# Nasopharyngeal Carcinoma

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## 10.1 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 the fourth and sixth decades (Bray et al. 2008; Wei and St Sham 2005). Males are more frequently affected than females, with 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. In pediatric series, median age is around 15 years (Dourthe et al. 2018). 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 (Dittmer et al. 2008; Sultan et al. 2010; Cheuk et al. 2011; Huang et al. 2018).

## 10.2 Symptoms

Young patients with nasopharyngeal carcinoma frequently present with symptoms resulting from a mass effect from the primary tumor as well as frequent cervical lymph node metastasis (Fig. 10.1). Nasal symptoms, such as epistaxis and nasal obstruction, are almost always present and are secondary to the presence of the tumor in

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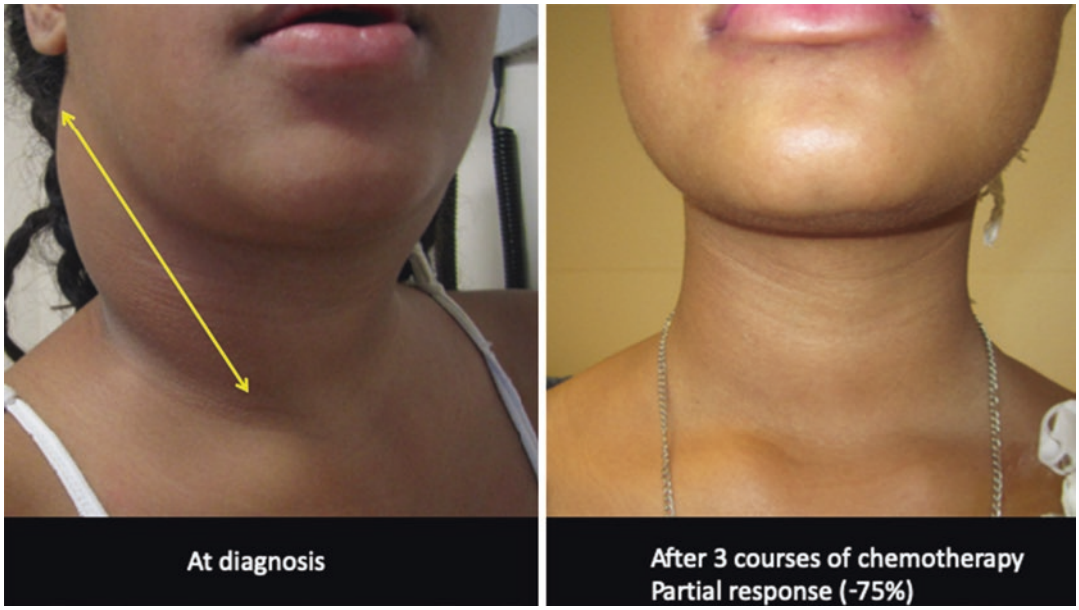


**Fig. 10.1** Cervical lymphadenopathy in a 13-year-old girl with stage IV nasopharyngeal carcinoma

the nasopharynx. The second most common symptoms are 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. The third most common symptoms are cranial nerve palsies, mostly of the fifth and sixth cranial nerves, resulting from cranial extension of the tumor and skull base erosion; in addition, patients may experience headache, diplopia, facial pain, and numbness. A retrospective analysis of 4768 patients identified the following symptoms at presentation: neck mass (75.8%), nasal symptoms (73.4%), aural symptoms (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%) (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. Indeed, up to 90% of NPC patients present with lymph node metastases. Distant metastases are rare and can be detected in 5–10% of patients at diagnosis and most commonly involve bones (67%), liver (30%), bone marrow (23%), lungs (20%), and mediastinum (Altun et al. 1995; Ayan et al. 2003).

## 10.3 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, LMP1, and LMP2 as well as the EBERs. In vitro and in vivo models have shown that LMP1 and, in particular, LMP2 as well as viral miRNAs, especially BART miRNA, play a major role in the malignant transformation of the NPC cells (Lo et al. 2012).

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 cur-

rent 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).

### 10.3.1 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).

### 10.3.2 Genetic Factors

Three independent genome-wide association studies have consistently identified single nucleotide polymorphisms in the MHC region to be strongly associated with an increased risk for NPC (Su et al. 2013). A consistent association between NPC and the prevalent Chinese HLA-A2 subtype (HLA-A*0207) but not the prevalent Caucasian subtype (HLA-A*0201) has been detected (Hildesheim et al. 2002). The HLA types 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).

