Scientific Paper Compilation

1st NATIONAL CONFERENCE OF NASOPHARYNGEAL CARCINOMA

“Prevention is Better than Cure”

Toba Beach Hotel, Samosir
October 18–20, 2018

Editor: Farhat

Reviewer: Marlinda Adham
Bambang Hermani
Widodo Ario Kentjono
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USU press
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PREFACE

First of all, thanks to The Almighty God for all of His blessings and guidance in finishing this **Scientific Paper Compilation: 1st National Conference of Nasopharyngeal Carcinoma**, which has published at 18th of October.

This book consists of articles and ideas regarding the nasopharyngeal carcinoma by many Head and Neck Oncologist from various study center in Indonesia. We do hope that this book will benefit everyone to develop further study especially about nasopharyngeal carcinoma.

Lastly, we sincerely apologize for any mistakes. We are looking forward for your critics and suggestions for the sake of the better future.

Chairman,
Center of Excellence Nasopharyngeal Carcinoma
Universitas Sumatera Utara

Dr. dr. Farhat, M.Ked(ORL-HNS), Sp.T.H.T.K.L.(K).
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THE DEVELOPMENT OF NASOPHARYNGEAL CARCINOMA IN INDONESIA

Farhat, Ashri Yudhistira

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In International Agency for Research on Cancer World Health Organization (WHO) in year 2018 there are roughly 129,079 new cases of nasopharyngeal carcinoma and 72,987 death in year 2018. Based on the data, it is stated that nasopharyngeal carcinoma became a rare case in the world. Around 92% new cases of nasopharyngeal cancer occured in developing country. Guangdong Province (Kwangtung) has the highest prevalence of nasopharyngeal cancer in the world, around 20-40 cases per 100,000 lifes. One of the highest incidence occured among Kanton “pesanir race” with the incidence 54,7/100,000 lifes. (Jemal, 2011) (Adham, 2012).

Several countries in South East Asian has a several to high incidence of nasopharyngeal cancer. Data from Guangdong found that the native Bidayu race in Serawak, Malaysia also had a high incidence of nasopharyngeal carcinoa (23,1/100.000). Other South East countries such as Singapore (15/100.000), Malaysia (9,7/100.000), Vietnam (7,5/100.000) and Philipines (6,4/100.000). Epidemiologically, nasopharyngneal carcinoma has became an interesting cancer due to geographical effect, racial distribution, genetic, social and environment. (Adham, 2012).

Based on International Agency for Research on Cancer World Health Organization (WHO) in 2018 there are 348,809 new cancer cases. Prevelance of nasopharyngeal carcinoma in Indonesia is quite high, which is on the 5th place after breast cancer, cervix, lungs and liver, with 17,992 new cases. Incidence of patients suffering from nasopharyngeal carcinoma more often found in male than female with ratio 3:1 (Adham, 2012).

Nasopharyngeal carcinoma frequency prevale in almost every Indonesia regions. There are more than 100 cases per year was found in Cipto Mangunkusumo Hospital Jakarta. In Hasan Sadikin Bandung around 60 cases per year, Makassar 25 cases per year, Palembang 25 cases per year, Denpasar 15 cases per year and in Padang 11 cases per year. The frequencies found in Medan, Semarang, Surabaya and other cities in Indonesia are not much different. This shows that malignancy incidence prevail in whole Indonesia. (Soepardi, 2007)

In the last one and a half century, nasopharyngeal carcinoma has caused many death. (Clifford, 1970). The oldest pathological specimen from nasopharyngeal carcinoma originated from Northeast and Middle East Africa...
population around 3500-3000 B.C (Wells, 1963), (Krogman, 1940), (Smith dan Dawson, 1924), dan (Derry, 1909). Wells (1964) stated that only 3 or 4 definite cases of carcinoma which was found from tens of thousands ancient Egypt mummies has been researched. These specimens shows defect of posterior alalveolus left maxilla near hard palate and lamina pterygoid. (Picture 1)

Based on Smith and Dawson (1924) research, Wells (1964) concluded that the found specimen was not a pictured condition of nasopharyngeal carcinoma. Smith and Dawson (1924) found in Rome-Egypt population case, male pre-Christian Nubian specimen had a wide defect in basis cranii from cribiform plate to occipital base, almost reached the foramen magnum. The location and presence of destruction showed a case of sphenoidal sinus carcinoma case or nasopharyngeal carcinoma. These case is difficult to be differentiated even with physical examination. Evidence which was found untill now is still far from assurance that nasopharyngeal carcinoma had been experienced by the Northeast and Middle East African population around 5000 years ago.

Picture 1. Photograph of skull specimen No. 236. Dotted line indicates the nasopharyngeal boundaries on the right side (R). Destruction of bone is limited to the floor of the left maxillary sinus and adjacent hard palate and pterygoid laminae.

Since the majority of nasopharyngeal carcinoma was found in Kwantung, China, thus nasopharyngeal carcinoma was aptly named Kwantung Carcinoma. This can be found in an Ancient Chinese medical literature. In a book titled “Dalam sebuah buku volume 50, “Aetiology and Symptomatology of Various Disease”, written by Chou Uen Fung also known as Chou Yuan Fang, an emperor physician from the Sui Dynasty (A.D 589-617), contain some description about the types of
superficial tumor swellings. Jung and Yu (1963) found an impossibility to differentiate the “lo li” case (enlargement of neck glandular in chinese writings) is a malignancy or tuberculosis disease or other disease. In a Chinese Medical encyclopedia that was edited by Wu (1921), there is a disease called “shih ying” or “shih jung” which defines a lack of nutrition that was described as one of four fatal disease with clinical symptom such as:

A mass was found in front or behind the ear part of the neck. Hard consistency, immobile, hot or cold when touched and painless in the beginning, and getting bigger and more painful progressively. Sero-sanguineous discharge but no pus. At the end phase, necrotic fiber was formed and great pain is suffered during this phase. Bleed easily from ulcer and can cause massive hemorrhage even death. There’s no more debate that this clinical presentation is a form of metastasis, not tuberculosis, lymph node and high possibility of primer nasopharyngeal carcinoma. No report was found in the encyclopedia when was this disease first reported in Chinese medical writing.

First Medical Journal about nasopharyngeal carcinoma was described in Durand Fardel (1837), Michaux (1845) and Bosworth (1889). Jackson (1901) reported primer nasopharyngeal case and reviewed 13 cases which was collected from England, France, Italy and German, including six cases belonged to Bosworth. Jackson concluded in his report that irritation is not the cause of nasopharyngeal carcinoma development significantly, because even though the nasopharynx was exposed to smoke and dust, larynx carcinoma is exposed even more. (Clifford, 1970).

Most of South East Asia Countries had contact with Chinese people, it’s because of war or trading. In other side, Chinese people marries the locals. Nasopharyngeal carcinoma has a high incidence rate among the Chinese immigrants in Thailand, Singapore, Malaysia, Indonesia, Phillipines and Vietnam. These incidence is much lower compared to Chinese people that was born and raised in south China. (Clifford, 1970) (Asroel, 2002).

Nasopharyngeal carcinoma is affected by EBV virus, enviroments and genetic as its etiology. Migration from high risk country to low risk country cause the incidence in said country to rise. Implication of an area and or genetics and the possibility of EBV virus infection can be an important causage of nasopharyngeal carcinoma. EBV was first identified by Sir Epstein and colleagues in 1964 by lymphoma Burkitt tumor. This virus became the first virus to be linked with oncogenesis because it’s linked to the appearance of Burkitt lymphoma and some other causage of lymphoma and epitelial malignancy. (Adham, 2012) (Jemal, 2011).

In Indonesia, 100% of 5 year old children which is infected by EBV virusand became latent infection for the rest of their lives.Primary infection often found in children and is assymptomatical or a upper respiratory tract infection. After being infected, EBV infiltrate the submucos and transforms B cell lymphocytes
until it becomes latent infection which is persistent in nasopharynx mucosa (Adham, 2012).

Nasopharyngeal carcinoma is not too easy to associate with EBV infection. More than 95% adult in the whole ethnic group all over the world also has been infected by EBV. Other research reported that the rising risk of nasopharyngeal carcinoma is related to the food that is being eaten such as spices that contains nitroso and nitrosamines compound. Yu’s research (1981) stated that salted fish consumption that contains nistrosamine in kanton people becomes the main risk factor of nasopharyngeal carcinoma compared to smoking. Malaysian Chinese community consumes cow’s liver, with salted fish and salted egg shows a significant relation with the appearance of nasopharyngeal carcinoma (Jemal, 2011) (Adham, 2012).

Until now, radiotherapy is still the main therapy for nasopharyngeal carcinoma since 1982. Radiotherapy is a main therapy for cancer which haven’t reach far metastases. The radiation that was given is hoped to improve the quality and prolonged the live of the patient. (Kentjono, 2003).

Epidemiological research shows that the consumption of fresh fruits and vegetables can prevent the occurrence of nasopharyngeal carcinoma. Vitamin C can prevents nitroso metabolism and reactivate of EBV. The daily consumption of dried salted fish of Indonesian community, foods that contains formaline compounds and poliaromatic coloring compounds in local food can become carcinogenic and must be avoided. Smoking tobacco and other inhaler which is common in Indonesia, can also become a co-carcinogenic compound from enviroments. Repetitive exposure to those compounds can increase the risk of EBV latent infection and the risk of nasopharyngeal carcinoma occurrence. (Adham, 2012).
NASOPHARYNGEAL CARCINOMA
UNDERSTANDING THE ANATOMY, EBV MARKER, AND CLINICAL PRESENTATION

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1. NASOPHARYNGEAL CARCINOMA
1.1. Anatomy of the nasopharynx and the lymphogenic spread of nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is a rare malignancy in most parts of the world and it is one of the most confusing, commonly misdiagnosed and poorly understood diseases.

The nasopharynx (NP) is defined as the part of the pharynx, which lies behind the nasal fossa and extends inferiorly as far as the level of the soft palate (Fig. 1). The NP is a hollow, air-containing passageway. The posterior wall occupies the angle between the base of skull above and the vertebral column. Anterior, the NP communicates with the nasal cavity through the posterior nares or choanae. The lower part of the anterior wall is formed by the soft palate. The lateral wall is formed by the superior constrictor muscles. The Eustachian tube ostium is situated in the lateral wall of the NP and the lateral pharyngeal recess or fossa of Rossenmuller. In this area stratified squamous and ciliated epithelia meet. This is called the transitional zone and is liable to metaplastic and neoplastic changes.

It has been shown that opening of the Eustachian tube is dependent on the action of the musculus tensor veli palatini. Interference with its action by tumor infiltration is associated with tubal dysfunction and middle ear problems with hearing loss, which is an early sign of NPC. Its inaccessible location underlines the problem of the otolaryngologist in performing a thorough examination of the area.

The NP is the site of marked aggregation of lymphoid tissue and forms part of a lymphoid ring i.e. the Waldeyer’s ring. The lymphatic drainage system is correspondingly extensive. A dense capillary network in the mucosa exists throughout the pharynx and gives origin to three main groups of sub-mucosal collecting trunks. The retropharyngeal space needs some more attention in that it contains the median and lateral groups of retropharyngeal lymph nodes including the node of Rouviere. A good understanding of this extensive lymphatic system is of great importance in tumor staging and management of tumor spread and it should be noted that lymphatic channels do cross the midline.
The Anatomy of nasopharynx and connection with other structures in the back of the nasal cavity.

1.2. Epidemiology of the tumor

NPC has a remarkable racial and geographical distribution with complex interactions of genetic, viral, environmental and dietary factors.

There was an estimated incidence of 84,400 cases of NPC and 51,600 deaths in 2008, representing about 0.7% of the global cancer burden. This disease may be considered as one of the rarer cancer forms globally, ranking as the 24th most frequently diagnosed cancers worldwide and 22nd within the developing world.

NPC is a relatively rare malignancy in most parts of the world. It is more frequent in males than females in both the developing and developed world, with incidence rates commonly 2 to 3 times higher in males in higher resource countries. It accounts for 2% of all head and neck squamous cell carcinomas, with an incidence of 0.5 to 2 per 100,000 in the United States. However, it is endemic in many geographical regions, including Southern China, Southeast Asia, Indonesia, Japan, the Middle East/North Africa and Eskimos in arctic regions. Some North-East parts of India have a high incidence of NPC as well. Ho et al. reported that NPC is the third most common malignancy among men, with an incidence of 50 per 100,000 in the Guangdong province of Southern China. Some references report much higher incidences of 50-150 cases per 100,000 in Southern China, particularly in Hong Kong and Guangzhou (formerly known as Canton, and the capital of the province of Guangdong). Indeed, this malignancy is often referred to as “Cantonese cancer” or “Kwangtung tumor”. Emigration from high to low incidence areas such as the United States and Canada reduces the incidence of NPC in first generation Chinese, but it still remains at seven times the rate compared to Caucasians. Chinese of southern origin have a uniquely high risk up to 10-20 /100,000 for males resulting in around 20,000 new cases yearly in China. The highest recorded NPC incidence is found in the Bidayu people of Borneo Island (Kalimantan), with an age-adjusted incidence of 35/100,000. In Indonesia it is the
most frequent cancer in the head and neck and ranks as number 4 in males with an incidence of 6.2/100,000 and has been added to the Globocan overview of WHO-IARC only recently, because of prior lack of specific diagnostic facilities and data\textsuperscript{16}. The epidemiology and etiology specifically for Indonesia will be discussed in detail in chapter 2\textsuperscript{17}.

1.3. Etiology and risk factors

NPC presents as a complex disease caused by an interaction between chronic infection with an oncogenic gamma herpes virus, the Epstein-Barr virus (EBV) and environmental and genetic factors, involving a multistep carcinogenic process\textsuperscript{6}. EBV exists worldwide, infecting over 95\% of the global adult population\textsuperscript{18}. In Hong Kong, 80\% of the children are infected by 6 years of age, and almost 100\% have seroconverted by 10 years of age\textsuperscript{19}. Although primary EBV infection is typically subclinical, the virus is associated with the later development of several malignancies including NPC\textsuperscript{7}. It is transmitted by saliva, and its primary infection occurs during childhood with replication of the virus in the oro-pharyngeal lining cells, followed by a latent infection of B lymphocytes (primary target of EBV). Epstein-Barr virus initiates an early active (or lytic) infection; the virus then persists in a latent state until it is reactivated under certain conditions of immunosuppression or illness. Elevated titers of EBV-associated antigens (especially of IgA class), a latent EBV infection identified in neoplastic cells of virtually all cases of NPC, the clonal EBV genome consistently detected in invasive carcinoma and high-grade dysplastic lesions suggest a critical role of EBV in the pathogenesis of NPC in endemic areas\textsuperscript{6}.

Environmental factors and dietary habits are also reported to be related to NPC. Salted fish consumption in early childhood has been correlated with an unusually high incidence of nasopharyngeal cancer in the boat communities of Hong Kong’s harbors\textsuperscript{12,20}. N-nitrosodimethylamine in salted fish, perhaps in combination with vitamin deficiency, has been considered a likely carcinogen\textsuperscript{10,12,21}. The process of salt preservation is inefficient, allowing fish and other foods to become partially putrefied. As a result, these foods accumulate significant levels of nitrosamines, which are known to be carcinogenic in animals\textsuperscript{22}. Salt preserved fish also contain bacterial mutagens, direct genotoxins, and EBV-reactivating substances\textsuperscript{23,24}, any or all of which could also contribute to the observed association.

Occupational hazards, including exposures to formaldehyde, dust and smoke particles and certain aromatic hydrocarbons, have been investigated as risk factors for nasopharyngeal cancer\textsuperscript{25–27}. Formaldehyde is a recognized nasal cavity carcinogen in rodents. Smoke particles from incomplete combustion of coal, wood, and other materials are also of the size and weight to be deposited mostly in the nasopharynx\textsuperscript{28}. Several studies conducted in high- and low-risk populations during the past decade have obviously indicated the nasopharynx as a tobacco susceptible
cancer site, and that exposure to parental smoking during childhood plays a role. Ever smokers exhibit a roughly 30%-100% excess risk compared with life-long non-smokers. In low risk populations, data on risk factors are scarce. Also, a proportion of cases of NPC are of the differentiated type (WHO type I) and the etiology of these tumors is different from that of the UCNT. A case-control study conducted in the USA on 231 cases and 246 controls revealed that only differentiated NPCs (118 cases) were clearly related to heavy drinking and tobacco. A strong dose response relationship between cigarette smoking and the risk of differentiated squamous cell carcinoma was observed. The use of certain Chinese medical herbs has been suggested to increase the risk for NPC by reactivating EBV infection in the host.

A genetic predisposition is suggested by a high incidence of NPC in patients with specific histocompatibility complex profiles, including HLA-A2, HLA-B46 and HLA-B58. AW19, BW46 and B17 have also been reported to be associated with an increased risk, whereas HLA-A11 is associated with a decreased risk. In rare familial cases, inherited genetic alterations could be the first “hit” and EBV infection may contribute to the second “hit”. Therefore these familial cases usually occur with a younger age of onset. The finding of translocation, amplification and deletion of 3p, 5p and 3q indicates that genetic aberrations are possibly contributing to NPC development.

Viral infection by EBV together with environmental co-carcinogens rather than genetic predominance is believed to be the strongest etiological forces for the development of NPC.

1.4. Histopathology

According to WHO classification, NPC is histopathologically divided into 3 categories i.e. keratinizing squamous cell carcinoma (type 1), non-keratinizing carcinoma (type 2), and undifferentiated carcinoma (type 3). The pathology of the different NPC types is presented in figure 2. EBV is more deeply related to the undifferentiated type of carcinoma. This type has a better prognosis than the differentiated non-keratinizing and keratinizing types of carcinoma. This is related to the higher (chemo-) radiosensitivity of undifferentiated carcinomas. Undifferentiated NPC has a higher local tumor control rate, despite a higher incidence of distant metastasis compared to differentiated carcinomas.

A “Working Formulation Classification” based on the degree of anaplasia and pleomorphism of different cell types was suggested by Yeh. Tumors with cells with marked nuclear hyperchromatism and or evident variation in nuclear size were designated as Type A, whereas those with little to moderate pleomorphism and hyperchromatism were designated as Type B.

Both cell types and the degree of anaplasia reflect important prognostic significance and further impact on the patient’s outcome. Tumors with evident anaplasia and or pleomorphism (Types A) have a significantly less favorable
outcome with a 5 year survival of 30-40% than their counterparts with mild anaplasia (Types B) with a 5 year survival of 60-72%.

Published data indicate a higher proportion of keratinizing squamous cell carcinoma among all NPC cases in non-endemic compared with endemic areas. Some studies reported that WHO type 1 accounts for approximately 25% of all NPC in North America, but only 1% in endemic areas; whereas undifferentiated carcinoma, WHO type 3, accounts for 95% of all cases in high incidence areas and 60% of cases in North America.

2A. Nasopharyngeal keratinizing squamous cell carcinoma (WHO-1). The island of tumor shows invasion into the stroma. The tumors cells show obvious squamous differentiation and keratinization and round prominent nucleoli and eosinophilic cytoplasms.

2B. Nasopharyngeal non-keratinizing, differentiated carcinoma (WHO-2). The tumor cells show differentiation with some cytokeratin expression, but in which squamous differentiation is not evident by light microscopy.

2C. Nasopharyngeal non-keratinizing, undifferentiated carcinoma (WHO-3). The tumor cells in syncytial arrangements show round nuclei, pleomorphic, vesicular with prominent nucleoli and spindle cell with dark staining nuclei and inconspicuous nucleoli.
2D. EBER-RISH showing positive expression in nuclei of NPC tumor cells in the routine paraffin-embedded histopathology specimen

**Picture 2. A,B,C, and D Histopathology pictures of different Types of WHO classification (Courtesy of Lisnawati Rachmadi. MD Path, her own work in Histopathology UI Jakarta )**

1.5. Clinical Presentations

Wei and Sham\(^1\) divided symptoms presented by NPC patients into four categories (1) symptoms caused by the presence of a tumor mass in the nasopharynx (epistaxis, nasal obstruction, and discharge), (2) symptoms associated with dysfunction of the Eustachian tube (hearing loss), (3) symptoms associated with the superior extension of the tumor (headache, diplopia, facial pain, and numbness), and (4) neck masses. The clinical appearance of NPC is depicted in figure 3. Since the nasopharynx has an abundant supply of regional lymphatic vessels, metastases are frequently found. Cervical lymphadenopathy is often the only clinical manifestation of NPC in patients. Because symptoms, related to NPC in the early stage, are usually nonspecific, most NPC patients are diagnosed in advanced stage. Spread to the neck nodes occurs in a predictable manner; upper levels first, mid jugular and supraclavicular chains later\(^1,4,44\). Paulino et al. found that a unilateral neck mass was the most common presenting sign, occurring in 80\(^\%\)\(^45\) of the patients.

Cranial nerve involvement, subsequent to invasion of the skull base is seen in 25\(^\%\) of cases\(^46\). The two principle cranial nerve syndromes associated with nasopharyngeal carcinoma are the **retroparotid syndrome** (involving cranial nerves IX, X, XI and XII) and the **petrosphenoid syndrome** (involving cranial nerves III, IV, V, and VI). Occasionally, cranial nerve II becomes involved through the foramen lacerum\(^43\). Isolated cranial nerves most commonly affected was the III, V, VI and XII\(^{\text{th}}\) nerves, with symptoms of diplopia, trigeminal neuralgia and or deviation of the tongue\(^1,44\). Headache can be explained by extension into sphenoid, middle cranial fossa and intracranial extension.

NPC produces its clinical features by invading adjacent structures locally and spreading to neck nodes regionally. Extension of local spread is associated with adverse prognosis. The presence of bulky cervical lymphadenopathy is predictive for distant metastasis. Lung, followed by bone, are the most common sites for metastasis\(^11\).
1.6. Diagnosis and staging

Diagnosis of nasopharyngeal carcinoma is primarily based on the history, physical examination and imaging. For definitive diagnosis a biopsy of the lesion is required. Biopsy can be performed in the office or in the operating room by rigid or flexible endoscope and has a high specificity (99.6%)\(^2\). Endoscopy gives adequate information of the local status of the disease. Endoscopic evaluation gives the possibility to take a direct biopsy of the lesion for histopathological examination. As long as the tumor involves the mucosa it will be visible by direct endoscopy. Sub-mucosal tumor extension is more difficult to evaluate by endoscopy (Picture 4.) due to the fact that the extension of the lesion is hardly visible. Imaging is indispensable for this reason.\(^1,47\)

The primary tumor extent should be evaluated by CT scan and/or MRI. MRI is the preferred modality of choice for the imaging of NPC\(^48,49\). MRI is more sensitive than CT scan for the detection of the extension of the primary tumor. It can reveal soft tissue extent, regional nodal metastasis and perineural growth and may help to depict subclinical NPC missed at endoscopy. MRI is better than CT in displaying both superficial and deep nasopharyngeal soft tissue and for differentiating tumor from soft tissue. MRI is also more sensitive for assessment of retropharyngeal and deep cervical nodal metastases and it can detect bone marrow infiltration\(^11,50-52\). Bone marrow infiltration is associated with an increased risk of distant metastases\(^53\). CT scan is considered as a better tool for defining bone erosion\(^1\). CT has been used for long in staging NPC (Fig.5), especially for the detection of skull base tumor involvement with lytic or sclerotic lesions\(^54,55\), but now it has been largely replaced by MRI for primary tumor and nodal staging. However, CT scan is still used for radiotherapy planning and, in some centers, it is used together with PET using 18F-FDG. PET/CT scan has been shown to be of great value in NPC staging, where the main advantage is for the detection of distant metastasis\(^56\). It is also used for monitoring patients post-treatment and detecting NPC recurrence. In case a PET scan is not available, chest radiography, hepatic
ultrasonography and bone scanning can be used in the assessment of metastatic disease and, ultimately, the staging of this malignancy.\cite{57}

**Picture 4.** Endoscopic appearance shows tumor involvement of the fossa of Rosenmuller, obstruction of the Eustachian tube and extension into the nasal cavity through the choanae (first picture), and tumor from the left side of nasopharynx involved the roof of nasopharynx with extension to the right side of nasopharynx.\cite{4}

**Picture 5.** T1 (former T2a) Nasopharyngeal Carcinoma: tumor from the Left Fossa of Rosenmuller spreading to the nasal cavity

Clinical staging of the tumor represents 4 stages (Table.1) According to the AJCC 2010 7th edition, stage I is T1N0, local disease in soft tissue only. Stage II represents stage I with N1 disease, which is uni or bilateral- retropharyngeal nodes, or unilateral upper neck nodes not greater than 6 cm, or primary tumor extension (T2) into the parapharyngeal region. Stage III is stage II plus N2 disease, which is bilateral upper neck nodes <6 cm, or local tumor invasion (T3) with minimal bone invasion or into the paranasal sinus. Stage IV is stage III with N3 disease, which is nodal involvement in the supraclavicular fossa, or lymph nodes greater than 6 cm, or local disease (T4) with cranial nerve involvement, extension to intracranial, or to the hypopharynx, infratemporal fossa, orbit or oropharynx.\cite{58,59} In comparison to the 6th edition a few changes have been made. First, patients with nasal cavity or oropharynx involvement who were classified as T2a in the 6th edition are now classified as T1 and T2b, which in case of parapharyngeal extension has become T2. Second, the role of retropharyngeal lymph node is clarified in the staging
system, and (uni- or bilateral) retropharyngeal lymph node invasion is staged as N1. Third, the addition of the term “masticator space” (as a synonym for infratemporal fossa), which was introduced in the 6th edition, has been abandoned, and anatomic masticator space involvement is staged as T4.

