MANAGEMENT OF NASOPHARYNGEAL CARCINOMA IN DR. ZAINOEL ABIDIN GENERAL HOSPITAL BANDA ACEH

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Abstract

Introduction: Most of the patients who are at an advanced or final stage of an illness usually comes from middle to low economic level. Right now, nasopharyngeal carcinoma management in Dr. Zainoel Abidin General Hospital Banda Aceh only has chemotherapy to treat patients. Actually patients need to also undergo radiotherapy treatment which unavailable in our hospital yet, so we will refer it to another hospital located in North Sumatera or Jakarta. Therefore, the Acehnese government is preparing to build an oncology center which includes radiotherapy, so that we can treat our patients here.

Objective: The purpose of this research is to report management of NPC in Dr. Zainoel Abidin General Hospital Banda Aceh from January 2016 to October 2018.

Method: Data was taken from medical records of patients diagnosed with NPC from January 2016 to October 2018. 73 patients was diagnosed with NPC and underwent chemotherapy.

Result: There were 73 patients NPC, 44 (60.3%) patients are male (60.3%) and 29 patients are female (39.7%). The youngest patient is 13 years old and the oldest is 79 years old. Most common average age are between 36-65 years old. The highest number is from Banda Aceh 10 patients. WHO histopathology classification reported that 26 (35.6%) patients with type I and type III as well, and 21 (28.8%) patients with type II. While 30 (41.1%) patients underwent chemotherapy for 6 cycles, 43 (58.9%) patients dropped out due to lack of living cost, long distance from hospital, or worsen of general condition.

Conclusion: It was reported 73 patients NPC, 44 (60.3%) male and 29 (39.7%) female. The youngest 13 years old and the oldest 79 years old. Most common average age between 36-65 years old. The highest number was from Banda Aceh 10 patients, WHO histopathology classification reported 26 (35.6%) patients with type I and type III as well, and 21 (28.8%) patients with type II. While 30 (41.1%) patients underwent chemotherapy 6 cycles, 43 (58.9%) patients dropped out due to lack of the cost of. This study reported 4 (13.3%) patients who survived after underwent chemotherapy full dose with average range of 19-26 months.

Article Info

Keywords:

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1. INTRODUCTION

The Dr. Zainoel Abidin General Hospital, which is a referral and teaching hospital located in the center of Aceh that treats Head & Neck cancer patients. All cases were histologically classified by standardized biopsy and staged according to the 2002 American Joint Committee on Cancer (AJCC) criteria using clinical assessment and CT scan work-up. The work-up of nasopharyngeal carcinoma includes a history, physical examination, nasopharyngeal examination and biopsy, dental evaluation, and appropriate diagnostic imaging studies (e.g., MRI and/or CT with contrast). These studies are important to determine the full extent of tumor in order to assign the stage appropriately and to design radiation ports that will encompass all the disease with appropriate doses. A chest x-ray should also be obtained. Chest CT should be considered for patients at high risk of or thoracic metastases. Imaging for distant metastases (i.e., chest, liver, bone) may include ultrasonography and/or CT. According to NCCN guidelines, modalities of management for NPC are radiotherapy, chemotherapy, and chemoradiotherapy.

We reported 73 patients registered between January 2016 to October 2018, we analyzed NPC cases treated at our hospital from which sufficient data were available. These reports include citizens who are not all permanent residents of Banda Aceh but also include patients who come from district hospitals. As a referral hospital, we treat patients not only from Banda Aceh and surrounding areas but also from other district and regions surround Banda Aceh. Some patients from more distant underdeveloped rural areas lacked long-term follow-up.

1.1 Epidemiology and Etiology

Nasopharyngeal carcinoma (NPC) is a malignant head and neck cancer, it differs from other head and neck cancers because of its unique characteristics in terms of epidemiology, etiology, clinical presentation, and prognostic factors [1, 2]. It is a frequent cancer in Indonesia, with as the fourth most common tumor after cervical cancer, breast cancer, and skin cancer, and is the most common malignancy in the head and neck [3]. NPC is endemic in Southeast Asian countries ethnic

Chinese especially from the province of Guangdong province, where the incidence rates range from 30 to 50 in 100,000 patients [3-8]. NPC in the Western hemisphere (the Americas and Europe) is rare with an annual incidence of around 0.5/100,000, accounting for 1-2% of all head and neck cancers [9].

