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Epidemiology and Outcomes of Nasopharyngeal Carcinoma

Gamal Abdul Hamid

Abstract

Nasopharyngeal carcinoma (NPC) is a rare head and neck neoplasm worldwide. It is common among the southern Chinese with significant geographical variation with the highest incidence being in Southeast Asia up to 6.4/100,000 males and 2.4/100,000 females in these regions and the Epstein Barr virus (EBV) is associated closely with NPC. This disease has peculiarities in its etiopathogenesis, presentation, risk of nodal and distant metastasis, response to therapy and overall survival (OS) outcomes that stand out as compared to other head and neck cancer subsites. NPC is mainly treated by RT and is profoundly radiosensitive and radiotherapy treatment is the spine of treatment for all stages of NPC without far off metastases. Many advances in RT techniques and schedules are attempted to improve outcomes of the disease starting from intracavitary brachytherapy, intensity modulated RT to simultaneous modulated accelerated RT, all showing some promise with most significant benefit seen with addition of chemotherapy, especially in intermediate (Stage II) and advanced (Stage III, IVA, IVB) cases. At a time when modern radiation treatment like *intensity-modulated radiotherapy* (IMRT) are accomplishing great good local control, distant metastases are getting to be the transcendent design of treatment failure, particularly in patients with locally progressed illness. There are numerous results from clinical trials looking at combined radiation treatment (RT) and chemotherapy for NPC. Survival rates significantly differ between NPC patients according to stages of disease.

Keywords: nasopharyngeal carcinoma, epidemiology, risk factors, Epstein-Barr virus, clinical outcomes

1. Introduction

Nasopharyngeal carcinoma (NPC) is a rare disease and one of the most common types of malignancies that appear in the nasopharynx, which is the narrow tube passage behind the nasal cavity and one of the malignancies associated with the Epstein-Barr virus (EBV) and is considered one of the malignant and rare tumors in most parts of the world and is distinguished by distribution geographical and ethnic [1]. In southern China, it is one of the leading causes of death and morbidity. Notwithstanding the common burden of NPC in some endemic areas, the etiology and prevention of NPC is relatively unknown.

In 1978 the histopathological classification of nasopharyngeal carcinoma proposed by the World Health Organization was adopted, which divided tumors into three types. Type 1 was typical of squamous cell carcinoma, similar to the rest of the upper gastrointestinal tract. The second type included non-keratinized squamous cell carcinoma and the third type was undifferentiated carcinoma. In

epidemiological research this classification is more applicable and has been shown to have a predictive effect. Undifferentiated carcinomas have a higher rate of localized tumor control during treatment and a higher rate of distant metastases.

Among cancers of the head and neck, nasopharyngeal carcinoma is one of the most common type of cancers [2]. It is also a virulent disease that has been accounted for to occur in many parts of the world with a uniform incidence rate for age and sex, one of every 100,000 every year [3]. This malignant growth has an unequal geographical distribution with the incidence rate on one continent higher than on other continents, which was very high in Asia (80%) and 10% in Africa. The rest 10% have been accounted for somewhere in the world, and Southeast Asian nations represent 67% of cancer burden worldwide. In addition to geographical differences, some ethnic gatherings might be in danger of creating nasopharyngeal malignancy. For example: Bidayuh on Borneo Island, Inuit in the Arctic and Nagas in Northern India, with an old norm of more than 16 for every 100,000 every year for men [4].

