Management of Recurrent Regional Nasopharyngeal Carcinoma

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ABSTRACT
Treatment result for nasopharyngeal carcinoma has improved drastically due to introduction of chemotherapy and radiotherapy combination. However, regional failure is still a common finding which occurs to 3-10% patients. Local failure can be divided into 2, residual and recurrent disease. Residual or recurrent disease is defined as confirmations of disease occurring within 6 months following treatment. A 45-year-old male presenting with a neck mass, nosebleed, and obstructed nose. From physical examination there were multiple cervical lymph nodes enlargement in level 3 and 4 and an exophytic mass on the the roof of nasopharyng. We evaluated the patient using CT scan and biopsy. The patient was diagnosed with WHO III T2N2M0 nasopharyngeal carcinoma. Following chemoradioation, patient still complained of neck mass. PET scan showed sign of malignancy and metastasis. Patient underwent neck dissection. Histology examination showed no viable tumor cell therefore patient was diagnosed with nonspecific chronic lymphadenopathy. Following treatment for nasopharyngeal carcinoma, clinician must assess extent of disease or distant metastasis by CT scan, MRI, or PET scan. In case of which residual, recurrent, persistent, or progressive disease is confirmed, then patient had to undergone neck dissection or systemic therapy (radiation or chemotherapy). Study by Chen et al showed that selective neck dissection (SND) procedure had a favorable overall survival, disease-free survival, and regional-free survival compared to radical neck dissection (RND). Other study by Yang et al showed that adjuvant chemotherapy did not have significant correlation with overall survival, failure-free survival, local relapse-free survival, and distant metastasis-free survival. For treatment of recurrent nasopharyngeal carcinoma, clinician must consider the need for adjuvant chemotherapy or neck dissection procedure. Study showed that SND had a better effectivity compared to RND. However, it still can't be concluded whether SND procedure is better than adjuvant chemotherapy.

Keywords: *recurrent nasopharyngeal carcinoma, neck dissection, adjuvant chemotherapy.*

1. INTRODUCTION

Nasopharyngeal carcinoma is a common malignancy found in Indonesia. There are 13.000 new case of nasopharyngeal carcinoma every year, contributing to 28.4% of all head and neck malignancy. It is the most common head and neck malignancy, affecting 20-30 per 100.000 population [1-3]. There is various factor that increased the risk of this malignancy. Some which have been proven are Epstein Barr virus (EBV) infection, smoking, and history of first-degree family member with nasopharyngeal cancer [1, 3-7].

Diagnosis of pharyngeal carcinoma is rather difficult because patient's clinical presentation varies. Most patients present with progressive and metastasic disease, making treatment more difficult [8-10]. Treatment for nasopharyngeal carcinoma has improved drastically due to introduction of combination therapy. However, local failure is still a common finding, occurring in 3-10% patients. Local failure can be divided in to 2, residual disease and recurrent disease. Recurrent disease is defined as confirmations of disease within 6 months after treatment. The incidence of recurrent disease is between 7-13% [11]. It is still an underexposed problem, especially in developing country like Indonesia.

1.1. Cervical Lymph Node Anatomy

Cervical lymph node system is divided into three functional unit, Waldeyer's ring, transitional lymph node which located in head and neck, and cervical lymph node [12]. The Waldeyer's ring is divided into palatine tonsil, lingual tonsil, adenoid, and surrounding submucosal lymph node [12]. Transitional lymph node is consisted of submental, submandibular, parotid, retroauricular,

occipital, retropharyngeal, and sublingual lymph node [12].

Based on American Academy Otolaryngology Head and Neck Surgery (AAO-HNS), the cervical lymph node is grouped into 6 level: I which consists of IA (submental) and IB (submandibular), II (upperjugular) which consists of IIA (jugulodigastric) and IIB (supraspinal accessory), III (middle jugular), IV (lower jugular), V (posterior triangle) which consists of VA (spinal accessory) and VB (transverse cervical), VI (central or related to thyroid gland) [12,13].

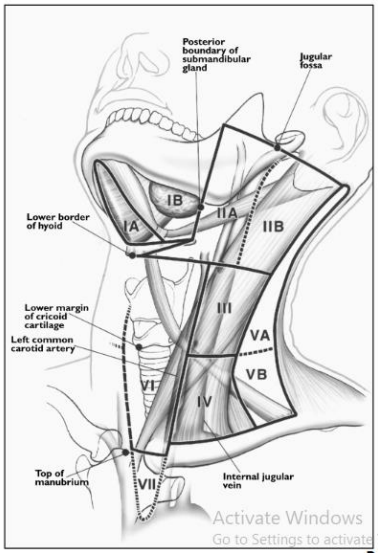

Figure 1 Cervical lymph node level [14]

Each lymph node level has its own lymphatic drainage. If lymphadenopathy due to malignancy is suspected, the cervical lymph node level can be used to determine the origin of metastasis.

