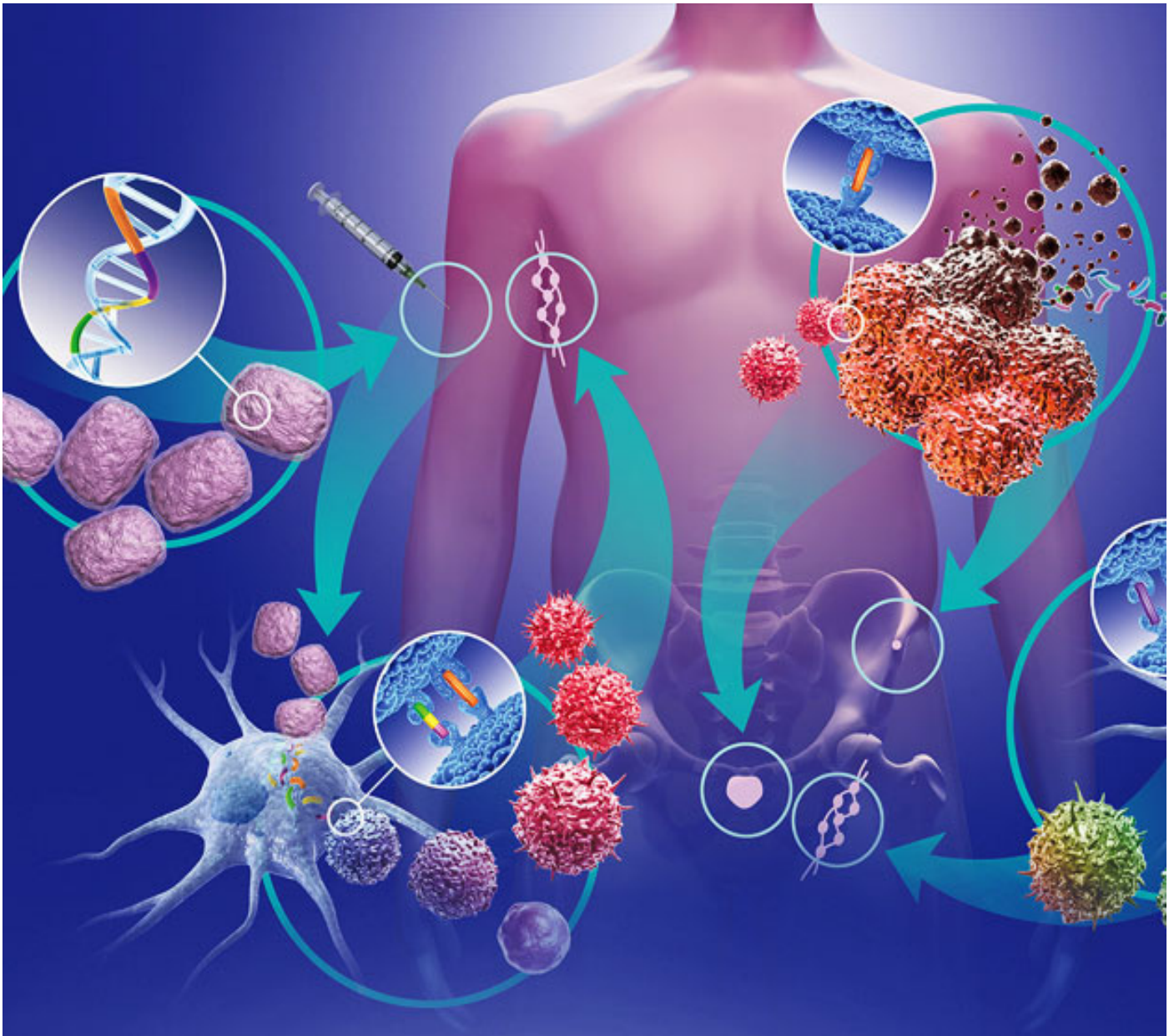

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Pediatric Nasopharyngeal Carcinoma

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Introduction

Nasopharyngeal Carcinoma (NPC) is very rare in children less than 10-years [1]. It constitutes to 1% of all pediatric malignancies and 35-50% of nasopharyngeal malignancies in children [2]. It usually arises from the Rosenmullar fossa of nasopharynx. NPC can invade the base of skull and commonly presents with bilateral cervical lymphadenopathy. Distant metastases are rare at presentation. NPC being chemo and radiosensitive tumor, both modalities are used currently in the management of these patients.

