



## Consensus Recommendations for Nasopharyngeal carcinoma in children and adolescents

**Final version (V. 9)**

### The Partner Project:

PARTN-ER aims to create a European Registry dedicated to children and adolescents with very rare tumors (VRT) linking existing national registries and to provide a registry for those countries not already having a registry for VRT in place. The European Registry will be an essential part of the activity of the VRT subnetwork part of the ERN PaedCan. The possibility to link the registry with a virtual consultation system and the elaboration of diagnostic/treatment recommendations will create a platform that can be easily accessed by EU Health care providers. The increasing expertise in VRT based on the data collected in the European registry will increase the capacity to provide international consultation and define standard of treatment recommendations. This will ultimately result in improved patients' care and reduce currently existing inequalities in cancer outcome across EU member states.



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**Summary:**

Pediatric very rare tumors (VRT) constitute an extremely heterogeneous group of neoplasms. Some of them are typical of pediatric age, while other more commonly arise during adulthood and only rarely develop in children. Using the definition *any solid malignancy or borderline tumor characterized by an annual incidence <2/million children <18 years old and/or not already considered in other clinical trials*, the European Cooperative Study group for Pediatric Rare Tumors (EXPeRT) has initially identified a number of pediatric VRT (1). Due to the low number of patients it is very difficult – or even impossible - to conduct clinical trials on them, and this makes it hard to arrive to evidence-based treatment guidelines. As a consequence, the treatment of patient with VRT is often individualized.

**Background:**

Nasopharyngeal carcinoma (NPC) is a rare pediatric tumor, accounting for 1% of childhood malignancies<sup>1,2</sup>. NPC in children is often diagnosed during adolescence, and usually presents in advanced local disease<sup>3</sup>. Distant metastases, usually to the lung, mediastinum, liver or bones at presentation are rare, and account for less than 10% of newly diagnosed pediatric NPC. The conventional treatment of NPC includes chemotherapy and radiotherapy. Most children with NPC will become long-term survivors, but many will have long-term morbidities due to therapy-related effects. Data on the biology and epidemiology of pediatric NPC is scarce. Several collaborative studies performed over the last decades showed improved results compared to historical data<sup>4-7</sup>, but standardized guidelines for diagnosis and management of pediatric NPC are still unavailable.

**Objective:** To establish internationally recognized recommendations for the diagnosis and treatment of children and adolescents with NPC (WP6 – “Standard of care recommendations for children with VRT”). This constitutes one of the deliverables of PARTN-ER project (ERN-PAEDCAN Partner Paediatric Rare Tumours Network – European Registry), an EU funded project.

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# 1. METHODOLOGY

According to Consensus conference Standard Operating Procedure methodology the grade of evidence can be classified from Grade I to V <sup>8</sup>.

**Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System [1])**

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts' opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

EXPeRT/PARTN-ER’s members recognized that due to the rarity of this tumor, no evidence of level I to II exists. Therefore, recommendations for VRTs are developed based on the evidence collected from some prospective studies (level III) published, and more frequently retrospective series (Level IV), case reports (Level V) and personal expertise (Level V). The “strength” of recommendations will be categorized by additional grading (Grade A to E).

To identify tumors that need shared recommendations, PARTN-ER members designed the following procedure:

- Identification of the tumor of interest on the base of its relevance, and previous PARTN-ER experience, (i.e. data analysis and publication). Tumors should be classified as VRT (i.e. <2/100000/inhabitants/y), not already analyzed in previous Expo-r-Net project (pleuropneumoblastoma, pancreatoblastoma, salivary gland tumors, thymic tumors, rare sarcomas), not included in specific international protocols and frequent enough to be of interest <sup>9</sup>.
- Designation of two main coordinators for each VRT on the basis of their experience (data analysis, publications, personal experience).

Coordinators have to:

- Analyse the medical literature and select the relevant papers.
- Propose a series of recommendations in a form of a first draft of recommendations.
- Identify the main diagnostic and therapeutic problems for the designated VRT.

The first drafts will be shared and discussed, along with the relevant publications, into a selected expert group of PARTN-ER members, and annotated.

- A mature version of recommendations will be produced, taking into account proposals from the group of selected PARTN-ER members.
- The annotated draft will be then proposed to external experts identified by the coordinators on the basis of a recognized experience on the tumor (pediatricians, medical oncologist, radiotherapist, surgeon and others).
- The final version will be validated by the whole PARTN-ER group. In case of remaining disagreements, a vote will be done, during a physical consensus meeting, to agree on in a final consensus.
- Validated version will be submitted to publication in a peer review international journal.

The final document including recommendations will be available on PARTN-ER website.

**Warning:** These guidelines may change over time according to new data available. Local clinicians remain responsible for the care of their patients. The EXPeRT/PARTN-ER members are not responsible for results or complications related to their use. If necessary, medical discussions are possible with EXPeRT members of these groups via the expert website: <https://vrt.cineca.it>

## 2. BACKGROUND

Nasopharyngeal carcinoma (NPC) is a rare malignant epithelial tumor of the nasopharynx <sup>2,3</sup>. NPC accounts for less than 1% of childhood tumors but represents 20-50% of nasopharyngeal malignant tumors in children, after rhabdomyosarcoma and non-Hodgkin lymphoma. The incidence of NPC varies widely depending on geographic areas, from less than 1/100.000 inhabitants per year in low-risk countries – such as Europe and North America – and up to 40/100.000 person per year in endemic areas (i.e. southern parts of China, South-east Asia, Alaska and the Mediterranean Basin). NPC is mostly diagnosed in the 5<sup>th</sup> and 6<sup>th</sup> decades <sup>10-12</sup>, with a second minor peak in adolescence/early adulthood reported in low and intermediate-incidence countries <sup>13-15</sup>. Median age at diagnosis for pediatric NPC is between 12 to 15 years depending on series <sup>2,7,16</sup>.

According to the historical World Health Organization (WHO) classification <sup>17</sup>, three histologic subtypes of NPC are described:

- Type I: keratinizing squamous cell carcinoma, which is rarely seen in the pediatric setting;
- Type II: non-keratinizing squamous cell carcinoma;
- Type III: undifferentiated carcinoma (previously called lymphoepithelioma), which is the most common histologic type in the pediatric population, representing more than 90% of cases under 16 years of age <sup>2,7,16</sup>.

Familial clustering of NPC has been described and suggests that the development of NPC may result from a complex interaction between multiple susceptibility genes and environmental factors. Nevertheless, no predisposing syndrome has been reported to date <sup>18</sup>. Risk factors associated with NPC include certain human leukocyte antigens (HLA) types, as well as smoking, salted fish consumption and occupational exposures <sup>19</sup>. Pediatric NPC is associated with C-kit expression, as compared to P53 and Bcl2 mutations, seen more often in the adult NPC cases, indicating different

mechanisms of tumorigenesis<sup>20</sup>. Childhood undifferentiated NPC (type III), is consistently associated with evidence of Epstein-Barr Virus (EBV) infection, including circulating viral DNA, positive serological studies and presence of viral proteins in NPC tumor samples<sup>2,3</sup>.

Most children with NPC present with advanced locoregional disease. Distant metastases are rare at presentation, accounting for less than 10% of cases. Metastases are usually confined to the lungs, mediastinum, liver and bones<sup>4-6,16,21,22</sup>. Due to the nature of the tumor spread and its complex anatomical location, NPC is almost always unresectable at diagnosis.

NPC is radiosensitive, and radiotherapy has been the foundation of the treatment of NPC for decades. Doses of >65 Gy were historically used to achieve tumor control, resulting in severe short- and long-term sequelae, including stomatitis, dental caries, hypothyroidism and other endocrine abnormalities, xerostomia, hearing loss (related to both radiotherapy and cisplatin treatment) and growth development abnormalities as well as secondary malignancies<sup>3,22</sup>. Cisplatin-based Induction Chemotherapy (IC) has proved to be efficient in reducing tumor mass, thus reducing radiation volumes in good responders, with improved long-term survival and less long-term morbidities. Concomitant chemoradiotherapy in addition to IC has been reported in several non-randomized prospective pediatric studies to have additional benefit in long-term survival, although this issue is still controversial<sup>5,6,21-23</sup>. Recent studies reported the use of reduced radiation doses of 45 Gy to 59.4 Gy, with an emphasis on response-based dosing, with very favourable results<sup>5,6,16</sup>. Maintenance therapy with Interferon Beta (IFN- $\beta$ ) is being used by the German Pediatric Oncology and Hematology (GPOH) group for the last 3 decades as part of 2 consecutive prospective trials (NPC-91-GPOH, NPC-2003-GPOH/DCOG) with excellent outcomes<sup>5,6</sup>.

Thanks to multimodal treatment strategies combining chemotherapy and radiotherapy, overall prognosis of pediatric NPC has improved, reaching more than 90% of overall survival (OS) and progression-free survival (PFS) at 5 years, even with primary advanced locoregional disease<sup>4-6,21,23,24</sup>. Nevertheless most of these children will be burdened with long-term treatment related effects, with



a 15-year cumulative incidence of any morbidity of 84% according to a retrospective study at St Jude Children’s Research Hospital and from Israel <sup>22,25</sup>.

