

Bone Metastases in Nasopharyngeal Carcinoma

Ni Ketut Susilawati^{1*}, Hamsu Kadriyan²

¹Department of Otorhinolaryngology-Head and Neck Surgery Praya General Hospital, Central Lombok, Indonesia

²Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Mataram University/West Nusa Tenggara General Hospital, Indonesia

Abstract

Introduction: The incidence of bone metastases is as much as 20% of all distant metastases in nasopharyngeal carcinoma (NPC). However, the publication regarding bone metastasis is limited.

Case Report: Reported a 58-year-old male patient with a mass on the right upper jugular neck lymph node. According to history taking, physical examination, radiology, and histopathology work up, concluded that the patients were established as nasopharyngeal cancer with the thoraco-lumbar bone metastasis. The physician was starting the chemotherapy; however, due to the advanced stage, this patient was death after the second chemotherapy.

Conclusion: In this article presented a nasopharyngeal carcinoma case with bone metastases that have been diagnosed with stage IV B nasopharyngeal carcinoma. This article also described the pathophysiology, diagnosis, and treatment of bone metastases in nasopharyngeal carcinoma.

Article Info

Article history:

Received: 19th August 2020

Received in revised form: 3rd September 2020

Accepted: 4th September 2020

Keywords:

Bone metastases, NPC, pathophysiology, diagnosis, therapy

*Corresponding author:

Address: Jl. H. Lalu Hasyim, Bunut Baik, Praya, Kabupaten Lombok Tengah, Nusa Tenggara Bar. 83511

e-mail: susilawatiketut88@gmail.com

1. CASE REPORT

Reported a 58-year-old male patient who came to the Praya General Hospital on January 13, 2019 with the main complaint of a lump in the right neck since 8 months ago accompanied by the weakness of the whole body, including all four limbs since 3 months ago. In the last 1 month, the complaint slowly began to propagate. Three days prior to the hospital visit, the patient could not walk and sat, only lying down on the bed. The patient also complained that he could not urinate and defecate. He remains could be taking food and water. The lump in the neck was initially small and multiple; however, gradually it getting bigger, denser, and fixed, without any fever and pain. The other accompanied complaints were headache, tinnitus, nasal congestion, sometimes accompanied by nasal bleeding. There were no complaints such as difficulty when opening the mouth, bumps in the armpits and groin, hoarseness, difficulty on breathing, tingling in the face, and double vision.

This patient previously has visited a private practice of ENT specialist, and a nasopharyngeal biopsy was done on November 17, 2018. CT scan of the head and neck with contrast has been performed with the result there is a mass in the nasopharynx. According to those results, the patient is advised to the West Nusa Tenggara General Hospital for further treatment. Unfortunately, the patient chose alternative medicine until it finally comes with a weak condition.

Based on the history of daily life found that he was a smoker for more than 20 years, often consume salted fish and furniture maker. There was no history of similar disease or malignancy on the family.

Physical examination showed a general state was weak, blood pressure 140/100 mmHg, pulse 88x/minute, respiration rate 20x/minute, temperature 36.5 °C. Examination of ENT-HN obtained both the external auditory canal and eardrum within normal limit. However, the cone of light on the right ear was decreased. There was no deformity of the nasal aperture: the nasal cavity, inferior turbinate, and middle turbinate and nasal septum within normal limits. On throat examination, pharyngeal mucosa, palatum, and tonsil within normal limit. There was a mass on the right nasopharynx and enlargement of the right upper jugular with the size 8x8x4 cm, solid, fixed, without any pain when palpated.



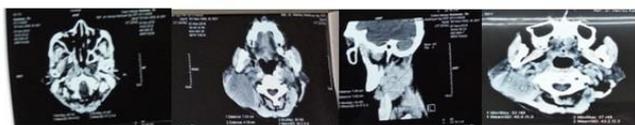
Picture 1. Enlarged lymph nodes on the right upper jugular node

The neurology examination regarding the eye movement was normal; there was no ptosis. The other cranial nerve within normal limits found a motoric tetra spastic paresis. Hypesthesia sensibility from toe to C3-4 dermatome, and there was a vegetative retentio uri et alvi.

