A radiological and radiotherapeutic approach for paediatric
tumours in the head and neck area

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Introduction
Cancer is the second leading cause of death in children older than one year of age1. Haematological malignancies (lymphoma, leukaemia) constitute about 40% of all paediatric cancers1. The most common solid tumours are brain tumours, followed by neuroblastoma, Wilms’ tumour, sarcomas and primary rhabdomyosarcoma2. This review briefly describes diagnostic procedure, radiation treatment and follow-up in most common paediatric tumours in the head and neck area.

Lymphoma
Lymphoma constitutes approximately 15% of all paediatric neoplasms3. In case of suspected lymphoma, initial imaging includes ultrasound, chest X-ray and computed tomography (CT) of the affected area1. Definite diagnosis requires histological analysis.

Staging is based on the Ann Arbor staging system for Hodgkin and the St Jude staging system for non-Hodgkin lymphomas (NHL)4,5. Upon histological confirmation, work-up includes bone marrow biopsy and a contrast-enhanced neck/chest/abdomen/pelvis CT6. Positron emission tomography (PET) is recommended for Hodgkin’s lymphoma and all intermediate and aggressive subtypes of NHL as it changes staging and management in 32% of children7–11. Furthermore, PET/CT is essential for radiotherapy planning12. Whole-body magnetic resonance imaging (MRI) is also a promising technique8.

Assessment of response is evaluated by CT scans of the affected areas and/or PET in specific timelines, according tumour histology3,13. These methods also apply for final restaging after completion of therapy13. It must be noted that PET is the imaging modality of choice for differentiation between viable tumour, necrotic tumour or scar tissue4.

Surveillance includes CT scan of the affected area and chest X-ray in selected timetables according tumour histology plus annual CT scans for areas not previously involved and liver–spleen ultrasound. PET is recommended to confirm the absence of lymphoma in a persistent CT abnormality or when laboratory tests are abnormal but CT scans are negative14. The radiological diagnosis and staging together with follow-up procedure is shown in Table 16–14.

Central nervous system tumours
Central nervous system (CNS) tumours constitute 25% of paediatric tumours, being the commonest solid tumours3,15. In clinical suspicion of CNS tumour; MRI is the examination of choice, as it precisely depicts the lesion, provides the differential diagnosis and gives information on the most appropriate area for biopsy17 (Figures 1, 2). However, acutely ill children may initially undergo a head CT or a brain ultrasound if they are newborns18. The role of advanced neuroimaging is also evolving. Diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI) and fibre tractography, perfusion MRI and magnetic resonance spectroscopy (MRS) are used more often nowadays, but further studies are required in order to fully evaluate their potential role in paediatric CNS tumours19–27. PET or PET/CT is also currently under investigation, as it may have a role in differentiating high-grade from low-grade tumours21,22. Biopsy (depending, of course, on the site of the tumour) should also be performed for histological classification and tumour grading28.

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Paediatric CNS tumours are not staged typically, as they do not metastasize, except via cerebrospinal fluid; therefore, spinal imaging is required in certain tumours (e.g. medulloblastoma and ependymoma). Prognosis is influenced by the World Health Organization histological tumour classification, tumour size and location, residual disease after surgery and child’s age and operating level. Additional bone scan studies must be performed in patients with medulloblastoma/embryonal tumours and supratentorial primitive neuroectodermal tumour (PNET).

After surgical removal of the tumour, contrast-enhanced MRI is indicated immediately postoperatively (24–72 h) to check for residual disease. MRI is also the examination of choice in long-term follow-up. The frequency of examinations depends on the histology of the tumour and presence of residual tumour. MRS, PET or PET/CT may have a role post-treatment to differentiate between residual tumour, recurrence and treatment-associated lesions. PET is most helpful in the determination of transformation of a lower-grade tumour to a higher-grade neoplasm and differentiation of post-therapy (especially post-radiation) treatment effects from tumour progression. MRS is sometimes used alternatively to PET, but further studies are required. Diagnostic and follow-up approach in summary is shown in Table 1.