In North American whites its frequency is 0.25% of all cancers, while in American Chinese is 18%. Chinese born in America have a lesser incidence than those born in China. One of the aetiological factors of NPC frequently referred to is the consumption of salted fish. Dried salted fish, common in the Indonesian diet. This may be related to the carcinogenic compound, nitrosamine content, detected on the salted fish. The preservation process is thought to increase levels of carcinogenic nitrosamines. Burning of incense or wood (polycyclic hydrocarbon), use of preserved salted fish (nitrosamines) along with vitamin C deficient diet (vitamin C blocks nitrosification of amines and is thus protective) may be other factors operative in China [3, 10, 11].

Another etiologic of nasopharyngeal carcinoma is the Epstein Barr virus (EBV). It is associated with malignancies and has a characterized geographical distribution. In southern China, it is one of the major causes of morbidity and mortality. Despite the heavy public health burden of NPC in southern China and other endemic areas, relatively little is known about the etiology and prevention of NPC [11].

Chan et al. reported that the EBV genome is present in approximately 90% of NPCs observed in endemic regions, and is considered to play an important role in many aspects of NPC development. Interestingly, human papillomavirus infection has recently been identified in EBV-negative NPCs in non-endemic regions; however, the true biologic implications of these observations remain to be fully characterized [12].

Other environmental risk factors associated with NPC have also been identified, such as alcohol drinking and tobacco smoking, intake of chemical carcinogens, formalin and phorbol esters, occupational exposures, and some herbal medicines. Notably, a stronger association between tobacco smoking and NPC is observed in populations outside endemic regions than within high-risk populations. Concordantly, this occurs with differentiated versus undifferentiated or EBV-positive versus EBV-negative NPC [11, 12].

In contrast, high consumption of fresh fruits and vegetables has been shown to decrease an individual's risk of NPC, which could be attributed to many components within these food products, such as fiber, vitamins, folate, and carotenoids. Although EBV is likely an early event in EBV-associated nasopharyngeal tumorigenesis, there is also mounting evidence suggesting that preexisting genetic abnormalities (e.g., loss of chromosomal regions on 3p and 9p) may be required to support the persistent infection of premalignant or malignant epithelial cells of the nasopharynx [11, 12].

1.2 Histopathology

The World Health Organization (WHO) classifies NPC into three histopathological types based on the degree of differentiation. There have been many classifications proposed for nasopharyngeal carcinoma, and the World Health Organization (WHO) originally described three types according to histopathological in 1978. In practical terms, epidemiological and clinical features broadly define two groups, the squamous cell carcinomas (SCC) of varying degrees of differentiation and the undifferentiated carcinomas of nasopharyngeal type. The WHO type tumors are the most poorly defined with no clear morphological distinction between these and the undifferentiated carcinomas [3, 9, 13].

Table 1. Histopathological classification of nasopharyngeal tumors [9]

WHO Classification	Histopathological Classification
WHO type I	Keratinizing squamous cell carcinoma
WHO type II	Non-keratinizing (differentiated) carcinoma
WHO type III	Undifferentiated carcinoma

Type I, Squamous Cell Carcinoma (SCC), included those typical keratinizing sees with intercellular bridges, is seen in 5%-10% of cases of NPC and is characterized by well-differentiated cells that produce keratin and demonstrated the presence of intracellular bridges when observed under the electron microscope. Type II included non-keratinizing epidermoid carcinomas, varies in cell differentiation (from mature to anaplastic cells) but does not produce keratin, but without definite squamous differentiation. Type III included undifferentiated carcinomas or poorly differentiated carcinoma. These cells have indistinct cell margins with hyperchromatic nuclei, is also non-keratinizing, but is less differentiated, with highly variable cell types (clear cell, spindle cell, anaplastic) [3, 13]. The histopathological around the world is different. In North America, around 25% of patients have a tumor with type I, 12% with type II, and 63% with type III. In southern Chinese 3% of patients with type I, 2% type II, and 95% type III [3, 13].

An alternative classification divided tumors into two histopathological types, namely, sees and undifferentiated carcinomas of the nasopharyngeal type (UCN'Ts). This second classification took into consideration the correlation of the tumor with EBV serology. Patients with SCCs have a lower EBV titer, while those with UCN'Ts have elevated titers. On clinical grounds, biopsies obtained from patients suffering from NPC sometimes show a mixed histopathological pattern. The recent WHO classification has taken this mixed pattern into account as well as the association of the EBV with type II and III tumors [3].