Lymph nodes in level 1 drain the lip, buccal mucosa, anterior nasal cavity, and soft tissue on the cheek. IA and IB are differentiated due to difference in their drainage area. IA drains mouth floor, lower lip, ventral tongue, and anterior nasal cavity while IB drains oral cavity. Level II drains oral cavity, nasal cavity, pharing (nasopharyng, oropharyng, and hypopharyng) laryng, and parotid gland [13,15].

Level III drains oral cavity, nasopharyng, oropharyng, hypopharyng, and laryng. Level IV draines hypopharyng, laryng, thyrod, and anterior part of eesophagus. Level V drains nasopharyng, cutaneous scalp tissue, and posterior of the neck. Level VI drains thyroid gland, laryngeal glottis and subglottis, apex of piriform sinus, and anterior part of the esophagus (Figure 1) [13,15].

Based on AAO-HNS, level VII lymph nodes is not part of the cervical but mediastinal lymph node [13].

1.2. Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma is a malignancy of the nasopharyngeal epithel [4]. The global incidence of nasopharyngeal carcinoma is 80,000 new cases every year, contributing to only 0.7% of all malignancy cases. In Europe and North America, the incidence of this malignancy is only 1 per 100,000 population. However, in endemic country such as Hongkong and Southeast Asia, the incidence can be as high as 20-30 cases per 100,000 population [1].

In Indonesia, nasopharyngeal carcinoma is the most common head and neck malignancy (28,4%) with incidence of 13,000 new cases every year and prevalence of 6.2 per 100,000 population [2,8].

Data from Dharmais Hospital showed that nasopharyngeal carcinoma is one of top ten of most common cancer. In 2013, there were 134 new cases of nasopharyngeal carcinoma and 38 deaths because of it [16].

There are various risk factors associated with nasopharyngeal carcinoma, such as Epstein Barr virus (EBV) infection, salted fish consumption (contained macromolecule lignin which activate EBV), smoking, alcholol consumption, exposure to dust, smoke, and formaldehydie, and family history of nasopharyngeal cancer [5-7, 9]

Based on its histopathology, the World Health Organization (WHO) classified nasopharyngeal cancer into three subtype, WHO 1: squamous cell carcinoma, WHO 2: differentiated non keratinized squamous cell carcinoma, WHO 3: undifferentiated carcinoma, and squamous sel basaloid carcinoma [9,17].

The goal of classifying this malignancy based on its histopathology characteristic is to determine whether malignancy really originated from nasopharyng or other organs in nasal and oral cavity [17].

Beside histopathology classification, nasopharyngeal carcinoma is also classified based on its stage according to AJCC (primary tumor characteristic, involvement of regional lymph node, and distant metastasis) [8].

Nasopharyngeal carcinoma mostly originated from Rosenmuller fossa [2,9]. It is very difficult to recognize, especially in early stage [8]. Clinical manifestation of nasopharyngeal carcinoma is usually cervical lymphadenopathy which is a metastases condition. Other clinical manifestation includes obstructed nose, mild epistaxis, trismus, pain, otitis media, nasal regurgitation due to soft palate paresis, hearing problem, tinnitus, feeling of fullness in ear, trigeminal neuralgia, and cranial nerve paresis (nerve III, IV, V, VI) [3, 8-10].

Nasopharyng examination using fiber or rigid nasopharyngoscopy is needed to evaluate local status (Figure 2). CT scan/MRI of the nasopharyng is needed to evaluate pathologic anatomy (Figure 3). Pathology anatomy examination of nasopharyngeal biopsy is the gold standard in diagnosing nasopharyngeal carcinoma. To check distant metastases, clinician must perform thorax x-ray examination, bone scan, and abdominal ultrasonography. Fine needle aspiration biopsy is performed if there is an enlarged lymph node. Narrow band imaging examination is needed for treatment follow-up [3,8,10].