Table 1. Classification criteria and stage grouping by different systems. Changes in the AJCC/UICC staging system (7th edition) for nasopharyngeal cancer.

<table>
<thead>
<tr>
<th>Classification criteria and stage grouping by different systems.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AJCC/UICC 5–6th edition</strong></td>
</tr>
<tr>
<td>T1: Nasopharynx</td>
</tr>
<tr>
<td>T2: Oropharynx or nasal fossa</td>
</tr>
<tr>
<td>T2a: without parapharynx</td>
</tr>
<tr>
<td>T2b: with parapharynx</td>
</tr>
<tr>
<td>T3: Bony structure, paranasal sinuses</td>
</tr>
<tr>
<td>T4: Intracranial extension, cranial nerve, hypopharynx, orbit, infratemporal fossa (masticatory space)</td>
</tr>
<tr>
<td><strong>N-category</strong></td>
</tr>
<tr>
<td>N0: None</td>
</tr>
<tr>
<td>N1: Unilateral node, 6 cm, above supraclavicular fossa</td>
</tr>
<tr>
<td>N2: Bilateral node, 6 cm, above supraclavicular fossa</td>
</tr>
<tr>
<td>N3a: 6 cm</td>
</tr>
<tr>
<td>N3b: in supraclavicular fossa</td>
</tr>
<tr>
<td><strong>AJCC/UICC 7th edition</strong></td>
</tr>
<tr>
<td>T1: Nasopharynx, oropharynx, or nasal fossa</td>
</tr>
<tr>
<td>T2: Parapharyngeal extension</td>
</tr>
<tr>
<td>T3: Bony structure, paranasal sinuses</td>
</tr>
<tr>
<td>T4: Intracranial extension, cranial nerve, hypopharynx, orbit, infratemporal fossa (masticatory space)</td>
</tr>
<tr>
<td>N0: None</td>
</tr>
<tr>
<td>N1: Unilateral cervical, uni/bi-lateral parapharyngeal, 6 cm, above supraclavicular fossa</td>
</tr>
<tr>
<td>N2: Bilateral cervical node, 6 cm, above supraclavicular fossa</td>
</tr>
<tr>
<td>N3a: 6 cm</td>
</tr>
<tr>
<td>N3b: in supraclavicular fossa</td>
</tr>
</tbody>
</table>

Narrow-band imaging (NBI) endoscopy is a promising tool to differentiate non-malignant from malignant nasopharyngeal lesions on the basis of the morphologic findings of mucosal capillary vessels in vivo. In addition, NBI may increase the diagnostic value of endoscopy in populations at high risk for NPC.

For diagnosis and typing, EBER in situ hybridization is the most reliable method for determining if a lesion is EBV associated and considered as the gold standard for detecting and localizing latent EBV in tissue samples.

1.7. Treatment of NPC

NPC is more sensitive to radiotherapy and or chemotherapy than other head and neck cancers. The 5 years overall survival rates for stage I, II, III and IV disease is 90%, 80%, 70% and 50% respectively. Since NPC is highly radiosensitive, radiotherapy (RT) has always been the main treatment of choice for this cancer. The major limitations of 2D planning for nasopharyngeal carcinoma can now be overcome with 3D conformal radiotherapy and intensity-modulated radiotherapy (IMRT). The main aim of using 3D-CRT (Conformal Radiation therapy) and IMRT is to produce isodose curves with high conformity for the target volume, while decreasing the dose into surrounding tissues. Consequently, acute and late morbidity will decrease, while increasing the dose to the target volume. Prophylactic neck treatment is recommended for NPC without clinical neck nodes,
because 30% - 40% of these patients will develop regional disease if the neck is not treated.

For early stage disease (T1N0M0), radiotherapy is given to the nasopharynx and the neck\textsuperscript{1,6}. For advanced stage (T1N1-3M0 and T2-4N0-3M0), chemoradiation is the treatment of choice. Chemotherapy can be administered as neoadjuvant or concurrent to radiation. The standard agent used in concurrent chemoradiotherapy is cisplatin. This provides a benefit in terms of overall survival and on both loco-regional and distant control\textsuperscript{66–72}. While three cycles of adjuvant cisplatin-5FU has been a standard part of many concurrent chemoradiotherapy regimens, the actual benefit of the adjuvant cycles are uncertain and toxic effect is substantial\textsuperscript{73}. Cisplatinum based induction chemotherapy has been shown by some studies to improve disease-free survival and may be considered in locally advanced disease although it is not seen as a standard treatment\textsuperscript{74}

Radiotherapy is applied with a dose of 65-75 Gy to the primary tumor and 65-70 Gy to the involved neck nodes, whereas the dose for prophylactic treatment for the node-negative neck is 50-60 Gy. This treatment has successfully controlled T1 and T2 tumors in 75-90% of cases and T3 and T4 tumors in 50-75% of cases\textsuperscript{61,75–78}. For T1 and T2 tumors, a booster dose by use of intracavitary brachytherapy can improve tumor control by 16%\textsuperscript{79}.

Nodal control is achieved in 90% of N0 and N1 cases, but the control rate drops to 70% for N2 and N3 cases\textsuperscript{74}. Evaluation is performed with CT scan or MRI, ultrasound of the neck and endoscopy of the nasopharynx 8-12 weeks post treatment to assess the tumor response. For patients with distant metastasis, platinum based combination of chemotherapy or radiotherapy for brain metastasis and weight bearing bones can be considered.

To minimize the risk of late toxicity (particularly, to adjacent neurological structures), fractional dose >2 Gy per day and excessive acceleration with multiple fractions >1.9 Gy/fraction should be avoided. IMRT may offer improvement in local tumor control, and reduction in radiation xerostomia in early-stage disease.

It is well demonstrated that once radiotherapy has started the full course of radiation should be given in 45-47 days, due to the fact that the number of clonogenic cells in cycle will increase once radiotherapy is started. Interruptions have been shown to be hazardous for the expected outcome of radiotherapy, due to a phenomenon known as accelerated repopulation which occurs in the tumor tissue\textsuperscript{80}.

Complications of treatment are hearing deficits due to chemotherapy, reduced smell and vision due to decreased function of olfactory and optical nerve, vascular stenosis and or induced malignancy by the radiotherapy it self. Radiotherapy also effects dental hygiene, due to a reduction of the function of the salivary glands.
1.8. **Follow-up after primary treatment.**

The modalities commonly used in the follow up of patients with NPC include clinical examination, endoscopy and imaging. Inspection with a flexible or rigid endoscope plays a primary role in follow up examination. However, mucosal reactions after radiotherapy make it difficult to find early recurrent lesions. Secretions and crust covering the nasopharyngeal mucosa also hamper the early detection of local recurrence. Detection of sub-mucosal or deep-seated recurrent lesions is difficult with endoscopic examinations only.

For the imaging after initial treatment, CT and MRI are widely used for the detection of recurrent or residual lesions. MRI is superior to CT in the detection of soft tissue abnormalities. The baseline MRI or CT study is conducted 2 to 3 months after termination of the initial treatment. After the baseline evaluation, close follow up is recommended every 3 to 6 months for the first 2 years post-treatment. FDG-PET in the detection of residual or recurrent NPC lesions has been reported from several institutes. FDG-PET is increasingly being used for detection of recurrent lesions and may distinct tumor from post irradiation changes, such as tissue necrosis, fibrosis, and edema. Liu reported that sensitivities for CT, MRI, PET for the detection of residual or recurrent NPC lesions were 76, 78, and 95% respectively. This suggests that PET can be a useful tool for the detection of recurrent or residual NPC lesions, but there are also limitations with the use of PET for the detection of early recurrent NPC lesions. FDG uptake can be increased by inflammatory reactions in the early period after radiotherapy. For the detection of distant metastases, the use of serum EBV DNA has been shown to be more sensitive and reliable than other options.

Narrow Band Imaging (NBI) is a novel technique that enhances the diagnostic sensitivity of endoscopes for characterizing tissues using narrow-band width filters in a sequential red-green-blue illumination system. Superficial mucosal carcinoma lesions, which are rarely detected using conventional endoscopy, can be observed with NBI by viewing the non-angiogenic, microvascular proliferation pattern. Lin and Wang reported that early recurrent lesions of NPC after radiotherapy were successfully detected by NBI coupled with conventional endoscopy.

1.9. **Treatment of locoregional recurrent and persistent NPC.**

Based on retrospective analysis on diagnosis of recurrent regional disease, the recommended procedure after curative intent chemo-radiotherapy is a FNAC and CT scan. When positive nodes are detected, radical neck dissection is the preferred treatment. When the FNAC is negative or inconclusive, excision biopsy of the affected node should be done, preferably with frozen sections in combination with neck dissection if malignant cells are found. Radical neck dissection offers better results than re-irradiation. The overall 5 years survival rate for treatment with radiation is around 20%. Radical neck dissection as salvage procedure has
achieved a 5 years tumor control rate of 66% in the neck and a 5 year actuarial survival of 38%. When tumor in the neck node extends beyond the confines of the lymph node, brachytherapy should be applied to the tumor bed in addition to radical neck dissection.

Locally persistent and recurrent tumors after radiotherapy or chemoradiation can be addressed by re-irradiation, brachytherapy, stereotactic radiotherapy, photodynamic therapy or surgically. Surgery can be performed either through a minimal invasive (endoscopic) approach, or with open surgery by a mandibular or maxillary swing procedure or infratemporal approach from the lateral aspect, transpalatal, transmaxillary, and transcervical approaches from the inferior aspect. Surgery remains a challenge due to the hidden position of the nasopharynx. The 5 year actuarial control of tumors in the nasopharynx is about 65% and the 5 year disease free survival rate is around 54%. Nasopharyngectomy is usually offered when there is only evidence of local recurrence or persistent disease.

Re-irradiation can also be used as therapy for local recurrent NPC, although its use is limited by the cumulative dose toxicity. Re-irradiation can be given by external beam RT, stereotactic radiotherapy or brachytherapy. The use of brachytherapy and surgery has generally resulted in better outcomes compared to external re-irradiation for the small recurrent lesions. Stereotactic radiotherapy, when used for the management of limited residual or recurrent tumor, is associated with a 2 year local tumor control rate of 72%.

Photodynamic therapy is a relatively new modality for treating NPC, with good results for local failures of NPC. PDT is an established non-invasive treatment modality for incurable head and neck cancer. A photosensitizer is administered to the patient followed by illumination of the tumor with a specific wavelength. This causes tumor destruction. Several clinical trials with first generation haematoporphorin-derived photosensitizers (HpD or Photofrin) have shown that PDT is effective in destroying NPC, with good local tumor control and complete responses in the majority of patients with limited recurrent or persistent disease, while achieving long-term palliation in cases with extensive recurrence. Although these results were encouraging, PDT for NPC has not yet been considered as a breakthrough in this field. The two major drawbacks of these studies were (1) the light delivery and (2) the selection of photosensitizer. First, light delivery in the nasopharynx is extremely difficult. It is almost impossible to illuminate the whole tumor area with a lens fiber, guided with endoscopes or transorally with a mirror system. The problem of proper illumination of the nasopharyngeal cavity has now been solved by the development of a special applicator, which allows one-stage illumination of the entire nasopharynx. The second drawback is the use of HpD/Photophrin (the first generation photosensitizer). This photosensitizer has a limited depth penetration of <5 mm and a prolonged light hypersensitivity of several months. Temoporfin (Foscan®), a
second-generation photosensitizer and approved in Europe for treatment of incurable head and neck cancer, has a depth penetration of 1 cm and light hypersensitivity of only a few weeks. Research in NPC cell lines by Yow et al confirmed that Temoporfin showed much better PDT efficiency as compared with HpD. These authors also observed significant photo destruction of the mitochondria, especially in Foscan® mediated PDT. Mitochondria are an important sub-cellular target and may play a role in cell death. Temoporfin, in combination with the special designed nasopharyngeal applicator for proper illumination, has the potential to effectively treat recurrent and or residual NPC also in the current Indonesian medical system.

1.10. Distant metastases

The frequency of distant metastasis is 4.4% to 7% at diagnosis and 20% to 27% during follow up\textsuperscript{50,107,108}. In case of metastatic NPC (stage IVC) only palliative treatment remains. In chemo-naïve patients, platinum-based regimens are the first choice and give the best results\textsuperscript{109}. Chen et al showed the benefit of a combination chemotherapy with radiation for loco-regional disease in case of distant metastases at diagnoses\textsuperscript{110}. When the above mentioned strategies have failed, limited options are left. Best response rates for palliative chemotherapy only were found with gemcitabine, capecitabine or docetaxel, with a median survival of 9.5-15 months\textsuperscript{111}. Apart from the poor outcome, combination chemotherapy in metastatic NPC in general results in increased toxicity\textsuperscript{112}.

1.11. Targeted therapy

Epidermal growth factor receptor (EGFR) is highly expressed in NPC. A strong expression is associated with poor survival outcome\textsuperscript{113}. Combination of the monoclonal antibody against EGFR, cetuximab, with carboplatin in patients with metastatic NPC who have failed prior platinum-based therapies achieved a response rate of 12% and a clinical benefit rate of 60%\textsuperscript{69}. Cetuximab has been combined with cisplatin and IMRT in locoregionally advance NPC, demonstrating good tolerability despite a significant incidence of radiation dermatitis, mucositis and dysphagia\textsuperscript{114}. The approach of adding EGFR-targeted therapy to conventional treatment approaches is being actively studied in locoregionally advanced NPC.

Overexpression of the markers associated with hypoxia, including hypoxia-inducible factor 1 Alpha (HIF-1A), carbonic anhydrase 9 (CA-9) and vascular endothelial growth factor (VEGF), is associated with poorer survival outcome in NPC\textsuperscript{115}. VEGF and VEGF Receptor targeted therapies, including use of Bevacizumab (Avastin) and small molecule or DNAzyme inhibitors\textsuperscript{116}, are underway to limit neovascularization in NPC.

In undifferentiated NPC, EGFR overexpression was up to 83% and was found to correlate with primary tumor stages of disease and locally aggressive diseases\textsuperscript{117}. 

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Overexpression of epidermal growth factor receptor (EGFR) has been correlated with alterations in cell cycle progression, increased invasive capacity, enhanced angiogenesis, and decreased apoptosis of tumor cells. Overexpression also associated with larger and advanced stage tumor and poor prognosis, while EGFR activation associated with resistance to radiation\textsuperscript{118,119}. Study in five NPC cases, has found the effectiveness of EGFR blockade in tumors without deleterious skin toxicity (skin rash) commonly found in treatment with other EGFR inhibitors\textsuperscript{120}.

The viral antigens expressed by the tumor cells are attractive targets for immunotherapy and may be a potential avenue for the development of new therapies for the treatment of NPC\textsuperscript{121,122}.

When cytotoxic T-lymphocytes (CTL) are added, the EGFR concentration in the tumor cell membranes (EGFRs) is suppressed and the activity of EGFR declines during CTL immunotherapy, which is consistent with the finding of Yuan et al\textsuperscript{123,124}.

The combination of nimotuzumab (anti-EGFR) and radiotherapy in head and neck cancer is well tolerated and can enhance tumor radiocurability. The addition of nimotuzumab to standard modalities might increase the response and survival rates without significantly potentiating toxicity. A recent study showed combination of nimotuzumab and radiation achieved a highest tumor volume reduction of 98\%, and drastic reduction of more than 90\% in nodal volume\textsuperscript{114}.

2. EPSTEIN-BARR VIRUS AND NPC

2.1. Introduction to EBV

EBV is the first discovered human tumor virus and is associated with variety lymphomas and carcinomas. In these tumors EBV is actively present in all tumor cells resulting in an increased proliferation and decreased apoptosis. More than 95\% of adult population throughout the world is EBV positive as defined by serology. However, presence and active role of EBV in NPC pathogenesis can be detected by a rise of IgA titers to EBV antigens. The aberrant serology correlates with tumor development, remission and recurrences\textsuperscript{125–127}. Viral DNA load in plasma has been shown as promising alternative marker\textsuperscript{128–132}, although EBV DNA in whole blood samples does not appear to have similar diagnostic value\textsuperscript{133}. Furthermore, viral DNA load in nasopharyngeal (NP) brushings is a direct reflection of aberrant local viral NPC activity in the nasopharynx\textsuperscript{134–136}. Besides EBV DNA load in NP-brushings, altered methylation of tumor suppressor gene promoter regions is indicative of tumor presence in situ\textsuperscript{137–139}. Therefore, the presence of aberrant antibody responses to EBV and viral presence and activity in all tumor cells may enable us to use the virus and virus-induced changes as biomarker(s) for early detection of NPC, monitoring of therapy outcome/efficacy and prediction of recurrences or distant metastases. The studies presented in this thesis were planned
in part to evaluate viral biomarkers contributing to the clinical decision making for patients with NPC.

2.2. **Epstein-Barr virus**

The Epstein-Barr virus (EBV) was discovered 50 years ago by electron microscopy examination of cells cultured from Burkitt’s lymphoma tissue by Epstein, Achong and Barr\textsuperscript{140}. Four years later, EBV was shown to be the etiologic agent of heterophile-positive infectious mononucleosis\textsuperscript{141}. Aberrant anti-EBV antibody responses in NPC patients were a first hint for EBV involvement in NPC\textsuperscript{142,143} and EBV DNA was detected in the tumor cells in tissues from patients with NPC in 1970\textsuperscript{144}. In the 1980s and 1990s, EBV was shown to be associated with B-cell non-Hodgkin’s lymphoma and so-called lymphoproliferative disease (PTLD) in transplant recipients receiving immunosuppressive medication as well as with brain lymphomas and oral hairy leukoplakia in patients with the acquired immunodeficiency syndrome (AIDS)\textsuperscript{145–147}. Since then, EBV DNA, RNA and proteins have been detected in tissues from other cancers, including T-/NK-cell lymphomas and Hodgkin’s disease and B-cell lymphomas arising in other immune compromised patients\textsuperscript{148–151}.

EBV is a human herpesvirus (HHV) with a 172 kb long, double-stranded DNA genome that encodes >80 genes\textsuperscript{152}. As for other herpesviruses, EBV represents an enveloped virus that consists of a protein core wrapped with DNA surrounded by an icosahedral nucleocapsid and a tegument layer enclosed by a lipid envelope containing glycoprotein spikes for cell attachment. There are 3 main subclasses within the HHV family; alpha-herpesviruses including herpes simplex I and II and Varicella-Zoster virus, beta-herpesviruses including cytomegalovirus (CMV) and HHV6, HHV7 and gamma-herpesviruses including EBV and Kaposi sarcoma herpesvirus (KSHV) or HHV8. EBV is also known as HHV4 and has unique DNA structure and coding sequences separating it from the other HHVs. The gamma herpesviruses can be subdivided into gamma-1 (lymphocryptoviruses, EBV) and gamma-2 (Rhadinoviruses, HHV8). These are the only HHVs directly associated with human tumor formation. Human tumors have been attributed to both human herpesvirus 8 (Kaposi’s sarcoma, primary effusion lymphoma and Castleman’s disease) and to EBV (Burkitt’s lymphoma, various types of classic Hodgkin lymphoma, as well as extranodal NK- and T-cell non-Hodgkin Lymphoma, nasopharyngeal carcinoma, gastric adenocarcinoma, immunodeficiency associated B cell Lymphoma and most recently B cell non-Hodgkin’s lymphomas in elderly\textsuperscript{153,154}. Humans serve as the only natural host for EBV with target cells predominantly being B cells and epithelial cells\textsuperscript{155}. 
2.3. Biology of EBV

EBV infects nearly all humans (>90%) by the time they reach adulthood, but infection occurs mostly at early age\textsuperscript{142,156}. EBV can infect a number of different cell types, including B cells and epithelial cells. Under certain condition, it may infect T cells, natural killer cells, monocytes, and smooth muscle cells as well. The mechanisms for entering these cells are different.

EBV enters B lymphocytes by binding with its envelope gp350/220 protein to the CD21 receptor (also known as CR2), which is located at the surface of B cells, whereas viral gp42 interacts with cellular MHC class II molecules as co-receptor. This triggers fusion of the viral envelope with the cell membrane, allowing EBV to enter the B cell\textsuperscript{155,157–159}. Entry into epithelial cells is considered to involve cell contact from EBV producing plasma B cells and epithelia, or binding of virions to integrin beta-1 via the envelope BMRF2 protein containing RDG motif and subsequent membrane fusion via gH/gL and gB glycoprotein interaction with other integrins\textsuperscript{155,160,161}. Indirect transfer of the virion via monocytes has been described as well as transfer of IgA coated virions via IgA receptors on polarized epithelial cells as alternative routes\textsuperscript{162,163}.

During acute infection, EBV primarily infects B lymphocytes in the sinonasal lymphoid tissue and replicates in the stratified squamous epithelium of the oropharynx\textsuperscript{155,164,165}. The infected individual remains a lifelong carrier of the virus and EBV establishes persistent infection in the host, residing in a small fraction of memory B lymphocytes\textsuperscript{166}.

Primary infection with EBV typically occurs within the first few years of life, usually asymptomatic and ranges from a mild self-limiting disease in children to infectious mononucleosis (IM) in adolescents and adults in more developed areas. EBV is transmitted by salivary exchange (e.g. pre-chewing food, kissing, etc.), but not every person will get IM symptoms after contact with an EBV carrying individual. EBV infection will result in transient viremia followed by a rapid immune response that will control EBV for life in a permanent well balanced dynamic equilibrium between virus reactivation and immunological control\textsuperscript{167,168}. EBV will remain in a dormant state in most humans for long time without serious consequences.

This persistent infection with EBV is reflecting the virus lifelong balance with its human host and where it hides from the immune system via latent infection of B lymphocytes. The latency state allows the virus to be maintained in cells with a highly restricted viral gene expression, which is needed for survival without being recognized and eliminated. The expressed essential viral latency proteins are low immunogenic and have properties to evade the immune system\textsuperscript{169–171}.

Although EBV exists in 95% of the world population without symptoms and EBV has a strong capacity to immortalize infected host cells, strong host immune responses prevent outgrowth of such potentially dangerous cells. However, in a minority of infected individuals EBV is linked to the development of a variety
of lymphoid and epithelial malignancies. EBV is biologically active in the malignant cells of these tumors and each type of tumor has a distinct pattern of EBV gene expression. The EBV genome within the tumor cells shows different patterns (latent) gene expression characteristics for each tumor and reflecting defined episodes (stages) of normal viral activity, as will be described here below.

2.4. The life cycle of Epstein-Barr virus.

2.4.1. General features

EBV infection of lymphocytes leads to two alternate outcomes. Firstly, EBV can infect naive B cells and let them grow out into memory B cells, which persist with the virus in long-term latency expressing only few of its genes. On the other hand, these B cells can differentiate upon antigen stimulation toward plasma cells that then can produce new infectious virions and will die. Thus, the EBV infection has two different phases, a latent persistent and lytic reproductive phase\(^{167}\). Lifelong infection of the human host relies on this dual phase of infection. Viral replication is naturally enriched in the oral mucosa where memory B cells are routinely stimulated to differentiate after exposure to foreign antigens. The role of mucosal epithelial cells in viral persistence and reactivation is still under debate\(^{172,173}\).

2.4.2 EBV infection (primary infection and persistence)

![A Schematic presentation of EBV infection in healthy carriers (adopted from Udumade et al.\(^{142}\)).](image)

Picture 6. A Schematic presentation of EBV infection in healthy carriers (adopted from Udumade et al.\(^{142}\)).
Primary EBV infection begins in the oral cavity and affects epithelial cells and naïve B cells. The Waldeyer’s lympho-epithelial region in nasopharynx and oropharynx, is considered as the location for primary EBV infection, viral replication and EBV persistence. EBV genome will transport into naïve B-cell nuclei followed by B cell immortalization and creation of a B cell memory niche through epigenetic modulation of the host cell. Activation of B cell growth program by EBV gene products will drive proliferation of blasting B cells, at the same time countered and controlled/eliminated by T cells primed by EBV antigens on B cells, acting themselves as the antigen-presenting cells. In the blood, memory B cells with largely quiescent viral genomes will circulate and occasionally enter lymphoid tissues in the head & neck region, to be triggered into activation as plasma cells and switching-on lytic replication. This results in transfer of virus to susceptible epithelial cells further amplify virus production and shed virus into the saliva.

The oropharynx is rich in aggregates of lymphoid tissue, such as the lingual, palatine and pharyngeal tonsils (Waldeyer’s Ring). During primary infection, the virus can infect B cells within the tonsillar crypts (squamous epithelium covering tonsils which dips into the connective tissue beneath), thereby entering the “growth program”, expanding the number of virus infected cells before entering the latency program (Fig. 6). EBV may also persist and replicate in oropharyngeal epithelial cells. EBV latent infection of B lymphocytes is necessary for virus persistence, subsequent infectious replication in epithelial cells, and release of infectious virus into saliva. EBV replication in latently infected B cells needs additional triggering by chemical agents or immunoglobulins receptors.

2.4.3. Replicative cycle

The virus is periodically replicated in most asymptomatic carriers of EBV and infectious virions can be recovered in oral secretions. EBV lytic replication will produce infectious virus in mucosal epithelia, after being activated in circulating memory B cells that have re-entered the oropharyngeal lymphoid tissue and upon triggering by antigen or other (chemical or hormonal) triggers that drive B cells to differentiate into plasma cells. This triggering ultimately results in expression of more than 80 viral proteins.

