# Diagnosis and Treatment of Nasopharyngeal Carcinoma in Children and Adolescents – Recommendations of the GPOH-NPC Study Group

## Diagnose und Behandlung des Nasopharynxkarzinoms bei Kindern und Jugendlichen – Empfehlungen der GPOH-NPC Studiengruppe

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### Abstract

Nasopharyngeal carcinoma (NPC) is a rare malignant tumor arising from epithelial cells of the nasopharynx. Its incidence is highest in Southeast Asia. Age distribution of NPC is bimodal, with one peak in young adolescents and another in patients 55–59 years of age. EBV appears to be the primary etiologic agent in the pathogenesis, environmental factors such as nitrosamines and genetic factors are contributory. NPC is most commonly diagnosed in locally advanced stages, with lymph node metastases occurring in up to 90% of patients. About 5–10% of patients present with distant metastases. Diagnosis of NPC is made histologically, supported by an abnormal anti-EBV-VCA IgA titer and elevated plasma EBV-DNA load. Superior results in children and adolescents with advanced locoregional NPC, with overall and event-free survival rates > 90%, have been achieved by neoadjuvant chemotherapy with 5-fluoruracil and cisplatin, followed by synchronous radiochemotherapy and subsequent maintenance therapy with interferon-ß as demonstrated by the 2 prospective studies GPOH-NPC-91 and -2003. Response to therapy can be assessed by PET-imaging and in patients with complete remission after neoadjuvant chemotherapy, the radiation dose to the primary tumor can be safely reduced from 59.4 to 54.4 Gy. Since the majority of long term sequalae such as xerostomia, skin and tissue fibrosis are caused by high radiation dosages, radiotherapy modalities such as intensity-modulated radiotherapy should be used to efficiently spare non-tumorous tissue. For patients with metastatic disease and relapse, survival chances are low. New treatment strategies, such as the application of EBV-specific T-lymphocytes should be considered for these patients.

### Zusammenfassung

Das Nasopharynxkarzinom (NPC) ist ein seltener maligner Tumor, der aus Epithelzellen des Nasopharynx hervorgeht. Der Tumor tritt am häufigsten in Südostasien auf und zeigt einen Altersgipfel in der Adoleszenz und einen zweiten im Alter zwischen 55–59 Jahren. Dem Epstein-Barr-Virus (EBV) kommt eine Schlüsselfunktion bei der Entstehung des NPC zu, dazu kommen Umweltfaktoren, wie die Aufnahme Nitrosamin-haltiger Speisen und bestimmte genetische Polymorphismen. Bei Erstdiagnose sind bis zu 90% der Tumoren bereits lymphogen metastasiert, bei 5–10% lassen sich Fernmetastasen feststellen. Die Diagnose des NPC erfolgt histologisch und wird durch eine abnorme IgA-Immunantwort gegen EBV-VCA und den Nachweis einer hohen Plasma EBV-DNA-Last gestützt. Die besten Behandlungsergebnisse bei Kindern und Jugendlichen mit fortgeschrittenem lokoregionären Befall, mit Gesamt- und Ereignis-freien Überlebensraten > 90% wurden durch eine neoadjuvante Chemotherapie, gefolgt von einer Radiochemotherapie und anschließender Erhaltungstherapie mit Interferon-ß erreicht, wie in den GPOH-Studien NPC-91 und 2003 dargestellt. Da der Großteil von Spätkomplikationen wie Xerostomie und Haut- und Gewebsfibrose auf hohe Strahlendosen zurückzuführen ist, sollten bei der Strahlentherapie Verfahren wie die Intensitäts-modulierte Strahlentherapie eingesetzt werden, um die Streustrahlung auf gesundes Gewebe in der Tumorumgebung zu minimieren. Die Heilungsaussichten für Patienten mit Fernmetastasen und einem Rezidiv sind gering. Hier sollten neue Behandlungsverfahren wie die Gabe EBV-spezifischer T-Zellen zur Anwendung kommen.

