Nasopharyngeal Carcinoma

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17.1 Introduction

Nasopharyngeal carcinoma (NPC) is a rare malignant tumor in childhood not only in Europe but also in Asia, where the highest incidence of NPC in adult patients is seen. NPC represents one of the most frequent epithelial tumors of the child in intermediate risk regions. However, distinguishing malignant tumors from the more common and numerous benign causes of neck masses in childhood is crucial, as many malignant conditions have an excellent prognosis with appropriate oncological management. The worldwide incidence of NPC in children and adolescents between 0 and 14 years is 0.1 per 100,000 and follows a bimodal age distribution with a first peak between 10 and 20 years and a second peak between that fourth and sixth decades (Bray et al. 2008; Wei and St Sham 2005). Males are more frequently affected than females, with

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a male to female ratio of 2:1. In the United States, the incidence is higher in African-American children than in children of other races, but this racial predilection is lost in older ages. While 10–15% of cases occur in patients younger than 30 years of age, it makes up only 1% of childhood malignancies. NPC has a distinct epidemiology, etiology, and clinical course compared with other head and neck squamous cell carcinomas, and its pathogenesis is multifactorial. Genetic predisposition and epigenetic alterations particularly related to Epstein–Barr virus (EBV) infection play a major role in the initiation and progression of NPC (Sultan et al. 2010; Cheuk et al. 2011; Dittmer et al. 2008; Wong et al. 2004).

17.2 Symptoms

Young patients with nasopharyngeal carcinoma frequently present with symptoms resulting from mass effect. Nasal symptoms, such as epistaxis and nasal obstruction, are almost always present and are secondary to the presence of the tumor in the nasopharynx. Secondly, otologic symptoms, such as hearing loss and tinnitus, which are related to the dysfunction of the Eustachian tube caused by the lateroposterior extension of the tumor into the paranasopharyngeal space. Thirdly, cranial nerve palsies, commonly the fifth and sixth cranial nerves, resulting from the extension of the tumor superiorly, leading to skull base erosion; the patient might experience headache, diplopia, facial pain, and numbness. A retrospective analysis of 4,768 patients identified the symptoms at presentation as neck mass (75.8%), nasal (73.4%), aural (62.4%), headache (34.8%), diplopia (10.7%), facial numbness (7.6%), weight loss (6.9%), and trismus (3.0%). The physical signs present at diagnosis were enlarged neck node (74.5%) and cranial nerve palsy (20.0%) (Ozyar et al. 1994; Lee et al. 1997). Since the nasal and auditory symptoms are nonspecific and a thorough examination of the nasopharynx is not easy, the majority of NPC patients are only diagnosed when the tumor has reached an advanced stage. Therefore, young patients had significantly more advanced-stage disease compared with the group of adult patients. Mostly neck masses are observed, usually appearing first in the upper neck. NPC is characterized by a very important locoregional extension as well as a high rate of distant metastases (Mertens et al. 1997; Tang et al. 2010).

17.3 Pathogenesis

NPC presents as a complex disease caused by an interaction of the oncogenic gammaherpesvirus EBV chronic infection, environmental, and genetic factors, in a multistep carcinogenic process.

A monoclonal EBV infection is found in more than 98% of preinvasive lesions. The EBV-infected epithelial cells express the EBV-antigens EBNA1, LMP 1, and 2 as well as the EBERs. In vitro and in vivo models have shown that LMP1 and, in particular, LMP2 play a role in the malignant transformation of the NPC cells (Raab-Traub 2002).

While nasopharyngeal carcinoma is a rare malignancy in most parts of the world, it is one of the most common cancers in Southeast Asia. Epidemiologic studies conducted in that region have provided an invaluable insight into our current understanding of NPC pathogenesis. The pathogenesis of NPC is influenced by three major factors: environmental factors, such as certain herbs and salted fish consumed in regions with an elevated incidence of NPC; genetic factors, as documented by familial cases that suggest a genetically determined susceptibility; and infectious factors, as documented by the evidence of early EBV infection (Ren et al. 2010).

17.3.1 Environmental Factors

A large number of case-control studies conducted in diverse populations in Southeast Asia, Alaska, the Mediterranean basin, and North America have shown that consumption of salted fish and other preserved foods containing large amounts of nitrosodimethylamine may predispose to the development of NPC (Chang and Adami 2006).

17.3.2 Genetic Factors

Studies in Southeast China demonstrated an increased risk of NPC for individuals with HLA-A2. A recent study detected a consistent association between NPC

and the prevalent Chinese HLA-A2 subtype (HLA-A*0207) but not the prevalent Caucasian subtype (HLA-A*0201) (Hildesheim et al. 2002). The HLA types of AW19, BW46, and B17 have also been reported to be associated with an increased risk, whereas HLA-A11 is associated with a decreased risk (Liebowitz 1994). Significant complex multiple chromosome aberrations are often demonstrated.

17.3.3 Epstein–Barr Virus

EBV is consistently detected in NPC patients from regions of high and low incidence. Using EBV-encoded RNA (EBER) in situ hybridization, EBER signal was present in virtually all tumor cells. Premalignant lesions of the nasopharyngeal epithelium have also been shown to harbor EBV, and the EBV DNA is clonal, suggesting that EBV infection occurs in the early phases of carcinogenesis (Gulley 2001). In the past, NPC was called lymphoepithelioma, as the malignant epithelial cells of the nasopharynx frequently intermingled with lymphoid cells in the nasopharynx (Godtfredsen 1944). The histological classification of nasopharyngeal carcinoma proposed by the World Health Organization (WHO) in 1978 categorized tumors into three types. Type I were the typical keratinizing squamous cell carcinomas similar to those found in the rest of the upper aerodigestive tract. Type II included nonkeratinizing squamous carcinomas and type III carcinomas were the undifferentiated carcinomas (Micheau et al. 1978; Shanmugaratnam 1980; Marks et al. 1998).

Table 17.1 shows the WHO classification modified by Krüger and Wustrow indicating the varying degrees of lymphoid infiltration, whereby the undifferentiated NPC with lymphoid infiltration corresponds to the entities described in 1921 as lymphoepithelioma by Schmincke and nonkeratinizing epithelium carcinoma by Regaud. Histological variants are strictly associated with increased titers against EBV antigen (Krueger and Wustrow 1981).

Table 17.1 WHO classification modified by Krüger and Wustrow

Squamous cell carcinoma (keratinizing)	Type I
Squamous cell carcinoma (nonkeratinizing)	
– Without lymphoid infiltration	Type IIa
– With lymphoid infiltration	Type IIb
Undifferentiated (anaplastic carcinoma)	
– Without lymphoid infiltration	Type IIIa
– With lymphoid infiltration	Type IIIb

17.4 Staging Systems

There are various ways of staging nasopharyngeal carcinomas. At present, the American Joint Committee on Cancer Staging and End Result Reporting/International Union Against Cancer (the 6th edition of the *AJCC staging*) system is preferred in Europe and America. This staging system follows the classical TNM criteria. The Ho's system is frequently used in Asia (Lee et al. 1999).

17.4.1 Primary Tumor (T)

T1 Tumor confined to the nasopharynx
T2 Tumor extends to soft tissues of oropharynx and/or nasal fossa
T2a Without parapharyngeal extension
T2b With parapharyngeal extension
T3 Tumor invades bony structures and/or paranasal sinuses
T4 Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, orbit, and direct invasion of first or second cervical vertebra, hypopharynx, orbit, or masticator space

17.4.2 Regional Lymph Nodes (N)

N0 No regional lymph node metastasis
N1 Unilateral metastasis in lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa
N2 Bilateral metastasis in lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa
N3 Metastasis in lymph node(s)
N3a >6 cm in greatest dimension
N3b Extension to the supraclavicular fossa

17.4.3 Distant Metastasis (M)

M0 No distant metastasis
M1 Presence of distant metastasis

Table 17.2 Stage-related definition of risk groups

Stage grouping	
Stage I	T1 N0 M0
Stage IIA	T2a N0 M0
Stage IIB	T1-2 N1 M0
	T2b N0-1 M0
Stage III	T1-2 N2 M0
	T3 N0-2 M0
Stage IVA	T4 N0-2 M0
Stage IVB	Any T N3 M0
Stage IVC	Any T Any N M1

17.4.4 Definition of Risk Groups

Staging directly correlates with outcome, and in general, two large groups of patients are identified based on rates of local control and risk of metastatic disease. Patients with stages I–IIA have an excellent outcome, with survival rates in excess of 75–80%, whereas patients with stages IIB–IV have lower survival (Lee et al. 1992; Wee et al. 2005; Ali and al-Sarraf 2000; Al-Sarraf et al. 1998) (Table 17.2) (Figs. 17.1 and 17.2).