Biology and epidemiology

NPC originates from the surface epithelium. Three histologic subtypes are recognized by the World Health Organization (WHO) which include, Type I - keratinizing squamous cell carcinoma, Type II - nonkeratinizing squamous cell carcinoma, Type III - undifferentiated carcinoma. Undifferentiated Carcinoma is the most common histology seen in children developing NPC [3]. Pediatric NPC has an endemic distribution among well-defined ethnic groups (inhabitants in Southeast Asia Mediterranean basin & Alaskan Eskimos). It occurs rarely in the west [4]. NPC has a bimodal age of incidence with an early peak between 10 and 20 years and a second peak between 40 and 60 years. Pediatric Nasopharyngeal carcinoma resembles endemic NPC in adults with universal type-3 histology and Epstein - Barr Virus (EBV) positivity. Children with HLA A2Bsin2 haplotype has a higher risk of NPC.

Role of EBV in pathogenesis

EBV infection observed by expression of EBER RNAs has been shown in high-grade, pre-invasive lesions in the nasopharynx, but not in low-grade or histologically normal nasopharyngeal epithelium [5].Multiple genetic modifications have been reported in NPC, with regular deletion of chromosomes 3p, 9p, 11q, 13q, and 14q, and promoter of hypermethylation of particular chromosomes 3p (RASSF1A, RARβ2) and 9p genes (p16, p15, p14, DAP-kinase).Both 3p and 9p deletions have been reported in the absence of EBV infection in low-grade dysplastic lesions and in typical high-risk individuals with nasopharyngeal epithelium, indicating that these genetic events arise early in NPC pathogenesis and may predispose to subsequent EBV infection [6]. A stable EBV infection in the nasopharyngeal epithelium requires an altered undifferentiated cellular environment. Such an altered environment is predisposed by the occurrence of loss of heterozygosity in early NPC pathogenesis among patients with environmental exposures such as salted fish which result in low-grade pre-invasive lesion. These low-grade pre-invasive lesions become susceptible to EBV infection after additional genetic and epigenetic events. Once the cells have been infected, latent EBV genes provide growth and survival effects, resulting in the development of NPC.

Role of EBV detection in NPC

Real-time PCR is more sensitive in the detection of circulating, cell-free EBV DNA. Pretreatment concentration of EBV DNA correlates with tumor load of NPC [7]. It also helps in identifying patients with a higher chance of disease recurrence. Serial plasma EBV DNA analysis is also a useful tool for monitoring response to treatment and early detection of disease recurrence. Patients with rapid clearance of EBV DNA from the circulation had a better survival probability compared with a slower clearance. Also, post-treatment EBV DNA levels can predict NPC patients with a high chance of recurrence.

Histopathology of NPC

Nasopharyngeal carcinomas are malignant neoplasms arising from the nasopharyngeal mucosa showing histological, ultrastructural or immunophenotypic evidence of squamous differentiation and most are positive for EBV and a minority for HPV [8].

Gross description: Most common site is the nasopharyngeal recess (Fossa of Rosenmuller) or a metastatic cervical node(most commonly the Jugulo-diagastric group), most specimen are tiny endoscopic biopsies or needle cores without any specific findings. On resection specimen which is rare albeit the gross appearance is variable though and be an infiltrative mass or a nodule with surface ulceration or an occult primary invisible to the naked eye [8,9].

Microscopic description: WHO classification of histological subtypes of nasopharyngeal carcinoma.

Type 1: Keratinizing subtype: Morphologically is indistinguishable from keratinizing squamous cell carcinoma of other sites, with obvious features such as squamous pearls and intercellular bridges. Prominent desmoplastic reaction and mononuclear infiltrate is noted [8].

Compared to non-keratinizing carcinoma, the tumour is more commonly advanced(76% vs 55%), whereas has a lower propensity of lymph node metastasis(29% vs 70%), also worth noting is that keratinizing variants are less responsive to radiation and a worse prognosis compared to non-keratinizing counterparts [10,11].

Type 2A: Non-keratinizing, Differentiated subtype: Morphologically consists of interconnecting cords and trabeculae with little or no keratinization with cellular stratification and pavementing often with a plexiform growth pattern reminiscent of high grade urothelial carcinoma. The individual tumour cells are relatively smaller with fairly defined cellular borders with an inconspicuous nucleoli. The surrounding stroma shows variable lympho-plasmacytic infiltrate and little to no desmoplastic reaction[8].

Type 2B: Non-keratinizing, Undifferentiated subtype: This is the most common histological variant(>60%) with near consistent association with EBV. It is characterized by islands and sheets of large-undifferentiated tumour cells with indistinct cell borders, round to ovoid vesicular nuclei and large prominent nucleoli. Apoptosis and brisk mitotic activity is always noted but necrosis is hitherto rare. In around 12% of cases PAS positive amyloid globules are noted and can be intracytoplasmic, intercellular or stromal and be an aid in the diagnosis of nasopharyngeal carcinoma as it is practically never seen in other pathologies. A prominent peri and intratumoral lymphoplasmacytic infiltrate or non-caseating granulomas may be noted [8].

