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International Guideline for Paediatric Radiotherapy Services

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INTERNATIONAL GUIDELINE FOR PAEDIATRIC RADIOTHERAPY SERVICES

FOREWORD

Childhood cancer represents a significant global health challenge, with an estimated 300,000 new cases diagnosed annually worldwide. Despite remarkable advancements in cancer treatment, paediatric radiation oncology remains a complex and evolving field, demanding tailored approaches to ensure optimal outcomes for young patients. High-quality radiotherapy treatment plays a pivotal role in the management of childhood cancer, offering curative potential and symptom relief for a wide range of malignancies. As such, enhancing the quality of radiotherapy treatment is of paramount importance in improving survival rates, minimizing long-term toxicities, and maximizing quality of life for paediatric cancer survivors.

In this spirit, the International Atomic Energy Agency (IAEA) presents this publication, which highlights the key considerations of radiotherapy in paediatric oncology care. Through collaborative efforts and unwavering dedication, one strives to ensure that every child facing cancer receives the highest standard of care, thus fostering a brighter and healthier future for the youngest patients worldwide.

The IAEA acknowledge to all those who have contributed to the development and refinement of this document, with special recognition bestowed upon the Paediatric Radiation Oncology Society. Their invaluable expertise and meticulous review have ensured the accuracy and relevance of the information presented, particularly in addressing the specialized needs of paediatric radiation oncology patients.

As one navigates the complexities inherent in the realm of paediatric cancer care, it is imperative that one continue to harness collective knowledge and expertise to propel progress forward. This publication serves as an indispensable resource for practitioners, policymakers, and researchers alike, providing a robust foundation upon which to build and innovate.

The IAEA commends the dedication and diligence of all those involved in the creation of this document, and one are confident that its insights will inform and inspire advancements in paediatric cancer care on a global scale for years to come.

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CONTENTS

1. SETTING THE SCENE

Providing a radiotherapy service which best meets the needs of children offers multiple challenges in comparison with adult services. Evidence has shown that radiotherapy plays an essential role in the excellent outcomes achieved in paediatric oncology in the past 50 years [1]. However, sadly it is evident that several factors conspire to contribute to enhanced side effects from treatment: children are at more risk of late effects because more normal cells are growing and dividing, more children are cured than adults and, if cured, children have more years to live to develop late sequelae. Combined, these factors make a compelling case to strive for excellence in paediatric radiotherapy, with specialized resources in all parts of the service. These include:

(a) Multidisciplinary team (MDT) working, with paediatric radiation oncologists (ROs) fully integrated in clinical decision making.
(b) Development of infrastructure which meets the needs of children and families.
(c) Acquisition of radiotherapy equipment suitable for the treatment of children.
(d) An appropriate workforce with sub-specialty training for all radiation medicine professionals treating paediatric patients.
(e) Support for the child patient and parents to enable co-operation with treatment.
(f) Delivery of specialized radiotherapy techniques, some of which are uncommon in the adult population.
(g) Clinical governance and quality measures designed for paediatric radiotherapy.
(h) Follow up care of children after radiotherapy.
(i) Research and audit to improve outcomes and reduce sequelae.
(j) Assessment of the costs and effectiveness of services.

The aim of this document is to describe the key considerations in each of these domains which can contribute to an excellent service. It is hoped that this can support oncologists, hospital directors and healthcare planners aiming to develop or enhance paediatric radiotherapy services.

1.1 INTRODUCTION

1.1.1 What is a child?

Many international institutions and national authorities use different age limits to define child, adolescent and young people based on different demographic, economic and socio-cultural settings. Unless otherwise specified, this document defines paediatric and children as children and adolescents up to 19 years of age, to reflect the medical point of view and for consistency with the World Health Organisation (WHO) [2].

Over the past half-century, the demographics of world population has changed significantly with diverse patterns of age distribution and pace of population growth. In 2023, the overall population exceeded eight billion, with 2.65 billion (32.9%) being children (0-19 years old) [3]. The proportion of children in the total population varies widely across geographical regions and income groups. High-income countries (HICs) show a demographic shift towards older-age populations due to declining birth-rate and increasing longevity, whereas low and middle-income countries (LMICs) have relatively younger populations with higher fertility rates. In Africa in 2023, half of the total population (50.3%) were children; this ratio was 30.8% in Latin America and the Caribbean, 30.5% in Asia, 29.8% in Oceania, 23.9% in Northern America and 20.9% in Europe. Nine out of ten children (90.4%) in the world lived in LMICs: 397 million in low-income countries (LICs), 1.97 billion in middle-income countries (MICs) and only 270 million in HICs. Children constitute 52.4% of population in LICs, 32.8% in MICs and 21.5% in HICs [3].

1.1.2 Cancer among children

Cancer is mainly a disease of adults; malignancies in children form only a small portion of the global cancer burden. According to the International Agency for Research on Cancer data in 2020, it was estimated that there were 277,000 new childhood cancers in a worldwide total of 18 million new malignancies [4]. Although worldwide only 1.5% of all new cancer patients are younger than 19 years old, there are significant differences among income levels of the countries. Whilst only 0.6% of cancer cases in HICs and 1.9% in MICs are children, the percentage is 6.9% in LICs, such that 1 in every 14 cancer patients in those countries are in the paediatric age group. Overall, 84% of childhood cancers occur in LMICs. The diagnosis and treatment of childhood cancers require specialized personnel, additional infrastructure, and equipment in child sizes; thus, many LMICs with high numbers of childhood cancers struggle to provide optimal services for these patients. Furthermore, most scientific research in childhood cancer has been conducted, and treatment protocols developed in HICs, and may not directly meet the needs in LMICs.

1.1.3 Epidemiology of childhood cancers

The frequency of various cancer types in children is heterogeneous across age, geographical regions, and income levels (Fig. 1). Globally, more than 29.1% of all cancers of paediatric ages are

leukaemias, followed by brain and central nervous system (CNS) tumours (11.1%), non-Hodgkin lymphomas (9.0%), kidney tumours (5.3%), Hodgkin lymphoma (4.8%), gonadal malignancies (4.1%) thyroid cancers (3.8%) and liver cancers (2.0%) [4]. Leukaemias, brain and CNS tumours, non-Hodgkin and Hodgkin lymphomas and sarcomas are common in all age groups of children. However, a unique group of tumours with embryonal origin (Wilms' tumour, neuroblastoma, hepatoblastoma, germ cell tumours, and retinoblastoma) are more frequent among infants and small children, whereas carcinomas such as thyroid and nasopharyngeal cancer are more often diagnosed among adolescents.

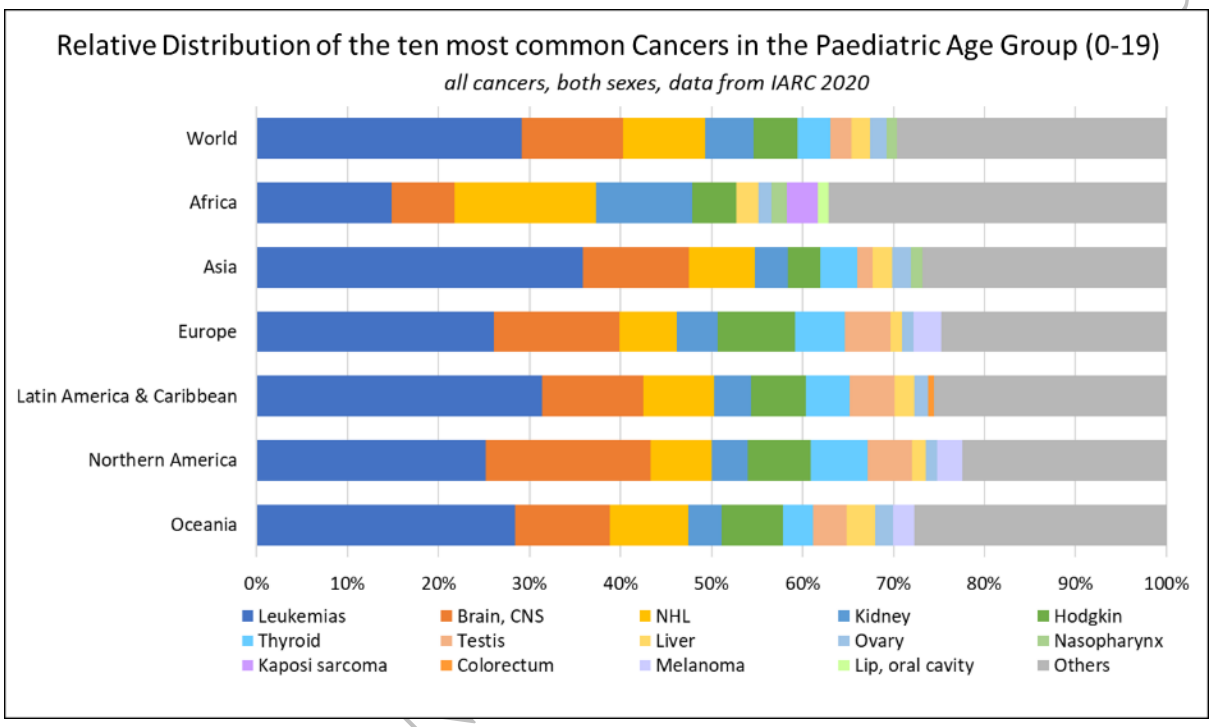

FIG. 1. Relative distribution of the ten most common cancers in paediatric age group

Variations of cancer incidence across age, geographic distribution and income levels should be taken into consideration when planning national and regional cancer services for children. Leukaemias are the most common malignancy among children in all continents except for Africa, followed by brain and CNS tumours.