### 10.3.3 Epstein–Barr Virus

Epstein–Barr virus (EBV) or human herpes virus 4 (HHV4) is an oncogenic c-herpes virus. Under normal circumstances, EBV infection is restricted to humans, although some types of monkeys can be infected experimentally (Bornkamm 1984). EBV is consistently detected in NPC patients from regions of high and low incidence. Its ability to establish latent infection of host cells and to induce proliferation of the latently infected cells is directly involved in NPC pathogenesis (Niedobitek and Young 1994).

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).

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 (Huang et al. 2018). 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 proteins 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).

## 10.4 Pathology

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 are the typical keratinizing squamous cell carcinomas similar to those found in the rest of the upper aerodigestive tract. Type II includes nonkeratinizing squamous carcinomas and type III carcinomas are the undifferentiated carcinomas (Micheau et al. 1978; Shanmugaratnam 1980; Marks et al. 1998). In children and adolescents, the majority of NPC is WHO type III, whereas type I is not encountered (Ozyar et al. 2006; Jouin et al. 2019).

**Table 10.1** 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 |

Table 10.1 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. These histological variants are strictly associated with increased titers against EBV antigen (Krueger and Wustrow 1981).

## 10.5 Staging System

For staging, the classification of the American Joint Committee on Cancer Staging (eighth edition of the *AJCC stage groupings and TNM definitions*) is internationally accepted (Amin et al. 2017).

### 10.5.1 Primary Tumor (T)

| | |
|---|---|
| T0 | No tumor identified, but EBV-positive cervical node(s) involvement |
| T1 | Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement |
| T2 | Tumor with extension to parapharyngeal space and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles) |
| T3 | Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses |
| T4 | Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle |

### 10.5.2 Regional Lymph Nodes (N)

| | |
|---|---|
| N0 | No regional lymph node metastasis |
| N1 | Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage |
| N2 | Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage |
| N3 | Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage |

### 10.5.3 Distant Metastasis (M)

| | |
|---|---|
| M0 | No distant metastasis |
| M1 | Presence of distant metastasis |

### 10.5.4 Definition of Risk Groups

Risk groups are defined by the AJCC (eighth edition). 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–II have an excellent outcome, with survival rates in excess of 80–90%, whereas patients with stages III–IV have lower survival (Lee et al. 2005a, b; Wee et al. 2005; Chen et al. 2011) (Table 10.2) (Figs. 10.2 and 10.3).

## 10.6 Diagnosis

Clinical examination, including endoscopic examination of the nasopharynx, can provide very valuable information on mucosal involvement and local tumor extension and allows nasopharyngeal tumor biopsy. A definitive histological diagnosis should require a positive biopsy taken from the tumor in the nasopharynx, although a cervical nodal biopsy in the appropriate context may also be diagnostic. Major differential diagnoses of malignant tumors in the nasopharyngeal region in children are rhabdomyosarcoma and lymphoma.

**Table 10.2** 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 |
| | (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 |

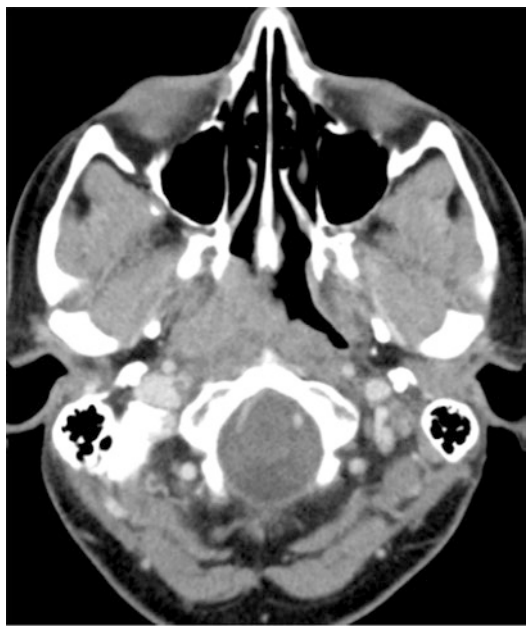

**Fig. 10.2** Axial MRI shows the typical primary tumor of NPC (T3) extending into the right infratemporal fossa

Clinical examination cannot, however, determine a deep extension of the tumor, such as skull base erosion and intracranial spread (Colevas et al. 2018). 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). In addition, head and neck MRI helps to detect frequent cervical regional nodal involvement. 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; Buehrlen et al. 2012).