However subclassification into differentiated or undifferentiated subtypes has no bearing on the prognosis or treatment [8].

Type 3: Basaloid subtype: Least common histological variant, characterized by invasive lobular masses and festoons of ovoid basaloid cells with high N:C ratio, inconspicuous nucleoli, scant cytoplasm. Peripheral palisading and central comedo-type necrosis is common. EBV positivity is noted in high-risk ethnic & geographical groups [8].

Immunophenotype: The tumour cells are diffusely positive for p63, p40, and HMW-CK such as CK5/6, while are negative for EMA, CK7, CK20 & p16. Detection of EBV using EBER-ISH is highly specific and found in >90% of cases [8,12].

EBV-LMP1 & EBV PCR are less sensitive and reliable with a variable staining pattern and false positive results in view of EBV-Positive bystander lymphocytes [12].

Differential diagnosis: The closest mimics of nasopharyngeal carcinoma are poorly differentiated squamous cell carcinoma(p40 & p63 positive , while negative for CK5/6 & EBER-ISH), sinonasal undifferentiated carcinoma(p63 positive, CK7 positive, p40 & CK5/6 negative, EBER-ISH negative), extranodal NK/T cell lymphoma(p63/p40 negative, CD3/56 positive, EBER-ISH positive), malignant melanoma(p40 negative, SOX10/HMB45/melan A positive, EBER-ISH negative), INI1 deficient sinonasal carcinoma(p63 positive, INI1/SMACRCB1 loss, EBER-ISH negative), & NUT midline carcinoma(p40/p63 positive, NUTM1 positive, EBER-ISH negative) [8,12].

Assessment of post treatment biopsy: The need to distinguish between persistent tumor versus radiation induced atypia in non-neoplastic tissue: Post-radiation tumour cells show signs of injury in the form of nuclear enlargement, nuclear pleomorphism, nuclear hyperchromasia, but with a maintained N:C ratio. Presence of persistent carcinoma cells within 10 weeks of completion of radiotherapy does not necessarily mean disease persistence nor is it an indication for treatment escalation. A negative biopsy is defined as two consecutive negative biopsies atleast twelve weeks post-therapy. Radiation induced changes

in normal nasopharyngeal mucosa can mimic carcinoma characterized by nucleomegaly, bizarre hyperchromatic nuclei but these cells tend to occur singly amongst normal looking epithelial cells (random cellular atypia) with maintained N:C ratio and absence of mitotic activity. Radiation induced changes shoudn't persist beyond 12 months post-therapy and any uncertainties in the biopsy can be resolved by an EBER-ISH test with positivity favoring persistent carcinoma [8,13,14].

Another potential pitfall is the presence of atypical stromal fibroblasts which are large, ovoid with hyperchromatic smudged chromatin and persist for years post-therapy, these tend to occur singly and are consistently negative for cytokeratin and EBER-ISH [8,13,14].

Clinical features

Nasopharyngeal carcinoma commonly occurs in adolescent male children [15]. The most common presentation of NPC in children is unilateral or bilateral, bulky cervical lymphadenopathy (80%), although nose bleeds, nasal congestion, and obstruction may be the earliest manifestations of NPC which often remains unrecognized. NPC presents with locoregionally advanced disease, larger primaries, and higher nodal stage in children compared to adults. When the disease invades the base of skull it may lead to headache, cranial nerve palsy, and raised intracranial pressure. The lateral extension of the tumor may involve the eustachian tube resulting in otalgia, otitis media, and may spread along the parapharyngeal space into infra-temopral, pterygopalatine fossa. Involvement of temporomandibular joint may lead to trismus. Distant metastasis occurs rarely in NPC and involves Lungs, Bones and/or Liver. Table-1 shows the common differential diagnosis of a nasopharyngeal mass in children.

Table 1: Differential diagnosis of nasopharyngeal carcinoma in children.