In Africa, non-Hodgkin lymphomas are the most frequent, due to the high incidence of Burkitt lymphoma. Hodgkin lymphoma, thyroid cancers and melanoma are commoner in Europe, Northern America, and Australia and New Zealand than other regions.

1.1.4 Outcomes of treatment for children with cancer

Recent decades have brought significant improvements in outcomes for children treated for cancer in HICs. Improved diagnostic methods, advanced treatment modalities, better supportive care and, importantly, integrated multi-modal management through the implementation of dedicated MDTs has led to significant improvement in survival rates, such that more than 80% of children in HICs can now be expected to become long-term survivors. Sadly however, cure rates remain significantly lower

in most LMICs (15-45%). As an example, data from three cancer registries in East Africa indicate a three-year survival rate for Wilms tumour of 22.9 to 38.7% [5]. For neuroblastoma, survival rates in South Africa were relatively good for low-risk disease, but inferior to those achieved in HICs for high-risk disease [6].

Centralisation of childhood cancer services has been noted to be associated with better outcomes [7]. Survival rates vary by tumour type [8]; 5-year survival data from the United Kingdom for patients treated between 2012-2016, are 99.1% for retinoblastoma, 94.1% for Wilms tumour, 88.3% for leukaemias, 68.6% for medulloblastoma, and 40.2% for brain stem gliomas. Even within a major category, the probability of survival depends on stage and other prognostic factors used for risk stratification. Outcomes therefore display significant heterogeneity, not only in relation to the characteristics of the cancer type or era of treatment, but also by geography and socioeconomic and healthcare related factors, including the availability of treatments such as radiotherapy [9-12].

1.2 OVERVIEW OF CANCER MANAGEMENT IN CHILDREN

1.2.1 Multidisciplinary management

Success in the management of cancer patients depends on multidisciplinary management including diagnosis, treatment, supportive care, and follow-up. Optimum management of childhood cancer patients can only be provided through coordinated work by a team of professionals in these fields (see Section 3).

The first step in management is clinical evaluation of the patient. A child with a suspected cancer diagnosis is usually referred directly to a paediatric oncologist or a paediatrician experienced in childhood cancers. Typically, this specialist evaluates the patient and orders a series of laboratory and imaging tests followed by biopsy of the tumour.

High quality diagnostic imaging is essential for the diagnosis and staging of cancer. This may include not only plain radiography, ultrasonography, and cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI), but also nuclear medicine techniques including positron emission tomography (PET) for complete assessment in some cancers. Interventional radiology may also be required for biopsy, central line insertion, and some other therapeutic procedures. Later in management, repeated imaging is valuable for response assessment and surveillance after treatment. In all cases, paediatric imaging protocols specific to children should be used to minimize repeated radiation exposure.

Accurate diagnosis and risk group assignment for children with cancer requires advanced histopathologic evaluation, including not only conventional techniques but also immunohistochemistry and access to molecular and genomic tests. Childhood cancers differ from adult cancers and a pathologist experienced in paediatric tumour pathology is an essential member of the childhood cancer management team.

Cancer treatment in children continues to rely predominantly on three essential modalities: surgery, chemotherapy, and radiotherapy. Each can cause serious early and late toxicities in children. Largely due to coordinated clinical research studies on both sides of the Atlantic, extraordinary advances in multimodality therapy to ensure comprehensive treatment for childhood cancer patients have been

achieved. Today, a multimodality treatment approach is considered the backbone of paediatric cancer treatment.

1.2.2 The Expert Team

The best treatment sequence and combination can only be achieved by evaluation of the individual patient and decision making in a multimodal setting. This involves a large group of physicians including paediatric oncologists and haematologists, ROs, surgeons with expertise at specific anatomical sites (e.g., neurosurgery, urology, orthopaedics and otolaryngology/head and neck surgery), radiologists, pathologists, and nuclear medicine specialists. These professionals meet regularly to discuss the diagnosis of new patients, define the applicable risk group, and prepare a treatment plan. The team also re-discuss patients at appropriate decision-making points, such as to assess response to induction chemotherapy and determine if it is appropriate to proceed to surgery, or for histopathological review after surgery to decide whether radiotherapy is indicated.

In addition to the physicians, a wide range of other healthcare professionals are required for the most comprehensive service: nurses, pharmacists, nutritionists, radiographers, physio- and occupational therapists and more. These allied medical workers clearly have a critical role in childhood cancer treatment. In children between the ages of five to ten who undergo radiotherapy, the requirement for anaesthesia is influenced by the approach of all the team taking care of the child.

However, while representation of all these specialists and staff groups in the management team may represent the ideal situation, financial and other constraints mean they may not all be available everywhere, and individuals may have wide practises with less scope for specialisation within children's cancer. There are fewer ROs in LMICs, compared to HICs, and they are less likely to specialize solely in paediatric cancers [12]. Adapted clinical guidelines, for use in resource challenged settings, have been developed for some tumours, such as medulloblastoma and low-grade gliomas [13,14]. Additionally, guidance has been developed for the best use of radiotherapy for AYA in LMICs [15].

1.2.3 Treatment sequencing and timing

Surgery, radiotherapy, and chemotherapy are used in various combinations in childhood cancer. A typical example is to start with induction chemotherapy, followed by surgery and postoperative radiotherapy and maintenance chemotherapy. However, factors such as age may influence the sequencing and timing of treatment. As an example, when treating medulloblastoma, surgery followed by immediate radiotherapy and post-irradiation chemotherapy is standard in older children, but in small children radiotherapy may be deferred to minimize long term complications, and postoperative chemotherapy recommended to reduce the risk of disease progression.

Such complex schedules require precise scheduling and timing, which may be further complicated by the availability of each modality and access to the treatment facilities. Since childhood cancers form only a small portion of the overall cancer load in oncology centres, not all professionals and equipment are available everywhere, and patients can often be transferred to different centres for some part of their management. Planning childhood cancer services at regional or national level is thus extremely important to ensure children can receive seamless and high-quality treatment, and to allow cost-effective clinical management.

1.3 RADIOTHERAPY IN CHILDHOOD CANCERS

Radiotherapy is the medical specialty of using ionizing radiation to kill cancer cells. Since its first application in a stomach cancer in 1896, the use of radiotherapy has historically been one of the outstanding achievements in the treatment of childhood cancers, especially in acute lymphoblastic leukaemia, Hodgkin lymphoma, rhabdomyosarcoma, Wilms tumour, and Ewing sarcoma. It is currently one of the main pillars in cancer management both for cure and palliation, whether used alone or in combination with chemotherapy and surgery.

Although radiotherapy targets cancer cells, it also has detrimental effects on healthy cells in the treatment volume and may cause permanent late toxicity in adjacent healthy organs. In children, these toxicities are more evident because tissues and organs are still developing and growing, and survivors live long enough to develop the late side effects of the treatment which increase with time. Therefore, radiotherapy in AYA should be used cautiously, for proper and evidence-based indications only. Several methods of radiotherapy are available, and the best option should be carefully selected for each child.

1.3.1 Radiotherapy methods

Methods of delivering radiotherapy have evolved rapidly in the last two decades thanks to technological developments. The most suitable method for each individual patient is determined by considering the dose distribution, risks of toxicity, availability of equipment and experienced staff, ease of applicability and day to day reproducibility of the technique. The location and size of the tumour, patient age and sometimes the gender are patient related factors in decision making.

1.3.2 External beam radiotherapy

External beam radiotherapy with megavoltage X-rays typically in the 6-15 MV range or gamma rays from a Cobalt-60 source are the types of radiotherapy used most frequently worldwide. Linear accelerators have almost entirely replaced cobalt-60 machines in HICs (Fig. 2), but cobalt machines are still used in many LMICs. There is a hierarchy of treatment complexity of external beam radiotherapy, ranging from a single direct field, through a parallel opposed pair of fields, to three-dimensional (3D) conformal and intensity modulated radiotherapy (IMRT) techniques [16]. CT simulators which allow 3D planning and virtual simulation have largely replaced conventional simulators.