Bibliography
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## Introduction

Nasopharyngeal carcinoma (NPC) is a rare neoplasm arising from epithelial cells of the nasopharynx. Its incidence varies between geographical locations, with the highest incidence occurring in adults in Southeast Asia. The age distribution of NPC is bimodal, with one peak arising in young adolescents and another one in patients between 55 and 59 years of age [9]. In Germany, NPC makes up about 0.2% of all neoplasms under the age of 18, with an incidence rate of 0.1 per 100 000 persons between 15 and 17 years of age [17]. Epidemiological studies from the United Kingdom report an incidence of about 0.3–0.4 per 100 000 persons across all age groups resulting in about 200 newly diagnosed patients per year [33]. In Southeast Asia environmental factors such as the consumption of certain herbs, salted fish and smoking have been described to be associated with an increased risk for NPC [14]. In addition, genetic factors, indicated by the occurrence of familial cases, association of NPC with certain HLA-subtypes and polymorphisms in host innate immune sensor genes influence the predisposition for this tumor [31, 47].

## Pathogenesis

NPC presents as a complex disease caused by an interaction of the oncogenic gamma-herpes virus EBV, environmental, and genetic factors, in a multistep carcinogenic process [25]. A monoclonal EBV infection is found in more than 98% of pre-invasive lesions [37]. The EBV-infected epithelial cells express a restricted group of latent genes (type II latency) such as *EBNA1*, *LMP1, LMP2A* and *EBERs* [52]. *In vitro* and *in vivo* models have shown that especially LMPs play a major role in malignant transformation of infected nasopharyngeal epithelial cells. More recently, evidence that the EBV BART microRNAs contribute to the malignant transformation has accumulated [24]. An aberrant immune response to EBV with high titers of IgA against viral capsid antigen and early antigen is seen early in disease and has been used together with circulating plasma EBV-DNA for screening in high-risk areas [26, 57, 58]. EBV strains found in NPC induce an unusually strong virus replication in infected cells that could explain this immune response [51]. Furthermore, these strains infect epithelial cells much more efficiently than strains found elsewhere, suggesting that NPC is caused by particular EBV strains [51]. Next-generation sequencing of NPC tumors revealed a distinct mutational signature with alterations in pathways responsible for chromatin modification, autophagy and ERBB-PI3K signaling [23].

## Clinical Presentation

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, auditory symptoms such as hearing loss and tinnitus occur, which are related to dysfunction of the Eustachian tube caused by latero-posterior extension of the tumor into the paranasopharyngeal space. Thirdly, cranial nerve palsies are present, commonly affecting the fifth and sixth cranial nerves and resulting from upward extension of the tumor leading to skull base erosion; patients also might experience headache, diplopia, facial pain and numbness. A retrospective analysis of 4768 patients identified the following symptoms at presentation: 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%) [44]. Since nasal and auditory symptoms are nonspecific and a thorough examination of the nasopharynx is not easy to perform, the majority of NPC patients are only diagnosed when the tumor has reached a locally advanced stage. Indeed, up to 90% of patients present with lymph node metastases. In about 5–11% of patients distant metastases are detected at diagnosis involving bones (67%), lungs (20%), liver (30%), bone marrow (23%) and mediastinum [2, 3].

**Table 1** Cervical lymph node grouping according to the American Head and Neck Society and the American Academy of Otolaryngology – Head and Neck Surgery [39].

| | |
|---|---|
| Sublevel IA | Submental |
| Sublevel IB | Submandibular |
| Sublevels IIA and IIB | Upper jugular |
| Level III | Middle jugular |
| Level IV | Lower jugular |
| Sublevels VA and VB | Posterior triangle group |
| Level VI | Anterior compartment group |

