Childhood Nasopharyngeal Carcinoma (NPC): A Review of Clinical-Imaging Features and Recent Trends in Management

Mark Yoi Sun Soo*

Clinical Senior Lecturer and VMO Radiologist, Department of Radiology, Westmead Hospital Campus, Centre for Biomedical Imaging Research and Development (CBIRD), and University of Sydney, NSW, Australia 2145

Abstract: *Introduction*: Nasopharyngeal carcinoma (NPC) in children and adolescents is a relatively rare yet highly malignant disease. Clinical presentation of NPC in this age group is non-specific and varied leading to a predominantly late diagnosis. The objective of this paper is to explore and clarify the tumour's ambiguity and assess the precision of imaging in mapping its morphology and loco-regional extension and possible distant metastases. Treatment regimes that minimize adverse radio-therapeutic effects on surrounding structures will be highlighted.

Method: Retrospective analysis and observations of literature (in English) between 2004 to December 2017 was performed. A search was performed using the Medline data-base. The following are the search terms: "children", "nasopharyngeal carcinoma", "symptoms', "imaging" and "therapy".

Material: Of the 43 papers found on the primary search only 36 satisfied the search criteria. Four review papers of the primary search were retained as sources of reference. The core material comprised 22 papers on NPC's clinical presentation and the role of imaging in diagnosis and prognostication. There were three papers on advanced imaging in adults. The rest of the seven comprised selected articles on chemo-radiation, radiotherapy and related late toxicities.

Results: The clinical presentations range from nasal stuffiness, otalgia to unilateral or bilateral neck masses. Symptoms can last from a few weeks to 6 months; by then disease can be advanced. A WHO high-grade undifferentiated squamous cell carcinoma is the commonest lesion in clinical practice. Data from magnetic resonance imaging (MRI) focusing on tumour extensions and tumour volume are markers of long-term prognosis. Diffusion weighted MRI by assessing microscopic changes of NPC can determine the ultimate outlook of adults afflicted with NPC. Treatment of paediatric NPC consists of induction chemotherapy followed by radiotherapy with dosage up to 65-70 Gy.

Morphologically, the main mimicker of childhood NPC is an embryonic parameningeal rhabdomyosarcoma arising from the pharyngeal and nasal space. Both have inclination to invade the skull base.

Conclusion: Despite NPC's varied and nonspecific presentations, the clinician must be vigilant because treatment of the disease in different stages of severity has a higher response rate than its adult counterpart. Contrast MRI and computed tomography (CT) are precise in showing skull base invasion, loco-regional and distant metastases. The application of diffusion weighted MRI has a role in determining the tumour's microscopic contents and long-term prognosis. Use of intensity modulated radiation therapy (IMRT) in addition to induction chemotherapy and irradiation treatment regime has decreased the incidence of the dreaded late sequelae.

Keywords: Nasopharyngeal carcinoma, childhood, symptoms, Imaging, therapy.

1. INTRODUCTION

Childhood nasopharyngeal carcinoma (NPC) is an aggressive disease, characterised by a myriad of nonspecific presentations leading to late confirmation of its pathological identity. A singular feature of childhood NPC is its low incidence compared to adults particularly in the disease's moderately prevalent regions in the Mediterranean basin where countries like Egypt, Tunisia and Morocco are particularly affected [1]. Regions with the highest prevalence of NPC are in Guangdong province of South China including Hong Kong. Southeast Asian countries such as Vietnam, Indonesia, Brunei, Singapore and Malaysia are also among those with a high incidence [2]. But NPC among children in endemic countries is rare to the point where the lesion is clinically unsuspected [3]. The length of the symptoms can last between four weeks to a few months. By the latter instance the disease would be advanced [4].

The paradox of NPC in children and adolescents is that even if it was discovered at an advanced stage, its response to treatment excels that of adults [3, 5]. Thus, to make a firm diagnosis of NPC among young children and adolescents the clinician must be vigilant. Clinically mundane and vague symptoms must be viewed with a high index of suspicion because therapy for those at early stages yield excellent results in terms of overall survival (OS) and disease free survival (DFS) [3].

1.1. Clinical Features

Common but nonspecific symptoms such as nasal congestion/stuffiness, otalgia and ear discharge are described in numerous case series and reports [5-8].

*Address correspondence to this author at the Westmead Hospital, Cnr Darcy Road and Hawkesbury Road, Westmead NSW 2145, Australia; Tel: + 61 2 8890 6522; Fax: +61 2 9687 2109; E-mail: yoisunsoo@iprimus.com.au

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Sometimes with the tumour at an early stage and in a submucosal position, nasoendoscopy can be negative. In contrast, Noorizan *et al.* [6] found only adenoid enlargement leading to a late diagnosis. Trismus has been noted as a rare symptom in children of a young age [9]. Yet on occasions this complaint is a manifestation of an advanced stage NPC that has infiltrated the masticator muscle [10].

