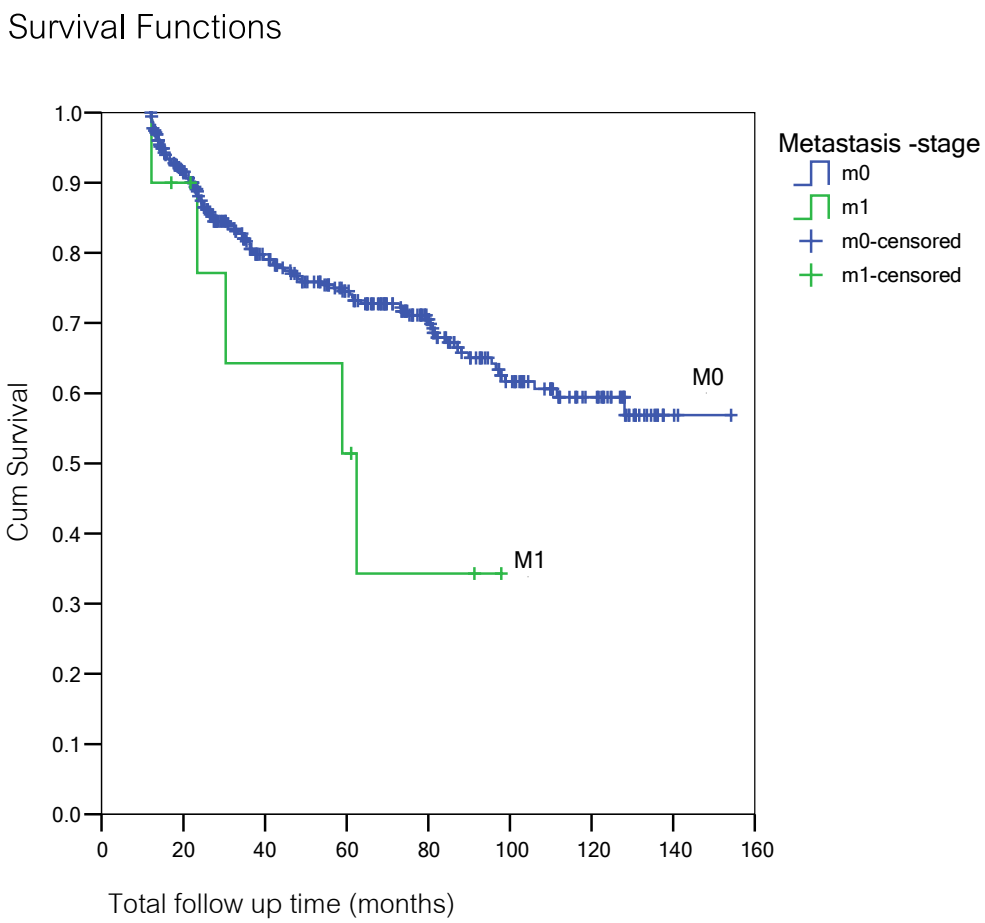


**Figure 10** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by metastasis stage. (p = 0.077)

**Overall Stage grouping**

The 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients with stage I+II, stage III, stage IV without metastasis and stage IV with metastasis were 19.11%, 22.52%, 31.98 and 48.57%, respectively. The median recurrence time in patients with stage IV with metastasis was 62.47 months. There were significant differences among the survival curves of recurrence rates of nasopharyngeal carcinoma patient with different stage (p = 0.022). (Table6)

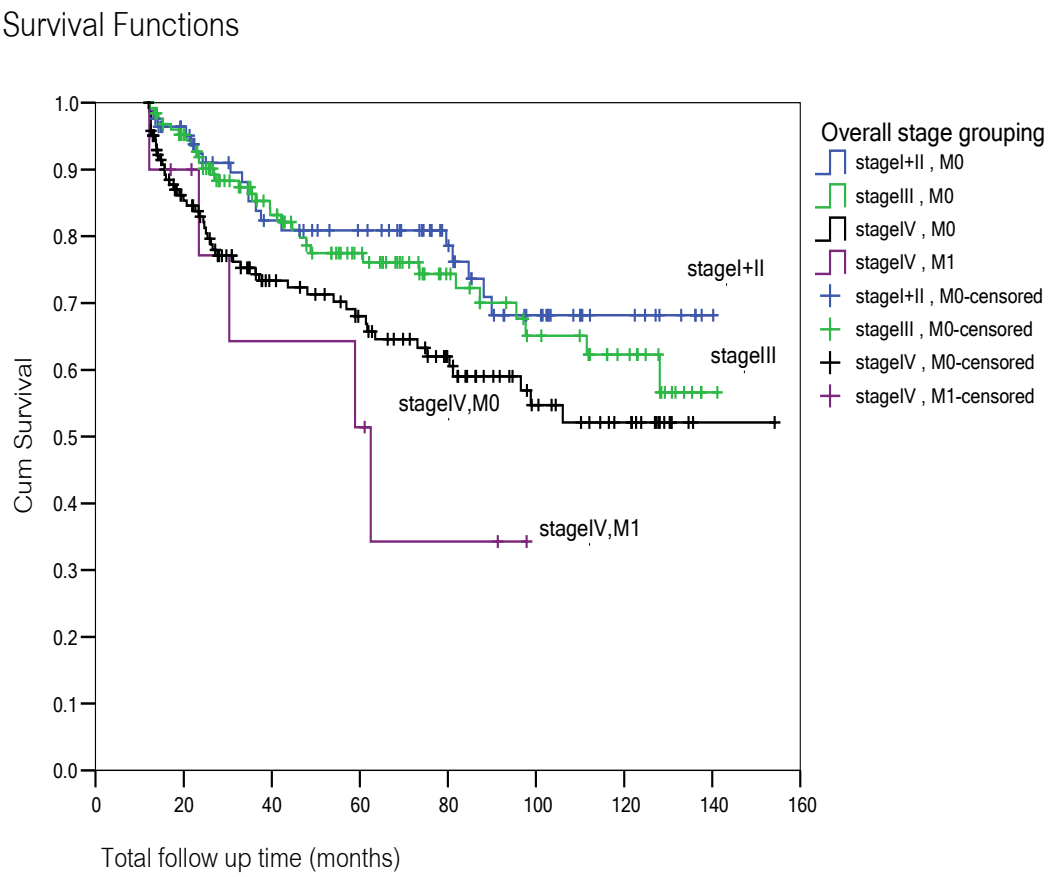


**Figure 11** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by overall stage grouping. (p = 0.022)**.**

**Histological cell type**

The 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients were 19.61%, 23.43% and 31.24% for well differentiate carcinoma type (WHO I), poor differentiate carcinoma type (WHO II) and undifferentiated carcinoma type (WHO III), respectively. There were not significance differences of survival curves of recurrence rates of patients by histological cell type (p = 0.263). (Table6)