### 3. RECOMMENDATIONS

#### 3.1 INITIAL TUMOR ASSESSMENT

Since NPC arises in the deep region of nasopharynx, it may remain asymptomatic for a long time, and diagnosis is often made at an advanced local stage, although metastases remain rare at presentation <sup>2</sup>. The diagnosis of NPC could be challenging as there are no specific signs and symptoms. NPC should be suspected when a child presents with a mass located in the nasopharynx, usually associated with uni- or bilateral large painless non inflammatory cervical lymphadenopathy. Other symptoms may include nasal symptoms (obstruction, bleeding), auditory symptoms (otalgia, hearing impairment), other pain symptoms (headaches, neck pain), or less frequently neurological symptoms such as cranial nerve palsy that should lead to search for a skull base involvement by the tumor <sup>3</sup>.

When NPC is suspected – based on clinical and radiological findings – a histological diagnosis through a surgical procedure or core needle biopsy must be obtained [Level V; Grade A]. Biopsy of the primary tumor is preferred, although a biopsy from an involved cervical lymph node in the presence of nasopharyngeal mass is acceptable [Level V; Grade A]. Due to the anatomical complexity of the nasopharynx and proximity to various vital organs and major vessels, care should be taken in planning and performing tumor biopsy under general anesthesia during endoscopic examination [Level V; Grade A].

**Staging investigations include:****a. Primary tumor and its loco-regional tumor extension:**

Appropriate imaging studies at diagnosis are essential to assess the disease stage, extent of locoregional spread, skull-base and possible major cervical vessels and nerve involvements.

Loco-regional evaluation should include <sup>2</sup>:

- Full **clinical examination** including cervical and supraclavicular lymph nodes area evaluation and neurological examination [Level V; Grade A];
- Accurate delineation of locoregional disease is mandatory for both staging and treatment (the Growth Target Volume (GTV) definition). Anatomical imaging by **magnetic resonance imaging (MRI) or computed tomography (CT) scan** of the head and neck area including supraclavicular fossa is necessary [Level V; Grade A]. MRI has shown to be superior to conventional CT in the evaluation of the primary tumor and involved cervical and retropharyngeal lymph nodes in several studies in adult NPC <sup>26–29</sup>, as well as pediatric NPC <sup>30</sup> [Level III based on adult studies, IV based on pediatric study; Grade A]. When skull base invasion remains doubtful on MRI, additional CT scan may be helpful.
- **FDG PET/CT** has excellent diagnostic performance for detecting lymph nodes and distant metastases in patients with NPC <sup>31</sup>. Recently, the use of **PET/MR** devices has shown to be more accurate for tumor staging than combination of head and neck MRI and PET/CT in 2 prospective studies in adult patients, and may be used as a single-step staging modality <sup>32,33</sup> [Level III; Grade B]. There are no data on the use of **PET/MR** in pediatric NPC.
- **Nasopharyngeal endoscopic examination** with precise description of the primary tumor and its extension and potential complications (such as bleeding) is recommended [Level V; grade B]. **Biopsy** of the primary tumor is classically performed during this

endoscopic exploration [Level V; Grade A]; alternatively, a large cervical lymph node could be biopsied [Level V; Grade B].

- **Nodal staging** is based on clinical and radiologic findings. Lymph nodes are classified as invaded when their short-axis diameter is >10 mm or when obvious central necrosis or extra-capsular spread is identified by MRI or CT scan, or when pathological uptake is depicted by FDG-PET. In doubtful situations, the cytological examination of enlarged cervical lymph nodes can provide useful information<sup>34–36</sup> [Level IV; Grade B].

#### **b. Distant metastasis**

When NPC spreads, it mainly metastasizes to thoracic regional nodes and less frequently to bones, lungs and liver. Evaluation for distant metastatic disease at presentation of NPC should include:

- **Chest and abdominal (liver) CT scan with iodine contrast** [Level IV; Grade A].
- **FDG PET/CT** – based on adult studies<sup>26,37–40</sup> and a single pediatric study<sup>30</sup> – was shown to be superior to Technetium bone scintigraphy in the detection of lung and bone lesions [Level III based on adult studies, V for pediatric population; Grade A]. FDG PET/CT can add information to MRI studies in planning radiation therapy, based on a large retrospective study by Liu *et al.* and one limited randomized trial published by Wang *et al.*<sup>41,42</sup>. Cheuk *et al.* reported advantages of FDG PET/CT for monitoring disease clearance and follow-up in children<sup>30</sup>. Several studies support the value of metabolic derived parameters of FDG PET/CT as prognostic parameters for event-free survival (EFS) and OS in adult patients. There are no studies to support its role in pediatric NPC<sup>43–46</sup>. If FDG PET/CT is not available, combined CT and technetium bone scintigraphy could be used<sup>37</sup> [Level V; Grade C].

### c. Additional assessments

Pretreatment evaluations should include, in addition to classic biologic screening (i.e. hematological, hepatic and renal function):

- Oral and Dental evaluation. Short and long-term effects of therapy can result in significant oral and dental complications including mucositis, dental caries and life-long xerostomia. Baseline evaluation will allow for urgent treatments if required prior to treatment initiation [Level IV; Grade A].
- **Audiometric evaluation**, since the primary tumor can itself cause hearing impairment and before cisplatin-based chemotherapy or skull base radiotherapy [Level IV; Grade A].
- Whenever possible, **dihydropyrimidine dehydrogenase (DPD) deficiency research** before 5-Fluorouracil (5-FU)-based treatment, including phenotyping (direct or indirect measurement of enzyme activity) or genotyping (detection of inactivating polymorphisms on the *DPYD* gene) test. 5-FU can result in severe toxicity in some patients, which is often the result of reduced activity of the key metabolic enzyme DPD, mostly caused by genetic variants in the gene encoding DPD (*DPYD*). Before the use of 5-FU, DPD deficiency research is recommended to propose genotype-based dose reductions if necessary and avoid severe toxicity <sup>47,48</sup> [Level III based on adult studies; Grade A].
- **Fertility preservation options** depending on the age of the patient should be discussed with patients and families prior to initiation of treatment <sup>49</sup> [Level V; Grade A].

**Additional tests** could be considered to analyze the tumor biology and genetics:

- EBV-related studies, with serum and plasma DNA analyzes (tumor assessment for EBV is discussed on the “Diagnosis” section – 3.2). It is now well-known that EBV infection is associated with childhood undifferentiated NPC <sup>50</sup>. High titers of IgG and IgA against early antigen (EA) and viral capsid antigen (VCA) or other viral proteins are frequently seen at diagnosis <sup>2,5,51</sup> and could have post-therapeutic prognostic impact <sup>52</sup>. Similarly, high levels

of circulating viral DNA are almost always detected at diagnosis <sup>53,54</sup>. The surveillance of the plasma EBV DNA level has been described, mainly in adult cohorts, as a marker for tumor burden and could be a useful prognostic factor <sup>55-62</sup>. One retrospective pediatric study including 89 patients has shown the prognostic impact of pretreatment plasma EBV DNA level <sup>63</sup> [Level IV; Grade C].

- Molecular biology studies – such as whole exome – for germline and somatic mutations could be proposed for further understanding of tumor biology but are to date limited for research <sup>64,65</sup> [Level V; Grade C].

**Diagnosis** is often made at an advanced local stage.

Main symptoms result from a mass located in the nasopharynx ± cervical nodal enlargement.

Other symptoms may include nasal, auditory or less frequently neurological symptoms.

**Initial tumor assessment** should include:

- **Full clinical examination** [Level V; Grade A];
- **Head and neck MRI or CT scan with contrast media** including supraclavicular fossa [Level V; Grade A]
- **Nasopharyngeal endoscopic examination with biopsy** of the primary tumor [Level V; Grade A]; alternatively, a large cervical lymph node could be biopsied ([Level V; Grade B];
- **Chest and abdomen CT scan with iodine contrast** [Level IV; Grade A] (an alternative to systematic upper abdomen CT scan could be a liver ultrasound, or MRI).
- **FDG PET/CT** [Level III for adult studies, V for pediatric population; Grade A]; if FDG PET/CT is not available, technetium bone scintigraphy could be used [Level V; Grade C].

**Pretreatment investigations** should include:

- **Classic biological screening** (hematological, hepatic and renal function) [Level V; Grade A];
- **Audiometric evaluation** [Level IV; Grade A];
- **DPD testing** if feasible (phenotyping or genotyping) [Level III based on adult studies; Grade A];
- **Fertility preservation options** [Level V; Grade A].

**Additional assessment for research** could include:

- Serum and plasma EBV DNA analysis, with potential prognostic impact [Level IV; Grade C];
- Optional studies for germline and somatic mutations [Level V; Grade C].

## 3.2 DIAGNOSIS

Histology is mandatory for the diagnosis of NPC, since nasopharyngeal cytology sensitivity after fine needle aspiration is limited <sup>66</sup> [Level IV; Grade B]. It should especially distinguish NPC from other benign or malignant tumors occurring in this location during childhood, such as rhabdomyosarcoma or lymphomas. Revision of the histological slides by a pathologist with proved experience in pediatric and head and neck tumors and especially in NPC is highly recommended [Level IV; Grade B]. Frozen tissue could be stored for potential molecular profile [Level IV; Grade C].

Even if nasopharyngeal cytology is not enough to set up the diagnosis, the cytological examination of enlarged cervical lymph nodes can provide useful information for initial metastatic staging in case of positivity <sup>34–36</sup> [Level IV; Grade B].