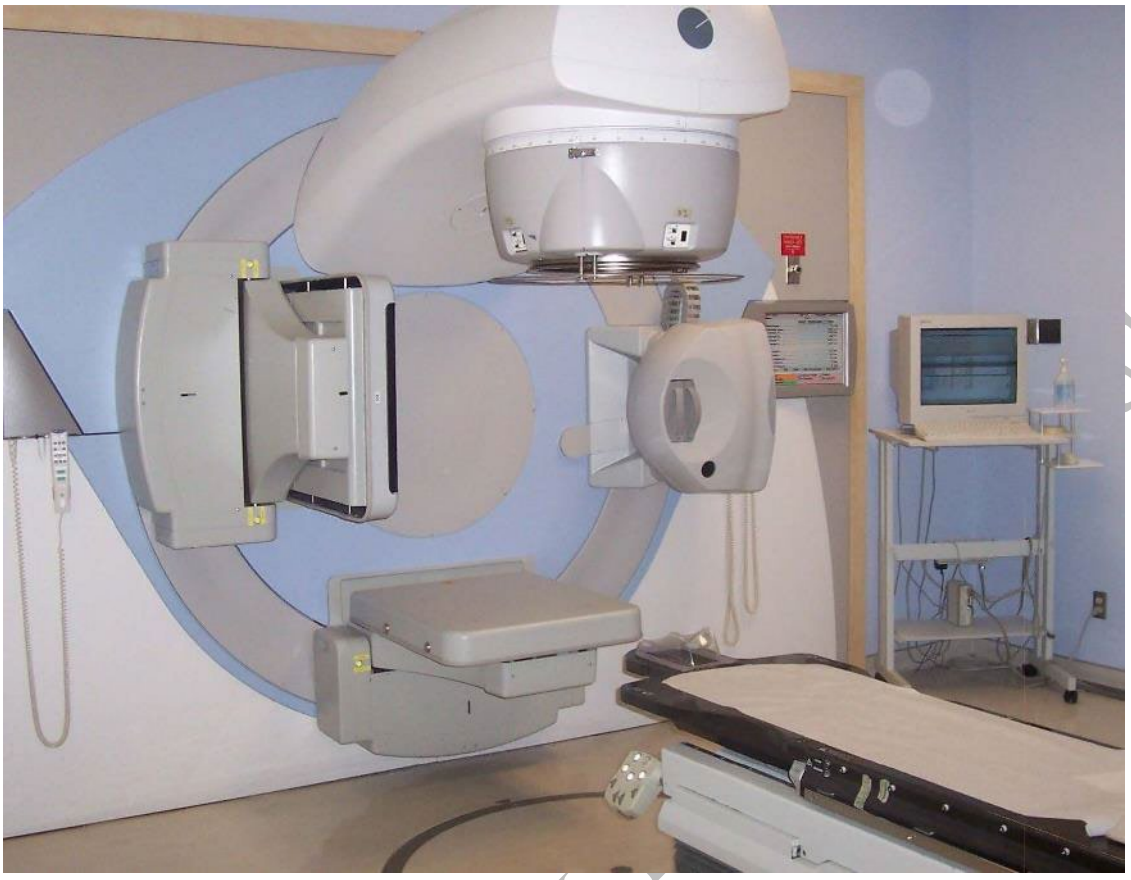

FIG. 2. A modern linear accelerator with online portal imaging system. Courtesy of Susan Awrey R.N., BScN. SickKids/Princess Margaret Cancer Centre

Advanced methods of dose delivery by IMRT techniques, including volumetric arc therapy (VMAT), provide more individualized radiotherapy, with tighter margins and better sparing of adjacent tissues from high doses. This offers potential to reduce late effects but necessitates great care in the quality assurance (QA) of planning and treatment delivery, or else "geographical miss" may occur, and the chance of local control be reduced. For this reason, regular image guidance, with verification of field placement, is now the norm. In centres which can deliver image guided radiotherapy, this has become the standard of care.

There are still circumstances however, when wide-field radiotherapy is indicated, rather than a conformal volume. Examples include total body irradiation for bone marrow transplantation in leukaemia, craniospinal irradiation (CSI) for medulloblastoma and some other CNS tumours, and whole lung or whole abdominal/pelvic radiotherapy in selected patients with advanced Wilms tumour.

Low-energy radiation in the 50-300 kV range, sometimes referred to as superficial or orthovoltage radiation, still has a role in the treatment of some superficial tumours such as skin lesions, but otherwise is no longer recommended as a curative cancer treatment.

1.3.3 Stereotactic radiotherapy

Stereotactic radiotherapy is a method of external beam radiotherapy employed for the treatment of small, well-defined targets in the brain or the body, delivered in a single treatment or with few fractions. It can be referred to as radiosurgery in the context of brain lesions, which include benign conditions such as arteriovenous malformations as well as tumours, or stereotactic ablative body radiotherapy in the context of extracranial disease. Typically, patients with small primary lung cancers or oligometastatic disease may be treated with this approach. Experience with these techniques in children is limited.

Modern linear accelerators may be very versatile, capable of delivering diverse techniques including total body irradiation, rotational IMRT, stereotactic radiosurgery, stereotactic ablative body radiotherapy and electron treatments. However, some departments are equipped with equipment specifically dedicated to individual modalities. Use of specialized techniques may also be limited by the numbers and training of the personnel required for safe delivery of radiotherapy.

1.3.4 Proton beam therapy

In the last 20 years, there has been a proliferation of centres able to deliver high-energy proton beam therapy (PBT) [17]. The main benefit of PBT in comparison to photon radiotherapy relates to the dose distribution, as most of the energy is deposited at a certain depth – the Bragg peak – and there is no dose beyond that. Proton therapy technology has advanced from a fixed beam with passive scattering and a range modulator, to rotating gantries and intensity modulated PBT. Paediatric cancers represent one of the main indications for PBT, as normal tissue sparing is improved, and hence late effects, particularly in eloquent areas of the brain, and the risks of secondary radiation-induced cancers are reduced. In most cases, PBT offers no greater chance of cure than conventional photon radiotherapy. The exception to this may be for some highly radioresistant tumours, such as clival chordoma and chondrosarcoma, where it is possible to deliver a higher dose than with photons. However, while advantageous in certain circumstances, PBT is much more expensive than photon radiotherapy, and is not a panacea. There are still some uncertainties in relation to dose distribution and variations in relative biological effectiveness, and unanticipated toxicities have been seen. Planning requires these uncertainties to be considered, to ensure that the risk of late toxicity is minimized. Further research is needed to optimize the use of PBT, which is currently unaffordable for most countries [18].

1.3.5 Brachytherapy

Brachytherapy is a form of radiation delivery where radioactive sources are placed inside or adjacent to the tumour. As with other treatment modalities, the technical aspects have developed over the decades. Direct placement of radioactive sources has been replaced by insertion of catheters for automated after loading, and treatment planning has become more complex to allow prescription to a defined volume rather than a single point. There are various options of low-dose-rate, pulsed-dose-rate and high-dose-rate equipment. Brachytherapy is best suited to treat small, well-defined tumours accessible to intracavitary, intraluminal, or interstitial implantation. Sometimes catheter placement requires an image guided interventional radiology procedure or else may be undertaken at surgery following complete or partial tumour removal. Close cooperation with surgery departments and a high degree of technical skill is required, hence centralisation of paediatric brachytherapy in

specialized units is prudent. Indications in paediatric practice include bladder/prostate [19], vaginal/uterine rhabdomyosarcoma, limb sarcomas [20], retinoblastoma and head and neck tumours [21].

1.3.6 Radionuclide therapy

Molecular radiotherapy, or radionuclide therapy, has a small but important place in paediatric cancer treatment. It is the systemic administration of a radiopharmaceutical which is selectively deposited in tumour cells through biological targeting [22]. The oldest and best example is the use of radioactive iodine (131-I) in differentiated thyroid cancer. Other examples include the use of 131-I meta-iodobenzylguanidine (mIBG) in neuroblastoma, and 177-Lu or 90-Y labelled somatostatin analogues in neuroendocrine tumours. An experienced team of nuclear medicine specialists, radio pharmacists and medical physicists (MPs) is required.

1.3.7 Immobilization and anaesthesia

Proper positioning and immobilization of patients are necessary for good quality radiotherapy. Lasers and positioning aids are used to ensure the patient is still during treatment; however, providing good immobilization in children can be challenging. Some are not old enough to understand and cooperate with the team and should be treated under general anaesthesia. Even for older children, anaesthesia or sedation may be required since uncontrolled pain, fear of hospitals from prior bad experiences, learning difficulties and other factors can affect compliance. The use of a play specialist is invaluable in preparing children for treatment and can reduce the need for daily general anaesthesia.

1.3.8 Delivering high quality paediatric radiotherapy

A high-quality radiotherapy service should be the goal of every radiation oncology centre, and this should be provided for paediatric radiotherapy applications as well. The first requirement of a high-quality service in paediatric radiotherapy is a RO with experience in childhood cancers, who should be a key member of the multidisciplinary management team. The knowledge base of a RO treating children includes a comprehensive understanding of the management of childhood cancers, including multimodal treatment protocols, the indications and evidence base for radiotherapy and optimal radiotherapy techniques in children. It necessitates consideration of the best probability for local control and cure, as well as options to minimize late side effects and provide the best functional outcome. The RO should have additional experience and training in this less common and complex area of practice. Paediatric radiation oncology is not currently recognized as a subspecialty, but children are usually treated by ROs with a specialist interest and training in the field.

The quality of treatment cannot however depend on one person, as radiotherapy is a team effort where diverse professionals work together. In many radiotherapy departments paediatric cancers are only a small fraction of service load and as with the RO, other staff are not specific to paediatric practice. It is recommended that a paediatric radiotherapy team is established, including a RO, MPs with experience in paediatric radiotherapy planning, radiotherapy technologists (RTTs) and a nurse with paediatric experience. Additional education and training should be provided to all members of this team. Other elements of quality include proper equipment and standard procedures specific for

paediatric patients. A comprehensive quality management system (QMS) including external audits and accreditation is recommended. Children are often treated far from home, so the provision of a hostel or family accommodation is helpful; advocacy groups including cancer associations may assist with this. Radiotherapy staff should also operate in collaboration with paediatric services to ensure other parts of care are provided, for instance concomitant chemotherapy, nutritional support and treatment of myelosuppression, infection, and sepsis. A comprehensive radiotherapy report should accompany the child back to the paediatric oncology unit at completion of treatment.