Laboratory work up on 13 January 2019: leucocyte 15.02 k/uL, Haemoglobin 11.5 g/dL, platelets 474 k/uL, blood sugar 93 mg/dl. Electrolyte Sodium 122 mmol/L, Kalium 4.7 mmol/L, Chloride 87 mmol/L.

Radiologic examination of the head and neck CT scan with contrast appears mass in the right nasopharyngeal extends to the right parafaring. Lymphadenopathy right colli with the largest dimension 7.8 cm.

The treatment is IVFD NaCl 3% 24 drops/minute, cefotaxim 2x1 gram, amlodipine 1x10 mg, paracetamol 6x500 mg, codeine 6x10 mg.



Picture 2. Head and neck CT scan with contrast

On January 15, 2019 patient was referred to West Nusa Tenggara General Hospital for CT Scan, staging, and chemoradiotherapy plans. The liver function test was examined on 26/1/2019: SGOT 24 u/L, SGPT 10u/L, albumin 3.2 mg/dL, Alkaline phosphatase 97.8. Kidney function test revealed BUN 24 mg/dl, SC 0.6 mg/dL.

Thoracolumbar CT scan with contrast was performed on January 24, 2019. According to this examination found the appearance of lytic lesions on the anterior corpus vertebra L2 and vertebra compressi Th10.



Picture 3. Thoracolumbar CT scan with contrast

Finally, patients were diagnosed with Nasopharyngeal carcinoma Stage IV B (T2N3M1), based on AJCC 8th edition, 2017. The treatment was initialized with correcting the general conditions; then the next treatment plan was chemotherapy or chemoradiation with platinum-based combination through a concurrent technique. On February 6, 2019, first cycle chemotherapy was started with paclitaxel 267.75 mg and cisplatin 122.4 mg. The second chemotherapy was given on March 2, 2019 with the similar doses. On March 23, 2019 was planned to the third cycle chemotherapy but the patient did not come because he already death on March 15, 2019.

2. DISCUSSION

Nasopharyngeal carcinoma (NPC) is a malignant tumor that appears in the nasopharynx (the area above the throat and behind the nose), especially in fossa Rosenmuller and roof nasopharynx which shows evidence of mild or ultrastructural microscopic squamous differentiation [2].

In Indonesia, NPC is the 4th most malignancy after breast cancer, cervical cancer, and lung cancer [3]. In the head and neck area NPC was the most prevalence (NPC was composed the 60% of tumors in the head and neck area, followed by 18% malignant on nasal and paranasal sinuses, the rest 16% were larynx and malignancy of oral cavity tumors, tonsils, hypopharynx) [4].

Metastases are the growth of cancer into the lymph node and other organs, through the lymphogens or hematogenous. Metastases clinically is the most important properties of cancer growth and it will altered the prognosis [5,6].

The percentage of distant metastases in nasopharyngeal cancer (NPC), consecutively to pulmonary, bone, liver, kidney, and brain was 20%, 20%, 10%, 0.4%, 0.4%. The most metastases are on the regional neck node [6]. The general prognosis of NPC is poor. For stage I, the five years of survival rate was 83.7%, stage II 67.9%, and stage III 40.3%, whereas in advanced cases with metastases, only around 22.3% [6,7].