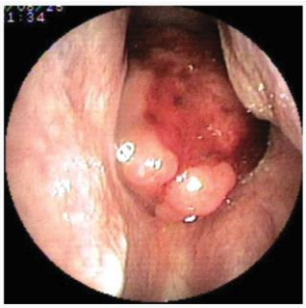

Figure 2 Nasopharyngeal carcinoma on nasopharyngoscope [18]

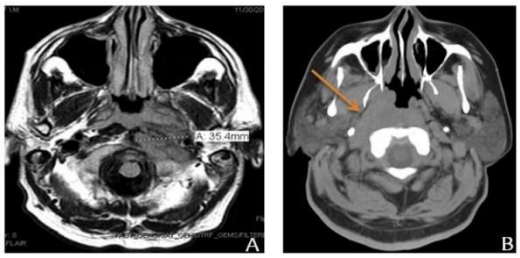

Figure 3 Stage IV Nasopharyngeal carcinoma on MRI [19]

Treatment of nasopharyngeal carcinoma involved many divisions. Based on Pedoman Nasional Pelayanan Kedokteran (PNPK) Kanker Nasofaring, treatment recommendation include radiation, chemotherapy, and/or combination of both. The goal of treatment is divided into 2, curative and palliative [10].

Prognosis of nasopharyngeal cancer is based on its stage. The 5-year survival rate is 82% for localized nasopharyngeal carcinoma and 51% for metastases disease [20].

1.3. Imaging Role in Post Treatment Surveillance

Imaging for nasopharyngeal cancer evaluation can be performed using CT and/or MRI with contrast and FDG PET/CT examination. CT and/or MRI can be obtained within 3-4 months after definitive treatment in order to establish a new baseline for future comparison. Physical examination is difficult in patient with altered anatomy. If patient showed an incomplete response, then CT and/or MRI can be performed at 4-8 weeks or even immediately [21].

FDG PET/CT should be performed within 3-6 months of definitive therapy to identify residual or recurrent tumor. FDG PET/CT performed in less than 12 weeks showed a high false-positive result and therefore should be avoided if there is no sign of recurrence or progression [21].

1.4. Recurrent Nasopharyngeal Carcinoma

Recurrent nasopharyngeal carcinoma is defined as confirmation of disease which occurs within 6 months following treatment. Study by Wang M et al showed that T staging, N staging, presence of cervical lymph node metastasis, and size and laterals of positive neck nodes was correlated to local failure. Patient which had a primary tumor that infiltrates the bone had a higher risk of residues and recurrence [22].

After patient had completed systemic therapy or radiotherapy, a clinical assessment is performed within 4-8 weeks. If patient had residual or recurrent, persistent disease, or progression, clinician must performed CT or MRI with contrast or FDG PET/CT to assess extent of disease or distant metastasis. In patient with confirmed residual or recurrent with resectable tumor, resection of residual or recurrent primary and/or neck dissection is performed. If the tumor is unresectable, patient will undergo reirradiation in addition to systemic therapy and supportive care [21].

If patient response to therapy, FDG PET/CT examination can be performed at minimum of 12 weeks and CT scan or MRI with contras at 8-12 weeks. Patient with negative FDG PET/CT or CT or MRI examination can be observed according to NCCN recommendation. If FDG PET/CT examination is equivocal, then patient is observed and repeat of FDG PET/CT was performed at 3- months. If FDG PET/CT, CT, or MRI result is positive, then biopsy, resection of primary tumor, or neck dissection is performed [21].

NCCN follow-up recommendation involved of history and physical examination, TSH examination, dental evaluation, EBV DNA monitoring, supportive care and rehabilitation, and imaging. Patient was evaluated by history and physical examination every 1-3 months during the first year, every 2-6 months during the second year, every 4-8 months during the third to fifth year, and every 12 months after 5 year. TSH level is checked every 6-12 months if the neck is irradiated. Dental evaluation is performed to assess oral cavity and sites exposed to significant treatment. Supportive care

and rehabilitation include speech/hearing and swallowing evaluation, nutritional evaluation and rehabilitation, surveillance for depression, and smoking cessation and alcohol counselling.