Lytic EBV replication is rarely associated with disease except in oral hairy leukoplakia and chronic active EBV syndrome and more recently in chronic periodontitis.

While EBV latency is dominated by few genes driving cell growth and survival while maintaining the viral genome as a mini-chromosome, the lytic cycle, or productive phase of EBV infection, involves the expression of up to 80 genes and results in the production of new infectious virions. EBV can undergo lytic replication in both B cells and epithelial cells. In B cells, lytic replication normally only takes place after reactivation from latency. In epithelial cells, lytic replication often directly follows viral entry. Virus-encoded DNA polymerase and accessory
proteins are required for linear viral DNA replication during the lytic phase of the viral life cycle. This contrasts with latency, when host DNA polymerase copies the viral genome\textsuperscript{175}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{epstein-barr-virus-life-cycle.png}
\caption{Life cycle of the Epstein-Barr virus (Adapted from Tsurumi\textsuperscript{180}).}
\end{figure}

Lytic gene products are produced in three consecutive stages: immediate-early, early, and late. Immediate-early lytic gene products act as transactivators, enhancing the expression of lytic viral genes as well as host genes. Immediate-early (IE) lytic gene products include BZLF1 (also known as EB1, Zta or ZEBRA) and BRLF1 (Rta or EB2) are part of the IE products that act as transcriptional activators of multiple (methylated) virus and host genes in an auto-stimulatory fashion\textsuperscript{180–182}. Early lytic gene products have many more functions, preparing the cell for viral DNA replication, enhancing nucleotide metabolism, and blockade of antigen processing. Early lytic gene products include BMRF1, BALF2 and BALF5 that have functions for replication, BGLF5, BNLF2a, and BILF1 that, function in RNA metabolism and blockage of antigen processing. Late lytic gene products tend to code for structural proteins, like viral capsid antigens (VCA p18, p40, p160, encoded in BFRF3, BDRF1 and BcLF1, respectively), which form the viral capsid, membrane antigens (MA gp350/220, gp125/110 encoded in BLLF1 and BALF4) that form the viral envelope and gene products for apoptosis resistance, like BHRF1 and BALF1, and immune evasion like BCRF1, the viral IL-10 homologue\textsuperscript{142}.

The gp350/220 envelope protein binds to CD21, to mediate EBV attachment to B cells\textsuperscript{183,184}. Besides the VCA capsid proteins, the gp125/110 (BALF4), or gB homologue, is believed to be the major immunogen of the VCA complex\textsuperscript{185}. Gp350/220 is a target for neutralizing antibodies, but also a prominent constituent of the plasma membrane of the EBV-producing cell and can serve as a target antigen for EBV specific ADCC\textsuperscript{186}.
Unlike lytic replication for many other viruses, EBV lytic replication does not inevitably lead to lysis of the host cell because EBV virions are produced by budding from the infected cell.

2.5. Latency phase of EBV

Three different programs of latent viral gene expressions are defined (Table 2) and can be observed in defined EBV-linked disease entities, as well as certain cell lines in vitro.

Type I latency is characterized by a limited spectrum of latent viral gene expression, namely non-coding EBER and BART transcripts along with EBNA1 protein. This pattern is found in circulating memory B lymphocytes of healthy viral carriers. Burkitt’s lymphoma is an EBV-related tumor characterized by latency type I gene expression.

Type II latency is mostly seen in tumors arising in immunocompetent hosts characterized by EBNA1, LMP1 and LMP2 protein expression in addition to the presence of non-coding EBER and BART transcripts, as seen in Hodgkin’s disease, T cell Lymphoma, and NPC, with the later also expressing the BARF1 protein. EBV associated gastric carcinoma (GC) shows similar type-II latent gene expression with BARF1 but without LMP1.

Type III latency is mostly seen in B cell lymphoproliferative diseases and lymphoma immunocompromised hosts and refers to the full spectrum of latent viral gene expression as found transiently in acute infectious mononucleosis. The higher EBNA proteins (EBNA2, 3a, 3b, 3c, 5) are highly immunogenic and therefore this latency pattern is only observed in the absence of an adequate T cell response as in immunocompromised hosts. In immunocompromised individuals, EBV is related to post-transplant (PTLD) and AIDS-related lymphoproliferative disorders, autoimmune lymphomas and lymphomas in the elderly, but not particularly with NPC. In HIV carriers Hodgkin’s disease is virtually always EBV positive as it is in most developing countries.
**Table 2.** Expression of EBV latent genes in disease (adopted from Cohen\textsuperscript{190}).

<table>
<thead>
<tr>
<th>Pattern</th>
<th>EBNA 1</th>
<th>EBNA 2</th>
<th>EBNA 3</th>
<th>LPM1</th>
<th>LPM2</th>
<th>EBERs</th>
<th>BARTs</th>
<th>DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td>Type 2</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NPC, GC, Hodgkin’s disease, periphereal T-cell lymphoma</td>
</tr>
<tr>
<td>Type 3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>PTLD, X-linked LPD</td>
</tr>
<tr>
<td>Other</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>Healthy carrier</td>
</tr>
</tbody>
</table>

2.5.1. **Function(s) of EBV latent genes.**

Latent infection in benign and malignant cells is characterized by limited expression of viral proteins to avoid immune recognition and destruction. Most latent protein functions have been defined in the background of EBV-infected and immortalized B-cells as cultured in vitro. The resulting lymphoblastoid cell lines (LCLs) express most latent EBV gene products, like six nuclear proteins (EBNA-1, EBNA-2, EBNA-3A, EBNA-3B, EBNA-3C and EBNA-LP), three membrane proteins (LMP-1, LMP-2A, LMP-2B), EBV-encoded small RNAs (EBER1 and EBER2) and rightward transcripts from the BamHI A region (BARTs).
<table>
<thead>
<tr>
<th>Gene products</th>
<th>Function</th>
</tr>
</thead>
</table>
| **EBNA1** | Maintenance of EBV episome in dividing cells through sequence-specific binding at OriP and linking EBV genome to chromosomes.  
Inhibits proteosomal degradation and presentation to MHC class I via gly-alal repeat.  
Destabilises p53 via interaction with cellullar ubiquitin-specific protease (USP7) and interferes with PML-bodies affecting DNA damage repair.  
Enhances cellular gene transcription and induces surviving expression. |
| **EBNA2** | EBV transcriptional enhancer and oncogene required for B cell transformation together with EBNA-LP (and LMP1).  
Interact with RBP-Jκ to transcriptionally activate cMyc, Runx-5, CD23 and other cellular genes as well as viral LMP1 and LMP2 early after infection. |
| **EBNA-LP** | Upregulation of transcription factors needed for B cell transformation and growth. |
| **EBNA-3A** | Essential for EBV-mediated transformation of primary B lymphocytes and interacts with RBP-Jκ, balancing EBNA2 binding to RBP-Jκ transcription factor.  
Together with EBNA3C prevents pro-apoptotic Bim expression in Burkitt cells with enhanced c-Myc expression, stimulating survival. |
| **EBNA-3B** | Transcriptional regulator, not essential for initial transformation |
| **EBNA-3C** | Essential for EBV-mediated transformation of primary B lymphocytes and interacts with RBP-Jκ.  
Promotes LMP1 expression in the presence of EBNA2. |
| **LMP1** | Essential for EBV transformation of B cell in vitro and drives proliferation through NF-κB, AP-1 and JAK/STAT pathway activation.  
Mimics CD40 activity by providing growth and differentiation signals to B cell.  
Up-regulation of anti-apoptotic proteins (Bcl-2, A20).  
Induces malignant transformation in human cells and transgenic mice.  
Activates transcription of epidermal growth factor receptor (EGFR) in epithelial cells. |
| **LMP2A** | Inhibits signaling through BCR and promotes the proliferation and survival of B cells. |
Promotes migration and stem-cell characteristics in epithelial cells.

LMP2B   Modulator of LMP2A

Counteracts the anti-viral effects of interferon and PKR activation in infected B cells. Induces TLR3 signaling in external recipient cells, stimulating innate immunity.

BARF1   Induce tumorigenicity and malignant transformation in primary epithelial cells.
Induces apoptosis-resistance via up-regulating Bcl-2.
Share homology with c-Kit, binds CSF1 and modulates monocytes activation.

BARTs   Encode >40 miRNAs that regulate EBV latent infection and modulate host immune responses by targeting a variety of viral and cellular messenger RNAs.

**Epstein-Barr nuclear antigen 1 (EBNA1)**

EBNA1 is a DNA-binding nuclear phosphoprotein which is required for the replication and maintenance of the episomal EBV genome in dividing cells through binding to the origin of plasmid replication (Ori-P) on the viral genome. The tethering of the viral genome to the host chromosome is mediated via so-called AT-hook domains within GR-repeats of EBNA1, allowing the replication of EBV during cell division by the replication machinery of the host. EBNA1 also functions as a transcriptional enhancer, driving defined host promoters into altered activity and induces Survivin expression leading to apoptosis resistance. EBNA1 is the only EBV protein that is expressed in all latently EBV-infected cells. Although EBNA1 is a foreign protein to the host, EBV-infected cells expressing EBNA1 are not killed by CTLs. This is due to a inhibitory effect of the protein’s Gly-Ala repeat on proteasomal processing thereby preventing endogenous MHC class I-restricted presentation. EBNA1 is capable of inducing genomic instability and interferes with p53 stability and DNA repair mechanisms, enhancing the risk for genomic alterations in the host cell, thus increasing the potential for cancer development.

**Latent membrane protein 1 (LMP1)**

LMP1 is considered the major EBV oncogene and functions as a viral mimic of the TNFR family member CD40. LMP1 signals constitutively without the need for a ligand and thereby exhibits properties of a classical oncoprotein, inducing promotion of cell growth and inhibition of apoptosis in a variety of cell types in vitro. The regulation of LMP1 expression occurs both at the transcriptional and post-translational level and LMP1 is secreted into exosomes. LMP1 is often present in NPC and can be detected in pre-invasive lesions of nasopharynx. LMP1 is considered to, have an important role in the pathogenesis NPC and its
detectable expression showed to correlate with poor prognosis\textsuperscript{204}. LMP1 induces expression of the epidermal growth factor receptor (EGFR) in epithelial cells and EGFR is expressed at high level in NPC\textsuperscript{205}. The induction of EGFR expression may be an important contributing factor to the deregulated cellular growth in this epithelial tum

LMP1 induces secretion of IL-6 in epithelial cells and decreases expression of cytokeratins and E-cadherin\textsuperscript{206}. LMP1 inhibits apoptosis in B-lymphocytes triggering expression of the Bcl-2\textsuperscript{207}. LMP1 achieves its wide-ranging phenotypic effects through the activation of multiple signaling cascades. Its activates the NF-kB, JNK and JAK/STAT pathways through direct interaction with pathway intermediary proteins\textsuperscript{208,209}. LMP1 induces expression and secretion of MMPs thereby promoting metastatic behaviour, and induces cytokine secretion thereby providing growth stimuli (IL-6), neo-angiogenesis (IL-8) and immunosuppression (IL-10). Secreted in exosomes, LMP1 may have modulatory functions in recipient cells in the tumor cell microenvironment and mediate immune evasion\textsuperscript{171,210–212}.

Latent membrane protein 2a and 2b (LMP2a and -2b)

EBV LMP2A prevents reactivation of EBV from latently infected cells by blocking B-cell receptor tyrosine kinase phosphorylation\textsuperscript{205}. LMP2 is not required for B cell transformation, but essential for long term persistence for the viral episome by providing B cell survival signals in the lymphoid organs\textsuperscript{150,213}. LMP2b modulates the function of LMP2a in regulating BCR signaling, driving the latently infected B cells to lytic reactivation\textsuperscript{150}. In epithelial cells LMP2a is considered to contribute to migration and invasion and induce stem-cell like characteristics\textsuperscript{214–216}. LMP2a is considered to cooperate with LMP1 in epithelial transformation and carcinogenesis\textsuperscript{217,218}.

BamHI rightward frame 1 (BARF1) protein

The EBV-encoded BARF1 gene is located in the BamHI-A fragment of the EBV genome and has oncogenic activity, encodes 221 amino acids\textsuperscript{219}. BARF1 functions as a viral oncogene, immortalizing and transforming epithelial cells of different origin by acting as a mitogenic growth factor, inducing Cyclin-D1 expression, and up-regulating anti-apoptotic Bcl-2, stimulating host cell growth and survival\textsuperscript{220}. Since BARF1 is expressed in tissues of various EBV-associated epitheloid malignancies, the possibility cannot be excluded that BARF1 expression in EBV-associated epitheloid malignancies reflects spontaneous induction of the lytic cycle in carcinoma cells. Because expression of the BARF1 gene is induced on the induction of the lytic cycle in EBV-positive cell lines\textsuperscript{221,222} and in Burkitt’s lymphoma cell lines, expression of BARF1 in NPC tissues is thought to reflect spontaneous induction of the lytic cycle in carcinoma cells. Quantitative real-time RT-PCR assay revealed that BARF1 was highly expressed in nasopharyngeal carcinoma (NPC) and EBV-positive gastric carcinoma tissues in the absence of
expression of lytic gene BARF1 is expressed in NPC and EBV-positive gastric carcinoma tissues as a latent gene and suggest that BARF1 plays a role in the pathogenesis of these malignancies\textsuperscript{135,223,224}. BARF1, an intracellular and secreted protein, has multiple pathogenic functions and also can function as a target for immune responses\textsuperscript{220}.

**EBV-encoded small RNAs (EBERs)**

The EBV encoded small RNAs (EBERs) comprise the highly abundant EBER1 and EBER2 molecules of 162-176 nucleotides in size. EBER transcripts are expressed in all latency states and represent a reliable target for detecting and localizing EBV in tissue sections by RNA in situ hybridization\textsuperscript{225}. The EBERs are expressed in many of the malignancies linked to EBV, including NPC and presumably contribute in some way to the maintenance of latency in vivo\textsuperscript{226}.

The high level of sequence conservation, suggests that EBERs are important in EBV biology, even though EBERs do not play a role in establishment of latent viral infection and replication\textsuperscript{227}. EBERs were found to interact with cellular proteins that play a key role in antiviral innate immunity. EBERs can be secreted from EBV-infected cells in exosomes and protein-RNA complexes and are recognized by toll-like receptor (TLR) 3, leading to induction of type-I IFNs and inflammatory cytokines, and subsequent immune activation\textsuperscript{228}. Furthermore, EBER1 was detected in sera of patients with active EBV disease, suggesting that activation of TLR3 signaling by EBER1 can account for some pathogenic characteristics of reactive EBV diseases\textsuperscript{229}.

EBER in situ hybridization is the gold standard for detecting and localizing latent EBV infected cells in tissue samples in every benign and malignant lesion\textsuperscript{63}. EBER in situ hybridization is often helpful in making the correct diagnosis\textsuperscript{230,231}. In cases of metastatic cancer of unknown origin, it is reasonable to consider NPC if EBV is present in the tumor cells\textsuperscript{232}.

**Rightward transcripts of the BamHI-A region of the viral genome (BARTs)**

BARTs are abundant transcripts derived from the BamHI-A fragment of the viral genome and expressed in all EBV infected cells and have elevated levels in NPC and GC. Structural analysis of the BARTs revealed the presence of several open reading frames. These are RPMI-1 and -2, A73 and BARF0 or depending on the splicing of the transcript RK-BARF0\textsuperscript{233,234}. However the protein products of these putative genes remain undefined\textsuperscript{235}. The function of most of the BARTs is still under investigation, but their detection in infected B cells and in many EBV-associated malignancies suggests that they might have an important role in viral persistence and pathogenesis\textsuperscript{150}. Recently BARTs were found to encode for about 40 individual microRNA species, that are abundantly expressed in NPC and other EBV-driven cancers\textsuperscript{236–238}. MicroRNAs (miRNAs) are small non-coding RNAs that play important roles in post-transcriptional gene regulation. In animal cells,
miRNAs regulate their targets by translational inhibition and mRNA destabilization\textsuperscript{239}. Recent findings show that miRNAs can also modulate the cell microenvironment, enabling immune escape and metastasis\textsuperscript{240,241}.

### 2.6. EBV is linked to NPC carcinogenesis

EBV related malignancies primarily arise from infected lymphocytes and epithelial cells, leading to lymphomas and carcinomas, respectively. The tumors are latently infected with EBV yet express distinct subsets of viral proteins that are contributing to growth, survival and immune evasion. In some of the viral cancers, viral proteins are barely expressed, but the viral small and miRNAs can alter growth by decreasing expression of negative regulators of cell growth such as tumor suppressors and cellular proteins that induce apoptosis\textsuperscript{242} (Picture 8).

In Southern China NPC is the third most common malignancy among men, where the incidence is approximately of 30–80/100,000 in the Cantonese region around Guangzhou, Province of Southern China\textsuperscript{9,243}. Genetic as well as environmental factors play a role in the cause of the disease\textsuperscript{1}. The disease is classified by World Health Organization (WHO) into three histological types: I, squamous; II, non-keratinizing; III, undifferentiated\textsuperscript{244}. Circular EBV is present in NPCs with a latency type II. High titers of serum IgA to EBV viral VCA and EA antigens have diagnostic value. Rise in IgA titers may be evident several years before the development of an undifferentiated NPC\textsuperscript{126}. The link between EBV and NPC was initially based on serological findings\textsuperscript{143,245}, and later confirmed by detection of viral DNA, RNA and protein in the tumor cells in situ using nucleotide probes and specific antibody reagents\textsuperscript{144,246,247}. High titer antibodies to VCA and early antigen especially of IgA class, or high titers that persist after therapy, where found to be associated with a poorer prognosis\textsuperscript{248}. Detection of EBV DNA in peripheral blood plasma is an important risk factor that indicates a significantly high likelihood of developing distant metastasis as well as poor survival\textsuperscript{249,250}. 
The pathogenesis of NPC involves 3 factors. First, early and repeated EBV infection and chronic triggering of aberrant viral replication by exposure to environmental factors like dietary components such as nitrosamines in salty fish; Secondly, loss of heterozygosity (LOH), usually occurring early in the NPC pathogenesis and possible induced by EBNA1 expression as outlined above, will produce low-grade pre-invasive lesions. Thirdly, accumulation of epigenetic and genetic lesions in key regulatory genes leading to loss of cell cycle control and enhanced survival\(^\text{138}\).

In EBV positive NPC and GC, the tumor cells carry monoclonal viral genomes, which indicates that EBV infection must have occurred prior to expansion of the malignant cell clone\(^\text{253}\). EBV infection has been detected both by EBER RNA in situ hybridization and by the presence of monoclonal EBV genomes in high-grade pre-invasive lesions (severe dysplasia and carcinoma in situ) in the nasopharynx, but not in low-grade disease\(^\text{203}\). Multiple genetic changes have been found in NPC, with frequent deletion of regions on chromosomes 3p, 9p, 11q and 14q and promoter hypermethylation of specific genes on chromosomes 3p (RASSFIA and retinoic-acid receptor B2) and 9p. Deletions of some chromosomal regions of low-grade dysplastic lesions from high-risk persons in the absence of EBV infection in those lesions, indicate that genetic defects may occur earlier than EBV infection. Therefore in the pathogenesis the genetic events caused by exposure
to chemical carcinogens might cause predisposition to subsequent EBV infection leading to NPC\textsuperscript{254}. Interestingly, recent data indicate that the EBV genome is more stably maintained in epithelial cells aberrantly expressing Cyclin D1, which may be an initiating event in the pathogenesis of NPC\textsuperscript{255}.

2.7. Immune response to EBV and evasion of the immune system by the virus

Infection of humans with EBV results in both lifelong humoral and cellular immunity to the virus. Although the finding of antibodies directed against virus structural proteins and the EBNAs is important for the diagnosis of infection, the cellular immune response is more important for the control of EBV infection. Natural killer cells and CD4+ and CD8+ cytotoxic T cells control proliferating EBV-infected B cells during primary infection\textsuperscript{168}. After recovery from acute infection, HLA-restricted cytotoxic T cells are important in controlling EBV, and CD8+ T cells are targeted both replicative and latent antigens. Many of the cytotoxic T cell responses directed against latent proteins are targeted to the EBNAA3 proteins controlling the potentially dangerous latency-III stage of infection\textsuperscript{168,256}.

The ability of EBV to persist, despite potent immune effector responses against it, indicates that the virus has evolved strategies to elude the immune system. EBV encodes a cytokine and a cytokine receptor that may be important for modulating the immune system to allow persistent infection. The BCRF1 protein mimics the activity of interleukin-10 by inhibiting interferon-\(\gamma\) synthesis by human peripheral-blood mononuclear cells in vitro\textsuperscript{257}. The EBV BARF1 protein functions as a soluble receptor for Colony-Stimulating Factor 1. Since Colony-Stimulating Factor 1 normally enhances the expression of Interferon-\(\alpha\) by monocytes, BARF1 protein may function as a decoy receptor or scavenger to block the action of the cytokine\textsuperscript{220,258}. Since interferon-\(\gamma\) and Interferon-\(\alpha\) inhibit the outgrowth of EBV-infected cells in vitro, the BCRF1 and BARF1 proteins may help the virus to evade the host’s immune system during acute EBV infection or reactivation of virus from latently infected cells.

EBNA1 has been shown to block its own degradation by proteasomes in the cell\textsuperscript{197}. Since viral proteins are normally broken down by proteasomes to peptides for presentation to cytotoxic T cells, the ability of EBNA-1 to inhibit its degradation may allow the protein to avoid triggering the activation of cytotoxic T cells. In addition, lytic phase proteins encoded in BGLF5, BILF1 and BNLF2a genes interfere with antigen processing and presentation in MHC-I avoiding elimination of cells that switch to virus production\textsuperscript{259–261}.

EBV encodes at least two proteins that inhibit apoptosis. The EBV BHFR1 protein, expressed early during lytic reactivation and some stages of viral latency is a homologue of the human Bcl-2 protein, which also blocks apoptosis\textsuperscript{262}, whereas EBV LMP1 up regulates the expression of several cellular proteins that inhibit apoptosis, including Bcl-2 and A20\textsuperscript{263}. In addition, LMP1 contains an immunosuppressive domain, which –upon LMP1 secretion–, can interfere with T-
cell activation. In vivo evidence for local evasion of cellular immune responses by NPC tumor cells is illustrated by induction of silencing Treg cells in the tumor, not present in the circulation. Together these data indicate that, although NPC tumor cells express potentially immunogenic viral proteins, the tumor cells exhibit several ways of evading these responses, resulting in extended survival and continued growth. However, raising the level and activity of anti-EBV immunity by vaccination or immunotherapy, may provide future options for intervention.

Humoral responses to EBV antigens are broad and strongly elevated, in both IgG and IgA classes. Predominant antigens recognized by these antibodies include the latent EBNA1 protein as well as EA, VCA antigens. High level neutralizing antibodies exist in NPC patients. It is considered that the humoral immune response to EBV antigens in NPC is reflecting antigen expression during tumor development, rather than being protective. However, these aberrant anti-EBV antibody responses are very useful in diagnosis of NPC, as outlined below.

2.8. EBV related laboratory tests

The fact that EBV is present and active in almost all NPC cases makes EBV an ideal tumour marker for NPC. Quantitative analyses of EBV antibodies and EBV DNA have been shown to be clinically useful for the early detection, monitoring and prognostication of NPC. Early detection is essential since patients with NPC usually enter the clinic with an advanced stage of disease decreasing therapy success rate. Population screening for high-risk individuals would allow the recognition of early-stage NPC. To aid the clinical diagnosis, early detection can be achieved by new EBV-based serodiagnostic tests and parallel molecular diagnostic tests. The viral markers could also be used for the prediction of recurrence in addition to monitoring therapy responses to guide the clinicians in decision making. A wide variety of diagnostic approaches for prediction, diagnosis and prognosis of EBV-associated diseases have been described.

2.8.1. Serodiagnostic approaches

The initial link between EBV and NPC was based on identification of EBV-specific serological abnormalities in NPC patients to viral antigens present in newly discovered Burkitt Lymphoma cells. In particular the presence of IgA antibodies to several EBV antigen complexes defines NPC patients, as confirmed in larger studies by the Henles. For diagnosis of acute versus past EBV infection and definition of EBV carriernesship in immunocompetent hosts EBV-specific serological testing is the gold standard. EBV-specific serology involves the analysis of antibody responses to distinct viral antigens, originally defined by patterns of immunofluorescent staining on Burkitt-lymphoma cells, comprising the viral capsid antigen complex (VCA), the EBV nuclear antigen complexes (EBNA) and the early antigen complex (EA), the latter divided into diffuse (EAd) and restricted
(EAr) complexes, with different serological implication. In recent years the molecular basis of EBV serology has been defined, gradually leading to replacement of the laborious and poorly reproducible immunofluorescence tests to more defined and reliable assays. Early serological studies in South-East Asia and Indonesia have shown that at age 5 nearly 100% of Indonesians are infected by EBV. Serological test consists of agglutination tests, immunofluorescence, immunoblot or enzyme immunoassays (EIA) and more recently automated and multiplex tests which allow accurate definition of acute or convalescent EBV infection.

At the time of acute infection IgM anti-VCA will arise first, followed by IgG anti-VCA and IgG anti-EA, with symptoms of primary infection and a positive heterophile test. After symptoms resolve around 2 months post infection, remote infection is characterized by persistent IgG-EBNA and VCA without IgG-EA, reflecting lifelong EBV carriage. IgG-EA may reappear without symptoms upon viral reactivation or EBV related neoplasia few years later.