Picture 1. Light microscopic appearance of nasopharyngeal carcinoma [14]

(A) Keratinizing squamous cell carcinoma; hematoxylin and eosin (H&E) stain, (B) Nonkeratinising carcinoma, differentiated subtype; H&E stain, (C) Non-keratinizing carcinoma, undifferentiated subtype; H&E stain, (D) Detection of Epstein-Barr virus-encoded small RNA by in-situ hybridization.

2. MATERIAL AND METHODS

This report was a descriptive study and the purpose of this study to reported patients diagnosed with nasopharyngeal carcinoma in the ORL-HNS department of Dr. Zainoel Abidin General Hospital Banda Aceh from January 2016 to October 2018. The sampling technique in this study used Consecutive Sampling. We classified criteria of patients according to gender, age, demographic, histopathological result and patients who underwent chemotherapy.

3. RESULT

It was reported 73 Nasopharyngeal Carcinoma patients who admitted to the ORL-HNS department of Dr. Zainoel Abidin General Hospital Banda Aceh from January 2016 to October 2018. Which were 35 patients in 2016, 24 patients in 2017 and 14 patients till October 2018. There were 44 (60.3%) male and 29 (39.7%) female for 3 years.

Graphic 1. Ratio male and female of nasopharyngeal carcinoma in Dr. Zainoel Abidin General Hospital Banda Aceh from January 2016 to October 2018.

Distribution of age from 73 patients NPC, the youngest age 13 years old and the oldest 79 years old. Most common average age between 36-65 years old about 49 (67.4%).

Graphic 2. Distribution of age of nasopharyngeal carcinoma in Dr. Zainoel Abidin General Hospital Banda Aceh from January 2016 to October 2018.

Distribution based on the region in Aceh province, from 73 Nasopharyngeal Carcinoma patients who came to the ORL-HNS department of Dr. Zainoel Abidin General Hospital Banda Aceh from January 2016 to October 2018, the highest number was from Banda Aceh 10 (13.6%) patients, followed by Aceh Barat Daya 9 (12%) patients.

Graphic 3. Distribution of regional of nasopharyngeal carcinoma in Dr. Zainoel Abidin General Hospital Banda Aceh from January 2016 to October 2018.

Based on histopathological WHO classification, we reported type I was 26 (35.6%) patients as well as type III, and type II 21 (28.8%) patients.

Graphic 4. Histopathological WHO classification of Nasopharyngeal Carcinoma in Dr. Zainoel Abidin General Hospital Banda Aceh from January 2016 to October 2018.

Seventy-three patients with Nasopharyngeal Carcinoma who admitted to the ORL-HNS department of Dr. Zainoel Abidin General Hospital Banda Aceh from January 2016 to October 2018. There were 30 (41.3%) patient underwent chemotherapy for 6 cycles, 43 (58.9%) patients who underwent incomplete chemotherapy.

Graphic 5. Patients underwent chemotherapy of Nasopharyngeal Carcinoma in Dr. Zainoel Abidin General Hospital Banda Aceh from January 2016 to October 2018. **Table 2.** Patients underwent chemotherapy of nasopharyngeal carcinoma in Dr. Zainoel Abidin General Hospital Banda Aceh from January 2016 to October 2018

Chemotherapy	Amount
Complete Chemotherapy	30
Incomplete Chemotherapy	43
Total	73

From the 30 patients who had underwent 6 cycles of chemotherapy at Dr. Zainoel Abidin Hospital, 4 patients were in good condition and still being followed, 7 patients died and 4 patients who continued radiotherapy (1 patient died, 2 patients relapsed and one patient had no signs and symptoms of recurred until now), the rest of patients cannot be evaluated because they cannot be contacted.

4. DISCUSSION

In our study, the ratio of male and female was 1.5:1 (60.3% male, 39.7% female). In Indonesia, Marlinda et al. reported a similar predominance, with 70.4% male and 29.6% female cases yielding a 2.4:1 ratio. In Indonesia NPC is the most frequent cancer in the head and neck and ranks as number 4 in males with the incidence of 6.2/100.000 [15]. The causes of the height of male sufferers than women in this cancer remain unclear. It might be men tend to be more often exposed to carcinogens in working environment compared to women, so more at risk for cancer [15].

