Head and neck cancers in paediatric population including recent advances

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Καρκίνος της κεφαλής και του τραχήλου σε παιδιατρικούς ασθενείς. Νεώτερες εξελίξεις

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Review
Ανασκόπηση

SUMMARY: Addressing health issues in paediatric population poses a major challenge to health care providers due to lack of child's capability in expressing varied range of symptoms through which they undergo which may be of utmost diagnostic significance, thereby delaying early diagnosis. Unfortunately, Cancer is well known to be a common cause for increase in mortality rates in children. To achieve early diagnosis, careful attention to constellation symptoms portrayed by chid and/or parents suggestive of malignancy may aid in earlier diagnosis.

With no disparity between early and late diagnosed cases, treatment modalities such as radio/chemotherapy and surgeries poses risk of recurrence, short and long term effects due to chemo/ radiation. To overcome all the aforementioned facts, new perspectives like targeted immunotherapy and Proton beam therapy proves beneficial and prevents children from emotional and physical trauma and primarily, from peer pressure. Updating with common head and cancers and advances in treatment may facilitate health care professionals in early diagnosis thereby, preventing disease progression. This article briefs about commonly occuring head and neck tumors in paediatrics, latest updates, advancements and an overview of impact of Global pandemic on current oncology practices with special concern on outcomes to be faced post pandemic.

KEY WORDS: *Head and neck cancers, Lymphoma, TNM classification, Targeted therapy, Proton beam therapy and Covid-19*

ΠΕΡΙΛΗΨΗ: Η αντιμετώπιση θεμάτων υγείας στον παιδιατρικό πληθυσμό αποτελεί σημαντική πρόκληση για τους παρόχους υγειονομικής περίθαλψης λόγω της αδυναμίας των παιδιών να εκφράσουν τα συμπτώματα τους, πολλές υψηλής διαγνωστικής σημασίας, καθυστερώντας έτσι την έγκαιρη διάγνωση. Δυστυχώς, ο καρκίνος είναι γνωστό ότι είναι μια κοινή αιτία για την αύξηση των ποσοστών θνησιμότητας στα παιδιά. Για να επιτευχθεί έγκαιρη διάγνωση, η υψηλή κλινική υποψία για τα συμπτώματα που αναφέρονται από το παιδί και/ή τους γονείς και που υποδηλώνουν κακοήθεια μπορεί να βοηθήσει στην πρώιμη διάγνωση. Χωρίς σημαντική διαφορά μεταξύ των περιπτώσεων πρώιμης και όψιμης διάγνωσης, οι τρόποι θεραπείας όπως η ακτινοθεραπεία, η χημειοθεραπεία και οι χειρουργικές επεμβάσεις ενέχουν κίνδυνο υποτροπής, βραχυπρόθεσμων και μακροπρόθεσμων επιπτώσεων λόγω χημειοθεραπείας/ακτινοβολίας. Για να ξεπεραστούν όλα τα προαναφερθέντα, νέες προοπτικές όπως η στοχευμένη ανοσοθεραπεία και η θεραπεία δέσμης πρωτονίων αποδεικνύονται ευεργετικές και ελαττώνουν το συναισθηματικό και σωματικό τραύμα στα παιδιά, μέρος του οποίου οφείλεται και στους συνομηλίκους/συμμαθητές τους. Η ενημέρωση για τους συχνότερους καρκίνους της κεφαλής στα παιδιά και οι πρόοδοι στη θεραπεία μπορεί να διευκολύνουν τους επαγγελματίες υγείας στην έγκαιρη διάγνωση και θεραπεία, αποτρέποντας έτσι την εξέλιξη της νόσου. Αυτό το άρθρο συνοψίζει τη βιβλιογραφία σχετικά με τους συνήθεις όγκους κεφαλής και τραχήλου στην παιδιατρική και τις τελευταίες εξελίξεις. Επιπλέον γίνεται μια επισκόπηση του αντίκτυπου της παγκόσμιας πανδημίας στις τρέχουσες ογκολογικές πρακτικές με ιδιαίτερη μνεία στα αποτελέσματα που πρέπει να αντιμετωπίσουμε μετά την πανδημία.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Καρκίνος κεφαλής και τραχήλου, λέμφωμα, ταξινόμηση TNM, Στοχευμένη θεραπεία, θεραπεία δέσμης πρωτονίων, Covid-19*

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INTRODUCTION

Child, one of the God's benevolent creation who is not just a miniature but a dynamic organism undergoing constant physical and emotional changes (1). In children, cancer tops the list of mortality rates especially in age group who are less than fourteen years (2). To achieve early diagnosis in paediatric cancers, careful attention to signs or symptoms what child / parents mention, is of utmost important (3). Failure in recognizing constellation of signs and symptoms portrayed by chid or parents suggestive of malignancy may cause diagnostic delay, disease progression, intense therapies, secondary malignancies, parental anger and importantly, disappointment with medical provider. Table 1 gives us an overview of common clinical presentations which has been missed out resulting in delay in diagnosis (4). Few factors related to diagnostic delay are as follows: child's age during diagnosis, parents education status, cancer type and presentation of symptoms (5). Though, it is not feasible to follow a diagnostic protocol for each and every complaint, certain clinical presentations require definite evaluation because of risk of malignancy (4). Often, paediatric tumors are confused with non – neoplastic head and neck masses such as congenital malformations, haemangiomas, lymphangiomas, vascular malformations, inflammation and infections, thus further complicating diagnosis (6). However, aquisition of scientific knowledge and update with recent advancements not only make diagnosis easier, but also enables in providing quality care to child, saves time, money and child from emotional trauma (1). Paediatic head and neck cancers commonly occurs in age group between 10 and 19. Of note, Incidence rates were found to increase in girls between age group of 10 and 14 years, whereas in boys, 0 and 9 years is the most commonly affect age group (7). Cancer incidence rates were found to increase, whereas death rates were found to harbour a decline in trends during the past few decades. 5-year relative survival rate improved from 58% to 84% through 2015 for children (8). Lymphomas were the most common malignancy in paediatrics followed by rhabdomyosarcoma and then the nasopharyngeal carcinoma. Of the lymphomas, non-Hodgkin's lymphoma is predominant. Other malignancies like thyroid carcinoma and mucoepidermoid carcinoma were found to occur less frequently (9).

