

CHARACTERISTICS OF NASOPHARYNGEAL CARCINOMA IN CHILDREN AND ADOLESCENTS IN DR. ZAINOEL ABIDIN GENERAL HOSPITAL BANDA ACEH

by Benny Kurnia

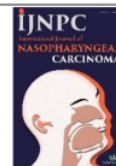
Submission date: 09-Nov-2021 11:58AM (UTC+0700)

Submission ID: 1697477216

File name: N_CHILDREN_AND_ADOLESCENTS_IN_DR._ZAINOEL_ABIDIN_GENERAL_HOS.pdf (656.56K)

Word count: 4477

Character count: 24356



CHARACTERISTICS OF NASOPHARYNGEAL CARCINOMA IN CHILDREN AND ADOLESCENTS IN DR. ZAINOEL ABIDIN GENERAL HOSPITAL BANDA ACEH

Lily Setiani^{1*}, Fadhlia¹, Benny Kurnia¹, Yerni Karnita²

¹Medical Staff of Oncology Division Departement of Otorhinolaryngology Head and Neck Surgery Dr. zainoel Abidin General Hospital

²Otorhinolaryngology Head and Neck Surgery Resident of Otorhinolaryngist Head and Neck Surgery Departement of Dr. zainoel Abidin General Hospital

Abstract

Introduction: Nasopharyngeal Carcinoma (NPC) is a malignant tumor arising from epithelial cells that cover the nasopharynx. NPC is a rare malignancy in children. The incidence of NPC varies by age, geographical and ethnic factors which indicate both genetic and environmental factors contribute to the tumor growth. NPC in children has several features different from adults.

Objective: To assess characteristics of nasopharyngeal carcinoma in children and adolescents in dr. Zainoel Abidin general hospital Banda Aceh from 2014-2019.

Methods: The study was conducted in dr. Zainoel Abidin general hospital Banda Aceh. This study is a descriptive with cross sectional retrospective design. The data collected from medical records of patients diagnosed with nasopharyngeal carcinoma from January 2014-September 2019. The variable including regional distribution, gender, age (between 0-25 years), histopathologic types, stage and chemotherapy regimen used. The sampling was done by total sampling method.

Results: The result showed that there was 17 patients of nasopharyngeal carcinoma in children and adolescents with the highest case came from Bireuen and North Aceh district 3 (17.7%) patients, respectively. South Aceh and West Aceh district 2 (11.8%) patients, respectively. Nasopharyngeal carcinoma mostly infected 9 (53%) male patients than 8 (47%) female with a sex ratio of 1.1 : 1. The age most affected is at the end of childhood between 17-25 years were 9 (53%) patients and between 12-16 years were 8 (47%) patients with the average age range was 17.2 years (range 13-22 years). Most of histopathologic types found in the type of undifferentiated carcinoma (WHO type III) as many as 7 (41.1%) patients with stage IV being the most frequent 9 (53%) patients. Most of the histopathologic type found in this study was undifferentiated carcinoma (WHO type III; 41.1%; n=7) with stage IV (53%; n=9). The most widely used chemotherapy regimen were combination of Cisplatin and Docetaxel with 10 (62.5%) patients.

Conclusion: Nasopharyngeal carcinoma in children generally occur at the end of childhood with the most common histopathological type of undifferentiated carcinoma (WHO type III) and stage IV which associated with advanced locoregional disease and higher rates of distant metastasis.

Article Info

Keywords:

Nasopharyngeal carcinoma, characteristics, children, adolescents.

*Corresponding author:

Address: Jl. Teuku Tanoh Abee, Kopelma Darussalam, Syiah Kuala, Kopelma Darussalam, Kec. Syiah Kuala, Kota Banda Aceh, Aceh 24415

e-mail: lily_setiani70@yahoo.co.id

1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a tumor arising from the epithelial cells that cover the nasopharynx [1]. Multiple factors participate in the etiology of NPC including Epstein-Barr virus (EBV) activation, genetic susceptibility and exposure to environmental carcinogens. Specifically, risk factors consistently associated with NPC in endemic areas include early childhood salted fish consumption, preserved foods consumption, lack of fresh fruit or leafy vegetables intake, prior chronic respiratory tract conditions, and exposure to cooking fumes [2]. The incidence of pediatric NPC varies greatly by age, ethnic and geographic factors. The incidence variations of NPC between different geographical and ethnic groups indicate that both genetic and environmental factors contribute to its growth [3,4,5,6]. Nasopharyngeal carcinoma is a rare malignancy in children. Pediatric NPC constitutes 1-5% of all pediatric cancers and 20-50% of all primary nasopharyngeal malignant tumors in children [7].