2.1 Pathophysiology

Osteoclasts are originated from precursor cells in the monocyte-macrophage line of the hemopoietic system. Osteoclasts are activated to reabsorb the bone and then undergo apoptosis. Cytokines, systemic hormones, and conditions around the bone play a role in osteoclast formation through the production of macrophage colony-stimulating factors and receptor activator of nuclear- κ B ligand (RANKL) by stromal cells or osteoblasts. RANKL then released by the T cells are activated and expressed to the surface by osteoblasts and stromal cells. The function osteoclast was to reabsorb bone in normal or pathological conditions by secreting proteases

that dissolve the bone matrix and produce acids, which release bone minerals into the extracellular space below the osteoclast plasma membrane. This plasma membrane is directly facing the bone surface. The attachment of osteoclasts to the bone surface is very important in the process of bone resorption because there is a factors that can inhibit resorption bone like cathepsin k. The osteoblast is a cell forming derived bone from mesenchymal stem cells. Bone protein is an important factor in stimulating the growth of osteoblast to be osteocytes [8]. Cancer cells migrate to the bone microenvironment that causes the occurrence activity of osteoclasts to absorb bone minerals. Furthermore, the destruction of the cortex bone was initiated. The venous system on plexus paravertebral Batson is the main way on the spreading of tumor cells to the bone because bone does not have channel lymph [9]. Malignant tumors of the head and neck, breast, kidney, and the adrenal gland has a relationship with the vertebral venous system so metastases bone from this tumor could happen along this vein without through system porta, lung and vena cava [10].

2.2 Diagnosis

The diagnosis of bone metastases should be determined based on clinical, laboratory, and imaging workup. Definitive diagnosis is established by histopathology examination of the organ involved, but it is rarely done. Histopathology only in bone metastases lesions where the primary lesion is not known. This needs to be done. According to the NCCN 2006 version 1:9 if there are radiographic abnormalities in bone without pain in patients less than 40 years, then the patient should be referred to an orthopedic oncologist for biopsy. For those who up to 40 years must do the comprehensive workup due to a possibility of a bone metastases. A routine bone scan, chest x-ray, pelvic abdominal CT scan, must be done. Clinically, the main complaint of bone metastasis usually pain. On the circumstances, the neurology disturbance, fracture signs, dislocation could be found depends on the location of metastases. On the laboratory, exploration may found an enhancement of alkaline phosphatase, calcium, and LDH; however, this is not specific. On imaging, a routine bone scanning and X-ray/bone survey should be performed. In advanced, in specific cases, the additional examination could be performed, such as myelography, CT scan, and MRI [8, 9].

2.3 Treatment

Based on the guideline of the 2018 NCCN in NPC with bone metastases, the treatment plan should be a combination of platinum-based chemotherapy or chemoradiation with a concurrent technique. The aim of radiation therapy on bone metastases is palliative, and it's vital for patients with bone pain. However, the radiation depending on the origin of the primary tumor. More than three-quarters of the number of patients with the pain can be relieved by radiation. Furthermore, the radiation treatment on bone metastases is useful to eliminate the pain, prevent the fracture, prevent the neurological disturbance, and the final goal is the patient could be care ambulatory. The right time to give radiation could prevent pathological fracture. In case of fracture, then it should be fixed immediately because mechanic pain or bone dislocation will attenuate by radiation. Bisphosphonate should be administered as an inhibitor of osteoclasts activity, so it could reduce pain symptoms and pathological fracture. The medicine should be given to the patient with the results abnormal bone scan, photo plain, abnormal CT or MRI. On the other hand, if bone lesions are not seen in plain photos or CT/MRI, bisphosphonate administration is not recommended [11]. Regular bone scan in asymptomatic patients are usually performed on follow-up patients, it is not recommended to provide radiation to patients without symptoms because the goal of palliative treatment is to relieve symptoms [12].

The patient on this case was a 58-year-old male. NPC could be found at all ages, but rarely under 20 years. The incidence of NPC began to increase at the age of 20-24 years and is often found in the productive age of 30-59 years (around 80%) with peaks between 40-49 years [6]. The incidence of NPC is higher in men than women with a ratio of 2-3:1 [13]. In Lombok, the age of the patient with NPC, mostly up to 40 years old (67%) with the gender ratio 75% was male [14].