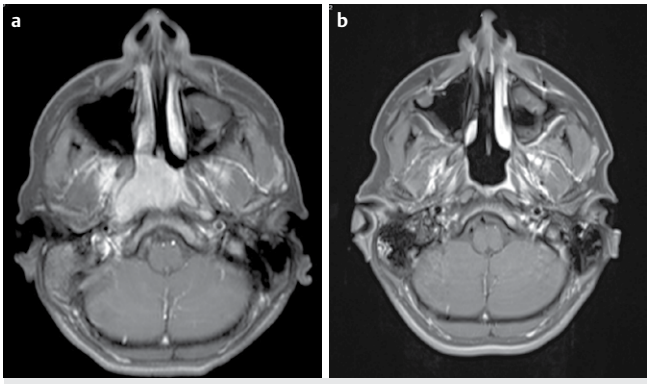


**Fig. 1** Contrast enhanced T1-weighted MRI of a 13 year-old boy with right-sided nasopharyngeal carcinoma (TNM: T4, N2, M1, stage IVC) before **a** and 2 years after radiochemotherapy **b**.

## Diagnosis

Histological analysis of a biopsy specimen is mandatory for the diagnosis of NPC. Prior to biopsy, mirror examination of the nasopharyngeal space for direct visualization of the tumor and MRI of the nasopharynx, skull base and neck including all cervical and supraclavicular lymph node regions are recommended (**Table 1**). MRI is preferred over CT, since it more precisely describes deep primary tumor infiltration (**Fig. 1**) [22]. Nasopharyngeal carcinomas are categorized along the WHO classification modified by Krüger and Wustrow [19] (**Table 2**). The classification indicates the degrees of lymphoid infiltration, whereby undifferentiated NPC with lymphoid infiltration corresponds to the lymphoepithelioma described by Schmincke in 1921 and non-keratinizing carcinoma with lymphoid stroma to the tumor characterized by Regaud in the same year [16, 38]. In children and adolescents most tumors are of type III histology,

**Table 2** WHO classification of nasopharyngeal carcinoma modified by Krüger and Wustrow [19].

| | |
|---|---|
| Typ I | Squamous cell carcinoma |
| Typ IIa | Non-keratinizing carcinoma without lymphoid stroma |
| Typ IIb | Non-keratinizing carcinoma with lymphoid stroma |
| Typ IIIa | Undifferentiated carcinoma without lymphoid stroma |
| Typ IIIb | Undifferentiated carcinoma with lymphoid stroma |

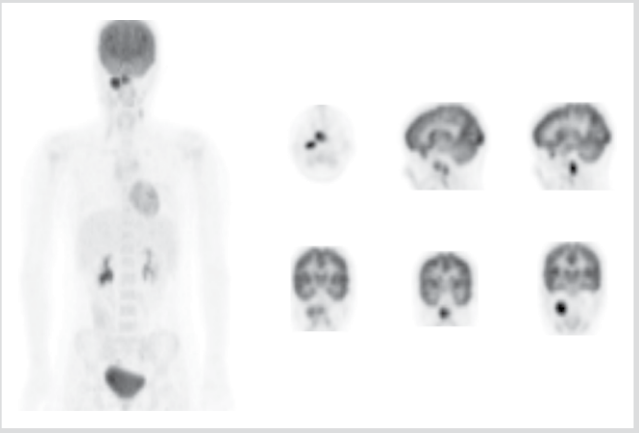

**Fig. 2** 13-year-old girl with nasopharyngeal carcinoma and right cervical lymph node metastasis at diagnosis. 3D reconstruction (left) and images of all 3 directions (right). 18FDG uptake by the lymph node metastasis is higher than by the primary tumor.