Benign conditions	Mycobacterial Lymphadenopathy
	Infectious Mononucleosis
	Juvenile Angiofibroma
Malignant conditions	Lymphomas
	Parameningeal Rhabdomyosarcoma
	Nonrhabdomyomatous soft tissue sarcoma
	NUT carcinoma
	Esthesioneuroblastoma
	Rosai Dorfman disease

Diagnosis and evaluation

A typical clinical presentation of an adolescent with bulky cervical lymphadenopathy and a nasopharyngeal mass should raise a suspicion of nasopharyngeal carcinoma. Nasal endoscopy and biopsy of the mass or cervical nodal biopsy helps in confirming the diagnosis. Magnetic Resonance Imaging (MRI) of the head and neck up to supraclavicular fossa is the preferred local imaging modality. Computerized Tomography (CT) of the head may help in delineating the skull base erosion by the disease. Metastatic workup includes computerized tomography of the thorax to look for lung and mediastinal nodal spread and Bone scan to detect bony metastasis. Recently FDG PET-CT has been used by many pediatric co-operative groups for initial staging workup and response assessment in nasopharyngeal carcinoma. In a retrospective study of 18 pediatric NPC patients, a better concordance between magnetic resonance imaging and PET/CT in N staging than in T staging at diagnosis helps to detect metastasis and clarified ambiguous findings [16]. In the same study, among patients who achieved complete remission, FDG PET-CT showed disease clearance 3-6 months earlier than MRI.

Staging system

The 7th edition of American Joint Committee of Cancer (AJCC-2010) staging system is the commonly used classification for children with NPC [17] (Table-2). More than 90% of children and adolescents with nasopharyngeal carcinoma present with advanced disease (stage III/IV or T3/T4). Metastatic disease (stage IVC) at diagnosis is uncommon.

Table 2: The AJCC Staging system for pediatric nasopharyngeal carcinoma.

Variables	Definition
Primary Tumor (T)	
T1	Tumor confined to the nasopharynx or tumor extends to oropharynx and/or nasopharynx without parapharyngeal extension
T2	Tumor with parapharyngeal extension
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 infratemporal fossa/masticator space
Regional Lymph nodes (N)	
N1	Unilateral metastasis in cervical lymph node(s) ≤6cm in greatest dimension above supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymphnodes ≤6cm in greatest dimensions
N2	Bilateral metastasis in cervical lymphnodes ≤6cm in greatest dimension, above the supraclavicular fossa
N3	Metastasis in Lymph node(s) >6cm and/or to supraclavicular fossa
N3a	>6cm in dimension
N3b	Extension to the supraclavicular fossa
Metastasis (M)	
M0	No distant metastasis
M1	Distant Metastasis
Staging	
Stage I	T1N0
Stage II	T1N1, T2N0, T2N1
Stage III	T1N2,T2N2,T3N0,T3N1,T3N2
Stage IVA	T4N0, T4N1, T4N2
Stage IVB	Any T, N3
Stage IVC	Any T, Any N, M1

Treatment

Nasopharyngeal carcinomas being unresectable, radiotherapy and chemotherapy are the main modalities used in the treatment.

Radiotherapy

Nasopharyngeal carcinomas are highly radiosensitive and radiotherapy is considered to be the primary treatment modality [18]. Higher doses (>65Gy) are required for good loco-regional control. Regional lymph nodes in the entire head and neck, structures surrounding the nasopharynx, and the entire neck are included in the RT field. The traditional radiation plan consists of delivering a high dose (66 to 70Gy) on the primary tumor and involved lymph node areas and a prophylactic dose (45 to 50Gy) on uninvolved bilateral cervical lymph node areas including supraclavicular areas. Loco-regional and distant recurrence correlates with the size of the primary Tumor (T) and the Nodal (N) staging. Tumors of undifferentiated histology (WHO type III) are more radiosensitive, correlates with better outcome. Disease control rates with radiotherapy are stage dependent with Overall Survival (OS) of 65–85 % for patients with stage II and <50 % for patients with stage IV disease.

In a multicentre study NPC-2003-GPOH/DCOG [19] recruited 45 patients (8 years to 20 years) with nasopharyngeal cancer. 1 patient was stage II and 44 patients were staged as III/IV. The stage II patient received EBRT of 59.4Gy. Patients staged III/IV received 3 cycles of Neoadjuvant Chemotherapy (Cisplatin, 5FU, Folinic acid) followed by re-assessment. 5 patients achieved complete response with NACT and received an EBRT dose of 54Gy and remaining 40 patients received an EBRT dose of 59.4Gy. All the patients received concurrent Cisplatin as radio sensitizer. Interferon beta was prescribed for all patients. 43 patients achieved complete response after completion of the treatment. All patients tolerated the multimodality treatment well with superior outcomes.

A study by Ayan et al [20] concluded that the overall survival in Pediatric Nasopharyngeal Cancer(PNPCs) increased the 5 year survival upto 70-90%. A study by Pao et al [21] concluded that EBRT dose 55Gy-60Gy was sufficient for stage I/II to achieve a good disease control. 56 patients with PNPCs were evaluated by Serin et al [22] and concluded that radiotherapy alone increased the Locoregional tumor control rate and reduced the Locoregional tumor failure rate. They also concluded that the addition of chemotherapy reduced the systemic failure rates.