This patient also has risk factors related to the etiology of NPC, such as active chronic smokers, salted fish consumption history, and as wood dust exposure due to furniture employer for a long time. Several studies revealed that the risk of NPC in smokers was 30% -100% higher compared to

nonsmokers [15,16]. Salted fish exposure as a carcinogenic factor at an early age are at high risk for the occurrence of NPC [16,17]. The other risk factor is Formaldehyde, which is widely used as a solvent, disinfectant, and preservative solution [17,18]. Formaldehyde gas (CH₂O) is a combustible, colorless, and widely used compound in the manufacture of resins, wood coatings, photo films, and tissue preservatives. Formaldehyde can irritate the eyes and upper respiratory mucosa with a concentration of 0.5-1 ppm [19,20].

Another factor is exposure to wood dust that accumulates over a long period of time. Wood dust causes irritation and inflammation in the nasopharyngeal epithelium, so it could fuse the mucociliary work and may change the epithelial cells in the nasopharynx. Exposure to smoke resulting from burning firewood and incense smoke for more than 10 years can increase the incidence of NPC by about 6 times [19].

Epstein Barr Virus (EBV) infected more than 90% of the entire world population, but the primary infection of the Epstein Barr virus remains inactive and has not shown clinical symptoms [13]. The relationship between NPC and Epstein Barr virus was found in 1966 based on the results of research in serology through the discovery of EBV DNA and EBV nuclear antigen (EBNA) in NPC patients [19]. Genetic factors also take a role. The analysis of the relationship between human leukocyte antigen (HLA) haplotypes and NPC showed an increased risk in individuals with HLA-A2 positive in the Chinese population [13, 20].

The main complaint of this patient was the mass in the neck. According to the literature, most patients present with complaints of a neck mass. This symptom indicated that the patients were coming at an advanced stage (stage IV). In the common case, it is difficult to detect early cases of NPC due to the hidden nasopharyngeal position; the initial symptoms are not typical like the common cold. The process of metastasis in the neck gland is in accordance with the flow of lymph from the nasopharynx to the retrofaring lymph nodes, which then enter the superior jugular lymph node [3].

On examination of the nasopharyngeal biopsy obtained the results of undifferentiated carcinoma (WHO type 3). Based on the WHO Head and Neck 4th Ed 2017 establishes three forms of nasopharyngeal carcinoma histopathology, keratinizing squamous cell carcinoma, non-keratinizing squamous cell carcinoma, and basaloid squamous cell carcinoma [21].

Keratinizing squamous cell carcinoma, characterized by the differentiation of squamous cells with intercellular bridge or keratinization. Tumors grow in the form of islands associated with desmoplastic stroma with varying infiltration of inflammatory cells such as lymphocytes, plasma cells, neutrophils and eosinophils. Tumor cells are polygonal and stratified. The boundary between cells is clear and separated by intercellular bridges. Cells in the central part of the island show eosinophilic cytoplasm, which many sign of keratinization. Keratin pearls are found [21].

Non-keratinizing squamous cell carcinoma is characterized by a cell that shows clear inter-cell boundaries and sometimes, a faint intercellular bridge is found. Compared with undifferentiated carcinoma, the cell size is smaller, the ratio of the cytoplasmic nucleus is smaller, the nucleus is more hyperchromatic and the core child is not prominent [21].

Basaloid squamous cell carcinoma this type has two components, namely basaloid cells and squamous cells. Basaloid cells are small with a hyperchromatic nucleus, and no nucleus is found and little cytoplasm. Grow in a solid pattern with lobular configurations and at some cases, found palisading peripherals. Components of squamous cells can be in situ or invasive. The boundary between the basaloid and squamous components is clear [21].