**Table 3** TNM-classification of nasopharyngeal carcinoma according to the International Union against Cancer (UICC) and American Joint Committee of Cancer (AJCC) system [32].

| | |
|---|---|
| **Primary tumor (T)** | |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma in situ |
| T1 | Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension (eg, without posterolateral infiltration of tumor) |
| T2 | Tumor with parapharyngeal extension (posterolateral infiltration of tumor) |
| T3 | Tumor involves bony structures of skull base and/or paranasal sinuses |
| T4 | Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space |
| **Regional lymph nodes (N)** | |
| NX | Regional nodes cannot be assessed |
| NO | No regional lymph node metastasis |
| N1 | Unilateral metastasis in cervical lymph nodes ≤ 6 cm in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral retropharyngeal lymph nodes ≤ 6 cm in greatest dimension (midline nodes are considered ipsilateral nodes) |
| N2 | Bilateral metastasis in cervical lymph nodes ≤ 6 cm in greatest dimension, above the supraclavicular fossa (midline nodes are considered ipsilateral nodes) |
| N3 | Metastasis in a lymph node > 6 cm and/or to the supraclavicular fossa (midline nodes are considered ipsilateral nodes) |
| N3a | > 6 cm in dimension |
| N3b | Extension to the supraclavicular fossa |
| **Distant metastasis (M)** | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

**Table 4** Stages of nasopharyngeal carcinoma according to the International Union against Cancer (UICC) and American Joint Committee of Cancer (AJCC) system [32].

| Stage | T | N | M |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| I | T1 | N0 | M0 |
| II | T1 | N1 | M0 |
| | T2 | N0 | M0 |
| | T2 | N1 | M0 |
| III | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N0 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |
| IVA | T4 | N0 | M0 |
| | T4 | N1 | M0 |
| | T4 | N2 | M0 |
| IVB | T Any | N3 | M0 |
| IVC | T Any | N Any | M1 |

the remaining ones type II [3]. Both type II and III tumors are EBV-associated, whereas type I is not [5].

## Staging

Staging should include PET(/CT), chest-CT and MRI-abdomen for detection of distant metastases (**Fig. 2**). In case of lesions suspicious of bone involvement on PET or MRI, a technetium bone scan is recommended. Also, EBV-serology, including anti-VCA-IgA and EBV-PCR are recommended. Tumor stages are defined by the classification of the International Union against Cancer (UICC) and the American Joint Committee of Cancer (AJCC) [32] (**Table 3,4**). MRI, PET(/CT), anti-EBV-VCA-IgA and EBV-PCR are useful parameters for monitoring response to therapy and are recommended to be repeated after neoadjuvant chemotherapy, after radiotherapy and after maintenance therapy with interferon-ß. In the NPC-2003 study all tumors were PET-positive at initial diagnosis or at relapse [6]. Changes in 18F-FDG uptake during therapy have been shown to be of prognostic value [54]. As shown in the NPC-2003 study the dose of radiotherapy to the tumor could be safely reduced from 59.4 to 54.4 Gy in patients who are in complete remission by MRI and PET after neoadjuvant chemotherapy.

## Treatment

As NPC is a radiosensitive neoplasm and tumors are usually not amenable to complete surgical excision due to their location, radiotherapy has been traditionally the treatment of choice. Several randomized trials over the last 20 years have shown a benefit for concomitant radiochemotherapy in loco regionally advanced disease in adults with regards to overall survival, event-free survival and relapse rate [4]. Radiation dosages of around 70 Gy to the primary tumor and 50 Gy to the lymph nodes are considered as standard in adults; combinations of cisplatin and 5-fluorouracil are mostly used for chemotherapy. With this concept 5-year progression free survival rates of about 70 % have been achieved [41]. Currently, the role of sequential therapy consisting of induction chemotherapy, adjuvant chemotherapy

or both is being investigated in several phase III clinical trials in adults.