NPC is relatively common in South China, Southeast Asia, North Africa [5,6,8]. According to the International Agency for Research on Cancer (IARC), the worldwide crude rate for NPC for 0-14 years old is 0.1/100,000. The most affected continent is Asia with 891 cases per year, followed by Africa with 469, America with 167, and Europe with 45 cases in 2002 [5]. The annual incidence of NPC in the UK is 0.3 per million at age 0-14 years, and 1 to 2 per million at age 15-19 years and the incidence was 0.1 to 1.5 per million in the United States [1,9].

The incidence of NPC has been observed to occur at two peaks, the first between 10 and 20 years of age and the second between 40 and 60 years [10]. Generally, occurs at the age more than 40 years and rarely occurs in children (<1%).

The graphic shows that the incidence of NPC in children occurs at the end of childhood [3]. Hu et al, found the age range between 9-20 years with an average age was 16 years with male sex more common than women by a ratio of 1.63: 1 [6]. Mauden et al, found the average age is between 7-16 years, an average of 12 years with a male is more at 76% [4]. According to the study of Casanova et al, they found that the most frequent age was 16 years ranging from 10-21 years [5].

Nasopharyngeal carcinoma in children has several different features from adults. Generally, NPC in children tends to be diagnosed at advanced stage but has a better prognostic [11]. Generally, NPC in children also has a histopathological type of undifferentiated carcinoma that is associated with advanced locoregional disease and has a higher rate of distant metastasis and the majority of patients who relapse with distal metastases occur during a short period of time after treatment. It was said that nasopharyngeal carcinoma in children is more closely related to Epstein Barr Virus (EBV) infection [3,4,10].

Nasopharyngeal carcinoma in children generally presents with the most frequent symptom is cervical lymphadenopathy [9]. Other symptoms such as hearing loss/tinnitus, headache, bleeding nose, and nasal obstruction [4].

Management of nasopharyngeal carcinoma in children and adolescents generally follows the protocol established in adults due to lack of clinical trials in the pediatric population [7]. Nasopharyngeal carcinoma in children generally has better survival than adults, although it is usually diagnosed at advanced stage but has a risk of long-term complications higher length associated with the treatment [11]. So that earlier diagnosis will reduce the long-term morbidity of treatment.

The aims of this study is to assess the characteristics of nasopharyngeal carcinoma in children and adolescents in dr. Zainoel Abidin general hospital Banda Aceh Period 2014-2019.

2. MATERIAL AND METHODS

This study was a descriptive with cross sectional retrospective design. The study was conducted in dr. Zainoel Abidin general hospital Banda Aceh. The data collected from medical records of patients diagnosed with nasopharyngeal carcinoma in children and adolescents between the ages of 0-25 years with undergoing treatment at RSUD Dr. Zainoel Abidin general hospital Banda Aceh from 2014-2019. The population was all cases of nasopharyngeal carcinoma in children and adolescents based on histopathological examination in the pathology anatomic laboratory of RSUD Dr. Zainoel Abidin general hospital Banda Aceh. The sampling was done by total sampling method. The data was tabulated and the percentage of each dependent variable was calculated and the characteristics of nasopharyngeal carcinoma patients were found in the form of a regional distribution, gender, age, histopathologic types (used the American Joint Committee on Cancer Seventh Edition (AJCC 7) classification), stage (used World Health Organisation (WHO) classification) and chemotherapy regimen used.

3. RESULT

The researchers identified 17 patients reported with nasopharyngeal carcinoma who were diagnosed at RSUD dr. Zainoel Abidin general hospital Banda Aceh from Januari 2014 to September 2019. The number of nasopharyngeal carcinoma cases based on regional distribution can be seen in Figure 1.