A CT-Scan with contrast is useful for staging. According to the head and neck CT scan obtained tumors located in right nasopharynx expanding to the right parafaring, enlargement right colli lymph node with the size 7.8 cm at level II (jugular superior). This examination can also determine the spread of the tumor to the surrounding tissue which is not too wide, and detect base cranium erosion and perineural spread through the foramen ovale as intracranial extension to the mainline [22].

The enlargement regional lymph nodes indicated that NPC has an ability to invade and related tightly with the lymphoid network. Metastases to cervical lymph nodes are commonly found, its occur on 65-86.6% patient. Furthermore, this complaint is the often reason that brings the patients to seek the medication. The most common location is latero-superior deep cervical lymph nodes located just below the mastoid tip, behind the mandibular angles, in the medial part of the upper end of the sternocleidomastoid muscle, next to mediosuperior deep cervical lymphoma. NPC can spread to the lateral retropharyngeal lymph nodes. Limfogen metastases pathways are starting from lymphatics, cancer cells

carried to the station of the first regional lymph nodes through afferent channels to a certain place where cancer cells can grow into cancer metastases. Then, the cancer cell can reach the next lymph node station [22].

In determining distant metastases, an examination of lungs, liver, and bone was obtained patient with metastases L2 vertebral corpus. According to a lumbar CT scan, a lytic lesion is found in the anterior vertebra corpus L2, which is suspected bone metastases. Bone metastases may due to the hematogenous process. Hematogenous metastases occur when cancer cells reach the blood vessels. The penetrated blood vessels determine where metastases will occur. If it stops at certain places in the capillary area of the circulating cancer cells, it will make a cancer embolism. This principle may explain the specific pattern of metastases or specific metastatic sites. Nasopharyngeal malignant tumor cells can enter the right internal jugular vein or subclavian vein through vasa efferent cervical lymph nodes, which then enter the jugular trunk. This spread gives rise to distant metastases. Sheng et al. (2007) said that around 5-10% of patients with nasopharyngeal carcinoma experience distant metastases [22]. Barnes et al. (1996) said that distant metastases is usually preceded by locoregional recurrence, but the fact that is found is 10-20% of patients who experience distant metastases without locoregional recurrence first [23]. Cancer cell migrates to the microenvironment of bone and leads to occurrence activity of osteoclasts to absorb bone minerals. If it happens, the destruction of the bone cortex will happen. The venous system on plexus paravertebral Batson is the main spread of tumor cells to the bone because bone does not have channel lymph. Malignant tumors head and neck, breast, kidney, and the adrenal gland have a relationship with the vertebral venous system. So, bone metastases from this tumor could happen along this vein without system porta, lung, and vena cava [24].

Metastases on the vertebral corpus L2 may cause the symptoms of micturition and defecation disturbance. Initially, patients experience urine retention and alvi but after the care was given, this symptom is gradually improved and patient already could urinate and defecate. The other possibility in this condition, it may influence by electrolyte decreases (hyponatremia) so the function of the nerve is disturbed, and after corrected, all the function has become normal on the next examination. Tetraparesis spastic as a consequence existence emphasis on the C 3-4 vertebral corpus could not confirm yet from result of the cervical spine CT-Scan examination.

According to the 2018 guideline of the NCCN, the patient was planned to be treated with platinum-based chemotherapy or chemoradiation with a concurrent technique [11]. The standard for NPC therapy is radiotherapy. The advantage of providing radiotherapy as a single regimen in stage I and II cancers will provide 5 years of life expectancy of 90-95%, but the problem is most patients come with advanced stages (stage III and IV), some even with bad conditions. Aside from NPC is known as a malignancy that has high potential to make regional and distant metastases. The success of therapy is strongly influenced by the stage; the delay in starting adequate treatment may cause the results of therapy to be far from encouraging. Another alternative for treating patients with head and neck squamous cell carcinoma, which is a locally advanced stage, is induction chemotherapy followed by chemoradiotherapy as radical therapy, especially in patients with a good response to induction chemotherapy [6, 9].