In children and adolescents with NPC, sensitivity to chemotherapy has been shown as early as in the mid-70s [12]. There have been several retrospective studies on children and adolescents with NPC, most of them with less than 50 patients, mostly heterogenous for the type of chemotherapy used and the dosage of radiotherapy applied, reporting a 5-year overall and disease-free survival of 41-91 % and 47-85 %, respectively [1, 13, 34, 35, 43, 48, 55, 59]. NPC in children and adolescents has so far been prospectively studied only in 5 clinical trials [6, 7, 12, 29, 40]. Due to the low incidence of the disease in children and adolescents, none 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 [12]. 11 patients had locally advanced tumors; one had systemic metastases at diagnosis. Chemotherapy contained doxorubicin, cyclophosphamide and 5-fluorouracil and was given before radiotherapy in 4 patients and with or after radiation in 8 patients in 3 week cycles for up to 2 years. Radiation dosages to the primary tumor site were between 59 and 68 Gy and to the neck between 59 and 66 Gy. 9 patients remained tumor free 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 nasospharyngeal cancer were evaluable for analysis [40]. One patient with stage II disease was only irradiated, 16 patients with stage III/IV NPC received 4 cycles of neoadjuvant chemotherapy with methotrexate, cisplatin and 5-fluorouracil. 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 45.0 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 years during the years 2000 to 2009 [7]. Of these all but one patient had lymph node involvement and 5 had distant metastases. Patients received 3 cycles of neoadjuvant chemotherapy with cisplatin and 5-fluorouracil 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.

The NPC-91-GPOH study was the first multicenter study for the treatment of nasopharyngeal carcinoma in children, adolescents and young adults [29]. 68 patients were registered, among them 5 patients with metastatic disease. Of the 59 protocol-patients (58 "high risk" patients and one "low risk "patient, median age 13 years, range 8–25) the high risk patients were treated with induction chemotherapy consisting of 3 cycles of methotrexate, cisplatin and 5-fluorouracil, radiotherapy with a dosage of 59 Gy to the primary tumor and 45 Gy to loco regional lymph nodes and maintenance therapy with interferon-ß 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. Therefore, methotrexate was omitted in the NPC-2003 study [6]. In addition, due to results on the benefit of concomitant radiochemotherapy in adults [21] cisplatin was given for 2 weeks during radiotherapy. A third change to the NPC-91 study in 2003 was the reduction of the radiation dose 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 %. Follow up after 52 months showed an overall survival of 93 % and an event-free survival of 92 % (unpublished) (**Fig. 3**).

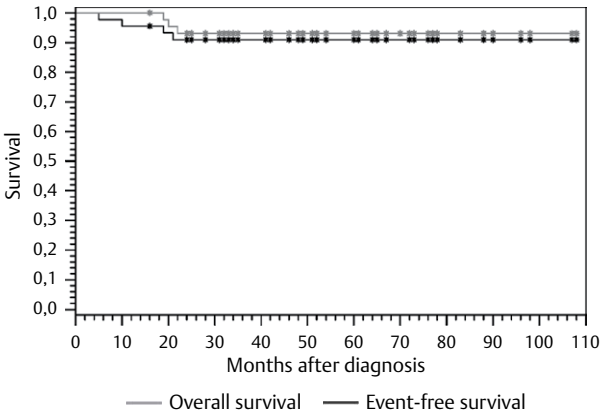


**Fig. 3** Kaplan-Meier curve illustrating overall and event-free survival for patients of the GPOH-NPC-2003 study after a median follow up of 52 months. Asterixes indicate censored observations. [non published].

The NPC-91 and NPC-2003 studies are unique for the following 4 reasons: (1) both together encompass the largest number of children and adolescents with NPC treated in a prospective study. (2) The NPC-93 and NPC-2001 trials are the only trials for NPC which use interferon-ß as maintenance therapy. The latter fact was mainly due to the unavailability of this drug in other countries than Germany. (3) Overall and event-free survival in the 2 studies are higher compared to the ones reported by other prospective trials on NPC. Since in the Italian study, 5 of the 46 patients had metastases at diagnosis, outcome for their patients with loco regional disease appears to be similar. (4) Compared to the other prospective trials, the dosage of radiation to the primary tumor is lowest in the NPC-2003 trial.

Based on the last 2 arguments we recommend treating children and adolescents with nasopharyngeal cancer along the concept of the NPC-91 and 2003-studies. The suggested treatment is outlined in the following paragraphs.