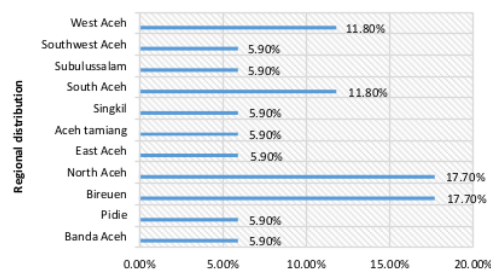


Figure 1. Distribution of nasopharyngeal carcinoma based on regional distribution

Based on Figure 1, the most nasopharyngeal carcinoma cases came from Bireuen district and North Aceh that is 3 (17.7%) patients, respectively. The second area is South Aceh and West Aceh district that is 2 (11.8%) patients, respectively. The lowest incidence occurred in Banda Aceh, Subulussalam, Singkil, East Aceh, Aceh tamiang, Southwest Aceh and Pidie each with 1 (5.9%) patients.

The highest distribution of nasopharyngeal carcinoma by age was found at the end of childhood, between 17-25 years that is 9 (53%) patients and 12-16 years that is 8 (47%) patients. The most common age is 16 years with 4 patients and 19 years with 3 patients with an average age was 17.2 years. The most common distribution of nasopharyngeal carcinoma by sex was in males with 9 (53%) patients compared to females with 8 (47%) patients. The number of nasopharyngeal carcinoma cases based on age distribution can be seen in Figure 2.

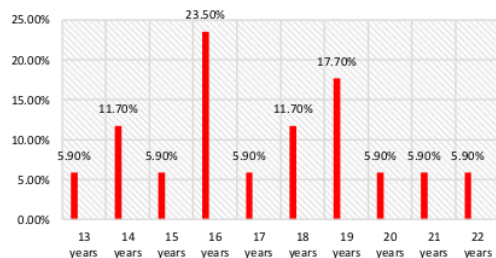


Figure 2. Distribution of nasopharyngeal carcinoma based on age

The results showed that the most histopathological type was undifferentiated carcinoma (WHO type III) 7 (41.1%) patients, non-keratinizing squamous cell carcinoma (WHO type II) 6 (35.3%) patients and the lowest is keratinizing squamous cell carcinoma (WHO type I) 4 (23.6%) patients. Most of the patients had advanced disease with stage IV in 9 (53%) patients, stage III in 7 (41.1%) patients and stage II in 1 (5.9%) patient and 1 patient. In this study, the classification used according to the most recent version of the American Joint Committee on Cancer Seventh Edition (AJCC 7). Most of the patients performed chemotherapy using a combination regimen of cisplatin and docetaxel in 10 (62.5%) patients, a combination of ifosfamide, cisplatin, uromitexan, paclitaxel in 3 (18.75%) patients, a combination of cisplatin, docetaxel and 5-fluorouracil in 2 (12.5%) patients, and a combination of cisplatin and 5-fluorouracil in 1 (6.25%) patient. And 1 new patient was diagnosed with nasopharyngeal carcinoma and had not undergone chemotherapy. There were no patients with undergoing radiotherapy treatment.

Table 1. Distribution of nasopharyngeal carcinoma.

Characteristics	n	%
Male	9	53 %
Female	8	47 %
Stage II	1	5.9 %
Stage III	7	41.1 %
Stage IV	9	53 %
WHO type I (Keratinizing squamous cell carcinoma)	4	23.6 %
WHO type II (Non-keratinizing squamous cell carcinoma)	6	35.3 %
WHO type III (Undifferentiated squamous cell carcinoma)	7	41.1 %
Cisplatin+Docetaxel	10	62.5 %
Cisplatin+Docetaxel+5-Fluorouracil	2	12.5 %
Cisplatin+5-Fluorouracil	1	6.25 %
Ifosfamide+cisplatin+uromitexan+paclitaxel	3	18.75 %

4. DISCUSSION

The results showed that nasopharyngeal carcinoma was found frequently in Bireuen and north Aceh each of 3 (17.8%) patients and in South and West Aceh each 2 (11.8%) patients. Majority of these patients have a low economic status and lived close to the sea. The high incidence of NPC in their district suggested because of the habit of consuming foods containing preservatives or marinated related to nitrosamine levels. Majority population in Aceh have had habit of consuming salted fish as a daily diet.