Patients should be treated, where possible, according to standardized internationally agreed protocols and enrolled, if feasible, into clinical trials which will enhance the evidence base for practice in the future. Involvement in these trials may also ensure prospective radiotherapy QA is undertaken (see Section 9).

1.3.9 Follow-up of survivors and monitoring late effects of radiotherapy

Survivors of childhood cancers are at risk of a wide range of late effects of the treatment. These vary depending on the anatomical site treated, the radiotherapy technique used, the dose administered, the use of chemotherapy, the extent of surgery and the age of the patient at the time of treatment (see Section 7). Minimizing these late effects remains the most challenging issue, and monitoring the development of late side-effects is essential. Evidence-based recommendations for the organization of long-term follow-up (LTFU) care have been developed [23]. At present, almost 80% of children who are diagnosed with cancer in HICs survive at least 5 years; sadly two-thirds of childhood cancer survivors will experience at least one late effect in their lifetime and 30 years after diagnosis, four out of every ten survivors may develop a severe condition related to treatment late effects [24]. A recent study found that adult survivors of childhood cancer are four times more likely to develop severe and disabling, life-threatening health conditions than their siblings at the same age [25]. Children have developing tissues and organs which are prone to permanent impairment by radiation and chemotherapeutic drugs. The risk of developing secondary cancers is also five-fold higher in these individuals than in the general population [26]. Survivors of childhood cancer live much longer than adult patients, contributing to the increased incidence of secondary cancers.

Survivorship care is already recognized and practised in many HICs but is not prioritized in most LMICs yet. A survey conducted in India showed that only 25% of radiotherapy centres provided adequate care to childhood cancer survivors [27]. India, where 10-15% of all childhood cancer will occur [28], has recently made rigorous efforts in supporting the childhood cancer survivorship scheme and may provide a good example of the implementation of this care in LMICs. There are numerous non-governmental organizations supporting childhood cancer management, focusing on a public education campaign, provision of cancer services and supporting resources, human resource development and evidence-based advocacy. These non-governmental organizations also provide support for survivors.

There is an urgent need to consider the role of civil society and patient support groups, particularly in the holistic management of childhood cancer survivors. Engagement and collaboration amongst diverse stakeholders, is essential, with the ultimate objective being integration of childhood cancer survivors into society.

2. INFRASTRUCTURE, MEDICAL EQUIPMENT AND SUPPLIES REQUIRED FOR PAEDIATRIC SERVICES IN A RADIOTHERAPY CENTRE

A radiation oncology facility that will be treating paediatric patients requires additional specialized equipment and infrastructure. This section will discuss the necessary radiation infrastructure, devices, and supply requirements as well as technical considerations to be taken into account when treating children.

When considering the establishment and/or improvement of a radiation oncology centre where children will be treated, several members of the medical community should be involved the infrastructure planning team from the start. The team should include a medical manager, RO, MP, RTT, paediatric anaesthesiologist and nurse. Ideally, all should have experience in the treatment of children; if they do not, external experienced staff should be drafted into the group to advise.

2.1 INFRASTRUCTURE REQUIREMENTS

The buildings, bunkers, treatment machines and treatment planning systems to treat children do not differ from those used for adults. A radiotherapy centre dedicated only to treatment of children is a rare situation; in most centres children are treated in the same building and with the same equipment as adults. However, some modifications to the infrastructure and additional equipment are required to allow radiotherapy of children. These are summarized in Table 1.

FIG. 3. A Playroom as an essential component of required infrastructure for the waiting area. Courtesy of Susan Awrey R.N., BScN. SickKids/Princess Margaret Cancer Centre

2.1.1 Waiting rooms

It is ideal if the centre can create a child-friendly space within the waiting room that may include play and activity areas for various ages (Fig. 3). This helps to alleviate the anxiety of visiting a medical facility, especially if it is primarily designed for adults. The centre should also consider space for parents accompanying the child every day during the treatment course.

Consideration should be given as to whether to use the waiting room as a consultation room in a situation when a child will have emotional difficulty in handling complex information about radiotherapy. It could be useful to consult with parents separately but close by, while the child is engaged in play or other activities in a separate space. Ideally, the centre should designate an isolation area for children attending with compromised immunity.

TABLE 1. SUMMARY OF INFRASTRUCTURE MODIFICATIONS REQUIRED TO ACCOMMODATE PAEDIATRIC RADIOTHERAPY

Area	Requirement
Waiting room	Play and activity area Space for accompanying parents Isolation area for immuno-compromised children Induction/recovery rooms for anaesthesia (ideally separate rooms)
Bunker	Adequate space to accommodate additional staff and anaesthesia equipment Oxygen and suction equipment with paediatric modifiers Anaesthesia cart with paediatric drugs and equipment Resuscitation trolley with paediatric equipment Audio-visual equipment to monitor child from control room
CT simulator	Additional space to accommodate additional staff and anaesthesia equipment Imaging software and protocols developed for paediatric patients Paediatric immobilization devices
Medical equipment	Paediatric equipment including Blood Pressure cuffs in child sizes, thermometers, resuscitation equipment, scales, growth charts

2.1.2 Simulation

Imaging for simulation is now usually undertaken with CT scanners. Software equipped with adequate optimisation protocols should be used to minimize the radiation dose to child (e.g. image-

gently protocols [with reference to: https://www.imagegently.org/]). Additionally, the centre will require specific immobilization devices such as thermoplastic masks, moulds, vacuum bags, etc. These devices are commonly available for the immobilization of adults, but may be difficult to obtain in paediatric sizes, necessitating additional finance and logistical planning to ensure an uninterrupted supply.

2.1.3 Radiotherapy bunkers

Radiotherapy bunkers should be equipped with oxygen and suction for all patients. In addition, for paediatric patients, the bunker should be equipped with anaesthesia and paediatric resuscitation equipment (see below) for emergency situations.

A two-way audio-visual communication system is essential, to allow staff to monitor the patient and communicate with the child from outside the bunker. The anaesthesia team also need to be able to see both the patient and the monitors attached to the child during treatment. The centre should ensure that there is enough space within the bunker and control area to accommodate the anaesthesia equipment and staff.

2.1.4 Medical equipment

Examination rooms should be equipped with paediatric cuffs for blood pressure, child-friendly thermometers, and devices for measuring patient height. It is desirable to have child-friendly decorations and play areas.

The centre needs to have paediatric emergency response equipment (defibrillator pads), pharmacy for Paediatric Advanced Life Support (PALS) as part of paediatric resuscitation equipment ("Paediatric Code Cart"). There should be enough PALS trained staff to provide uninterrupted clinic coverage when children are treated.

2.2 PAEDIATRIC ANAESTHESIA REQUIREMENTS IN RADIATION ONCOLOGY CENTRES

While designing a Radiation Oncology Centre where children will be treated, special attention should be taken to create facilities and infrastructure for implementation of general anaesthesia and/or sedation. A working group under the patronage of European Society for Paediatric Oncology has been created in 2023 with the aim of formulating recommendations on infrastructures, devices, human resources, and techniques for general anaesthesia in radiation centres.

Anaesthesia should be administered only by an anaesthesia team experienced in paediatric patients. Repeated anaesthesia/sedation exposes the sick child to a multitude of risks including respiratory pharmacological, neurological, infectious, and psychological toxicities; thus, anaesthesia techniques can be adapted to limit harmful consequences.

Some radiotherapy centres are located at a distance from the paediatric unit or hospital which hampers the availability of a specialized paediatric anaesthesia team. Additional resources should be allocated to allow the team to be fully operational at the site.

2.2.1 Facilities

Mandatory: One room/area dedicated to anaesthesia preparation, induction, and post-anaesthesia recovery (Fig. 4), large enough for induction of anaesthesia in safe and comfortable circumstances with space for equipment (minimal surface: 15 – 20 m^2), containing sink and other decontamination means (hydro-alcoholic solution).

Ideally: A busy paediatric radiation centre should have 2 separate fully equipped rooms: An induction room and a recovery room. The number of beds of the latter may vary according to legislation of the respective countries (e.g., four beds are required in France).

FIG. 4. Paediatric patients' recovery space. Courtesy of Susan Awrey R.N., BScN. SickKids/Princess Margaret Cancer Centre

2.2.2 Equipment

Anaesthesia can be administered in different ways using various drugs, the most common methods being intravenous and gas anaesthesia. The anaesthesiology team should select the most appropriate option for the patient. Since radiotherapy is painless, and the child needs to stay only a few minutes

under anaesthesia, sedation may be sufficient to keep child motionless on the treatment table. However, whatever method is used, all rooms including the simulator, radiotherapy bunker and induction and recovery rooms should be equipped with oxygen, suction, monitoring devices, and emergency equipment and medicines. These are summarized in Table 2.