NPC is defined as a carcinoma arising in the nasopharyngeal mucosa that shows light microscopic or ultrastructural evidence of squamous differentiation. The current 4<sup>th</sup> edition of the WHO classification for NPC includes the following subtypes <sup>67,68</sup>:

- Keratinizing squamous cell carcinoma (i.e. type I);
- Non-keratinizing carcinoma, which is divided in two subtypes:
  - Non-keratinizing differentiated carcinoma (i.e. type II, also called type 2a);
  - Non-keratinizing undifferentiated carcinoma (i.e. type III, also called type 2b);
- Basaloid squamous cell carcinoma (new subtype added in the 3<sup>rd</sup> edition).

Keratinizing squamous cell carcinoma (ex-type I) is characterized by a conventional squamous differentiation with intercellular bridges and/or keratinization over most of the tumor, and different degrees of differentiation (well, moderately and poorly differentiated). Tumor cells are arranged in irregular islands, the stroma shows various degrees of inflammatory infiltration with lymphocytes, plasma cells, neutrophils and eosinophils. This histological subtype is rarely seen in

the pediatric population. Non-keratinizing carcinoma shows irregular islands, dyscohesive sheets and trabeculae of carcinoma cells, and variable lymphocytes and plasma cells infiltrate. The undifferentiated subtype (ex-type III), the most frequent in childhood and early adulthood, is characterized by large tumor cells, with prominent large nuclei, scant cytoplasm, and prominent mitotic activity.

Immunohistochemistry is required to demonstrate the carcinomatous nature of the tumor (expressions of cytokeratins reactive with pan-cytokeratin antibodies like AE1/AE3) and its squamous differentiation (expression of cytokeratins 5/6, expression of transcription factors p63 and p40). Staining for low molecular weight cytokeratin (CAM5.2) is often weaker, cytokeratin 7 and 20 are both negative, epithelial membrane antigen (EMA) is often only focal. Tumor cells are negative for lymphoid markers CD20/CD5. Additional markers might be useful to rule out differential diagnoses (synaptophysin and chromogranin A for neuroblastoma, desmin and myogenin for RMS, NUT for NUT carcinoma, CD99 for Ewing sarcoma).

The stroma is composed of a mixture of T and B cells, and a variable number of S100 positive dendritic cells.

Childhood undifferentiated NPC is associated with EBV infection in almost all cases, and footprints of EBV infection can be found in NPC cells, such as the viral proteins EBNA1, LMP2, and LMP1 by immunohistochemistry, and the EBV small noncoding RNAs, Epstein-Barr Encoding Region (EBER) by hybridization in situ<sup>69–71</sup> [Level IV; Grade B].

There are no specific serum tumor markers available. Plasma EBV serological and DNA studies are discussed on the “Additional assessments” section – 3.1.c.

**Histological diagnosis**

**Histology** is mandatory for NPC diagnosis; cytology sensitivity is not enough [Level IV; Grade B].

Revision of the histological slides from an **experienced pathologist** especially in NPC is highly recommended [Level IV; Grade B].

**Frozen tissue** could be stored for potential molecular profile [Level IV; Grade C].

**Cytology of enlarged cervical lymph nodes** can help for initial staging [Level IV; Grade B].

**HES examination and immunohistochemistry** for cytokeratin (AE1/AE3, cytokeratin 5/6, 34BE12, CAM5.2), epithelial membrane antigen (EMA), transcription factors p63 and p40 and lymphoid markers (CD20/CD5) should be performed [Level V; Grade B].

**Footprints of EBV infection** should be searched, with immunohistochemistry including the viral proteins EBNA1, LMP2, and LMP1, and/or EBER hybridization in situ [Level IV; Grade B].

**Additional immunostaining and somatic molecular complementary analysis** should exclude other head and neck malignant tumors [Level V; Grade B].



### 3.3 STAGING SYSTEM

The use of the 8<sup>th</sup> edition of American Joint Committee on Cancer staging system is recommended [Level IV; Grade A] <sup>72–75</sup>.

The **AJCCC edition** proposes that:

*“Clinical assessment uses information available from clinical history, physical examination, imaging, endoscopy, biopsy of the primary site, surgical exploration, or other relevant examinations. Clinical (pretreatment) (cTNM) : Diagnostic data including symptoms, physical examination, imaging, endoscopy; biopsy of primary site; resection of single node/ sentinel node(s) with clinical T; surgical exploration without resection; other relevant examinations. The staging systems presented are all clinical staging, based on the best possible estimate of the extent of disease before first treatment. Imaging techniques [computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasonography] may be utilized and, in advanced tumor stages, have added to the accuracy of primary tumor (T) and nodal (N) staging, especially in the nasopharyngeal and paranasal sinuses, primary sites, and regional lymph nodes. Endoscopic evaluation of the primary tumor, when appropriate, is desirable for detailed assessment of the primary tumor for accurate T staging. Fine-needle aspiration biopsy (FNAB) may confirm the presence of tumor and its histopathologic nature, but it cannot rule out the presence of tumor.”*

***For nasopharyngeal cancer:***

*Cross-sectional imaging in nasopharyngeal cancer is mandatory to complete the staging process. Magnetic resonance imaging (MRI) often is the study of choice because of its multiplanar capability, superior soft tissue contrast, and sensitivity for detecting skull base and intracranial tumor spread. Computed tomography (CT) imaging with axial and coronal thin section technique with contrast is an alternative. Radiologic nodal staging should be done to assess adequately the retropharyngeal and cervical nodal status.”*

American Joint Committee on Cancer staging system	
Primary Tumor	
T1	Tumor confined to the nasopharynx or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension
T2	Tumor with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid, and/or prevertebral muscles
T3	Tumor invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle
Nodes	
N1	Unilateral metastasis, in cervical lymph node(s) above the caudal border of cricoid cartilage, and/or unilateral or bilateral metastasis in retropharyngeal lymph nodes, 6 cm or less
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or less above the caudal border of cricoid cartilage
N3	Metastasis in cervical lymph node(s) greater than 6 cm in dimension and/or extension below the caudal border of cricoid cartilage
Distant Metastases	
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases
Stage	
I	T1 N0 M0
II	T1-2 N1 M0, or T2 N0 M0
III	T3 N0-1 M0, or T1-3 N2 M0
IVA	T1-4 N3 M0, or T4 N0-2 M0
IVB	Any T, N, M1

Some recent adult studies have reported the prognostic value of pretreatment plasma EBV DNA level integrated to TNM staging but this remains at a research level today, and standardized quantitative assays and cut-off for EBV DNA levels are required <sup>76-78</sup> [Level IV; Grade C].

**Staging** should follow the **8<sup>th</sup> edition of AJCC** [Level IV; Grade A].

Incorporation of plasma EBV DNA level to TNM staging has been recently proposed [Level IV; Grade C].

## 3.4 TREATMENT

### General considerations:

- Multidisciplinary team discussions are mandatory at diagnosis and during therapy [Level IV; Grade A].
- Patients/families should be proposed the enrolment in a prospective trial if available and data collection in national or international databases [Level IV; Grade B].
- Treatment of NPC includes chemotherapy and radiotherapy [Level III; Grade A] <sup>2,3</sup>.
- Most long-term effects after the treatment of NPC, including secondary malignancies, are related to initial disease extension, chemotherapy-related effects and the high dosage of radiotherapy <sup>79–81</sup>. Chemotherapy is used to increase survival and to try to reduce radiation exposure in young patients.
- The type of treatment depends on the tumor stage according to the 8<sup>th</sup> Edition of the American Joint Committee on Cancer Staging System, and response to induction chemotherapy (IC) [Level III; Grade B].

#### a. Surgery

NPC is mostly diagnosed at an advanced local stage. Due to the nature of the tumor spread and its complex anatomical location, primary NPC is considered to be unresectable [Level III; Grade A]. Surgery can be discussed in the rare setting of very limited disease at presentation (stage T1/T2, N0, M0) or in selected cases of oligometastases in disease relapse situation [Level IV; Grade C].

#### **Surgery**

There is **no place for surgery** in the treatment schedule of primary NPC [Level III; Grade A]. Surgery can be discussed in selected cases of very limited disease or oligometastatic disease relapse [Level IV; Grade C].

## b. Medical therapy

- NPC is usually a chemosensitive tumor, however the optimal standard chemotherapy regimen has yet to be defined <sup>82–86</sup>.
- Several retrospective studies and six prospective non comparative studies since 2000 in pediatric NPC (see Table) showed good response to cisplatin-based chemotherapy regimens and it is now considered as standard care.

Additional chemotherapy drugs with evidence for efficacy in NPC include: 5-fluorouracil (5FU), bleomycin, doxorubicin, vinblastine, vinorelbine, paclitaxel, irinotecan and cyclophosphamide <sup>2–6,16,21,23,24,87,88</sup>.