For EBV related malignancies serology alone appeared not to be adequate for diagnosis. Although patients with EBV associated tumor shave often higher titers of IgG antibodies against EBV proteins, this is not always related to tumor presence and is not specific for malignancy as it can also be found in autoimmune disease, chronic EBV infections and other immune disfunctions. In contrast, NPC often associates with elevated levels of IgG-VCA antibodies, particularly against the lytic VCA-p18 protein and the EBNA1 protein, and IgA antibodies against early antigen (EA).

IgA antibodies against EBV antigens in serum of patients with NPC, reflect the tumor’s origin in the mucosa of the nasopharynx. The anti-viral capsid antigen IgA antibody (IgA-VCA), measured by indirect immunofluorescence or ELISA, is the most widely used antibody marker for diagnosis and screening. The preferred assay is based on ELISA, since the interpretation of the immunofluorescence assay is subjective and the technique needs expert skills. EBV-IgA testing, combining VCA with EBNA1 or VCA with EA antigens successfully used for defining high risk population of NPC and to evaluate prognosis and detection of recurrences after completion of therapy. The first mass-screening studies were performed in complete city populations in Southern China by Zeng Yi, followed by multiple large-scale studies confirming the use of IgA-VCA (and –EA) for NPC diagnosis. The sensitivity of EBV-IgA in the diagnosis of WHO type II and II NPC in areas both endemic and non-endemic for the disease has been reported to be 85-90%. The EBV-IgA markers frequently precede the appearance of NPC and may serve for early-stage NPC detection and possibly also serve as markers of remission and relapse.

Ji et al confirmed that elevation of the EBV antibody levels preceded the clinical onset of NPC by as much as prior to the clinical onset, and that the antibody level is subsequently elevated and maintained at high levels. Most IgG of healthy
EBV carriers recognize a restricted pattern of EBV proteins in immunoblot, which includes strong IgG reactivity against VCA-p18 and EBNA1. In many NPC patients IgA antibodies against EBV proteins are detectable, even before the carcinoma becomes clinically evident. These antibodies are reflecting the abnormal activity of EBV within the nasopharynx. Both IgA-VCA and IgA-EAd have been proposed for NPC follow-up monitoring post treatment.

![EBV Infection Kinetics](image)

**Picture 9.** with permission Cyto-Barr BV, Netherlands

### 2.8.2. Molecular diagnostic approaches

Next to the indirect serological assays for NPC detection, a direct measurement of NPC presence could be obtained by detecting and quantification of the viral genome within the tumor cells. EBV DNA levels in nasopharyngeal brushings from NPC patients are significantly higher than in brushing from healthy controls. NPC may be more directly reflected by elevated viral DNA levels plus carcinoma-specific viral transcriptional activity at the site of the primary tumor, this hypothesis is analyzed in recent reports, showing elevated EBV DNA loads in NP brush samples in NPC patients using non-standardized PCR techniques.

Patients with active infection or EBV-related cancer tend to have high levels of EBV DNA in the cell-free fraction of blood (plasma or serum), whereas in healthy carriers the virus is restricted to the intracellular compartment of the blood. Quantitative EBV DNA measurement is essential for differentiating the low-level infection of healthy carriers from the high levels characteristic of EBV-related disease.

EBV DNA levels began to rise within 2 weeks after primary infection after which the viral load declines to nearly undetectable levels. In most EBV infected healthy individuals EBV DNA is undetectable in plasma or serum or remains low positive for life. The viral DNA load will increase according to the development of
EBV related malignancy, decreases after treatment rapidly, and showed elevated levels again if the tumor relapsed. Most clearly this is seen in transplant recipients developing EBV-driven PTLD, where DNA viral load in whole blood showed, rising levels prior to diagnosis and clinical relapse, and declining levels indicate success of treatment\textsuperscript{295–297}.

EBV viral load and circulating free EBV DNA is a marker of tumor burden in NPC patients where it is useful for diagnosis, prognostication and monitoring of the disease in response to therapy\textsuperscript{249,269,298–300}. Plasma EBV DNA appears more sensitive and reliable than whole blood cell EBV DNA for diagnosis staging and therapeutic effect evaluation at a molecular level in NPC clinical practice\textsuperscript{133,269}. Levels of plasma EBV DNA may rise before clinical diagnosis, implying that screening in high-risk groups, might be beneficial for early-stage NPC detection\textsuperscript{132,193,301–304}.

The detection of plasma EBV DNA might directly reflect tumor growth and decline\textsuperscript{130,305,306}, and has proven to be an important and sensitive index in diagnosing the residual and relapse of NPC\textsuperscript{129,301,302}. Successful therapy is marked by a decline to baseline, and rising levels may serve as a relapse\textsuperscript{305}. The increased number of EBV DNA copies in blood during the initial phase of radiotherapy suggests that viral DNA was released into the circulation after cell death\textsuperscript{193,300}. The plasma EBV DNA load may improve the accuracy of diagnosing NPC in high-risk individuals, but it appears to have limited value in screening patients who have early stage NPC and predicting NPC development\textsuperscript{307}.

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NASOPHARYNGEAL CARCINOMA BOOK WRITING IN INDONESIA

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INTRODUCTION

Nasopharyngeal Carcinoma Book (KNF) Head Surgery Study Oncology Group
The security neck of all Kodi members and multidisciplinary other sciences such as radiotherapy, radiology, anatomical pathology, clinical nutrition, and hemato-oncology.

The KNF book here is complete by the end of 2018 and startmultiplied in 2019 and will be translated in 2019.

KNF BOOK WRITING GUIDE:

1. Title
   - Made in Indonesian.
   - The use of abbreviations or formulas should be avoided.
   - The term foreign language is written in italics (italic).
   - Title is written in Times New Roman with a size of 14 single spaces and bold.
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2. Author's name
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3. Heading
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4. Bibliography
   Written according to Vancouver's writing method. Bibliography is identified in a script with Arabic numerals and given a serial number in accordance with the order of appearance in the text. All authors' names are included, if there are more
than 6 authors, the names of the first 6 authors are followed by et al. Bibliography is limited to a maximum of 30.

Example of writing a bibliography:


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5. The manuscript
Submitted in CD form and typed using the Microsoft Word program with Times New Roman font size 12 with a space of 1.5 or via email to oncologyhnsstudygroup@yahoo.co.id.

6. Paper size
Paper size is A4 (20.99 x 29.69 cm)
- Pitch (margin) above: 4 cm from the edge of the paper
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7. Space
- The distance between lines is 1.5 spaces.
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METHODS OF NPC EARLY DETECTION AND SCREENING IN INDONESIA

Sagung Rai Indrasari, Camelia Herdini

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Nasopharyngeal carcinoma has a unique and striking geographical distribution throughout the world. Although rare in most regions, it is very common in Southern China and South East Asia. In Indonesia, the estimated incidence of nasopharyngeal carcinoma is 6.2 per 100,000 population. Undifferentiated carcinoma (WHO type III) is the most common type of NPC and among the five most prevalent cancers overall. Due to unspecific symptoms and the hidden localization of the primary tumor at the early stage, more than 80% of the patients come to the hospital at a late stage (III or IV), when they already have metastasis in the cervical lymph node. Whereas late-stage disease has a poor prognosis and requires combined chemo-radiotherapy, early stage NPC may reach complete remission by radiotherapy. Therefore, treatment results tend to be poor. For this reason, a screening program to detect nasopharyngeal carcinoma at an early stage will be crucial for decreasing disease burden and increasing treatment efficacy. The success of screening depends on the availability of specific tests and the existence of a well-defined population at high risk for developing the disease.

Epstein Barr Virus (EBV) has long been implicated in the pathogenesis of NPC. Old et al. first made the association of EBV with NPC using immunodiffusion when patients with undifferentiated NPC showed elevated immunoglobulin G (IgG) and immunoglobulin A (IgA) antibody titers against EA-D (early antigen-diffuse) and VCA (viral capsid antigen). Using in situ hybridization techniques, EBV DNA has also been confirmed in NPC tumor cells.

The close relationship between EBV and nasopharyngeal carcinoma is highlighted by the presence of viral DNA, RNA, and protein in all tumor cells, viral reactivation and the aberrant antibodies against EBV antigens in patient sera. Aberrant antibodies against EBV antigens such as viral capsid antigen (VCA), DNase, early antigen (EA), and EBV nuclear antigen 1 (EBNA1) have benefit in clinical diagnosis. Aberrant seroreactivity in nasopharyngeal carcinoma is detectable prior to onset of clinical manifestation of the disease. Studies in China and Taiwan have shown the feasibility of using EBV serology as a predictive marker for disease development.

Although EBV is the strongest risk factor for NPC, there are additional exogenous factors, which are also closely linked with the malignancy. Food such as salted fish, other preserved foods, and herbal medicine have been linked to nasopharyngeal carcinoma but not consistently. Several compounds in food have...
been demonstrated to induce in vitro EBV reactivation suggesting their capability of initiating enhanced in vivo virus replication. Furthermore, tobacco smoke, passive smoke, alcohol consumption, occupational dust, and other inhalants are among environmental factors related to nasopharyngeal carcinoma.

A family history of nasopharyngeal carcinoma has also been associated with increased risk of the disease. First-degree relatives of patients have 6- to 19-fold excess risk of developing the disease compared to those without a family linkage. This effect observed among cases is the strongest compared to other cancers. An increased risk for EBV-associated nasopharyngeal carcinoma and other infectious agent-related cancers were recorded among families with a history of nasopharyngeal carcinoma especially among the multiplex cases. This suggests an increased frequency for viral reactivation among family members of EBV-associated cases. Aberrant EBV reactivation among family members was also indicated by studies on EBV immunoglobulin A (IgA) detection in the sera among core family members of cases. These studies indicate that both genetic and environmental factors responsible for the aberrant EBV IgA are shared in the family.

Because involvement of both genetic and environmental factors in carcinogenesis has been proposed, it is reasoned that healthy individuals from families with members affected by nasopharyngeal carcinoma might have an EBV antibody profile that is distinct from that seen in healthy individuals from the community at large. A peptide-based ELISA has been developed for measuring EBV IgA in (dried) blood samples, allowing finger prick sampling on paper filters, that may serve as tool for early screening. The first step to define the usefulness of this assay in a screening approach is to validate it in families with nasopharyngeal carcinoma cases versus controls without a family history.

Recently, an EBV IgA ELISA is developed based on a combination of VCA p18- and EBNA1-derived synthetic peptides which is routinely used as an NPC diagnostic test in Sardjito Hospital, Yogyakarta, Indonesia. This EBV IgA ELISA combines the separate features of IgA VCA and IgA EBNA1, each of which has its value in NPC diagnosis. The combination of these markers in a single assay provided sensitivity and specificity of 85.4% and 90.1%, respectively. The presence of NPC-related serological abnormalities can be confirmed by immunoblotting to reveal the spectrum of antibody responses, which has diagnostic value by itself. The combined EBV IgA ELISA and immunoblot assay showed increased sensitivity and specificity and positive predictive value (PPV) and negative predictive value (NPV) of more than 95%. Because immunoblot studies revealed a diagnostic value of multiple EBV proteins, in particular certain EBV-EA markers, a separate IgA EA ELISA using native EA proteins is developed. In addition to their role in primary diagnosis, anti-EBV IgA responses, in particular the IgA EA response, also have a distinct role for posttreatment follow-up monitoring, as declining responses correlate with a good prognosis and
increasing responses are related to persistence of relapsing tumor. The availability of two distinct and biochemically well-defined EBV IgA ELISA systems addressing responses to different EBV antigens for NPC specific serology may add to further standardization.

Universitas Gadjah Mada now is developing a rapid test tool for NPC screening, namely NPC G Strip. This tool works by detecting immunoglobulin G (IgG) antibodies in the blood or serum or plasma of patients who then react with the protein Epstein Barr Virus (EBV), especially the early antigen (EA) that has been attached to the strip. The method used in this examination is known as the immunochromatography method. Antibodies to EBV protein are used as markers for several malignancies, one of which is NPC. The use of EA in the manufacture of NPC Strip G because the molecular size of this protein complex is quite large, so that it can be mobilized in the pores of the membrane strip. NPC Strip G requires only 10ml of blood from a fingertip prick or using 2ml of blood serum or plasma which is then placed on the strip using a loop, then the strip is dipped into the buffer and waited for 3 minutes for the value of the result. If two lines are formed, it indicates that the EBV IgG titer in the patient is above normal. This is not necessarily that the patient is suffering from NPC, but the patient can be referred to ENT Specialist for further examination such as nasoendoscopy and CT scan. If there is a suspected tumor in the nasopharynx followed by nasopharyngeal biopsy to get the right histopathology. But if there is no clinical abnormality, then the NPC Strip G examination can be repeated every 6 months for 2 years.

For a screening program to be successful, not only must it be applied to a disease with characteristics appropriate for screening, but also a suitable screening test must be available. This NPC Strip G appears to fulfill some of the criteria as a screening tool. It is relatively inexpensive, easy to administer and imposes minimal discomfort on the screening. A screening test must also be valid, reliable and reproducible.

In conclusion, screening should be focused on populations at high risk of developing NPC. These high-risk groups include individuals with; (1) There are one or more cases of NPC in the family, (2) Specific chronic complaints in the head and neck area, and (3). Environmental related risks (diet and non-diet).

Treatment outcome of nasopharyngeal carcinoma is stage-dependent. Up to 85% cure can be achieved for early stage of disease whereas the cure rate is 30% for advanced disease. There is no good evidence currently supporting or against NPC screening but we hope to detect the disease at an early stage and improve the cure rate.
REFERENCES


INTRODUCTION

Nasopharyngeal carcinoma (NPC) is the most common head and neck cancer. NPC is a cancer that grows on the posterior nasal cavity and palate. The area with a high risk of developing the NPC is mainly Southern China, Southeast Asia, the Southwest of India, North Africa, Eskimo, and Alaska.\(^1\)

NPC is considered one of the most common cancers in Indonesia, placing 4\(^{th}\) after cervical cancer, breast cancer, and skin cancer, also the most common cancer of the head and neck region. NPC derived from the fossa Rosenmüller where the transitional zone of the cuboidal to squamous epithelium exist.\(^1\)

Statistical data showed that the Chinese ethnic has the highest incidence rate. The prevalence rate in Singapore is 15/100,000 populations, 9.7/100,000 populations in Malaysia, 7.5/100,000 populations in Vietnam, and 6.4/100,000 populations in The Philippines. NPC ranked 4\(^{th}\) in Indonesia.\(^2\)

METHOD

This is a descriptive study to map the demography and epidemiology of NPC patients in Sanglah Denpasar General Hospital dated 1\(^{st}\) January up to 30\(^{th}\) September 2018. The population and sample of this study is all the NPC patients who came to ENT clinic within 1\(^{st}\) January - 30\(^{th}\) September 2018. The data will then be presented descriptively with table and narration.

RESULTS

Within 1\(^{st}\) January to 30\(^{th}\) September 2018, 53 cases were reported which suited the inclusion criteria. The statistical data showed that range of the NPC patients is 18-72 years old, majority are the patients age 51-60 (33.96%), while the lowest are 11-20 years old (3.77%). The youngest patient is 18 years old and the oldest is 72 years old. Men consists of 36 people (67.92%) and women 17 people (32.08%).
Table 1. Age and Gender

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Graph 1. Range of Age
Bali province consists of 8 districts which are Badung, Tabanan, Gianyar, Buleleng, Karangasem, Jembrana, Klungkung, Bangli, and Denpasar. This study categorized the data based on the districts in Bali and outside of Bali. Majority of patients were from Bali, 14 people (21.41%) and the lowest rate is from Bangli District and Klungkung District both only 2 cases (3.77%).

<table>
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Graph 3. Demography

Picture 1. Demography Mapping
DISCUSSION

NPC is a cancer that grows on the posterior nasal cavity and palatum of mouth. The area with a high risk of developing the NPC is mainly Southern China, Southeast Asia, the Southwest of India, North Africa, Eskimo, and Alaska.¹

The statistical data showed that range of the NPC patients is 18-72 years old, majority are the patients age 51-60 (33.96%), while the lowest are 11-20 years old (3.77%). The youngest patient is 18 years old and the oldest is 72 years old. Men consists of 36 people (67.92%) and women 17 people (32.08%). Statistical data showed that the Chinese ethnics has the highest incidence rate. The prevalence rate in Singapore is 15/100,000 populations, 9.7/100,000 populations in Malaysia, 7.5/100,000 populations in Vietnam, and 6.4/100,000 populations in The Philippines. NPC ranked 4th in Indonesia.²

According to the data in Cipto Mangunkusumo Hospital, there were 6,000 cases of malignancies of Head and Neck recorded within 1995-2005. Among them there were 1,121 cases of NPC, consisting of 789 men and 332 women.²

NPC patients in several countries have the range of 4-91 years old with the peak incidence 50-60 years old. Loh et., al., showed that the highest prevalence rate of NPC in China is those who were 50-60 years old.³

CONCLUSION

This study consists of 53 people, 36 men (67.92%) and 17 women (32.08%), majority age groups is 51-60 years old (33.96%), while the lowest rate are 11-20 years old group. (3.77%). The clinical signs that mostly manifested is the swelling of neck (30.18%). Patients mostly are from Denpasar (21.41%).

Demography pattern of the NPC is important to understand the epidemiology and spreading of NPC in Bali Province and can be use as the early detection of NPC.

REFERENCE

ANATOMY AND PHYSIOLOGY OF NASOPHARYNX

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ANATOMY

Pharynx is an irregularly tubular structure, extending from base of the skull base to the esophageal inlet, pharynx has anterior opening into the nasal and oral cavities, inferiorly it open into the larynx and esophagus. Pharynx consist of three segments; Nasopharynx, Oropharynx, and Hypopharynx. There is a three Pharyngeal muscles begin from Superior constrictor is suspended from base of the skull, medial pterygoid plate, Pterygomandibular raphe, Mylohyoid line of the mandible, and the lateral of tongue, Middle constrictor muscle anterior attaches to hyoid bone and stylohyoid ligament, also Inferior constrictor attaches to the thyroid & cricoid cartilages.

Nasopharynx is an nasal part of the pharynx that continuous anteriorly through the choanae with the nasal cavities, is an open cuboidal chamber that lies beneath the base of the skull at the posterior aspect of the nasal fossa. It measures 4.0 to 5.5 cm transversely and 2.5 to 3.5 cm in the anteroposterior dimension and is roughly 4.0 cm in height. The close proximity to the nose and pharynx plus its connection with the middle ear via eustachian tube, identify the nasopharynx as the central hub around which the specialty of otorhinolaryngology revolves. Region of the nasopharynx according to UICC in 1963 Anteriorly, it borders the posterior nares, within which lie the posterior ends of the middle and inferior turbinates. The roof is a sloping concave surface formed by the posterior body of the sphenoid, basilar component of the occipital bone, and anterior arch of the atlas. The nasopharyngeal tonsil lies in the midline in the roof and posterior wall. The superior pharyngeal constrictor and fascia complete the posterior wall. The floor of the nasopharynx is composed of the soft palate. The lateral walls contain important structures such as the pharyngotympanic tube, situated 10 mm behind and slightly below the level of the posterior part of the inferior turbinate. The lateral walls consist of only two layers: the mucous membrane and the pharyngeal aponeurosis. The cartilaginous eustachian tube passes through this aponeurosis, opening into the fossa of Rosenmüller. Lateral to the lateral wall, the mandibular nerve exits the foramen ovale into the infratemporal fossa. Posterior to the eustachian tube is the retroparotid space, which contains the pharyngeal lymph nodes, internal carotid artery, internal jugular vein, and glossopharyngeal, vagus, spinal accessory, and hypoglossal nerves as well as the cervical sympathetic nerve.
Understanding the relative contents and locations of the foramina surrounding the nasopharynx allows the clinician to predict the extent of tumor spread based on cranial nerve examination. Six foramina are adjacent to the wall of the nasopharynx: (1) foramen lacerum, (2) foramen ovale, (3) foramen spongiosum, (4) carotid canal, (5) jugular foramen, and (6) hypoglossal canal. The foramen lacerum and the foramen ovale offer little resistance to tumor spread into the cranium, and their close proximity to the cavernous sinus and cranial nerves II, III, IV, and VI explains the frequency of cranial nerve palsies at diagnosis. The lymphatics of the nasopharynx drain either through direct efferent channels to the deep lymph nodes of the posterior triangle or first through the lateral pharyngeal wall to the retroparotid or lateral pharyngeal lymph nodes and then on to the upper jugular chain. Some channels may pass directly to the jugulodigastric chain. Lymphatic channels often cross the midline and offer ready access to both sides of the neck.\textsuperscript{1,2}

**PHYSIOLOGY**

The nasopharynx is not, as is commonly supposed an immobile entity, is only a small area anterior to the Eustachian tube orifices which has rigid bony walls. Vigorous contractions even in the areas of the tubal eminence and the fossa of rosenmuller, below this level the nasopharynx is a muscular tube, constantly participating in active contraction during swallowing and speech especially in the region of the isthmus.\textsuperscript{1,2}
NASOPHARYGEAL WALL

The wall of nasopharynx are composed of the muscular, Fibrous, mucosal layer. The Muscular layer comprises outer oblique and inner longitudinal component derived from the superior constrictor muscle. Between the upper edge of the muscle and the base of the skull, the muscular layer is absent, the deficiency being strengthened by a thickening of the fibrous layer. The Fibrous Layers comprises two layers which provide an outer and inner lining for the constrictor muscles. Both layer are continuous with the general fascia of the neck. Outer layer or buccopharyngeal fascia covers the superficial aspect of the superior constrictor muscle. The inner component or pharyngeal aponeurosis, which lies between the mucosal layer and the contrictor muscle is part of the pharyngobasilar fascia. Both fascial layers unite at the upper edge of the superior constrictor muscle and ascend towards the base of skull as a single entity.1,2,3

The mucosal layer, in adult nasopharynx is lined mainly by pseudostratified columnar ciliated mucosa near the choanae and adjacent part of the roof. While the lower and posterior regions of the nasopharynx, the lining assumes a stratified squamous character. Areas of transitional epithelium are encountered at the junctional zone located on the roof and lateral walls. The lamina propria is frequently infiltrated by lymphoid tissue, while the submucosal layers contains serous and mucous glands.1,2,3

SPECIAL FEATURES

Pharyngeal Tonsil is detectable beneath the mucous membrane at the junction of the roof and posterior wall of the nasopharynx. Rapid hypertrophy takes place in early childhood followed by gradual regression after the age of 8-10 years. The lymphoid mass is triangular in shape with the apex pointing towards the posterior free margin of the nasal septum, the surface is irregular with several prominent ridges interrupted by deep furrows lined with epithelium. The lymphoid follicles embedded beneath the surface epithelium contains T and B lymphocytes,
reticular cells and fibroblasts. Large adenoid masses may extend laterally into the fossa rosenmuler.\textsuperscript{2,3,4}

Torus Tubarius, the pharyngeal orifice of the Eustachian tube lies 1 - 1.25 cm behind and below the posterior end of the inferior turbinate. The orifice is partially shielded especially on its posterior and superior aspects, by prominent comma shaped elevation termed the Eustachian cushion which is formed by the medial extremity of the cartilaginous part of tube. The Eustachian tube 3 to 4 cm in length runs laterally and backwards from the nasopharyngeal orifice to the tympanic cavity. The anteromedial two third are composed of cartilage and connective tissue whereas the posterolateral one third is bony. The cartilaginous segment occupies a groove between the greater wing of sphenoid and the petrous temporal bone. The cartilage of the tube is elastic in type and has the shape of an inverted U, the inferior deficiency being closed by connective tissue. The cartilaginous portion of the tube is lined by pseudostratified columnar ciliated epithelium while the bony segment has non ciliated cuboidal epithelium.\textsuperscript{2,3,4}

Fossa rosenmuller, immediately above and behind the tubal elevation lies the pharyngeal recess or fossa rosenmuller. It extends laterally into the sinus of Morgagni immediately above the upper limit of the superior constrictor muscle of the pharynx. The fossa is variable in size and depth and is conical or slit-like in shape. Usually occur bilaterally, one such diverticulum measured in 2.5-3 cm in vertical height and 2.5 cm in depth. In large diverticula the lining may appear smooth or granular and varying degrees of epithelial metaplasia may be evident on histological examination. The fossa rosenmuller is of great importance since it represents by far the commonest site of origin of the nasopharyngeal carcinoma. More over its inaccessible location underlines the problems of the otolaryngologist in performing a thorough examination of the area. Relations of the fossa as tumour spread generally radiates from the fossa of rosenmuller the anatomical relations are the great clinical significance, anteriorly is Eustachian tube, anterolateral levator veli palatini muscle, posterior is retropharyngeal space, superior is foramen lacerum, medialy the petrous apex and carotid canal, posteriorly the foramina ovale and spinosum anterolateraly, Lateral is tensor veli palatine muscle, pharyngeal space, inferior is superior constrictor muscle. The close proximity of the fossa to the foramen lacerum and other important structures at the skull base readily accounts for the ease and rapidity with which tumour can spread and cause serious neurological complications.\textsuperscript{2,3,4}
IMPORTANCE COMPARTMENT

The Formation of a number of compartments which are of great importance to the clinician. The Retropharyngeal space lies behind the nasopharynx separating it from prevertebral (alar) fascia. The firm midline attachment between the buccopharyngeal fascia and the prevertebral (alar) fascia divides the space into two segments. Laterally the space is sealed by the attachment of both these fascial layers to the carotid sheath. The space is of special importance in as much as it contains the median and lateral groups of retropharyngeal lymph nodes, including the node of Rouviere. The Parapharyngeal space is triangular on cross section and lies immediately lateral to the pharynx, extending from the base of skull above, to the superior mediastinum below. In its upper part, it is related laterally to the ascending ramus of the mandible and medial pterygoid muscle in front and to the parotid gland further back. The space is sub divided into two compartments by the styloid process and attached muscles together with the fascial connection between the carotid sheath and prevertebral (alar) fascia. The Prestyloid compartment is related in its upper part to the lateral wall of the nasopharynx and fossa rosenmuller and contains the maxillary artery and inferior dental, lingual and auriculo temporal nerves. The retrostyloid compartment is more deeply placed and contains the carotid sheath and its contents, the upper deep cervical lymph nodes, the cervical sympathetic chain and the last four cranial nerves. ¹
BLOOD VESSELS, NERVES AND LYMPHATICS

The major arteries supplying the nasopharynx ascending pharyngeal, ascending palatine, descending palatine, and pharyngeal branch of the sphenopalatine. All originate from external carotid artery and its various branches. A venous plexus situated beneath the mucous membrane communicates with the pterygoid plexus superiorly and the posterior facial or internal jugular veins below.