17.5 Diagnosis

Clinical examination, including endoscopic examination of the nasopharynx, can provide very valuable information on mucosal involvement and local tumor extension. A definitive histological diagnosis should require a positive biopsy taken from the tumor in the nasopharynx, although a nodal biopsy in the appropriate context may also be diagnostic. Clinical examination cannot, however, determine a deep extension of the tumor, such as skull base erosion and intracranial spread.

Cross-sectional imaging has revolutionized the management of NPC. In terms of contribution to staging, MRI can identify the paranasopharyngeal extension as one of the most common modes of extension of NPC and perineural spread through the foramen ovale as an important route of intracranial extension (Sham et al. 1991). Perineural spread through the foramen ovale also accounts for the CT evidence of cavernous sinus involvement without skull base erosion (Chong et al. 1996). Positron emission tomography (PET) may provide an additional tool for the initial diagnosis and staging and help in the evaluation of disease response after therapy (King et al. 2008).

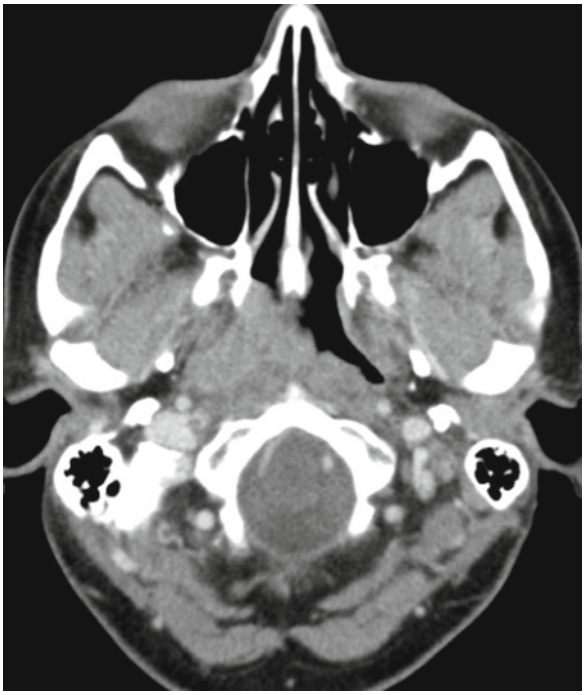

Fig. 17.1 Axial MRI shows the typical primary tumor of NPC (T3) extending into the right infratemporal fossa

17.5.1 Epstein–Barr Virus

Epstein–Barr virus (EBV) or human herpes virus 4 (HHV4) is an oncogenic c-herpes virus associated with malignancies that develop in NPC. EBV is consistently detected in patients with nasopharyngeal carcinoma, and its ability to establish latent infection of their host cells and to induce proliferation of the latently infected cells is directly involved in NPC pathogenesis (Niedobitek and Young 1994). Under normal circumstances, EBV infection is restricted to humans, although some types of monkeys can be infected experimentally (Bornkamm 1984).

EBV-encoded RNA signal has been shown to be present in nearly all tumor cells, whereas EBV RNA is absent from the adjacent normal tissue, except perhaps for a few scattered lymphoid cells. Premalignant lesions of the nasopharyngeal epithelium have also been shown to harbor EBV RNA, which suggests that the infection occurs in the early phases of carcinogenesis. Detection of a single form of viral DNA suggests that the tumors are clonal proliferations of a single cell that was initially infected with EBV (Lo et al. 2000).

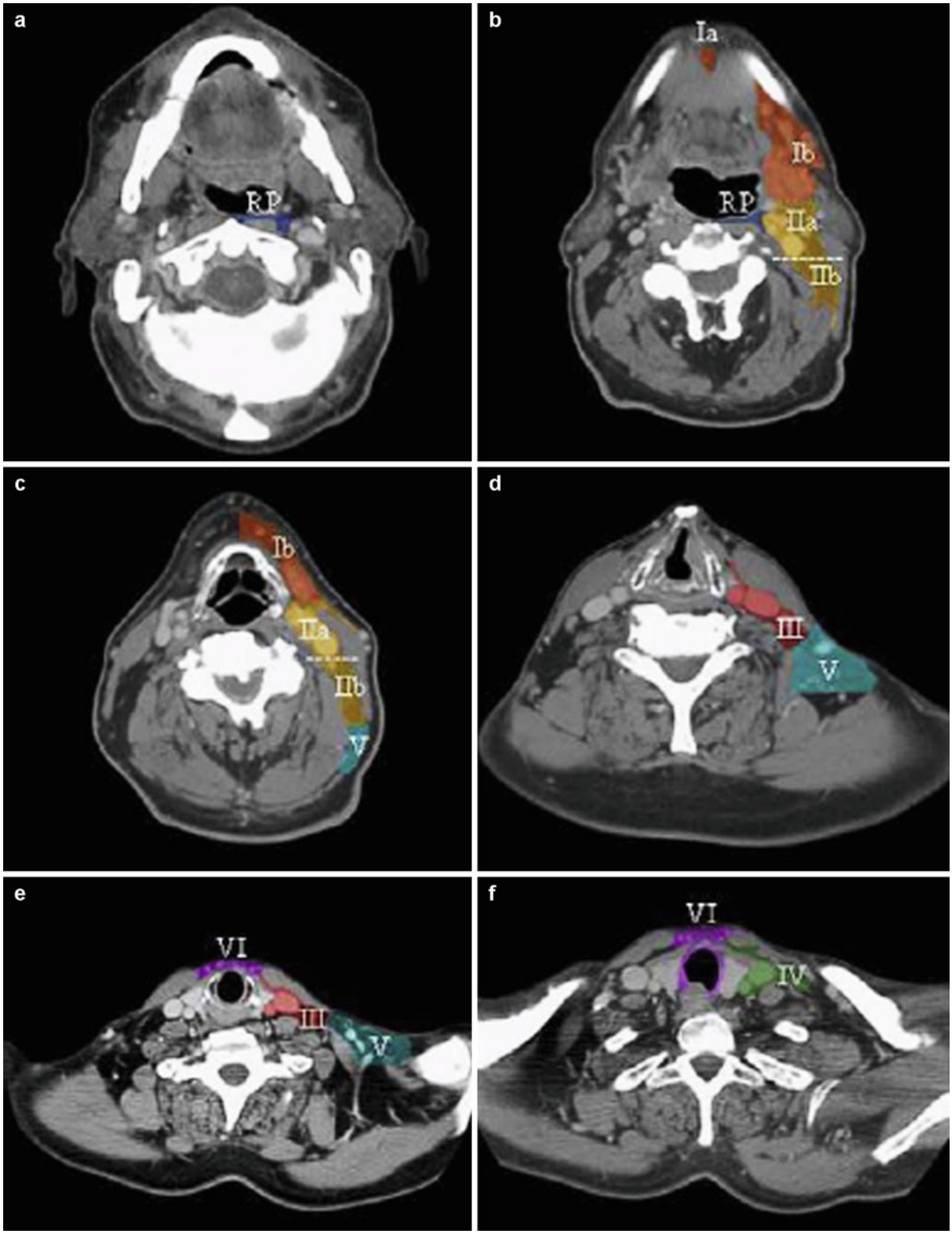

Fig. 17.2 (**a**) Parapharyngeal (**b**) Level IIa+IIb : jugular LN (**c**-**d**) Level III , IV: jugular LN (**e**-**f**) Level V: supraclavicular LN, level VI: LN around the thyroid gland

The EBV protein, latent membrane protein 2A (LMP2A), is expressed in NPC and can modulate epithelial proliferation, transformation, and differentiation and as such may promote malignancy. A key regulator of epithelial cell differentiation is the transcription factor p63, a member of the p53 family. The corresponding latent viral proteins (latent membrane protein 1 and 2) have substantial effects on cellular gene expression and cellular growth, resulting in the highly invasive, malignant growth of the carcinoma (Fotheringham et al. 2010).