- Different schedules for chemotherapy administration have been evaluated for NPC in adults and children, although there are no comparative studies that have been performed in children, adolescents and young adults (AYA) to date <sup>2,84,86,89,90</sup>.
- Available treatment plans include:
  - **Induction chemotherapy (IC)**, prior to radiotherapy with the aim of reducing tumor mass, preventing metastatic dissemination and thus try to allow decrease radiation doses and long-term radiation related toxicities;
  - **Concomitant chemotherapy during radiotherapy (CCRT)**, in order to sensitize the tumor to irradiation;
  - **Adjuvant therapy**, following radiotherapy, as a maintenance treatment with the aim to control minimal residual disease.
- Initial tumor staging and tumor response assessment are used to **adapt treatment strategy**.
- Early nutritional status evaluation and continuous supportive care are recommended. [Level III; Grade B]. Systematic gastrostomy placement prior to therapy initiation can be discussed with patients and families at diagnosis to ensure for continuous nutritional support

throughout treatment, taking into account the expected high risk of significant mucositis with chemo-radiotherapy [Level IV; Grade C].

- Central venous access insertion is recommended before chemotherapy administration [Level III; Grade B].

### ***Medical therapy for localized disease (stages I-II, N0)***

Only rare stages I-II (N0) disease could be treated without any chemotherapy [Level IV based on adult studies, no pediatric study; Grade B].

High cure rates for stage I disease were reported using radiotherapy alone <sup>91</sup>.

According to some studies, patients with stage II disease may benefit from addition of IC or concomitant cisplatin to radiotherapy <sup>91,92</sup>. Yet, in a recent meta-analysis, stage II NPC only benefited from CCRT when two-dimensional radiotherapy was employed but non-significant difference in survival outcomes were shown between CCRT and radiotherapy alone when intensity modulated radiotherapy (IMRT) was adopted <sup>93</sup>.

### **Medical therapy for localized disease (stages I-II, N0)**

Treatment for **stage I** could be **exclusive radiotherapy** [Level IV based on adult studies, no pediatric study; Grade B].

For **stage II N0** disease **additional cisplatin chemotherapy** may be considered, but its benefit is **not certain** compared to IMRT alone [Level IV adults, Grade C, no data on pediatric NPC].

### ***Medical therapy for locoregional disease (stages II N1, III-IVa)***

#### **Induction chemotherapy**

In adults, large phase III trials and meta-analysis comparing different IC regimens versus no IC showed inconclusive results <sup>82,90,94–97</sup>. Although the impact of induction therapy on overall survival remains controversial, it has been shown to achieve the highest distant control, and tolerance was acceptable. In children, no prospective comparative studies (with and without initial chemotherapy)

have been performed to scientifically analyze the precise role of IC in addition to locoregional radiotherapy. However, due to poor historical outcome after exclusive radiotherapy for locoregionally advanced NPC, and severe acute and long-term toxicities, the induction cisplatin-based chemotherapy was introduced for the pediatric population, with promising results <sup>2</sup>. A recent large retrospective study with matched cohort analysis reported a trend in favor of IC versus CCRT alone, but this result did not reach statistical significance <sup>98</sup>. Since 2000, several non-randomized prospective studies (including 18 to 111 patients each) have assessed the efficacy of IC ± CCRT ± maintenance treatment with several modalities of chemotherapy and radiotherapy, reporting improvement in overall survival compared with historical radiotherapy treatment (reaching more than 80% at 5 years versus 20% to 40%) <sup>4-6,21,23,24</sup>. The only prospective randomized phase II study on young patients with NPC showed that the addition of docetaxel to cisplatin + 5FU during induction therapy did not provide any benefit in terms of local control rate and outcomes in children and adolescents, leading to consider that this drug does not add to this combination for primary pediatric NPC <sup>24</sup>.

Despite the lack of evidence-based data with randomized studies in the pediatric population, **IC is currently considered as standard of care for locoregionally advanced disease (stages III-IVa)**, in order to avoid metastatic dissemination and thus prevent metastatic relapse, and to enable de-escalation of radiotherapy in good responders (and thus reducing acute and long-term toxicities) [Level III; Grade A]. Therapy usually includes **3 cycles of cisplatin and 5FU** [Level III; Grade B]. Tumor response should be assessed radiologically by MRI and/or PET/CT following the second or third chemotherapy cycle (time at evaluation has to be defined in order to begin RT 3 weeks after the third cycle) [Level III; Grade B].

**Table. Prospective main clinical studies published in childhood NPC since 2000**

Studies	Inclusion Period	Patients Number	Median Age (Range) (y)	Induction Chemotherapy Regimen	Overall Response Rate to Induction Chemotherapy	Radiation Therapy Doses and Fields	Concomitant Chemoradiotherapy	Maintenance Treatment	EFS	OS	Reported Toxicities
Mertens 4	1992 to 2003	59	13 (8-25)	MTX-cisplatin-5-FU 3 courses	94.9%	59.4 Gy: PT +ILN 45 Gy: ULN	—	Interferon beta for 6 mo	DFS: 91% at 108 mo 4 y EFS: 77%	OS: 95%	Severe stomatitis: 4 patients, cardiotoxicity: 2 patients
Rodriguez Galindo 3	1990 to 1994	18	13	MTX-cisplatin-LV-5-FU 4 courses	93.75%	61.2 Gy: PT +ILN 50.4 Gy: ULN	—	—	5 y EFS: 75%	4 y OS: 77%	Myelosuppression, stomatitis
Casanova 19	2000 to 2009	46	13 (9-17)	5-FU-cisplatin 3 courses	91%	60/65 Gy: PT+ILN 45 Gy: ULN	Cisplatin	—	5 y EFS: 79.3%	5 y OS: 80.9%	One patient died from respiratory failure. No other major acute toxicities. Most common late effects: hypothyroidism, xerostomia, neck fibrosis, trismus
Buehrlen 5	2003 to 2010	45	15 (8-20)	Cisplatin-LV-5-FU 3 courses	98%	Stage I, II: 59.4 Gy: PT 45 Gy: ULN Stage III, IV: 59.4 Gy: PT +ILN 45 Gy: ULN	Cisplatin	Interferon beta for 6 mo	EFS: 92% at 30 mo	OS: 97% at 30 mo	During neoadjuvant chemotherapy: mucositis 53%, nausea 36%, neutropenia 63% During chemoradiotherapy: severe mucositis 42%, ototoxicity 16 to 19% During IFN treatment: grade 3-4 leucopenia in 12 patients. Late effects: ototoxicity 14%, hypothyroidism 25%
Casanova 21	2007 to 2008	75	16 (9-21)	Cisplatin-5-FU or cisplatin-5-FU-docetaxel 3 courses	TPF: 88% PF: 88%	Not evaluated	Not evaluated	Not evaluated	3 y OS: 78% in PF, 85.7% in TPF	5 y OS: 88.2%	Hematologic disorders: 14% TPF, 16% PF. Gastrointestinal SAE: 14% TPF, 0% PF
Rodriguez-Galindo 22	2006 to 2013	111	14 (3-18)	Cisplatin-5-FU 3 courses	Not evaluated	61.2 Gy if complete or partial response 71.2 Gy if stable disease	Cisplatin	Not evaluated	5 y EFS: 85.5%	5 y OS: 88.2%	Not evaluated

DFS, disease-free survival; EFS, event-free survival; ILN, involved lymph nodes; LV, leucovorin; MTX, methotrexate; ORR, NPC, nasopharyngeal carcinoma; overall response rate; OS, overall survival; PF, cisplatin-5-FU; POG, Pediatric Oncology Group; PT, primitive tumor; SAE, severe adverse event; TPF, cisplatin-5-FU-docetaxel; TREP, rare tumors in pediatric age; ULN, uninvolved lymph nodes.

*From Dourthe et al., J Pediatr Hematol Oncol, 2017*

**- Response to treatment evaluation**

Radiological response to medical treatment should be analyzed by **MRI or CT-scan** according to either **WHO** criteria <sup>99</sup> using bidimensional measurements or **RECIST 1.1** criteria using unidimensional measurements <sup>100</sup> [Level IV; Grade B]. WHO was initially considered superior to RECIST for evaluation of therapeutic response in patients with irregularly shaped NPC <sup>100</sup>. However, using the tumor volume measurement as a reference in a recent adult prospective study, Chen *et al.* reported the superiority of unidimensional measurement for both primary and lymph nodes assessment <sup>101</sup>. These authors also showed that the single MR coronal dimension was the most consistent with the volume. Whatever the method used, the appropriate threshold values should be used, which are different between uni- and bidimensional methods (i.e., partial response “PR” is defined as >30% decrease with RECIST but >50% with WHO, and progressive disease “PD” is >20% increase with RECIST and >25% with WHO). One difficult issue is the use of very

good partial response “VGPR”, which is not defined neither in the WHO nor in the RECIST1.1. Although the prognostic value of tumor response has been demonstrated<sup>102,103</sup>, there is no evidence that a single measurable threshold defining VGPR is significantly related to survival.

Encouraging results were published regarding the use of PET/CT to assess response to IC<sup>104</sup>. Preliminary results showed that both <sup>18</sup>F-FDG and <sup>18</sup>F-FLT PET have the potential to monitor and predict tumor regression. However, the actual prognostic significance of metabolic response to IC is not yet confirmed.