The sensory nerves supply of the nasopharynx including the posterior part of soft palate, is derived from cranial nerves IX excepting an ill defined area of the nasopharyngeal roof adjacent to the tubal orifices which is supplied by cranial nerve V through its maxillary division. The glossopharyngeal component is mainly derived through several small branches, including a communicating twig from the tympanic branch of the nerve which follows the course of the greater superior petrosal nerve. The supply to the upper surface of the soft palate and adjacent nasopharynx comes directly from the glossopharyngeal nerve as it descents in close proximity to the tonsillar fossa.

The trigeminal component leaves the maxillary division of the nerve in the pterygopalatine fossa and after traversing the pterygopalatine ganglion, it enters the tiny palatinovaginal canal to reac the roof of the nasopharynx. The motor innervation is supplied by way of the pharyngeal plexus, comprising cranial nerves IX and X together with branches of the cervical sympathetic. The main innervation to the pharyngeal musculature is derived from the cranial root of the XI nerve passing via cranial nerve X. The nasopharynx is site of a marked aggression of lymphoid tissue, concentrated mainly in the pharyngeal tonsil, which form part of the lymphoid ring of waldayer. The drainage area of the middle collecting trunks includes the soft palate and palatine tonsils but it may extend upwards as far as the Eustachian tube orifice. The lymphatic channels run outwards traversing the lateral wall of pharynx to terminate in the lateral retropharyngeal node. The retropharyngeal nodes are located in the retropharyngeal space between the posterior wall of the
nasopharynx and the prevertebral fascia. They are prominent in the newborn and in early childhood but tend to atrophy with age and some nodes may disappear by adult life. They comprise two group, median and lateral, the medial retropharyngeal nodes are of limited importance being inconstant and often absent in adulthood. They consist of one or two small applied directly to the posterior surface of the nasopharynx lying in the course of the median group of collecting trunks. The lateral groups of nodes is larger and more constant than the median group usually consist of a single node on either side often referres to as the node of rouviere.¹

**ROUTES OF TUMOUR SPREAD**

The direction of spread is partly dependent on the site of origin of the neoplasm but in large tumours this may be difficult to determine. Tumours arising near the midline may spread to one or other side but more often spread bilateraly. Tumours of the lateral wall however also occasionaly transgress the midline so that bilateral or even contralateral spread may occur. Intralumenary expansion is common and as the growth enlarges it may spread from the nasopharynx into the pharynx into the nose causing resorption of adjacent tissue with occasional destruction of the palate, maxillary sinus or orbit.

Retropharyngeal space is frequently the first route spread. Lymphatic spread to the node of rouviere is commonest but direct invasion also occurs. Further extension of the tumour may result in compression or infiltration of the retrostyloid space and its contents or destruction of the lateral mass of the atlas vertebra. Parapharyngeal space is compose of prestyloid compartment, normaly taken place by direct extension of the tumour. Disturbances of the sensory root of the trigeminal nerve followed later by motor root may become evident. Trismus is also encountered due to invasion of the ptregoid muscles while asymmetry of palate in the resting position due to infiltration of the levator muscle is frequently encountered. Facial paralysis due to damage to cranial nerve VII is rare. Further spread of the tumour may take place to the palate, sinuses, parotid gland, the pterygomaxillary fissure and the infratemporal fossa while very large tumours may invade the maxillary or frontal sinuses.²,³,⁴

Retrostyloid Compartment, invasion of the retrostyloid space by direct or lymphatic spread may result in paralysis of the last four cranial nerves and the cervical symphatetic chain. The internal carotid artery and jugular vein may also be compressed or infiltrated. Upward spread from the parapharyngeal space may lead to erosion of the base of skull, including sphenoid body and sinus, foramina ovale, spinosum and roundum also the greater wing of the sphenoid. In extensive growths tumour deposits may penetrate the pterygoid muscle and gain acces to the infratemporal fossa. Further migration by this route into the orbit and maxillary sinus is possible. Downward extension of the tumour result in invasion of the palate causing associated ear problems, and the parotid and submandibular salivary glands may also be infiltrated.²,³,⁴
REFERENCE
CLINICAL PRESENTATION AND DIAGNOSIS OF NASOPHARYNGEAL CARCINOMA

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is unique in its epidemiologic pattern. It is common in certain ethnic groups. The risk factor for NPC are genetic, environment and EBV infection. Eighty percent patient come in a late stage. The symptoms depend on tumor expansion. Symptoms can be nasal obstruction, epistaxis and bloody saliva. Superior expansion reveals neurologic complain such as diplopia, ptosis and dysphagia. Otitis Media with effusion caused by lateral expansion of nasopharyngeal carcinoma. The most common symptoms is palpable neck lump caused by metastasis of the cancer to neck lymph node. The gold standard for NPC diagnosis is nasopharyngeal biopsy.

INTRODUCTION

Nasopharynx is posterior to the nose and the upper part of the pharynx. The superior part borders are the base of the brain and the posterior is the cervical vertebra. Because of the Capacity for tumor growth in nasopharynx, the space also difficult to see without endoscopic, patients generally come in an advanced stages. These tumors usually reach a certain size before causing symptoms in the patient. Almost all patients with nasopharyngeal carcinoma have symptoms at the time of diagnosis, only 1 percent of the cases detected are accidentally when the patient checks for periodic check ups or during imaging examinations that show the presence of masses in the nasopharynx.1

PREVALENCE

Nasopharyngeal carcinoma are found in certain ethnic groups. This cancer often occurs in China and Hong Kong. The highest incidence of nasopharyngeal cancers found in Guang Zhou China with prevalence rates is 30/100,000 population, in Hong Kong 20.2/100,000 in men and 7.8 / 100,000 in women. In China, most are from Cantonese and Fujians ethnic, while in Hong Kong the most are Cantonese. In Singapore the prevalence of NPC patients is 10.8/100,000 population. In the past 10 years, the incidence of nasopharyngeal cancer began to decline, this is associated with changes in diet.1,2

Nasopharyngeal cancer is rare in white people. Seventy-five percent of NPC patients are male. More than 80% of cases are between 30-60 years old.1 In
Indonesia Nasopharyngeal carcinoma is the highest malignancy of the head and neck cancer.

**ETIOLOGY**

The main factors related to nasopharyngeal cancer are genetic factors, environment and Epstein Barr Virus infections.\(^1\)\(^2\)

*Genetic and nasopharyngeal carcinoma*

Many studies revealed a link between genetic factors and nasopharyngeal cancer (NPC). Ung et al, confirmed that NPC patients who have a family history is 15.5%, have a probability 8 times higher than the normal population without a history of NPC. Sibling have a 70% higher risk compared to 30% for parents and children. The presence of NPC patients in the family group is said to have the same genes, but some argue because they are also affected by the same environment. \(^1\)

The Incidence of NPC in the Chinese population in the United States shows influential environmental factors. These factors are related to modified diet, especially in children's, ventilation, occupational exposure to dust and smoke. Dymethyllnitrosamine in salted fish causes upper respiratory tract cancer in studies with mice.\(^2\)

*Human Leucocyte Antigen (HLA) and nasopharyngeal cancer*

The relationship between HLA and nasopharyngeal cancer has been presented since 1975. The human leucocyte antigen is HLA class I, including HLA A, B and D groups on chromosome 6. HLA A2, Bw46, B17, Bw58, DR3 and DR 9 are obtained by a significant amount of nasopharyngeal carcinoma with the highest risk was found in people who had high HLA A2 and Bw46. Most patients with Chinese races with NPC have predominantly HLA A0207, which is different from the dominant white people who have HLA A0201.\(^1\)

*Genetic Changes and Chromosome*

Studies shows that Chromosome changes are loss of chromosomes 3, 9 and 11. The loss of chromosomes causes loss of certain functions such as chromosome 9p21 which functions as a regulator for cell cycle development such as p15 and p16. P 16 itself is not active in NPC patients.\(^1\)\(^2\)

*Environment Factor and NPC*

The most influential environmental factor is the high diet of preservatives like salted fish. Carcinogens in salted fish are nitrosamines. Other environmental factors are wood dust and chemical substances. Some literature reveals the link between smoking and NPC and is associated with higher cancers of squamous cell carcinoma and not with differentiated carcinomas.\(^2\)
EBV is an encapsulated herpesvirus. Infection occurs in children or adolescents. Infection in children can be asymptomatic, but infection at adolescence will have symptoms. The symptoms are like mononucleosis. Once the man is infected with EBV, he will be immune to this infection, but EBV is present in B lymphocytes for life and is transmitted through saliva. Immunoglobulins M and G will increase in the acute phase. The antigen in this virus is the Early Antigen (EA) and Viral Capsid Antigen (VCA). In patients with NPC, IgA VCA and EA increase and are used as tumor markers. EBV antigen is also found in nasopharyngeal cancer cells both lytic and nuclear antigen. Lytic antigens include LMP1, 2 and 3. Nuclear antigen is Epstein Barr Nuclear Antigen (EBNA) 1 to 6. Both EBNA 1 and LMP1 are always expressed in significant amounts. EBNA functions to maintain viral episomes in tumors and LMP 1 plays a role in increasing cell growth. NPC patients also always express Epstein Barr Encoded Ribonucleosid Acid (EBER) in the cytoplasm. These antigens and EBERs are not obtained in normal nasopharyngeal cells.1,3

CLINICAL PRESENTATION AND NASOPHARYNGEAL CARCINOMA

Symptoms of nasopharyngeal cancer are neck lumps, blood in the saliva, epistaxis, nasal obstruction, hearing loss and cranial nerve disorders.

The most common symptom in nasopharyngeal carcinoma is a neck lump. Sixty percent of patients come to the doctor with this complaint. This neck lump is a metastasis or spread of this tumor in the neck lymph nodes. Lymph node metastasis usually has the upper part of the neck and posterior neck (at level II and level V), it also can be seen on level III and rarely at level IV. Some literature mention NPC with the spread of lumps in the parotid lymph nodes. Sometimes there is central necrosis of the lymph nodes and is followed by the formation of abscesses in the gland. NPC patients who come on treatment usually have 80% have metastasis in the lymph nodes, because there are 20 percent of the glandular metastases that are not palpable but detected on imaging such as CT scans.1
The second most common symptom is blood saliva. Epistaxis was also reported in 23% of patients. Another symptom is feeling full in the ear and hearing loss. This is due to impaired tubal function due to the closure of the fallopian tubes by the tumor and will form fluid in the ear and up as conductive hearing loss. With the tuning fork examination, it is found that there is a weber lateralization to the affected ear and the negative rhinne on the affected side. On otoscopic examination, there is an air bubbles in the tympanic membrane. Tympanometry examination shows type B.¹

Persistent headache complaints were also found in patients with intracranial extension or clivus erosion. Cranial nerve paralysis is found in 10 percent of cases. The nerves that are often affected are nerves to 5, 6, 9, 10 and 12. In endemic areas such as in China, if there is a strabismus cause by nerve VI disorders, nasopharynx should be evaluated with an endoscope and CT scan to evaluate the presence of NPC.¹

Endoscopic examination shows an exophytic mass in the nasopharynx area. But in 10 percent of cases, NPC is submucosal and nasopharyngeal appearance can be within normal limits or only slightly irregular. In endemic areas, patients with neck lumps, blood-mixed saliva, unilateral deafness should be considered the possibility of NPC and will be evaluated to look for the presence of NPC until it is proven not NPC.¹

Pain in NPC is obtained due to compression of trigeminal nerve because the tumor erodes the bones and base of the brain. Pain is usually in the face, occipital and temporal areas. Pain when lifting the head is felt by the patient if the tumor has infiltrated the prevertebral muscles.²
CLINICAL INVESTIGATION

Computer tomography Scan (CT-Scan) can show the nasopharynx, clivus and basic erosion of the brain. Magnetic resonance imaging (MRI) is superior compare with CT scan because it can better to see soft tissue changes and see intracranial involvement. When looking at the MRI, radiologist should be able to look to extension nasopharyngeal cancer to superior border: to the cavernous sinus, meninges, the foramen laserum, rotundum and ovale. Posteriorly, they should assess the clivus and sphenoid. To the Anterior part, they should investigate Involvement in the sinuses, To the lateral expansion, investigate the pterygopalatine fossa, and the infratemporal fossa involvement. The retropharyngeal gland is assessed and assessed as a central neck gland that is classified as N1 and also assesses the supraclavicular and mediastinal glands and axilla.¹

Chest X ray, liver ultrasound, and bone scan should be performed to see distant metastases. The most common metastasis is bone. Positron emission therapy (PET) has been widely used to assess local, regional and metastatic tumors, but PET cannot replace the superiority of MRI which can see the meninges, foramen in skull base. Positron emission therapy will be very useful when combined with MRI.

Audiogram and tympanometry examination is performed as a basic examination, this is important because the patient can experience hearing deterioration due to chemotherapy and xerostomia post radiation. IgA EA examination that is specific for NPC and IgA VCA that are sensitive to NPC. This examination does not replace a biopsy but can be used as a follow-up to assess recurrence, assess the therapeutic response and or can be for tumor markers.¹

NASOPHARYNGEAL CARCINOMA DIAGNOSIS

Gold standard for NPC diagnosis is histopathology through nasopharyngeal biopsy. Biopsy can be performed with local anesthesia. The tumor is biopsied through the nose with the rigid endoscope guidance. In some cases, general anesthesia should be done for nasopharyngeal exploration. This procedure is perform if the result of Fine needle aspiration biopsy (FNAB) is metastasis/spread from carcinoma and the previous biopsy show no cancer in nasopharynx. This procedure is repeated by taking deeper biopsy. Imunohistochemical examinations such as cytokeratin, EBER can help differentiate NPC from sinonasal tumors that are undifferentiated carcinoma types.¹

HISTOLOGICAL CLASSIFICATION OF NPC

According to WHO, the classification of nasopharyngeal cancer is squamous cell carcinoma, non-keratinized squamous cell carcinoma and non-keratinized carcinoma.²
STAGING OF NASOPHARYNGEAL CARCINOMA

Table 1. Union International Centre Cancer Tumor of NPC:

<table>
<thead>
<tr>
<th>T Classification</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor unable to be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Confined to nasopharynx or extend to oropharynx and/or nasal cavity</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extend to parapharyngeal space</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor involved sinus or skull based</td>
</tr>
<tr>
<td>T4</td>
<td>Intracranial, infratemporal/masticator space involvement, cranial nerve involvement orbit or hypopharynx.</td>
</tr>
</tbody>
</table>

Table 2. Union International Centre Cancer Nodes of NPC:

<table>
<thead>
<tr>
<th>N Classification</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No nodal involvement</td>
</tr>
<tr>
<td>N1</td>
<td>Unilateral cervical lymph nodes ≤ 6cm, or unilateral or bilateral retropharyngeal nodes ≤ 6cm above fossa supraclavicular</td>
</tr>
<tr>
<td>N2</td>
<td>Bilateral lymph nodes ≤ 6cm above supraclavicular fossa</td>
</tr>
<tr>
<td>N3A</td>
<td>Lymph node &gt; 6cm</td>
</tr>
<tr>
<td>N3B</td>
<td>Supraclavicular lymph node</td>
</tr>
</tbody>
</table>

Table 3. Union International Centre Cancer Metastases of NPC:

<table>
<thead>
<tr>
<th>M Classification</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant including mediastinum node</td>
</tr>
</tbody>
</table>

Table 4. Union International Centre Cancer Staging of NPC:

<table>
<thead>
<tr>
<th>Stadium</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>II</td>
<td>T1N1M0, T2N0M0, T2N1M0</td>
</tr>
<tr>
<td>III</td>
<td>T3N0M0, T3N1M0, T3N2M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4, any N, M0</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T, N3M0</td>
</tr>
<tr>
<td>IVC</td>
<td>Any T, Any N, M1</td>
</tr>
</tbody>
</table>

After the stadium is determined, the NPC will be treated according to the guidelines made by NCCN.
REFERENCE
INTRODUCTION

Nasopharyngeal carcinoma (NPC), one of the most common cancer in the head and neck area, is a cancer arising from the epithelium and usually develops at the fossa of Rosenmuller and invades adjacent spaces or organs. Nasopharyngeal cancer worldwide prevalence is less than 1/100,000. However, it is a malignant disease and a leading cause of death in several regions, such as Asia and Africa. There were 86,691 cases of nasopharyngeal carcinoma worldwide with Southeast Asian countries contributed large number of those cases in 2012. Indonesia has the second highest number (13,084 cases) of nasopharyngeal carcinoma in the world after China (42,100 cases) with at least 5.7 per 100,000 in males and 1.9 per 100,000 in women. Men are two to three times at risk of nasopharyngeal carcinoma than women.\(^1\)

Beside its relatively high incidence, nasopharyngeal carcinoma is one of the leading cause of death in five countries worldwide, respectively. In 2012, Indonesia had the highest standardized mortality rate (3.3 per 100,000 people) followed by Vietnam (3.3 per 100,000 people), Singapore (2.8 per 100,000 people), Malaysia (2.5 per 100,000 people), and Brunei (2.1 per 100,000 people). One of the main causes of the high mortality rate in Indonesia, as a developing countries, is the delay in diagnosis and most of the patients come with an advanced stage of the disease. The prognosis for advanced stage is very weak and it has higher risk for relapse, especially in elderly.\(^2\)

Treatment of choice for nasopharyngeal carcinoma is radiotherapy, with chemotherapy combination or not. However, local failure occurs in 10 to 30% of the patients.\(^1\) It is a challenging situation for treating the local failure of nasopharyngeal carcinoma. The difficulties arise from the anatomy of the residual or recurrent carcinoma, involvement of surrounding structures, and the therapy-related complications. The treatment for recurrent nasopharyngeal carcinoma follows the guidelines of the 2016 National Comprehensive Cancer Network. The treatment options varies from surgery, re-irradiation by external beam, stereotactic radiotherapy or brachytherapy, and chemotherapy. However in Indonesia, there are still minimal data on the outcome of recurrent nasopharyngeal carcinoma after the treatment. This review will explore more on the outcomes of salvage surgery and re-irradiation in recurrent nasopharyngeal carcinoma.
RECURRENT NASOPHARYNGEAL CARCINOMA

The management of recurrent NPC is still challenging in the medical field. Some of the things that cause difficulty in treating recurrent NPC are the location of the cancer adjacent to the vital structures i.e. brainstem, temporal lobe, and optic apparatus. On the other hand, long-term complications due to re-irradiation can also occur and damage the surrounding organs, therefore the selection for managing the recurrent NPC should be carefully thought out and weigh all possible risks. Management for recurrent NPC is currently following the guidelines of the 2016 National Comprehensive Cancer Network but the selection of treatment depends on the condition of each patient. Some things that need to be considered in choosing a treatment for recurrent NPC are the size, stage, connection with the surrounding tissue, whether it can be resected or not, and the availability of experts and surgical instruments.

All patients must be fully evaluated before deciding which treatment to choose. Re-staging must be done and discussed in a multidisciplinary team. The doctor must also make plans regarding the handling of teeth, nutrition, and evaluation of health behavior and intervention. For patients who will undergo surgery, surgical procedures, operating margins, and reconstruction plans must be discussed carefully with the ultimate goal is tumor-free margin.

RE-IRRADIATION

There are various types of radiotherapy modalities to treat NPC, including brachytherapy, stereotactic radiation, and radiation of external beams. The choice of treatment of re-irradiation in patients with recurrent or persistent NPCs needs to be done very carefully. Every benefit and complication that may occur must be
thought through carefully because each patient is in different conditions. For example, re-irradiation does improve control of the tumor, but if the interval time of re-irradiation is too close from the last one, it can cause high levels of toxicity to the surrounding organs. Some things that need to be considered in re-radiation are the interval between initial radiation and re-irradiation, tumor volume, and the general condition. The choice of re-irradiation is thought only for groups of patients who have no other curative treatment options or just as an addition to surgery. Short time intervals, greater tumor volume, and poor general patient conditions associated with a poor prognosis.9,10

Brachytherapy was first used for the treatment of NPC in the 1920s and is one type of radiotherapy that gives high doses of radiation to the target area with very high doses to avoid high-dose toxic effects on the surrounding tissue. For residual KNF, it can be used with intersisial gold implants or by using an applicator (intracavitary brachytherapy).4

Stereotactic radiation is used for NPC management with local failure. The use of stereotactic radiation is different for each patient and is generally used if brachyt herapy or nasopharyngectomy cannot be performed in these patients. There are two types of stereotactic radiation, namely single doses and multiple fractions.4

The use of intensity-modulated radiation therapy (IMRT) generally varies depending on the patient's condition, if the patient has a severe disease condition, it can be used around 66 to 74 Gy, while for subclinical diseases can be given as much as 50 to 60 Gy. The radiation field for radiotherapy in NPC covers the superior limit of cranial base, including the sphenoid sinus, the vocal cords in the inferior border, the spinous process for the posterior boundary, and 2 to 3 cm from the tumor border for the anterior border, including the pterygoid and 1/3 posterior maxillary sinus.9

One of the requirements for doing re-irradiation is the 6 months interval from the last radiotherapy. Re-irradiation can cause complications in the form of organ poisoning due to the level of radiation received. The study from Barnett et al (2009) states that there are two types of toxicity, which are early and late toxicity. Early toxicity occurs within a few weeks from the first radiotherapy, while late toxicity occurs after 6 months to several years after radiotherapy begins.10

Side effects related to radiotherapy can occur in all organs of the body. There are 6 toxicity levels from 0 to 5. Level 0 means there are no side effects or within normal limits, level 1 means mild side effects, level 2 means moderate side effects, level 3 means severe side effects, level 4 means life threatening, and level 5 can cause death. The side effects of acute toxicity to the skin are in the form of hyperemia, dry and wet desquamation, ulceration; in hair is in the form of alopecia; on the mucosa are in the form of erythema, edema, patchy and confluent mucositis; in the esophagus is in the form of retrosternal pain due to esophagitis; on the salivary glands is in the form of reduced amount and viscosity of saliva, and the pH becoming so acidic. While the side effects of chronic toxicity to the skin and mucosa are telangiectasia, fibrosis, tissue necrosis; in the esophagus is fibrosis,
necrosis or perforation of the fistula; in the salivary gland is fibrosis and does not respond to stimulation; in the brain are in the form of mild to severe headaches, convulsions, or paralysis and coma; in the eye are in the form of cataracts, keratitis, panophthalmitis, blindness; in the larynx are in the form of edema, condritis, necrosis. From Tian YM's study (2017), the incidence of severe acute toxicity (grade III acute mucositis) reached 12.7%, while the side effects of late toxicity in the form of grade III mucosal necrosis reached 26.9%. The high toxicity that occurs due to re-irradiation has led experts to look for other alternatives in the form of surgery for the management of recurrent NPC.¹¹

**NASOPHARYNGECTOMY FOR LOCALLY RECURRENT**

Nasopharyngectomy plays an important role in patients with recurrent or persistent NPC. Nasopharyngectomy is surgery on the nasopharynx and surrounding tissue. Surgery can reduce the long-term toxic effects that occur as a result of re-irradiation, such as multiple cranial nerve palsies, osteoradionecrosis, cervical subcutaneous fibrosis, hearing loss, temporal lobe damage; therefore surgery is chosen as an alternative treatment for recurrent NPC with an early stage (rT1-2). There are various ways and various access routes for nasopharyngeal surgery, starting with open surgery to a minimally invasive approach. Various options for surgery will be discussed below.¹²

**MAXILLARY SWING APPROACH**

The maxillary swing approach was first introduced by Wei et al in 1991 and is a very good surgical method for looking at the entire nasopharynx and the area of the ipsilateral parapharynx. This approach performs surgery through the anterolateral side and can be used for tumors with retropharyngeal lymph node metastases.⁵