Circulating free EBV DNA is commonly seen in patients with nasopharyngeal carcinoma, and the increased number of copies of EBV DNA in the blood during the initial phase of radiotherapy suggests that the viral DNA was released into the circulation after cell death (Hong et al. 2004).

The quantities of EBV DNA copies before and after treatment are significantly related to the rates of overall and disease-free survival. Several studies have reported that the levels of posttreatment EBV DNA compared with pretreatment EBV DNA are good predictors of progression-free survival (Wagner et al. 2009; Hong et al. 2004).

17.5.2 Structure of EBV and Its Genome

Epstein–Barr virus (EBV)-encoded RNA signal is present in all nasopharyngeal carcinoma cells, and early diagnosis of the disease is possible through the detection of raised antibodies against EBV. The quantity of EBV DNA detected in blood indicates the stage and prognosis of the disease. With regard to the clinical data, EBER expression in NPC was shown to be a strong independent predictor of overall and progression-free survival. Recently, it has been shown that miRNA dysregulation is implicated in the carcinogenesis of many human cancers. In cancer cells, the upregulated/downregulated miRNA could function as oncogenic/tumor-suppressing modulators. In the case of NPC, however, the critical miRNA changes involved in its carcinogenesis are not yet clearly defined (Sengupta et al. 2008).

17.5.3 EBV DNA

Circulating free EBV DNA can be detected by polymerase chain reaction (PCR) in patients (Mutirangura et al. 1998). A significant EBV DNAemia in plasma but not in cellular compartments of the peripheral blood was investigated. The EBV DNA is directly released from the tumor tissue. Ninety-five percent of patients are positive for EBV DNA in plasma at diagnosis. Moreover, the course of EBV DNA in plasma reflects the course of the disease:

Patients receiving complete remissions become negative for EBV DNA in plasma, whereas patients with persistent or progressive disease remain positive or even show increasing EBV DNA concentrations in their plasma.

The increased number of copies of EBV DNA found in the blood during the initial phase of therapy suggests that the viral DNA was released into the circulation after cell death (Leung et al. 2003). For the detection of distant metastases, the use of serum EBV DNA has been shown to be more sensitive and reliable than other options. The quantities of EBV DNA copies before and after treatment are significantly related to the rates of overall and disease-free survival (Chan et al. 2003). There was a study reporting that the levels of posttreatment EBV DNA when compared with pretreatment EBV DNA had a better prediction for progression-free survival (Lin et al. 2004).

17.5.4 VCA IgA

EBV-VCA-IgA antibodies have been identified as diagnostic and EBV-DNA in the serum or plasma as diagnostic and prognostic markers for NPC, high titers during diagnosis and with relapse is found very specific. The rise in IgA titers to these antigens can be noticed before the development of NPC and correlates with tumor burden, remission, and recurrence Therefore, this method of measuring patients' EBV-specific IgA antibodies is useful in screening for early detection of NPC (Leung et al. 2004; Li et al. 2010; Cohen et al. 2008).

17.5.5 EA (Early Antigen) IgA

Seventy percent of the patients with NPC exhibit an anti-I/O antibody of the IgA type; this is in contrast to only 3% of the patients with other malignancies. IgA can contribute to the diagnostic identification of an NPC of the undifferentiated type and/or for the proof of a relapse even before the occurrence of a clinical manifestation (Cai et al. 2010).

17.5.6 Ultrasound

US should widely be used as the initial imaging technique in the assessment of extracranial head and neck masses in children.

The frequent superficial location of head and neck tumors make them readily accessible to US examination. Technical developments in high-resolution gray-scale (B-mode) ultrasound have improved the ability of US to characterize the internal architecture of masses, beyond simply distinguishing cystic from solid lesions (Leung et al. 1991). The additional use of color Doppler ultrasound (CDUS) and power Doppler allow assessment of vascularity within the lesion, particularly helpful in the assessment of hemangioma and vascular malformations and also contributory in the assessment of enlarged lymph nodes (Imhof et al. 2004).

17.5.7 Computed Tomography

Computed tomography (CT) technology allows rapid and detailed examination of the entire neck with the ability to produce multiplanar reformatted images.

Assuming the airway is not compromised, the child should be scanned supine with the neck in the neutral position.

The region scanned extends from the top of the sphenoid sinus to the sternoclavicular joints. A bone algorithm, in addition to a standard soft tissue algorithm, is particularly important for tumors that may involve the skull base. The presence of calcification or fat within the lesion is well demonstrated on CT and helps with lesion characterization. Intravenous contrast administration is mandatory to delineate the mass, or lymphadenopathy, from adjacent normal structures. Enhancement patterns may be helpful in characterizing some masses, such as vascular tumors (Cellai et al. 1990; Yabuuchi et al. 2002; Lloyd and McHugh 2010).

17.5.8 Magnetic Resonance Imaging

The superior soft tissue resolution of MRI makes it an excellent modality in imaging of head and neck masses. It is particularly useful in delineating intracranial extension of disease. The examination is performed with the child supine in quiet respiration. Standard examination should include a T2-weighted fast spin echo (FSE) sequence in axial and coronal planes, a T2-weighted fat suppression or inversion recovery sequence, and a plain T1-weighted FSE or spin echo (SE) sequence (Lloyd and McHugh 2010). In evaluating mass lesions, a further fat-saturated T1-weighted SE sequence following gadolinium administration will often improve characterization of the mass. Additional diffusion-weighted imaging appears to also have a role in characterizing head and neck masses. A recent study found a significant difference in apparent diffusion coefficients (Olmi et al. 1995; Dillon et al. 1984).

17.5.9 Positron Emission Tomography

The increasing availability of PET-CT allows improved localization and definition of disease activity. The role of PET and PET-CT in childhood malignancies continues to be defined, but it is widely used in the staging and follow-up of lymphoma and may also have a role in soft tissue (Xie et al. 2010; Yen et al. 2009; Nakamoto et al. 2003).

17.6 Therapy

17.6.1 Chemotherapy

The mean survival rate of patients suffering from nasopharyngeal carcinoma ranges between 24% and 90%, depending on the tumor stage. While modern radiotherapy like IMRT achieves good local control, distant metastases become the predominant pattern of failure, especially among those with locoregionally advanced disease. NPC is also chemosensitive. There is a long history of clinical studies investigating combined radiotherapy (RT) and chemotherapy for NPC. Most of the early studies in pediatric patients with NPC were nonrandomized (Harrison et al. 1991; Turner and Tiver 1993; Chan et al. 1995; Teo et al. 1995; Garden et al. 1996; Lee et al. 2009). Randomized trials on combined chemotherapy and RT for NPC are reported in adult patients only (Rossi et al. 1988; Chan et al. 1995; International Nasopharynx Cancer Study Group 1996; Garden et al. 1996; Chen et al. 2008). However, randomized multi-institutional studies are necessary to standardize the treatment of the NPC in childhood. Each trial used a different approach with respect to drug combination, time sequence of chemotherapy and RT, and RT technique and dose. In the early trials, induction chemotherapy is the most often

studied approach (Chua et al. 1998; Wee et al. 2005; Lee et al. 2005; International Nasopharynx Cancer Study Group 1996). The rationale for induction chemotherapy is to reduce locoregional tumor load before start of RT and also early use of systemic treatment for eradication of micrometastases.