A single institution study from MSKCC [23] evaluated 33 patients with PNPCs (stage I-IV). 13 patients received EBRT (mean Radiation dose of 66Gy in both arms) alone and 20 patients received a Combined modality Treatment Of Chemoradiation (CTRT). They concluded that addition of chemotherapy to EBRT did not influence the Locoregional recurrence rates but had a significant influence on distant metastasis rates(84%vs 35% , $p < 0.01$) and improved 10 year overall survival rates (78%vs 33% , $p < 0.05$). The recommended EBRT dose is about 65Gy (Range 50Gy-75Gy) for patients above 10 years. For patients below 10 years usually a dose reduction of 5-10%(59.4 Gy) [24] is suggested.

Radiotherapy planning by Conformal Intensity Modulated Radiotherapy (IMRT) technique is preferred over the conventional 2 D or 3DCRT (3 dimensional Conformal Radiotherapy). IMRT technique helps in achieving a very good tumour control doses and at the same time decreases the dose received to normal structures significantly. A study by Guo et al [25] evaluated 90 patients of PNPCs to receive NACT followed by Radiotherapy by IMRT technique. The reported 4 year over all survival was 90.8%, Progression Free Survival (PFS) was 79.4%. The study also concluded that the use of IMRT in PNPCs resulted in lesser rates of Xerostomia, Neck fibrosis and hearing loss than conventional 2D/3DCRT techniques.

The Multicentre NPC-2003-GPOH study also recommends radiotherapy contouring volumes. The Gross Tumour Volume (GTV) includes the primary tumour region and metastatic lymph nodes. Clinical Target Volume (CTV)- High risk region is generated with a 1 cm margin to the GTV,CTV- intermediate risk) includes the entire nasopharynx, retropharyngeal lymph nodes, and jugular level II in stage I/II. For Patients in stage III/I the inclusion of jugular nodes level III, IV, V and supraclavicular region is suggested. The Planning Target Volume (PTV) is generated by giving a margin of about 5 mm to the CTV. It is recommended that Cone Beam Computed Tomography (CBCT) is done atleast every 5 fractions of EBRT to detect any errors in positioning of the patient.

Chemotherapy

With radiotherapy alone, relapses occur in many patients with advanced-stage disease. NPC being chemosensitive, generally, chemotherapy is used in the treatment of advanced-stage disease. Methotrexate, Bleomycin, 5-fluorouracil (5-FU), cisplatin (CDDP), carboplatin are agents with the best activity against NPC. Table-3 shows different chemotherapy regimens used in the treatment of nasopharyngeal carcinoma. CDDP containing combination regimens showed a clear advantage over non-CDDP containing regimens in adult studies. Chemotherapy during NPC treatment is commonly administered in 3 settings, 1.Neoadjuvant, 2.Concurrent, and 3.Adjuvant setting. Neoadjuvant chemotherapy induces immediate response resulting in symptom alleviation and allows more time for radiation planning. Concurrent Chemoradiation (CCR) with Cisplatin enhances radiation toxicity to NPC cells by inhibiting the repair of sublethal damage, reoxygenation, and recruitment of cells into a proliferative state, radiosensitization of hypoxic cells. Administration of cisplatin during radiation therapy has shown a survival advantage compared with radiation alone. A meta-analysis of studies involving adult locally advanced nasopharyngeal carcinoma found a 20% long term survival benefit with concurrent chemoradiation [26]. Neoadjuvant chemotherapy was also found to improve survival as it decreased distant and local relapses. However adjuvant chemotherapy has shown no survival benefit and it was associated with more toxicity and compliance issues. Most pediatric study groups incorporate neoadjuvant chemotherapy (Cisplatin and 5-FU) f/b concurrent chemo-RT (with single-agent Cisplatin). Current overall survival rates of pediatric nasopharyngeal carcinoma approach 80-90%.

Three major pediatric co-operative groups prospectively evaluated radiation dose reduction in locally advanced nasopharyngeal carcinoma in children based on response to induction chemotherapy. Three to four cycles of Cisplatin and 5-Fluorouracil Induction chemotherapy and Cisplatin-based concurrent chemoradiation was used in the management of locally advanced NPC. In the Italian Rare Tumor in Pediatric Age (TREP) Project [27] 60Gy was given T1 and T2a tumors and 65Gy to T2b T3,T4 primary. Involved nodes were given 65Gy and 45Gy to uninvolved nodes. Forty-six patients were enrolled over a 10year period with 45 patients with node involvement and 5 with distant metastasis. Objective Response to primary chemotherapy was noticed in 90%. The 5-year OS and PFS rates were 80.9% and 79.3% respectively. Distant metastases were associated with poor outcomes.