Radiotherapy

Paediatric radiation therapy encompasses a wide variety of patient ages, diseases, treatment sites and tumour volumes. In modern paediatric protocols, the volume targeted to receive the prescription dose, the planning target volume (PTV), is defined based on the specific diagnosis, location and extent of disease, relevant imaging studies and clinical- and treatment-related factors including prior surgery, the use of chemotherapy and the risk of treatment-related side effects. Considering the International Commission on Radiation Units and Measurements (ICRU 50–62) definitions, relevant imaging studies are required to define the gross tumour volume (GTV), which is expanded by an anatomically confined margin to form the clinical target volume (CTV). CTV is meant to account for potential subclinical invasion of the tumour and defines the volume at risk. Ideally, CTV would receive a tumouricidal dose of radiation and no other tissue would be irradiated.

Unfortunately, this ideal situation cannot be archived because the tumour is often imbedded within or adjacent to organ at risk (OARs).

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**Table 1** Radiological approach for diagnosis and follow-up concerning tumours in childhood for head and neck area

<table>
<thead>
<tr>
<th>Disease</th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
<th>PET-CT</th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
<th>PET-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Follow-up</td>
<td>Diagnosis</td>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>+</td>
<td>+</td>
<td>+ (for staging)</td>
<td>+</td>
<td>+/- (when indicated)</td>
<td>+</td>
<td>(when indicated)</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>+</td>
<td>+</td>
<td>+/- (under investigation)</td>
<td>+</td>
<td>+</td>
<td>+/- (when indicated)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1**: Sagittal T2-weighted (a), non-contrast T1-weighted (b) and contrast enhanced T1-weighted MRI (c) scan demonstrates a large suprasellar craniopharyngioma with extension in interpeduncular and preopticine cistern and mass effect on the third ventricle, causing hydrocephalus.
Irradiated OARs may limit the dose that can be prescribed without serious complications. In addition, due to possible temporal variation in the position, shape and size of CTV, an internal margin (IM) must be taken into account, ideally on serially acquired on treatment imaging. A set-up margin (SM) is also required to account for all the variations and uncertainties in the daily patient positioning and beam delivery. Minimization of SM may be achieved using various daily localization schemes. IM and SM are combined and added to the CTV, giving rise to PTV. An IM and SM are also added to each OAR to give a planning risk volume (PRV)29.

The need to understand the manipulation of these margins has become increasingly clear as high dose conformal radiation therapy, including intensity modulated radiation therapy30 and proton therapy31, enter the mainstream for children.

**Doses and fractionations**

Radiotherapy quality assurance (QA) is particularly important in the treatment of children. Because of the high cure rate for most childhood cancers, it is important to achieve local control avoiding a ‘geographical miss’32. It is also important to avoid unnecessarily large field sizes to minimize long-term effects.

**Lymphomas**

The survival for children with Hodgkin lymphoma is approximately 90%28,1. For several years, wide field radiation therapy (RT)—such as mantle technique—used widely in adults has been avoided in children. Nowadays in the optimization era, low intensity chemotherapy and low dose involved field RT are the protocols used in America and Europe. The dose prescribed is 35 Gy in 20 fractions33–35.

Compared with adults, a different spectrum of NHL is seen in children. The majority of children have either T cell lymphoblastic lymphoma, Burkitt’s or anaplastic large cell lymphoma. Survival rates are currently more than 80%1. Therapy is based on intensive multiagent chemotherapy including CNS prophylaxis. There is no routine role for RT in the management of NHL33–35.

Moreover, there are studies36–38 showing abnormal timing of menarche in survivors of RT. Armstrong et al. studied 235 female survivors of CNS tumours and they provided self-reported data on age and menarche. The radiation dose for each anatomical region of the brain was estimated. The conclusion was that radiation confers a significant risk for early and late timing of menarche. We should mention that the application of the RT was not done with advanced techniques39. Radiation-induced toxicity is shown in Table 2.

**Leukaemia**

Currently, more than 70% are long-term survivors40,41,1. Current treatment is stratified according to risk status based on presenting white count and cytogenetic profile. Chemotherapy is the main treatment. CNS prophylaxis, generally with intrathecal methotrexate is the next step, but cranial RT is now no longer employed expect for patients presenting with CNS involvement by leukaemia. The total dose is 24 Gy in 15 fractions of 1.6 Gy daily33–35.

**Figure 2:** Sagittal T2-weighted (a), non-contrast T1-weighted (b) and coronal FLAIR (c) MRI scan demonstrates a tectal glioma (arrow), causing aqueductal obstruction and hydrocephalus.
Laningham et al. reviewed the methods of systemic therapy of CNS leukaemia and tried to correlate the therapies with acute and late toxicity. The intrathecal and high doses of chemotherapy are not innocuous and are related with neurological consequences, such as altered mental status and chloromas. The study by Winick showed the same results.