In non endemic regions, during last 50 years, incidence of poorly or undifferentiated NPC raised [5, 6]. However, this was supposed to be mostly related to the increase of migration flows towards these areas from endemic regions rather than an augmented exposure of residents to risk factors for NPC development. Indeed, in low incidence countries, the risk of development of NPC in immigrants is estimated to be around 30-fold greater than in residents. The association between Epstein-Barr virus (EBV) and nasopharyngeal carcinoma (NPC), has marked geographic and ethnic differences in its incidence [7]. The Over population in Asia, responsible for the increased rate of death by NPC, from 45,000 (in 1990) to 65,000 (in 2010) [8]. In Africa and some regions of East Asia, the nasopharyngeal carcinoma is more common and the incidence rate is generally lower from 1 for every 100,000 persons [9]. However, there are around 25 per 100,000 people in southern China, which is 18% of all cancers [10]. In Asia, NPC occurs in all ages but more common in the middle-aged population, although there is a high incidence of cases in children in Africa. A study on NPC and EBV showed a particular association between natural factors such as viral antibody factors, genetic factors and diet [11].

NPC is one of the highly invasive neoplasia and malignancies that spread early to regional lymph nodes [12]. Radiation therapy (RT) is also seen as an essential supportive treatment for management because of the sensitivity of the radiation to the type of disease. In advanced stages of disease, chemotherapy (CT) has been used for more than 20 years and some studies confirmed the benefit of chemoradiotherapy (CRT) in stages II to IV [13].

2. Global trends

In 2012, 86,691 nasopharynx cancer cases occurred in the world and 50,831 nasopharynx death cases, and in 2018 there were around 130,000 accidents and more than 73,000 deaths from nasopharyngeal carcinoma (NPC) worldwide [14]. The global NPC incidence and mortality distribution reported very high rates (more than 20-30/100,000 men and 10/100,000 women) in Southeast Asia [15], some regions of southern China, [16], Singapore, [17] Hong Kong, [18] Taiwan, [19] Selected Chinese immigrants (mainly to North America), [20, 21] and the Middle East [22]. In most of the western countries, Latin America and Japan that are non-endemic areas, the incidence rate of NPC showed less than 1/100,000 [23]. Recent studies have shown the incidence of NPC is high in cities like Zhongshan, Zhuhai, Hong Kong, and Jiangmen (standard age: 12.8-25 per 100,000 per year for men) in southern China [24–26] (**Figure 1**).

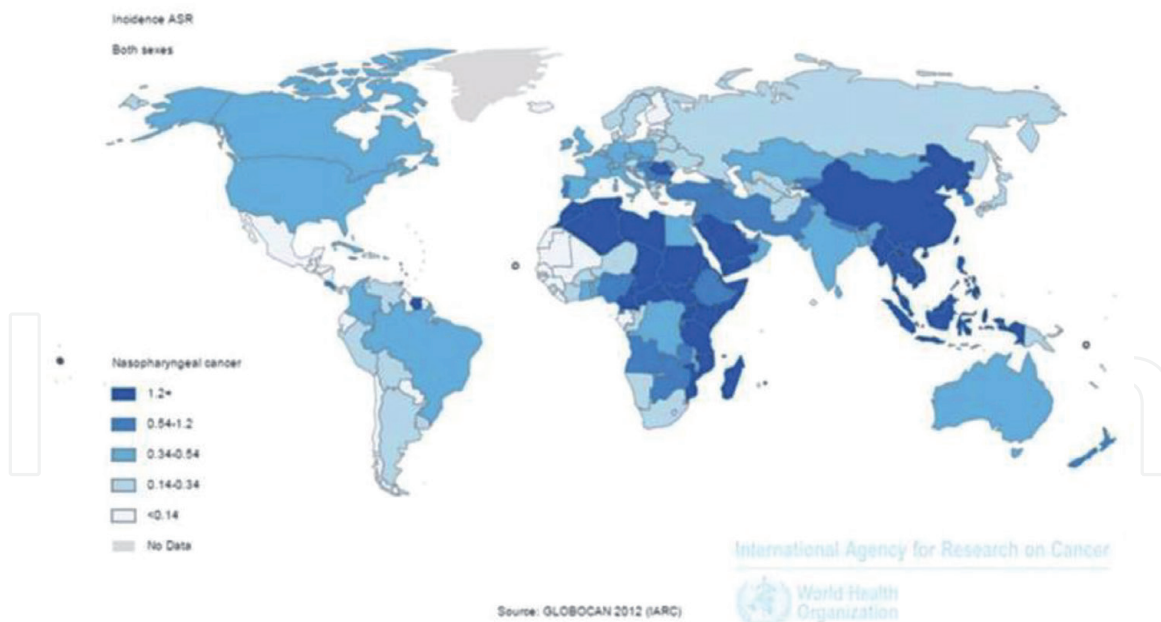


Figure 1.
 Incidence of Nasopharyngeal carcinoma (2012) (GLOBOCAN 2012) [26].