LYMPHOMA:

Neoplasm of the reticuloendothelial system affecting either lymphocytes or histiocytes in varying degrees of differentiation exhibiting varied clinical presentations, being multicentric in nature, diffuse or nodular and regional or generalized (10).

NON-HODGKIN'S LYMPHOMA:

One of the most common lymphoma in males with increase in incidence rate as age progresses. Abdomen is the most commonly affected site. Based on tumor aggressiveness, it is sub-classified into the following grades, i.e., low, high and intermediate (11). Classification of lymphoma aids clinicians not only in diagnosis, better treatment planning and staging but also renders a significant prognostic value. Revised European American Lymphoma (REAL)/ World Health Organization (WHO) Classifies Lymphoma (2001) based on the type of each cell lineage and its specific morphology, in which, B-cell neoplasms were sub-classified into two groups, namely, Precursor B-cell neoplasm and Peripheral B-cell neoplasms. Similarly, T-cell and putative Natural killer-cell neoplasms were sub-divided into Precursor T-cell neoplasm and Peripheral T-cell and NK-cell neoplasms (10). Murphy and Ann arbor staging schema stages lymphoma based on the number of lymph nodes or single extranodal organ or site involved (12). French-American-British/LMB system is specifically designed for classification of B-cell non-hodgkin lymphoma (13).

BURKITTS LYMPHOMA:

An uncommon, fast growing, aggressive B- cell lymphoma affecting children often involves body parts other than the lymph nodes. It is often curable and comprises of 2 varieties: Sporadic and Endemic. Endemic, as the name suggests, with high incidence in equatorial Africa named endemic Burkitt's lymphoma, whereas sporadic occurs in other regions of the world. Endemic cases are 95% related to Epstein Barr Virus (EBV), highly involves jaw bones, a distinct characteristic that is not found in sporadic. On the contrary, sporadic were not found to be strongly linked with EBV, involves bone marrow rather than jaws. Histopathologically, tumors cells are characterized by the presence of monomorphic cells. Tumor cells are usually medium – sized with well-defined round nuclei and multiple nucleoli. Cytoplasm is basophilic, thereby giving tumor cells, an appearance of small non – cleaved cells scattered around the germinal centers of each of the secondary lymphoid follicles. Ingestion of apoptotic tumor cells by macrophages imparts a pathognomic histologic feature of 'Starry sky pattern' appearance' (1).

DIAGNOSIS: Incisional biopsy of the affected lymph node along with histopathologic analysis were more accurate than Fine Needle Aspiration Biopsy (FNAC). Fresh biopsies were preferred for Immunohistochemistry (IHC) and flow cytometry (11). Radiologic techniques such as Computed Tomography and Magnetic Resonance Imaging studies are commonly used for staging of tumors. Radionucleotide bone scans are usually indicated only in cases wherein a bone involvement or metastasis comes arises a suspicion (13). Advanced techniques, which mainly evolves around the principle of perfusion and spectral imaging Computed Tomography,

Table 1: Common clinical presentations often mis-diagnosed[4]

Persistent presentation	Mis-diagnosed as	Common final diagnosis
Constitutional symptoms	Viral infection	Lymphoma
Respiratory symptoms	Sinusitis, Pneumonia	Lymphoma
Abdominal pain	Constipation	Burkitt's Lymphoma
Enlarged single node	Reactive nodes	Lymphoma, other solid tumors
Cervical adenopathy	Viral illness	Lymphoma

Table 2: French-American-British/LMB staging schema for b-cell non-hodgkin lymphoma

Stratum	Disease manifestation
A	Resected stage I & stage II
B	Multiple extra-abdominal site Non-resected stage I, II, III and IV (< 25% marrow blasts, no CNS involvement)
C	Mature B- cell ALL (>25% blasts in marrow) and /or CNS disease)

Abbreviations: ALL, Acute Lymphoblastic Leukemia: FAB, French-American-British; LMB, Lymphoma Malignancy B-cell13

enables clinicians in assessment of properties of tumor by not only just characterizing its size but also serves as a valuable tool in development of precise functional images. With specific consideration to MRI techniques, which works on the ideas of perfusion, elastography , diffusion-weighted and spectroscopy, facilitates investigation of tumor, metabolism and its functions (14). ^{99m}Tc bone scintigraphy or PET scans which uses 18F-fluoro-deoxyglucose as a marker is useful in cases of skeletal metastases, staging and response (15).