### 10.6.1 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 is observed, and it is assumed that the EBV DNA is directly released from the tumor tissue. Ninety-five percent of patients are positive for EBV DNA in plasma at diagnosis (Leung et al. 2006). Various clinical studies have demonstrated that circulating EBV DNA concentrations correlate positively with disease stage as well as exhibit prognostic importance in NPC (Leung et al. 2003; Chan et al. 2003; Lin et al. 2004; Wagner et al. 2009). A meta-analysis comprising 14 prospective and retrospective studies with a total of 7836 NPC patients found that high pre-DNA, detectable mid-DNA, detectable post-DNA, and slow EBV DNA clearance rates were all significantly associated with poorer OS, with hazard radios (HRs) equal to 2.81, 3.29, 4.26, and 3.58, respectively. Pre-DNA, mid-DNA, and post-DNA had the same effects on PFS, distant metastasis-free survival (DMFS), and local relapse-free survival (LRFS) (Zhang et al. 2015). Usually, patients achieving a complete remission become negative for EBV DNA in plasma, whereas patients with persistent or progressive disease remain positive or even show increasing EBV DNA plasma concentrations.

### 10.6.2 EBV Serology

Patients with EBV show an aberrant antibody response against EBV proteins. IgA antibodies against the EBV viral capsid antigen (VCA) and early antigen (EA) have been demonstrated to