3. Age and gender

The incidence of nasopharyngeal carcinoma increases two to three times more frequently in men than in women [27]. Male predominance in the population is a common trait among NPC patients. Male dominance in the incidence of NPC can be partly explained by biological or gender differences or different lifestyles in the prevalence of some environmental risk factors, such as smoking and hazardous occupational exposure [28].

The nasopharyngeal carcinoma incidence in most low-risk groups is consistent with increasing age [29]. On the other hand, in the 50 to 59 age group, the incidence of NPC increases because these groups are more susceptible, and then decreases [30], which is related to the exposure of these groups to carcinogens in the early life stages [31].

It can take several decades for nasopharyngeal carcinoma to develop malignant cells. After that, the signs appear. Therefore, the outcome of carcinogens exposure in early life will have a sizeable effect on the development of this cancer [28].

4. Risk factors

Since the first case of this malignancy was recorded in 1901 [32], the etiology of the NPC has not been identified as a mystery. Risk factors for NPC, most commonly in men [33], include a family history of NPC, EBV infection, low intake of fresh vegetables and fruits, high consumption of salt-canned fish, smoking and Cantonese races [34]. On the other side, a reduced risk may be associated with a history of infectious mononucleosis (IM) and HLA genotypes [35]. Other potential risk factors are the genetic polymorphism in glutathione S-transferase M1 (*GSTM1*), *GSTT1*, cytochrome P450 2E1 (*CYP2E1*) and *CYP2A6* [36], possibly high consumption of other preserved foods [37, 38] and the history of chronic respiratory diseases. The exposures to dust and formaldehyde, nickel exposure and consumption of herbal medicine are less established risk factors [39].

4.1 Epstein-Barr virus (EBV)

The relationship of NPC to EBV-associated is known and proven, and EBV infection is one of the common infectious agents in the population. This relationship concluded the hypothesis that an EBV subtype of NPC plays a role in increasing the incidence of NPC in the epidemic regions. The association between EBV infection and nasopharyngeal carcinoma is very strong and has been demonstrated in several studies [40].

In the nucleus of malignant cells there are approximately 30 copies of the EBV gene. Most versions refer to the presence of "small circular chromosomes" called episomes. In some cases, these episomes are adjacent to the viral DNA releases. The use of serological and virological tests is recommended to diagnose and study the populations at risk. In areas with an increased incidence of nasopharyngeal carcinoma, high levels of IgA antibodies with EBV capsid antigen and Epstein-Barr nuclear antigen are considered to be a valuable screening test or the new prediction model combining VCA/IgA and EBNA1/IgA which will improve diagnosis of NPC and could identify high-risk population [41].