A recently published meta-analysis of chemotherapy in nasopharyngeal carcinoma included eight randomized trials which had completed accrual before end of 2001 and thus excluded the more recent trials from Asia. In the meta-analysis, there were four trials that investigated induction chemotherapy (+ adjuvant chemotherapy in one trial), three trials that investigated concurrent chemoradiotherapy (+ adjuvant chemotherapy in two trials), and one trial that investigated adjuvant chemotherapy alone. Overall, an absolute survival benefit of 6% at 5 years from addition of chemotherapy was observed (from 56% to 62%). A significant interaction was observed between the timing of chemotherapy and overall survival, with the highest benefit resulting from concurrent chemoradiation. The results concur with findings from meta-analysis on other head and neck cancers also (Baujat et al. 2006). Two of the four neoadjuvant studies reported improvement in relapse-free and in overall survival. The others reported no improvement generally (Pignon et al. 2009).

A pivotal study was reported by the Head and Neck Intergroup in 1998, using concurrent RT with cisplatin (100 mg/sqm D1, 22, 43) followed by adjuvant cisplatin and 5-fluouracil (5-FU) (cisplatin 80 mg/sqm D1 and 5-FU 1,000 mg/sqm/D, D1-4, Q4 weeks cycles for 3 cycles). Compared with RT alone, chemoradiation significantly improved progression-free survival and overall survival. The pattern of disease failure showed reduction of both locoregional and distant failure with chemoradiation (Al-Sarraf et al. 1998).

In contrast to the trials of NPC in adults, the neoadjuvant chemotherapy was often favored in treatment of NPC of childhood. In 2005, Rodriguez et al. published a successful series of 19 patients with NPC treated with four courses of neoadjuvant chemotherapy and irradiation (Rodriguez-Galindo et al. 2005). The Society for Pediatric Oncology and Hematology (GPOH) developed uniform therapy concepts for the treatment of NPC in Germany with children and young people from Germany, Austria, and Switzerland, including Dutch Oncology Group, and thus obtained excellent healing rates. In the NPC-91-GPOH and NPC-2003-GPOH, all juvenile patients are to be treated. High-risk patients received neoadjuvant chemotherapy consisted of cisplatin (CDDP) 100 mg/m^2 d1 and 5-fluorouracil (5-FU) 1,000 mg/m^2 daily 1–5. After three courses and irradiation, a recombinant or nature interferon β were given over a half year. The 9-year disease-free survival for patients treated on this study was 91% (Mertens et al. 2005).

Because of the rarity of this disease in children, only a multi-institutional trial may result in an improved treatment strategy. In the follow-up study NPC-2003-GPOH, the dose of radiotherapy was reduced in patients with an effective neoadjuvant chemotherapy.

The use of concurrent or, and especially, neoadjuvant chemotherapy with radiation therapy has significantly improved the outcome of advanced nasopharyngeal cancers. Because of the rarity of NPC, there are almost no reported multicenter studies for the treatment of NPC in children.

17.6.2 Radiotherapy

Radiotherapy is still the standard therapy of NPC. The major limitations of conventional 2D radiotherapy for NPC can now be overcome with three-dimensional (3D) conformal radiotherapy and IMRT. IMRT is an advanced form of 3D conformal radiotherapy, conforming high dose to tumor while conforming low dose to normal tissues (Wu et al. 2004).

IMRT planning and dose optimization is fully computerized, a process known as inverse planning, thus, it is much preferred over the more expertise-dependent forward planning in 3D conformal radiotherapy (Hsiung et al. 2002).

The use of IMRT in treatment of NPC has multiple advantages. IMRT can be used for organ preservation, e.g., sparing the parotids of high-dose radiation will preserve salivary function after radiotherapy. IMRT can achieve good dose differential between the tumor and the dose-limiting organs and thus can achieve a high dose in the tumor without overdosing the normal organs. As the fractional dose will affect the biological effectiveness of radiation, there is a component of biological modulation of radiation besides just modulating the physical radiation dose in IMRT (Withers and Thames 1988).

Simultaneous modulated accelerated radiotherapy (SMART) employs this principle for accelerated radiotherapy with IMRT. IMRT resolves the problem of dose uncertainty at the junction between the primary tumor and neck lymphatic target volumes in conventional radiotherapy (Cheng et al. 2001).

Different series reported excellent local control of more than 90% in NPC achieved with IMRT, even among patients with advanced T3-4 diseases (Pow et al. 2006). Reports also showed preservation of salivary function and improve quality of life of survivors after IMRT (Wu et al. 2004). A series of cases in which hypofractionated radiotherapy was used in combination with conventional 2D radiotherapy produced a 60% actuarial risk of complication and a 28% risk of neurological complications (Kam et al. 2007; Butler et al. 1999; Wolden et al. 2006). Cutting down late complications of treatment should be one of the main objectives of future clinical trials.

All patients in the NPC-2009-GPOH study received irradiation according to the guidelines of the study. The patients are treated with IMRT to the primary tumor, including the base of the skull and the regional lymphoid areas. In high-risk patients, the supraclavicular region should be treated by single anterior portal with a midline block at 45 Gy and the base of skull was included in the target volume. The dose to the spinal cord is limited to 40 Gy. Radiotherapy is delivered daily in single doses of 1.8 Gy. All primary tumor-bearing areas are given an additional dose of 14.4 Gy to a total dose of 59.4 Gy. In the stage II patient, the nasopharynx and regional lymph nodes are irradiated with 45 Gy and the pituitary gland is excluded.

17.6.3 Interferon Therapy

The combination of cisplatin and 5-fluorouracil in combination with radiotherapy is the most widely used therapy regimen for nasopharyngeal carcinomas. In addition, β-interferon is also only used in the German study.

In the German study NPC-91-GPOH and NPC-2003-GPOH, all patients underwent 6 months of recombinant IFN-beta or native IFN-beta treatment after completion of radiation therapy, receiving a dose of 10^5 U per kg body weight (max dose 6×10^6 U) intravenously three times a week. It is a nonrandomized study with a good result of 90%.

17.7 Metastasis

The NPC usually metastasizes lymphatics but also has hematogenous spread. The lymphatic spread is initially described by Frommonhold and Grauwerk as rear upper rail and drainage flows into the lymph nodes of the intersection group, which is partly located behind the posterior edge of C2 vertebral body (Frommhold and Gauwerk 1972). The high number of metastases, despite sufficient local therapy, represents a major problem in the treatment of NPC. The development of metastases occurred early, usually in the first 2 years after diagnosis, and is the most important factor of risk for the survival of patients.

Despite the use of chemoradiotherapy, distant metastases remain the major cause of failure, especially in stage IV patients. However, induction chemotherapy showed significant reduction of distant failures. Thus, there is now revival of interest in using induction and concurrent chemotherapy in treatment of NPC (Cheng et al. 2000).

17.8 New Treatment Strategies

17.8.1 T Cell Therapy

EBV-specific cytotoxic T cell (CTL) lines can readily be generated from individuals with NPC, notwithstanding the patients' prior exposure to chemotherapy/radiation. In a pilot study, patients diagnosed with advanced NPC were treated with autologous CTLs. All patients tolerated the CTLs, although one developed increased swelling at the site of preexisting disease. The administration of EBV-specific CTLs to patients with advanced NPC was feasible, appears to be safe, and could be associated with significant antitumor activity.

The EBV-specific CTLs used in this study were reactivated using LCLs that express all EBV latent antigens. LCLs are excellent antigen-presenting cells that are readily available for all patients, as only a limited amount of blood are required to establish an LCL line. As expected using this method, only a minority of the infused lines contained cytotoxic T cells specific for LMP2 (an EBV antigen usually expressed by NPC tumor cell mononuclear cells). Although there was no persistent rise in the frequency of circulating T cells

specific for LMP2 after infusion, the CTLs appeared to show significant anti-tumor activity.)