TREATMENT: Rituximab, a specific antibody which targets antigen CD20 and R-CHOP regimen which is inclusive of Rituximab, Cycophosphamide, Doxorubicin, Vincristine and Prednisone forms the frontliner in treatment. EPOCH-R which include drugs namely, Cyclophosphamide, Etoposide, Prednisone, Vincristine, Doxorubicin and Rituximab also support the treatment protocol (13). Immunomodulators including thalidomide and lenalidomide with impressive antitumor effect have shown promising outcomes (16). Vorinostat, first FDA approved Histone deacetylase inhibitors were found to yield an enormous and profound outcomes in the lines of treatment planning and prognosis in groups of cutaneous T-cell lymphoma (17). Blockade of intracellular signalling by temsirolimus (mTOR inhibitor), enzastaurin, a protein kinase C beta inhibitor and bortezomib, a proteasome inhibitor, is also under study18. Bortezomib, another FDA approved drug which works by the mechanism of proteasome inhibition were found to exhibit promising effects in tumor groups of mantle cell lymphoma. Targeted therapies which were under investigation are as follows: Sorafenib (Nexavar®), a multi-kinase inhibitor targeting kinases followed by Pazopanib, axitinib and tivozanib (VEGF-R inhibitors) and quizartinib and crenolanib [fms-like tyrosine kinase receptor (FLT3)] inhibitors (18).

HODGKIN'S DISEASE:

Hodgkin's disease, as the name suggests, came into literature manuscript in the year 1832 by Thomas Hodgkin (10). It is common in males and have a bimodal distribution in adolescence and adulthood. Asymptomatic cervical adenopathy with or without accompanying symptoms such as pyrexia and night sweats is one of the early manifestation (11). It commonly affects lymph nodes of cervical area, axilla, inguinal regions and waldeyer ring. Involved nodes are firm, rubbery in consistency and the overlying skin tends to be normal. Based on prominent histopathologic feature, it is classified as follows: Nodular sclerosis, Mixed, Lymphocyte-depleted, Lymphocyte-

rich and Nodular lymphocyte-predominant Hodgkin's disease (12).

DIAGNOSIS: Lymph node biopsy is effective since FNAC exhibits low diagnostic yield (11). Staging is important for planning treatment, estimating prognosis and confirmation of working diagnosis. A detailed and comprehensive case history taking and assessment, followed by physical examination, radiographic techniques and hematologic laboratory tests may aid clinicians in arriving out a definite provisional diagnosis. Nowadays, determining the site and extent of involvement of disease progression using PET scans is becoming a gold-standard protocol in tumor management. Invasive surgeries such as exploratory laparotomy is mandatory to be carried out only if the determined surgery would have an serious impact on the outcomes of tumor staging, prognosis and treatment planning (19).

TREATMENT: BEACOPP and ABVD Chemotherpy regimens forms the main course of treatment. Salvage chemo regimens, such as ICE, DHAP, ESHAP and GVD also have proven beneficial. Targeted therapy such as Pembrolizumab, Nivolumab and Brentuximab Vedotin were found to improve outcomes in relapsed/refractory (R/R) cases and increase Complete Response Rate (CRR) on pretransplant FDG PET, a strong predictor of post transplant outcome (20). Nivolumab's adverse reactions were in the form of autoimmune effect and Pembrolizumab's adverse effects were pneumonitis and thyroid disorder. Recently developed newer biological agents in management of lymphoma are yet to yield fruitful outcomes in near future (21). CD123 antigen were found to exhibit high therapeutic inheritance capacity in a preclinical in vivo model of Hodgkin lymphoma which targets CAR T cells.i.e., autologous T cells. AFM13, targets natural killer cells by binding of CD16A on natural killer cells, thereby results in activation of natural killer cells, its subsequent termination and tumor cell lysis. Lenalidomide, everolimus (mTOR inhibitors), Panobinostat (pan-deacetylase inhibitor) integration into ancient lines of therapy will cause relapse or facilitate durable remission is yet to be evaluated. One of the most recent modification from the basic model of Involved Field technique to Involved Site Radiotherapy technique were found to lessen the adverse effects of conventional radiotherapy in which the radiotherapy field size is drastically minimized, hence targeting only the the defined pretreatment dimension of involved tumor sites (22).

RHABDOMYOSARCOMA:

Rhabdomyosarcoma is one of the malignant tumor of striated muscle in children (10). It exhibits itself as a discrete and asymptomatic mass or swelling affecting orbital region followed by localized and/or generalized regions of oral cavity and pharynx. It is much more common in age groups younger than 5 years and between 10 and 18 years (11). Four forms of rhabdomyosarcoma are: Pleomorphic, Alveolar, Embryonal and Botryoid

Embryonal: It is commonly occurring sub-type in children and have marked predilection for head and neck. Histopathologic features shows tumors cells with characteristic eosinophilia. The tumor cells are of spindle shaped, arranged in the arbitrary pattern of interlacing fascicles and/or bundles. Few tumor cells were also found to be round in shape and large and/ or intermediate in size. Occasionally, cells with small-sized nucleus and a more coarse and granular cytoplasm, were found to be interspersed in the background of other tumor cells.

Pleomorphic: This spindle cell neoplasm constitutes mainly of tumor cells arranged in a haphazard fashion. Large distinctive bizarre cells with nuclei placed towards its expanded end gives a typical 'racquet' shape whereas 'strap' shaped cells show evidence of cytoplasmic vacuoles with processes of streaming cytoplasm.

Alveolar: A sub-type with harbouring worse prognosis consists of poorly differentiated round cell clusters separated by fibrous septa. Center compartment of the cellular clusters lack cohesion, while peripheral cells will be evident in the form of a monolayer adhering to the septal walls.

Botyroid: This sub-type demonstrates myxoid matrix with minimal ratio of scattered primitive mesenchymal cells. A hallmark feature of 'cambium layer' i.e., peripheral zone of increased cellularity is usually found. Regardless of the histologic subtypes, special stains like trichrome stains differentiates rhabdomyosarcoma from other neoplasm, however, histopathologic analysis forms the gold standard diagnostic method (10,23).