4.2 Familial history and genetic susceptibility

It is known that families with a history of cancer, particularly nasopharyngeal carcinoma, are 4 to 10 times more likely to develop nasopharyngeal carcinoma. Some studies have reported that familial clustering is stable in areas with a high incidence of NPC [42] and in areas with low to moderate incidence [43]. In southern China, where NPC is endemic, more than 5% reported NPC with a positive family history of NPC in cases with first-degree family history [44]. Evidence and studies of previous case control studies have shown indifferent populations that the odds ratios for people between 2 and 20 with history of NPC and history of first-degree family were compared to people without such a medical history [45]. This size of association is among the highest in any malignant disease. In nasopharyngeal carcinoma the genetic research focuses on genes of human leukocyte antigen. Where it occurred in subjects with presence of EBV and weak HLA allele, the antigens likely increased the risk of developing nasopharyngeal carcinoma. The development of NPC less likely in people with the presence of EBV associated with strong HLA allele. In etiology of NPC, it is possible that genetics and environmental exposure play a common role. Four correlation studies with susceptibility sites of 4p15.1_q12, 6p2153, 3p21.31e21.2 and 5p13 in NPC families of a single major susceptibility gene were observed and reported, supported by the results of NPC complex family segregation analysis, indicating that this the pathogens of NPC includes the interaction of many environmental and genetic factors [46, 47].

The genetic factor is one of the notable features of the race distribution in the cantonese population. The shared roles of environmental factors, lifestyle and genetics should not be ignored. Whether familial NPC cases differ significantly from sporadic cases in terms of clinical features (such as histopathology, stage of disease, and prognosis), gender, race, age, EBV sera, genetic risk factors, and environmental risk factors [48].

4.3 Exposure to carcinogens

4.3.1 Salt-preserved foods and fish

Several studies have reported that eating fish with salt is considered a risk factor for cancer. For the Chinese, the relative risk of developing pharyngeal cancer is lower among weekly consumers than those who use very little or no salt-canned

fish. Overall it was about 1.4 to 3.2 [36, 37]. The relative risks are between 1.8 and 7.5 for those who consume daily [49, 50]. The risk of developing nasopharyngeal carcinoma is higher with other canning foods such as fruits, vegetables, eggs and meat in Southeast Asia, Southern China, the Middle East, North Africa and the Arctic [51]. This preservative food is also implicated in people found in low-incidence areas of northern China and the United States [52].

4.3.2 Exposure to smoking and occupational products

The direct relationship between nasopharyngeal carcinoma and smoking was confirmed by reports that people who had smoked cigarettes for ten years or more were more likely to develop NPC [53]. Several studies have confirmed that cigarette smoking is linked to nasopharyngeal carcinoma. The relationship pattern between the risk of developing nasopharyngeal carcinoma and smoking depends on the dose, especially in well-differentiated nasopharyngeal carcinoma [54]. Lin et al. [55] compared the surroundings of NPC patient with those of neighboring controls in Taiwan and found that cigarettes were smoking and working in poorly ventilated rooms was closely related to the NPC.

Another study found that long-term cigarette smoking was linked to the NPC, but only to a minor extent exposure to cigarette smoke through passive exposure to smoking and alcohol consumption is not associated with a disease risk [56].

4.3.3 Oral hygiene

There is a connection between poor oral hygiene in the elderly and cancers of the head, neck, esophagus and stomach [57]. In NPC, periodontal disease can increase recurrent inflammation and thus increase possibility of developing NPC as the inflammatory response may be on the way to promoting carcinogenesis, Zhiwei Liu et al 2016 suggested poor oral health may increase risk of NPC [58]. In addition, When more teeth are lost, the bacterial load also increases. Some types of bacteria are involved in the increased production of nitrosamine, which is thought to be carcinogenic and has been linked to the development of NPC. Poor oral hygiene can also increase the risk of NPC by EBV stimulation and proliferation, as evidenced by higher viral loads in people with periodontitis more than others [59].

4.3.4 Other risk factors

The relationship between alcohol consumption and nasopharyngeal carcinoma has been documented in complicated ways. Several studies have documented that there is no clear confirmation of a relationship between the risk of nasopharyngeal carcinoma and alcohol consumption [60]. Other studies confirmed the relation between nasopharyngeal carcinoma and the exposure to wood dust. Several studies have shown an increased risk of developing nasopharyngeal carcinoma after exposure to formaldehyde [61]. Exposure to other chemicals or stimuli such as smoke, steam, cotton dust, chemicals, flammable products, or solvents such as chlorophenol and phenoxy acid increases the risk of developing nasopharyngeal carcinoma [62]. An association between nasal cavity and sinus cancer and the textile work has also been reported [63]. In addition, several other non-dietary risk factors for nasopharyngeal carcinoma have been included [64]. It has been reported that occupational exposure to combustion products and cotton dust is independently related to NPC risk. The risk of developing NPC also increases through occupational exposure to formaldehyde and not through exposure to wood dust [65]. However, this association appears to be specific to squamous cell carcinoma. In addition,