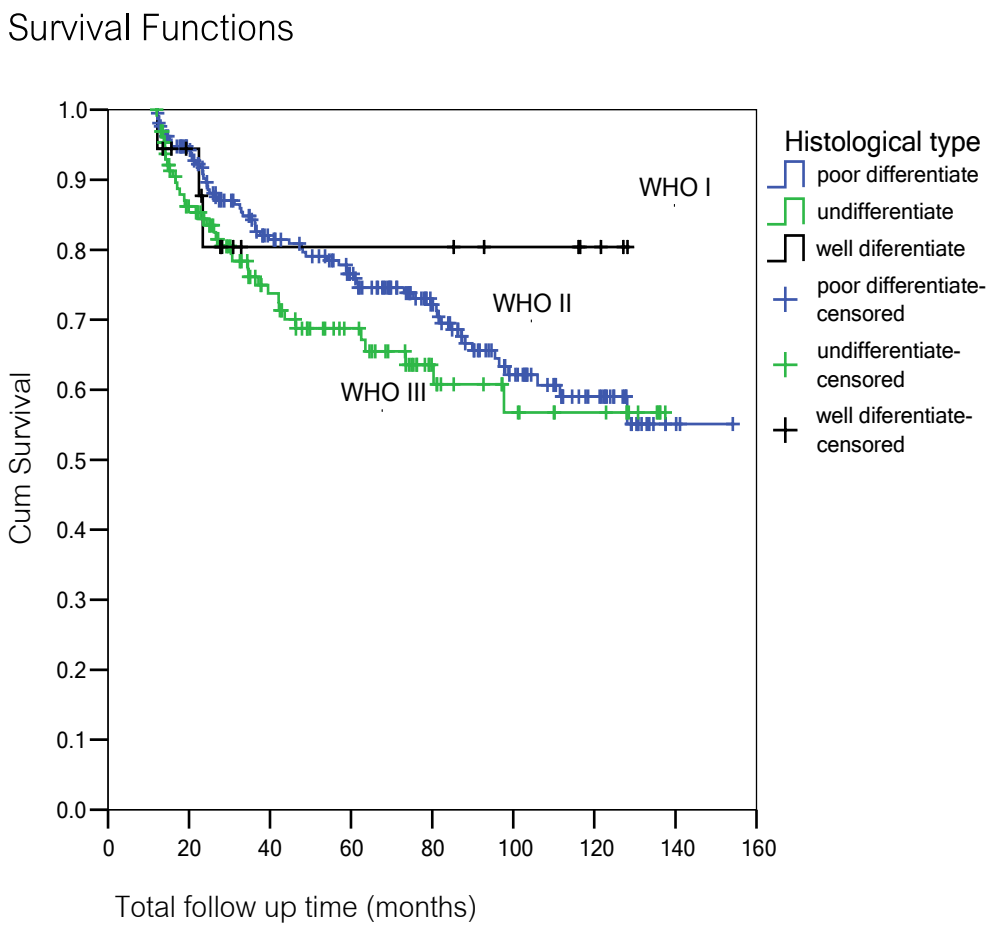


**Figure 12** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by histological cell type. (p = 0.263)

**Chemotherapy received**

The 5-years cumulative of recurrence rates of nasopharyngeal carcinoma patients with received chemotherapy and no received chemotherapy were 27.65% and 21.86% respectively. The difference of survival curves of recurrence rates of nasopharyngeal carcinoma patients with received and no received chemotherapy were not statistically significant (p=0.677). (Table6)

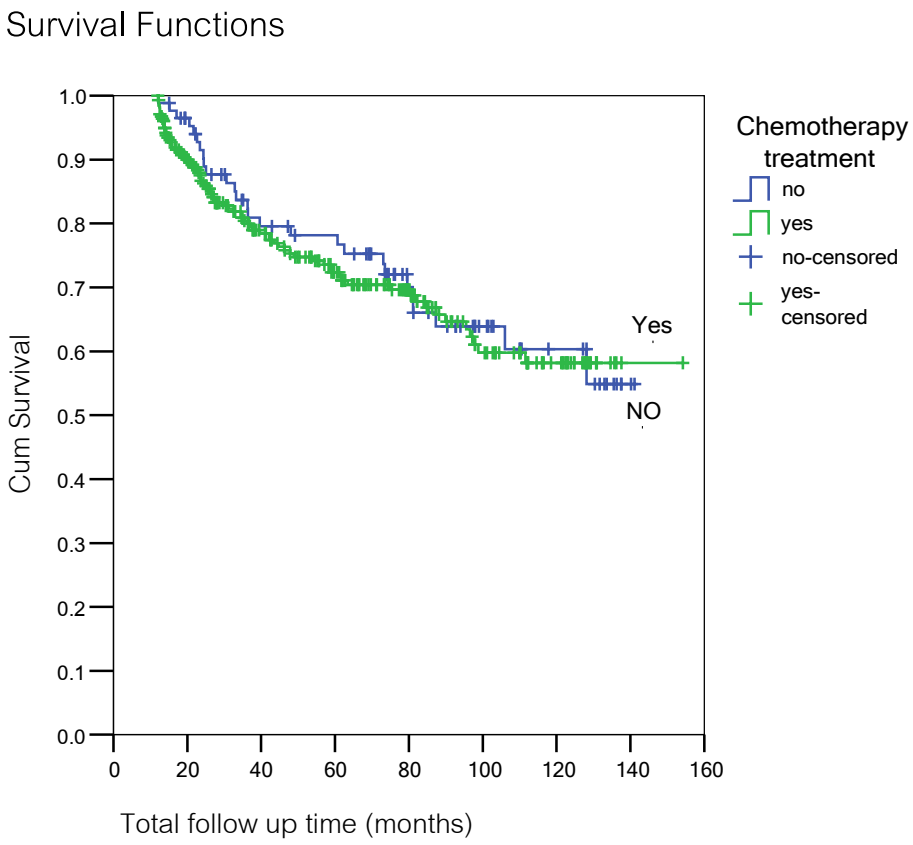


**Figure 13** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by chemotherapy received. (p = 0.677)

**Lymph node level involvement**

The 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients with no lymph node involvement, upper lymph node level involvement, mid lymph node level involvement and lower lymph node level involvement were 17.66%, 24.00%, 32.33% and 39.46%, respectively. The median recurrence time in patients with lower lymph node involvement was 62.47 months. There were no significant difference of survival curves of recurrence rates of nasopharyngeal carcinoma patients among different lymph node level involvement (p=0.265). (Table6)