The prognosis of this patient is poor. In these cases, survival is only for 13 months since the first complaint. In NPC with distant metastases reported that five years survival rate is only 22.3%. It was found that type 1 nasopharyngeal carcinoma (squamous cell carcinoma) had a worse prognosis than type 2 and 3. This may occur due to type 1 is easier to metastases. Overall, the 5-year survival rate is 45%. The prognosis is exacerbated by several factors, such as the advanced stage, age more than 40 years, gender, Chinese race than in the white race, an enlargement of neck nodes, the presence of cerebral nerve palsy, skull bone damage, and distant metastases [6].

3. CONCLUSION

Reported a 58 years old male patient with nasopharyngeal carcinoma stage IV B. This patient was planned to be treat as advanced stage management. NPC often comes at an advanced stage because symptoms were not specific. The location of nasopharyngeal difficult to evaluated finally altered the prognosis of the diseases. To prevent other cases in the future, the strengthening of early detection in community and primary health care facilities become important. Furthermore, the physician could increase the prognosis.

REFERENCE

- [1] Lee AWM, Lydiatt M, Colevas AD, Glastonbury CM, Le QTX, Sullivan BO, et al. Nasopharynx. In: Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, et al editors. AJCC Cancer Staging Manual. 8th ed. Switzerland:Springer Nature;2017.103-110
- [2] Chan JK, Pilch BZ, Kuo TT, Wenig BM, Lee AW. Tumours of the nasopharynx. In: Barnes EL, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumours. Kleihues P, Sobin LH, series editors. World Health Organization Classification of Tumours. Lyon, France: IARC Press; 2005. 85–97
- [3] Adham M, KurniawanAM, MuhtadiAI, Roezin A, Hermani B, et al. Nasopharyngeal carcinoma in Indonesia: epidemiology, incidence, signs, and symptoms at presentation. Chin J Cancer. 2012; 31 (4). DOI: <https://doi.org/10.5732/cjc.011.10328>
- [4] Roezin A., Adham M. Nasopharyngeal Carcinoma. In: Soepardi EA, Iskandar N, Bashiruddin J, Restuti RD, editors. Otorinolaryngology Head and Neck Book. 6th ed. Jakarta: Indonesia University Medical Faculty, 2007.p.182-190.
- [5] Bosman FT. Fundamental aspects of cancer. In: van de Velde CJH, Bosman FT, DJTh Wagener. Oncology. Edition 5. Yogyakarta: Gajah Mada University Press; 1999. 10-14.
- [6] Kurniawan P, Yusuf M. Metastatic Processes in Head and Neck Malignancies. Journal ENT-HN.2014. (7):1.37-46
- [7] Djuita F, Defrizal. Radiation of Bone Metastases. Indonesian Journal of Cancer 2007; 4: 135-139.
- [8] Roodman GD. Biology of osteoclast activation in cancer. Journal of Clinical Oncology [internet]. 2001;19(15):3562-71. DOI: <https://doi.org/10.1200/JCO.2001.19.15.3562>
- [9] Lovey G, Hennigs SP, Gerdes CH, Trenn G. Percutaneous vertebroplasty in combination with external beam radiotherapy for vertebral metastases [internet]. Radiotherapy and Oncology. 2004; 73(S355). DOI: [https://doi.org/10.1016/S0167-8140\(04\)82698-7](https://doi.org/10.1016/S0167-8140(04)82698-7)
- [10] Savelli G, Maffioli L, Maccauro M, De Deckere E, Bombardieri E. Bone scintigraphy and the added value of SPECT (single photon emission tomography) in detecting skeletal lesions. The Quarterly Journal Of Nuclear Medicine. 2001;45(1):27-37.