TABLE 2. SPECIFIC ANAESTHESIA EQUIPMENT REQUIRED FOR PAEDIATRIC RADIOTHERAPY

Mandatory, in each room/setting (induction, treatment, recovery)	**Ideally**
Centralized Oxygen, air, and negative pressure (suction)	Anaesthesia machine with capacity of ventilating children of below 10 kg
Supplementary oxygen cylinder and suction system	Anaesthetic scavenging system
Oxygen administration system (inspiration air/oxygen blender, tubes, prongs)	Patient-heating system
Monitoring of blood oxygenation (arterial oxygen saturation), electrocardiogram, respiratory rate, blood pressure. Portable Monitoring devices should be present	Monitoring of End-tidal Carbon Dioxide, Tidal Volume, Minute Volume, concentration of anaesthetics in airways, apnoea, airway pressure (usually included in modern anaesthesia machines)
Visual monitoring of devices on remote screen in the control room	N/A
Trolleys with drugs and devices for anaesthesia and emergency	N/A
Video surveillance of treatment room	N/A
Thermometer	N/A
Stethoscope	N/A
Beds with slatted bars and stretchers for induction, transport, and recovery, adapted to critical care procedures	N/A

Abbreviations: N/A: not applicable

2.2.3 Disposable materials

Disposable equipment used for paediatric radiotherapy includes paediatric facial masks, oropharyngeal cannulas, suction tubes and syringes, and medicines for anaesthesia. Sustainability of these disposable materials throughout a radiotherapy programme which may extend for several weeks is necessary. This requires advance planning and stock control. These are summarized in Table 3.

TABLE 3. DISPOSABLE MATERIALS REQUIRED FOR PAEDIATRIC RADIOTHERAPY

Mandatory	**Ideally, strongly recommended (adapted to different weights)**
Facial masks for bag ventilation and for simple oxygenation	Laryngeal masks
Ventilation bags (0,5 – 1 l)	N/A
Oropharyngeal cannulas (Guedel) Airway filters	N/A
Oxygen/air connecting tubing system/circuit	N/A
Suction tubes	N/A
Syringes	N/A
Intravenous infusion lines and fluids (usually normal saline)	N/A
Volume-controlled devices for intravenous fluids	N/A
Peripheral venous catheters	N/A
Needles	N/A
Special connecting (**Huber**) needles to implanted venous access devices	N/A
Sterile dressings and means for sterile chain during procedures on central venous catheters	N/A
Anaesthesia recording charts	N/A

Abbreviations: N/A: not applicable

FIG. 5. A modern linear accelerator treating a paediatric patient. Courtesy of Susan Awrey R.N., BScN. SickKids/Princess Margaret Cancer Centre

2.2.4 Drugs

Selecting the most appropriate drug for the child is extremely important. Since the treatment time is short anaesthetic agents having effect for a short duration are usually preferred. Children receive daily anaesthesia for up to 5-6 weeks, which is a unique situation among all anaesthesia applications. During the repeated anaesthesia sessions many patients develop resistance to anaesthetic drugs used and increase of the drug dose within the tolerance limits or switching to another drug may be required. A spectrum of anaesthetic medicines should be ready to be selected for daily administration (Table 4).

TABLE 4. DRUGS REQUIRED FOR PAEDIATRIC RADIOTHERAPY

Drugs	Mandatory	Ideally
Anaesthetics	Intravenous anaesthetics/hypnotics (i.e., propofol, midazolam)	Volatile anaesthetic (halogens, i.e., sevoflurane), opioids, and intravenous/intranasal/sublingual sedative (i.e., dexmedetomidine)
Resuscitation drugs	Epinephrine, nor-epinephrine, atropine, ephedrine	N/A
	Myorelaxants (fast acting curares, i.e., suxamethonium)	N/A
	Normal saline 50 ml to 500 ml, glucose 10%, 30%, polyionic infusion fluids	N/A
	Bronchodilators and rescue inhalers	N/A
	Corticosteroids	N/A
	Antihistamine drugs, intravenous and orally	N/A
	Antiemetic drugs, intravenous and orally	N/A
	Antibiotics (if needed)	N/A
	Analgesics, intravenous and orally	N/A

Abbreviations: N/A: not applicable

2.2.5 Resuscitation

Anaesthesia procedures during radiotherapy are relatively safe but can always carry some risk and the department should be prepared for emergency situations (Table 5). Some cancer patients are more prone to risks of anaesthesia than others due to airway obstruction resulting from tumour compression, decreased respiratory capacity or increased anaesthetics doses due to repeated administration extending to weeks. Emergency equipment should be ready and easily accessible during all procedures.

TABLE 5. REQUIREMENTS FOR PAEDIATRIC RESUSCITATION DURING RADIOTHERAPY

Mandatory (adapted to different weights)	**Ideally**
Means for tracheal intubation (laryngoscopes, endo-tracheal tubes, connecting systems)	Intraosseous catheters with insertion devices (drill)
Gastric tubes	Devices for difficult intubation: video-laryngoscopes, gum elastic bougies
Bag valve mask resuscitator	N/A
Transport ventilator adapted for children including toddlers weighing less than 10 kg	N/A
Tourniquets	N/A
Infusion pumps with respective syringes and connecting systems	N/A
Defibrillator	N/A
Established and consolidated protocols, pathways, and agreements for transfer to oncological or intensive care units of critical patients after clinical stabilization	N/A
Prepared personal to support in management of patient in critical condition (need for medical simulation training)	N/A

Abbreviations: N/A: not applicable

2.2.6 Other considerations

This list is not exhaustive. Specifically, it does not mention the additional facilities and requirements to address the comfort and well-being of children undergoing repeated anaesthesia, and their parents. These issues are covered in Section 4.

A bibliography of references and guidelines on paediatric anaesthesia is provided in the Appendix.

3 THE PAEDIATRIC RADIOTHERAPY TEAM

3.1 INTRODUCTION

Planning and delivery of paediatric radiation treatment has a multi-professional nature, including ROs, RTTs, MPs, nurses, and non-clinical administrators. The roles of these professionals are discussed below. However, teamworking is also required with many staff in other clinical specialties including paediatric specialists in oncology, anaesthesia and endocrinology, specialist nurses in paediatric oncology and anaesthesia and play specialty teams [29].

Children also need support from diverse medical specialties outside the oncologic field. These may include physiotherapists and occupational therapists, nutritionists, psychologists, psychiatrists, social workers, protocol coordinators, play (child life) specialists, reaction therapists and spiritual leaders. It is important to offer family centred care, as attention to the needs of the entire family will directly benefit the paediatric patient, who is highly dependent on the support of parents and siblings. A dedicated paediatric team including a nurse, play therapist, and RTT will enhance the experience of the child and family. This team can assist with compliance and comfort level, and critically may decrease the need for anaesthesia. With preparation, teaching and daily involvement, the child may co-operate with treatment without anaesthesia, reducing risk and discomfort and benefitting departmental workflow.

3.2 WORKFORCE PLANNING

There are no existing staffing guidelines specific to paediatric radiotherapy. It is rare for a radiotherapy centre to serve only children; typically, children receive radiotherapy in centres which also serve adults. Thus, generic staffing guidelines developed for radiotherapy centres are applied to paediatric radiotherapy as well.

The IAEA provide staffing guidelines in radiotherapy for different levels of service [29,30]. In planning a national radiotherapy service, one RO is recommended for each 200-250 patients treated annually, no more than 25-30 patients should be under treatment by a single RO. One MP is recommended for each 400 patients treated annually, and two RTTs per megavoltage machine plus additional staff for simulation, mould room and other duties. These recommendations can form a baseline for the workforce planning of a centre. However, they represent minimum staffing levels needed to initiate or sustain a basic service, and do not allow for complexity in techniques, technology, and services. To address this, the IAEA developed an interactive programme where the recommended staffing to operate a radiotherapy department can be calculated by an activity-based approach which allows for multiple parameters including planning and treatment technique, positioning, simulation, image guidance and equipment. [30].

The European Society for Radiotherapy and Oncology has also proposed guidelines for radiotherapy staffing through its QUAntification of Radiation Therapy Infrastructure and Staffing Needs project, where one RO per 200-250 patients, and one MP per 450-500 patients annually were recommended. Although these numbers are very similar to the IAEA guidelines, QUAntification of Radiation

Therapy Infrastructure and Staffing Needs also suggest variations depending upon the complexity of the treatment. [31,32].

It should be kept in mind that neither of those guidelines were developed for children; even the activity-based staffing calculations of the IAEA lack parameters such as anaesthesia, play therapy, paediatric immobilization etc. which are more demanding on staff time. Significant numbers of paediatric patients in the radiotherapy workload necessitate additional staff and a reduced workload for the professionals involved.

3.3 ROLES OF THE TEAM MEMBERS

Paediatric radiotherapy requires a team effort. The roles and responsibilities of each team member should be clearly defined for the harmonized work of the team and the success of the treatment.

3.3.1 Medical Director or leader

The paediatric radiation oncology leader of an institute should work in conjunction with all the team members in different subspecialties and other stakeholders including the institute management, regional and national health authorities, radiotherapy equipment suppliers, technical personnel of the institute, directors of other paediatric oncology institutions, and civil society and patients' support groups to provide a high-quality service. It is the leader's responsibility to create a culture of safety and quality, and to empower team members to participate actively in improving clinical practice without fear of reprimand or reprisal. They should develop and adopt policies to enhance performance and increase professional competency and expectation through discussing quality improvement methodology and appropriate use of resources with all staff members [29-31].

3.3.2 Radiation Oncologist

The RO is a medical professional responsible for recommending, prescribing, and supervising treatment with radiation, and for the supportive care of the patient during radiotherapy. They should contribute effectively to the tumour board or MDT meeting through discussion of the role of radiotherapy in patients' management and the scheduling of radiotherapy, systemic therapy and surgery in patients treated with combined modality therapy.