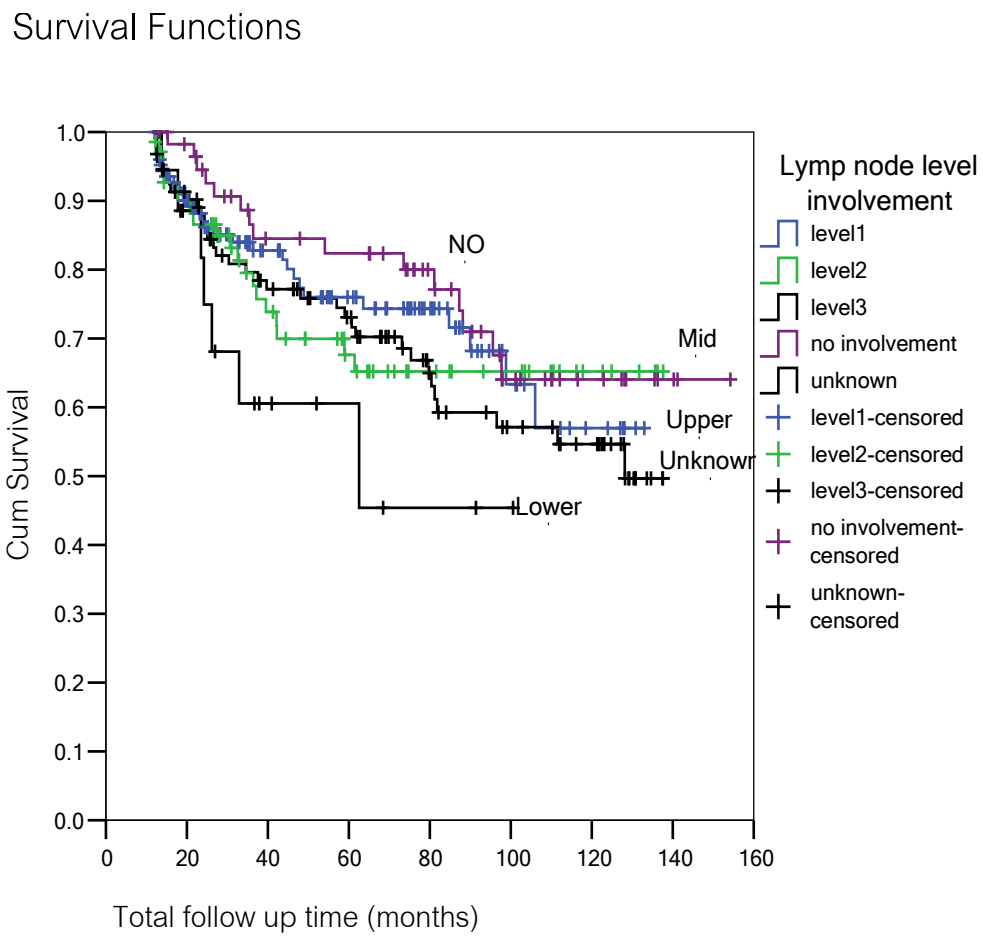


**Figure 14** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by lymph node level involvement. (p = 0.265)

**EBV IgG-VCA titer**

The 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients had EBV IgG-VCA titer ≥ 160 and patients had EBV IgG-VCA titer < 160 were 17.00% and 11.50%, respectively. The difference survival curves of recurrence rates among patients were statistically significant (p=0.004). (Table6)

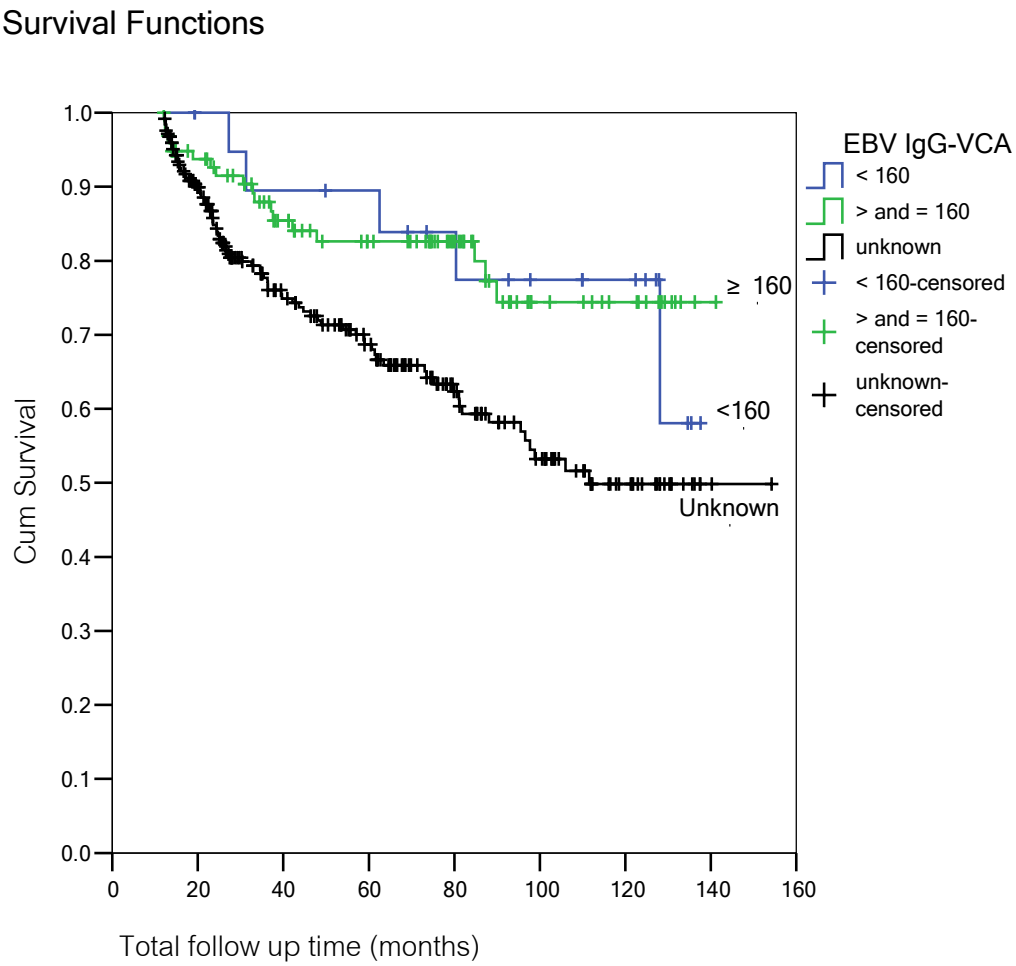


**Figure 15** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by EBV IgG-VCA titer. (p = 0.004)

**EBV IgA-VCA titer**

The 5-years cumulative of recurrence rates of nasopharyngeal carcinoma patients had EBV IgA-VCA titer ≥ 40 and patients had EBV IgA-VCA titer < 40 were 28.08% and 24.89%, respectively. The difference of survival curves of recurrence rates among patients were not statistically significant (p=0.584). (Table6)