The EBV-specific CTLs were biologically active in vivo, reducing levels of EBV DNA in peripheral blood (Louis et al. 2010; Comoli et al. 2005).

Another approach to reduce distant failure is by adding targeted therapy to chemotherapy. In a recently closed phase II trial (RTOG 0615), bevacizumab (a monoclonal antibody directed against vascular endothelial growth factor) was added to the concurrent and adjuvant phases of therapy.(Louis et al. 2010) It was hoped that adding on antiangiogenic agents to the chemotherapy can destroy distant micrometastases in primary treatment. Finally, the antitumor effect of taxanes has been shown in several studies in adult NPC, and its incorporation into the frontline management of this malignancy may provide additional cure options (Radiation Therapy Oncology Group of the American College of Radiology 2006).

17.9 Long-Term Sequelae

Survivors of NPC following radiotherapy or chemoradiation have impaired the health-related quality of life. Patients may suffer from a variety of late complications, many of which result from the effects of radiation on the dose-limiting organs situated adjacent to the nasopharynx and cervical lymph node (Huang et al. 1994). NPC survivors almost uniformly develop hypothyroidism secondary to neck irradiation and also are at risk for panhypopituitarism resulting from pituitary damage. A close endocrine follow-up is thus required for early diagnosis and intervention (Fang et al. 2002). Ototoxicity is also very common, and its incidence is particularly higher in patients receiving chemotherapy in addition to radiation, which often involved the auditory apparatus. A small proportion of the long-term sequelae represent the effects of unhealed residual damage by the tumor, such as residual cranial nerve palsies and serous otitis media resulting from persistent disturbance of the Eustachian tube function (McMillan et al. 2004).

In up to 8,5% of the NPC patients, subsequent malignancies developed 8.6–27 years after NPC diagnosis. The 15-year cumulative incidence of any morbidity, sensorineural hearing loss, primary hypothyroidism, and growth hormone deficiency related to the stage were 84%, 53%, 43% and 14%, respectively. There are dose-response relationships between RT dose and primary hypothyroidism and growth hormone deficiency (Ulger et al. 2007).

17.10 Juvenile Nasopharyngeal Angiofibroma

17.10.1 Introduction

Juvenile nasopharyngeal angiofibroma (JNA) is a rare tumor with prominent vascularity and *benign histological* features. It originates from the superior margin of the sphenopalatine foramen, which is also a route for the sphenopalatine artery branching from the internal maxillary artery (Schuon et al. 2007; Tosun et al. 2006).

The reported incidence is between 1 in 6,000 and 1 in 60,000 otolaryngology patients and accounts for 0.5% of all head and neck neoplasms (Mann et al. 2004; Glad et al. 2007). JNA accounts for 0.5% of all head and neck neoplasms, and it is considered to be the most common benign neoplasm of the nasopharynx. Evidence of intracranial spread occurs in 10–20% of cases. The average age at onset of symptoms is 15 years (Midilli et al. 2009; Paris et al. 2001).

Although histologically benign in appearance, JNAs are locally aggressive and destructive, spreading from the nasal cavity to the nasopharynx, paranasal sinuses, and orbit skull base with intracranial extension. The pathogenesis of JNA is unknown.

The tumor may grow towards the nasal fossa and extend to the posterior portion of the middle turbinate, which becomes a common part of the tumor mass. The angiofibroma may extend laterally towards the pterygomaxillary fossa and destroy the posterior wall of the maxillary sinus. Eventually, the tumor may invade the intratemporal fossa and the middle cranial fossa. This is a general view of the growth of this tumor. The actual modes of invasion into local structures may be unpredictable and far from a typical pattern (Paris et al. 2001; Marshall and Bradley 2006).

17.10.2 Symptoms

The most common presenting symptom is persistent nasal obstruction with repetitive epistaxis.

Further classical clinical presentation is unilateral nasal block and/or rhinorrhea, and occasionally pain. Because of its invasive nature, the tumor may cause facial deformity and proptosis, changes in visual acuity, and cranial nerve palsy if it reaches the orbit and intracranial region (Weprin and Siemers 1991; Tyagi et al. 2007).

17.10.3 Pathogenesis

The gender selectivity of JNA*, with a high male-to-female ratio,* and the relatively young age at diagnosis suggest hormone-dependent development. Hormonal disorders have been reported in patients with JNA, and androgen and estrogen receptors have been identified in tumor tissue; however, a hormonal influence on JNA is controversial. Recent studies have attempted to further delineate the pathogenesis of JNA through analysis of genetic and molecular changes. While JNA is known to be sensitive to androgens, there are likely intermediary cytokines and/or growth factors that mediate aggressive stoma cell proliferation and angiogenesis. Transforming growth factor beta1 (TGF-beta1) is a polypeptide that is secreted in an inactive form, cleaved to produce an active form, and then deactivated in the tissues. The localization of activated TGF-beta1 to the fibroblasts and endothelial cells within JNA tumors suggests that TGF-beta1 may play a role in the stromal cell proliferation and angiogenesis associated with JNA. The expression of estrogen receptor beta by the tumor cells recently has been demonstrated (Lee et al. 1980; Liang et al. 2000; Saylam et al. 2006; Ngan et al. 2008; Zhang et al. 2003).

17.10.4 Diagnosis

The diagnosis of JNA is based on a precise clinical history and examination of the patient, and imaging (CT or MRI). Tissue biopsies should be avoided due to the highly vascular nature of the tumor. Angiography is used to define the feeding arteries of the tumor and to provide information for embolization (Nicolai et al. 2003; Jacobsson et al. 1989).

JNA is classified as Type I when the tumor is restricted to the nasal cavity and the nasopharynx without bone destruction; Type II when the tumor invades the pterygomaxillary fossa and maxillary, sphenoidal, and ethmoid sinuses with bone destruction; Type III when the tumor invades the intratemporal fossa, the orbit, and the parasellar region but remaining lateral to the cavernous sinus; and Type IV when the tumor invades the cavernous sinus, the optic chiasma, and the pituitary fossa (Howard et al. 2001).

Andrews staging system for juvenile nasopharyngeal angiofibroma (1989)

Stage	
I	Tumor limited to the nasal cavity and nasopharynx
II	Tumor invading the pterygopalatine fossa or maxillary, ethmoidal, and sphenoid sinuses; with bone destruction
III	Tumor invading the infratemporal fossa or orbital region: (a) Without intracranial involvement and (b) With extradural intracranial involvement
IV	Tumor with intradural intracranial involvement: (a) Without or (b) with infiltration of cavernous sinus, pituitary fossa, or optic chiasma

17.10.5 Therapy

The management of JNA has changed during the last decades. It is generally agreed that surgery is the treatment of choice for JNA. Preoperative selective arterial embolization is almost always indicated as it helps decrease the risk of intraoperative hemorrhage and facilitates the resection of large tumors. The management of JNA should be planned by an experienced head and neck surgeon, as part of a multidisciplinary team, preferably in a tertiary referral setting. Surgery aims for a complete and safe resection of tumor, with minimal morbidity and loss of blood. A transpalatal, transmaxillar (lateral rhinotomy or midfacial approach) is usually performed (Dubey and Molumi 2007; Belmont 1988).

For stages I and II, a transpalatal approach results in good outcome when the lesion is limited to the nasal cavity, nasopharynx, and paranasal sinuses. For patients with intracranial extension, the LeFort I surgical technique should be used. Involvement of the orbit, middle cranial fossa, and base of the pterygoid by the primary JNA results in a higher incidence of recurrent tumor (Borghei et al. 2006; Yiotakis et al. 2008).

Recurrence rates as high as 50% (ranging from 6% to 50%) have been reported (Reddy et al. 2001). During the last decade, the increased understanding of

angiogenesis has allowed the development of new therapeutic approaches. Since strong vascularity is a common feature of JNAs, it has been suggested that antiangiogenic therapies ought to be considered in the management of selected cases (Hashizume et al. 2010). Other methods that have been used as primary treatment include hormone therapy, chemotherapy, and radiotherapy.