The etiology of NPC is multifactorial. Ethnic, environmental and EBV seem to play an important role in the causes of NPC [1]. The literature explained that genetic and environmental factors contribute to the tumor growth [8]. One of the environmental factors is food. High risk foods that can develop nasopharyngeal carcinomas such as salted fish, canned food and burnt meat. Consuming salted fish is related to carcinogenic compounds which nitrosamines contained in salted fish. A case study has found that the consumption of salted fish every week before the age of 10 years is associated with a threefold increased risk of developing NPC [12]. Nasopharyngeal carcinoma in children has a difference from adults, it has a close relationship with EBV [11,13]. Detection of nuclear antigens associated with Epstein Barr Virus (EBNA) and DNA virus in NPC types II and III has revealed that EBV can infect epithelial cells and associated with viral transformation [1]. A previous retrospective study found that EBV DNA was detected in plasma in about 96% of non-keratinizing type NPC patients compared with only 7% of control patients [1]. Another risk factors are smoking, and tobacco [11].

Nasopharyngeal carcinoma is a relatively rare malignancy of childhood. In our study we found that male is more frequent than female with a ratio of 1,1 : 1 with an average age range of 17,2 years (range 13-22 years). According to study by Kupali et al, they found the incidence of NPC was more frequent in male than female with age range of 13 years (7-17 years) [13]. Study by Yan et al, they also found the highest prevalence of NPC was in male as much as 71.4% [11]. Study by Mouden et al, they found that males are more frequent than female [4].

Our study found undifferentiated NPC was the most frequent histological type in childhood. Nasopharyngeal carcinoma was diagnosed histopathologically based on World Health Organization (WHO) classification criteria which has been biopsy in primary tumors [4]. Three subtypes of NPC are recognized in the World Health Organisation (WHO) classification, keratinizing squamous cell carcinoma (type I), non-keratinizing squamous cell carcinoma (type II) and undifferentiated carcinoma (type III) [1]. Most cases

in childhood and adolescence based on WHO classification is type III, with a few type II cases [1]. Undifferentiated carcinoma is classically associated with a more advanced locoregional disease and with more frequent distant metastases [4]. Study retrospective found, about 90% children with NPC had histopathology type undifferentiated carcinoma with a more aggressive nature but had better survival than adults [3,5]. Daoud et al, found that 56.3% patients were classified as type III NPC [10]. According to Hu et al, 85 (89.5%) patients had type III and 10 patients with type II [6]. The same result by Kupeli et al, they found more patients with type III was 96.4% [14]. But according to study Mouden et al, they found all patient had subtype histopathological undifferentiated carcinoma [4]. The literature, revealed that type II and III has associated with the elevation of Epstein-Barr Virus titers, but type I is not [1].

This study found that most of the patients were stage IV (n=9; 53%) and we found 7 patients classified as stage III (n=7; 41.1%). This is likely due to the habit of the children not being aware of their illness or sometimes a lack of attention from parents so that most patients came with advanced disease. The NPC staging has evolved over the past decades. The classification used according to the most recent version of the American Joint Committee on Cancer Seventh Edition (AJCC 7) [4]. Study by Mauden et al, they found about 12.5% had T1-T2 stages with N0-N1 around 26.6% [4]. Other studies found, the most patients with stage IV [5]. According to NPC-2003-GPOH/DCOG, more patients with stage III-IV around 99% and most of them were undifferentiated [8]. Study by Yan et al, most patients with advanced stages were stage III (43.8%) and stage IV (47.0%) [11]. Nasopharyngeal carcinoma usually originate from the lateral wall of the nasopharynx in the rosen-muller fossa. The tumor can extend within or out of the nasopharynx to the contralateral wall and/or postero-superiorly to the base of the skull or the palate, nasal cavity or oropharynx [1]. Tumors can metastasize to lymph nodes of the neck or metastases to distant organs such as bones, lungs, mediastinum, and less frequently to the liver [1]. Cervical lymphadenopathy is the initial presentation in many patients [14]. Symptoms related to the primary tumor include trismus, pain, otitis media, nasal regurgitation due to paresis of the soft palate, hearing loss and cranial nerve palsies [1,3,4]. Because of the location of nasopharynx, small tumors usually do not cause symptoms and unspecified initial symptoms. Therefore, some patients present with advanced stages with distant locoregional disease and distant metastases [8,13]. According to a study by Mauden et al, they found all of the patients had cervical lymphadenopathy [4]. Study of Casanova et al, stated that 6.6% of patients had distant metastases [5]. Study of Mauden et al reported that most of the patients with NPC had advanced stage T, regional lymph node metastases, and about 2 (3%) patients had distant metastases to the lungs, liver and bones [4]. Nasopharyngeal carcinoma may extend into the skull base and cause dysfunction of cranial nerves VI and XII, resulting in diplopia or dysphonia [15].