## Treatment for patients with localized disease

### Patients with Stage I disease

Patients rarely present with small, localized tumors without evidence of metastases (T1N0M0). High cure rates can be achieved without chemotherapy (20). We therefore recommend treating these patients as in the NPC-93 study with radiotherapy followed by IFN-ß maintenance therapy (**Fig. 4**).

### Patients with Stage II, III and IV disease

Stage II disease is also very rare in children and adolescents, with only 2 patients registered in the 2 NPC-GPOH studies. These 2 patients have been successfully treated with only radiotherapy and radiochemotherapy, respectively. However, since a large retrospective study from Hongkong, encompassing 141 pa-

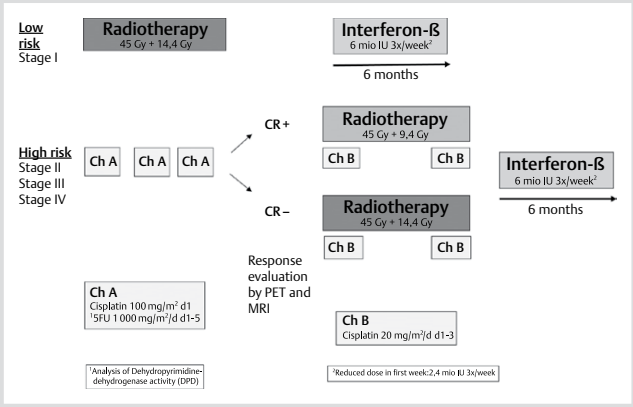


**Fig. 4** Treatment overview for patients with localized disease.

tients with NPC stage I and II showed that patients with stage II T2N0 and T1,2N1 had a 10y-OS and -DFS of only 72 and 55 %, respectively, when treated with radiotherapy alone [20], we recommend to treat the rare patient with stage II disease as the ones with stage III and IV disease which consists of 3 cycles of neoadjuvant chemotherapy with cisplatin and 5-fluorouracil, followed by concomitant radiochemotherapy, and maintenance with interferon-ß for 6 months (**Fig. 4**).

## Chemotherapy

Neoadjuvant chemotherapy is given in 3 cycles at 3-week intervals. Each cycle contains cisplatin 100 mg/m² as infusion over 6 h on day 1. Immediately after the end of the cisplatin infusion, leucovorin 25 mg/m² is given as an intravenous bolus every 6 h for 6 doses. 30 min after the first leucovorin bolus, 5-fluorouracil (5-FU) 1 000 mg/m²/d is started as continuous infusion over 5 days. Adequate hydration before, with and after cisplatin is most important for preventing nephrotoxicity. In addition, mannitol should be given according to the German product information ("Fachinformation") immediately before cisplatin and during pre- or post-hydration in case of insufficient urinary output. The role of mannitol in protecting against cisplatin-induced nephrotoxicity, however, has been questioned over the last years. In one study 49 women with ovarian cancer, who received 75 mg/m² cisplatin every 3 weeks, were randomized to 3 hydration arms, each one containing 2L of normal saline, one in addition furosemide, the other in addition mannitol; when comparing creatinine clearances on day 6, the ones in the normal saline + mannitol (50 g) group were significantly lower than the ones in the other 2 groups [42]. 2 recent studies, however, support the use of mannitol with cisplatin chemotherapy [28, 30]; though both studies are retrospective, the 143 and 139 patients, respectively, received the same higher dose of cisplatin as in our treatment regimen (100 mg/m²), more hydration fluid (3L) and less mannitol (12.5 and 25 g, respectively). In both studies, patients with mannitol had less renal toxicity by multivariate analysis. In case of ototoxicity CTC grade 2 or more or nephrotoxicity with a creatinine clearance < 50 ml/min/1.73 m², cisplatin should be replaced by carboplatin (500 mg/m² iv over 1 h). In patients with severe mucositis (grade 4) the duration of treatment with 5-FU (1 000 mg/m²/d) should be reduced to 4 days. Since cardiac toxicity of 5-fluoruracil has been linked to low activity of the enzyme dihydropyrimidine-dehydrogenase (DPD), screening for genetic variants of DPD before initiation of chemotherapy is recommended. In patients with DPD genotypes suggesting a low activity phenotype, dose modifications for 5-FU should be made [8].