This surgical procedure begins with the Weber-Ferguson incision then the incision is extended to reach the anterior zygoma area and is carried along the midline of the hard palate to reach the connection of the hard and soft palate. Then an incision is made on the lips until it reaches the gingivobuccal sulcus laterally then turns medially to the maxillary tuberosity until it meets the hard palate incision. After the zygoma anterior and maxilla separation incisions have been performed, the maxilla remains left attached to the anterior cheek skin and then it can be pulled laterally to provide a clear field of view of the nasopharynx and parapharynx area. There are several additional procedures to expand the contralateral nasopharyngeal field, one of which is posterior septectomy. After resection is performed, the maxilla will be repositioned using a titanium plate. Some complications that may occur from this procedure are middle ear effusion (37.8%), trismus (9.2%), facial numbness (7.4%), epiphora (6.5%), palate fistula (4.3%), nasal blockade, and ectropion (1.8%).⁵,¹³
Data from Wei et al (2011) study of a total of 246 patients with 229 patients with undifferentiated carcinoma, 8 patients with squamous cell carcinoma (KSS), and 9 differentiated SSC patients, found that 5-year local control after surgery with maxillary swing technique is 74% with 5-year overall survival reaching 56%. Data from Hao et al (2015) study found that 5-year total control of 53.6% with 5-year overall survival reaching 48.7%. Study of Chan et al (2013) stated that the rate of local recurrence was higher in patients with a positive surgical margin on previous nasopharynectomy.13, 14

MIDFACIAL DEGLOVING

The midfacial degloving procedure is a safe approach for midface lesions with low complication rate and excellent cosmetic outcomes. It lacks of facial incision and no disruption of palatal function. It was first suggested by Portmann in 1927 but it was first done by Casson and colleagues in 1974. This technique was reported to be useful in allowing adequate bilateral maxillary and lower nasal cavity exposure, therefore midfacial degloving is widely used to expose and treat lesions of the facial cavities, orbits, central compartment of the anterior and middle cranial fossae, paranasal sinuses, and nasopharynx.5

The degloving approach is performed with an incision in the maxillary vestibular mucosa and bilateral intercartilaginous incision, complete transfixion, and bilateral piriform apperture to elevate the entire midface skin and expose the skeleton. The incision in intercartilaginous will divides the cartilages to upper and lower part. The upper lateral cartilage will remain attached to the skeleton, whereas the lower cartilage will be displaced during the procedure. The operator then made an incision along the inferior border of the upper lateral cartilage and meet the transfixion incision of the nasal columellar and this incisions would allow the separation of soft tissue of the nasal alar, nasal tip and the nasal bone. After the separation, the whole midface, soft tissue could be elevated to the infraorbital foramen and exposed all of the bony anterior midface and midfacial osteotomies can be performed. This procedure has narrow view of nasopharynx, therefore bilateral medial maxillectomies (Denker’s procedure) could be performed to improve the exposure of the nasopharynx.13

Temporary infraorbital anesthesia or hypesthesia are common complications to the midfacial degloving procedure. The other complications that may arise are nasal obstruction and epiphora. However, the infraorbital anesthesia for most patients are fully recover within 5 months and the rate of permanent infraorbital anesthesia is less than 3%.13 The study of To et al in 7 rT1 patients, 5 rT2 patients, and 3 rT4 patients showed that 80% of the results of surgery using this procedure had a negative surgical margins.13
INFRATEMPORAL FOSSA APPROACH

This technique was first performed by Ugo Fisch in 1979 in 7 rT4 patients, 4 persistent T1 patients, and 2 T2 patients. This technique uses a neuro-otology approach. This procedure starts with a retroauricular skin incision, transection of the external canal and the facial nerve will appear in the parotid area. Then the skull bone in the part of the cranial fossa of the media is removed so that the structure of the infratemporal fossa which consist of the eustasia tube, external pterigoid muscle and media, and palatine tensor muscle are seen. Hen the branch of the trigeminal nerve must be separated and the pterygoid muscle must be removed from the lateral pterygoid plate so that the internal carotid artery can be identified and can be protected when the resection is performed and this is one of the advantages of this procedure. However, the operator cannot see the contralateral part of the nasopharynx and this is one of the disadvantages of using this procedure.\(^5\)\(^15\)

Possible complications are cranial nerve palsies, including the mandibular branch trigeminal nerve, facial nerve, glossopharyngeal and vagus nerves. From a study conducted by Fisch in 1983 on a total of 13 patients who experienced local failure, 6 patients with an early stage T1-2 did not experience recurrence within two to five years after surgery, but all patients with early stages of T4 experienced local recurrence and died within three years.\(^15\)

TRANSPALATAL APPROACH

Tu et al first introduced this technique in 1988 to 9 patients who experienced recurrence in stage rT1 to 2. This procedure uses an inferior approach by making a ‘U’ flap on the palate mucosa. Then separation between the hard and soft palate and posterior retraction is performed. After that the nasopharynx can be seen and resection can be done. After resection is performed, the palate flap is then sutured back to the anterior portion of the hard palate and the wound is closed.\(^5\)\(^12\)

Study conducted by Fee in 37 patients in 2002 showed that the 5-year survival rate was 52% and the 5-year local control was 67%. Fee also compared the results between treatment using transpalatal surgery with re-irradiation, it was found that the results were comparable or even better using surgery than re-irradiation for local control.\(^5\)

TRANSCERVICO-MANDIBULO-PALATAL APPROACH

This procedure was first performed by Morton et al in 1996 in 7 patients with rT1-2. This procedure uses an inferolateral approach. Initially begins with the separation of the lips with mandibulotomy, then the incision is extended to the upper ipsilateral neck. The incision is then carried out at the floor of the mouth and the soft palate is separated from the hard palate to obtain an adequate nasopharyngeal field. This procedure has the advantage of being able to easily search for the internal carotid artery from the neck to the base of the skull, therefore the internal carotid artery can be protected during the resection. However, this procedure causes
extensive tissue damage compared to other procedures and endoscopic techniques.\textsuperscript{5,16}

Morton's study in 1966 stated that of the 7 patients who underwent surgery using this technique, one patient had an early recurrence within one year after surgery and one patient had a late recurrence within 10 years after nasopharyngectomy.\textsuperscript{16}

**ENDOSCOPIC APPROACH**

Endoscopic technique, as one of the approach for recurrent NPC, was first introduced by Yoshizaki et al in 2004. Endoscopic approach surgery has several advantages compared to open approach surgery, that are minimal bleeding, no scarring, minimal surrounding tissue damage, and recovery period faster.\textsuperscript{17}

There are 3 types of nasopharyngeal resection using endoscopy. Type 1 begins with a resection of the posterior part of the nasal septum until it reaches the base of the sphenoid and pharyngobasilar sinus bones or inferior prevertebral fascia. While type 2 is carried superiorly until it reaches the anterior wall and the base of the sphenoid sinus. Type 3 incision is carried out laterally to reach the lateral nasopharyngeal wall and Eustasia tubal cartilage. Then a medial maxillectomy is performed with removal of the inferior conca, the media maxillary wall, and the naso-lacrimal duct, and then the incision is extended along the piriform aperture. After the sphenopalatine artery, the major palatine artery, and the palato-vaginal artery are clearly visible, cauterization can be performed, leaving the septal branch of the sphenopalatine artery for the nasopharyngeal flap. Doppler ultrasound guidance can be used to identify the internal carotid artery. Then the frozen section analysis is carried out and nasoseptal flap is returned to cover the defect.\textsuperscript{18}

The choice of endoscopic treatment depends on the location and stage of the NPC. For recurrent NPC, endoscopic surgery is generally performed if the tumor is located on the nasopharyngeal palate with minimal lateral invasion. Thus, endoscopic surgery is generally performed on NPC rT1-2 and in recurrent tumors that are not too close to the base of the skull and internal carotid artery. The study of MY Chen in 72 patients consisting of 32 rT1 patients, 27 rT2 patients, and 13 rT3 patients showed a 5-year overall survival of 77.1% and a 5-year loco-regional relapse free survival of 67.4%. In this study no serious complications were found, but 22% of patients experienced otitis media. Study from Hao et al (2008) performed endoscopic surgery on a total of 53 patients with details of 27 rT1 patients, 9 rT2 patients, 9 rT3 patients, and 8 rT4 patients showing a 5-year overall survival of 48.7% and 5-year local control of 53.6%. Contraindications to surgery using endoscopy are massive intracranial involvement, invasion of orbital contents, and location of the tumor covering the internal carotid artery. It is necessary to conduct pre-operation examination and planning before selecting a treatment so that the selection of management can be done appropriately.\textsuperscript{19}
### Tabel 1. Comparison of nasopharyngectomy and radiotherapy therapy results in recurrent nasopharyngeal carcinoma.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient (n)</th>
<th>T Stage (%)</th>
<th>Management</th>
<th>Local Control (%)</th>
<th>Survival (%)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>King et al, 2000¹³</td>
<td>31</td>
<td>rT1: 65</td>
<td>Transpalatal, maxillary swing, transmandibular</td>
<td>LRFS: 85.8 at 5 years</td>
<td>44.9 at 5 years</td>
<td>Hemorrhage: 47/132</td>
</tr>
<tr>
<td>Fee et al, 2002¹³</td>
<td>37</td>
<td>rT1: 59</td>
<td>Transpalatal</td>
<td>67 at 5 years</td>
<td>52 at 5 years</td>
<td>5% experienced death and permanent dysphagia</td>
</tr>
<tr>
<td>Hao et al, 2008¹⁴</td>
<td>53</td>
<td>rT1-2: 66</td>
<td>Endoscopic</td>
<td>53.6 at 5 years</td>
<td>48.7 at 5 years</td>
<td>2 patients died from massive bleeding</td>
</tr>
<tr>
<td>Chen MY et al, 2009¹⁷</td>
<td>37</td>
<td>rT1: 17</td>
<td>Endoscopic</td>
<td>LRFS: 86.3 at 2 years</td>
<td>84.2 at 2 years</td>
<td>1 patient died from distant metastasis and 1 patient had intracranial infection</td>
</tr>
<tr>
<td>Roeder et al, 2011¹³</td>
<td>17</td>
<td>rT3-4: 36</td>
<td>IMRT, FSRT</td>
<td>69 at 2 years</td>
<td>37 at 3 years</td>
<td>Grade 3 late toxicity: 29%</td>
</tr>
<tr>
<td>Qiu et al, 2012¹³</td>
<td>70</td>
<td>rT3-4: 57</td>
<td>IMRT</td>
<td>65.8 at 2 years</td>
<td>67.4 at 2 years</td>
<td>Cranial nerve palsies: 24.3%; Trismus: 17.1%; Deafness: 17.1%</td>
</tr>
</tbody>
</table>

IMRT: intensity-modulated radiation therapy  
FSRT: fractionated stereotactic radiotherapy  
LRFS: local relapse-free survival

### SURGERY FOR NODAL RECURRENCES IN NPC

Management of patients with NPC recurrence and lymph node involvement has a poor prognosis with re-irradiation. Obtained data for 5-year overall survival only reached 19.7%. In addition re-irradiation is associated with an increased risk of toxicity due to excessive radiation doses. Therefore, experts are looking for alternative ways to manage NPC with lymph node recurrence. The study of Wei et al (2001) stated that 70% lymph node recurrence has extra capsular spread so Wei proposes an alternative way of radical neck dissection. While the study of Khaffid et al proposed the use of imaging to increase accuracy in performing modified or selective neck dissection. Chen et al used selective neck dissection for NPC with lymph node recurrence and found 5-year overall survival of 66.81% and 5-year regional free survival of 78.67%⁵.
CONCLUSION

Currently surgery for nasopharyngeal carcinoma is still a challenge in the medical field. Advances in technology today make surgical techniques more developed and the use of conventional surgical techniques are abandoned. Nasopharyngectomy with a transpalatal procedure is a simple surgery, but the field of view of the nasopharynx is very limited and the complication rate of oronasal fistula is high. The transmandibular approach also has a narrow visual field of the superior nasopharynx because of the inferior approach. However, the internal carotid artery can be clearly seen with this approach. The maxillary swing procedure and midface degloving are anterior approaches, these types of procedure is best for tumors located in the nasopharynx with minimal parapharyngeal involvement. While endoscopic use is indeed limited to the location and size of certain tumors. It can be combined with a neurosurgical approach to obtain a good visual field in NPC surgery, as an example of the subfrontal approach to provide a superior visual field.

Surgery plays an important role in the management of recurrent NPC without metastasis. Compared with re-irradiation, surgery for early stage recurrent NPC is preferred as the main treatment because it can reduce the effects of toxicity that can occur due to re-irradiation. However, the management of patients with recurrent NPC varies depending on the patient’s condition and tumor extension. It should be noted that positive post resection margins are associated with a poor prognosis and administration of radiotherapy to patients with a positive post resection margin does not improve survival rates in patients with recurrent NPC.
REFERENCES


RIGID NASOPHARYNGOSCOPY AND FLEXIBLE ENDOSCOPY
EVALUATION FOR DIAGNOSIS AND RECURRENT
NASOPHARYNGEAL CARCINOMA

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Faculty of Medicine, Universitas Gadjah Mada

Nasoendoscopy involves evaluation of the nasal and sinus passages with direct vision using a magnified high-quality view. It is a commonly performed procedure in the otolaryngologist’s office and serves as an objective diagnostic tool in the evaluation of nasal mucosa, sinonasal anatomy, and nasal pathology. Nasoendoscopy may be accomplished with either a flexible fiberoptic endoscope or a rigid endoscope. When performed by experienced practitioners, both flexible endoscopy and rigid endoscopy are usually well tolerated.

The fiberoptic telescope has the advantage of being flexible and generally smaller in diameter, which means that it is readily manipulated in multiple directions to permit visualization of tight areas. However, flexible endoscopy requires 2 hands for manipulation of the instrument and is thus a more difficult procedure. Traditionally, flexible endoscopy has provided inferior visualization, but this drawback has been overcome with the development of digital flexible endoscopes.

The rigid endoscope provides superior image clarity, facilitates culture and tissue sampling, control epistaxis better, and affords the doctor to be able to perform surgery.\(^1,2\) Rigid endoscopes for the nose come in diameters of 2.7-4 mm and have tips of different angles (generally 0-70º), allowing the physician to visualize various sinuses and areas within the nasal cavity and sinuses.

Indications for nasoendoscopy are; (1) Initial identification of disease in patients experiencing sinonasal symptoms (eg, mucopurulent drainage, facial pain or pressure, nasal obstruction or congestion, or decreased sense of smell), (2) Evaluation of patients’ response to medical treatment (eg, resolution of polyps, inflammation after treatment with topical nasal steroids, post chemo-radiation), (3) Evaluation and biopsy of nasal massed or lesion, (4) Evaluation of nasopharynx, eustachian tube problems and nasal obstruction, (5) Evaluation of CSF leak, and (6) Evaluation and treatment of epistaxis and nasal foreign bodies.

No absolute contraindications to nasoendoscopy exist; however, some patient populations are at increased risk for complications. In patients who have a history of a bleeding disorder or are receiving anticoagulants, nasal endoscopy should be performed carefully so as not to provoke bleeding. Additionally, in an anxious patient or a patient with cardiovascular disease, there is a risk of a vasovagal episode.
Rigid endoscopes are made in various angles (0º, 30º, 45º, and 70º). The angled telescopes are used to see around corners and to evaluate areas not easily examined under direct vision. The 4 mm 30º scope has been shown to provide sufficient illumination and an adequate field of vision and may therefore be the most useful telescope in an average patient. Nasal endoscopes also come in pediatric sizes (2.7 mm), which are also available in various angles and which may be used for increased comfort in adults.

In addition to affording superior visualization, nasal endoscopy provides improved illumination, greater magnification, and the ability to navigate directly to pathologic areas. As a result, examiners obtain a more accurate and thorough diagnostic evaluation. In one study, rigid nasal endoscopy identified nasal pathology in almost 40% of patients who had normal examinations on anterior rhinoscopy. Endoscopy plays an important role in the preoperative, postoperative, and medical management of patients with sinonasal complaints.

Steps of nasoendoscopy preparation are; (1). Equipment preparation, 0º scope is needed for evaluating nasopharynx, light source, and light cable, (2) appropriate positioning, (3) Before nasoendoscopy, nasal cavities are often sprayed with a nasal decongestant, such as oxymetazoline and xylocaine 4% spray. Anesthetics are typically applied either with a spray atomizer or directly on a cotton pledget. Before application, patients should be questioned about medication allergies. The topical anesthetic should be applied to the inferolateral surface of the middle turbinate, to the surface of the inferior turbinate, and to any other sites where pressure may be exerted by insertion of the scope. (4) Ask the patient to breath through his/her mouth to avoid blurred vision, (5) Gently insert the endoscope into the nose along the base of the nose to the nasopharynx, (6) Evaluate the Rossenmuller fossa, torus tubarius, and eustachian tube, (7) If masses are seen in the nasopharynx, do biopsy.

Overall, nasoendoscopy is a safe and low-risk procedure. Potential complications associated with the procedure include an adverse reaction to the topical decongestant or anesthetic, pain or discomfort, epistaxis, and vasovagal episodes. Before the topical medications are administered, the patient’s allergies should be verified.

Narrow-band imaging (NBI) is a novel optical technique that enhances the diagnostic sensitivity of endoscopes for characterizing tissues by using narrow-bandwidth filters in a sequential red–green–blue illumination system. The central wavelengths of each band are 415 and 540 nm. The narrowband blue light, which has a short wavelength (415 nm), penetrates the mucosa and highlights the superficial vasculature. Furthermore, the blue filter is designed to correspond to the peak absorption spectrum of hemoglobin, and thus enhances the image of the capillary vessels on the surface mucosa. Thus, superficial mucosal lesions that usually cannot be detected by regular white-light endoscopy can be identified on the basis of their neoangiogenetic vasculature pattern by using blue light in NBI.
The literature review showed that the effectiveness of NBI in the early detection of head and neck squamous cell carcinoma (SCC) over the mouth floor, larynx, oropharynx, and hypopharynx, have been documented through the years. It is now generally accepted that NBI is of great benefit in detecting superficial mucosal lesions over the pharyngeal mucosa. Except for one case that we reported previously of irradiated NPC with early recurrence successfully detected by NBI coupled with conventional endoscopy, there has been still no documentation of its application to primary NPC and the screening performance of NBI for high-risk populations.

There are five distinctly different findings that need to be examined by NBI: Type I: brownish spots, Type II: irregular microvascular pattern (IMVP), Type III: light crests, Type IV: side-difference, Type V: presence of either IMVP or side-difference, of which last three (Type III–V) were a new concept. Previous studies showed that Type I pattern is ordinarily observed in superficial cancers of the oropharynx and hypopharynx. Even Type II pattern is encountered in carcinoma of the oropharynx, hypopharynx, esophagus and stomach.

NBI can identify the microvascular architecture and mucosal microsurface structure, including detecting tortuous microvessels, a fine white line on the crests of the surface, and easily compare the both side difference of nasopharynx. Therefore, NBI reduced the number of false-negative cases except for one with mainly downward invasive NPC.

The utility of NBI as an adjunctive technique to perform NPC screening in a high-risk population is recommended. Even though large-scale screening program should be established to verify the accuracy of this technique in the daily practice, nonetheless its low cost, easy of use, and non-invasiveness seem quite encouraging.

REFERENCES
FNAB’S AND INCISIONAL BIOPSY ON NASOPHARYNGEAL CANCER

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INTRODUCTION

The cases of nasopharyngeal cancer (NPC) frequently found in advanced stage. This happened due to location of nasopharynx is isolated in the posterior part of nasal cavity, under the skull bases and above oropharynx. According to American Joint Committee on Cancer (AJCC), the stages of NPC divided into stage 1 to 4. Stage 1 define as a tumor localized on nasopharynx without any enlargement of lymph node on the neck. On the other hand, stage 2 or higher, the neck node must be appear at least on one side with the diameter less than 3 cm or bigger.¹

The management of neck lymph node is one of the important things on the management of nasopharyngeal cancer. There is some question appear related to management of neck lymph node on the case of its enlargement. Is it necessary to manipulate the neck node or are there any benefit of fine needle aspiration biopsy (FNAB) or incisional biopsy on the presentation of neck lymph node? This paper will describe about the benefit and disadvantages as well as indication to perform FNAB and incisional biopsy of the neck lymph node and its relation to nasopharyngeal cancer management.

EPIDEMIOLOGY OF NASOPHARYNGEAL CANCER

The incidence of nasopharyngeal cancer is found difference between one country to the others. The high incidence is found in South China and Southeast Asia, including Indonesia. In Indonesia, the incidence is 6.2/100,000 or almost 15,000 cases will be find annually², furthermore, in West Nusa Tenggara Province with 4.8 million population³, the number of cases predicted about 300 per year.

According to epidemiologic data in West Nusa Tenggara Hospital, from January to December 2015 found 48 patients. The cases became from all district in West Nusa Tenggara with the highest incidence in west Lombok (27%). The most cases found in male with the male to female ratio 3:1. Based on age category, the most cases found under 50 years old (69%) with the peak incidence in 40 years old. The detailed data as showed on table 1.⁴

Recent study found that most cases found on the advance stage, Xing Li et al (2018) found on their research about 61% were found on stage 3 and 4. According to AJCC, on stage 3 and 4, the neck node must be appear.⁵ Pelealu et al (2015) found the cervical node enlargement on 26 patients (50%) nasopharyngeal cancer.⁶
Although not all of enlargement of lymph node on the cervical are cancer, the fact showed that most of them are the spreading of others disease from the other site of body. Zbaren et al (1993) found that 80% metastasis lymph node on the neck is originated from ear, nose and throat region. Ten percent of them is originated from bronchus and esophagus. In advance, Adoga et al (2009) found almost 80% of patients with cervical lymph node enlargement are originated from nasopharyngeal cancer.

Table 1. Distribution of nasopharyngeal cancer in West Nusa Tenggara Province (January-December 2015)

<table>
<thead>
<tr>
<th>District</th>
<th>Frequency N (%)</th>
<th>Gender</th>
<th>Age category</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td>&lt;50</td>
<td>&gt;50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mataram</td>
<td>6 (13)</td>
<td>5 (11)</td>
<td>1 (2)</td>
<td>5(11)</td>
<td>1(2)</td>
</tr>
<tr>
<td>West Lombok</td>
<td>13 (27)</td>
<td>8 (17)</td>
<td>5 (11)</td>
<td>8(17)</td>
<td>5(11)</td>
</tr>
<tr>
<td>Central Lombok</td>
<td>12 (25)</td>
<td>8 (17)</td>
<td>4 (9)</td>
<td>9 (19)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>East Lombok</td>
<td>8 (17)</td>
<td>5 (11)</td>
<td>3 (7)</td>
<td>5(11)</td>
<td>3(7)</td>
</tr>
<tr>
<td>North Lombok</td>
<td>2 (4)</td>
<td>2 (5)</td>
<td>0 (0)</td>
<td>1(2)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Sumbawa</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1(2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>West Sumbawa</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1(2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dompu</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1(2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bima</td>
<td>3 (6)</td>
<td>2 (5)</td>
<td>1 (2)</td>
<td>2(5)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Bima city</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Province</td>
<td>48 (100)</td>
<td>32 (67)</td>
<td>16 (33)</td>
<td>33 (69)</td>
<td>15 (31)</td>
</tr>
</tbody>
</table>

Based on the fact above, all physician should be aware to looking for the primary site of cervical lymph node enlargement. A complete work up should be done to explore the primary site, including history taking, physical examination especially ear nose and throat as well as surrounding organ such as eyes and nerve disorder, additional examination such as imaging with CT scan or MRI with contrast, endoscopic view and serologic for Epstein Barr virus (EBV). On the history taking, the questions should be arrange to explore several symptoms that may appear, such as epistaxis, nasal blocking, eye problem, headache, etc. A detailed physical examination such as rhinoscopy anterior and posterior as well as otoscopy are needed to view the nasal cavity, oral cavity, nasopharynx and the eardrum in order to directly find the primary site (Balm et al, 2010; NCCN, 2018).

Imaging on nasopharynx and surrounding structures are very important to decides the primary site and also for the staging of the malignancy in enlargement of cervical lymph node. However, the gold standard for diagnosis of nasopharyngeal carcinoma is the biopsy nasopharynx itself.
FINE NEEDLE ASPIRATION BIOPSY

The cytology examination from the cervical lymph node aspiration can be done to make an early diagnosis and to eliminate such differential diagnosis of cervical lymph node. FNAB is an easy, simple and quick as well as low price procedure which can be done on outpatient setting. This procedure is frequently used to diagnose the thyroid mass. The equipment including the 10 ml spuit, alcohol swab, object glass, hematoxylin eosin staining and microscope. The result can be obtained in 1-2 days. The pain may occur after FNAB, however, visual analog scale (VAS) is relatively low with the mean 36±16.

The sensitivity, specificity and diagnostic accuracy of FNAB in head and neck lesion (excluding thyroid) is excellent. Goret et al (2013) found in his research, the sensitivity 94.6%, specificity 97.9% and accuracy 96.7%. This result similar with research by Alam et al (2009), consecutively the found 93.3%, 94% and 95.65%

On the National comprehensive cancer network (NCCN) guideline version 2.2018, FNAB is one of the recommendation in nasopharyngeal carcinoma workup. However, the most important thing is a biopsy on the primary site with the endoscopic guided biopsy in nasopharynx.

INCISIONAL BIOPSY ON CERVICAL LYMPH NODE

Neck node biopsy should be avoided although a direct effect on tumor recurrence has not been demonstrated (Balm et al, 2010). Pastor M, et al (2018), emphasized that Incisional cervical biopsy should be avoided as this procedure will negatively impact the subsequent treatment. Incisional cervical lymph node biopsy is only indicated to those who repetitive negative or non-diagnostic FNAC as well as repetitive negative imaged guided true cut biopsy on the primary tumor.