Waber et al. evaluated late neuropsychological toxicity in children treated for acute lymphoblastic leukaemia (ALL) who were randomly assigned to receive either cranial radiation therapy (CRT) with intrathecal (IT) chemotherapy or intensive triple IT chemotherapy without CRT. They revealed small differences 6 years after diagnosis between the two groups. If the efficacy can be achieved without CRT, it is preferable to do so. However, CRT at lower doses may not add significant neurotoxicity (Table 2).

CNS Tumours
RT for children with CNS tumours is technically challenging. Initially, the treatment for CNS tumours is the surgical resection, as complete as is considered safe. This may be relative for tumours arising in the cerebellum than those arising from the optic tract or optic chiasm. The dose prescription for low-grade tumours are 54 Gy in 30 fractions specified to ICRU reference point 28, and this is the dose

<table>
<thead>
<tr>
<th>Studies</th>
<th>Diseases</th>
<th>Toxicity</th>
<th>Special disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref.36</td>
<td>Lymphoma</td>
<td>Puberty timing</td>
<td>Endocrine-related cancer, metabolic syndrome, structural abnormalities, altered growth, functional deficits, or cancer, behavioural disorders, early sexual debut and potential abuse</td>
</tr>
<tr>
<td>Ref.37</td>
<td>Lymphoma</td>
<td>Precocious puberty</td>
<td>Behaviour problems, such as aggressive and hyperactive behaviours and dysphoric adjustment</td>
</tr>
<tr>
<td>Ref.38</td>
<td>Lymphoma</td>
<td>Low peak bone mass</td>
<td>Areal bone mineral density, low body weight</td>
</tr>
<tr>
<td>Ref.39</td>
<td>Lymphoma</td>
<td>Early and late puberty</td>
<td>Premature epiphyseal fusion and shortened final height, behavioural problems, increased social withdrawal, potential sexual abuse, low bone mineral density and long-term risk for osteoporosis, incomplete sexual development and reduced fertility</td>
</tr>
<tr>
<td>Ref.42</td>
<td>Leukaemia</td>
<td>Neurotoxicity</td>
<td>Neuroendocrine and neurocognitive dysfunction, secondary cancers, myelosuppression, mucositis, nephrotoxicity, hepatotoxicity, neurotoxicity, hemiparesis, aphasia, paraplegia, neurogenic bladder, vascular thromboses, CNS infections, posterior reversible encephalopathy syndrome</td>
</tr>
<tr>
<td>Ref.43</td>
<td>Leukaemia</td>
<td>Neurotoxicity</td>
<td>Neurocognitive outcome, training difficulties</td>
</tr>
<tr>
<td>Ref.44</td>
<td>Leukaemia</td>
<td>Neurotoxicity</td>
<td>Late neuropsychological toxicity</td>
</tr>
<tr>
<td>Ref.45</td>
<td>CNS</td>
<td>Second malignancies</td>
<td>Infections, endocrine and sensory dysfunction, neuropsychologic impairment, infarcts, haemorrhages, hydrocephalus, venous thrombosis leucoencephalophathy, second malignancies</td>
</tr>
<tr>
<td>Ref.46</td>
<td>CNS</td>
<td>Neurotoxicity</td>
<td>Physical, endocrinological, neurological (strokes, seizures, moyamoya disease, peripheral neuropathy and motor dysfunction), sensory, secondary malignancies, neurocognitive late effects</td>
</tr>
<tr>
<td>Ref.47</td>
<td>CNS</td>
<td>Second malignancies</td>
<td>Non-melanoma skin cancer and meningiomas, breast, thyroid cancer, sarcoma, leukaemia, bone, melanoma, lymphoma, gastrointestinal carcinomas</td>
</tr>
<tr>
<td>Ref.48</td>
<td>CNS</td>
<td>Neurologic damage</td>
<td>Gliomas, meningiomas, desmoid tumours, myelodysplastic syndromes, basal cell carcinomas, leukaemia, malignant fibrous histiocytoma and thyroid carcinoma</td>
</tr>
</tbody>
</table>