#### - **Concomitant chemotherapy and radiotherapy**

In adults, several trials and meta-analyses have confirmed the role of CCRT in loco-regionally advanced NPC in term of locoregional/distant control as well as survival. The standard agent used in concurrent chemoradiation is cisplatin. A meta-analysis of the chemotherapy benefit in NPC (MAC-NPC) was reported by the Collaborative Group. A total of 8 randomized trials (for a total of 1753 patients) compared cisplatin-based chemotherapy plus radiotherapy versus radiotherapy alone in locally advanced NPC. A significant benefit was found for OS (+6% at 5 years) and EFS (+10% at 5 years) with the addition of chemotherapy, especially with CCRT<sup>86</sup>. An update published in 2015, on 19 trials and 4806 patients, confirmed that the addition of concomitant chemotherapy to radiotherapy significantly improved survival (absolute benefit at 5 years +6.3%), either with or without adjuvant chemotherapy<sup>84</sup>. In adults studies, the most frequently used regimens are: cisplatin 100 mg/m<sup>2</sup>/every 3 weeks (standard treatment) or weekly cisplatin (40 mg/m<sup>2</sup>/weekly) and it was defined that the optimal cumulative total dose of concurrent cisplatin should be higher than 200 mg/m<sup>2</sup><sup>105,106</sup>.

There are no randomized control studies in pediatric NPC that evaluated the role of CCRT versus radiotherapy alone. Several prospective trials in pediatrics used different regimens for cisplatin-based chemotherapy during radiotherapy with improved results compared to historical data<sup>3,6,7,16,21,23,79</sup>. Of note, the use of chemotherapy during irradiation is related with additional acute toxic



effects, mainly mucositis and need of nutritional support, with potential delays in the radiation therapy <sup>7</sup>. For these reasons, some national groups, such as the French group, considered the possibility to omit CCRT in patients in CR or VGPR after IC. On the other hand, in the COG ARAR0331 study report, patients treated with 3 versus 2 cycles of cisplatin concurrent chemoradiotherapy had improved 5-year EFS <sup>23</sup>. However, due to increased toxicity in this study, the dose of cisplatin during chemoradiation was reduced from 300 mg/m<sup>2</sup> to 200 mg/m<sup>2</sup>. Therefore, an optimal strategy regarding CCRT remains debatable in children [Level I for adult studies, III for pediatric population; Grade C]. Current regimens of CCRT in children include **cisplatin given either in 21 days cycles or weekly schedules** [Level III; Grade B].

- **Maintenance treatment**

The role of maintenance therapy following chemotherapy and radiotherapy is still uncertain <sup>5-7</sup>. Two prospective single arm studies performed by the GPOH have used 6 months of IFN- $\beta$  maintenance therapy after completion of 3 blocks of cisplatin-based IC and subsequent radio(chemo)therapy <sup>5,6</sup>. The two single arm studies comprised 104 patients with non-metastatic NPC. Overall, EFS and OS were >90% in both studies, although radiation dosages were lower compared to other pediatric NPC protocols. In the GPOH-NPC-91 and -2003 studies, patients received Fiblaferon®, natural IFN- $\beta$ , licensed for the treatment of NPC in Germany up to 2010. In 2010, the production of Fiblaferon® was stopped for non-medical reasons. Since then, the use of recombinant IFN- $\beta$  1a, Rebif®, licensed for the treatment of multiple sclerosis but not NPC, was recommended by the GPOH-NPC study committee <sup>107</sup>. Rebif® has the same amino acid sequence as endogenous human IFN- $\beta$ . It is produced in mammalian cells (Chinese hamster ovary) and is therefore glycosylated like the natural protein. The recommended dosage in pediatric NPC is 6x10<sup>6</sup> IU subcutaneously three times a week. It is recommended to use 50% of the dose in the first week of treatment. The drug is usually well tolerated, side effects are mainly flu-like symptoms and leukopenia <sup>6</sup>. IFN- $\beta$  is contraindicated in patients with depressive disorders. Other reports on

the use of IFN- $\beta$  maintenance therapy also come mainly from a retrospective analysis by the French pediatric rare tumor group (FRACTURE) and from a pilot study in adults, in which none of the 17 pediatric NPC patients and 6 adult patients treated with IFN- $\beta$  maintenance therapy had disease relapse<sup>7,108</sup>. No comparative data are available to confirm the role of IFN- $\beta$  in improving outcome [Level III; Grade B/C (no consensus reached)].

### **Medical therapy for locoregional disease (stages III-IVa)**

Although comparative evidence-based data are scarce in children, major current pediatric protocols propose for patients with locoregionally advanced NPC:

**1. Induction chemotherapy** in order to rapidly decrease tumor volume, reduce microscopic distant tumor spread and to allow de-escalation in the radiation therapy in good responders [Level III; Grade A].

It could include 3 to 4 cycles of cisplatin and 5-fluorouracil (5FU) [Level III; Grade B].

Tumor response should be assessed (MRI  $\pm$  FDG-PET/CT) after the third cycle [Level III; Grade B].

**2. Adapted radiotherapy** according to tumor response to initial chemotherapy (see after);

**3. Concomitant chemoradiotherapy** in order to sensitize the tumor to irradiation, taking into account potential additional acute side effects and the risk of delay in radiotherapy [Level I for adult studies, III for pediatric population; Grade C].

It could include cisplatin given either in 21 days cycles or weekly schedules [Level III; Grade B].

**4. Maintenance treatment with IFN- $\beta$**  to be discussed in patients with loco-regionally-advanced disease and/or unfavourable response to induction chemotherapy [Level III; Grade B/C].

### **Medical therapy for progressive/refractory disease**

The experience on these patients is very limited. As a general principle, after poor response to initial first line chemotherapy, **concomitant chemoradiotherapy** should be used in case of locoregional disease. In the setting of refractory disease, whenever possible, patients should have the possibility to participate in an **experimental protocol**.

Analysis of prognostic factors, such as performance status, disease-free interval, and site of metastatic disease may help to select the chemotherapy regimen and to choose between single-

agent and combination chemotherapy or sometime palliative therapy. The chemotherapy agents which were shown to demonstrate antitumor activity in patients with highly advanced or metastatic NPC for both chemo-naïve and for those treated previously with platinum compounds include: 5FU, capecitabine, taxanes (paclitaxel, docetaxel), gemcitabine, methotrexate, bleomycin, ifosfamide, anthracyclines, irinotecan, pemetrexed and vinorelbine<sup>109–119</sup>. Objective response rates of up to 74% were reported when these agents were used in combinations, including a platinum compound in patients who had not received it earlier<sup>115–117</sup>. For patients who become refractory to cisplatin-based therapy, a second-line chemotherapy based on other chemotherapy agents provides an acceptable treatment option<sup>110,111,120</sup>.

**EBV specific cytotoxic T-cells** (EBV-CTLs) have been shown to have some anti-tumor activity in metastatic and/or recurrent NPC mainly in adults, although further data are needed for evaluation of efficacy, including in refractory situations<sup>121–124</sup> [Level III; Grade C].

The programmed cell death ligand 1 (PD-L1) expression is present in nearly all NPC tumors. High PD-L1 expression or co-expression of PD-L1 and programmed cell death protein 1 (PD-1) has been associated with worse disease-free survival in NPC<sup>125</sup>. **PD-1/PD-L1 checkpoint inhibitors** were reported to have potential benefit in recurrent and metastatic diseases in adult NPC (see after)<sup>126</sup> and could be also promising for refractory diseases, although there are no current studies in the pediatric population [Level III for adults studies, no data available in children; Grade C].

### **Medical therapy for metastatic disease at diagnosis (stage IVb)**

Distant metastases at diagnosis are rare (less than 10%). Outcomes of patients with metastatic disease are poor, with most historical studies reporting a 5-year overall survival of less than 25%, although a recent report from the COG ARAR0331 study showed a 5-year EFS of 57%<sup>2,23</sup>. Nevertheless, high chemosensitivity of NPC provides a rationale for the use of **systemic**

**therapy with the use of various potential chemotherapy agents** as listed in the upper section. In adults, Jin *et al.* have reported, through a retrospective review comparing five regimens for metastatic patients, that combinations of cisplatin, 5FU, gemcitabine and/or paclitaxel could be a reasonable option <sup>118</sup> [Level IV for adult studies; Grade C, no data available for children]. Zhang *et al.* conducted a randomized phase III trial showing the superiority of cisplatin + gemcitabine over cisplatin + 5FU <sup>119</sup> [Level IV for adult studies; Grade C, no data available for children]. No specific study has been conducted in children with metastatic NPC at diagnosis. However, in adult patients with metastatic NPC, who have a good performance status and who have achieved a good response to IC, an intense multimodal approach involving chemoradiotherapy to the primary tumor and local treatment (such as surgery, thermal ablation) to the site of oligo-metastases followed by maintenance therapy in selected cases may significantly prolong the outcome <sup>127–131</sup> [Level V; Grade C].

Again, the place for immunotherapy including **EBV-CTLs** and **immune checkpoint inhibitors** for metastatic patients has to be defined but could be promising. As an example, in a recent meta-analysis conducted by Masterson *et al.*, camrelizumab combined with chemotherapy achieved an objective response in 91% of patients in first-line treatment for patients with metastatic NPC, but with a high level of grade 3 and 4 toxicity <sup>126</sup>.

### ***Medical therapy for relapsed disease***

Local and regional failures are rare (around 7%) with contemporary protocols, in contrast with distant metastatic or combined relapses which represent the major pattern of failure <sup>3</sup>.

Relapses mainly occur within two years after the end of treatment and the interval between the end of primary therapy and the relapse is an important predictor of survival.