The RO should take a focused history of the child, undertake a clinical examination, evaluate the relevant imaging and laboratory tests, and review the MDT diagnosis and treatment recommendations. He/she should apply hospital, national or international guidelines in the management of an individual patient and should appreciate the potential interactions of radiotherapy with other parts of the treatment plan such as surgery and systemic therapies. They should explain the radiotherapy strategy to the patient and family and discuss treatment options, goals of treatment, pre-treatment procedures such as dental review, simulation including immobilization and the use of contrast agents, the treatment regimen and acute toxicities and supportive measures, as well as the probabilities and consequences of potential late effects.

At the time of radiotherapy planning, the RO determines and defines the target volumes (TVs) and organs at risk (OAR) using appropriate diagnostic imaging techniques including CT, MRI, and PET/CT. In collaboration with MPs and RTTs, he/she will evaluate radiotherapy treatment plans generated by MPs using relevant guidelines for prescribing, recording, and reporting dose, critically evaluating the dose distribution in the tumour volumes and OAR, ensuring that dose constraints for normal tissues are not exceeded and exploring options if required for improving unsatisfactory plans. The RO takes overall responsibility for approving the final treatment plan and verification of radiotherapy treatment, using techniques for real-time image guidance, if available, to check the accuracy of patient set up and make necessary adjustments. They assess and manage early radiation reactions in patients and modify treatment, if required, to adjust for gaps, applying radiobiology principles. It is recognized that adequate RO staffing is one of the most significant factors in the delivery of safe high-quality radiation therapy [33]. Increased staffing is needed to cope with the use of advanced technology and increasing treatment complexity, and the more complex the treatment, the greater the necessity for staff to have time for education, training, quality control (QC) and assurance to achieve and maintain competency and safety.

3.3.3 Medical Physicist

The MP is involved in many activities including dosimetry measurements, radiation safety, treatment planning, QC and equipment selection [34]. Structured training for medical physics duties specific to paediatric cancers is not available everywhere, and MPs taking responsibility for paediatric patients usually learn from seniors and through postgraduate training events such as courses, workshops, and conferences. Radiotherapy planning for childhood cancers differs considerably from adults for several reasons including the smaller anatomy, presence of developing organs, different tumour types with specific spread patterns and different dose constraints for OAR. MPs should be aware of all these aspects to generate a radiotherapy plan with the optimal dose distribution. Additional specific dosimetry and QA/QC requirements might also be considered with some paediatric radiotherapy procedures, such as total body irradiation or CSI.

3.3.4 Radiation Technologist

These staff are termed therapy radiographers or manipulators in some countries. The RTT is responsible for understanding and interpreting the radiotherapy treatment prescription to prepare the patient and deliver treatment accurately. Their duties include:

- Treatment planning procedures including simulation (conventional, CT, and MRI Sim),
- Patient positioning, immobilization, and use of shielding devices
- Setting up fields and planes of origin
- Verification of daily set up according to the department policy and making necessary adjustments.
- Accurate delivery of external beam radiotherapy
- Operating remote afterloading brachytherapy machine when employed
- Maintenance of daily records and updating relevant information
- Monitoring patients and reporting physical or psychological changes that may require action.

As the person who interacts with the patient daily, the RTT should respect the privacy and dignity of the patient. He/she may take responsibility for professional communication between all members of the team [6].

3.3.5 Radiation Oncology Nurse

Nurses offer the care required to ensure that the patient and family will cope with and adapt to radiotherapy and its side effects. The role of the radiation oncology nurse includes assessment and education of the patient and family, focusing on the patient's total cancer experience and not just radiotherapy. This will include knowledge and prevention of side effects, psychological support and liaison with other healthcare professionals including paediatric oncology.

During the treatment, nurses see the children more frequently than the RO and can play a significant role in early detection of physical and psychological problems necessitating intervention. Nurses may also assist the RTTs during simulation and treatment and the anaesthesia team when it is required. They can share a rehabilitation programme for the patient, help with creation of educational tools and resources and participate in clinical nursing research [35].

3.3.6 Anaesthesia team

Daily anaesthesia of the children requires an experienced anaesthesia team including an anaesthesiologist and anaesthesia technicians. These staff are usually not members of the radiation oncology department but should be considered as the part of the paediatric radiotherapy team. The anaesthesia team should be available five days a week to allow for standard fractionation and whenever necessary in case of an emergency.

3.3.7 Play Therapist

A qualified hospital play therapist has an important role in preparing the child for radiotherapy by facilitating communication through play. A play therapist is trained in the developmental needs of children at different ages and selects appropriate measures to assist the child through planning and treatment. Play therapists may be required to support the child in the first consultation meeting and at different appointments including planning and treatment. The play therapist can help to prepare the child and reduce misconceptions, anxieties, and fear. The play therapist uses distraction techniques and coping strategies with children enabling them to cope more effectively with treatment. Furthermore, the play therapist enables the child to express his feelings safely and to convey them to the RO and psychologist if needed [36].

3.3.8 Psychology/psychiatry team

Around 25%–30% of paediatric cancer patients have significant psychosocial problems including distress during treatment that may persist for years after treatment is completed [37]. Children and parents may also experience longer-term depression, anxiety, and poorer quality of life [38]. Distress may impact parents' well-being and caregiving abilities and indirectly affect the mental and physical health of the sick child. A Psychology/psychiatry team specialized in paediatric cancer patients is

essential for the supportive care of the children and improving both the psychological and physical outcomes.

3.3.9 Dietician

Dieticians play a critical role in the management of paediatric cancer patients [39]. A consultation should take place with the dietician before the start of the radiotherapy schedule, and the dietician should evaluate child's nutritional status and energy needs. This assessment should take account of previous morbid treatments such as major surgeries and intensive chemotherapy, the treatment site(s) and radiotherapy volumes and the duration of the planned radiotherapy to decide on the nutritional support.

Reversing malnutrition and optimizing nutrition status throughout radiotherapy and other oncologic treatments in paediatric patients can play an important role in improving outcomes. Children undergoing radiation may be required to fast for six to eight hours prior to daily anaesthesia. Abdominal irradiation may decrease gastrointestinal absorption secondary to mucosal damage, diarrhoea, and skin breakdown [40]. Preventing dehydration and weight loss is important in all patients receiving radiotherapy and has been shown to improve their tolerance to future treatment and survival outcomes.

In summary, it is well known that radiotherapy care delivery for children has more complexities than that for adult practice. More time is required for consultation, preparation, planning, and treatment delivery and additional areas of expertise, including anaesthesia, psychological support, play therapy, and other specialists may be needed. The whole team should endeavour to empower the child, helping them to understand the procedure and allowing them to develop individualized coping strategies. Paediatric practice ranges from babies through toddlers and primary school children to teenagers up to 18 years of age. Each group requires management in an age and developmentally appropriate way [41].

4. ENSURING A PROPER PAEDIATRIC APPROACH TO RADIATION THERAPY

This section will cover areas related to providing care to the child and family during their radiation therapy treatment. It includes practical ideas for making the process more comfortable and less stressful for all involved.

Treating children with radiotherapy differs significantly from treating adults and brings greater challenges. Besides the consideration of growth and development at all stages, communication with small children and anxious parents and guardians requires a professional approach and experience. Most paediatric cancer patients are treated with complex and detailed treatment protocols which combine surgery, radiotherapy, and chemotherapy. In this aspect, paediatric cancer management is more demanding since careful follow-up of the ongoing treatment is essential by all members of the treatment team at all stages of the treatment. Radiation treatment does not hurt and once set up in the treatment position, the children are not disturbed. However, the treatment can be a stressful time for the child and family. Radiotherapy usually means a change of daily routines and attending a new hospital environment with new staff. The thought of radiation can itself cause anxiety to both the child and parents, due to fear of the unknown. In addition, in most stages of a child's cancer journey the parents can be with the child physically, but with radiotherapy there is separation during the beam-on time when no-one else is permitted in the treatment bunker.

4.1 THE PHYSICAL ENVIRONMENT TO SUPPORT THE CHILD

Creating a safe and friendly space for children in the radiotherapy department is recommended, ideally with a separate area for teenagers. This space should be designed as a playground, equipped with age and developmentally appropriate toys and other distractions. The treatment units should also be child friendly making the space feel safe for them in a scary situation. Try to remove any unnecessary equipment in the consulting room, the anaesthesia area and the bunker that may scare the child or feel them uncomfortable. Store necessary equipment, especially fixation devices that may appear scary, discreetly. A pleasant, child friendly, clean area with additions that will relax the child and make them feel comfortable is ideal.

4.2 INFORMATION PROVISION/EDUCATION FOR THE CHILD AND FAMILY: WHAT TO EXPECT DURING TREATMENT

Children deserve to be carefully informed in an honest and straightforward way about what is happening to them. This can include illustrated booklets, videos, and models of equipment. Full, accurate and reliable information is needed for parents. It is important to have teaching tools which are geared to the age range and cognitive development of the child. The child needs to be told in an age-appropriate manner why the treatment is being done, and how one hope it will help, with the parent or guardian's support of course. There are currently resources available on-line [42] which can utilize and supplement information in the radiation department. Pictures of the centre, the people they may meet, the waiting area, and planning and treatment rooms will give the child and family some basic information on what to expect. It can also be helpful to have pictures and videos, or even to meet other children getting to planning or treatment. A short, guided visit to the department with a

therapist would usefully complement this information. Pre-recorded music or a beloved story played during treatment can also help lessen the anxiety created by unfamiliar surroundings.