TREATMENT: Surgical excision of the tumor is the main stay of treatment. Resection needs to be combined with radiotherapy / chemotherapy in residual disease (11). Main chemotherapy regimens include IVA and VAC. TABLE 3 illustrates some of the molecular targeted drugs useful in rhabdomyosarcoma. Lipid-prostamine-siRNA nanoparticles targeting one of the fusion protein PAX-FOXO1 expressed in rhabdomyosarcoma inhibits the formation of fusion transcript, thereby, decreasing the proliferation of tumor. Entinostat, a class-I HDAC, inhibits formation of PAX3-FOXO1. Due to the mechanism of Entinostat induced sensitization to chemotherapy, PAX3-FOXO1 mRNA undergoes destabilization (vitro/vivo), thereby favouring PAX-FOXO1 as a potential therapeutic target (24). ^{99m}Tc bone scintigraphy have significant prognostic value in evaluation of distant/ skeletal metastases and tumor staging (15).

NASPHARYNGEAL CARCINOMA:

This head and neck tumor has its origin from the nasopharyneal epithelial cells. Its incidence rates exhibits a bimodal pattern with one peak affecting much more

Table 3: Molecular targeted drugs in Rhabdomyosarcoma

Treatment	Target molecule
Pazopanib	PDGF-α, VEGF-1, 2, 3, c-kit
Bevacizumab	VEGF
Sorafenib	VEGF-2,3, PDGFR-β, FLT3, and c-KIT
Crizotinib	MET, ALK, ROS1 and RON
Temsirolimus	mTOR
Cixutumumab	IGF-1R

ALK, anaplastic lymphoma kinase;ROS1,ROSproto-oncogene1receptor tyrosine kinase; RON, Recepteur d'Origine Nantais; IGF-1R, insulin-like growth factor 1 receptor15

young adolescent age group whereas another affecting the mid-50s. It is found to have a high incidence in Southeast Asia and has been associated with environmental agents such as intake of specific herbs, fishes and smoking (25). Epstein Barr Virus (EBV) elevated titer values were found to be associated with extensive disease. It presents with features of epistaxis, nasal obstruction and auditory dysfunction including, a diminuition in hearing capacity and tinnitus, a characteristic feature of Eustachian tube dysfunction which occurs due to the spread of the lesion into the paranasopharyngeal space. Another common finding is fifth and sixth cranial nerve palsies which arises as a result of tumoral cells spread in an upward direction resulting in erosion of skull base. Other symptoms include headache, diplopia, facial numbness and enlarged lymph nodes. Since ear and nose related sign and symptoms are vague, non-specific and often neglected at an earlier stage, majority of NPCs are often diagnosed during its late stage (11).
DIAGNOSIS: Direct visvualization and examination of nasopharyngeal space for nasopharyngeal tumor is mandatory. MRI of skull base is preferred over CT, since it clearly delineates the extent of invasion of primary tumor infiltration into the deeper structures. NPCs fall into three categories as per WHO classification modified by Kruger and Wustrow: Squamous cell carcinoma followed by Non-keratinizing tumors without and/or with presence of lymphoid stroma and Undifferentiated types. Staging and grading of nasopharyngeal carcinomas are based on gold-standard TNM-classification (25). If suspicion of bone metastasis arises, a bone scan will usually suffice. Polymerase chain reaction to determine the viral loads of EBV and anti-EBV-IgA, MRI and PET not only aids us in monitoring therapeutic response to treatment protocol and also, requires mandatory repeatation after every neoadjuvant chemo and/or radiation therapy. Changes in the uptake of 18F-FDG by tumoral lesional cells during the ongoing course of therapies have found to significantly affect prognostic value.
TREATMENT: Surgery and radiotherapy forms the main course of treatment. Non-keratinizing sub-types are sensitive to both radiotherapy and chemotherapy. Those tumors at an earlier stages are usually treated with radiotherapy while concomitant chemoradiation is standard for advanced tumors. Intense Modulated Radiotherapy (IMRT) along with concomitant chemotherapy have improved outcome. Nasopharyngeal cancer is sensitive to cisplatin-based regimens. Induction chemotherapy combines cisplatin, 5-FU, and epirubicin with or without bleomycin. Recurrence might be cured with re-irradiation or salvage surgery; in most patients palliative platinum-based polychemotherapy is the treatment. Bone metastases should be irradiated (26). Late complications including xerostomia, ototoxicity, fibrosis, osteoradionecrosis, necrosis and destruction of regions of temporal lobe, bulbar palsy, hypogonadism (hypothyroidism and hypopituitarism) and secondary cancers tend to occur. MRI and EBV-serology/DNA deducts relapse (25).

THYROID CARCINOMA:

Thyroid cancers were common in paediatric population less than 18 years (27). It usually arises as an asymptomatic mass/swelling in the regions of the neck, with/without cervical adenopathy, with accompanying dysnoea and/or hyperthyroidism. Increased malignant potential of this tumor, especially in pediatric age groups which is opposite in adolescents necessitates nodule identification at a very earlier stage. Papillary thyroid carcinoma (PTC) constitute 90% and follicular sub-type contribute to 10% of thyroid cancers. Paediatric thyroid cancers follows an aggressive course, high recurrence, metastases,