eating canned foods has been linked to NPC at a young age and risk in all population groups [33]. Studies and data on inhalation of different types of smoke/fumes/dust show that inhalants can play an important role, although they can secondary as a catalyst is the high incidence of NPC in various geographic regions of the world.

5. Treatment

5.1 Radiation therapy

Radiation therapy is the first type of cancer treatment method for non-invasive nasopharyngeal carcinoma (NPC) due to anatomical limitations and high sensitivity to radiation. One of the treatment method is with two-dimensional radiation therapy (2DRT), which has been converted to 3D compliant radiation therapy, and particularly highly modified radiation therapy (IMRT), is an important step forward in the treatment of NPC.

IMRT use was first reported in 2000 by the University of California at San Francisco. The results with 100% local control and a 4-year operating system are a dramatic 94%.

The second phase of II trails 0225 by the Radiation Oncology Group then showed that it is possible to transfer IMRT to a multi-institutional setting [66]. Three comparative randomized trials studies of IMRT and 2DRT have been applied. Chen et al. The studies confirmed a significant improvement in the therapeutic ratio by IMRT: The use of IMRT in patients with NPC demonstrated an improved terminal therapeutic ratio compared to 2DRT over a follow-up period of more than 10 years with significant improvement in OS, FFS, and L-FFS [67].

5.2 Adjuvant and neoadjuvant chemotherapy

While chemotherapy given concurrently with RT offers consistent benefits, the adjuvant chemotherapy role after alternative chemoradiotherapy is uncertain. The chemotherapy induction attempts for cases with local metastasis which include concomitant chemotherapy and radiation therapy, followed by adjuvant chemotherapy, in which an increased rate of NPC relapse in remote locations was observed in a large proportion of patients. These studies have shown the usefulness of this strategy for the OS. The administration of adjuvant chemotherapy was associated with significant toxicity, with 25-45% of the patients exhibiting high grade toxicities [68]. In addition, some research studies evaluating chemoradiotherapy protocols without adjuvant chemotherapy which provided similar results to studies using simultaneous and adjuvant chemotherapy, raising questions about the actual results and benefits of adjuvant chemotherapy for NPC control [69].

In theory, novel chemotherapy can prevent micrometastases earlier and also facilitate the mapping of RT by decreasing local metastasis, especially in large tumors. So far, phase III studies on novel adjuvant chemotherapy with post-radiation therapy alone have proven no difference in OS compared to RT [70]. An up to date meta-analysis of MAC-NPC contained data from a number of induction chemotherapy studies and showed statistically excellent results in survival without disease progression, but not in OS [71]. Increased cases with leukopenia and neutropenia rates observed during the CRT period [72]. This confirms the primary interest in the new induction/adjuvant approach, which could interfere with the delivery of chemotherapy with effective doses and/or radiation therapy during the period of CRT or increased toxicity and outweigh the potential benefits of the induction-based approach.

5.3 Treatment in advanced NPC

Although chemotherapy concurrently with radiation has resulted in many improvements with significant outcomes in NPC patients, and improve survival in locally advanced NPC over 5 years in 50-70%. A large proportion of patients have relapsed either locally or in distant sites, or both. Adding more chemotherapy drugs to available protocols is not a viable approach as CRT already exhibits significant toxicity. Instead, more research aims to identify the possibility of recurrence or relapse before treatment or at the end of the CRT assessment, who can focus on additional research methods. Second, the use of personalized target therapy in conjunction with radiation therapy or chemotherapy is assessed.