Older children will often readily accept an explanation from the radiation oncology team. Assistance from additional team members can assist with teaching younger children through development-appropriate communication tools. It is important to give the child as much autonomy as possible and say, "I am going to speak to mom or dad now about the treatment, don't worry if there are words you don't understand and if there is something else you would like to ask me, let me know". Asking a younger child to draw a picture and write their name down is usually a good idea when you take the conversation to parent level. File this picture so the child sees that their contribution is important to you. Make sure you establish a rapport with both the child and the parents or guardian from the outset and that they know your role in the team and know what to call you. If you are comfortable allowing the child to use the easiest name you have, your first name or nickname, it can help establish trust, but in whatever connection or rapport you establish make sure it's one you are sincere about. Children have great radar for insincerity.

4.3 HELPING A CHILD THROUGH RADIATION THERAPY

4.3.1 How do you work with children?

On arrival in the radiotherapy department, most children with cancer have already experienced several painful diagnostic and treatment procedures including surgery and chemotherapy. They may anticipate and fear the unknown of yet another new procedure and in many cases, this fear prevents the child from cooperating, especially if they are of a very young age. It is important to communicate openly and honestly with the child. Building a strong connection through talking and answering their questions, helps them to feel secure and supported. If a child is prepared for what to expect during appointments, this will help in gaining his/her trust and cooperation and may avoid the need for anaesthesia during simulation and treatment. The radiation team in collaboration with paediatricians, paediatric nurses and play therapists are valuable resources in preparing a child for radiation. A special toy or video, blanket or favourite dress may help the child through this difficult time, and they should be encouraged to bring one along with them.

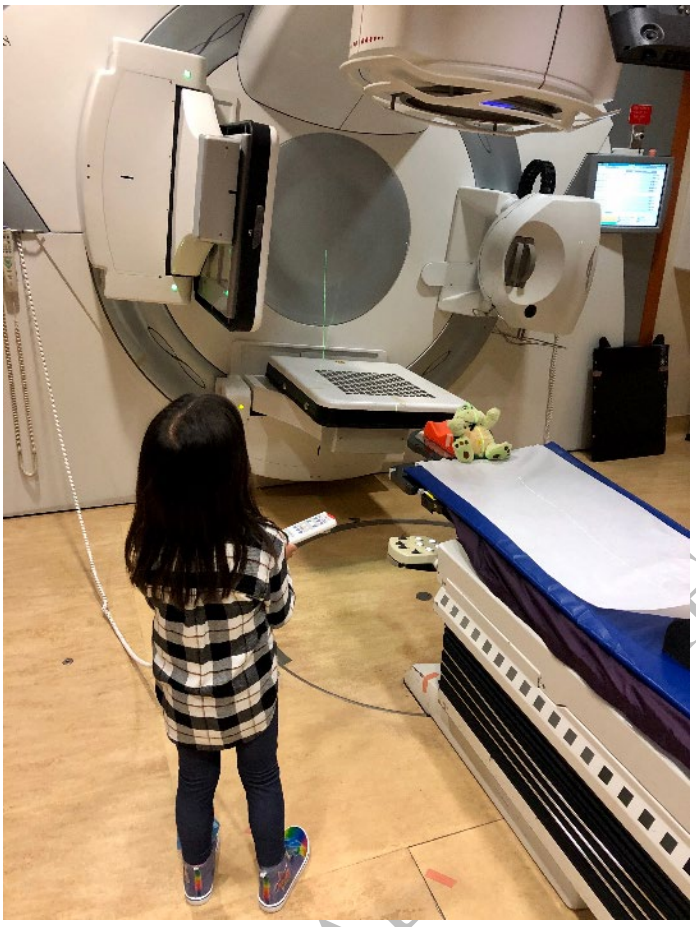

FIG. 6. A play time at the treatment room. Courtesy of Susan Awrey R.N., BScN. SickKids/Princess Margaret Cancer Centre

Treating children requires a team approach with health care professionals, the children, and their families working together. Understanding the needs of the child and family assists in decision making. Children usually know nothing about the radiotherapy process, and it should be explained in an appropriate way. Many children are accustomed to teaching, and teaching techniques may help them to learn about the radiotherapy procedures. Play time, including a favourite toy or distraction, especially around intimidating machinery or procedures may help to make treatments easier (Fig. 6). New techniques to make treatment easier can always be considered. Sometimes a reward system may help to gain the co-operation of the child. It is important to limit the number of people in the room, since too many people may make the child anxious, and safety issues should be always kept in mind when the parents are inside the treatment room.

4.3.2 A child-friendly team

Part of making the environment optimal for children and families is continuity of care, and ideally the same RTTs should treat the child each day to establish a trusting relationship. Other ways to provide this comfort include asking the child to bring along a favourite stuffed toy or blanket that can be with them in the bunker during treatment. Children love to make choices especially when they do not have a choice about whether to accept chemotherapy or radiation therapy. Little things like which

side of the treatment couch to climb up on or choosing a daily sticker for a sticker/check mark calendar can greatly assist them to count down to the end of treatment. If there is access to audio-visual equipment, this also helps by keeping them distracted and more comfortable.

Novel ideas providing security to the child should be welcomed. A ribbon with one end held onto by the child and the other by the parent may help the child feel connected to their parent even when separated in the CT scanner or treatment bunker. For children tolerating their simulation without sedation, it is important to keep talking to them once everyone leaves the room and, if possible, to allow their guardian to talk to them through the intercom. Once again, communicating with the child and explaining why it's so important to do this well with their help, gives them autonomy.

4.4 SPECIAL SITUATIONS FOR PAEDIATRIC RADIOTHERAPY

4.4.1 Immobilization during planning and treatment

Immobilization of the child on the treatment couch for precise radiation treatment is critical. It is important to consider the age of the child, the area for treatment and the need for a mask or intravenous contrast infusion prior to the planning simulation. Novelty masks such as those painted as ballerinas or superheroes may make the mask slightly more appealing. As they go through treatment, most children will begin to tolerate the immobilization device but it's important that the mask or body foam and the set-up is good from the start. Paediatric headrests and small mask sizes need to be readily available. Opening the eye sections of the masks may help the child feel more comfortable and less scared of what is happening around them. This will increase their compliance with lying still. General anaesthesia will be needed for the youngest children, but with time and very careful preparation, even quite young children can be coached to cooperate voluntarily with what is required of them for treatment.

4.4.2 Clinical care of the child during treatment

A consultation with the RO is scheduled at least once a week during radiation treatment to examine the child, manage acute side effects, give further explanations to parents, and direct them to other members of the team for supportive care when necessary. Listening to the child as well as the parents at these treatment checks is very important.

Paediatric ROs are familiar with the medical care of children, such as acute side effects of radiation treatments; however, they are not trained paediatricians. Supportive care ranging from nutrition to treatment of concurrent infections and bone marrow depletion need the expertise of paediatric doctors and nurses especially when children are receiving concurrent chemotherapy. Assistance from the dietician may also be essential when children are receiving anaesthesia as they will fast for several hours daily before the anaesthesia. These specialists should work together in their respective areas to address any clinical need. Increasingly, a paediatric palliative care (PC) team may also be integrated into clinical care early in the child's illness, as palliation has a role from the time of diagnosis in many cases.

5. SERVICES FOR ADOLESCENTS AND YOUNG ADULTS

Teenagers and young adults, often termed adolescents and young adults (AYA) are a special group of patients who do not fit into either the paediatric group, or the adult patient group. AYA have some specific challenges and special needs when it comes to diagnosis, treatment, supportive care and follow up. The aim of identifying AYA as a separate group in cancer management is to improve outcomes in these patients.

For children with cancer aged below fifteen years, survival has improved dramatically over the past half century, largely due to coordinated research in the paediatric oncology communities. However, despite cancer being more common in the AYA group, the same improvements and inclusion in research studies have not been evident. Over the past decade and a half, many HICs have developed specialized units for management of these patients and have managed to effect definite improvements in outcome in almost all groups of cancers [43]. In resource constrained environments, however, this is seldom the case, and these patients fall between the paediatric and adult services depending on their age, diagnosis, and various other local factors [44].

5.1 HOW IS AYA DEFINED?

There is no universally agreed definition of the AYA. As mentioned in Section 1, WHO and the United Nations define 'adolescence' as the phase of life between childhood and adulthood, from ages 10 to 19, and 'youth' as the phase between the ages of 15 and 24. [45]. In the United Kingdom teenagers are defined as 13–18 years and young adults as 19–24 years [46]. The National Comprehensive Cancer Network and National Cancer Institute define AYA as 15–39 years [47, 48]. Other scientific and health organizations, including the WHO [49] restricted the age range to 15–25 years and the Surveillance, Epidemiology and End Results programme defined 15–29 years as the limit of AYA [50]. Barr et al [51, 52] suggested that the flexibility in age range is made to serve certain purposes; early to mid-twenties for the provision of active treatment, 29 or 30 years for epidemiology, and 39 or 40 years to accommodate clinical follow-up.

Using the wider age range may have major implications in terms of descriptive analysis, such as a dramatic effect on disease prevalence and distribution that is markedly influenced by the prevalence of epithelial tumours, the most prevalent tumours among adults. However, accumulating evidence suggests that although many of AYA may have histologically similar epithelial tumours, these may be biologically distinct from what appears to be the same neoplasm in older persons. AYA cancers may therefore have different aetiologies and require different therapeutic strategies.