extrathyroid extension and lymph node involvement rather than adolescents. Larger tumor size with bilateral and multifocal disease in childhood poses the need of comprehensive surgery in pediatric patients resulting in transient/ permanent hypoparathyroidism and recurrent laryngeal nerve damage. Radio-active Iodine therapy (RAI) is associated with an increase in second primary malignancy, especially salivary cancer (28). As childhood thyroid is radiosensitive, thyroid cancers tend to occur in those population who are exposed to radiation at a tender age. Example, after Chernobyl accident and nuclear bombings in Hiroshima and Nagasaki, thyroid cancers incidence were high in children since they have been exposed to high dose of ^{131}I. Secondary thyroid carcinoma after radiotherapy to the neck has been reported after a regular follow-up for a period of 30 years once the diagnosis of HL is made (29). Flow chart 1 gives an comprehensive overveiw of how to initially evaluate, approach and follow-up a paediatric thyroid nodule. FNAC are categorized based on Bethesda schema. Non-diagnostic cytopathology specimens with minimal cellularity and poor preservation places requirement of a repeat FNAC as a better option. However, it must be delayed for atleast a span of 3 months to minimize the effects of the characteristic features of cellular atypia that may eventually arise during regeneration and repair. Levothyroxine (LT4) suppression were found to reduce nodule size and the risk of subsequent nodule formation. Thyroid hormone supplementation in radiation-induced thyroid nodules decreased subsequent nodule formation. Taking into account, high false-negative rate of FNAC and to simplify follow-up, surgery is mandatory in FNAC-documented benign nodules >4cm. Ultrasound examination, CT or MRI are the standard diagnostic modalities. In cases, wherein, an iodinated contrasts are used, a delay in 2–3 months before starting the treatment course with RAI is mandatory until quantity of total body's iodine declines. CT has shorter image acquisition times and reduces the need for conscious sedation in children. In evaluation and investigation of newly diagnosed tumors, thyroid nuclear scintigraphy should come into play only if patient exhibits a suppressed TSH (30). Total thyroidectomy is the main modality of treatment. Adequate thyroid tissue must be left spared in cases of near-total thyroidectomy to prevent any iatrogenic complications posed to vital structures those found in the vicinity, i.e., recurrent laryngeal nerve. In case scenarios, where distant metastases were found to involve those structures in the central or lateral neck regions, removal of thyroid gland intoto combined with a neck dissection is required. Assessment of tumor size and its focality determines the need of a prophylactic neck dissection. High risk of recurrence is found in solid/trabecular/follicular sub-types followed by non-invasive follicular lesions with papillary-like nuclear features (31). Re-operation is needed if there is increase in size and subsequent loss of central hilum. Doppler findings suggestive of Presence of peripheral vascularity and characteristic micro calcifications harbours high risk for malignancy. Before proceeding with lymph node dissection, in addition to lymph nodes assessment using USG, an aspiration cytology to rule out metastasis involving lateral lymph nodes of the regions of the neck is required. In cases of persistent locoregional involvement, ATA enforces the usage of radioactive iodine therapy. Indications for radioactive iodine therapy differ between adult age and paediatric population. As derived from the publication of NCCN, radioactive iodine therapy in indicated in adults with PTC, whose primary tumor size >2–4 cm, extra thyroidal invasion and involvement of regional lymph nodes. Some of the ill- effects of ^{131}I include sialadenitis, dry mouth, stomatitis, xerophthalmia and obstruction of nasolacrimal ducts. Bone marrow supression may follow but deranged hematologic parameters will revert back to normalcy with an approximate time period of 30 to 60 days after ^{131}I exposure (30). Vandetanib, cabozantinib, lenvatinib, sorafenib, combination of dabrafenib/trametinib and larotrectinib have received FDA approval (31). Targeted radiotherapy with somatostatin analogs or ^{131}I - Meta-IodoBenzylGuanidine (MIBG) has its own limitations (26).

MUCOEPIDERMOID CARCINOMA (MEC):

This common salivary gland neoplasm, is usually aggressive with high incidence rates in parotid and minor salivary gland. An enlarging mass in the regions of head and neck, especially if rich in typical cellular features of salivary glands must arise a clue of MEC. MEC, as the name suggests, consists of a mixture of mucous and epidermoid cells. Intermediate cells are also found in varying proportions. Clear cell change is seen in epidermoid cells, due to glycogen accumulation. Being cystic to solid, tumors proliferates intraluminally. MECT1-MAML2 translocation were the main drivers of tumor. FNAC and needle core biopsy helps is establishing diagnosis (32). Wide surgical excision is usually adequate. In those cases of high grade tumors with evidence of positive margins and minimal residual disease, in addition to wide surgical excision of tumor, an adjuvant therapy is mandatory to avoid relapse in near-future. In histopathologic specimens, where there is evidence of close margins after tumor excision, a re-surgery is necessary (33).

Various challenges exist in the platform of evidence based research especially in the field of paediatrics. First and fore-most challenge faced in research and recent advancements pertaining to paediatric community is the small disease cluster, when compared to adults in which cancers were found to be 40 times more common (18). Enforcing more sensible and specific therapies with features of less damage and/or side effects in children,

which differ in terms of adult cancers is of prime significance (34). With respect to Imaging and diagnostics, due to the high risk of carcinogenic effects of radiation, diagnostic aids including ultrasound is used, especially in those wherein a definite provisional diagnosis of cancer is yet to be established. Even cases with a confirmed diagnosis, minimizing the exposure to radiation and its effects by strictly adhering to the principles of ALARA by optimizing radiologic parameters in diagnositic imaging may prove beneficial (15). Updation in diagnostic modalities with latest advancements in perspective of radiotherapy delivery systems allows an efficient control over loco-regional involvement and better tumor delineation by targeting smaller tumor volumes. However, clinically and pathologically malignant free regions those in vicinity to the sites of radiation therapy are prone to develop secondary tumors due to the late effects of non-targeted ionizing radiation which will eventually hamper children normal organ growth, development and cellular metabolism (35). To avoid all aforementioned drawbacks, some of the recent advancements in radiation therapies were come into play.