References

Ali H, al-Sarraf M (2000) Chemotherapy in advanced nasopharyngeal cancer. Oncology 14(8):1223–1230

Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, Forastiere AA, Adams G, Sakr WA, Schuller DE, Ensley JF (1998) Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 16(4):1310–1317

Baujat B, Audry H, Bourhis J, Chan AT, Onat H, Chua DT et al (2006) Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol Biol Phys 64(1):47–56

Belmont JR (1988) The Le Fort I osteotomy approach for nasopharyngeal and nasal fossa tumors. Arch Otolaryngol Head Neck Surg 114:751–754

Borghei P, Baradaranfar MH, Borghei SH, Sokhandon F (2006) Transnasal endoscopic resection of juvenile nasopharyngeal angiofibroma without preoperative embolization. Ear Nose Throat J 85:740–743, 746

Bornkamm GW (1984) Virologisch-serologische Diagnostik des Nasopharynxkarzinoms. In Nasopharynx-Tumoren. Urban & Schwarzenberg, München-Wien-Baltimore, pp 15–21

Bray F, Haugen M et al (2008) Age-incidence curves of nasopharyngeal carcinoma worldwide: bimodality in low-risk populations and aetiologic implications. Cancer Epidemiol Biomarkers Prev 17(9):2356–2365

Butler EB, Teh BS, Grant WH 3rd, Uhl BM, Kuppersmith RB, Chiu JK et al (1999) Smart (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys 45(1):21–32

Cai YL, Zheng YM, Cheng JR, Wang W, Zhang YN, Wang WH, Wu YS, Zhong WM, Li J, Mo YK (2010) Relationship between clinical stages of nasopharyngeal carcinoma and Epstein-Barr virus antibodies Rta/IgG, EBNA1/IgA, VCA/IgA and EA/IgA. Nan Fang Yi Ke Da Xue Xue Bao 30(3):509–511

Cellai E, Olmi P, Chiavacci A, Giannardi G, Fargnoli R, Villari N et al (1990) Computed tomography in nasopharyngeal carcinoma: Part II: Impact on survival. Int J Radiat Oncol Biol Phys 19(5):1177–1182

Chan AT, Teo PM, Leung TW, Leung SF, Lee WY, Yeo W et al (1995) A prospective randomized study of chemotherapy adjunctive to definitive radiotherapy in advanced nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 33(3):569–577

Chan KH, Gu YL, Ng F, Ng PS, Seto WH, Sham JS, Chua D, Wei W, Chen YL, Luk W, Zong YS, Ng MH (2003) EBV specific antibody-based and DNA-based assays in serologic diagnosis of nasopharyngeal carcinoma. Int J Cancer 105(5):706–709

Chang ET, Adami HO (2006) The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev 15(10):1765–1777

Chen Y, Liu MZ, Liang SB, Zong JF, Mao YP, Tang LL et al (2008) Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of china. Int J Radiat Oncol Biol Phys 71(5):1356–1364

Cheng SH, Jian JJ, Tsai SY, Yen KL, Chu NM, Chan KY et al (2000) Long-term survival of nasopharyngeal carcinoma following concomitant radiotherapy and chemotherapy. Int J Radiat Oncol Biol Phys 48(5):1323–1330

Cheng JC, Chao KS, Low D (2001) Comparison of intensity modulated radiation therapy (IMRT) treatment techniques for nasopharyngeal carcinoma. Int J Cancer 96(2):126–131

Cheuk DK, Billups CA, Martin MG, Roland CR, Ribeiro RC, Krasin MJ, Rodriguez-Galindo C (2011) Prognostic factors and long-term outcomes of childhood nasopharyngeal carcinoma. Cancer 117(1):197–206

Chong VF, Fan YF, Khoo JB (1996) Nasopharyngeal carcinoma with intracranial spread: CT and MR characteristics. J Comput Assist Tomogr 20(4):563–569

Chua DT, Sham JS, Choy D, Lorvidhaya V, Sumitsawan Y, Thongprasert S et al (1998) Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma: Asian-Oceanian Clinical Oncology Association Nasopharynx Cancer Study Group. Cancer 83(11):2270–2283

Cohen F, Monnet O, Casalonga F, Jacquier A, Vidal V, Bartoli JM, Moulin G (2008) Nasopharyngeal carcinoma. J Radiol 89(7–8 Pt 2):956–967

Comoli P, Pedrazzoli P, Maccario R et al (2005) Cell therapy of stage IV nasopharyngeal carcinoma with autologous Epstein-Barr virus-targeted cytotoxic T lymphocytes. J Clin Oncol 23:8942–8949

Dillon WP, Mills CM, Kjos B, DeGroot J, Brant-Zawadzki M (1984) Magnetic resonance imaging of the nasopharynx. Radiology 152(3):731–738

Dittmer DP, Hilscher CJ, Gulley ML, Yang EV, Chen M, Glaser R (2008) Multiple pathways for Epstein-Barr virus episome loss from nasopharyngeal carcinoma. Int J Cancer 123(9): 2105–2112

Dubey SP, Molumi CP (2007) Critical look at the surgical approaches of nasopharyngeal angiofibroma excision and "total maxillary swing" as a possible alternative. Ann Otol Rhinol Laryngol 116:723–730

Fang FM, Chiu HC, Kuo WR, Wang CJ, Leung SW, Chen HC et al (2002) Health-related quality of life for nasopharyngeal carcinoma patients with cancer-free survival after treatment. Int J Radiat Oncol Biol Phys 53(4):959–968

Fotheringham JA, Mazzucca S, Raab-Traub N (2010) Epstein-Barr virus latent membrane protein-2A-induced DeltaNp63 alpha expression is associated with impaired epithelial-cell differentiation. Oncogene 29(30):4287–4296

Frommhold H, Gauwerk F (1972) Zur Strahlenbehandlung der Epipharynxtumoren. Strahlentherapie 144:509–514

Garden AS, Lippman SM, Morrison WH, Glisson BS, Ang KK, Geara F et al (1996) Does induction chemotherapy have a role in the management of nasopharyngeal carcinoma? Results of treatment in the era of computerized tomography. Int J Radiat Oncol Biol Phys 36(5):1005–1012

Glad H, Vainer B, Buchwald C, Petersen BL, Theilgaard SA, Bonvin P, Lajer C, Jakobsen J (2007) Juvenile nasopharyngeal angiofibromas in Denmark 1981–2003: diagnosis, incidence, and treatment. Acta Otolaryngol 127:292–299

Godtfredsen E (1944) Chapter III: on the histopathology of malignant nasopharyngeal tumours. Acta Pathol Microbiol Scand 32(Suppl 59):38–56

Gulley ML (2001) Molecular diagnosis of Epstein-Barr-virus-related diseases. J Mol Diagn 3(1):1–10

Harrison LB, Pfister DG, Bosl GJ (1991) Chemotherapy as part of the initial treatment for nasopharyngeal cancer. Oncology (Williston Park) 5(2):67–70

Hashizume H, Falcon BL, Kuroda T, Baluk P, Coxon A, Yu D, Bready JV, Oliner JD, McDonald DM (2010) Complementary actions of inhibitors of Angiopoietin-2 and VEGF on tumor angiogenesis and growth. Cancer Res 70:2213–2223

Hildesheim A, Apple RJ, Chen CJ, Wang SS, Cheng YJ, Klitz W, Mack SJ, Chen IH, Hsu MM, Yang CS, Brinton LA, Levine PH, Erlich HA (2002) Association of HLA class I and II alleles and extended haplotypes with nasopharyngeal carcinoma in Taiwan. J Natl Cancer Inst 94(23):1780–1789