Outcomes are very poor for adult and pediatric patients with recurrent disease <sup>7,16</sup>. No standard second-line treatment is supported by literature, especially in children, and whenever

possible, patients should have the possibility to participate in an **experimental protocol**. Some data have shown long-term survivals after relapses in patients treated with intense **multimodal therapy**. DeRenzo *et al.* have proposed an oxaliplatin-containing regimen in combination with gemcitabine as a reasonable choice for first-line salvage therapy in a multicentric retrospective review of 14 pediatric patients <sup>132</sup> [Level IV; Grade C]. **Local excision of oligometastatic disease, thermal ablation of lung metastases and/or re-irradiation of metastatic sites** in selected cases should be discussed in a multidisciplinary team.

Clinical trials investigating molecularly targeted therapies or various immunotherapy approaches are options for patients who have progressed on chemotherapy. Among targeted therapies, the **VEGF inhibitors**, especially pazopanib and axitinib, have demonstrated promising clinical activity in phase II trials in adult patients with recurrent or metastatic NPC <sup>133,134</sup>. Disease control after treatment with axitinib was relatively durable and the grade 3 or 4 toxicities were uncommon, thus axitinib may be suitable for combination with immune checkpoint inhibitors <sup>134</sup>. To the contrary, several agents targeting the epidermal growth factor receptor (EGFR) have shown disappointing results <sup>135,136</sup> [Level V Grade C].

Therapies with **PD-1 inhibitors** – camrelizumab, pembrolizumab and nivolumab – have shown promising results in patients with heavily pretreated NPC <sup>137–140</sup>. Other clinical trials investigating anti-PD1 immune agents in patients with NPC are ongoing <sup>126</sup>. However, there are no current studies in the pediatric population [Level III for adults' studies, no data available in children, Grade C].

In recurrent NPC, as in metastatic NPC in adults, **EBV-CTLs** have been shown to have some anti-tumor activity <sup>121–123</sup> [Level III for adults' studies, no data available in children; Grade C].

Again, further data is needed for evaluation of safety and efficacy in children and therefore these treatments (EBV-CTLs and immune checkpoint inhibitors) have to be only delivered as part of a prospective protocol [no data available in children; Grade B].

**Medical therapy for high-risk tumors (refractory, relapsed or initially metastatic diseases)**

The experience on those patients is very limited and outcomes are poor.

Whenever possible, these patients should be offered to participate to an **experimental protocol** [Level V; Grade B].

**In case of progressive disease or relapse** following initial chemotherapy, concomitant chemoradiotherapy should be used in case of locoregional disease [Level I for adult studies, III for pediatric population; Grade C]; various regimens may be proposed, including gemcitabine or taxanes in case of distant metastasis [Level IV; Grade C].

Second-line chemotherapy for **relapsed tumors** may include oxaliplatin or taxanes (such docetaxel) and gemcitabine [Level IV; Grade C].

In the situation of **initially metastatic disease**, a multimodal strategy with initial chemotherapy (which could include cisplatin, 5FU, gemcitabine, paclitaxel or docetaxel), locoregional radiotherapy, focal treatment of metastatic sites and maintenance therapy with IFN- $\beta$  should be discussed [Level V; Grade B].

**Immune-based therapy** could be a promising treatment in case of high-risk tumors, with EBV specific cytotoxic T-cells (EBV-CTLs) with or without previous lymphodepleting regimen and/or PD-1/PD-L1 checkpoint inhibitors, but further data are needed for evaluation of efficacy and safety in children. These therapies should be considered in prospective controlled trials [Level III for adult studies, no data available in children; Grade B].

### c. Radiotherapy

- Radiotherapy is one of the cornerstones for the treatment of NPC which are usually radiosensitive tumors and intensity modulated radiotherapy (IMRT) technique should nowadays be used <sup>3</sup> [Level III; Grade A].
- In the rare case of stage I and for selected patients with N0 stage II, treatment could be exclusive radiotherapy [Level IV based on adult studies, no pediatric study; Grade B], while stages III-IV patients are treated with chemotherapy and radiotherapy various combinations [Level III; Grade A].

### Target volume definition

The Growth Target Volume 1 (GTV1) includes the primary nasopharyngeal carcinoma, retropharyngeal nodes, and gross nodal disease. The Growth Target Volume 2 (GTV2) is defined by the residual tumor (primary tumor or/and nodes) after neoadjuvant chemotherapy. The Clinical Target Volume 1 (CTV1) includes the GTV1 and the potential areas of microscopic spread of disease. It should include the entire nasopharynx, half (posterior) of nasal cavity, entire sphenoid sinus, posterior third of ethmoid sinuses, clivus, pterygoid fossae, parapharyngeal spaces, skull base, but also lymph nodal groups involved at diagnosis. The Clinical Target Volume 2 (CTV2) includes the GTV2 and a 3 to 5 mm margin. Prophylactic radiotherapy is usually recommended in levels Ib, II, III, IV, V, VII. The planning target volumes PTV is defined as the CTV with a margin of 3 to 5 mm [Level V; Grade A].

### **Total radiation dose**

No data exists on the optimal dose of radiotherapy in NPC. High cure rates are achieved with historical high doses (up to 65-70 Gy to the high-risk areas) but severe long-term effects including xerostomia, dental caries, growth abnormalities in younger children, hypothyroidism and secondary malignancies have been reported in many children<sup>7,16,25</sup>. Therefore, and taking into account the good prognosis for non-metastatic patients, adapted dosage protocols with dosage reduction after favorable tumor response (i.e. CR or VGPR) following initial chemotherapy have been developed in children and AYA and should be preferred<sup>4-7,16,21,23</sup> [Level III; Grade A].

Total dosage to the primary tumor should be between 54 Gy to 67 Gy depending on nodal status and response to therapy, with 1.8 Gy daily fractions [Level III; Grade B].

**Radiotherapy techniques**

Randomized studies in adults have reported a clear clinical benefit (in terms of survival and quality of life) for Image Guided Radiotherapy (IGRT) and Intensity Modulated Radiotherapy/Volumetric Modulated Arc Therapy (IMRT/VMAT) compared to 2D-conformal radiation therapy<sup>80,141,142</sup>. Several reports in childhood are also in favor of IGRT and IMRT/VMAT use for NPC treatment, considering the decrease of acute and late toxicities and a better survival<sup>3,143,144</sup>. Thus, these techniques should be recommended as a standard of care for NPC [Level II based on adult trials, IV based on pediatric literature; Grade A].

Little data is available about the potential benefit of proton therapy for NPC treatment (few studies in adults based on dosimetric data, no study in children), but it suggests similar tumor coverage with better sparing of critical organs<sup>145–148</sup>. Protons could be of interest and should be more investigated to evaluate the long-term benefit in term of late effects as these remain highly frequent and severe, especially after treatment in childhood and adolescence [Level V; Grade C].

**Radiotherapy**

**Image-Guided Radiotherapy (IGRT) with intensity modulated radiotherapy (IMRT/VMAT)** should be recommended as a standard of care for NPC [Level II based on adult trials, IV based on pediatric literature; Grade A].

**Adapted dosages protocols** with de-escalation after favorable tumor response following IC should be proposed [Level III; Grade A].

The optimal **dose** of radiotherapy in NPC has yet to be defined. Total dosage should be between 54 Gy to 67 Gy depending on nodal status and response to therapy, with 1.8 Gy daily fractions [Level III; Grade B].

If **proton therapy** could be of interest with a better sparing of critical organs, further data is needed to evaluate its long-term efficacy (in terms of survival and late effects) [Level V; Grade C].



## 4 GENETIC CONSIDERATION

Genetic counseling is not indicated for pediatric NPC, but this option may be discussed on an individual basis depending on family history and family preferences. There are no genetic predisposing syndromes and no excess risk for overall cancer that have been reported to date <sup>15,18</sup> [Level IV; Grade B].

**Genetic counselling** for patients with NPC is **not mandatory** and may be considered on an individual basis [Level IV; Grade B].

## 5 LONG TERM FOLLOW-UP RECOMMENDATIONS

Due to the possibility of frequent long-term toxicities in survivors of pediatric NPC, a strict follow-up more than 5 years is strongly advised. Baseline neuroendocrine testing and audiograms are useful for the assessment of late therapy-related effects. Periodic follow-up includes audiograms and renal studies after treatment with platinum compounds and regular monitoring of dental and endocrine functions following radiotherapy. Possible long-term effects include thyroid and pituitary dysfunctions; neck fibrosis, xerostomia, ototoxicity; dental caries and dental fragilities; odynophagia and development growth abnormalities of exposed areas <sup>16,22,80,81,144</sup> [Level IV; Grade A].

Radiation-induced secondary cancers have been reported, sometimes decades following therapy and thus require very long follow up of patients. The role of proton therapy in reducing long-term therapy-related effects is still unknown, and further prospective studies are needed <sup>7,16,21,22</sup> [Level V; Grade C].

A **long-term follow-up** is highly recommended, especially for **auditory symptoms, neuroendocrine functions, head and necks consequences** (fibrosis, xerostomia, dental impairment...), and potential secondary malignancies [Level IV; Grade A].