Table 2 Radiation-induced toxicity in childhood for tumours in head and neck area

also for high-grade tumours but post-operative. In high-grade tumours, independent of the total tumour dose of 60 Gy with conformal techniques, many children require craniospinal RT, which is one of the more complex techniques employed in most RT departments.33–35

The late effects after chemotherapy and radiotherapy treatments have been shortly discussed in the literature. We have previously reported various side effects involving the meningeal and the mental status.37–44 In addition, Koral et al., in a retrospective review, tried to assess the frequency of the low grade bone lesion development in the RT field in paediatric medulloblastoma/PNET (MB/PNET) survivors. They concluded that low grade bone lesions of calvarium are not very rare too.45

Vazquez et al. described the early and late effects of cancer therapy in the paediatric CNS and discussed the radiologic diagnosis to facilitate therapy and, in addition, the quality of life in these patients. Acute side effects mentioned were the infarct, haemorrhage, hydrocephalus, venous thrombosis and infections. Late side effects are related to ocular lesions, endocrine deficits, vasculopathy, leuconecephalopathy and neurological toxic effects. The authors insist that radiologists should be familiar with the main imaging patterns of the various side effects while minimizing the long-term consequences of the treatments.46 In addition, the application of advanced radiotherapy techniques contributed to reduction of acute and late effects.

Meadows et al. studied the reports of subsequent neoplasms (SNs) in the Childhood Cancer Survivor Study (CCSS) cohort. RT has been reported to increase the risk for second malignancies in the CCSS cohort. Radiation dose was associated with increased risk of subsequent glioma and meningioma. The possibility of second primary tumour it was according to the age of the primary childhood cancer diagnosis and the total dose of radiotherapy.47 The radiation morbidity in summary is shown in Table 2.

Discussion
Children should be treated by a multidisciplinary paediatric oncology team for a wide variety of diseases, which pose many different problems for patients and families. Management is not only related to the patient but also the family. RT plays an important part in the management of many children.

The anatomy of the head and neck regions is complex, with air cavities and important structures such as the brainstem, optic nerve, brainstem and spinal cord, in complicated arrangements, within a small volume. The treated volume plays a crucial role in the expression of late effects. A strong concentration must be set on target volume definition, delineation of OARs, choice of the optimal beam angles and dose distribution aiming at the reduction of dose to normal tissue and the kind of radiation.48

It requires the highest standard of RT planning and delivery, incorporating modern technical developments. IMRT allow coverage of the tumour target while minimizing the dose delivered to the normal tissues. Tumour behaviour and response vary according to primary site and histology. IMRT may be applied to escalate tumour dose as this technique provides sparing in normal tissue.

It has been demonstrated that there is a correlation between the amount of radiation dose and the induction of late effects49,50. The tolerance dose is different from organ to organ and also depends on the age of the child and the developmental status of the respective organ.48,49

The reduction of integral dose is a main concern in paediatric radiation oncology, and the physical properties of ion beams offer a benefit compared with even advanced photon techniques due to the low-dose deposition in the entry channel of the beam and the high local dose deposition within the Bragg peak. Brodin et al. studied intensity modulated proton therapy (IMPT), volumetric modulated arc photon therapy (VMAT) and conventional photon therapy without modulation. Their results are limited in their clinical meaningfulness; however, the modern technique with the conventional one has very heterogeneous dose distribution.51

Howell et al. studied both photon and proton in craniospinal irradiation (CSI). They concluded that proton CSI reduce the dose to normal tissue compared to photon CSI for paediatric patients.52

However, not many radiotherapy departments have an expert team of physicists and radiation oncologists and also the technology that can handle large volumes of IMRT patients. In addition, proton therapy is very expensive and quite rare spreading in radiotherapy centres.

The application of new techniques in radiotherapy will lead to an improved

Figure 3: Craniospinal irradiation with tomotherapy in sagittal (a) and in axial (b).
quality of life by decreasing the side effects and the appearance of second malignancies (Figures 3, 4). In future, we should compare modern radiotherapy techniques such as photon-beam IMRT and proton therapy in terms of dosimetric data and translate them into routine clinical practice. The irradiation dose deposited in normal tissues is really guiding the research efforts under the use of modern techniques.

References
19. Panagryah B, Blum I. Neuroimaging of pediatric brain tumors: from basic to advanced magnetic resonance imaging.

Figure 4: Radiotherapy in a chordoma case (1st and 2nd cervical vertebra) with tomotherapy.
Original research study

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