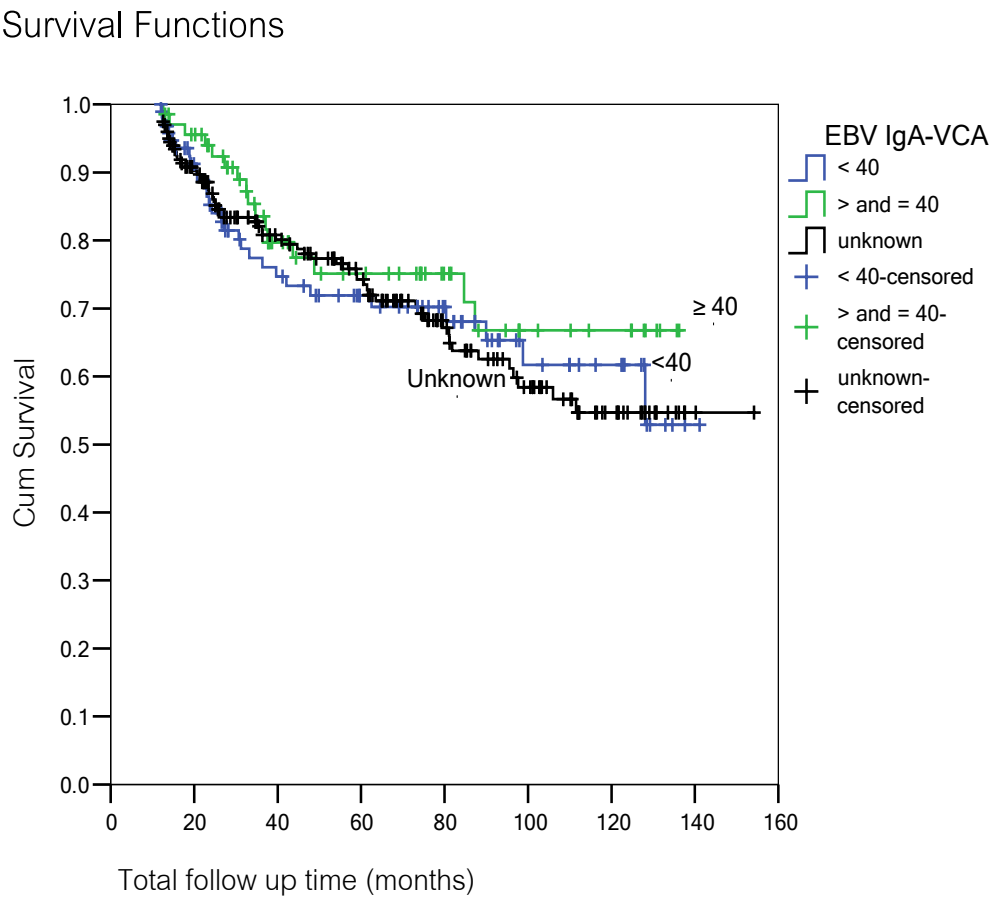


**Figure 16** Comparison survival curves of recurrence rates of nasopharyngeal carcinoma patients by EBV IgA-VCA titer. (p = 0.584)

**Table 6 Cumulative recurrence rates by 2, 3, 5 years followed by prognostic factors by using the Kaplan- Meier and the log rank test**

| Factor | 2-year Cumulative recurrence rates (%) | 3-year Cumulative recurrence rates (%) | 5-year Cumulative recurrence rates (%) | p-value |
|---|---|---|---|---|
| **Overall** | 12.16 | 18.80 | 26.11 | |
| **Gender** | | | | 0.532 |
| Male | 13.05 | 20.36 | 25.83 | |
| Female | 10.54 | 16.08 | 26.61 | |
| **Age** | | | | 0.913 |
| <45 | 11.36 | 19.87 | 28.53 | |
| ≥45 | 12.70 | 17.85 | 23.90 | |
| **Cigarette Smoking** | | | | 0.851 |
| No | 11.74 | 15.22 | 25.12 | |
| yes | 10.41 | 19.30 | 26.86 | |
| **Alcohol drinking** | | | | 0.845 |
| No | 11.15 | 16.45 | 25.85 | |
| Yes | 11.31 | 17.33 | 25.49 | |
| **Tumor stage** | | | | 0.875 |
| T1 | 8.84 | 17.47 | 28.82 | |
| T2 | 11.03 | 16.90 | 21.02 | |
| T3 | 13.36 | 19.04 | 27.82 | |
| T4 | 14.16 | 21.37 | 27.90 | |

**Table 6 Cumulative recurrence rates by 2, 3, 5 years followed by prognostic factors by using the Kaplan- Meier and the log-rank test (continued)**

| Factor | 2-year Cumulative recurrence rates (%) | 3-year Cumulative recurrence rates (%) | 5-year Cumulative recurrence rates (%) | p-value |
|---|---|---|---|---|
| **Lymph node stage** | | | | 0.098 |
| N0 | 6.17 | 12.88 | 14.77 | |
| N1 | 12.44 | 19.43 | 29.26 | |
| N2 | 12.70 | 17.99 | 25.02 | |
| N3 | 17.24 | 27.18 | 38.25 | |
| **Metastasis stage** | | | | 0.077 |
| M0 | 11.89 | 18.36 | 25.44 | |
| M1 | 22.86 | 35.71 | 48.57 | |
| **Overall stage grouping** | | | | **0.022** |
| Stage I+II | 7.59 | 14.75 | 19.11 | |
| Stage III | 9.00 | 13.66 | 22.52 | |
| Stage IV without metastasis | 17.05 | 24.71 | 31.98 | |
| Stage IV with metastasis | 22.86 | 35.71 | 48.57 | |
| **Histological cell type** | | | | 0.263 |
| Well differentiate carcinoma | 19.61 | 19.61 | 19.61 | |
| Poor differentiate carcinoma | 9.83 | 16.72 | 23.43 | |
| Undifferentiated carcinoma | 15.58 | 23.86 | 31.24 | |

**Table 6 Cumulative recurrence rates by 2, 3, 5 years followed by prognostic factors by using the Kaplan- Meier and the log-rank test (continued)**

| Factor | 2-year Cumulative recurrence rates (%) | 3-year Cumulative recurrence rates (%) | 5-year Cumulative recurrence rates (%) | p-value |
|---|---|---|---|---|
| **Lymph node level involvement** | | | | 0.265 |
| No involvement | 5.49 | 13.43 | 17.66 | |
| Upper lymph node level | 18.84 | 16.00 | 24.00 | |
| Mid lymph node level | 13.43 | 20.49 | 32.33 | |
| Lower lymph node level | 18.27 | 39.46 | 39.46 | |
| **EBV IgG-VCA titer** | | | | **0.004** |
| < 160 | 5.26 | 10.53 | 16.12 | |
| ≥ 160 | 7.38 | 11.50 | 11.50 | |
| **EBV IgA-VCA titer** | | | | 0.584 |
| < 40 | 14.76 | 22.57 | 28.08 | |
| ≥ 40 | 6.00 | 16.47 | 24.89 | |
| **Chemotherapy received** | | | | 0.677 |
| No | 8.53 | 16.33 | 21.86 | |
| Yes | 13.30 | 19.56 | 27.65 | |

p = log- rank test (p-value)

Results from univariate analysis by Kaplan –Meier method and log-rank test showed the significant factors related to recurrence rate of nasopharyngeal carcinoma were overall stage grouping (p = 0.022) and EBV IgG-VCA titer (p = 0.004) , while other factors did not demonstrate statistically significance. (Table6)

**4.4 Crude analysis of the association between prognostic factors and recurrence rate of nasopharyngeal carcinoma.**

Cox's proportional hazard model analysis was used to calculated crude hazard ratio (HR) with 95% confidence interval to demonstrate associations between prognostic factors and recurrence of nasopharyngeal carcinoma.

**Gender**

Risk of recurrence of nasopharyngeal carcinoma for being female patients were not significantly higher than that of being male patients (crude HR = 1.15, 95%CI= 0.78- 1.70, p= 0.475). (Table7)

**Age of diagnosis**

Risk of recurrence of nasopharyngeal carcinoma patients with age group 45 years and over were not significant higher than patients aged less 45 years. (crude HR = 1.04, 95%CI = 0.70 – 1.52, p=0.849). (Table7)

**Tumor stage (T stage)**

The primary tumor was not significantly associated with recurrence of nasopharyngeal carcinoma. The risk of recurrence of patients with T2, T3, and T4 were 0.92 (95%CI= 0.51- 1.65, p=0.799), 1.14 (95%CI= 0.63 – 2.04, p=0.681) and 0.96 (95%CI= 0.52 – 1.77, p=0.895), respectively compared to patients with T1 stage. (Table7)

**Lymph node stage (N stage)**

Risk of recurrence of nasopharyngeal carcinoma among patients with N3 stage was significant higher than patients with no lymph node involvement (N0) (crude HR = 2.10, 95%CI = 1.13 - 3.91, p = 0.020). The risk of recurrence of nasopharyngeal carcinoma patients with N1 stage and N2 stage were 1.56 (95% CI =

0.83 – 2.96, p = 0.176) and 1.33 (95% CI= 0.75 - 2.36, p=0.331) times compared to patients with N0 stage, but were not significant. (Table7)