In this study, the diagnostic tool used to determine the stage were Computed Tomography Scanning (CT-Scan) modality with contrast, Ultrasonography (USG) and thorax xrtongen. Contrast CT or MRI is a modality that should be used to assess the extent of local tumour growth and base of skull involvement [3]. MRI is more sensitive than CT for detection of the primary tumour and the extent of locoregional spread including nodal metastasis and perineural extension. CT scan is better than MRI for identification of bone erosion. Currently, investigators have recently utilized FDG PET alone or combined with CT (FDG PET/CT) to evaluate patients with NPC. The advantages of FDG PET can provide semiquantitative information about the functional activity of the tumor, detect areas of involvement that may overlooked by MRI, distinguish active tumor from scar tissue, and evaluate the whole body in a single imaging session. Some studies have found that FDG PET or FDG PET/CT can contribute to staging [14]. PET scans and PET-CT scans are also used as prognostic tools for NPC [8].

In this study most of patients has undergoing chemotherapy, and none of them has not undergoing radiotherapy. Most of their parents refuse to be referred to hospital that have radiotherapy facilities because of limited medical costs so the treatment only limited to chemotherapy. Most of patients undergo chemotherapy with combination regimen of Cisplatin and Docetaxel were 10 (62.5%) patients and combination of Ifosfamide, Cisplatin, Uromitexan, and Paclitaxel were 3 (18.75%) patients. The others regimen used were combination of Cisplatin and 5-Fluorouracil and combination of Cisplatin, Docetaxel and 5-Fluorouracil. The treatment recommendations for childhood NPC usually follow guidelines established for adults [6]. The survival benefit was predominantly observed with concurrent chemoradiotherapy using platinum-based agents [5,6]. Better

treatments are needed to improve the cure of advanced or recurrent disease and reduce long-term morbidities [9]. Although undifferentiated carcinoma is very sensitive to radiation, studies report cure rates range from 30% to 60% when radiation alone is used. The main problem is high dose radiation in children has been linked to significant long-term morbidity. This problem causes the involvement of chemotherapy in treatment strategies [3,13].

The survival of children with NPC has improved over past 4 decades with improved RT and chemotherapy. Combined therapy (adjuvant, neoadjuvant or concomitant chemotherapy) can significantly improve prognosis [9,13]. Based on multicenter study (Nasopharyngeal Carcinoma [NPC] 2003 German Society of Pediatric Oncology and Hematology/German Children's Oncology Group [NPC-2003-GPOH/DCOG]), NPC is highly radiosensitive and chemosensitive [8]. In recent years, most pediatric patients with NPC have been treated with a combination of chemotherapy and radiotherapy with various regimens around the world, usually containing Cisplatin and 5-fluorouracil. The survival rate is reported vary between 55% and 90% for overall survival (OS) and between 60.6% and 77% for disease-free survival (DFS) and event-free survival (EFS) [8].

According to Cassanova et al, induction chemotherapy before radiotherapy was received well in pediatric with NPC. Cisplatin and 5-fluorouracil are the most commonly used induction chemotherapy. The study of Casanova et al, they found that the addition of Docetaxel to the Cisplatin and 5-fluorouracil provides a complete response rate after 3 cycles which is higher (31%) compared to the cisplatin and 5-fluorouracil regimens only (20%) [5].