- [11] Colevas AD, Yom SS, Pfister DG, Spencer S, Adelstein D, Adkins D, Brizel DM, Burtness B, Busse PM, Caudell JJ, Cmelak AJ. NCCN guidelines insights: head and neck cancers, version 1.2018. Journal of the National Comprehensive Cancer Network. 2018;16(5):479-90. DOI: <https://doi.org/10.6004/jnccn.2018.0026>
- [12] Han LJ, Au-Yong TK, Tong WC, Chu KS, Szeto LT, Wong CP. Comparison of bone single-photon emission tomography and planar imaging in the detection of vertebral metastases in patients with back pain. European journal of nuclear medicine. 1998; 25(6):635-8. DOI: <https://doi.org/10.1007/s002590050266>
- [13] Guo X, Johnson RC, Deng H, Liao J, Guan L, Nelson GW, Tang M, Zheng Y, de The G, O'Brien SJ, Winkler CA. Evaluation of nonviral risk factors for nasopharyngeal carcinoma in a high - risk population of Southern China. International journal of cancer. 2009;124(12):2942-7. DOI: <https://doi.org/10.1002/ijc.24293>
- [14] Kadriyan H, Sulaksana MA, Lestarini IA, Susilawati NK, Punagi AQ, Pieter NA, Gaffar M. Incidence and characteristics of anemia among patients with nasopharyngeal carcinoma in Lombok, Indonesia. InAIP Conference Proceedings 2019.AIP Publishing LLC; 2199(1): p. 070015. DOI: <https://doi.org/10.1063/1.5141329>
- [15] Lu JJ, Cooper JS, Lee AW. Nasopharyngeal cancer: multidisciplinary management. London: Springer Science & Business Media; 2010.p.1-7
- [16] Sulaksana MA, Kadriyan H. Characteristics and Risk Factors of Patients with Nasopharyngeal Cancer in West Nusa Tenggara Hospital. International Journal of Nasopharyngeal Carcinoma 2019; 1(3): 83-85. DOI: <https://doi.org/10.32734/ijnpc.v1i03.2058>
- [17] Bishop JA, Thompson LDR. Malignant neoplasms of the nasal cavity, paranasal sinuses, and nasopharynx. In Head and Neck Pathology: A Volume in the Series: Foundations in Diagnostic Pathology. Amsterdam: Elsevier; 2019. p. 51-100.
- [18] Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiology and Prevention Biomarkers. 2006;15(10):1765-77. DOI: <https://doi.org/10.1158/1055-9965>
- [19] Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. Mortality from solid cancers among workers in formaldehyde industries. American Journal of Epidemiology. 2004;159(12):1117-30. DOI: <https://doi.org/10.1093/aje/kwh174>
- [20] Jia WH, Luo XY, Feng BJ, Ruan HL, Bei JX, Liu WS, Qin HD, Feng QS, Chen LZ, Yao SY, Zeng YX. Traditional Cantonese diet and nasopharyngeal carcinoma risk: a large-scale case-control study in Guangdong, China. BMC cancer. 2010;10(1): p. 1-7. DOI: <https://doi.org/10.1186/1471-2407-10-446>
- [21] Chan JKC, Bray F, McCarron P, Foo W, Lee AWM, Yip T, et al. Nasopharyngeal Carcinoma. In: Barnes L, Eveson JW, Reichart P, Sidransky D editors. WHO Classification of Tumours Pathology & Genetics Head and Neck Tumours. Lyon: IARCH Press. 2005. p.85-97
- [22] Ho SL, Fee WE. Malignant Nasopharyngeal Tumors. Department of otolaryngology Head and Neck Surgery, Wayne State University, Detroit Medical Centre. Last update: Dec. 2007;21.
- [23] Barnes L. Pathology of the Head and Neck: General Considerations. In: Myers E, Suen J, editors. Cancer of the Head and Neck. 3rd ed. Philadelphia: WB Saunders Company, 1996. p.17-32.
- [24] Resnick D, Niwayana G. Diagnosis of Bone and Joint Disorders. 2nd ed. Philadelphia: WB Saunders company. 1988, p 3998-4000.