Contrarily, epistaxis is more alarming [7] that instigates further investigation [4]. Similarly, a unilateral middle ear infection suggests there is a blockage of the Eustachian tube by a tumorous process, be it a benign focal adenoid mass of the nasopharynx [11] or a more sinister condition. Stambuk *et al.* [7] have described bilateral or unilateral neck masses caused by upper cervical lymphadenopathy in all 11 cases in their series. It is an indicator of lymphatic spread of the tumour beyond the confines of the nasopharynx. But the most prognostically unfavourable sign is cranial nerve palsies caused by tumour invasion of the skull base. Stambuk *et al.* [7] believe that the nasopharynx is a confined space walled off by a strong nasopharyngeal fascia, causing spread of tumour through the clivus or petro-clival fissure. The cranial nerves (CN) that are commonly affected are the V^{th} and VI^{th} nerves [12]. They stated that patients with extensive CN palsy had a worse survival than those with only upper or lower CN involvement. More recently, Afqir *et al.* [13] quoted 15% of their cohort of 42 adolescent patients had CN deficit without commenting on its prognostic significance. Yet a unique feature of childhood NPC is the manifestation of a paraneoplastic syndrome comprising hypertrophic pulmonary osteopathy and a decrease in pituitary function [14]. However, Ng *et al.* [15] regard this syndrome as rare and not entirely specific for NPC. They described a 67-year-old man with documented NPC presenting with peripheral neuropathy of the lower limbs and bowel and urinary incontinence. These workers also quoted instances in which the syndrome occurred without a neoplasm.

In summary, the clinician's suspicion of childhood nasopharyngeal cancer is heightened when progressive nasal obstruction and unilateral otitis media persist for more than 3-4 weeks in spite of treatment; particularly accompanied by enlarged neck nodes. Nasopharyngeal endoscopy and / or fine needle aspiration biopsy of the enlarged nodes is the next stage of investigation.

1.2. Imaging Features

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are complementary in the diagnostic workup when a patient is suspected of harbouring NPC [7]. Although CT can depict the skull base more clearly, MRI is the preferred modality in showing the soft tissue structures due to its superior contrast resolution. Contrast enhanced MRI not only shows the extent of the tumour in the nasopharynx but also can confirm or exclude regional lymph-node metastasis to the upper neck, supraclavicular fossa and organs in the thorax [1, 4, 7, 8]. MRI has an unerring precision in delineating tumour extent and margins as illustrated by the work of Stambuk *et al.* [7]. Thus retropharyngeal nodal disease and the extent of tumour invasion of the masticator muscle are well depicted. In this regard, Zhang *et al.* [16], in treating a cohort of 163 patients, used masticator space involvement to grade their overall survival. Their data revealed those affected had poorer overall survival and distant metastasis-free survival than those not. Masticator muscle invasion is deemed a crucial prognostic marker.

Calculation of the gross tumour volume at the primary site of NPC is regarded as a significant prognostic factor in children. The cut-off value is at 54.5 mL; for those with tumour volume in excess of this figure their overall survival (OS) and effect free survival (EFS) status are less favourable [17]. Moreover, clear display of lesional spread to the parapharyngeal spaces and beyond is mandatory in tumour staging prior to planning of radiotherapy [17, 18]. The latter investigators have taken this concept further by demonstrating in detail the value of 18 F-FDG PET/CT. This imaging technique has the added advantage as an almost real-time detection of tumour metabolic activities that is lacking in MRI. Its only disadvantage is limitation in demonstrating the degree of skull base invasion since detecting metabolic activity of the skull base/brain interface is imprecise. By itself 18F-FDG PET/CT is not as often used in paediatrics, since preparation and setup of the procedure are rather involved. Nevertheless, it is the modality of choice in detecting loco-regional and distant metastases as well as clarification of crucial findings in which the patients' MRI features are ambiguous [19].