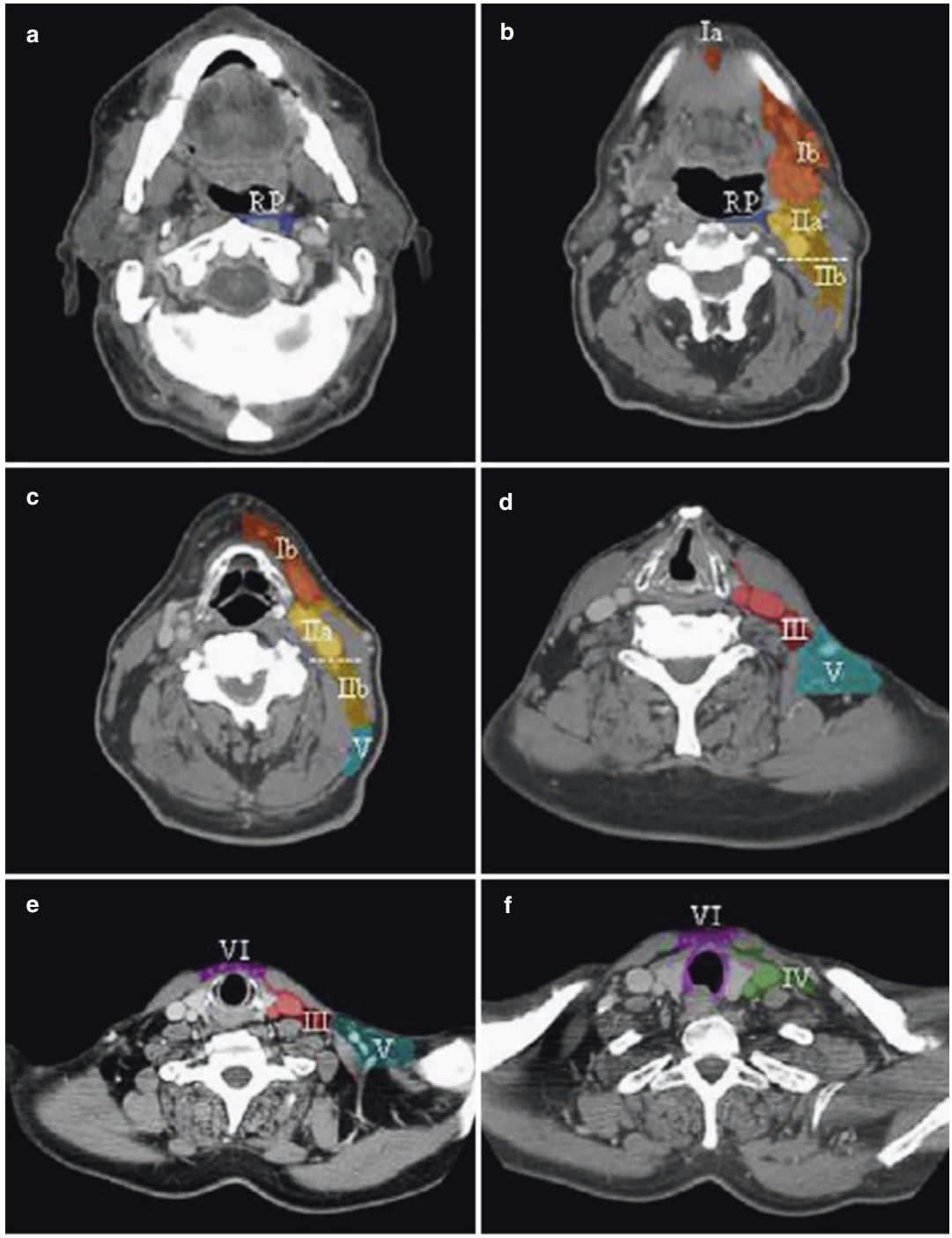


**Fig. 10.3** (**a**) Parapharyngeal. (**b**) Level IIa + IIb: jugular LN. (**c** and **d**) Level III, IV: jugular LN. (**e**–**f**) Level V, supraclavicular LN; level VI, LN around the thyroid gland

precede the development of NPC. In a large prospective study in Taiwan, men from the general population who tested positive for IgA antibodies against the VCA protein had an increased risk of developing NPC compared to VCA IgA-negative men, an association that persisted even ≥5 years after antibody measurement (HR = 13.9; 95% CI 3.1–61.7) (Chien et al. 2001). Therefore, both antibodies have been used to screen for NPC in endemic regions. EBV-VCA IgA and EA IgA titers also correlate with tumor burden (Cai et al. 2010; Yao et al. 2017). Rising titers of EBV-EA IgA antibody have also been shown to predict relapse (de Vathaire et al. 1988).

### 10.6.3 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 and prepares further radiotherapy delineation. 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. As MRI of the head and neck is nowadays the principal modality for delineation of the primary tumor and cervical lymph nodes, CT of the skull is only indicated if there is suspicion of bone invasion at the skull base (Colevas et al. 2018). Chest CT should be used for evaluation of pulmonary metastases either by itself or as part of FDG-PET/CT imaging.

### 10.6.4 Positron Emission Tomography

Various studies have investigated the use of [$^{18}$F]FDG PET/CT as imaging modality in patients with NPC. In the GPOH-NPC-2003 study, all tumors were PET positive at initial diagnosis or at time of relapse (Buehrlen et al. 2012). A comparison of PET/CT with MRI and CT for staging in children with NPC concluded that PET/CT may underestimate tumor extent and regional lymphadenopathy compared with MRI at the time of diagnosis, but it helps to detect metastases and clarify ambiguous findings (Cheuk et al. 2012). [$^{18}$F]FDG PET has been shown to be more sensitive than skeletal scintigraphy for detecting bone metastasis in endemic NPC at initial staging (Liu et al. 2008). A recent meta-analysis of 15 studies comprising 1938 patients with NPC confirms that high values of SUVmax, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) predicted a higher risk of adverse events or death in patients with nasopharyngeal carcinoma, despite clinically heterogeneous nasopharyngeal carcinoma patients and the various methods adopted between these studies (Lin et al. 2017). In addition, the decrease in the standardized uptake value (SUV) during therapy has been shown to be of prognostic value in NPC (Xie et al. 2010) and may help to better delineate tumor after chemotherapy to prepare radiotherapy plans. Therefore, [$^{18}$F]FDG PET/CT is considered a valuable imaging modality for the evaluation and monitoring of NPC in pediatric patients.

## 10.7 Therapy

### 10.7.1 Chemotherapy

In children and adolescents with NPC, sensitivity to chemotherapy has been demonstrated as early as in the mid-70s (Ghim et al. 1998). Outcome has been analyzed in several retrospective studies, most of them with less than 50 patients, mostly heterogenous for the type of chemotherapy used and the dosage of radiotherapy applied; the reported 5-year overall and disease-free survival range between 41–94% and 47–85%, respectively, with more recent studies showing a better outcome than older ones (Zubarreta et al. 2000; Ozyar et al. 2006; Orbach et al. 2008;

Afquir et al. 2009; Tao et al. 2013; Yan et al. 2013; Jouin et al. 2019). NPC in children and adolescents has so far been prospectively studied only in eight clinical trials (Ghim et al. 1998; Mertens et al. 2005; Rodriguez-Galindo et al. 2005; Buehrlen et al. 2012; Casanova et al. 2012; Casanova et al. 2016; Rodriguez-Galindo et al. 2016; Zaghloul et al. 2016). Due to the low incidence of the disease in children and adolescents, only one of these studies included a randomized question to be answered.