## 6 SPECIFIC CONSIDERATIONS FOR LHEAR COUNTRIES

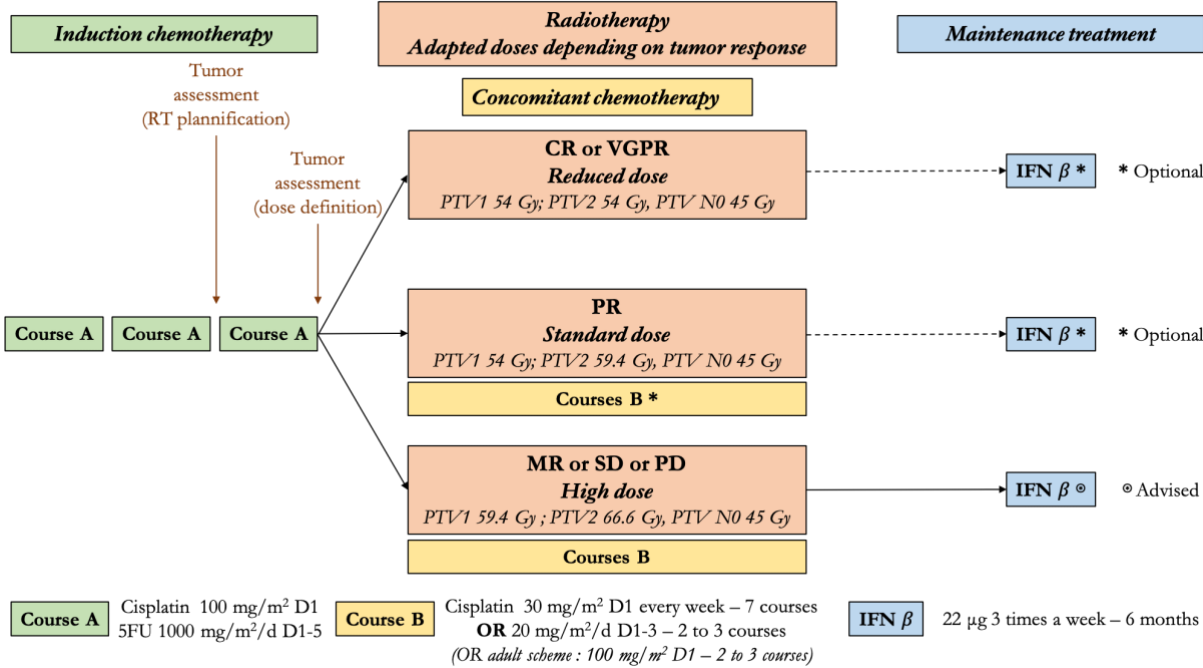
- If PET/CT is not available, initial tumor work up should include head and neck MRI, chest CT, and Technetium bone scan <sup>37</sup> [Level V; Grade C].
- If DPD deficiency testing is not available, initial 5FU doses administered should be reduced for first courses to test the tolerance <sup>47</sup> [Level V; Grade C].

## 7 MAIN OPEN QUESTIONS IN THE TREATMENT OF PEDIATRIC NPC

- Optimal definition of radiological tumor response criteria.
- Best dosage of loco-regional radiotherapy in case of favorable tumor response following IC.
- Role of proton therapy.
- Role and specific indications to maintenance with IFN- $\beta$  therapy.
- Treatment of patients with refractory disease, metastatic and relapsed tumors.
- Role of EBV- CTL and PD-1/PDL-1 checkpoint inhibitor treatment for primary metastatic, refractory or relapsed disease.
- Role of new targeted drugs for NPC patients.

### 8 NPC TREATMENT: THE PARTN-ER PROPOSAL

Even if many aspects of NPC treatment could not be fully supported by evidence-based medicine, the EXPeRT/PARTN-ER group proposes a possible overall strategy in order to help physician to treat patients. This therapeutic strategy should nevertheless be debated locally during multidisciplinary team discussion and adapted to level of proof discussed in this guidelines.



**Title:** Therapy summary proposed by the EXPeRT/PARTN-ER group.

**Abbreviations:** RT = radiotherapy, PTV = planning target volume (1 = before induction chemotherapy; 2 = tumor residue after induction chemotherapy; including invaded nodes at diagnosis), PTV N0 = prophylactic PTV for non-invaded nodes

**NB:** The proposal of dose de-escalation for RT is based on the French FRACTURE guidelines. Whenever possible, patients should be registered in an international specific registry in order to assess this question.

8.1 CHEMOTHERAPY REGIMENS

**Chemotherapy Course A**

Three courses A, every three weeks, are planned before radiotherapy.  
 Infusions will be delivered through a central venous access.



**Cisplatin 100 mg/m<sup>2</sup> over 6 h**

**5FU: 1000 mg/m<sup>2</sup>/d continuously over 5 days**

**1                    2                    3                    4                    5                    6                    days**

Day 1: Cisplatin IV 100 mg/m<sup>2</sup> over 6 hours with hydration

Days 1 to 5: 5-fluorouracil IV 1000 mg/m<sup>2</sup>/d in continuous infusion over 5 days

**Cisplatin:** 100 mg/m<sup>2</sup> = \_\_\_\_\_ mg over 6 hours (in 100 ml/m<sup>2</sup> of 0.9% NaCl)

**Pre- and concomitant hydration:** (starting 4 hours before, and during cisplatin infusion)

2000 ml/m<sup>2</sup>/16h = \_\_\_\_\_ ml

(2.5% Glucose / 0.45 % NaCl)

+ 20 mmol KCl / 1000 ml = \_\_\_\_\_ mmol

+ 10 mmol MgSO<sub>4</sub> / 1000 ml = \_\_\_\_\_ mmol

+ 12 g Mannitol / 1000 ml = \_\_\_\_\_ g

**Post-hydration:**

1750 ml/m<sup>2</sup>/14h = \_\_\_\_\_ ml

(2.5% Glucose / 0.45 % NaCl)

+ 20 mmol KCl / 1000 ml = \_\_\_\_\_ mmol

+ 10 mmol MgSO<sub>4</sub> / 1000 ml = \_\_\_\_\_ mmol

**5-Fluorouracil:** 1000 mg/m<sup>2</sup>/d = \_\_\_\_\_ mg/d in continuous infusion (in 0,9% NaCl protected from the natural light during infusion)

**Supportive care:**

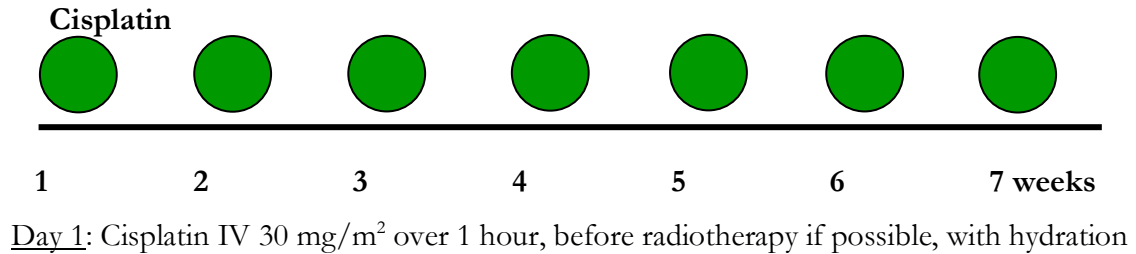
- If diuresis < 2/3 intake, give Mannitol 20% 40 ml/m<sup>2</sup>;
- Antiemetic drugs according to local habits.

**Adaptation:**

- Bi-weekly usual hematological monitoring;
- In case of severe mucositis (grade 3-4), shorten the infusion of 5FU over 4 days (1000 mg/m<sup>2</sup>/d over 4 days) in the following course of treatment. Pharmacokinetic monitoring can then be performed at H24, H48 and H72, and the adaptation modalities will be discussed with the center usual pharmacokinetic laboratory;
- Auditory monitoring by audiogram and interrogation (tinnitus, hearing loss) every 2 courses. In case of auditory toxicity  $\geq$  grade 2 of Brock, replace cisplatin with carboplatin over 1 hour (AUC = 6.6 mg/ml with pharmacokinetic, or 600 mg/m<sup>2</sup>);
- International guidelines before 5FU administration and in case of DPD deficiency should be strictly followed <sup>48</sup>.

## Chemotherapy Course B (option weekly)

The first course B starts at the beginning of radiotherapy, ideally at D21 of the third course A. Seven courses will be administered, every seven days.



**Cisplatin:** 30 mg/m<sup>2</sup> = \_\_\_\_\_ mg over 1 hour (in 20 ml/m<sup>2</sup> of 0.9% NaCl)

**Pre- and concomitant hydration:** (starting 1 hour before, and during cisplatin infusion)

2000 ml/m<sup>2</sup>/d over 2 hours = \_\_\_\_\_ ml

(2.5% Glucose / 0.45 % NaCl)

+ 20 mmol KCl / 1000ml = \_\_\_\_\_ mmol

+ 10 mmol MgSO<sub>4</sub> / 1000ml = \_\_\_\_\_ mmol

+ 12 g Mannitol / 1000ml = \_\_\_\_\_ g

**Post hydration:** (during 5 hours after cisplatin infusion)

2000 ml/m<sup>2</sup>/d over 5 hours = \_\_\_\_\_ ml

(2.5% Glucose / 0.45 % NaCl)

+ 20 mmol KCl / 1000ml = \_\_\_\_\_ mmol

+ 10 mmol MgSO<sub>4</sub> / 1000ml = \_\_\_\_\_ mmol

### Supportive care:

- If diuresis < 2/3 intake, give Mannitol 20% 40 ml/m<sup>2</sup>;
- Antiemetic drugs according to local habits.