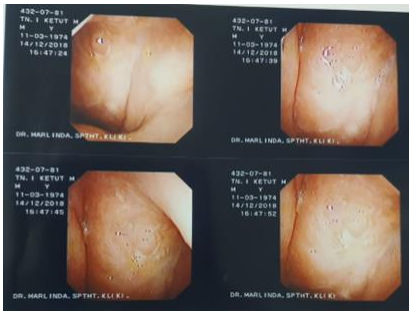

Figure 4 Endoscopy examination

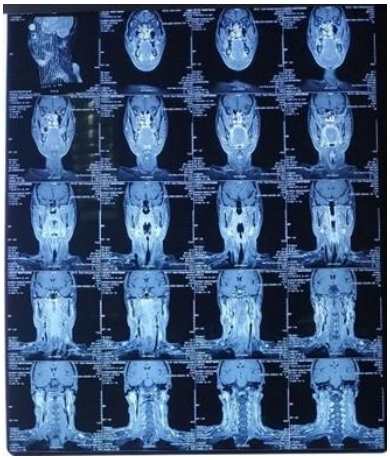

Figure 5 Nasopharyngeal MRI

2. CASE REPORT

A 45-year old male presented with one enlarged mass on the right side of the neck, nosebleed, and obstructed nose since 3 months ago. Physical examination showed multiple enlarged cervical lymph nodes on level 3 and 4, and easily bleed exophytic mass on the right and left roof of nasopharyng. Early diagnosis of this patient is cervical lymphadenopathy due to suspicion of nasopharyngeal carcinoma, treated with biopsy examination of nasopharyngeal mass.

Result of excision biopsy of the right cervical lymph node from previous surgeon was undifferentiated metastases carcinoma. On chest x-ray there was blast lesion on left anterior costae 5-6 with differential diagnosis of metastases disease. The diagnosis established for this patient was nasopharyngeal carcinoma WHO 3 Tis N2 M0 according to endoscopy examination (Figure 4) and MRI (Figure 5). Plan of treatment was adjuvant chemotherapy and radiation.

Therapy given to this patient was radiotherapy 6600 Gy and chemoradiation with Cisplatin 70 mg + Nimotuzumab 200 mg six times. After treatment, the mass shrinked, but patient still complained of epistaxis, tinnitus, and side effect of nausea. Patient was diagnosed with recurrent lymphadenopathy due to nasopharyngeal carcinoma. Patient was scheduled for further examination and treatment with lymph node extirpation and frozen section.

2.1. Clinical Question

What is the best treatment for post chemoradiation recurrent lymphadenopathy due to nasopharyngeal carcinoma?

2.2. Searching Method

Literature was searched on 11 March 2009 on three online databases, Pubmed, Cochrane, and EBSCO Host with additional hand searching. Medical subject heading terms used for searching were nasopharyngeal carcinoma, recurrent lymphadenopathy, and chemoradiation. Inclusion criteria for this study was study on human, written in English, and published within 5 years. Articles were screened from its title, abstract, and full text availability. Literature searching scheme can be seen on Figure 6.

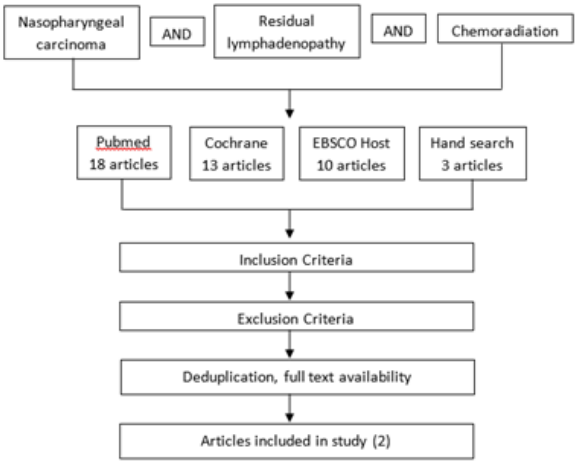

Figure 6 The scheme of literature searching

3. RESULT AND DISCUSSION

3.1. Result

3.1.1. Critical Appraisal

There are 2 articles included in this study. None of it was RCT, systematic review, or meta-analysis. The first article by Chen JY, et al. [23] is a prospective cohort study in China that evaluate the efficacy of selective neck dissection (SND) to treat residual or recurrent nasopharyngeal carcinoma compared with radical neck dissection (RND). The second article by Yang S, et al.

[24] is a retrospective cohort study in China. This study evaluated the effect of adjuvant chemotherapy on survival rate of patient with residual or recurrent nasopharyngeal carcinoma following chemoradiation. The result of critical appraisal can be seen on Table 1 below.