The first prospective study was a single institutional study conducted at Emory University Medical Center in Atlanta, USA, treating 12 patients aged 6–20 years during years 1976–1995 (Ghim et al. 1998). Eleven patients had locally advanced tumors; one had systemic metastases at diagnosis. Chemotherapy contained doxorubicin, cyclophosphamide, and 5-fluorouracil (5-FU) and was given before radiotherapy in four patients and with or after radiation in eight patients in 3-week cycles for up to 2 years. Radiation dosages to the primary tumor site were between 59 Gy and 68 Gy and to the neck between 59 Gy and 66 Gy. Nine patients remained in complete remission with a median follow-up of 9 years, one patient developed a secondary osteosarcoma of the mandible, one patient died of tuberculosis, and one patient was lost to follow-up in remission. In the Pediatric Oncology Group Study 9486, 17 patients below 22 years with nasopharyngeal cancer were evaluable for analysis (Rodriguez-Galindo et al. 2005). One patient with stage II disease was only irradiated, 16 patients with stage III/IV NPC received four cycles of neoadjuvant chemotherapy with methotrexate, cisplatin, and 5-FU. Irradiation was given after the end of chemotherapy with a dose of 61.2 Gy to the primary tumor and positive lymph nodes, whereas 50.4 Gy were applied to non-involved lymph nodes of the upper neck and 45 Gy to non-involved ones of the lower neck. The 4-year EFS and OS rates were 77% and 75%, respectively. The NPC study of the Italian rare tumors in pediatric age project (TREP) treated 46 patients aged 9–17 during the years 2000–2009 (Casanova et al. 2012). Of these all but one patient had lymph node involvement and five had distant metastases. Patients received three cycles of neoadjuvant chemotherapy with cisplatin and 5-FU followed by radiotherapy. Radiation dosages were 65 Gy for the primary tumor and involved lymph nodes and 45 Gy for non-involved ones. The 4-year PFS and OS rates were 79.3 and 80.9%, respectively, including metastatic patients.

The NPC-91-GPOH study was the first multicenter study for the treatment of nasopharyngeal carcinoma in children, adolescents, and young adults (Mertens et al. 2005). Sixty-eight patients were registered, among them five patients with metastatic disease. Of the 59 protocol patients (58 “high-risk” patients and 1 “low-risk “patient, median age of 13, range: 8–25), high-risk patients were treated with induction chemotherapy consisting of three cycles of methotrexate, cisplatin and 5-FU, radiotherapy with a dosage of 59 Gy to the primary tumor and 45 Gy to locoregional lymph nodes, and maintenance therapy with interferon-β for 6 months. The estimated overall survival for the protocol patients after 9 years was 95% and the disease-free survival 91%. Therapy was complicated by severe mucositis requiring total parenteral nutrition in 46% of patients and dose reductions in subsequent cycles of chemotherapy in 30% of patients. In the NPC-2003 study, methotrexate was omitted because of increased toxicity in the NPC-91 study (Buehrlen et al. 2012). In addition, due to results on the benefit of concomitant radiochemotherapy in adults, cisplatin was given for 2 weeks during radiotherapy. A third change to the NPC-91 study was the reduction of the radiation dose of the primary tumor to 54 Gy in patients with complete tumor remission after induction chemotherapy. The study resulted in an overall survival of 97% after a median follow-up of 30 months and an event-free survival of 92% for non-metastatic patients. Follow-up after 52 months showed an overall survival of 93% and an event-free survival of 92% (unpublished).

The only randomized comparative prospective study in children and adolescent was an international study which involved 75 patients and was conducted in 13 countries from 2007 to 2008. The randomized question to be answered was

whether the addition of docetaxel to the combination of cisplatin and 5-FU would increase the number of complete responses to induction chemotherapy. There was no significant difference in the overall response rates between the standard arm (ORR 80%) and the experimental arm (ORR 78%). Also, no significant difference in the 3-year overall survival was noted (Casanova et al. 2016).