Incisional biopsy can be done under local or general anesthesia, it depends on patient conditions including the renal and hepatic function, age and psychological status. Incisional biopsy is started with making an incision in the bigger palpable node, then goes deeper until the node is free from others tissue, so the node sample will easily to carry out. Finally, the tissue sample send to pathology laboratory to be proceeds for histopathologic examination. In Indonesia the result usually will be find in 5-7 days.

There are several effects of incisional biopsy on cervical lymph node, including scar formation which is occur in 100% cases, skin metastasis and distance metastasis are occur in 57% cases. (Adoga et al, 2009). In Indonesia, pathologic workup need about 5-7 days to be finished, furthermore, if cervical node biopsy was done and then followed by biopsy in the primary tumor, this will take at least 2 weeks to make a definitive diagnosis. A late start of radiotherapy and or chemotherapy will reduce the survival rate. Cai et al (1983) found that 5 years survival rate of patient with nasopharyngeal cancer who received the radiotherapy and or chemotherapy within 2 weeks after diagnosis will have a better survival rate.
(65%) than those who start the radiotherapy and or chemotherapy more than 2 weeks (45%).\textsuperscript{16}

Another research found there is no significant different between patient with and without incisional neck biopsy on the overall survival rate, loco-regional recurrence, or distance metastasis with intensity modulated radiotherapy (IMRT). They found the 4 years survival rate 88.4% and 92.3% consecutively in group with and without incisional biopsy with the p value 0.195. Loco-regional recurrence in both group consecutively 93.9% and 97.3% (p value 0.56). Distance metastasis 85.8% and 86.5% consecutively in both group with p value 0.58. IMRT is Relatively New Modality to Treat Nasopharyngeal Cancer.\textsuperscript{5}

In Indonesia, only a few hospitals using this modality, furthermore, not all province in Indonesia have the radiotherapy unit. Hiswara (2017) report in 2017 there are 33 radiotherapy center in Indonesia. Another obstacles in Indonesia are a period to waiting time for starting the radiotherapy was more than 3 month, and also pausing time when the equipment need a repair or maintenance.\textsuperscript{17} This make the prognosis of nasopharyngeal cancer will lower than others who use IMRT and starting the treatment within 2 week as well as there is no any pausing time.

**DISCUSSION**

According to several literatures above, FNAB is superior in early detection of type of lymph node on the neck. So, it can differentiate the node as an infection, benign or malignant mass with less invasive, economist and well tolerated procedure. On the other hand, incisional biopsy is superior in case of negative repetitive true cut biopsy. So, it can be as a final decision to make diagnosis in unknown origin head and neck cancer. According to the complication, FNAB has a minimal effect as a result of their simple procedure compared to incisional biopsy. The detailed comparison of these procedure as showed on table 2.
Table 2. Comparison of FNAB vs incisional biopsy

<table>
<thead>
<tr>
<th>Category</th>
<th>FNAB</th>
<th>Incisional Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure</td>
<td>Simple, unneeded the anesthesia</td>
<td>Complex, should use the anesthesia, sometime need a general anesthesia</td>
</tr>
<tr>
<td>Procedure impact</td>
<td>Minimal</td>
<td>Could be severe</td>
</tr>
<tr>
<td>Days to obtained the result</td>
<td>1-2 days</td>
<td>5-7 days</td>
</tr>
<tr>
<td>Indication</td>
<td>Early diagnosis</td>
<td>Repetitive negative result from true cut primary biopsy</td>
</tr>
<tr>
<td>Complication</td>
<td>Mild pain</td>
<td>Scar formation in the incision line, micrometasis, bleeding</td>
</tr>
<tr>
<td>Price</td>
<td>Low</td>
<td>Higher</td>
</tr>
</tbody>
</table>

Although both procedures have its superiority on head and neck cancer management, physician have a duty to find out the primary site of the tumor. According to NCCN guideline, the treatment should be focused on the primary tumor, the different primary tumor has their own management guideline. Finally, the definitive primary tumor and primary histopathologic finding is the most important things on management of head and neck cancer, including nasopharyngeal cancer.

REFERENCES
6. Pelealu O, Palandeng O, Adithia IPA, Rahardjo SP. Nasopharyngeal carcinoma at otolaryngology department Prof. RD Kandou hospital Manado
ABSTRACT

Introduction: Nasopharyngeal carcinoma (NPC) is malignancy of squamous cells on nasopharyngeal epithelial layer and the most common otorhinolaryngology malignancy found in Indonesia. Etiology of NPC is multifactorial including, food, environment, genetics, and Epstein-Barr virus infection. The study aimed to determine the highest risk factors on the incidence of nasopharyngeal carcinoma in Otorhinolaringology-Head and Neck Surgery Department dr. Hasan Sadikin General Hospital Bandung.

Methods: The study design was descriptive retrospective from medical record of NPC patients at Otorhinolaringology-Head and Neck Surgery Department, dr. Hasan Sadikin General Hospital Bandung in 2010–2015.

Result: There were 462 nasopharyngeal carcinoma patients in this research (265 men and 161 women) with three most common risk factors history of smoking (50.7%), mosquito coils use (43.2%), and consumption of salty fish (39.7%).

Conclusion: Smoking, mosquito coils, and consumption of salty fish affect the incidence of nasopharyngeal carcinoma.

Keywords: Risk factor, nasopharyngeal carcinoma, smoking, mosquito coils use, consumption of salty fish.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignancy of squamous cells on nasopharyngeal epithelial layer with Rosenmuller fossa is the most common predilection site. Nasopharyngeal carcinoma belongs to the top five malignancies after cervical cancer, breast cancer, lymph nodes, and skin.¹

The highest incidence of NPC is found in Asia and rarely found in American and Europe. ² Nasopharyngeal carcinoma can be found in all countries from five continents, but the highest incidence is in southern China, especially in Guangdong province, which is 17.8 per 100,000 population per year with a frequency 100 times higher than Caucasians.³

The prevalence of NPC in Indonesia is 4.7 new cases per 100,000 population per year or around 12,000 cases per year and is the most commonly found otorhinolaryngology malignancy in Indonesia. Comparison between men and women is 2–3: 1.⁴ There are 692 (43.7%) NPC patients in Hasan Sadikin General Hospital, Bandung within 2010-2014 with more male patients (65.7%) and occur most in the 46-55 age group (29.6%).
Etiology of NPC is multifactorial including genetic factors, Epstein Barr virus infection (EBV), environmental factors such as exposure to carcinogens (formaldehyde), wood dust and firewood fumes, smoking, and food (consume salted fish that contain nitrosamine).^6,7^

Research on the risk factors for NPC in Indonesia has never been done. On this basic researchers want to conduct research. The purpose of this study was to determine the risk factors for NPC at RSHS as a referral center Hospital in West Java.

**RESEARCH METHODS**

This research method is a retrospective descriptive based on medical record data of NPC patients that including the inclusion and exclusion criteria. The inclusion criteria were all patients diagnosed with NPC seeking treatment at the ORL-HNS outpatient ward subdivision of Head Neck Surgery, RSHS, Bandung within 2010 to 2015. Exclusion criteria are incomplete medical records.

**RESEARCH RESULT**

There were 482 patients with head and neck malignancy in ORL-HNS RSHS, 426 data for NPC and 56 data for non-NPC patients, with the results:

<table>
<thead>
<tr>
<th>Variable</th>
<th>NPC</th>
<th>Non-NPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.34 ± 14,351</td>
<td>53,553 ± 13,962</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>45</td>
</tr>
<tr>
<td>Range (min-max)</td>
<td>From 10.00 to 86,00</td>
<td>20.00-81,00</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>265 (62.2%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>161 (37.8%)</td>
</tr>
</tbody>
</table>

Based on these results, obtained a comparison of risk factors between NPC and non- NPC. Average for the NPC group, it was 43.34 ± 14,351 while in the non-NPC group it was 53.553 ± 13,962. Male (62.2%) in the NPC group was more than female (37.8%) while in the non-NPC group there was no difference between the gender.
Table 2. Risk Factors for NPC and Non-NPC

<table>
<thead>
<tr>
<th>Variable</th>
<th>NPC</th>
<th>Non-NPC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NPC</td>
<td>Non-NPC</td>
</tr>
<tr>
<td></td>
<td>N = 426</td>
<td>N = 56</td>
</tr>
<tr>
<td>Use of ONB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>184 (43.2%)</td>
<td>15 (26.7%)</td>
</tr>
<tr>
<td>No</td>
<td>242 (56.8%)</td>
<td>41 (73.3%)</td>
</tr>
<tr>
<td>Number of ONB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>24 (5.6%)</td>
<td>5 (33.4%)</td>
</tr>
<tr>
<td>2-4</td>
<td>160 (37.6%)</td>
<td>10 (66.7%)</td>
</tr>
<tr>
<td>Time of smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>77 (18.1%)</td>
<td>10 (17.8%)</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>139 (32.6%)</td>
<td>23 (41%)</td>
</tr>
<tr>
<td>Do not smoke</td>
<td>153 (35.9%)</td>
<td>19 (39.9%)</td>
</tr>
<tr>
<td>Passive</td>
<td>57 (13.4%)</td>
<td>4 (7.3%)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60 (14.1%)</td>
<td>20 (35.7%)</td>
</tr>
<tr>
<td>No</td>
<td>366 (85.9%)</td>
<td>36 (64.3%)</td>
</tr>
<tr>
<td>Family history of cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (7.0%)</td>
<td>2 (3.6%)</td>
</tr>
<tr>
<td>No</td>
<td>396 (93.0%)</td>
<td>54 (96.4%)</td>
</tr>
<tr>
<td>Salted Fish</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>169 (39.7%)</td>
<td>3 (5.4%)</td>
</tr>
<tr>
<td>No</td>
<td>257 (60.3%)</td>
<td>53 (94.6%)</td>
</tr>
</tbody>
</table>

Description: ONB = Mosquito coils

The risk factors that increase the incidence of NPC consists of a history of smoking (50.7%), use of mosquito coils (43.2%), history of consuming salted fish (39.7%), alcohol consumption (14.1%), and a family history of cancer (7%).

Table 3. Most Risk Factors in NPC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Research Group Year 2010-2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 426)</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>216 (50.7%)</td>
</tr>
<tr>
<td>Mosquito coils</td>
<td>184 (43.2%)</td>
</tr>
<tr>
<td>Consumption of salted fish</td>
<td>169 (39.7%)</td>
</tr>
</tbody>
</table>

The most risk factors for NPC group consisted of smoking history (50.7%) with smoking duration more than 10 years (32.6%), use of mosquito coils (43.2%), and consuming salted fish (39.7%)
Table 4. Most Risk Factors for non- NPC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Year 2010-2015 (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes</td>
<td>33 (58.8%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>20 (35.7%)</td>
</tr>
<tr>
<td>Mosquito coils</td>
<td>15 (26.7%)</td>
</tr>
</tbody>
</table>

In the non-NPC group the most risk factors consisted of smoking history (58.8%) with smoking duration more than 10 years (41%), alcohol consumption (35.7%), and use of mosquito coils (26.7%).

DISCUSSION

In this study showed male more than women with a ratio of 1-2 : 1 and the non-NPC group there is no difference based on gender. Based on the research that is not mentioned why men are more than women. The NPC occurred at age of 29-57 years of age and non-NPC groups at the age of 40-68 years. Based on the results of Septiani’s (2016), NPC patients have the range age between 50-59 years, men more than women. In the United States, age and sex are very important to determine the risk of carcinoma of the head neck. The average age of patients at diagnosis is 55-65 years, so it can be concluded that parents and older adults have a greater risk than children and young adults. Age and sex in NPC are associated with other factor etiology of NPC such as genetic, environmental, and EBV infection.

Risk factors for smoking in cases of NPC (50.7%) were lower than non-NPC cases (58.8%). Smoking and alcohol consumption are thought to be the dominant risk factors. Research conducted according to Stevens, smoking can increase the risk of NPC by 5.8 times, alcohol can increase the risk by 3.6 times, so both can increase the risk up to 19 times. Research conducted by Wen-Qiong Xue shows that smoking can increase the occurrence of NPC compared to non-NPC. Cigarettes contain carcinogenic substances such as nicotine and polycyclic aromatic hydrocarbons that cause gene mutations, and methylation so that there is a change in nasopharyngeal epithelial cells that are in direct contact with the mucosa during inhalation.

The use of mosquito coils in NPC patients was (43.2%) and non-NPC (26.7%). Based on Septiani's research (2016), mosquito coils have a 2.58 times risk of NPC. According to the 2013 Basic Health Research Basis, Indonesia is a country of use of mosquito coils at 48.8%. According to Moore MA, mosquito coils are the most common risk factor for NPC in Indonesia and Malaysia. The mosquito coils contain carcinogenic ingredients in the form of formaldehyde and acetaldehyde which can irritate the upper respiratory tract. According to the International Agency for Research on Cancer (IARC), formaldehyde and acetaldehyde are at risk
of developing NPC. Formaldehyde and acetaldehyde from mosquito coils bind to intracellular proteins that interfere with DNA replication and cause mutations in oncogenic, resulting in changes in morphology, cell function, and immunological reaction abnormalities in nasopharyngeal epithelial cells.  

Other risk factors that influence its high incidence of NPC is regularly consume salted fish. According to Tabuchi's research in Japan, the consumption of salted fish food regularly increases the incidence of NPC 3.15 times. Salted fish contains nitrosamine which appears in the process of salting and drying of salted fish under the heat of the sun. In the process, sunlight will react with nitrates in the salted fish meat and form nitrosamine compounds that increase carcinogenesis in nasopharyngeal epithelial cells.  

Nasopharyngeal risk factors are not only affected by one risk factor. In this study, not all NPC patients based on medical record data accompanied by data regarding NPC risk factors, this was one of the weaknesses of this study.

CONCLUSION  
The most risk factors that influence the occurrence of NPC at ORL-HNS RSHS Bandung outpatient ward in 2010-2015 consist of the use of mosquito coils, smoking and consumption of salted fish.

REFERENCE  
THE IMPORTANCE OF EARLY DETECTION
OF NASOPHARYNGEAL CARCINOMA: A CASE REPORT

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ABSTRACT

Introduction: Nasopharyngeal carcinoma (NPC) is the fourth most common cancer found in Indonesia. It is a malignant tumor arising from the epithelium of the nasopharynx. NPC may cause serious complications; therefore, an early detection and management is crucial. Physicians must be observant to detect NPC due to its tricky anatomical predilection site.

Case report: A 37-year-old man was admitted to ORL-HN outpatient’s clinic in Dr. Cipto Mangunkusumo Hospital with NPC. He had complained feeling of fullness in the left ear, spontaneous nosebleeding from left nostril, severe headache in his left side, numbness on his cheek, and double vision when looking to the left. In a series of approximately 2 years, the patient had underwent a septoplasty, an installation of tympanostomy tube, and a conchotomy to relieve the symptoms he experienced. Only 6 months ago, the patient was finally diagnosed with NPC.

Conclusion: It is very important for a physician to be more observant when meeting a patient with numerous chief complaints. They should not treat every symptoms the patient had, but to find out whether those symptoms are actually related to each other and treat the patient accordingly.

Keyword: nasopharyngeal carcinoma, early diagnosis

INTRODUCTION

The Nasopharynx is the highest part of the pharynx. It is connected to the nasal cavity via the choanae and to the middle ear by the eustachian tube orifice. The concavity behind the nasopharynx is termed the pharyngeal recess (Rosenmüller fossa).¹ This is the most common site of nasopharyngeal carcinoma (NPC) lesion.² The anatomical region is a very important clue to determine the extent of NPC size as the clinical manifestation is largely affected by the anatomy of nasopharynx. NPC is a malignant tumor arising from the epithelium of the nasopharynx.³
Southeast Asia has the highest number of NPC cases with the prevalence rate of 15-50 cases per 100,000 inhabitants. In Indonesia, NPC is the fourth most common cancer after cervical cancer, breast cancer, and skin cancer with the prevalence of 6 cases per 100,000 inhabitants. NPC is strongly related to Epstein Barr Virus (EBV) infection and its development is influenced by geographical distribution, race, genetic, sex, occupation, environment, culture, lifestyle, and socioeconomic status.

NPC may cause serious complications; therefore, an early detection and management is crucial. The gold standard for diagnosing NPC is biopsy whereas CT scan is important for detection of metastases. In this case report, we will discuss an unfortunate case of a patient with NPC that came to the tertiary hospital in Indonesia.

CASE REPORT

A 37-year-old man with NPC was admitted to ORL-HNS in Dr.Cipto Mangunkusumo Hospital. In 2015 (approximately two-and-a-half years ago) he experienced the feeling of fullness in his left ear. He denied any hearing disturbances, tinnitus, fluid oozing from the ear canal or pain in the ear. The patient also complained of frequent spontaneous nose bleeding from the left nostril. Usually, the bleeding stopped in one to two minutes. The blood sometimes omitted a foul odor. In addition, he experienced a severe headache, especially in the left region of his head. The headache could not be localized. The pain felt like the head was being stabbed, throbbed, and pressed by a heavy load at the same time. The patient denied history of hypertension, vision impairment, frequently carrying heavy weights, psychological problems, nausea, vomiting, trauma, and history of unilateral body weakness or facial asymmetry.

Two-years ago, patient finally went to an ENT surgeon and was suggested to undergo a head CT-Scan. The result revealed that he had a septal deviation. He underwent septoplasty procedure. After the surgery, the nosebleeds stopped. However, other symptoms persisted.
Four months later, during the patient’s control to the outpatient’s clinic, he mentioned that the feeling of fullness in his left ear persisted. The clinician then diagnosed the patient with glue ear. Thus, the patient underwent installation of tympanostomy tube (grommet tube) scheduled 5 months after the visit. However, his symptoms did not go away after the intervention.

Ten months ago, he went to a neurologist for his persistent cephalgia. He was diagnosed with trigeminal neuralgia and was recommended to do head MRI. The result revealed that patient suffered from sinusitis and suggested to undergo conchotomy.
Sixth months ago, conchotomy using CWL was conducted. After the surgery, his complained of cephalgia and feeling of fullness in his left ear still persisted, also felt an additional symptoms of numbness on his cheek and double vision when looking to the left.

He was then referred to another ENT surgeon. There, he was suggested a mastoid CT-scan. From the CT-scan, he was informed that he had an asymmetrical nasopharynx which suggested that he had a nasopharyngeal carcinoma (NPC). Then, he underwent biopsy of the nasopharyngeal mass. The result showed that he suffered from non-keratinizing squamous cell carcinoma, undifferentiated type. He went to Dr. Cipto Mangunkusumo Hospital for further treatments ever since.

**Discussions**

Our patient has been experienced the symptoms since approximately 2 years ago. In this case, he suffered from of fullness sensation in his left ear, spontaneous bloody discharge from left nostril, and severe cephalgia in the left region. Fullness sensation on his left ear suggested that there was a middle ear effusion of the blocked Eustachian tube which might be the result of compression from the enlarging tumor. Bloody discharge from the nostril suggested that the NPC grows anteriorly. In addition, this discharge was coming out only from the left nostril, and there was no history of epistaxis or trauma at the nostril before.
This increases the possibility that NPC was the cause of this bleeding. The cephalgia suggested that there was a skull base involvement as the tumor also grow superior-inferiorly. Therefore, it is common that the patient may also suffered from facial pain from unilateral trigeminal neuralgia. The five most common symptoms that appear in the first time in NPC patients in Indonesia are ear problem, nasal congestion, bloody discharge, cephalgia and bilateral lymph node enlargement. Since this patient was suffered from 3 out of 5 symptoms at the first time, therefore physicians must suspected NPC until proven otherwise.

Physical examination must involve not only the ear, nose, throat, head, and neck, but also other examinations such as ophthalmologic, neurologic, and complete general physical examination to find the metastasis. For instance, posterior rhinoscopy should be done in this patient earlier. Ear examination using otoscope and tuning fork examination are also needed to evaluate ear problem. Cranial nerve examination should also be done to examine the level of neurologic damage and find the extent of intracranial defect.

In this patient, the tuning fork examination revealed that the patient had a mixed of conductive and sensorineural hearing loss, indicated by a positive Rinne test, lateralization to the healthy ear (right ear), and Schwabach test similar to the examiner’s ear. The cranial nerves examination also showed that there is abnormality in the sensoric function of cranial nerve V, which means that there might be intracranial involvement in this patient.

It is very unfortunate for this patient that he was diagnosed with NPC only after numerous doctor’s appointments and even ENT specialist. He had underwent septoplasty, installation of typanostomy tube, and conchotomy before the physician found the NPC. If the physician were aware with the characteristic of the disease, he might not need to have those procedure done. Due to the fact that the patient’s diagnosis was formed late, currently, the patient had to suffer from complications of NPC.

Presentation of the nasopharyngeal carcinoma is variable. Patient’s can present with ontological, neck mass, nasal, or neurological features. Majority of the cases presented with unilateral or bilateral neck masses and/or deafness.

The importance of doing full ENT examination in cases of persistent middle ear disease, recurrent or persistent nasal symptoms, headache or neck swelling. A high index of suspicion with awareness of the disease is required to detect early tumors. Flexible endoscopic examination with documentation of the nasopharynx is the valuable procedure. This facility should be provided to the physicians and surgeons involved in the management of nasopharyngeal carcinoma, especially in areas where the disease is thought to be more prevalent. Health education and training for primary care physicians can also be of great help in early diagnosis of these cases, and it’s also important to give more hours to teach the Medical students since beginning how to understand the clinical presentation,
early sign about Head and neck cancer especially Nasopharyngeal carcinoma, because they are in the first basis patient’s search for treatment.

However the early diagnosis of nasopharyngeal carcinoma can be a difficult task because the post nasal space is relatively inaccessible to examination. The fact that the presentation of nasopharyngeal carcinoma is variable (headache, cranial nerve involvement, nasal obstruction or a neck mass due to nodal metastases). Patients may remain asymptomatic for a long time, given the often clinically occult site of presentation and patients consult doctors of different specialties who have little experience in managing NPC. It is not surprising that the diagnosis of NPC is delayed. While Van Hasselt stated only 10% of patients are diagnosed early at stage I.

CONFLICT OF INTERESTS
The authors declare no conflicts of interest.

REFERENCES
Van Hasselt A, Woo JKS. Nasopharyngeal carcinoma. Scott Brown’s Otorhinolaryngology and head and neck surgery, 7ed Ed.2008;2;ch188:2445-74
SYMPTOM IMPROVEMENT IN THE STAGE IV NASOPHARYNGEAL CANCER AFTER CHEMORADIATION

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ABSTRACT

Background: Nasopharyngeal cancer (NPC) is the most common cancer found in head and neck and most prevalently found in men. The prognosis of this cancer depends on tumor aggressiveness, and therapeutic intervention. The extent of local invasion, regional lymphatic spread, and distant metastases are reflected in the TNM stage. Due to the limitations of NPC anatomy and its high radio sensitivity, NPC is treated with chemoradiation therapy. Objective: To report the symptom improvement after chemoradiation for patients with stage IV nasopharyngeal carcinoma at dr. Kariadi Hospital. Cases: Male and female patients with stage IV nasopharyngeal cancer having ptosis and disorder movement eye symptoms. Treatment: Chemoradiation is performed. Summary: Chemoradiation provides improvement in stage IV nasopharyngeal cancer patients.

Keywords: Nasopharyngeal Cancer, Chemoradiation

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma of the nasopharyngeal epithelial layer. These neoplasms can appear from various sides of the nasopharynx and are more commonly seen in the fossa of Rosenmüller. One of the symptoms that can be caused is a disturbance in nerve III causing palpebral ptosis, and disorders in the nerve IV and VI causing ophthalmoplegia.

Mixed chemoradiotherapy has been accepted by most oncologists as a standard treatment for advanced NPC. There, however, is still controversy in the optimal medicine, time, dose and duration of chemotherapy. In general, there are three different ways to incorporate chemotherapy into curative therapy of the radiation therapy: before (neoadjuvant), while (concurrent), and after (adjuvant) radiation therapy.

So far, there is a few reports of symptom improvement in the stage IV nasopharyngeal cancer after chemoradiation at dr. Kariadi Hospital. Hence, this report is made to elevate the knowledge about stage IV nasopharyngeal cancer after chemoradiation.
CASE REPORT

The first case was a 44-year-old man coming to the ENT-HN clinic with a complaint of left and right stuffy nose. In the beginning, 8 months before, it was only left stuffy nose and it felt heavier time after time. It was weighing on the right nose and kept continuing. Nosebleeds were experienced and followed by the noisy on the left ear. Then, 4 months before, the patient experienced a headache and leisure, dual visions on the right and left eyes, and the right and left eyelids could not open. The results of examining the eyes showed that both eyes were ptosis and the movements of the eyes were limited. The examination of MSCT nasopharyngeal scan with facial contrast resulted the mass in the left and right side of nasopharynx spread to the left and right space of parapharyngeal, retropharyngeal space, right and left cavum nasi posterior, right and left ethmoidal sinus, right and left sphenoid sinus, right and left parasellar, oropharynx as high as the corpus vertebrae cervical 2 with destruction on the medial wall of the left maxillary sinus, os clivus, dorsum sella, processus of anterior-posterior clinoid, minor sphenoid wing, multiple lymphadenopathy level 2,3 of the right regio colli (size of ±1.91x0.89 cm at level 2) and lymphadenopathy level 2 of the left regio colli (size of ±2.35 x 1.18cm). The results of PA provide non-keratinizing carcinoma and undifferentiated subtypes

![1A](image1.png) ![1B](image2.png) ![1C](image3.png) ![1D](image4.png)

**Picture 1.** 1A Patient profile before chemoradiation, while 1B, 1C, 1D after chemoradiation

![2A](image5.png) ![2B](image6.png)

**Picture 2.** 2A MSCT before chemoradiation, while 2B after chemoradiation

Patient was treated in neoadjuvant chemoradiation with 6 series of paclitaxel-cisplatin chemotherapy and rays. After 3 times of chemotherapy, the
patient’s complaints began to improve. The patient’s eyelids were able to open and the eyeballs were able to move in all directions. Afterward, evaluation was conducted. The evaluation showed that the patient was no longer complaining the stuffy nose, noisy ears, double vision, nosebleeds, headaches. The physical examination showed there was no ptosis, the movement of the right and left eye balls could move in any direction, and there was no lump in the neck. MSCT Nasopharyngeal scan with contrast found nasopharyngeal mass spreading to the right-left parapharyngeal space, with a reduced size compared to the previous one, lymphadenopathy multiple 2.3 levels of the right regio colli (largest size of \(±23 1.23 \times 0.57\) cm) and level 2 of the left regio colli left (size of \(±1.54 \times 0.86\) cm).