FLASH RADIOTHERAPY:

This advanced radiotherapy is either based on the protocols of proton/photon radiation. It usually delivers an high dose of around 100 Gy/s within a short span of 60-120 seconds, thereby allowing an exposure of 1.8 Gy fractions. Exploitation of oxygenation levels in surrounding non-cancer cells shields nontargeted sub-sites and thereby, enables features of oxygen desaturation/ hypoxia which may lower the long term effects of hazardous radiation.

PROTON BEAM THEARPY (PT):

PT was introduced in the early 90s by Robert Wilson, which came into existence in the year 1958. The PPCR, a registry for proton therapy works with customized terms and conditions, allows gathering of dosimetric values in individuals undergoing proton therapy to expedite evaluation of PT in the pediatric population (36). PT directs irradiation to a deep especially targeted tumour region (37). PT, lowers the inflow and outflow of radiation doses, without deteriorating the therapeutic doses delivered to tumoral sites. Recent advancements which works on the principles of pencil beam and intensity modulation not only aids in effective and efficient dose conformation, and also lessens the effects of cross-contamination with neutrons. Unfortunately, this advanced therapy is expensive with a cost factor of 2.5, but, dosimetrically, it lessens doses delivered to surrounding non-tumoral organs. Children with incurable malignancies and less survival rates were known to be well-efficiently controlled with radiation. In specific scenarios where family members/ affected indivivuals may find it difficult to migrate and an unsound financial status with absence of insurance coverage continuing with RT, such as MR – linacs and guided brachytherapy may prove beneficial. PROS with membership of around 150 in number from 37 countries all around the globe including developing and developed nations is yet arrive at a standardized protocol in terms of radiologic imaging parameters for diagnosis and treatment planning in paediatric cancers. PT is associated with sparing of lymphocytes, reduced marrow and immune stem cell toxicity, hence can be comdined with other chemotherapy/ immunotherapy (35).

EFFECT OF GLOABAL PANDEMIC:

The corona virus disease has evolved into global pandemic, affecting cancer care amenities to its core especially in developing countries like India. Nationwide lockdowns to curb the spread of the infection have collapsed cancer care delivery services resulting in diagnostic delay, treatment initiation and/or rescheduling causing disease progression and poor survival. Cancer care delivery slowed down due to changing of cancer hospitals into dedicated COVID-19 hospitals and posting staffs to specifically work for COVID-19 patients resulting in lack of man power. Devices such as the Gamma knife, Cyber knife and proton beam machines are scarce and mostly owned by private institutes. Eventually, when Government resources were directed towards the care of COVID-19 patients, it poses difficulty on the poorer stratum of the society to start or continue their cancer treatment in private hospitals, which is beyond their means. Conversion from conventional to hypofractionated schedules in radiotherapy and weekly or two-weekly regimens to three-weekly regimens or from intravenous administrations to oral therapies were formulated to reduce the travel time of patients. Because of immature immune system, Children who are younger than 5 years are vulunerable to develop life threatening signs and symptoms rather than older age groups. Taking corona virus infection into major consideration, inpatient isolation must be strictly adhered especially in padiatric population undergoing intensive chemotherapy. However, in most health care systems, either due to lack of adequate knowledge and/or infrastructure, paediatric cancer community are most often treated as general outpatients. Hence, Minimising number of visitors entering cancer care systems on a daily basis and delaying the appointments or tele-medical team usage for non-critical paediatric community, E.g., children who were in long term follow-up or survivorship clinics, must come into routine clinical practice to reduce the number of visits (38). A study from Latin America reported that there was an indefinite delay of surveillance consultations followed by outpatient procedures, cancer surgeries, radiotherapy schedules, outpatient consultations and pain

and palliative oncology care. Also, Modification in drug regimens was in need due to lack of specific medicines distribution, production and ease of availability. Drastic reduction in paediatric health care system man-power, telemedicine consultations and short of life saving blood products was enlightened in different regions of the countries with much loaded travel restrictions. Patients distant from treatment center have transportation issue in accessing proper care. Family members, though well caring, may not be able to devote time as they wish to provide transportation. Transportation to doctor appointments or from hospital to residence is infrequently covered by insurance creating trouble to economically disadvantaged (39). Another Retrospective from Turkey shown decline trend in Out-pateints, chemotherapy and radiotherapy applications, surgical procedures and imaging studies thereby possibility of diagnostic delay may arise in up-coming years. In the same study, during chemotherapy, acquisition of COVID-19 resulted in demise of a child, while, other children recovered with mild symptoms necessitating efficient triage in practice and proper training of staff and patients/care givers during pandemic. Cancer care should not be neglected during pandemic and following waves of outbreaks poses challenge on health care to focus on post-Corona virus period, to fix the damages (40).

Pandemic has enlightened us the shortcomings of the cancer care delivery system in India and importance of mitigating them by establishing more cancer centers and to minimize disparities in access to cancer care experienced by the general population. Considering the pros and cons which were faced by oncology health care system in first wave of pandemic would have enabled the clinical practitioners in serving paediatric population in much more effective manner in this second wave of pandemic. With advent of vaccination against corona virus infection and its usage in groups affecting with paediatric cancers is yet to come into light.