In the COG study ARAR0331, 111 patients with NPC, aged 11 to 18, were treated between 2006 and 2013 with 3 cycles of 5-FU and cisplatin containing chemotherapy. This was followed by radiochemotherapy with a dose to the primary tumor of 61.2 Gy in patients with complete or partial tumor remission after induction chemotherapy and 70 Gy in patients whose tumor did not respond to induction chemotherapy. Cisplatin was given as a radiosensitizer during radiotherapy initially at a dose of 300 mg/m$^2$; however, it was subsequently reduced to 200 mg/m$^2$ because of toxicity. Five-year overall survival and event-free survival rates were 88.2% and 85.5%, respectively (Rodriguez-Galindo et al. 2016). A recent update of the study shows 5-year EFS and OS estimates of 84.3% and 89.2%, respectively. The 5-year EFS for stages IIb, III, and IV were 100%, 82.8%, and 82.7%, respectively. The 5-year cumulative incidence estimates of local, distant, and combined relapse were 3.7%, 8.7%, and 1.8%, respectively. Patients treated with 300 mg/m$^2$ of cisplatin during radiation therapy had improved 5-year post-induction EFS compared to those who received 200 mg/m$^2$ (90.7% vs. 81.2%, respectively, $p$ = 0.14) (Carlos Rodriguez-Galindo, personal communication).

In adults, the standard of therapy for locally advanced NPC has been for many years concomitant radiochemotherapy (Colevas et al. 2018). However, in the last years several large randomized studies have shown a benefit for induction chemotherapy (IC) followed by concomitant radiochemotherapy (CCRT) versus radiochemotherapy alone. Recently, pooled analysis of 4 randomized studies comprising 1193 patients with locoregionally advanced NPC from endemic regions also demonstrated the superiority of additional IC over CCRT alone, with the survival benefit mainly associated with improved distant control.

### 10.7.2 Radiotherapy

Radiotherapy is the main treatment modality of NPC. The aims are to irradiate the primary nasopharyngeal tumor together with the initially involved lymph nodes as well as to prophylactically irradiate the remaining cervical lymph node regions. The major limitations of conventional 2D radiotherapy for NPC can now be overcome with three-dimensional (3D) conformal radiotherapy and intensity-modulated radiotherapy (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; Wolden et al. 2006).

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; Jouin et al. 2019).

The use of IMRT in the 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 (Butler et al. 1999; 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 improved quality of life of survivors after IMRT (Wu et al. 2004). The superiority of IMRT versus conventional 2D radiotherapy was demonstrated in three prospective studies comparing the two treatment modalities in adult patients with NPC. Patients who underwent IMRT had significantly less late toxicities, especially hearing loss and xerostomia than patients who received conventional radiotherapy (Pow et al. 2006; Kam et al. 2007; Peng et al. 2012).

Considering the high incidence of severe late radiotherapy effects after NPC treatment even after IMRT, protons could be of interest in NPC, especially in children, adolescents, and young adults. The biological effect of protons is similar to photons, but the benefit expected is based on sharp dose fall-off, leading to a high therapeutic RT dose to the tumor with minimal exit dose, allowing for improved sparing of normal tissues (Taheri-Kadkhoda et al. 2008). The use of proton therapy, considered as the best technique for sparing critical organs, may induce less xerostomia and as a consequence less dental caries, as well as a potential reduction of ear and endocrine toxicities (Widesott et al. 2008). The place of this technique is still under investigation in pediatric NPC.

As cutting down late complications of treatment is one of the main objectives of pediatric clinical trials, another approach is adapting the dose of radiotherapy depending on the tumor response to induction chemotherapy. Such an approach has been taken by some national groups (French Group Fracture, German GPHO, or North American COG). Here, reduction of the dosage of radiation has been shown feasible in patients with a favorable response to induction chemotherapy, and it is assumed that this will lead to a decrease in long-term effects (Buehrlen et al. 2012; Rodriguez-Galindo et al. 2016; Jouin et al. 2019).