A spectrum of enhancement and signal intensities might typify NPC on MRI. Using a similar protocol Non Hodgkin Lymphoma (NHL) and the embryonic parameningeal rhabdomyosarcoma (RMS) can show

virtually identical findings. It has been argued that NHL of the head and neck enhances uniformly whereas a heterogeneous appearance favours NPC. Cho *et al.* [20] have observed the degree of contrast enhancement is more marked than that of NPC. Yet infiltration into deep structures such as the skull base is unlikely with NHL. Although reportedly infrequent, childhood B-cell lymphoma of Waldeyer's ring shares the same imaging features as NPC [21]. Lesions arising from Waldeyer's ring are symmetrically distributed whereas NPC is typically asymmetrical. Even at its early stage, B-cell lymphomas will invade the posterior nasal cavity and erode the hard palate and nasal septum [22]. Eighty per cent of childhood NHL are affected by predominantly painless cervical lymphadenopathy. Their T1W signal intensities are low to intermediate compared to neck muscles and high in T2W sequences, findings akin to those of NPC. Moreover, the pure bulk of the tumour without invasion of deep structures characterises NHL [20].

Childhood parameningeal rhabdomyosarcoma (RMS) is not as common as tumours of the NHL family. In head and neck RMS one of the commoner sites of origin is the nasopharynx. This malignant tumour affects younger children and is not usually associated with enlarged lymph nodes [1]. This is contrary to other researchers who regard bilateral cervical lymphadenopathy as part of the picture of RMS [23]. Moreover, the lesion's aggressiveness is exemplified by encasement of the cavernous internal carotid arteries and instances of tumour erosion of the entire middle cranial fossa have been observed. Surprisingly, metastasis to the brain is rare [23]. Contrast enhancement on MRI is variable: from strong and homogeneous to moderate heterogeneity, an indication of tumour cellularity, necrosis, and cavitations [23]. MRI findings are not conclusive in establishing a firm diagnosis of RMS.

Nonetheless, MRI has other positive applications in the assessment and prognostication of paediatric and adolescent NPC. In using diffusion MRI (DWI) to study 50 children, Youssef *et al.* [1] have shown there is invariable diffusion restriction in their group with NPC. The average apparent diffusion coefficient (ADC) value for undifferentiated carcinoma was 0.65×10^{-3} mm^2/sec and 0.8×10^{-3} mm^2/sec for squamous cell carcinoma. The diffusion restriction is caused by increased cellularity of the tumour. Thus, although the ADCs of nasopharyngeal carcinoma and lymphoma of the cavernous sinus region are decreased, the values are even lower in the latter group because of its greater cellularity [24]. Another application of DWI MRI is the use of ADC value in expressing NPC's response to treatment and ultimately prognosis [25]. One of the objectives is to observe a spectrum of microscopic components responsible for a raised ADC value in undifferentiated NPCs. Micro-necrosis, low cellularity and high stromal contents are mooted as causative factors [25]. A high ADC value is a likely marker of poor outcome compared with lesions with low values [25, 26].

1.3. Therapeutic Regimes

Chemotherapy and chemo radiation therapy are the main armaments in combating childhood NPC. Even in an earlier study by Haimi *et al.* [27] from Israel in 2005, they achieved an overall survival rate of 84% and EFS of 77% over a median follow up period of 6.15 years. Admittedly, their cohort of 13 patients with a median age of 14-years was small in numbers. Contrarily, Ozyar *et al.* [28] studied165 children and using a similar treatment protocol, their results of an actuarial five year overall survival (OS) of 77.4% had been encouraging. In multivariate analysis, they identified unfavourable factors as those over 14-years of age, male gender and a group of 21 who only received radiotherapy. A more recent study [29] of 30 children and adolescents with non-metastatic NPC treated with induction chemotherapy followed by radiotherapy showed a 5-year overall and event free survival rates of 77% and 63% respectively, figures regarded as favourable. They have also identified an Hb level of less than 11g and a prolonged radiotherapy course (>50 days) as factors that adversely affect overall survival. In regard to post treatment toxicities mucosities is the most frequent, amounting to 87%.

Casanova *et al.* [30] studied 46 children and adolescents who received three courses of induction chemotherapy followed by radiotherapy doses of 65 Gy with concomitant cisplatin. They achieved excellent results, with a 5-year overall survival of 80.9% and a progression free survival of 70.3%. In line with observations of others, they found the presence of distant metastases as the most significant prognostic indicator. Considering the high radiation dose given to these patients, they recorded a comprehensive list of sequelae ranging from xerostoma and hypothyroidism to hearing loss and growth hormone deficiency.

The use of intensity-modulated radiation therapy (IMRT) focuses on delivering a high dose of radiation to a target area with sparing of adjacent critical organs. The result is a reduction in the incidence of post

radiation toxicities. For this reason, the therapeutic regime advocated by Sahai *et al.* [31] had seen a gradual phase in of IMRT in eight of their 41 patients. Although the radiation dose had reached 70 Gy (in 36 fractions), the late sequelae were identical with other reports. There was one case of radiation myelitis. However, Liu *et al.* [3] found that in treating a subgroup of 58 patients (among a cohort of 158) with IMRT, there was a significant reduction of late toxicities such as trismus and xerostoma. A minor drawback of IMRT is a necessity for precision: patients are expected to remain very still during treatment. Presently, in view of the great awareness in prevention and minimisation of post radiation toxicities for children with head and neck malignancies, the advent of IMRT is a boon.