## Radiotherapy

The recommended clinical target volume should be based on pretherapeutic MRI and should include the primary tumor region and all visible macroscopic lymph node metastases with a 1 cm safety margin; in addition, the parapharyngeal lymph nodes and cervical lymph node levels II should be irradiated in all patients. In patients with stage III and IV disease, cervical lymph node levels III, IV, and V as well as the supraclavicular regions should be covered, too. Stage I patients should receive irradiation to the nasopharynx and respective cervical lymph nodes with a total dose of 45 Gy in daily single fractions of 1.8 Gy, 5 days a week, followed by a radiation boost to the primary tumor with 14.4 Gy. In patients with stage II, III and IV disease the boost dose to the primary tumor and lymph nodes metastases can be reduced from 14.4 to 9.4 Gy in patients who are in complete remission by MRI and PET after neoadjuvant chemotherapy. Concomitant cisplatin 20 mg/m²/day on 3 consecutive days should be given during the first and last week of irradiation. In order to spare radiation dosage to healthy surrounding tissue, intensity-modulated radiotherapy (IMRT) is highly recommended. In 2 randomized studies patients treated by IMRT had less severe late xerostomia than patients treated with conventional 3D-conformal radiation therapy [18, 36].

## Interferon-ß

After completion of chemotherapy and radiochemotherapy, all patients in the NPC-91 and NPC 2003- GPOH studies underwent 6 months of treatment with interferon-ß. Though there have not been any randomised studies examining the role of interferon-ß in patients with NPC, there are clear hints that interferon-ß is effective in the treatment of NPC as a) interferon-ß alone led to a complete response in a patient with metastatic NPC [50] b) EFS and OS of the NPC-91 and -2003 studies, which are the only ones applying interferon-ß prospectively, are higher than the ones in other trials or equal with lower radiation dosages applied than in the Italian study, and c) adult patients treated with interferon-ß had a better outcome than patients treated without in a retrospective analysis [53]. Up to 2010, patients received Fiblaferon®, natural interferon beta, licensed for the treatment of NPC in Germany. In 2010 the production of Fiblaferon® was stopped for non-medical reasons. Since then, the use of recombinant interferon-ß, Rebif®, licensed for the treatment of multiple sclerosis but not NPC, was recommended by the NPC study committee. Rebif® has been used before in the Netherlands where Fiblaferon® was not licensed. Since there are no data showing that the outcome of patients treated with Rebif® is inferior to the one of patients treated with Fiblaferon®, it is recommended to use Rebif® at a dose of 6 million IU 3 times a week subcutaneously. A lower dose of 2.4 million IU 3 times a week should be applied in the first week of treatment (**Fig. 4**). In Germany, costs for outpatient treatment with Rebif have been reimbursed by health insurance providers when applied for in advance.

## Treatment for metastatic disease

Metastatic disease at diagnosis is rare in patients with NPC. Between 2003 and 2010, only 3 patients with metastatic NPC have been registered at the GPOH-NPC-study center [6]. In general,