Distribution of age the youngest age 13 years old and the oldest 79 years old. Most common average age between 36-60 years old. This distribution of age of patients diagnosed with NPC differs substantially in areas with various incidences. Zeng et al. reported that the incidence of NPC is increased with age, while in the endemic areas, obviously after 30-years, range at 40-59 years. It has also been reported the incidence of NPC has a relatively small peak among adolescents and young adults [13]. In another research, NPC patients from various countries are described with ages ranging from 4 to 91 years, with average ages at 50 to 60 years of age in Chinese populations. Marlinda et al. reported that the age distribution of NPC patients from Dr. Cipto Mangunkusumo Hospital Jakarta, had average ages at 40 to 49 years, and more than 80% of patients were diagnosed between 30 and 59 years of age [15].

From the distribution of region, The highest number was from Banda Aceh 10 (13.6%) patients followed by Aceh Barat Daya 9 (12%) patients. In terms of distance and transportation to the hospital, it is very reasonable if patients who came from Banda Aceh was the highest number because our general hospital is located in Banda Aceh, so patients no need more effort such as transportation and lack of living cost. Long distances and relatively difficult geographical conditions such as having to pass through mountains and seas, making it difficult for patients to come to the hospital. Aceh province has 23 districts which is located between 010 58' 37.2"-060 04' 33.6" North Latitude and 940 57' 57.6"-980 17' 13.2" East Longitude with an average height of 125 meters above sea level. The borders of the Aceh Province, the North and East are bordered by the Malacca Strait, in the South with the Provinces of North Sumatra and the West with the Indonesian Ocean. Some patients who came from districts closer to North Sumatra, such as Eastern Aceh, Aceh Tamiang, Southeast Aceh and Singkil prefer to seek treatment in North Sumatra. Another people who come from regencies located on islands must travel by ship, patients from Sabang Island are more fortunate than those from Simeulu Island or Nasi Island, who have to travel more than one day from their place to Banda Aceh. The lowest number of patients from several districts does not necessarily indicate the actual conditions, many factors play a role including geographical problems. Further research is needed to look at ethnic relations with a high incidence of NPC in Aceh. Devi et al. reported that the highest recorded NPC incidence is found in the Bidayu people in Borneo Island (Kalimantan), with an age-adjusted incidence of 35/100.000 [16].

Histopathological WHO classification, the type I and type III was the same level at (35.6%) which both were 26 patients, followed by type II (28.8%) which were 21 patients. In Indonesia, Marlinda et al. reported which has an ethnically diverse population of 225 million patients, NPC is prevalent among different native patients and presents a major socioeconomic problem. Type III is most common, around 85.0% of cases proved to be undifferentiated carcinoma, and 12.7% WHO type I NPC tumors, only 2.3% of the cases were classified as WHO type II NPC tumors [15].

Based on NCCN guideline version 2.2018 for non-keratinizing or undifferentiated histology, consider testing for EBV in tumor and blood, for detecting EBV in pathologic specimens include in situ hybridization for EBV encoded RNA (EBER) or immunohistochemical staining for latent membrane protein (LMP). The EBV DNA load within the serum or plasma may be quantified using polymerase chain reaction (PCR) targetting genomic sequence of the EBV DNA such as BamHI-W, EBNA or LMP; these tests vary in their sensitivity. The EBV DNA load may reflect prognosis and change in response to therapy [17].

There is two options therapy for Nasopharyngeal recurrent, unresectable or metastatic disease, its a First line therapy and Subsequent line therapy. Preferred regimen for first line therapy is cisplatin or gincetabine (category 1), theres also other recommended regimens for first line therapy like a combination therapy (cisplatin

/5-FU, cisplatin or carboplatin/docetaxel, cisplatin or carboplatin/paclitaxel, carboplatin/cetuximab). Single agents (cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, gemcitabine, capecitabine).

For the subsequent line therapy, we can use combination therapy or single agents with option listed above for first-line therapy immunotherapy. Nivolumab can be used If previously treated, recurrent or metastatic non-keratinizing disease (category 2B), and Pembrolizumab if previously treated, PD-L1- positive recurrent or metastatic disease (category 2B).