Hong RL, Lin CY, Ting LL, Ko JY, Hsu MM (2004) Comparison of clinical and molecular surveillance in patients with advanced nasopharyngeal carcinoma after primary therapy: the potential role of quantitative analysis of circulating Epstein-Barr virus DNA. Cancer 100(7):1429–1437

Howard DJ, Lloyd G, Lund V (2001) Recurrence and its avoidance in juvenile angiofibroma. Laryngoscope 111: 1509–1511

Hsiung CY, Yorke ED, Chui CS, Hunt MA, Ling CC, Huang EY et al (2002) Intensity-modulated radiotherapy versus conventional three-dimensional conformal radiotherapy for boost or salvage treatment of nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 53(3):638–647

Huang TS, Huang SC, Hsu MM (1994) A prospective study of hypothalamus pituitary function after cranial irradiation with or without radiosensitizing chemotherapy. J Endocrinol Invest 17(8):615–623

Imhof H, Czerny C, Hormann M, Krestan C (2004) Tumors and tumorlike lesions of the neck: from childhood to adult. Eur Radiol 14:L155–L165

Institute Gustave Roussy, Rue Camille Desmoulins, Villejuif, France (1996) Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV(> or = N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. VUMCA I trial. Int J Radiat Oncol Biol Phys 35(3):463–469

Jacobsson M, Petruson B, Ruth M, Svendsen P (1989) Involution of juvenile nasopharyngeal angiofibroma with intracranial extension. A case report with computed tomographic assessment. Arch Otolaryngol Head Neck Surg 115:238–239

Kam MK, Leung SF, Zee B, Chau RM, Suen JJ, Mo F et al (2007) Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 25(31):4873–4879

King AD, Ma BB, Yau YY, Zee B, Leung SF, Wong JK, Kam MK, Ahuja AT, Chan AT (2008) The impact of 18F-FDG PET/CT on assessment of nasopharyngeal carcinoma at diagnosis. Br J Radiol 81(964):291–298

Krueger GRF, Wustrow J (1981) Current classification of nasopharyngeal carcinoma at Cologne University. In: Grundmann E, Krueger GRF, Ablashi DV (eds) Nasopharyngeal carcinoma, vol 5. Gustav Fischer Verlag, Stuttgart, pp 11–15

Lee DA, Rao BR, Meyer JS, Prioleau PG, Bauer WC (1980) Hormonal receptor determination in juvenile nasopharyngeal angiofibromas. Cancer 46:547–551

Lee AW, Poon YF, Foo W, Law SC, Cheung FK, Chan DK et al (1992) Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976–1985: overall survival and patterns of failure. Int J Radiat Oncol Biol Phys 23(2):261–270

Lee AW, Foo W, Law SC, Poon YF, Sze WM OSK, Tung SY, Lau WH (1997) Nasopharyngeal carcinoma: presenting symptoms and duration before diagnosis. Hong Kong Med J 3(4):355–361

Lee AW, Foo W, Law SC et al (1999) Staging of nasopharyngeal carcinoma: from Ho's to the new UICC system. Int J Cancer 84:179–187

Lee AW, Lau WH, Tung SY, Chua DT, Chappell R, Xu L et al (2005) Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol 23(28):6966–6975

Lee N, Harris J, Garden AS, Straube W, Glisson B, Xia P et al (2009) Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. J Clin Oncol 27(22):3684–3690

Leung SF, Metreweli C, Tsao SY, Van Hasselt CA (1991) Staging abdominal ultrasonography in nasopharyngeal carcinoma. Australas Radiol 35(1):31–32

Leung SF, Chan AT, Zee B, Ma B, Chan LY, Johnson PJ et al (2003) Pretherapy quantitative measurement of circulating Epstein-Barr virus DNA is predictive of posttherapy distant failure in patients with early-stage nasopharyngeal carcinoma of undifferentiated type. Cancer 98(2):288–291

Leung SF, Tam JS, Chan AT, Zee B, Chan LY, Huang DP et al (2004) Improved accuracy of detection of nasopharyngeal carcinoma by combined application of circulating Epstein-Barr virus DNA and anti-Epstein-Barr viral capsid antigen IgA antibody. Clin Chem 50(2):339–345

Li S, Deng Y, Li X, Chen Q, Liao XC, Qin X (2010) Diagnostic value of Epstein-Barr virus capsid-IgA in nasopharyngeal carcinoma: a meta-analysis. Chin Med J (Engl) 123(9):1201–1205

Liang J, Yi Z, Lianq P (2000) The nature of juvenile nasopharyngeal angiofibroma. Otolaryngol Head Neck Surg 123: 475–481

Liebowitz D (1994) Nasopharyngeal carcinoma: the Epstein-Barr virus association. Semin Oncol 21(3):376–381

Lin JC, Wang WY, Chen KY, Wei YH, Liang WM, Jan JS et al (2004) Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. N Engl J Med 350(24):2461–2470

Lloyd C, McHugh K (2010) The role of radiology in head and neck tumours in children. Cancer Imaging 10:49–61

Lo YM, Leung SF, Chan LY, Chan AT, Lo KW, Johnson PJ et al (2000) Kinetics of plasma Epstein-Barr virus DNA during radiation therapy for nasopharyngeal carcinoma. Cancer Res 60(9):2351–2355

Louis CU, Straathof K, Bollard CM et al (2010) Adoptive transfer of EBV-specific T cells results in sustained clinical responses in patients with locoregional nasopharyngeal carcinoma. J Immunother 33:983–990

Mann WJ, Jecker P, Amedee RG (2004) Juvenile angiofibromas: changing surgical concept over the last 20 years. Laryngoscope 114:291–293

Marks JE, Phillips JL, Menck HR (1998) The National Cancer Data Base report on the relationship of race and national origin to the histology of nasopharyngeal carcinoma. Cancer 83(3):582–588

Marshall AH, Bradley PJ (2006) Management dilemmas in the treatment and follow-up of advanced juvenile nasopharyngeal angiofibroma. ORL J Otorhinolaryngol Relat Spec 68:211–216

McMillan AS, Pow EH, Leung WK, Wong MC, Kwong DL (2004) Oral health-related quality of life in southern Chinese following radiotherapy for nasopharyngeal carcinoma. J Oral Rehabil 31(6):600–608

Mertens R, Granzen B, Lassay L, Gademann G, Hess CF, Heimann G (1997) Nasopharyngeal carcinoma in childhood and adolescence: concept and preliminary results of the cooperative GPOH study NPC-91. Gesellschaft für Pädiatrische Onkologie und Hämatologie. Cancer 80(5):951–959

Mertens R, Granzen B, Lassay L, Bucsky P, Hundgen M, Stetter G, Heimann G, Weiss C, Hess CF, Gademann G (2005) Treatment of nasopharyngeal carcinoma in children and adolescents: definitive results of a multicenter study (NPC-91-GPOH). Cancer 104(5):1083–1089

Micheau C, Rilke F, Pilotti S (1978) Proposal for a new histopathological classification of the carcinomas of the nasopharynx. Tumori 64(5):513–518

Midilli R, Karci B, Akyildiz S (2009) Juvenile nasopharyngeal angiofibroma: analysis of 42 cases and important aspects of endoscopic approach. Int J Pediatr Otorhinolaryngol 73:401–408

Mutirangura A, Pornthanakasem W, Theamboonlers A, Sriuranpong V, Lertsanguansinchi P, Yenrudi S, Voravud N, Supiyaphun P, Poovorawan Y (1998) Epstein-Barr viral DNA in serum of patients with nasopharyngeal carcinoma. Clin Cancer Res 4(3):665–669

Nakamoto Y, Osman M, Wahl RL (2003) Prevalence and patterns of bone metastases detected with positron emission tomography using F-18 FDG. Clin Nucl Med 28(4): 302–307

Ngan BY, Forte V, Campisi P (2008) Molecular angiogenic signaling in angiofibromas after embolization: implications for therapy. Arch Otolaryngol Head Neck Surg 134:1170–1176