Table 1 Critical appraisal based on Oxford University criteria

Article	Validity								Relevance			
	Year published	Study design	Number of sample	Randomization	Similarity between groups	Blinding	Comparable treatment	Intention to treat	Domain	Determinant	Result can be assessed	Level of evidence
Chen JY, et al.[23]	2015	Prospective cohort	69	-	+	-	+	-	-	+	+	2B
Yang S, et al. [24]	2015	Retrospective cohort	155	-	+	-	+	-	+	+	+	2B

Table 2 Result summary

Author	Inclusion Criteria	Comparison	End Point	Result	Summary
Chen JY, et al. [23]	Patient with stage II-III residual nasopharyngeal carcinoma that have completed radiotherapy or chemoradiation without evidence of distant metastases	RND vs SND (51 vs 18 patients)	Overall survival rate, disease-free survival rate, regional-free survival rate	5-year survival rate in SND group was higher compared to RND group (72.22% dan 66.30%) 5-year disease-free rate in RND group was higher compared to SND group 42.80%) 5-year regional-free rate in SND group was higher compared to RND group (86.27% dan 77.60%) Tumor stage, affected lymph node size, and number of lymph node metastases had significant correlation with overall survival Tumor stage, number of lymph node metastases, and carcinoma invasion had significant correlation with disease-free survival The number of affected lymph nodes and metastases lymph node had significant correlation with regional-free survival	SND is a more favorable procedure compared to RND
Yang S, et al. [24]	Patient with stage IV residual nasopharyngeal carcinoma that have completed chemotherapy	Adjuvant chemotherapy with cisplatin or nedaplatin for patient with previous history of chemoradiation	Overall survival, failure-free survival, local relapse-free survival, distant metastasis-free survival	1. Adjuvant chemotherapy did not improve 3-year overall survival, local relapse-free survival, and distant metastasis-free survival	The role of adjuvant chemotherapy for treatment of residual nasopharyngeal carcinoma was not clear

3.2. Discussion

Nasopharyngeal carcinoma is the most common head and neck malignancy in Indonesia. Indonesia is a part of South East Asia coutry which is an endemic area to nasopharyngeal carcinoma [8-10]. Patient was a 45-year-old male, consistent with demography profile by Adham et al that reported peak age of 40-49 years-old and male to female ratio of 2.4 for nasopharyngeal carcinoma [10].

Difficulty in diagnosis was caused by variety of clinical manifestations in early disease which caused misdiagnosis and treatment delay for about 6 months from initial symptoms [8, 19]. Wang et al study early symptoms in nasopharyngeal carcinoma patients. Wang et al divided symptoms into four category, ear problems including hearing loss and otitis media (42%), neck mass (40%), nose problems including obstructed nose and epistaxis (35%), and intracranial involvement including headache and neuropathy (13%) [19].

Patient in this case report complained of neck mass, obstructed nose, and epistaxis which were the second and third most common symptoms reported study by Wang et al. [19].

Nasendoscope examination might not visualize abnormality when most of the mass reside in submucosa tissue [25]. About 32% nasopharyngeal carcinoma patients showed normal result on their first endoscope examination [19].

Nasendoscopy examination is still the first diagnostic study for patient suspected with nasopharyngeal carcinoma [8, 25]. Nasendoscope or post nasal mirror examination will show the presence of exophytic tumor mass. In this study the author found an exophytic mass on the right and left roof of the nasopharyng.

The result of excision biopsy of the mass showed undifferentiated carcinoma (WHO 3). Adham et al reported that WHO 3 is the most common nasopharyngeal carcinoma found in South East Asia and other endemic area that have association with EBV infection [10].

Patient was diagnosed with stage IVA nasopharyngeal carcinoma with focal thickening of posterior wall of nasopharyng and mass obliterating to left Rosenmuller fossa (Tis), multiple lymphadenopathy level 3 and 4 (N2), and metastasis to the bone with blast lesion on chest x-ray.

Comprehensive and multidisciple treatment involved ENT, radiology, radiotherapy, pathologic anatomy, dentist, nutritionist, and rehabilitation specialist [8]. Metaanalysis result showed that chemotherapy induction before chemoradiation in patient with nasopharyngeal carcinoma can improve overall survival (pooled hazard ratio/HR 0.68, confidence interval 0.56-0.8), progression-free survival (HR 0.7, CI 0.61-0.79), reduce locoregional failure (risk ratio/RR = 0.81, CI 0.68-0.96), and control distant metastases (RR = 0.69, CI 0.58-0.82) [26].

PNPK kanker nasofaring also recommed chemotherapy combination which acts as radiosensitizer, and chemoradiation in T2-T4 and N1-N3 patient.