The second case was 41-year-old woman coming with a complaint of double vision of the left eye. In the beginning, 1 year before, the patient experienced noisy on the left ear getting more severe time after time. Then, the patient has experienced stuffy nose on the left nose for 2 months as well as dual vision of the left eye view for 4 days with headache which got heavier and the left eyelid could not open. The results of examining the eyes showed that the left eye was ptosis and left eye movement was limited. MSCT scan showed a solid mass in the left nasopharyngeal region spreading to the mucosal pharyngeal space, parapharyngeal space, carotid space, masticator space, left paracella, multiple lymphadenopathy in the regio colli level 2.3 of the right and left largest size of \(±AP 1.16 \times LL 1.43 \times CC 1.78\) cm. PA results provide non-keratinizing carcinoma and undifferentiated subtype.

The patient was treated with neoadjuvant chemoradiation with 6 series paclitaxel-cisplatin chemotherapy and rays. After 3 times of chemotherapy, the patient began to get better. The patient’s eyelids were able to open, and the eyeball
was able to move in all directions. Afterwards, the evaluation was conducted. The results of evaluation showed that the patient was no longer complaining stuffy nose, noisy ears, double vision, nosebleeds, headaches, and there was no lump in the neck. Nasopharyngeal scan MSCT with contrast was found to decrease the size of the regio nasopharyngeal tumor mass appeared to be smaller, malignant lymphadenopathy in the right and left regio colli was not seen anymore.

DISCUSSION

Nasopharyngeal cancer has typical symptoms and signs such as epistaxis, nasal congestion, noisy ears, swelling of neck lymph gland, and in stage IV tumors spreading to intra-cranial headaches, ptosis due to N III disorders, and eye movement disorders due to disturbances N III, IV, VI. The most common histopathology is keratinizing squamous cell carcinoma, Non-keratinizing Carcinoma, and undifferentiated carcinoma which has the most and has a better prognosis than these three histopathologies, i.e. undifferentiated carcinoma.

Mixed chemoradiotherapy has been accepted by most oncologists as a standard treatment for advanced NPC. There, however, is still controversy in the optimal medicine, time, dose and duration of chemotherapy. In general, there are three different ways to incorporate chemotherapy into curative therapy of the radiation therapy: before (neoadjuvant), while (concurrent), and after (adjuvant) radiation therapy.

One of nasopharyngeal cancer complications is petrosphenoidal jacob syndrome i.e. the tumor grows upward to the base of the skull through the foramen lacerum until the cavernous sinus suppresses N.III, N.IV, N.VI, and N.II which leads to trigeminal neuralgia (N.V) abnormalities. Trigeminal neuralgia is a pain on the side of the face that is characterized by a feeling like being exposed to electricity which is limited to the distribution area and trigeminal nerve, palpebral Ptosis (N.III), Ophthalmoplegia (N.III, N.IV, N.VI).

The malignancy stage is usually measured by clinical or pathological stage. However, because NPC is usually treated conservatively, it is usually done clinically based on the results of physical examination and radiology. It is important to recognize that the clinical stage is not only important in knowing the extent of the disease and predicting patient outcomes, but it is also important in determining the right management strategy.

SUMMARY

Neoadjuvant chemoradiation is one of the treatments for nasopharyngeal cancer that can improve symptoms in patients.
MANAGEMENT OF NASOPHARYNGEAL CARCINOMA

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a carcinoma type of malignancy derived from epithelial and lymphoid gland kriptae of the nasopharynx mucosal. Nasopharyngeal carcinoma frequently found in North Africa, Alaska, Southeast Asia including Indonesia, and South China specifically Guangdong province. The highest incident found in Guangdong South China reported 20-30/100,000/year, the lowest incident found in Western country reported 1/200,000/year.\(^1\) Incident of NPC in Indonesia reported 6.2/100,000/year, it was in rank four after cervical cancer, breast cancer and skin cancer.\(^2\) In head and neck malignancy, NPC is in the first place. According to previous study conducted in RSUD Dr. Soetomo Surabaya, based on electronic medical record (EMR) data of out patient department from 2010 – 2012 NPC case was 61.10% of total head and neck malignancy, meanwhile in RS. Cipto Mangunkusumo Jakarta from 1996–2005 NPC case was 28.40% of total head and neck malignancy.\(^2\)

The exact cause of NPC is still unknown, but already known that NPC has multifactorial etiologies. There are 3 factors that have important role in causing NPC, Epstein-Barr virus (EBV), environmental factor, and genetic factor. Overall the prognosis of NPC is getting better because of radiotherapy and chemotherapy technology development, local control can be achieved by both modalities especially in early stage. The problem that remains a challenge in managing NPC is cancer cell resistance to chemotherapy, radiotherapy, or both chemotherapy and radiotherapy. Cancer cell resistance is a cause for recurrence, residual tumour, or distant metastasis. Cancer cell resistance is the main cause of morbidity and mortality in NPC.\(^1\)

The better understanding of NPC management need to be improved in order to reach better therapy result, hence in this article is elaborated several topics which include the risk factors, clinical symptoms, diagnosis, histopathology, staging, therapy, and follow-up.

1. ETIOLOGY

The etiology factor of NPC is multifactorial. There are 3 factors EBV, environmental factor, and genetic factor. These 3 factors interacting with each other in synergy that can cause NPC (Figure 1).\(^3\)
Figure 1. Etiology factors of nasopharyngeal carcinoma. 

NPC : Nasopharyngeal carcinoma, EBV : Epstein Barr virus, HLA TCR : human leucocyte antigen, T cell receptor

1.1 Epstein-Barr Virus

Previous study proved that there is a close relation between EBV and NPC. Epstein-Barr virus mainly transmitted by saliva and also through blood transfusion. The transmission through saliva occurred because intimate oral contact and also saliva that left at glasses, plates, toys and other objects. The viral entrance is through oropharynx, in this area EBV replicates in many elements of parotid gland epithelial, pharynx, tongue, and B cell lymphocyte. After EBV replicates in B cell lymphocyte and human nasopharynx epithelial, turns out to be dormant for long periods of time without any symptom. The EBV must be activated in the first place before interfere the host become malignant and conduct replication without control.\(^2,3\)

Activation happens because of several factors, such as consuming salted fish, plant extracts that used in many traditional medications and low socio-economic level. Salted fish contains of nitrosamin, it is a carcinogenic that can activate the EBV. Nitrosamin also found in preserved food, fermented vegetable, smoked salmon that consumed by people in China. The habit of consuming salted fish is the main factor that can activated EBV. Plant extracts contain N-Butyric acid known as EBV promotor and activator.\(^3\)

Most of NPC patients are from low social-economy level, it relates with environmental factors and life style. Unhealthy environment such as a house with less ventilation can cause smoke trapped inside the house. Smoke can be derived from incense burning, insect repellent and certain kind of woods. Unhealthy life style such as cooking with certain ingredients, eating hot foods, lack of fruits and
vegetables. These conditions cause irritation and chronic inflammation at nasopharynx that makes mucosa more vulnerable to carcinogenic agent.  

1.2 Environmental Carcinogenic
Carcinogenic is a term that used to describe the substance that increase cancer incident. Carcinogenic not only activates EBV but also causes mutation. The carcinogenic substances are nitrosamine, benzo(a)pyrene, benzo(a)anthracene, chemical gas, and industrial smoke. Other environmental factors are smoking and alcohol. Many studies stated that smoking can increase the possibility 2-6 times higher than non smoking, and also stated about increase possibility in alcohol.  

1.3 Genetic Factor
The genetic susceptibility associated with NPC based on the fact that NPC found frequently in South China. Many studies conducted in Singapore chinese, Malaysia, Hongkong and China proved that HLA Bw 46 Bw 58 correlate with increasing risk. Genetic susceptibility relates with NPC based on the facts that many NPC cases in South China. A Study conducted in Jakarta found HLA-A24 and B63 as a suspicious cause of NPC in Indonesians. Someone with HLA-A24 has 4.96 times more susceptible of NPC. This is different with Malaysian, HLA-B17 and B18 are found. People with HLA-B17 3.4 times more susceptible of NPC and B18 4.4 times more susceptible of NPC.  

2. CLINICAL SYMPTOM
Clinical symptom of NPC devided into 4 groups: first, local symptom cause by primary tumour. The nasal symptoms such as flu, blocking nose, and bloody discharge or smelly pus. Tumour could expand to nose, throat, skull base, spread downward to soft palate and causing bombans. (figure 2A). Second, the ear symptoms are tinnitus, hearing loss, or repeating otitis media. (figure 2B). Third, tumour growth that infiltrated upward through foramen lacerum until duramater that cause severe headache. Upward infiltration also damage cranial nerves, when N.VI damage can cause diplopia, N.V can cause trigeminal neuralgia, N.III and IV can cause ptosis and ophthalmoplegy. (figure 3). Tumour can grow further through foramen jugulare and damage N. IX, X, XI and XII. Tumour that damage N.IX and X can cause soft palate paralysis, pharynx and larynx. The nerve damages cause eating disturbance, drinking disturbance and dysphonia.  

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Picture 1. A. Primary tumour block the choana B. Primary tumour block Eustachian tube.¹

Picture 3. Paralysis of trochlear nerve.¹

Four, lymph node metastasis can cause lymph node enlargement and usually bilateral/unilateral. The most frequent area is one-third upper jugular, seldomly at submandible or submental area. (figure 4). Common symptoms of malignancy are, anorexia, thin body, subfebrile, trismus, and swallowing disturbance. The symptoms of distant metastasis mostly found in liver, lungs, and bone.¹

Picture 4. Nasopharyngeal carcinoma through lymph node.¹
Nasopharyngeal carcinoma patients usually come to medical services in the late stage. Lymph node enlargement is the most common symptom found, followed by nasal blocking, epitaxis, hearing loss, proptosis, flu, vision disturbance, weight loss, ear pain, and cranial nerves paralysis.

3. DIAGNOSIS
Diagnosis based on history taking, physical examination, nasopharyngoscopy, and endoscopy. Additional examination including head and neck CT scan, magnetic resonance imaging (MRI) if there is any intracranial infiltration. Nasopharynx biopsy specifically at Rosenmuller fossa, continued with histopathology examination. Immunology test including indirect immunofluorescence for IgA anti viral capsid antigen (VCA) and early antigen (EA). The combination between these two examinations is sensitive and specific for screening, early detection and to evaluate the progressiveness, but commercially not available. 7

4. HISTOPATOLOGY
World Health Organization (WHO) in 1978 devided NPC in to 3 type based on histopatology findings.1

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<th>Classification</th>
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<td>Type 1</td>
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<tr>
<td>Type 2</td>
<td>Non keratinizing squamous cell carcinoma</td>
</tr>
<tr>
<td>Type 3</td>
<td>Undifferentiated carcinoma</td>
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5. STAGING
Staging needs to be done to define therapy and prognosis. Staging classification based on American Joint Committee on Cancer Staging and End Result Reporting/International Union Againt Cancer (AJCC/IUAC) 2011(table 2-5).8

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Table 3. Lymph node

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<tr>
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Table 4. Distant metastasis

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Table 5. Staging group

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<td>Stage IVa</td>
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<td>Stage IVb</td>
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<td>Stage IVc</td>
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6. THERAPY

Nasopharyngeal carcinoma therapy modality consist of radiotherapy, chemotherapy and surgery, single radiotherapy or combination with chemotherapy.

6.1 Radiotherapy

Radiotherapy is a method using ion light to eradicate carcinoma and preserve healthy tissue around. Until now radiotherapy is still a primary therapy for NPC, and even single therapy for early stage of NPC. The consideration to choose radiotherapy as treatment choice because histopatology findings of NPC (75-95%) undifferentiated type (WHO 3) and non-keratinizing type (WHO 2) which is more radio-sensitive in early stage. The other consideration is anatomy of nasopharynx that difficult to perform radical surgery. 9,10

Radiotherapy dose that used depends on therapy purpose. Curative radiotherapy given in all stages, except in distant metastasis. Radiotherapy target is primary tumour, neck and supraclavicle lymph nodes. Total dose given for T1-T2 is 65 Gy, can be raise to 70-76 Gy for T3-T4. The fraction is 1.8-2Gy per day given 5 times per week. Spinal cord dose can not be more than 45 Gy. Palliative radiotherapy given for tumour metastasis in bones and local recurrency. Radiotherapy dose in recurrency is 20-30 Gy. 10

There are 2 methods of radiotherapy transmissions, conventional 2 dimensional (2D) and conformal 3 dimensional (3D). The 2D technique is frequently use in developing country. In early stage, T1 and T2 give local control success for 75-90% of all cases, and for T3 and T4 give local control success for 50-75% of all cases. The weakness of this technique is low level of protection to the important organs near nasopharynx such as brain, spinal cord, fiber optic, and parotid. The side effects that might happen stomatitis, teeth caries, otitis media, external otitis, and trismus. The weakness of 2D technique could be take over by 3D and intensity modulation radiotherapy (IMRT). Intensity modulation radiotherapy is the development of 3D technique, which given high dose in tumour and low dose in normal tissue. Therapy result is better, higher local control, normal tissue preservation, and less complications. 1

6.2 Chemotherapy

Nasopharyngeal carcinoma relatively sensitive to radiotherapy, in early stage single radiotherapy is quite effective. In fact mostly NPC patients come in late stage, so that single radiotherapy won’t give satisfying result. The 5 years survival rate of late stage NPC is 34-52% with poor prognosis. Late stage NPC chemotherapy is very important because NPC not only radiosensitive but also chemosensitive and shows good response to chemotherapy agents. The chemotherapy combination with radiotherapy for patient with stage III/IV without metastasis based on consideration, first minimized distant metastasis risk by eradicating micrometastasis. Second, strengthen synergetic effect of radiotherapy
with chemotherapy as radio-sensitizer agents. Third, facilitate radiotherapy plan and increase local control with decrease tumour volume before radiotherapy.  

6.2.1 Route of transmission and regiment

According to priority there are 2 types of regiments, primary therapy and adjuvant therapy. Primary therapy means there is no additional therapy needed, whereas adjuvant therapy means accompanying primary therapy, which is surgery or radiotherapy. According to route of transmissions there are 3 types routes, induction, concurrent, and adjuvant. The choice depend on the purpose by considering the risks and benefits.

a. Neoadjuvant

Neoadjuvant chemotherapy is a chemotherapy given before the definitive radiotherapy. There are 3 important considerations in chemotherapy, the benefit for patient, duration, and survival. Survival based on staging, tumour size, physical status, and any other things relate to main disease. Some clinical trials recommend that only patients who give complete response get the clinical beneficial.

This type of chemotherapy has many benefits, reduce metastasis risk by eradicating micrometastasis dan locoregional microscopy. The better tissue preservation, easier surgery, less radical, reduce tumour size, strengthen radiotherapy, better vascularization, and become the success indicator of other therapy. There are many disadvantages including decrease of clinical status, tumour size getting bigger, need more time, toxicity, higher cost, and delay the definitive therapy.  

The standard regiment for neoadjuvant chemotherapy are cisplatin and 5 fluorouracil (FU). Regimen, dose and schedule of neoadjuvant chemotherapy can be seen at table 6.

**Table 6.** Regimen, dose, route of transmission neoadjuvant chemotherapy.  

<table>
<thead>
<tr>
<th>Induction Chemotherapy</th>
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<tbody>
<tr>
<td>Docetaxel (Taxotere) + cisplatin + 5-FU&lt;sup&gt;1,8,0&lt;/sup&gt;</td>
</tr>
<tr>
<td>Day 1: Docetaxel 75mg/m² IV + cisplatin 75mg/m² IV, plus Days 1-5: 5-FU 750mg/m² continuous IV infusion. Repeat cycle every 3 weeks for 4 cycles.</td>
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</tbody>
</table>

**General treatment notes:** Squamous Cell Cancers of the head and neck include lip, oral cavity, hypopharynx, glottis larynx, supraglottic larynx, ethmoid sinus, maxillary sinus, occult primary.
b. Concurrent

Concurrent chemotherapy is a chemotherapy that given combine with radiotherapy (chemoradiotherapy). Theoretically this type of chemotherapy is very useful, radiotherapy anti tumour strengthen simultaneously by radiosensitizer effect of chemotherapy. Systemic activity of chemotherapy could eradicate the micrometastasis at the area outside radiotherapy. Strengthen cell distribution that sensitive to chemoradiotherapy. Decrease tumour size and increase drug transmission.

Cell that resistant to any modality could be eradicate by other modality. The advantages of this treatment are, increase survival rate, increase local control, organ preservation, and shorter time. The disadvantages are, increase toxicity and side effects. 13 Regiment, dose and chemotherapy schedule can be seen at table 7.

Table 7. Regiment, dose, route of transmission concurrent chemotherapy.14

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>DOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Squamous Cell Cancers</strong></td>
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<tr>
<td><strong>Primary Systemic Therapy + Concurrent Radiotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Cisplatin (CDDP; Platinol) + radiotherapy 1-3</td>
<td>Days 1, 22 and 43: Cisplatin 100mg/m² IV + concurrent radiotherapy 2Gy/day to a total of 70Gy.</td>
</tr>
<tr>
<td>Cisplatin + paclitaxel (Taxol) 1,5</td>
<td>Day 1: Paclitaxel 30mg/m² IV (begin on Monday), plus</td>
</tr>
<tr>
<td></td>
<td>Day 2: Cisplatin 20mg/m² IV (every Tuesday). Time cycle every week for 7 cycles, plus</td>
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<td></td>
<td><strong>Radiotherapy:</strong> 70Gy, delivered in 35 fractions; plus</td>
</tr>
<tr>
<td></td>
<td>1 fraction delivered daily Monday-Friday.</td>
</tr>
<tr>
<td>Carboplatin (Paraplatin) + infusional 5-FU 1,6</td>
<td>Days 1-4: 5-FU 600mg/m²/day as continuous IV infusion + carboplatin 70mg/m²/day IV bolus. Repeat cycle every 3 weeks for 3 cycles given concurrently with radiotherapy</td>
</tr>
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</table>

c. Adjuvant

Adjuvant chemotherapy is a chemotherapy given after definitive radiotherapy. This type of therapy needed to prevent recurrency. Adjuvant chemotherapy has many advantages, such as increase locoregional control, eradicate residual tumour, and eradicate distant metastasis. Whereas there are also disadvantages such as poor vascular bed, increase toxicity, longer time.13 Regiment, dose, and chemotherapy dose can be seen at table 8.
Table 8. Regimen, dose, Route of transmission of adjuvant chemotherapy.  

<table>
<thead>
<tr>
<th>Nasopharynx Cancer</th>
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</thead>
<tbody>
<tr>
<td><strong>Chemoradiation Followed by Adjuvant Chemotherapy</strong></td>
</tr>
</tbody>
</table>
| Cisplatin + radiotherapy, followed by cisplatin and 5-FU[^13,10,11] | Cycles 1-3  
Day 1: Cisplatin 100mg/m² IV in concurrence with radiotherapy. Repeat cycle every 3 weeks, followed by  
Cycles 4-6  
Days 1-4: Cisplatin 80mg/m²/day + 5-FU 1,000mg/m²/day IV (by 96-hr infusion). Repeat cycle every 4 weeks for 3 cycles. |

**d. Sequential**

Sequential therapy is a combination of neoadjuvant chemotherapy followed with concurrent chemoradiotherapy. These combinations have advantages and disadvantages. As an example, the use of classic neoadjuvant chemotherapy in locoregional and distant metastasis. For distant metastasis, the purpose is to eradicate micrometastasis, whereas locoregional the purpose is to decrease tumour size before radiotherapy. The toxicity is less, but need more time for therapy. On the other hand, chemoradiotherapy increase the locoregional dose intensity to control the locoregional control. This is not effective because can increase the local toxicity and systemic significantly.  

**e. Targeted Therapy**

There are many targeted molecules identified in NPC and tested in order to increase therapy effect. A molecule that already known and recommended is anti-epidermal growth factor receptor (EGFR), although in clinical practice still need further evaluation. In head and neck malignancy include NPC 80-90% cases found excessive expression of EGFR molecules, that is why anti-EGFR therapy is needed. The use of anti-EGFR in NPC has already been tested. The use of anti-EGFR as single treatment is disappointed, therefore it must combine with other modality, including radiotherapy or chemotherapy. An example of anti-EGFR drug that already in market is cetuximab. Cetuximab recommended for head and neck malignancy squamous cell carcinoma type with metastasis, recurrent, or allergic to chemotherapy drugs. Cetuximab transmission with initial dose 400mg/m² continue 250mg/m² every week, given before chemotherapy or radiotherapy for 6 weeks.  

[^13]:  
[^10,11]:
7. FOLLOW-UP

After therapy given it should be evaluate with follow-up 3-4 weeks after therapy. The assessment of response can be seen from two aspects, survival rate and response rate. Response rate, the aspect regarded as covering diminution neck lymph node and decrease of primary tumour size in nasiphraynx. The assessment of therapy response was done based on the WHO criteria, complete response is when primary tumour disappeared 100%, partial response is when parimary tumour narrowed 50-100%, no response is when primary tumour narrowed less than 50% or remain the same, and progressive is when primary tumour is getting bigger than before or arising new lesion. Complete response including high response, meanwhile partial reponse, no response and progressive response including low response. The follow-up schedules are every 1-2 months in the first year, every 2-3 months in the second year, every 3-5 months in the third until fifth year, every 6 months in the fourth until seventh year, every 6 months – 1 year in the seventh year and beyond. Each follow-up schedule consist of history taking, physical examination, CT scan, and biopsy when needed.
SUMMARY

- History taking
- Complete physical examination
- Nasopharyngal examination & biopsy
- +/- FNAC of regional lymph nodes
- Baseline investigations (FBC, renal profile, random blood sugar, liver function test, chest X-ray and electrocardiogram)
- MRI of nasopharynx & neck (from base of skull to thoracic inlet) or CT with contrast
- PET-CT or CT thorax/abdomen or ultrasound and bone scan, as indicated
- Pre-treatment dental assessment
- Nutritional evaluation

**Stage I (T1N0M0)**
Treatment with definitive radiotherapy (RT) to nasopharynx & elective RT to neck
- Definitive RT:
  - Primary site: total of 66-70 Gy for 33-35 fractions, treated one fraction/day for 6-7 weeks (1.8-2.0 Gy/fraction)
  - Prophylactic neck: 54-60 Gy for 30 fractions, treated one fraction/day for 6 weeks (1.8-2.0 Gy/fraction)
- IMRT recommended to minimise dose to critical structures

**Stage II, III, IVA and IVB**
Concurrent chemoradiotherapy
- Cisplatin + RT
- Conventional fractionation:
  - Primary site: total of 66-70 Gy for 33-35 fractions, treated one fraction/day for 6-7 weeks (1.8-2.0 Gy/fraction)
  - Neck: 54-70 Gy for 30-35 fractions, treated one fraction/day for 6-7 weeks (1.8-2.0 Gy/fraction)
- IMRT recommended to minimise dose to critical structures

**Stage IVC (distant metastasis)**
Palliative treatment
- Consider clinical trial if available
- Palliative chemotherapy to be considered in patients with good ECOG performance status (0-2)
- RT to palliate symptoms
- Referral to palliative care/ palliative home care

**Follow-up and Surveillance**
- Multidisciplinary team involvement (ENT specialist, oncologist, speech therapist, audiologist, etc)
- Head & neck and systemic examination (including nasopharyngoscopy)

<table>
<thead>
<tr>
<th>Year</th>
<th>Intervals</th>
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<tbody>
<tr>
<td>First year</td>
<td>Every 1 to 2 months</td>
</tr>
<tr>
<td>Second year</td>
<td>Every 2 to 3 months</td>
</tr>
<tr>
<td>Third year</td>
<td>Every 3 to 5 months</td>
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<tr>
<td>Fourth to fifth year</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>After fifth year</td>
<td>Every 6 to 12 months</td>
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</tbody>
</table>

- Cross-sectional imaging in the initial 5 years
- Speech/swallowing assessment as clinically indicated
- Hearing evaluation & rehabilitation as clinically indicated
- Post-treatment dental management every 3 to 4 months by trained and experienced dental specialist
- Weight assessment on follow-up
- Annual thyroid function test (TFT) screening

**Picture 5. Management algorithm of NPC.**

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