Table 3. NCCN Guideline

Nasopharyngeal recurrent, unresectable or metastatic disease			
	Preferred Regimens	Other Recommended Regimens	Useful in certain circumstances
First-Line	Cisplatin/gemcitabine (category 1)	Combination therapy - Cisplatin/5-FU - Cisplatin or carboplatin /docetaxel - Cisplatin or carboplatin /paclitaxel - Carboplatin/cetuximab Single Agents - Cisplatin - Carboplatin - Paclitaxel - Docetaxel - 5-FU - Methotrexate - Gemcitabine - Capecitabine	None
Subsequent Line	None	Combination Therapy or Single Agents - See option listed above for first-line therapy immunotherapy - Nivolumab if previously treated, recurrent or metastatic non-keratinizing disease (category 2B) - Pembrolizumab if previously treated, PD-L1-positive recurrent or metastatic disease (category 2B)	None

However in our study from 73 patients, only 30 patients underwent chemotherapy 6 cycles, 43 patients dropped out. Usually, we use first-line regimen cisplatin+docetaxel. The thirty patients who had undergone 6 cycles chemotherapy at Dr. Zainoel Abidin Hospital are 4 patients still in good condition which are the first was a teenage 17 years old girl, was diagnosed as NPC stadium 4 with histopathology undifferentiated squamous cell carcinoma, underwent chemotherapy with regimen cisplatin+docetaxel full dose 6 cycles. The first cycle was on fifteen of June 2016 and finished on thirty of September 2016. Almost twenty-six months survived without radiotherapy, the second was a 50 years old man. He was diagnosed as NPC stadium 4 with histopathology undifferentiated squamous cell carcinoma who had undergone chemotherapy with regimen cisplatin + docetaxel full dose 6 cycles. The first cycle was on thirty of September 2016 and finished on eighteen of January 2017. Almost twenty-two months survived without radiotherapy, the third was a 22 years old girl. She was diagnosed as NPC stadium 4 with histopathology keratinizing squamous cell carcinoma who had undergone chemotherapy with regimen cisplatin+docetaxel full dose 6 cycles. The first cycle was on nine of June 2017 and finished on twenty-nine of April 2017. Almost nineteen months survived without radiotherapy, the last patient was a teenage 16 years old boy. He was diagnosed as NPC stadium 4 with histopathology non-keratinizing squamous cell carcinoma, underwent chemotherapy with regimen cisplatin+docetaxel full dose 6 cycles. The first cycle was on twenty-seven of April 2018 and finished on twenty of August 2018, during this time waiting for evaluating result as CT scan and histopathological as well after 3 months of chemotherapy.

Seven patients died which were with various condition such as acute/chronic renal failure, imbalance, and neutropenic fever. Four patients who continued underwent radiotherapy; 1 patient died because worsen condition during radiotherapy, 2 people relapsed after seven-month radiotherapy and 13 months after chemotherapy which signs and symptoms recurred as bloody rhinore and lumps in the neck. One patients had no signs and symptoms of recurred until now, the rest of patients (15 patients) can not be evaluated because they cannot be contacted.

According to NCCN guidelines the standard of therapy of NPC patients is radiotherapy alone or chemoradiotherapy or chemotherapy alone for advanced stage with distant metastasis. However, due to cost constraints, many patients refused to be referred to higher referral hospitals outside Aceh that provided radiotherapy because of the length of treatment and the amount of living costs incurred during chemoradiotherapy.

The frequency of distant metastasis is 4.4% to 7% at diagnosis and 20% to 27% during follow up [18]. In case of metastasis NPC (stadium IVC) only

palliative treatment remain. In chemo-naïve patients, platinum-based regimens are the first choice and give the best result [19]. Chen et al reported best response rates for palliative chemotherapy only were found with gemcitabine, capecitabine or docetaxel with a median survival of 9.5-15 months [20]. Apart from the poor outcome, combination chemotherapy in metastatic NPC in general result in increased toxicity [21].

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 diseases is 90%, 80%, 70% and 50% respectively [22, 23]. The numbers below were published in 2010 in the 7th edition of the AJCC Cancer Staging Manual and are based on patients diagnosed between 1998 and 1999 [24].

Table 4. Relative 5-years survival rate

.Stage	Relative 5-years survival rate
I	72%
II	64%
III	62%
IV	38%

These survival rates for the patients who underwent chemoradiotherapy and only estimates-they can't predict what will happen to any individual.

4.1 Limitations and future directions of study

The limitation in our study is our hospital only have chemotherapy facilities, meanwhile patient with 4th stage cancer according to NCCN guidelines need to be treated by chemoradiation. Furthermore not all patients who has completed chemotherapy can be followed. There were four patients that had been followed after completed chemotherapy, which are observed no sign or symptom appearance within 19-26 months, which actually have to be observed for survival at least until 5 years.

5. CONCLUSION

It is important to optimize therapy according to the guidelines. The availability of a radiotherapy center plays a very important role in getting good outcome for nasopharyngeal carcinoma patients and will increase survival rate.

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