**Metastasis (M stage)**

Metastasis stage was significantly associated with recurrence of nasopharyngeal carcinoma. The risk of recurrence of patients with metastasis or M1 stage was significantly higher than patient without metastasis or M0 stage (crude HR = 2.30, 95%CI= 0.96 – 5.51, p = 0.049). (Table7)

**Overall stage grouping**

The risk of recurrence of nasopharyngeal carcinoma patients with stage IV with metastasis was highest (crude HR = 3.18, 95% CI = 1.25 – 8.09, p = 0.040) when compared to patients with stage I+II, while risk of recurrence of nasopharyngeal carcinoma patients with stage IV without metastasis was 1.82 times (95% CI = 1.08 - 3.07, p = 0.023) compared to patients with stage I+II, with statistically significant. (Table7)

**Histological cell type**

The risk of the recurrence of nasopharyngeal carcinoma patients with poor differentiate carcinoma was 1.51 (crude HR = 1.51, 95%CI= 0.47 – 4.77, P = 0.518) and undifferentiated carcinoma was 2.04 (crude HR = 2.04, 95%CI= 0.64 – 6.43, P = 0.226) when compared to patients with well differentiated carcinoma type. Histological cell type was not significantly associated with recurrence of nasopharyngeal carcinoma. (Table7)

**Lymph node level involvement**

Lymph node level involvement was significantly associated with recurrence of nasopharyngeal carcinoma. The risk of recurrence of patients with lower lymph node level involvement was 2.87 (95%CI= 1.21 – 6.76, p = 0.033) when compared to patients with no lymph node involvement. (Table7)

**Chemotherapy received**

The chemotherapy received was not significantly associated with recurrence of nasopharyngeal carcinoma. The risk of recurrence of nasopharyngeal carcinoma patients received chemotherapy was 0.89 times (crude HR = 0.89, 95% CI = 0.57 – 1.38, p = 0.628) compared with patients no received chemotherapy but not statistically significant. (Table7)

**EBV IgG-VCA titer**

Risk of recurrence of nasopharyngeal carcinoma patients had EBV IgG-VCA titer ≥ 160 was not significant higher than patients had EBV IgG-VCA titer < 160. (crude HR = 1.03, 95%CI = 0.38 – 2.79, p=0.977). (Table7)

**EBV IgA-VCA titer**

EBV IgA-VCA titer was not significantly associated with recurrence of nasopharyngeal carcinoma. The risk of recurrence of patients had EBV IgA-VCA titer ≥ 40 was 0.84 (crude HR = 0.84, 95%CI= 0.46 – 1.54, p = 0.596) when compared to patients had EBV IgA-VCA titer < 40. (Table7)

**Table 7 Crude analysis of the association between prognostic factors and recurrence rates of nasopharyngeal carcinoma**

| Factor | Crude HR | 95% CI of HR | p-value* |
|---|---|---|---|
| **Gender** | | | |
| Male | 1 | | |
| Female | 1.15 | 0.78 – 1.70 | 0.475 |
| **Age of diagnosis** | | | |
| <45 | 1 | | |
| ≥45 | 1.04 | 0.70 - 1.52 | 0.849 |
| **Tumor stage ( T stage)** | | | |
| T1 | 1 | | |
| T2 | 0.92 | 0.51 – 1.65 | 0.799 |
| T3 | 1.14 | 0.63 – 2.04 | 0.681 |
| T4 | 0.96 | 0.52 – 1.77 | 0.895 |
| **Lymph node stage (N stage)** | | | |
| N0 | 1 | | |
| N1 | 1.56 | 0.83 – 2.96 | 0.176 |
| N2 | 1.33 | 0.75 – 2.36 | 0.331 |
| N3 | 2.10 | 1.13 – 3.91 | **0.020** |
| **Metastasis stage (M stage)** | | | |
| Without metastasis | 1 | | |
| With metastasis | 2.30 | 0.96 – 5.51 | **0.049** |

P* = Partial likelihood ratio test

HR = Hazard ratio of recurrence of nasopharyngeal carcinoma

**Table 7 Crude analysis of the association between prognostic factors and recurrence rates of nasopharyngeal carcinoma (continued)**

| Factor | Crude HR | 95% CI of HR | p-value* |
|---|---|---|---|
| **Overall stage grouping** | | | |
| Stage I+II | 1 | | |
| Stage III | 1.21 | 0.68 – 2.13 | 0.511 |
| Stage IV without metastasis | 1.82 | 1.08 – 3.07 | **0.023** |
| Stage IV with metastasis | 3.18 | 1.25 – 8.09 | **0.040** |
| **Histological cell type** | | | |
| Well differentiate carcinoma | 1 | | |
| Poor differentiate carcinoma | 1.51 | 0.47 – 4.77 | 0.518 |
| Undifferentiated carcinoma | 2.04 | 0.64 – 6.43 | 0.226 |
| **Lymph node level involvement** | | | |
| No involvement | 1 | | |
| Upper lymph node level | 1.29 | 0.69 – 2.39 | 0.433 |
| Mid lymph node level | 1.44 | 0.74 – 2.81 | 0.282 |
| Lower lymph node level | 2.87 | 1.21 - 6.76 | **0.033** |
| **Chemotherapy received** | | | |
| No | 0.89 | 0.57 – 1.38 | 0.628 |
| Yes | 1 | | |

P* = Partial likelihood ratio test

HR = Hazard ratio of recurrence of nasopharyngeal carcinoma

**Table 7 Crude analysis of the association between prognostic factors and recurrence rates of nasopharyngeal carcinoma (continued)**

| Factor | Crude HR | 95% CI of HR | p-value* |
|---|---|---|---|
| **EBV IgG-VCA titer** | | | |
| < 160 | 1 | | |
| ≥ 160 | 1.03 | 0.38 – 2.79 | 0.977 |
| **EBV IgA-VCA titer** | | | |
| < 40 | 1 | | |
| ≥ 40 | 0.84 | 0.46 – 1.54 | 0.596 |

P* = Partial likelihood ratio test

HR = Hazard ratio of recurrence of nasopharyngeal carcinoma

**4.5 Multivariate analysis of the association between prognostic factors and recurrence rate of nasopharyngeal carcinoma.**

Cox's proportional hazard analysis with enter methods was used to demonstrate adjusted hazard ratio (HR) of recurrence of nasopharyngeal carcinoma patients controlled for the effects of all variables in the model simultaneously.

After test for colineality between each independent variable, there were colineality between some variable such as lymph node level involvement, lymph node stage and overall stage grouping, So in multivariate analysis, variables with colineality with overall stage grouping were excluded some variable from analysis.

In the final model multivariate analysis included age of patients (<45/≥45), gender of patients (Male/female), overall stage grouping (stage I+II / stage III / stage IV without metastasis/ stage IV with metastasis), histological cell type (well/ poor/ undifferentiated) and chemotherapy received (no/yes).The statistically significant level was set at p-value < 0.05.