Table 3: Various chemotherapy regimens for NPC treatment in children.

Chemotherapy regimen	Drugs and Doses
PF	Cisplatin (100mg/m^2 on day-1 or 20mg/m^2 on day-1 to 5) + 5-Flurouracil (1gram/m^2 on day-1 to 5)
BEP	Bleomycin (15mg/m^2 IV bolus on day-1 and 12mg/m^2 on 24 hour infusion on day-1 to 5)+ Epirubicin (70mg/m^2 on day-1) + Cisplatin (100mg/m^2 on day-5)
MPF	Methotrexate (120mg/m^2 on day-1) + Cisplatin (100mg/m^2 on day-2) + 5 - Flurouracil (1gram/m^2 on day - 1 to 5)
PMB	Cisplatin (20mg/m^2 on day-1 to 5) + Methotrexate (50mg/m^2 on day -1,8 and 15) + Bleomycin (20U/m^2 on day-1,8 and 15)

Multicentric NPC-2003-GPOH study [28] used a strategy of radiation dose reduction in patients with Complete Response (CR) to induction chemotherapy with 45Gy to the nasopharynx and respective regional lymph nodes, including the whole jugular group and the supraclavicular region and a boost of 9Gy. Patients not achieving a CR post-induction chemotherapy were given 45Gy with a 14.4Gy boost. This study also incorporated 6-months of interferon-beta maintenance after completion of therapy. EBV positive nasopharyngeal carcinoma has impairment of T-cell immunity. Interferon-beta has an anti-tumor response by direct and indirect effects. Direct antitumor effects of Interferon-beta include antiproliferative, cytotoxic effects, and increased antigen expression by the tumor. Indirect effects include activation of macrophages &T-cells and anti-angiogenesis. Results of NPC-2003-GPOH is the best reported to date, with a median 30-month follow-up with EFS/OS of 92/97 %.

The recently concluded COG ARAR0331 study [29] evaluated the impact of Induction Chemotherapy (IC) and Concurrent Chemoradiotherapy (CCR) in locally advanced nasopharyngeal carcinoma (Stage IIb to IV). Patients with complete or partial response to induction chemotherapy received 61.2Gy to the nasopharynx and neck, and patients with stable disease received 71.2Gy. The 5-year event-free survival (EFS) and overall survival were 84% and 89%, respectively. The 5-year EFS for stages IIb, III, and IV were 100%, 83%, and 83%, respectively. The 5-year cumulative of local, distant, and combined relapse were 3.7%, 8.7%, and 1.8%, respectively. Although this study with Induction Chemotherapy and CCR resulted in excellent outcomes among locally advanced nasopharyngeal carcinoma in children, a trend toward decreased EFS was noticed for patients who received fewer doses of cisplatin during CCR. Thus an important observation among these recent studies is that for pediatric NPC patients with good response to induction chemotherapy, the radiation dose can be reduced to 55 to 60Gy without compromising local control rates [30].

Management of recurrent disease

Recurrence of nasopharyngeal carcinoma is usually associated with poor survival. Most recurrences occur within 1-2 years of diagnosis. Responses to taxanes and gemcitabine in recurrent nasopharyngeal carcinoma have been documented. Most salvage regimens incorporate agents in combination with carboplatin or oxaliplatin.

As a second line, adoptive transfer of EBV-specific cytotoxic T-cells has been utilized in clinical trials on recurrent NPC. EBV-specific cytotoxic T cells (EBV-CTLs) are safe and had antitumor activity in the relapsed setting. Locally relapsed did better compared to metastatic relapsed patients [31]. Ongoing trials utilize a combination of chemotherapy (Carboplatin and Docetaxel) and laboratory treated cytotoxic T cells in treating patients with refractory or relapsed EBV-Positive nasopharyngeal Carcinoma. Also, checkpoint inhibition with anti-PD1 antibodies (Pembrolizumab) has shown promising results in early clinical trials in recurrent NPC [32].

Late effects of NPC therapy

Radiation therapy remains the main reason for late sequelae among NPC patients. The most common long-term side effects are hypothyroidism, xerostomia, neck fibrosis, trismus, hearing loss, and growth hormone deficiency. Other long-term side effects include osteonecrosis, dental decay, esophageal stricture, cataract, vision loss, cranial nerve palsies, and second malignant neoplasms (Skin carcinoma, Salivary gland carcinoma, and Osteosarcoma) [33]. Cisplatin may result in renal tubulopathy. The use of IMRT instead of 2-dimensional conventional radiation therapy has proven to improve local control and reduce radiation-induced toxicities. Also reducing the radiation dose in good responders to induction chemotherapy may further reduce the long-term side effects. The use of proton radiation therapy may reduce the toxicity to the brain and skull base region without compromising disease control [34]. Survivors should be monitored for late effects by a multidisciplinary team.