Mouden et al, conducted a study using combinations of chemotherapy and radiotherapy for NPC patients. All patients were treated with three cycles of neoadjuvant chemotherapy every 21 days combining Bleomycine, Epirubicin, Cisplatin (BEC) and continued with followed by concurrent chemoradiation containing Cisplatin 30 mg/m²/week and radiotherapy (70 Gy to nasopharynx and the involved nodes and 50 Gy to the remainder cervical areas, 2 Gy/fraction in 7 weeks), they found about 78.1% of patients with a complete response to therapy [4].

Radiation is an appropriate therapy for NPC[3]. Retrospective research carried out by comparing radiation doses, they found that the radiation dose given >60 Gy 5-year disease free survival rate was reached to 70% in T1-T2 patients compared to only 20% in T3-T4. Retrospective research also found that radiation with 50-59Gy gave a 5-year Relapse Free Survival (RFS) rate of around 35% compared to 54% at a radiation dose of 70 Gy [4]. Evidence shows that RT doses less than 60Gy are proven to reduce survival [11]. But the RT doses to the cervical lymph nodes can be reduced to 50 Gy or less without affecting survival. A high RT doses is not needed for disease control but instead increases the incidence of mortality. Based on this evidence, they suggest RT 60-68Gy for primary lesions and 50-60Gy for neck lymph nodes [11]. Other opinions also revealed a doses of 50-72 Gy directed to the primary tumor are recommended for patients older than 10 years, and a 5-10% reduction in this dose is recommended for children younger than 10 years of age [3].

Study of Buehrlen et al, after chemotherapy and chemoradiotherapy, the treatment was continued with interferon- β (IFN- β) for 6 months. Patients received Flibaferon at a dose of 100,000 IU/kg intravenously over 30 minutes 3 days per week. The maximum single dose was 5 million IU for patients with a body weight >50 kg. IFN- β provides great benefits for the treatment results of NPC in children [7]. IFN- β administration can improved survival rates. It is known that T-cell immunity to EBV plays an important role in suppressing proliferating EBV-infected B cells. Patients with EBV-positive NPC were found to have a profound impairment in long term T-cell immunity to EBV. This IFN- β inhibits tumor cell angiogenesis. Angiogenesis is essential for tumor growth and is a key step for metastasis [8,13].

Study by Mouden et al, they found the long-term complications arising from the side effects of chemoradiotherapy were trismus (59.4%), hearing loss (51.6%), xerostomia (50%), neck fibrosis (37.5%) and radiation encephalopathy (4.7%) [4]. Other literature also found complications such as endocrine abnormalities, growth disorders, otitis media, mucositis, neutropenia, nausea, nephrotoxicity, ototoxicity undergoing chemotherapy and/or radiation [4,8,11]. Side effects that can arise due to interferon administration are leukopenia and fever [8,10].

5. CONCLUSION

Nasopharyngeal carcinoma in children generally have subtype of undifferentiated carcinoma with advanced stage, which is stage IV. Although the high rate of distant locoregional disease associated with undifferentiated carcinoma and NPC in children generally present with advanced stages, overall survival is not significantly different from adults and survival rates are better than adults.

Treatment for nasopharyngeal carcinoma in children generally follows the guidelines for adults with the results of therapy in children similar to that observed in adults, but the long-term toxicity is higher in children. Patients with stage I and II have very good survival. Presence of distant metastases results in a worse prognosis, despite the administration of combined treatment. Early diagnosis and prompt treatment are very important for better prognosis.