**Gender**

Risk of recurrence of nasopharyngeal carcinoma for being female patients were not significantly higher than that of being male patients (adjusted HR = 1.18, 95%CI= 0.79 – 1.74, p= 0.422). (Table8)

**Age**

The risk of recurrence of nasopharyngeal carcinoma patients with age 45 and over was not significantly higher than patients aged less 45 years (adjusted HR = 1.16, 95% = 0.78 - 1.72, p = 0.458). (Table8)

**Overall stage grouping**

Patients with stage IV with metastasis had higher risk to develop recurrence (adjusted HR = 3.35 95% CI = 1.22 – 9.19, p = 0.019), and patients with stage IV without metastasis also had a higher risk to develop recurrence (adjusted HR = 1.96, 95% CI = 1.10 – 3.50, p = 0.022) compared to patients with stage I+II. Patients

with stage III had higher risk to develop recurrence than patients with stage I + II, but no statistical significance (adjusted HR = 1.27, 95% CI = 0.69 – 2.32, p = 0.430). (Table8)

**Histological cell type**

The risk of the recurrence of nasopharyngeal carcinoma patients with poor differentiate carcinoma type (WHO type II) was higher than patients with well differentiated carcinoma type (WHO type I), but no statistical significance (adjusted HR = 1.43, 95% CI = 0.44 – 4.59, p = 0.550). The risk of recurrence of nasopharyngeal carcinoma patients with undifferentiated carcinoma type (WHO type III) was higher than patients with well differentiated carcinoma type (WHO type I) 2.06 times, but no statistically significance. (adjusted HR = 2.06, 95% CI = 0.63 – 6.73, p = 0.233). (Table8)

**Chemotherapy received**

The chemotherapy received was also no significantly associated with recurrence of nasopharyngeal carcinoma. The risk of recurrence of nasopharyngeal carcinoma patients who did not received chemotherapy was 0.95 times (adjusted HR = 0.95, 95% CI = 0.58 – 1.52, p = 0.824) when compared to patients received chemotherapy, but no statistically significance. (Table8)

**Table 8 Multivariate analysis of the association between prognostic factors and recurrence rates of nasopharyngeal carcinoma.**

| Factors | Crude HR | Adjusted HR | 95% CI of HR | p-value |
|---|---|---|---|---|
| **Gender** | | | | |
| male | 1 | 1 | | |
| female | 1.15 | 1.18 | 0.79 – 1.74 | 0.422 |
| **Age** | | | | |
| < 45 | 1 | 1 | | |
| ≥ 45 | 1.04 | 1.16 | 0.78 – 1.72 | 0.458 |
| **Histological cell type** | | | | |
| Well differentiate carcinoma | 1 | 1 | | |
| Poor differentiate carcinoma | 1.51 | 1.43 | 0.44 – 4.59 | 0.550 |
| Undifferentiated carcinoma | 2.04 | 2.06 | 0.63 – 6.73 | 0.233 |
| **Overall stage grouping** | | | | |
| Stage I+II | 1 | 1 | | |
| Stage III | 1.21 | 1.27 | 0.69 – 2.32 | 0.430 |
| Stage IV without metastasis | 1.82 | 1.96 | 1.10 – 3.50 | **0.022** |
| Stage IV with metastasis | 3.18 | 3.35 | 1.22 – 9.19 | **0.019** |
| **Chemotherapy received** | | | | |
| No | 0.89 | 0.95 | 0.58 – 1.52 | 0.824 |
| Yes | 1 | 1 | | |

HR = Hazard ratio of recurrence of nasopharyngeal carcinoma, adjusted for all variables in table 8

# CHAPTER V
# DISCUSSION

In Thailand, during past 5 years, incidences of nasopharyngeal carcinoma have been increasing and expected to become important among other sites of cancer. The important problem for nasopharyngeal carcinoma patients usually be the return of disease after initial treatment or called “recurrence of disease” (56). The recurrence of primary tumor is one of major cause of death from this disease, especially among patients with locally advanced tumor (57). The number of study of recurrence of nasopharyngeal carcinoma patients is quite small in Thailand and less than other countries. Most studies focused on identification of risk factors of the disease or the prognostic factors for treatment of nasopharyngeal carcinoma independently, in order that patients’ survival time could have been improved.

The aims of this study are to try to identify risk factors of recurrence of nasopharyngeal carcinoma patients in all stages. The recurrence rate of nasopharyngeal carcinoma varies widely according to several factors including size of tumor, histological cell type, stage of disease, and others e.g., treatment received methods, age, and gender (58). Risk factors of the recurrence of nasopharyngeal carcinoma included in this study were gender, age, TNM stage, overall stage of disease, histological cell types and types of treatment received.

## 5.1 Statement of the finding

### 5.1.1. Demographic and pathogenic characteristic of study population

The study population had mean age of 46.13 $\pm$12.15 years, and being male in 63.66%. Majority of them were in stage III to stage IV, and had poor and undifferentiated carcinoma cell types.76.50% received chemotherapy treatment which were considered as severe cases. It was found that there were 105 patients had recurrence of nasopharyngeal carcinoma with the followed up time ranged from 12.03 to 154.20 months (median follow up time was 60.20 months).

### 5.1.2 Recurrence rate of nasopharyngeal carcinoma

It was found that overall incidence density of recurrence rate of nasopharyngeal carcinoma was 5.72 per 100 person- years. Patients with stage IV with metastasis had the highest incidence density of recurrence rate of nasopharyngeal carcinoma among other stage, undifferentiated carcinoma cell types also had the highest the incidence density of recurrence rate among other types with was 7.10 per 100 person- years. Patients with lower lymph node level involvement had the highest incidence density of recurrence of nasopharyngeal carcinoma with 11.86 per 100 person- years compared to others. This study also found that the overall 2, 3 and 5-years cumulative recurrence rates of nasopharyngeal carcinoma patients were 12.16%, 18.80% and 26.11%, respectively.

Studies reported that recurrence rates of nasopharyngeal carcinoma after initial treatment ranged between 18% and 54% (59). However, approximately 19-56 % of patients develop a recurrent 5 years after their primary treatment. While this study found that the overall 5-years cumulative recurrence rate of nasopharyngeal carcinoma patients was 26.11%, which is nearly similar to the other studies. Study in Hong Kong reported the overall 5- years cumulative recurrence rate for patients was in 28.8% (45). While result from studies by in Brazil found among 173 patients in 32.3% (53), in China among 621 patients with nasopharyngeal carcinoma the overall 5- years local plus regional recurrence rate was 25%. And most of the studies that found overall 5-years cumulative recurrence rate of about 30 to 50% (39).

Although, most of recurrence lesion developed outside or at the margin of treatment portal within 3 years after receiving primary therapy, but some recurrence have been observed after a long time latent period (60, 61). Most of distant metastases recurrence also occurred within 3 years after treatment and the common sites of distant metastases were the bones and lung (62, 63). Similarly in our studies, it was found that the highest percentages of patients with recurrence of nasopharyngeal carcinoma were 42.18% during 1 - 3 years and 4.08% found that followed up time over 8 years after treatment. In China, study reported that some of the recurrence of nasopharyngeal carcinoma appeared between 6 to 10 years. They emphasized the importance of frequently careful follow up examination for at least 10 years (63).

### 5.1.3 Prognostic factors for recurrence of nasopharyngeal carcinoma

**Age**

Our study found that recurrence rates among patients aged <45 years was higher than the older of ≥ 45 years but no statistical significance. Beside, age was not risk factors of recurrence of nasopharyngeal carcinoma in both crude and adjusted analysis, and this is similar to several studies (64, 46, 45). In Taiwan, study also reported that age did not significantly associate with recurrence of nasopharyngeal carcinoma (≤ 50 years vs. > 50 years) (p = 0.170) (37).