After completing chemoradiation, patient was given adjuvant chemotherapy with Cisplatin + RT followed with Cisplatin/5-Fluorouracyl (5-FU) or Carboplatin/5-FU [8].

Chemoradiation given to patient was RT 6600 Gy and Cisplatin 70 mg and Nimotuzumba 200 mg 6 times. This regiment was consistent with PNPK kanker nasofaring that recommed the use of platinum based preparate 6 times every week [8].

Radiotherapy has long been chosen as the main treatment for nasopharyngeal carcinoma. PNPK recommend radiotherapy as a curative treatment. External radiation was performed covering the nasopharyngeal mass with margin of 2 cm above skullbase and lymph node with a total dose of 70 Gy on T3-T4, with addition of supraclavicular lymph node radiation with a total dose of 50 Gy [8].

Therapy response was evaluated by MRI with contrast and bone scan. Patient must have a routine check up every 1-3 months for the first year [8].

Following treatment, patient still had enlarged lymph node. We performed another biopsy on the lymph node. Frozen section examination showed no sign of malignancy therefore patient was diagnosed with nonspecific chronic lymphadenitis post stage IVA nasopharyngeal carcinoma. Further treatment for this patient was based on the pathologic anatomy result.

The result of treatment for nasopharyngeal carcinoma is known as Response Evaluation Criteria in Solid Tumor (RECIST) which consists of complete, partial, progressive, and stabile. Meanwhile, lymphadenopathy following treatment is classified into residual, recurrent, post treatment necrosis or hyaline fibrosis without tumor cell [27]. Residual, recurrent or persistent lymph node is defined as persistent lymphadenopathy without complete remission following complete treatment regimen. There is no time limit for this definition [27]. There are a few changes which occur to tissue following radiation, one of which is atrophy of lymph node structure and hyaline fibrosis formation [27, 28].

Toh et al. evaluate 12 patients with enlarged lymph node following treatment. Five out of 12 patients who were suspected for persistent lymph node due to nasopharyngeal carcinoma turned out had a negative

cytology result. Histology examination showed lymph node necrosis and hyalinization without viable tumor cell [27].

Surgical resection of localized persistent or recurrent disease (salvage surgery) is the treatment of choice for residual or recurrent nasopharyngeal carcinoma. There are several reasons for this claim. First, postirradiation lesions may not respond to external radiation and the side effects is significant. Second, treatment outcome with stereotactic radiation or brachytherapy is variable. Third, the efficacy of treatment depends on the extent of disease in the nasopharyng [29].

Chemotherapy is only indicated when lesions are too extended for surgery and radiotherapy. The preferred agent for chemotherapy is nonplatinum compound such as taxane, gemcitabine, and capacetabine. However, study Yang S et al. [24] showed that adjuvant chemotherapy did not have significant correlation with overall survival, failure-free survival, local relapse-free survival, and distant metastasis-free survival in patient with residual or recurrent disease.

Study by Chen JY et al. [23] showed that selective neck dissection (SND) procedure had a favorable overall survival, disease-free survival, and regional-free survival compared to radical neck dissection. Similar result was shown in study by Wang et al. Wang et al. [30] reported significantly longer 3-year and 5-year survival in patient underwent modified radical neck dissection (MRND) compared to RND. However, we still can't conclude whether neck dissection procedure is better than adjuvant chemotherapy. Further study comparing the efficacy of adjuvant chemotherapy and neck dissection procedure is needed.

4. CONCLUSION

Nasopharyngeal carcinoma is the most common head and neck malignancy in Indonesia. It is considered and endemic disease in South East Asia. There are various risk factors for nasopharyngeal carcinoma, one of which is EBV infection. Symtoms of nasopharyngeal carcinoma consists of ear problem, neck mass, nose problem, and cranial involvement. Histopathologic examination is important to established diagnosis and cancer subtype. Treatment was based on tumor stage. For stage IVA, the recommended treatment is chemoradiation. Prognosis for nasopharyngeal carcinoma is also based on its stage. The 5-year survival for metastasis disease is 51%. Persistent lymph node enlargement following complete treatment can be caused by residual or recurrent cancer on lymph node, recurrence, or hyaline fibrosis.

Clinician must consider the need for adjuvant chemotherapy or neck dissection procedure for residual or recurrent lymphadenopathy in patient with nasopharyngeal carcinoma. Study showed that selective neck dissection procedure had a better effectivity compared to radical neck dissection. However, further study to compare the effect of SND and adjuvant chemotherapy is needed.

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