Radiotherapy in pediatric and adult NPC patients is nowadays combined with chemotherapy, usually cisplatin. This is based on several trials in adults which have confirmed the superiority of radiochemotherapy versus radiotherapy alone in advanced locoregional nasopharyngeal carcinoma. A meta-analysis comprising data on 1834 patients included in 7 adult trials showed that overall as well as progression-free survival was significantly improved in patients with radiochemotherapy versus radiotherapy alone (Blanchard et al. 2015). However, concomitant radiochemotherapy is associated with significant morbidity like severe mucositis requiring nutritional support, leading to lower dosages of cisplatin in most pediatric protocols compared to adult ones (Casanova et al. 2012; Buehrlen et al. 2012; Rodriguez-Galindo et al. 2016). As the benefit of concomitant radiochemotherapy has been established in adults who have not received previous induction chemotherapy, its role in pediatric NPC patients whose treatment concept includes induction chemotherapy for most patients is less clear.

### 10.7.3 Interferon Therapy

Interferon-β was introduced as a maintenance therapy into the GPOH studies after a boy with a second systemic NPC relapse went into a long-lasting complete remission with interferon-β alone, and response rates of around 25% were achieved in NPC patients with refractory disease treated with interferon-β (Treuner et al. 1980; Mertens et al. 1993). In the GPOH-NPC-91 and NPC-2003-GPOH studies, event-free survival rates were >90%, although radiation dosages were lower compared to other pediatric NPC protocols (Kontny et al. 2016). As NPC relapses are predominantly systemic, it is assumed that interferon-β improves systemic disease control. Recent preclinical data show that interferon-β induces the expression of tumor necrosis factor-related apoptosis inducing ligand (TRAIL) in NPC cells which subsequently elicits apoptosis via an intact TRAIL signaling pathway in an autocrine and paracrine manner (Makowska et al. 2018). Interferon-ß also activates natural killer cells and increases their killing of NPC cells in vitro (Makowska et al. 2019a). In NPC patients, interferon-ß increases the killing activity of NK cells against NPC cells and also increases levels of circulating soluble TRAIL which could con-

tribute to the elimination of residual micrometastic disease (Makowska et al. 2019b).

In the German studies NPC-91-GPOH and NPC-2003-GPOH, all patients underwent 6 months of treatment with recombinant interferon-β or native interferon-β after completion of radiation therapy, receiving a dose of $10^5$ U per kg body weight (max. dose: $6 \times 10^6$ U) intravenously (native interferon-β) or subcutaneously (recombinant interferon-β) three times a week. The favorable results of this strategy plead in favor of the use of this drug, but one should take into consideration that no comparative studies have proved the precise value of the maintenance therapy in this disease in young patients yet.

## 10.8 Metastatic Disease

Distant metastases are present in about 10% of patients with NPC at diagnosis. Although tumors and metastases usually respond to induction chemotherapy, most patients relapse and eventually die of their disease (Leong et al. 2008). However, patients with solitary or few osseous metastases or isolated lung metastasis have been shown to achieve long-term remissions, if they were treated with chemotherapy and radiotherapy to the primary tumor and the metastatic lesions (Fandi et al. 2000). Recently, a large, randomized study in adults with metastatic or relapsed NPC demonstrated that the combination of gemcitabine and cisplatin as induction chemotherapy was superior to the cisplatin/5-FU regimen as it significantly prolonged median progression-free survival (7.0 months versus 5.6 months) (Zhang et al. 2016).

## 10.9 New Treatment Strategies

### 10.9.1 T Cell Therapy

EBV-specific cytotoxic T cell (CTL) lines can readily be generated from individuals with NPC, notwithstanding 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 (Comoli et al. 2005).

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 antitumor 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).

### 10.9.2 Checkpoint Inhibition

As tumors of NPC patients from endemic regions and tumors from children show marked infiltration by lymphomononuclear cells, one could assume that measures to increase an immune response against NPC could lead to control of the disease. Inhibition of host tumor immune responses by negative checkpoints, such as the PD-1/PD-L1 checkpoint, has been demonstrated in various tumors, and blockade of immune checkpoints has led to impressive results in the treatment of various diseases such as melanoma and Hodgkin's lymphoma. NPC tumor cells express the immune effector cell inhibiting ligand PD-L1 in about 95% of tumors; therefore, blocking of the PD-L1/PD-1 interaction was also hypothesized to increase antitumor immunity in NPC. In two phase II trials in which patients with therapy-refractory nasopharyngeal carcinoma

were treated with the anti-PD1 antibodies pembrolizumab or nivolumab, an overall response rate of 26% and stable disease rate of 42%, and 20% and 34.1%, respectively, were observed (Hsu et al. 2017; Ma et al. 2018). Currently, the addition of PD-1 checkpoint inhibition to standard treatment for NPC is evaluated in several randomized trials in adults with newly diagnosed NPC.