Conclusion

Pediatric nasopharyngeal carcinoma is highly aggressive and presents with advanced stage. It is commonly associated with EBV and undifferentiated Carcinoma. Despite advanced presentation in children and adolescents, outcomes of NPC are superior compared to adults with multimodal treatment.

References

1. Ayan I, Kaytan E, Ayan N. Childhood nasopharyngeal carcinoma: From biology to treatment. Lancet Oncol. 2003; 4: 13-21.
2. Dourthe ME, Bolle S, Temam S, Jouin A, Claude L, et al. Childhood nasopharyngeal carcinoma: State-of-the-art, and questions for the future. Journal of pediatric hematology/oncology. 2018; 40: 85-92.
3. Sultan I, Casanova M, Ferrari A, Rihani R, Rodriguez-Galindo C. Differential features of nasopharyngeal carcinoma in children and adults: A SEER study. Pediatr Blood Cancer. 2010; 55: 279-284.
4. Yan Z, Xia L, Huang Y, Chen P, Jiang L, et al. Nasopharyngeal carcinoma in children and adolescents in an endemic area: A report of 185 cases. Int J Pediatr Otorhinolaryngol. 2013; 77: 1454-1460.
5. Young LS, Dawson CW. Epstein-Barr virus and nasopharyngeal carcinoma. Chin J Cancer. 2014; 33: 581-590.
6. Lo KW, Chung GTY, To KF. Deciphering the molecular genetic basis of NPC through molecular, cytogenetic, and epigenetic approaches. Semin Cancer Biol. 2012; 22: 79-86.
7. Leung SF, Zee B, Ma BB, Hui EP, Mo F, et al. Plasma Epstein-Barr

viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. Journal of clinical oncology. 2006; 24: 5414-5418.

8. Chan J K. Virus-associated neoplasms of the nasopharynx and sinonasal tract: Diagnostic problems. Modern pathology : An official journal of the United States and Canadian Academy of Pathology, Inc. 2017; 30: S68-S83.

9. Loh KS, Petersson F. Nonexophytic nasopharyngeal carcinoma: High frequency of advanced lymph node and distant metastasis. Otolaryngology--head and neck surgery: Official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011; 145: 594-598.

10. Neel HB. Nasopharyngeal carcinoma. Clinical presentation, diagnosis, treatment, and prognosis. Otolaryngologic clinics of North America. 1985; 18: 479-490.

11. Reddy SP, Raslan WF, Gooneratne S, Kathuria S, Marks JE. Prognostic significance of keratinization in nasopharyngeal carcinoma. American journal of otolaryngology. 1995; 16: 103-108.

12. Franchi A, Moroni M, Mass D, Paglierani M, Santucci M. Sinonasal undifferentiated carcinoma, nasopharyngeal-type undifferentiated carcinoma, and keratinizing and nonkeratinizing squamous cell carcinoma express different cytokeratin patterns. The American journal of surgical pathology. 2002; 26: 1597-1604.

13. Kwong DL, Nicholls J, Wei WI, Chua DT, Sham JS, et al. The time course of histologic remission after treatment of patients with nasopharyngeal carcinoma. Cancer. 1999; 85: 1446-1453.

14. Nicholls JM, ShamJ, Chan CW, Choy D. Radiation therapy for nasopharyngeal carcinoma: Histologic appearances and patterns of tumor regression. Human pathology. 1992; 23: 742-747.

15. Hu S, Xu X, Xu J, Xu Q, Liu S. Prognostic factors and long-term outcomes of nasopharyngeal carcinoma in children and adolescents. Pediatr Blood Cancer. 2013; 60: 1122-1127.

16. Cheuk DK, Sabin ND, Hossain M, Wozniak A, Naik M, et al. PET/CT for staging and follow-up of pediatric nasopharyngeal carcinoma. European journal of nuclear medicine and molecular imaging. 2012; 39: 1097-1106.

17. Casanova M, Ferrari A, Gandola L. Undifferentiated nasopharyngeal carcinoma in children and adolescents: comparison between staging systems. Ann Oncol Off J Eur Soc Med Oncol. 2001; 12: 1157-1162.