In NPC patients, the epidermal growth factor receptor (EGFR) overexpression is 80% or more and associated with lower survival results [73]. Adding of cetuximab, a monoclonal chimeric antibody in patients with squamous cell carcinoma of the head and neck against EGFR in conjunction with RT of HNSCC in locally advanced stages, which reported improvement and significant in OS in comparison to RT alone [74]. The evaluation of cetuximab in concurrent with radiation therapy in comparison to standard CRT in NPC patients has not proven to be more effective due to the association with increased rates of mucositis [75]. The combination of IMRT radiation therapy and weekly cisplatin with cetuximab was more effective in patients in advanced stages [76].

5.4 Palliative chemotherapy for metastasis and relapses NPC

Palliative chemotherapy is very important and plays role in control of disease and keep patients in good conditions as well as in extending survival of patients with NPC metastases as NPC is very sensitive to chemotherapy cancer. Standard treatment includes chemotherapy with platinum in combination with other drugs such as 5-FU with cisplatin/carboplatin and paclitaxel with gemcitabine. Patients treated for long time with platinum chemotherapy, can achieve a significant response with rates of up to 80% and an average survival rate of 12 to 18 months [77]. There is a significant correlation between higher response rates with a combination therapy regimen than monotherapy, and platinum is a good treatment, but it is not the main criterion or standard treatment. Regardless of the treatment regimen chosen for the first line, the average progression time after 7 to 10 months remains relatively constant [78, 79]; This is related to the development of platinum resistance. The response rates for a triple therapy with paclitaxel/carboplatin/gemcitabine are impressive and close to 80%. However, the average response time is about 8 months, similar to two drug regimens [80].

5.5 Novel therapies: molecular-targeted agents

The past 10 years have seen the development of new treatments for NPC and this has been somewhat simultaneous with the development of treatment for other cancers. Little progress has been made in recent years beyond the usual cytotoxic approaches. EGFR-mediated signaling pathways inhibited by the molecular factors that lead to inhibition of cell growth and cell apoptosis which include tyrosine kinase inhibitors, for example gefitinib and monoclonal antibodies [81].

In a number of centers, Ueda and colleagues [82] investigating a combination treatment of carboplatin, paclitaxel and cetuximab in patients with metastatic or recurrent or with repeated platinum-resistant NPC showed good survival benefit, an overall response rate reach to 64 % and a median OS of 29.1 months with follow up for 30 months. The treatment with gefitinib had little response rates in

metastatic and recurrent NPC treated previously with platinum-based chemotherapy. The symptomatic improvement and disease stabilization were observed in some cases [83].

Multikinase inhibitors target tyrosine kinases such as fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR) and drugs such as pazopanib (VEGFR, PDGFR, FGFR, c-KIT), sorafenib (VEGFR, PDGFR, Raf kinases), and sunitinib (PDGFR, VEGFR, C-KIT), have been evaluated in NPC [84, 85].

6. Mortality and survival

6.1 Mortality of NPC

Global mortality rates of NPC estimated 51,000 deaths in 2012 among females and males were 0.04 per 10, 000 and 0.1 per 10,000, respectively.

The mortality rate were high in Southeast Asia, East Asia, East Africa North Africa and Micronesia. Nasopharyngeal carcinoma is the native cancer of Southeast Asia and the countries with the highest mortality were Malaysia, Singapore, Indonesia, Vietnam, and Brunei [26] (**Figure 2**).

6.2 Survival patterns of NPC

Early diagnosed NPC patients respond very well to radiation, and this treatment shows promise. Radiation therapy is the strategy treatment for treating NPC. However, approximately 70% of stage III or IV NPC patients are exposed to a local and/or regional condition of distant metastases or recurrences after radiation therapy [86]. Treatment with combination of chemotherapy and radiation therapy often required for advanced NPC [87].