REFERENCES

1. Tandon S and Rajeev K. Introduction to pedodontics. Tandon S. Textbook of Pedodontics, second ed, Paras, Hyderabad, 2008: 2.
2. Savary C, Kim A, Lespagnol A, Gandemer V, Pellier I, Andrieu C, Pages G, Galibert MD, Blum Y, Tayrac MD. Depicting the genetic architecture of pediatric cancers through an integrative gene network approach. Scientific reports 2020: 10: 1224.
3. Brasme JF, Morfouace M, Grill J, Martinot A, Amalberti R, Letouzey CB, Chalumeau M. Delays in diagnosis of paediatric cancers: a systematic review and comparison with expert testimony in lawsuits. Oncology 2012: 13: 445 -459.
4. Carberry AR, Hanson K, Flannery A, Fischer M, Gehlbach J, Diamond C, Wald ER. Diagnostic Error in Pediatric Cancer. Clinical Pediatrics 2017: 1-8.
5. Pedersen LH, Wahlberg A, Cordt M, Schmiegelow K, Dalton SO, Larsen HB. Parent's perspectives of the pathway to diagnosis of childhood cancer: a matter of diagnostic triage. BMC Health Services Research 2020: 20: 1-12.
6. Godzinski J and Brecht IB. Differential Diagnosis of Head and Neck Tumors. Schneider DT, Brecht IB, Olson A, Ferrari A, eds: Rare Tumors in Children and Adolescents, Springer, Berlin, 2012: 129-132.
7. Arboleda LPA, Mendonça RMH, Lopez EEM, Araujo ALD, Palmier NR, Paglioni MP, Fonseca JM, Hoffmann IL, Cardinalli IA, Chaves ALF, Aranda S, Brandao TB, Lopes MA , Ribeiro ACP, Troconis CCM, Silvaa ARS. Global frequency and distribution of head and neck cancer in pediatrics, a systematic review. Critical Reviews in Oncology/Hematology 2020: 148: 1-13.
8. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2020. Ca Cancer J Clin 2020: 70: 7–30.
9. Sengupta S, Pal R, Saha S and Bera P. Spectrum of head and neck cancer in children. Journal of Indian Association of Pediatric Surgeons 2009: 14(4): 200–03.
10. Rajendran R. Bengin and malignant tumors of the oral cavity. Rajendran R and Sivpathasundharm B. Textbook of Oral Pathology, seventh ed, Elsevier, New Delhi, 2012: 81-222.
11. Chadha K and Forte V. Pediatric Head and Neck Malignancies. Current Opinion in Otolaryngology & Head and Neck Surgery 2009: 17: 471–76.
12. Nagpa B, Hegde U, Archana S, Ghosh A, Nagpal A. Hodgkin's Lymphoma: A Comprehensive Review for Oral Health Care Practitioners. International Journal of Health Sciences and Research 2016: 6: 335-343.
13. Allen CE, Kelly KM, Bollard CM. Paediatric lymphomas and histiocytic disorders of childhood. Pediatric Clinics of North America 2015: 62: 139–165.
14. Rosolen A, Perkins SL, Pinkerton CS, Guillerman RP, Sandlund JT, Patte C, Reiter A, Cairo MS. Revised International Pediatric Non-Hodgkin Lymphoma Staging System. Journal of Clinical Oncology 2015: 1-9.
15. Morgenstern DA, Galindo CR, Gaze MN. Imaging in Pediatric Oncology: New Advances and Techniques. Voss, Stephan D, McHugh, Kieran, eds: Imaging in Pediatric Oncology, Springer, Switzerland, 2019: 1-7.
16. Khan AAC and Cheson BD. Lenalidomide for the Treatment of B-Cell Malignancies. Journal of Clinical Oncology 2008: 26: 1554-1552.
17. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, Frankel SR, Chen C, Ricker RJ, Arduino JM, Duvic M. Phase IIB Multicenter Trial of Vorinostat in Patients With Persistent, Progressive, or Treatment Refractory Cutaneous T-Cell Lymphoma. Journal of clinical oncology 2007: 25: 3109-3115.
18. Saletta F, Seng MS, Lau LMS. Advances in paediatric cancer