Nicolai P, Berlucchi M, Tomenzoli D, Cappiello J, Trimarchi M, Maroldi R, Battaglia G, Antonelli AR (2003) Endoscopic surgery for juvenile angiofibroma: when and how. Laryngoscope 113:775–782

Niedobitek G, Young LS (1994) Epstein-Barr virus persistence and virus-associated tumors. Lancet 343:333–335

Olmi P, Fallai C, Colagrande S, Giannardi G (1995) Staging and follow-up of nasopharyngeal carcinoma: magnetic resonance imaging versus computerized tomography. Int J Radiat Oncol Biol Phys 32(3):795–800

Ozyar E, Atahan IL, Akyol FH, Gurkaynak M, Zorlu AF (1994) Cranial nerve involvement in nasopharyngeal carcinoma: its prognostic role and response to radiotherapy. Radiat Med 12(2):65–68

Paris J, Guelfucci B, Moulin G, Zanaret M, Triglia JM (2001) Diagnosis and treatment of juvenile nasopharyngeal angiofibroma. Eur Arch Otorhinolaryngol 258:120–124

Pignon JP, le Maitre A, Maillard E, Bourhis J (2009) Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 92(1):4–14

Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH et al (2006) Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 66(4):981–991

Raab-Traub N (2002) Epstein-Barr virus in the pathogenesis of NPC. Semin Cancer Biol 12:4310

Radiation Therapy Oncology Group of the American College of Radiology (2006) A phase II study of concurrent chemoradiotherapy using three-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiation therapy (IMRT) + bevacizumab (BV) for locally or regionally advanced nasopharyngeal cancer. Radiation therapy oncology group, principal investigator : Nancy Lee, MD www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=7157

Reddy KA, Mendenhall WM, Amdur RJ, Stringer SP, Cassisi NJ (2001) Long-term results of radiation therapy for juvenile nasopharyngeal angiofibroma. Am J Otolaryngol 22:172–175

Ren ZF, Liu WS, Qin HD, Xu YF, Yu DD, Feng QS, Chen LZ, Shu XO, Zeng YX, Jia W (2010) Effect of family history of cancers and environmental factors on risk of nasopharyngeal carcinoma in Guangdong, China. Cancer Epidemiol 34(4): 419–424

Rodriguez-Galindo C, Wofford M, Castleberry RP, Swanson GP, London WB, Fontanesi J, Pappo AS, Douglass EC (2005) Preradiation chemotherapy with methotrexate, cisplatin, 5-fluorouracil, and leucovorin for pediatric nasopharyngeal carcinoma. Cancer 103(4):850–857

Rossi A, Molinari R, Boracchi P, Del Vecchio M, Marubini E, Nava M et al (1988) Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. J Clin Oncol 6(9): 1401–1410

Saylam G, Yucel OT, Sungur A, Onerci M (2006) Proliferation, angiogenesis and hormonal markers in juvenile nasopharyngeal angiofibroma. Int J Pediatr Otorhinolaryngol 70: 227–234

Schuon R, Brieger J, Heinrich UR, Roth Y, Szyfter W, Mann WJ (2007) Immunohistochemical analysis of growth mechanisms in juvenile nasopharyngeal angiofibroma. Eur Arch Otorhinolaryngol 264:389–394

Sengupta S, den Boon JA, Chen IH, Newton MA, Stanhope SA, Cheng YJ, Chen CJ, Hildesheim A, Sugden B, Ahlquist P (2008) MicroRNA 29c is down-regulated in nasopharyngeal carcinomas, up-regulating mRNAs encoding extracellular matrix proteins. Proc Natl Acad Sci USA 105(15): 5874–5878

Sham JS, Cheung YK, Choy D, Chan FL, Leong L (1991) Nasopharyngeal carcinoma: CT evaluation of patterns of tumor spread. AJNR Am J Neuroradiol 12(2):265–270

Shanmugaratnam K (1980) Nasopharyngeal carcinoma: epidemiology, histopathology and aetiology. Ann Acad Med Singapore 9(3):289–295

Sultan I, Casanova M et al (2010) Differential features of nasopharyngeal carcinoma in children and adults: a SEER study. Pediatr Blood Cancer 55(2):279–284

Tang LL, Li WF, Chen L, Sun Y, Chen Y, Liu LZ, Mao YP, Lin AH, Li L, Ma J (2010) Prognostic value and staging categories of anatomic masticator space involvement in nasopharyngeal carcinoma: a study of 924 cases with MR imaging. Radiology 257(1):151–157

Teo PM, Leung TW, Chan AT, Yu P, Lee WY, Leung SF et al (1995) A retrospective study of the use of cisplatinum-5-fluorouracil neoadjuvant chemotherapy in cervical-node-positive nasopharyngeal carcinoma (NPC). Eur J Cancer B Oral Oncol 31B(6):373–379

Tosun S, Ozer C, Gerek M, Yetiser S (2006) Surgical approaches for nasopharyngeal angiofibroma: comparative analysis and current trends. J Craniofac Surg 17:15–20

Turner SL, Tiver KW (1993) Synchronous radiotherapy and chemotherapy in the treatment of nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 27(2):371–377

Tyagi I, Syal R, Goyal A (2007) Recurrent and residual juvenile angiofibromas. J Laryngol Otol 121:460–467

Ulger S, Ulger Z, Yildiz F, Ozyar E (2007) Incidence of hypothyroidism after radiotherapy for nasopharyngeal carcinoma. Med Oncol 24(1):91–94

Wagner HJ, Mertens R, Reiter A, Gauch C (2009) Molecular and serological monitoring of pediatric patients with nasopharyngeal carcinoma treated by the protocol NPC-2003-GPOH of the German Society for pediatric oncology. Pediatr Blood Cancer. 53:751

Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T et al (2005) Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol 23(27):6730–6738

Wei W, St Sham J (2005) Nasopharyngeal carcinoma. Lancet 365:2041–2054

Weprin LS, Siemers PT (1991) Spontaneous regression of juvenile nasopharyngeal angiofibroma. Arch Otolaryngol Head Neck Surg 117:796–799

Withers HR, Thames HD (1988) Dose fractionation and volume effects in normal tissues and tumors. Am J Clin Oncol 11(3):313–329

Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ (2006) Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. Int J Radiat Oncol Biol Phys 64(1):57–62

Wong TS, Kwong DL, Sham JS, Wei WI, Kwong YL, Yuen AP (2004) Quantitative plasma hypermethylated DNA markers of undifferentiated nasopharyngeal carcinoma. Clin Cancer Res 10(7):2401–2406

Wu VW, Kwong DL, Sham JS (2004) Target dose conformity in 3-dimensional conformal radiotherapy and intensity modulated radiotherapy. Radiother Oncol 71(2):201–206

Xie P, Yue JB, Zhao HX, Sun XD, Kong L, Fu Z, Yu JM (2010) Prognostic value of 18F-FDG PET-CT metabolic index for nasopharyngeal carcinoma. J Cancer Res Clin Oncol 136(6):883–889, Pub 2009 Nov 20

Yabuuchi H, Fukuya T, Murayama S et al (2002) CT and MR features of nasopharyngeal carcinoma in children and young adults. Clin Radiol 57:205–210

Yen RF, Ting LL, Cheng MF, Wu YW, Tzen KY, Hong RL (2009) Usefulness of 201TL SPECT/CT relative to 18F-FDG PET/CT in detecting recurrent skull base nasopharyngeal carcinoma. Head Neck 31(6):717–724

Yiotakis I, Eleftheriadou A, Davilis D, Giotakis E, Ferekidou E, Korres S, Kandiloros D (2008) Juvenile nasopharyngeal angiofibroma stages I and II: a comparative study of surgical approaches. Int J Pediatr Otorhinolaryngol 72:793–800

Zhang PJ, Weber R, Liang HH, Pasha TL, LiVolsi VA (2003) Growth factors and receptors in juvenile nasopharyngeal angiofibroma and nasal polyps: an immunohistochemical study. Arch Pathol Lab Med 127:1480–1484