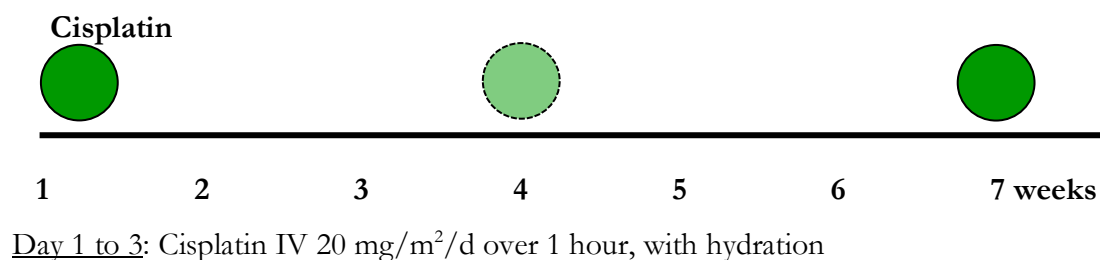
### Adaptation:

- Bi-weekly usual hematological monitoring;
- Auditory monitoring by audiogram and interrogation (tinnitus, hearing loss) every 2 courses. In the case of auditory toxicity ≥ grade 2 of Brock, replace cisplatin with carboplatin over 1 hour (AUC = 1.5 mg/ml equivalent of 100 mg/m<sup>2</sup>).

This cure can be done in outpatient basis if the digestive tolerance is good. If possible, administer cisplatin before the day's radiotherapy session.

### Chemotherapy Course B (option every 3 weeks)

The first course B starts at the beginning of radiotherapy, ideally at D21 of the third course A. Three courses will be administered, every 21 days. An alternative option is to deliver only 2 courses (in the first and last weeks of radiotherapy).



**Cisplatin:** 20 mg/m<sup>2</sup>/d = \_\_\_\_\_ mg/d over 1 hour (in 30 ml/m<sup>2</sup> of 0.9% NaCl)

**Pre- and concomitant hydration:** (starting 1 hour before, and during cisplatin infusion)

2000 ml/m<sup>2</sup>/16h = \_\_\_\_\_ ml

(2.5% Glucose / 0.45 % NaCl)

+ 20 mmol KCl / 1000 ml = \_\_\_\_\_ mmol

+ 10 mmol MgSO<sub>4</sub> / 1000 ml = \_\_\_\_\_ mmol

+ 12 g Mannitol / 1000 ml = \_\_\_\_\_ g

**Post-hydration:**

1750 ml/m<sup>2</sup>/14h = \_\_\_\_\_ ml

(2.5% Glucose / 0.45 % NaCl)

+ 20 mmol KCl / 1000 ml = \_\_\_\_\_ mmol

+ 10 mmol MgSO<sub>4</sub> / 1000 ml = \_\_\_\_\_ mmol

**Supportive care:**

- If diuresis < 2/3 intake, give Mannitol 20% 40 ml/m<sup>2</sup>;
- Antiemetic drugs according to local habits.

**Adaptation:**

- Bi-weekly usual hematological monitoring;

- Auditory monitoring by audiogram and interrogation (tinnitus, hearing loss) every 2 courses. In the case of auditory toxicity  $\geq$  grade 2 of Brock, replace cisplatin with carboplatin over 1 hour (AUC = 4 to 6.6 mg/ml equivalent of 400 to 600 mg/m<sup>2</sup>).

This cure can be done in outpatient basis if the digestive tolerance is good. If possible, administer cisplatin before the day's radiotherapy session.

The **adult scheme**, i.e. 3 courses of **Cisplatin 100 mg/m<sup>2</sup>/3 weeks**, can also be discussed. An adapted scheme for children and AYA who had received already 3 blocks of IC can be **2 blocks** of 100 mg/m<sup>2</sup> each.



## 8.2 INTERFERON THERAPY

Treatment with **Interferon Beta Rebif®** is the recommended recombinant interferon- $\beta$ -1a. It should be administered **subcutaneously 22  $\mu$ g (=  $6 \times 10^6$  IU), 3 times a week for 6 months.** However, during the first 3 weeks, this treatment is started at 50% of the dose i.e. 11  $\mu$ g (=  $3 \times 10^6$  IU), 3 times a week.

Premedication with Paracetamol is recommended to prevent influenza-like illness during at least first injections. Orally associated corticosteroids are contraindicated.

Rebif® is sold in easy-to-use pre-filled syringe: Rebif® 22, which contains 22  $\mu$ g per 0.5 ml.

In children <40 kg, discuss with the investigator a systematic dose reduction.

In case of poor clinical tolerance, despite Paracetamol, reduce the dose by 50% for 15 days then make an attempt to re-increase doses (if the side effect was not threatening).

Biological criteria for initiation:

- leukocytes >  $2 \times 10^9$ /L
- platelets >  $50 \times 10^9$ /L
- liver tests < 2xULN

Provide a blood test (ionogram - creatinine, NFS platelets and liver test) monthly.

8.3 RADIOTHERAPY

Radiation therapy will begin within 3-4 weeks after the third course A. The radiotherapy will be preceded by MRI evaluation post IC, after the third course to plan radiotherapy and to define the final doses. The radiation field will include the level of the nasopharynx and bilateral cervical ganglionic drainage areas (including initially pathological ones of course) in a systematic way and bilateral supraclavicular troughs. The total dose is dependent on the response to neoadjuvant chemotherapy:

- In case of CR or VGPR ( $\geq 80\%$  in 2 dimensions) after 3 courses A, the dosage to be delivered at the level of the cavum and at the cervical level will be reduce.
- In case of PR (volumetric reduction between 50-80%), the dose will be classical.
- Otherwise, in case of MR, SD or PD, the dose delivered at the level of the cavum and at the cervical level, will be high.

The recommended fractionation is as follows: 1.8 Gy per fraction, 5 days/7. The integrated boost is possible, but it is recommended to avoid doses per fraction  $>2$  Gy in this pediatric population.

The preferentially proposed technique will be a high compliance technique to reduce the doses of irradiation delivered to the salivary glands so as to avoid the hyposalia. Intensity radiotherapy modulation technics (classic, tomotherapy, arc therapy) are mandatory as the expected benefit in terms of salivary preservation and coverage of target volumes is major.

Oral dental restoration, if necessary, will be done before starting radiotherapy and even before chemotherapy if mouth opening allows. A gastrostomy/jejunostomy could be proposed before starting chemotherapy or radiotherapy according to the nutritional status of the patient.

<i>Cavum = T Lymph nodes = N</i>	<i>PTV2 Residual tumor following induction chemotherapy</i>	<i>PTV1 Macroscopic tumor and involved nodes prior to induction chemotherapy</i>	<i>PTV N0 Uninvolved nodal areas</i>
<u><b>Reduced dose:</b></u> <b>CR or VGPR</b> <b>&gt;80% (T and N)</b>	PTV T2 = 54.0 Gy (no boost) PTV N2 = 54.0 Gy (no boost)	PTV T1 = 54.0 Gy PTV N1 = 54.0 Gy	45.0 Gy
<u><b>Standard dose:</b></u> <b>PR</b> <b>[50-80%] (T or N)</b>	PTV T2 = 59.4 Gy (boost 5.4 Gy) PTV N2 = 59.4 Gy (boost 5.4 Gy)	PTV T1 = 54.0 Gy PTV N1 = 54.0 Gy	45.0 Gy
<u><b>High dose:</b></u> <b>MR (&lt;50%)</b> <b>or SD or PD</b>	PTV T2 = 66.6 Gy (boost 7.2 Gy) PTV N2 = 66.6 Gy (boost 12.6 Gy)	PTV T1 = 59.4 Gy PTV N1 = 54.0 Gy	45.0 Gy

Radiotherapy doses scheduled for patients with NPC according to response after IC  
*Abbreviations:* PTV, Planned tumor volume; Gy, grays.

## 8.4 EVALUATION OF THE RESPONSE TO INDUCTION CHEMOTHERAPY

The early radiological response will be done by comparing the pre-therapeutic examinations with those after 2 courses to allow early planning of the radiotherapy and will be repeated after the third course to define the final dose (which is the definitive point of reference for the response definition). The radiological response is defined by the response assessed at the nasopharynx primary. The radiological response is calculated by comparing the sums of the target tumor surfaces in the axial plane (primary lesion).

### **Very good response group:**

- Complete response (CR): no more measurable tissue mass at the primary site and no residual lymphadenopathy of small axis >1 cm.
- Very good partial response (VGPR): tumor reduction (cavum + lymphadenopathy) between 80 and 99% or isolated persistence of a thickening of the mucosa of the nasopharynx.

### **Partial response group:**

Partial response (PR): reduction of the overall tumor mass, i.e. cavum and lymph nodes between 50 and 80%.

### **Poor response group:**

- Minor response (MR): decrease of the overall tumor mass between 25 and 50%.
- Stable disease (SD): change of the overall tumor mass of  $\pm 25\%$ .
- Progressive disease (PD): tumor mass increase >25% and/or the appearance of distant metastases or new lymphadenopathies.

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