18. Chao KSC, Wippold FJ, Ozyigit G, Tran BN, Dempsey JF. Determination and delineation of nodal target volumes for head-and-neck cancer based on patterns of failure in patients receiving definitive and postoperative IMRT. Int J Radiat Oncol Biol Phys. 2002; 53: 1174-1184.

19. Buehrlen M, Zwaan CM, Granzen B, Lassay L, Deutz P, et al. Multimodal treatment, including interferon beta, of nasopharyngeal carcinoma in children and young adults: Preliminary results from the prospective, multicenter study NPC-2003-GPOH/DCOG. Cancer. 2012; 118: 4892-4900.

20. Ayan I, Kaytan E, Ayan N. Childhood nasopharyngeal carcinoma: From biology to treatment. Lancet Oncol. 2003; 4: 13-21.

21. Pao WJ, Hustu HO, Douglass EC, Beckford NS, Kun LE. Pediatric nasopharyngeal carcinoma: Long term follow-up of 29 patients. Int J Radiat Oncol Biol Phys. 1989; 17: 299-305.

22. Serin M, Erkal HS, Elhan AH, Cakmak A. Nasopharyngeal carcinoma in childhood and adolescence. Med Pediatr Oncol. 1998; 31: 498-505.

23. Wolden SL, Steinherz PG, Kraus DH, Zelefsky MJ, Pfister DG, et al. Improved long-term survival with combined modality therapy for pediatric nasopharynx cancer. Int J Radiat Oncol Biol Phys. 2000; 46: 859-864.

24. Ingersoll L, Woo SY, Donaldson S, Giesler J, Maor MH, et al. Nasopharyngeal carcinoma in the young: A combined M.D. Anderson and Stanford experience. Int J Radiat Oncol Biol Phys. 1990; 19: 881-887.

25. Guo Q, Cui X, Lin S, Lin J, Pan J. Locoregionally advanced nasopharyngeal carcinoma in childhood and adolescence: Analysis of 95 patients treated with combined chemotherapy and intensity-modulated radiotherapy. Head Neck. 2016; 38: E665-672.

26. Langendijk JA, Leemans CR, Buter J, Berkhof J, Slotman BJ. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: A meta-analysis of the published literature. J Clin Oncol Off J Am Soc Clin Oncol. 2004; 22: 4604-4612.

27. Casanova M, Bisogno G, Gandola L, Cecchetto G, Di Cataldo A, et al. A prospective protocol for nasopharyngeal carcinoma in children and adolescents: The Italian Rare Tumors in Pediatric Age (TREP) project. Cancer. 2012; 118: 2718-2725.

28. Buehrlen M, Zwaan CM, Granzen B, Lassay L, Deutz P, et al. Multimodal treatment, including interferon beta, of nasopharyngeal carcinoma in children and young adults: preliminary results from the prospective, multicenter study NPC-2003-GPOH/DCOG. Cancer. 2012; 118: 4892-4900.

29. Rodriguez-Galindo C, Krailo MD, Krasin MJ, Huang L, McCarville MB, et al. Treatment of childhood nasopharyngeal carcinoma with induction chemotherapy and concurrent chemoradiotherapy: results of the children's oncology group ARAR0331 study. Journal of Clinical Oncology. 2019; 37: 3369.

30. Orbach D, Brisse H, Helfre S, Klijanienko J, Bours D, et al. Radiation and chemotherapy combination for nasopharyngeal carcinoma in children: Radiotherapy dose adaptation after chemotherapy response to minimize late effects. Pediatric blood & cancer. 2008; 50: 849-853.

31. Louis CU, Straathof K, Bollard CM, Ennamuri S, Gerken C, et al. Adoptive transfer of EBV-specific T cells results in sustained clinical responses in patients with locoregional nasopharyngeal carcinoma. Journal of immunotherapy (Hagerstown, Md.: 1997). 2010; 33: 983-990.

32. Hsu C, Lee SH, Ejadi S, Even C, Cohen RB, et al. Safety and antitumor activity of pembrolizumab in patients with programmed death-ligand 1–positive nasopharyngeal carcinoma: results of the KEYNOTE-028 study. Journal of Clinical Oncology. 2017; 35: 4050-4056.

33. Sahai P, Mohanti BK, Sharma A, Thakar A, Bhasker S, et al. Clinical outcome and morbidity in pediatric patients with nasopharyngeal cancer treated with chemoradiotherapy. Pediatric blood & cancer. 2017; 64: 259-266.

34. Uezono H, Indelicato DJ, Rotondo RL, Sandler ES, Katzenstein HM, et al. Proton therapy following induction chemotherapy for pediatric and adolescent nasopharyngeal carcinoma. Pediatric blood & cancer. 2019; 66: e27990.