However, this result is not consistent with studies of Farias, T. et al., reported that patients with age older than 40 years at treatment had higher risk to have recurrence than the younger (p = 0.001) (53). And results from studies in retrospective analysis of 35 patients with nasopharyngeal carcinoma between 1994 - 2002 at Singapore found that patients with older age at diagnosis had higher risk of recurrence 1.06 times higher than younger (p = 0.02) (38). Similarly, studies of Ma, J. et al. reported that patients with age > 40 years old had higher risk of local recurrence than age < 40 years (HR = 1.02, 95 % CI = 1.01 – 1.04, P = 0.0385) (39). Some studies (35, 40) found that older age groups were also worse prognostic factors of recurrence of nasopharyngeal carcinoma because in the older age groups were often found to have more aggressive pathology, and presented themselves to physicians with the late stage cancer.

**Gender**

From this study, ratio of gender between males and females patient was 1.7: 1. Five years recurrence rate among gender was nearly the same, and gender was not significant prognostic factors of recurrence.

. From previous retrospective cohort study, gender ratio was 2 : 1 with a median age of about 50 years (39, 64, 55) which is similar to another study from Taiwan, gender was also not significant factor associated with recurrence of nasopharyngeal carcinoma (p = 0.39) (37). But in some studies, gender significantly associated with recurrence rate. For example, in the studies of Ma, J. et al. reported that recurrence rate of nasopharyngeal carcinoma of being male patients was

significantly higher than that of being female patients (HR = 1.17, 95% CI = 1.10 – 1.82, p = 0.033) (40). Also in other studies, gender was not significant associated with recurrence of nasopharyngeal carcinoma (64, 55).

By TNM system, tumor stage (T stage) did not demonstrate significant association with recurrence of nasopharyngeal carcinoma. From the previous study, the subgroup of TNM stage had independent effect on the incidence recurrence. For example, study evaluated 83 patients with nasopharyngeal carcinoma at the Tyen Mun hospital, Taiwan, reported that tumor stage of disease was a significant risk factors for recurrent of nasopharyngeal carcinoma favoring those with early stage (T1 and T2) disease (p = 0.040) (64).

Study of Cheng S. et al. reported that T4 stage independently predicted recurrent of nasopharyngeal carcinoma with the hazard ratio of 3.994 (p= 0.02) (37). Most of the studies showed better control for recurrence among patients with stage T1 – T2 than stage T3 – T4 (64, 46, 37, 45, 55).

From this study, lymph node stage (N stage) was significant factor for recurrence of nasopharyngeal carcinoma in crude analysis of hazard ratio (crude HR = 2.10, 95% CI = 1.13 – 3.91, p = 0.020), but not in multivariate analysis. Many studies reported that lymph node stage was associated with recurrence rate of nasopharyngeal carcinoma, such as univariate prognostic factor analysis revealed that (N2 vs. N0-1, p = 0.22, N3 vs. N0-1, p = 0.001, N3 vs. N2, p = 0.02) and multivariate analysis by Cox proportional hazard model showed that N3 stage were factors that independent predict recurrent of nasopharyngeal carcinoma, the hazard ratio were 3.39. (p= 0.01) (37), it was similar to a previous study (64, 55). Several researchers have reported that advanced clinical TNM stage is correlated with poor recurrence rate of nasopharyngeal carcinoma.

**Overall stage grouping**

Staging is the process of finding out how far cancer has spread. It is also one of the most important factors in selecting treatment options and estimating patients' outlook for recovery and survival. Result from this study showed that the 5

years cumulative recurrence rate of patients with stage I+II, III, IV without metastasis and stage IV with metastasis increased when stage increased by 19.11%, 22.52%, 31.98, and 48.57%, respectively. The difference in recurrence rates between stage I plus II, III and IV resulted in that the survival curves of recurrence rates of nasopharyngeal carcinoma patients by stages were significantly different (p = 0.022). Overall stage grouping of disease was significant factor for recurrence of nasopharyngeal carcinoma in crude analysis of hazard ratio, the result showed that risk of recurrence of nasopharyngeal carcinoma patients with stage IV with metastasis was highest (crude HR = 3.18, 95% CI = 1.25 – 8.09, p = 0.040) when compared to patients with stage I+II.

The multivariate analysis by Cox proportional hazard model showed that risk of recurrence of nasopharyngeal carcinoma patients stage IV with metastasis was highest when compare with patient with stage I+II. (adjusted HR= 3.35, 95% CI = 1.22 – 9.19, p = 0.019). When compared between patients with stage IV without metastasis and patient stage I+II, it was found that risk of recurrence of nasopharyngeal carcinoma patients with stage IV without metastasis had a higher than those patients with stage I+II. (adjusted HR = 1.96, 95% CI = 1.10 – 3.50, p = 0.022). It can be said that patients with stage I+II had the lowest recurrence rate of nasopharyngeal carcinoma, while patient with stage IV with metastasis had the highest recurrence rate of nasopharyngeal carcinoma.

As in many studies, Overall staging of disease was high potential prognostic factors for recurrence of nasopharyngeal carcinoma (64, 45, 35). In the present study, the clinical stage proved to be an independent prognostic factor for recurrence of nasopharyngeal carcinoma (35, 65). Our results identified that recurrence of nasopharyngeal carcinoma was significantly associated with stage of disease, especially in those who was in stage III-IV disease. The main reason for such results may be reflected by the fact that most patients with stage IV had poor prognostic factors for recurrence of tumor.

**Histological cell type**

Result from this study showed that the most common histological type of nasopharyngeal carcinoma was poor differentiated carcinoma (WHO type II) in 58.20% and 35.79% had undifferentiated carcinoma (WHO type III).

The risk of recurrence of nasopharyngeal carcinoma patients with undifferentiated carcinoma type (WHO type III) was higher than patients with well differentiated carcinoma type (WHO type I), but not statistical significant. (adjusted HR = 2.06, 95% CI = 0.63 – 6.73, p = 0.233). The highest recurrence rate of nasopharyngeal carcinoma was observed in patient with undifferentiated carcinoma type, while the lowest recurrence rate of nasopharyngeal carcinoma found in patient with well differentiate carcinoma.

However, this resulted was not consistent with some studies, such as study in Taiwan, which found that patients with poor differentiate carcinoma cell type or (WHO type II) had a greater risk of recurrence of nasopharyngeal carcinoma than patients with undifferentiated carcinoma or (WHO type III) with (adjusted HR = 3.55, p=0.054) (37). In the other hand, among Chinese, the majority of patients with nasopharyngeal carcinoma had cell type in undifferentiated carcinoma or WHO III), and there was no significant difference in survival rate and recurrence rate were observed with histological tumor type or degree of differentiation (36).

Many previous studies reported that the histological cell type was an independent prognostic factor for the recurrence of nasopharyngeal carcinoma (48 66). But, from the literatures, metastasis was higher in patients with poor differentiate carcinoma (WHO type II) or undifferentiated carcinoma (WHO III) tumor compared to patients with well differentiate carcinoma type (WHO type I) (26).

**Chemotherapy received**

In general, patients in early stage of nasopharyngeal carcinoma were usually treated by radiotherapy alone while those in advanced stage were treated by chemo-radiotherapy or combined treatment. For surgery therapy was treatment

indicated for patient who had recurrence or residual of nasopharyngeal carcinoma after radiotherapy.