2. DISCUSSION

In analysing 699 paediatric patients with NPC (in comparison with 16,618 adults) Richards *et al.* [32] have reconfirmed the marked predominance of advanced disease (with WHO type III histopathology of 62.3% in children compared to 19% in adults). It followed that in comparison with adults, NPC-related mortality in paediatric patients was reduced by more than 60%. Before theorising NPC in childhood and adolescents is a different disease from that of adults, they pointed out that paediatric patients would more frequently undergo multi-agent chemotherapy and radiotherapy than adult patients. Thus aggressive therapeutic regime could have accounted for the paediatric patients' overall improved survival. One point worth stressing is that these affected children have come from families residing in rural areas with low income and socioeconomic standing and that they have more advanced disease.

Casanova *et al.* [30], Liu *et al.* [3] and Sahai *et al.* [31] have detailed the objectionable, remote effects of high dose radiations essential in treating disease that had spread beyond the boundaries of the nasopharynx into skull base, the pterygo-maxillary fissures, nasal cavities and orbits. In this context, the common late sequelae will include hypopituitarism (mainly growth hormone deficiency), cranial nerve palsies and mal development of the facial structures. One must be sensitive to the psyche of these children and adolescents who will carry a psychological burden in them in future years. It falls on the clinician to show them a genuine sense of compassion and encouragement.

In terms of its morphology and uncertainty in its exact incidence, paediatric head and neck parameningeal rhabdomyosarcoma (RMS) holds a special interest for the imaging specialists. Some writers have reported that RMS arising from the nasopharynx is rare [33, 34]. Lalya *et al.* [33] described one case and commented on the condition's rarity by quoting only three references dating from year 2000. Contrarily, eight of 42 cases on paediatric head and neck RMS have originated from the nasopharynx in one recent series [35]. Both childhood NPCs and their RMS counterparts share a mutual aggressiveness typified by rapid skull base invasion and concomitant V nerve involvement with invariable peri-neural spread through its V2 and V3 divisions [23]. A salient feature of parameningeal RMS is that cure rates for orbital disease is superior to those arising from other facial structures [34]. There is a limited place for surgery: only focal lesions that do not have leptomeningeal spread and invasion of vital organ and structures are suitable for excision [34, 35].

A criticism of this paper may stem from its reliance on selected articles and reviews on adult patients. This is because there are relatively fewer publications devoted to the younger patients. By extrapolating the data on NPC in adults, one can reasonably apply these concepts to the management of paediatric patients. A clear example is the work of Zhang *et al.* [25] and Law *et al.* [26] in which a high ADC value in the primary tumour was associated with poor response of treatment to local disease. In summing up sources from the literature, Law *et al.* [26] stated that the calculated ADC values could determine the macroscopic and microscopic contents of the offending tumour. A high ADC value corresponds to an increase in tumour stroma, an unfavourable prognostic factor. It has been proposed that stroma-rich NPC is associated with increased risk of relapse and poor outcome. Finally Law *et al.* [26] found an increased tumour volume was indicative of poor outcome at the primary site. They cited a mean volume of 24.6 mL, a figure well below the accepted threshold of 54.4 mL. Another trend in therapy for NPC in adults dwells on immunotherapy [36]. Since NPC is associated with Epstein-Barr virus infection with peritumoural immune infiltrates there is a corresponding increased lethality amongst those with advanced NPC. Briefly, one of the targets of immunotherapy is to increase tumour antigenicity and improve immunological memory and therefore an improvement in treatment outcomes. The basic strategies consist of (i) harnessing the patient's inherent ability to mount and direct an immune response against the NPC, and (ii) a second category consists of direct targeting of cancer cells. Besides,

prior treatment with chemotherapy and radiotherapy can induce immunologic cell death. Cytotoxic T lymphocytes and cytokine are some of the immune cells that target cancer cells. To sum up, one is optimistic because recent research and applications of modern chemo radiation and immunotherapy for adults will soon be available in paediatric practice.

CONCLUSION

Even in non-endemic regions the clinician's awareness of NPC should be raised. Induction chemotherapy followed by radiation treatment for children and adolescents with high-grade squamous cell carcinomas has very good outcome. Contrast enhanced and diffusion-weighted (DWI) MRI is precise in assessing lesional size and extent. Application of apparent diffusion restriction values (ADC) is invaluable in creating reliable prognostic markers.

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