prognosis for patients with metastatic disease is poor, with 5y-OS rates of ≤20 % [7]. Since metastatic disease is usually responsive to chemotherapy at the beginning of therapy, initial treatment usually consists of chemotherapy followed by radiotherapy to the tumor, loco regional lymph nodes and distant metastatic sites, if feasible. EBV-specific cytotoxic T-cells (CTLs) have been shown to be safe and have anti-tumor-activity in refractory and recurrent NPC [27]. Recently, the application of EBV-specific CTLs to patients with metastatic NPC resulted in an increased survival compared to patients not receiving such cells [45]. Therefore, it is recommended to check for the frequency of EBV-specific T-cells at diagnosis. Patients should then receive 3 cycles of neoadjuvant chemotherapy as described for non-metastatic disease. After the third cycle of chemotherapy in patients with EBV-specific T-lymphocytes, isolation of these by lymphapheresis is suggested. In patients responding well to chemotherapy, a fourth cycle is recommended followed by radiochemotherapy. EBV-specific T-lymphocytes should be re-infused during radiotherapy. Maintenance therapy with interferon-ß is recommended as for patients with non-metastatic disease.

### Treatment of relapse

In the NPC-91 and 2003-studies, 8 patients with NPC relapsed [6,27]. Of these, 2 had only a local relapse; 6 had metastatic+/− local relapse. Most of the patients responded to chemotherapy again, but overall survival was poor. Major challenges to the treatment of relapse in NPC are the recurrence of disease at previously irradiated sites and maintenance of continuous remission after renewed chemotherapy. Therefore, strategies for treating patients with relapse should encompass the application of new methods of radiotherapy, e.g. proton-irradiation for local recurrences and new treatment modalities such as the application of EBV-specific T-cells for systemic recurrences or experimental allogeneic stem cell transplantation [11,15,49].

### Follow-up and late effects

After the end of treatment patients should be followed-up at regular intervals and observed for recurrences and late complications of therapy. MRI and EBV-serology/DNA are the main diagnostic modalities for the detection of relapse. Late complications include mainly xerostomia, hypothyroidism, ototoxicity, and skin and tissue fibrosis. An increased risk for osteoradionecrosis of the skull base, temporal lobe necrosis, delayed bulbar palsy, hypopituitarism, and secondary cancers has also been described but seems to be linked to higher radiation doses [6,46,56]. In the NPC-GPOH-2003 study, hypothyroidism was reported in 25 % of patients, and ototoxicity in 14 % after a median follow-up of 48 months [6]. Radionecrosis was not an issue with the recommended dose levels. Late effects, however, continue to arise even 10 years and later after therapy, and 15-year cumulative incidences of hypothyroidism and ototoxicity with 47 and 68 %, respectively, have been reported in a retrospective review in children with NPC treated with chemotherapy and similar doses of radiotherapy [10].

### Nasopharyngeal carcinoma registry and clinical trials

The GPOH registry for nasopharyngeal cancer collects in an observational study information on epidemiological aspects, course and outcome of patients with nasopharyngeal carcinoma. In addition, the study center focuses on assuring the highest quality of patient care by establishing guidelines for diagnostics, offering reference evaluation for histological specimen and imaging studies, as well as giving recommendations for treatment. Several biological studies will be launched to further investigate on genetic and immunological aspects of the disease. In order to further advance the treatment of patients with NPC, clinical trials are mandatory which will require a joint multidisciplinary and international collaboration.

## Conclusion

Nasopharyngeal carcinoma (NPC) is a rare malignant tumor in children and adolescents. About 95 % of patients are diagnosed with locally advanced stages. For these patients a therapy concept with neoadjuvant chemotherapy, followed by radiochemotherapy and subsequent maintenance therapy with interferon-ß has not only proved to show the highest overall and event-free survival rates (>90 %), but also to use the lowest dosages of radiotherapy. Since long term sequalae such as xerostomia, endocrine defects, tissue fibrosis and secondary neoplasms are mainly due to high-dosages of radiotherapy, future efforts to advance treatment of these patients should include strategies to further decrease radiation intensity. For patients with metastases or relapse new treatment strategies such as the use of EBV-specific T-cells or agents specific for newly identified targets by next-generation sequencing are warranted. New treatment strategies should be evaluated in clinical trials and will require international collaboration.

## Contributor's Statement

FM, GS, Provision of figures. UK, SF and RM writing of manuscript. All authors, development of concept for diagnosis and treatment of NPC.

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