treatment. Translational Pediatrics 2014: 3: 156-182.
19. Neville BW, Damm DD, Allen CM and Angela C. Hematologic disorders. Neville BW, Damm DD, Allen CM and Angela C. Oral and maxillofacial pathology, Fourth ed, Elsevier, St. Louis, 2016: 533-571.
20. Merryman RW and Case AL. Novel agents and immune invasion in Hodgkin lymphoma. Hematology 2019: 243-248.
21. Dumaswala K and Mehta A. Novel agents for the treatment of Hodgkin lymphoma. Expert Review of Hematology 2015: 8: 659–667.
22. Spinner MA, MD, Advani RH, Connors JM, Azzi J, Diefenbach C. New Treatment Algorithms in Hodgkin Lymphoma: Too Much or Too little? American Society of Clinical Oncology 2018: 626-636.
23. Parham DM and Barr FG. Classification of Rhabdomyosarcoma and Its Molecular Basis. Advances in Anatomic Pathology 2013: 20: 387-397.
24. Miwa S, Yamamoto N, Hayashi K, Takeuchi A, Igarashi K, Tsuchiya H. Recent Advances and Challenges in the Treatment of Rhabdomyosarcoma. Cancers 2020: 12: 1-18.
25. Kontny U, Franzen S, Behrends U, Buhrlen M, Christianse H, Delecluse H, Eble M, Feuchtinger T, Gademann G, Granzen B, Kratz CP, Lassay L, Leuschner I, Mottaghy FM, Schmitt C, Staatz G, Timmermann B, Vorwerk P, Wilop S, Wolff HA, Mertens R. Diagnosis and Treatment of Nasopharyngeal Carcinoma in Children and Adolescents – Recommendations of the GPOH-NPC Study Group. Klinische Padiatrie 2016: 228: 105–112.
26. Schrijvers D and Licitra L. Head and neck cancer. Cavalli F, Kaye SB, Hansen HH, Armitge JO, Piccart-Gebhart M. Textbook of medical oncology, Fourth ed, Informa, UK, 2009: 123-140.
27. Laser L, Lebenthal Y, Segal K, Steinmetz A, Strenov Y, Cohen M, Yaniv I, Gavan MY, Philip M. Pediatric Thyroid Cancer: Postoperative Classifications and Response to Initial Therapy as Prognostic Factors. Journal of Clinical Endocrinology and Metabolism 2016: 101: 1970–1979.
28. Cordioli MICV, Moraes L, Cury AM and Cerutti JM. Are we really at the dawn of understanding sporadic paediatric thyroid carcinoma? Society for Endocrinology 2015: 22: 311-324.
29. Qian ZJ, Jin MC, Meister KD, Megwalu UC. Pediatric Thyroid Cancer Incidence and Mortality Trends in the United States, 1973-2013. Journal of American Medical Association Otolaryngology–Head & Neck Surgery 2019: 145: 617-623.
30. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, Dinauer CA, Hamilton J, Hay ID, Luster M, Parisi M, Rachmiel M, Thompson GB, Yamashita S. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. The American Thyroid Association Guidelines Task Force on Pediatric Thyroid Cancer. Thyroid 2015: 25: 716-759.
31. Paulson AV, Rudzinski ER, Hawkins DS. Thyroid Cancer in the Pediatric Population. Genes 2019: 10: 1-20.
32. Dombrowskia ND, Wolter NE, Irace AL, Cunningham MJ, Mack JW, Marcus KJ, Vargas SO, Perez-Atayde AR, Robson CD, Rahbar R. Mucoepidermoid carcinoma of the head and neck in children. International Journal of Pediatric Otorhinolaryngology 2019: 120: 93-99.
33. Peraza A, Gomez R, Beltran J, Amarista FJ. Mucoepidermoid Carcinoma. An Update and Review of the Literature. Journal of Stomatology oral and Maxillofacial Surgery 2020: 1-38.
34. Grobner SN, Worst BC, Weischenfeldt J, Buchhalter I, Kleinheinz K, Rudneva VA, Johann PD, Balasubramanian GP, Segura-Wang M, Brabetz S, Bender S, Hutter B, Sturm D, Pfaff E, Hubschmann D, Zipprich G, Heinold M, Eils J, Lawerenz C, Erkek S, Lambo S, Waszak S, Blattmann C, Borkhardt A, Kuhlen M, Eggert A, Fulda S, Gessler M, Wegert J, Kappler R, Baumhoer D, Burdach S, Kirschner-Schwabe R, Kontny U, Kulozik AE, Lohmann D, Hettmer S, Eckert C, Bielack S, Nathrath M, Niemeyer C, Richter GH, Schulte J, Siebert R, Westermann F, Molenaar JJ, Vassal G, Witt H, ICGC PedBrain-Seq Project, ICGC mmmL-Seq Project, Burkhardt B, Kratz CP, Witt O, van Tilburg CM, Kramm M, Fleischhack G, Dirksen U, Rutkowski S, Frühwald M, von hoff K, Wolf S, Klingebiel T, Koscielniak E, Landgraf P, Koster J, Resnick AC, Zhang J, Liu Y, Zhou X, Waanders AJ, Zwijnenburg DA, Raman P, Brors B, Weber UD, Northcott PA, Pajtler KW, Kool M, Piro RM, Korbel JO, Schlesner M, Eils R, Jones DTW, Lichter P, Chavez L, Zapatka M, Pfister SM. The landscape of genomic alterations across childhood cancers. Nature 2018: 555: 321-27.
35. Weber DC, Habrand JL, Hoppe BS, Kayser CH, Laack NN, Langendijk JA, MacDonald SM, McGovern SL, Pater L, Perentesis JP, Thariat J, Timmerman B, Yock TI, Mahajan A. Proton therapy for pediatric malignancies: Fact, figures and costs. A joint consensus statement from the pediatric subcommittee of PTCOG, PROS and EPTN. Radiotherapy and Oncology 2018: 1-12.
36. Greenberger BA and Yock TI. The role of proton therapy in pediatric malignancies: Recent advances and future directions. Seminars in Oncology 2020: 47: 8-22.
37. Stephens FO and Aigner KR. Future Directions. Mersh TA, Hortobagyi G, Khayat D, Picksley SM, Sugarbaker P, Tagushi T, Thompson J. Basics of Oncology, Springer, Berlin, Second Ed, 2009: 315-328.
38. Shankar A, Saini D, Richa, Goyal N, Roy S, Angural H, Kaushal V, Bharati SJ, Upadhaya R, Durga T. Cancer Care Delivery Challenges in India during the COVID-19 Era: Are We Prepared for the Postpandemic Shock? Asian Pacific Journal of Oncology and Nursing 2021: 8: 1-4.
39. Vasquez L, Sampor C, Villanueva G, Maradiegue E, Lombardi MG, Gomez-Garcia W, Moreno F, Diaz R, Capellano AM, Portilla CA, Salas B, Nava E, Brizuela S, Jimenez S, Espinoza X, Gassant PY, Quintero K, Fuentes-Alabi S, Velasquez T, Fu L, Gamboa Y, Quintana J, Castiglioni M, Nunez C, Moreno A, Fineman SL, Luciani S, Chantada G. Early impact of the COVID-19 pandemic on paediatric cancer care in Latin America. Oncology 2020: 21: 753-54.
40. Kutluk MT, Ahmed F, Kirazli M, Bajin IY, Mungen E, Ekinci S, Yildiz F. The effect of the COVID-19 pandemic on paediatric cancer care: lessons learnt from a major paediatric oncology department in Turkey. ecancer 2021: 15: 1-16.

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