REFERENCE

- [1] Brennan B. Nasopharyngeal carcinoma. *Orphanet Journal of Rare Diseases* 2006; 1:23. doi:10.1186/1750-1172-1-23.
- [2] Busson P. Descriptive, Environmental and Genetic Epidemiology of Nasopharyngeal Carcinoma. LANDES. USA. 2013 ; 23-25.
- [3] Ayan I, Kaytan E, Ayan N. Childhood nasopharyngeal carcinoma: from biology to treatment. *Lancet Oncol* 2003; 4: 13–21.
- [4] Mouden K, Kababri ME, Kili A, Majjaoui SE, Kacemi HE, kebdani BE, et al. Nasopharyngeal Carcinoma in childhood: Analysis of a Series of 64 Patients treated with Combined Chemotherapy and Radiotherapy. *Canc Therapy & Oncol Int J* 9(2): CTOIJ.MS.ID.555758 (2018). DOI: 10.19080/CTOIJ.2018.09.555758.
- [5] Casanova M, Ozyar E, Patte C, Orbach D, Ferrari A, Follet CV, et al. International randomized phase 2 study on the addition of docetaxel to the combination of cisplatin and 5-fluorouracil in the induction treatment for nasopharyngeal carcinoma in children and adolescents. *Cancer Chemother Pharmacol*.2015. DOI 10.1007/s00280-015-2933-2.
- [6] Hu S, Xu X, Xu J, Xu Q, Liu S. Prognostic Factors and Long-Term Outcomes of Nasopharyngeal Carcinoma in Children and Adolescents. *Pediatr Blood Cancer* 2013;60:1122–1127. DOI 10.1002/pbc.24458.
- [7] Ozyar E, Selek U, Laskar S, Uzel O, Anacak Y, Arush MB, et al. Treatment results of 165 pediatric patients with non-metastatic nasopharyngeal carcinoma: A Rare Cancer Network study. *Radiotherapy and Oncology* 81 (2006) 39–46.
- [8] Buehrlen M, Zwaan CM, Granzen B, et al. Multimodal Treatment, Including Interferon Beta, of Nasopharyngeal Carcinoma in Children and Young Adults: Preliminary Results From the Prospective, Multicenter Study NPC-2003-GPOH/DCOG. *Cancer* 2012;000:000–000. DOI: 10.1002/cncr.27395.
- [9] Cheuk DKL, Billups CA, Martin MG, Ronald CR, Ribeiro RC, Krasin MJ, et al. Prognostic Factors and Long-Term Outcomes of Childhood Nasopharyngeal Carcinoma. *Cancer* January 1, 2011. DOI: 10.1002/cncr.25376.
- [10] Daoud J, Toumi N, Bouaziz M, Ghorbel A, Jilidi R, Drira MM, et al. Nasopharyngeal carcinoma in childhood and adolescence: Analysis of a series of 32 patients treated with combined chemotherapy and radiotherapy. *European Journal of Cancer* 39 (2003) 2349–2354. doi:10.1016/S0959-8049(03)00512-4.
- [11] Yan Z, Xia L, Huang Y, Chen P, Jiang L, Zhang B. Nasopharyngeal carcinoma in children and adolescents in an endemic area: A report of 185 cases. *International Journal of PediatricOtorhinolaryngology* 77 (2013) 1454–1460.
- [12] Wei WI, Chua DTT. *Nasopharyngeal Carcinoma in Bailey's Head and Neck Surgery-Otolaryngology* [edited by] Jonas T. Johnson, Clark A Rosen. 5th ed. Philadelphia. 2014. Volume 2. Hal 235.
- [13] Martens R, Granzen B, Lassay L, Buesky P, Hundgen M, Stetter G, et al. Treatment of Nasopharyngeal Carcinoma in Children and Adolescents: Definitive Results of a Multicenter Study (NPC-91-GPOH). *Cancer* 2005;104:1083–9. DOI 10.1002/cncr.21258.
- [14] Kupeli S, Varan A, Ozyar E, Atahan IL, Yalcin B, Kutluk T, et al. Treatment Results of 84 Patients With Nasopharyngeal Carcinoma in Childhood. *Pediatr Blood Cancer* 2006;46:454–458. DOI 10.1002/pbc.20433.
- [15] Cheuk DKL, Sabin ND, Hossain M, Wozniak A, Naik M, Galindo CR, et al. PET/CT for staging and follow-up of pediatric nasopharyngeal carcinoma. *Eur J Nucl Med Mol Imaging* (2012) 39:1097–1106. DOI 10.1007/s00259-012-2091-2.

CHARACTERISTICS OF NASOPHARYNGEAL CARCINOMA IN CHILDREN AND ADOLESCENTS IN DR. ZAINOEL ABIDIN GENERAL HOSPITAL BANDA ACEH

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4