### 10.9.3 Targeted Therapy

Like other squamous head and neck carcinomas, NPC tumors mostly express epidermal growth factor receptor (EGFR) (Fujii et al. 2002). However, neither the EGFR-blocking antibody cetuximab nor the tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib which inhibit the tyrosine kinase domain of the EGFR proved to have a significant effect on tumor growth in patients with recurrent or metastatic NPC in phase II trials (Perri et al. 2019). Vascular endothelial growth factor expression (VEGF-R) has been found in 60–70% of NPC tumors. Several VEGF-R-blocking TKIs have been investigated in phase II clinical trials in patients with recurrent or metastatic NPC with modest efficacy but significant toxicity (Elser et al. 2007; Hui et al. 2011; Lim et al. 2011).

## 10.10 Long-Term Sequelae

Survivors of NPC following radiotherapy or chemoradiation have impaired health-related quality of life. Patients may suffer from a variety of late complications, many of which result from the effects of radiation on 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 (Cheuk et al. 2011). 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 (Cheuk et al.2011). 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 radiotherapy dose and primary hypothyroidism and growth hormone deficiency (Ulger et al. 2007). In addition, three prospective studies comparing IMRT and conventional radiotherapy in patients with NPC all demonstrated that patients treated with IMRT had significantly less late toxicities than patients who underwent conventional radiotherapy (Pow et al. 2006; Kam et al. 2007; Peng et al. 2012). These frequent long-term toxicities associated with an overall nowadays good prognosis helped to propose adapted dose radiotherapy to induction chemotherapy in order to try to reduce sequelae in patients with favorable response.

## 10.11 Juvenile Nasopharyngeal Angiofibroma

### 10.11.1 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 of JNA is between 1 in 6000 and 1 in 60,000 otolaryngology patients. It accounts for 0.5% of all head and neck neo-

plasms, and it is considered to be the most common benign neoplasm of the nasopharynx (Mann et al. 2004; Glad et al. 2007). JNA predominately affects male children and adolescents between the ages of 9 and 19 (Gullane et al. 1992). 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 in 10–20%.

### 10.11.2 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). Differential diagnoses include parameningeal rhabdomyosarcoma, NPC, or diffuse lymphoma.

### 10.11.3 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 location 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 (Lee et al. 1980; Liang et al. 2000; Saylam et al. 2006; Ngan et al. 2008; Zhang et al. 2003).

### 10.11.4 Diagnosis

The diagnosis of JNA is based on a precise clinical history and examination of the patient and imaging (head and neck MRI or CT). 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).

Various staging systems have been proposed. In the Andrews staging system (Table 10.3), 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).

**Table 10.3** Stage-related definition of risk groups (AJCC, eighth edition)

| Stage grouping | |
|---|---|
| Stage I | T1 N0 M0 |
| Stage II | T0-1 N1 M0, T2 N0-1 M0 |
| Stage III | T0-1 N3 M0 |
| | T3 N0-2 M0 |
| Stage IVA | T4 N0-2 M0 |
| Stage IVB | Any T N3 M0 |
| Stage IVC | Any T Any N M1 |

### 10.11.5 Therapy

The management of JNA has changed during the last decades. It is generally agreed that surgery is the treatment of choice for all uncomplicated primary and recurrent JNA (López et al. 2017). Preoperative selective arterial embolization is almost always indicated as it helps to 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 or transmaxillar (lateral rhinotomy or midfacial) approach is usually performed (Belmont 1988; Dubey and Molumi 2007).

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). Radiotherapy may be considered for advanced, incompletely resectable cases and cases with a high morbidity of resection (López et al. 2017). Chemotherapy has been suggested for recurrences and selected cases with aggressive growth (Goepfert et al. 1985). In postpubertal patients, hormonal therapy with flutamide, an androgen receptor antagonist, has been used preoperatively to achieve tumor regression and facilitate surgical resection; this approach was successful in some but not all patients treated (Labra et al. 2004; Thakar et al. 2011). 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; however, clinical data have been lacking so far (Hashizume et al. 2010; López et al. 2017).

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