This study found that patients who had no received chemotherapy treatment had a lower recurrence rate compared to those who had received chemotherapy. (adjusted HR = 0.95, 95% CI = 0.58 – 1.52, p = 0.824), but received chemotherapy did not demonstrate significant association with recurrence of nasopharyngeal carcinoma. Similarly, study by Chan A. et al. showed treatment types was just having borderline statistical significance (p=0.061), patients who received radiotherapy alone had higher risk to have recurrence compared to those had received combine with chemotherapy with a recurrence ratio of 1.44 (95% CI = 0.98-2.1) (67). In contrast, several studies found that these factors were significantly associated with recurrence rates of nasopharyngeal carcinoma (51, 54).

For example, in the study of patients at Brazil, that the used combination chemotherapy – radiotherapy has been investigated, with a view to decreasing the rate of distant metastasis and recurrence of nasopharyngeal carcinoma (53).which were similarly to several results reported in the literature.

The result of this study from multivariate analysis showed that after adjusted for other factors, overall stage grouping of disease was significant factors for recurrence of NPC, while other variables were not significant.

Finally, recurrence of nasopharyngeal carcinoma is still an important issue in the patient care, and it still remains a serious issue in the management of patients with nasopharyngeal carcinoma.

**Limitation of the study**

Since the design of this study was retrospective cohort study. Secondary data from hospital records were used with unplanned for studying since the beginning of cohort. Some variables or factors were not be available such as viral infection, smoking and alcohol drinking which were also factors for recurrence according to the literature review. However, the researcher gathered the data with the best attempt, particularly for the data of independent factors. In multivariate analysis, missing data

resulted in lower number records excluded from the analysis such as EBV IgG-VCA titer and EBV IgA-VCA titer.

Some patients of nasopharyngeal carcinoma were referred from other hospital after received first treatment and started treatment again in to Ramathibodi hospital. So, in this case the recurrence time started from first date at treatment at Ramathibodi hospital until to recurrence occurred or the end of study. For those with unknown status or censored, follow up time finished at the last contact.

With the nature of university hospital in Bangkok, Thailand, patients, who came to receive treatment at Ramathibodi hospital, were from all over Thailand including referred cases. These can caused ill defined study population properly, and external validity of the study is in doubt.

# CHAPTER VI
# CONCLUSION

In this study, there were 366 nasopharyngeal carcinoma patients attending treatment at the Ramathibodi hospital during January 1, 1996 to December 31, 2006 with follow up time more than 1 year. The mean age of the patients was 46.13 years old (SD = 12.15) and ratio of male and female was 1.7: 1. Most of nasopharyngeal carcinoma patients (52.73%) were ≥ 45 year of age and 47.27% were age < 45 years old. The highest percentage of patient had residence in central region (59.84%), followed by Northeastern region (13.35%) and Southern region (11.75%). One hundred-eleven (30.33%) of patients had a history of tobacco consumption and 102 patients (27.875%) had a history of alcohol consumption. The most common histological type was poor differentiate carcinoma (58.02%) and most of patients (39.34%) were in stage IV without metastasis. The last status at the end of study it was found that 105 patients (28.69%) had recurrent and 77.31% had no recurrent or loss followed up. The highest percentage of recurrence type were distant metastasis alone (39.05%), 28.57% were local recurrence and 7.62% were regional recurrent The overall incidence density of recurrence rate of nasopharyngeal carcinoma was 5.72 per 100 person- years and the overall cumulative recurrence rates by 2, 3 and 5- year were 12.16%, 18.80% and 26.11%, respectively.

Results from univariate analysis by Kaplan- Meier and log rank test showed that the recurrence rate of nasopharyngeal carcinoma also had significant difference according to overall stage grouping (p = 0.022) and EBV IgG-VCA titer (p = 0.004). The 5-years cumulative recurrence rates of patients with stage IV with metastasis was highest (48.57%) with statistically significant differences among other stages (p=0.022).

According to Cox's Proportional hazard analysis with unadjusted or crude effects of hazard ratio (HR) with 95% confidence interval demonstrated factors such as lymph node level involvement, M stage, N stage, overall stage grouping of diseases were significantly associated with recurrence of nasopharyngeal carcinoma. The risk of recurrence of nasopharyngeal carcinoma patients with N3 stage was 2.10 times of patients with N0 stage (p = 0.020). The risk of recurrence of patients with M1 stage was significantly higher than patient with M0 stage (p = 0.049).The risk of recurrence of nasopharyngeal carcinoma patients with stage IV with metastasis was highest when compared to stage I+II (p = 0.040). The risk of recurrence of patients with lower lymph node level involvement was 2.87 times (crude HR = 4.12, 95%CI= 1.21- 6.76, p = 0.033) when compared to patients with no lymph node involvement of cancer.

Results from multivariate analysis by Cox' s proportional hazard model, adjusted effects or hazard ratio with 95% confidence interval demonstrated factors which significantly influenced on recurrence rate were still overall stage grouping. Patients with stage IV with metastasis had higher risk to develop recurrence was 3.35 times (adjusted HR = 3.35, 95% CI = 1.22 – 9.19, p = 0.019), and patients with stage IV without metastasis also had a higher risk to develop recurrence was 1.96 times (adjusted HR = 1.96, 95% CI = 1.10 – 3.50, p = 0.022) when compared to patients with stage I+II. Others prognostic factors did not demonstrated significant effects.

**Recommendation for results of application**

This study found overall stage grouping related to recurrence of nasopharyngeal carcinoma. The patients with advanced stage (stage IV with metastasis) had higher recurrence rates of nasopharyngeal carcinoma than patients in earlier stage (stage I+II). Risk of recurrence were increased when stage increased.

Results from this study recommended that supportive care should be provided to the high risk group in order to encourage them to received the complete the course of treatment. Early screening or recurrence should be emphasized, because patients with recurrent nasopharyngeal carcinoma tend to have a very poor prognosis if untreated. A complete follow up examination must be done continuously in order that early detection for recurrence can be found and treated with better prognosis.

From this study, it seem to be that prevention and control for this cancer among this group of patients was quite good. Most of patients were in early stage of disease before treatment, and there was high rates of recurrence of nasopharyngeal carcinoma found and reported mainly in patients with advanced stage before receiving treatment. So, it is suggested that early detection for cancer in early stage is the best way to prevent recurrence after treatment, especially before having distance metastasis or reached to advanced stage. Patients should be referred for appropriate treatment in early stage and can be decrease risk of recurrence of nasopharyngeal carcinoma after treatment.

This result may recommend screening program to identify high risk patients at early disease stage, screening for cancer of nasopharyngeal carcinoma, including the attending for annual examination with serological test against Epstein Barr Virus (EBV). Physical examination to exclude cervical lymphadenopathy and cranial nerve palsy, and endoscopic examination of the nasopharyngeal region by specialist should be emphasized.

The results of study provide information for further researches to improve the nasopharyngeal carcinoma at Ramathibodi hospital in the future.

**Recommendation for further study**

This study is a retrospective cohort study which has limitation in lacking details of in some important variables such as clinical information and treatment. The management of cohort study among patients with good quality of follow up data of outcome, exposure, and covariates should be reviewed and improved. Improvement of quality of medical records are so important for survival time study, the cancer registry should be reviewed.

Further research should include other variables such as antibody-dependent cellular cytotoxicity antibody (ADCC titer) and compare the effectives of different treatment modalities, such as neoadjuvant therapy, concurrent chemotherapy and palliative therapy that from our review literature found that these variables are related with prognosis of disease.

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