Studies have shown that intensity modulated radiation therapy (IMRT) often produces larger radiation dose distributions corresponding to improved tumor exposure and allows for lower doses of normal tissue for a variety of cancers that

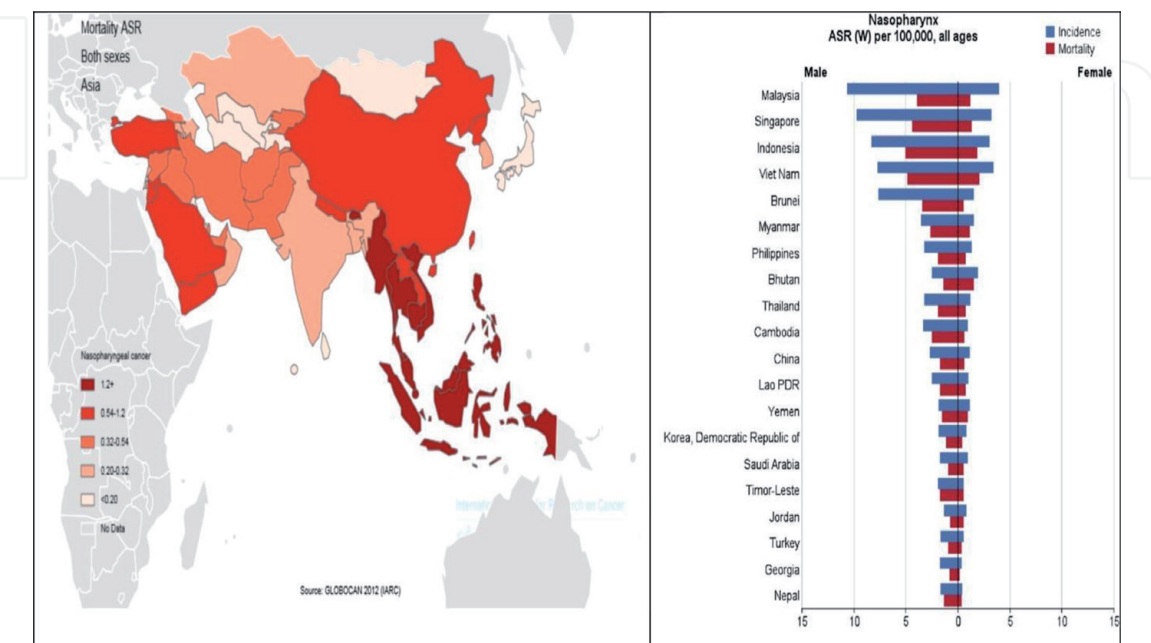


Figure 2. Mortality rate of nasopharyngeal carcinoma in Asia in 2012 (GLOBOCAN 2012) [26].

occur in the head and neck area [88]. In addition, the prognosis of NPC associated with many factors are, including age, sex, TNM stage, histology, radiation dose, leukopenia and anemia, and the type of combined chemotherapy [89]. Therefore, minimizing the risk of late complication and distant metastasis and maximizing the local control should be the key objects in designing future treatment.

7. Conclusions

Nasopharyngeal carcinoma is a rare head and neck malignancy and the native malignancy of Southeast Asia. Nasopharyngeal carcinoma (NPC), predominantly associated with Epstein-Barr virus (EBV), is characterized by remarkable geographical and racial differences in its incidence. The incidence of NPC is generally less than 1 per 100,000 individuals; however, in southern China it is around 25 per 100,000 individuals, accounting for 18% of all cancers. Epidemiological studies over the past few decades have shown a gradual decrease in incidence and a marked decrease in NPC mortality. However, the rise in population in Asia has increased the number of deaths caused by NPCs from 45,000 in 1990 to 65,000 in 2010.

The development of image diagnostic techniques and introducing chemoradiotherapy (chemo-IMRT) followed by adjuvant chemotherapy resulted in excellent locoregional control and increased survival rates among patients with NPC.


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