5.2 INCIDENCE AND SURVIVAL IN AYA CANCER

Most data available for assessment of incidence and survival in AYA cancers come from HICs as population-based registries are lacking in many LMICs. In HICs, cancer is the leading cause of disease-related death amongst AYA. Overall, the global number of new cancer cases in this age group is approximately 1,000,000 per year, most of whom live in LMICs. Registries in HICs show that the

incidence of cancer increases progressively from childhood to adulthood and is slowly rising, with the largest increases seen in thyroid cancer [53]. AYA survival rates are also slowly improving, albeit not as quickly as in younger children's cancer survivals which reach 80% across all types of cancers.

According to GLOBOCAN 2020, the worldwide estimate of cancer cases was 19,292,789 of which 187,242 (1%) fell in the AYA age range of 15–24 years. The AYA incidence rate was 21.4 and mortality rate 7.0 per 100,000 population [54] - higher than that estimated for the paediatric age group. In 2020, Miller et al estimated 89,500 new cancer cases and 9,270 cancer deaths in AYA in the United States of America (USA) and analysed the relative incidences in each age category (Table 6) [55].

TABLE 6. THE TEN MOST COMMON TYPES OF CANCER IN AYA DIFFERENT AGE GROUPS [55]

Age 15–19 year **5,800 patients (6.5 %)**		**Age 20–29 year** **24,900 patients (27.8 %)**		**Age 30–39 year** **58,800 patients (65.7 %)**	
Cancer type	%	Cancer type	%	Cancer type	%
Thyroid	13.8	Thyroid	18.9	Female breast	18.9
Hodgkin	13.8	Testicular germ cell	12.0	Thyroid	15.3
Brain	8.6	Melanoma	8.8	Melanoma	9.4
Non-Hodgkin	8.6	Hodgkin	8.0	Colon & Rectum	7.0
Testicular germ cell	6.9	Female breast	6.0	Testicular germ cell	5.3
Acute lymphoblastic leukaemia	6.9	Non-Hodgkin	5.6	Uterine Cervix	5.1
Bone tumours	6.9	Colon & Rectum	5.2	Non-Hodgkin	5.0
Soft tissue sarcoma	6.9	Brain	4.8	Kidney	4.1
Melanoma	3.4	Soft tissue sarcoma	4.0	Uterine Corpus	3.4
Acute Myeloid Leukaemia	3.4	Uterine Cervix	3.2	Brain	3.1

In Europe, USA and Japan, AYA experienced worse survival than children aged below 15 years for most cancers that occur in both age groups, while (with a few exceptions) they had better survival than adults for overlapping cancers. However, there are wide inter-geographic variations among AYA incidence, with the highest incidence of Kaposi sarcoma in Africa, the highest rates of liver cancer in African and Asian males, and an excess of Hodgkin lymphoma in North America, Europe, and South America. Each of these is underpinned by a genetic or environmental cause, or both [56]. In Jordan, a LMIC, adolescents and young adult cancer patients represent 16.3% of all new cancer cases. Girls are more represented than boys (1.44: 1) because of the frequency of thyroid and breast cancers. Five-

year survival rate for the AYA group was 72.4%, which was significantly better than that for adults aged ≥ 40 years (59.8%) but worse than that for paediatric patients aged below 15 years (79.2%) ($P < 0.0001$) [57].

AYA experienced a higher risk of long-term and late effects than older patients, including infertility, sexual dysfunction, cardiovascular disease, and delay in diagnosis for some secondary cancers. However, when compared with childhood cancer survivors, the risks of severe late effects are lower in AYA patients. [25,58-60]

5.3 TYPES OF CANCER SEEN IN AYA

The cancer types seen in in AYA differ from those of both the paediatric and adult populations. Embryonal tumours, such as neuroblastoma, nephroblastoma, medulloblastoma, hepatoblastoma, and retinoblastoma, are the most common childhood cancers but occur less frequently in AYA. In contrast, the incidence of bone sarcomas peaks in the AYA group and Hodgkin and non-Hodgkin lymphomas are much more prevalent. Melanoma and germ cell tumours are relatively common, and some carcinomas (especially of thyroid and breast in females) start to appear [61].

5.4 DISTINCT TUMOUR BIOLOGY

Existing data from studies on several AYA cancers showed evidence that tumours of AYA cancers may differ biologically from those in older and younger patients. Most of this evidence is still preliminary and large comprehensive studies to confirm and validate these findings are still undergoing. A better understanding of the AYA cancer biology facilitates the development of new diagnostic and predictive markers and may identify novel therapeutic targets and treatment approaches in the future [62].

One of the earliest examples of the evidence for the different nature of AYA tumour biology is colorectal cancer (CRC). The hallmark of hereditary nonpolyposis colon cancer, an inherited form of CRC (Lynch syndrome), is microsatellite instability due to mutations in the mismatch repair genes *MLH1* and *MSH2*. An analysis of microsatellite instability in 189 CRC patients with no familial evidence of hereditary nonpolyposis colon cancer, using four to five microsatellite markers per tumour, revealed that 58% of the tumours in patients aged 35 years or younger displayed microsatellite instability compared to only 17% in older patients [63]. In another study, tumours from 126 CRC patients aged 13–39 years were compared with those from 126 CRC patients aged over 60 years. The tumours from younger patients were characterized by poorer differentiation, a higher incidence of mucinous tumours and signet ring cells, more advanced stage at diagnosis and a significantly lower percentage of *p53* overexpression [64].

Breast cancer forms 4–5% of AYA cases. Although there is less evidence for unique biology, they are generally found to behave more aggressively than cancers in older patients. Tumours are usually larger at presentation, higher grade, and frequently triple-negative sub-type [65].

Differences in biological characteristics in AYA patients have also been found in acute lymphocytic leukaemia where the *TEL-AML1* translocation, which confers a favourable prognosis, occurs at much lower rates than in younger children, whereas the Philadelphia chromosome-like alteration, conferring a poor prognosis, is prevalent [66].

5.5 SPECIAL CHALLENGES WHEN TREATING AYA

Barr et al, [53] outline the following specific issues:

(a) **Delay in diagnosis**: In many cases, failure to recognize or failure to report symptoms or signs delays diagnosis in AYA cancer patients.
(b) **Adherence to therapy**: There is a general assumption that many AYA comply poorly to treatment regimens, especially with oral medication. Hanghøj et al [67] suggest that relationships with parents or peers, distractibility, poor planning, striving for normality, the complexities of treatment protocols and financial issues may all contribute to this.
(c) **Need for psychological support, rehabilitation, and exercise**: The disease itself and the adverse effects of its treatment, may seriously affect the normal process of maturation in AYA, and cause developmental regression. Early psychosocial support is necessary. After successful completion of therapy, ongoing support is needed to help AYA cancer patients regain normality and autonomy. There is evidence that both formal psychosocial support and physical exercise help in reduction of stress and promote an active lifestyle in AYA cancer survivors.
(d) **Sexuality and body image**: It is well-documented that cancer and its treatment have significant impact on AYA sexuality and may cause a negative body image. All possible measures should be considered to preserve normal sexuality and lessen the burden.
(e) **Onco-fertility**: Chemotherapy protocols using alkylating agents and abdominopelvic radiotherapy (especially in females), which are frequently used in the treatment of childhood and adolescent cancer, may cause gonadal injury, manifested as ovarian hormone insufficiency, premature ovarian insufficiency, early menopause, and infertility. Fertility preservation methods are extremely important, including psychological and ethical considerations and barriers.
(f) **Financial issues before, during, and after treatment**: Young people are often in financial transition from dependence on parents to separate financial security. This may affect AYA cancer patients prior to the diagnosis, during active treatment and after the end of therapy with possible late-effects and, sometimes, inability to resume normal education and/or employment.
(g) **Location of care and clinical trial enrolment**: In many centres and less well-resourced parts of the world, patients who exceed the upper limit of paediatric age are referred to adult services where they are treated on adult protocols. Older AYA patients are usually treated by 'adult' oncologists, while paediatric oncologists may deal with younger age groups. This creates a challenging issue for older paediatric patients and young adults who may be lost in between [68] or fail to transition. Furthermore, AYA patients are usually underrepresented in clinical trials which may contribute to the lack of progress in treatment outcomes in this age group [69] The enrolment of such patients in clinical trials is inadequate worldwide to the extent that in the USA, only 5% of 15-25 year old with cancer are entered onto clinical trials, in contrast to 60-65% of younger patients.

5.6 RADIOTHERAPY TOXICITIES IN THE AYA AGE GROUP

5.6.1 Acute and sub-acute toxicities

Psycho-emotional and social support is important during radiotherapy when the AYA group may feel somewhat isolated and vulnerable. Peer acceptance is crucial in this age group, and buy-in from school, with attendant peer support can make a huge difference. Pain management is crucial and can affect overall adherence to treatment. During treatment, particular monitoring is required for mucositis, myelosuppression, and skin toxicities, which are commonly potentiated with intense concurrent chemotherapy regimens.

There may be specific considerations regarding toxicities in this age group. For example, although the risk of radiation-induced CNS necrosis appears inversely proportional to age, the adolescent spinal cord may be particularly sensitive to chemo-radiotoxicity [70]. In addition, certain specific radiosensitizers, such as Melphalan and Busulphan, may predispose to increased cord toxicity. Carrie et al [71] reported on this toxicity in patients receiving treatment for Ewing sarcoma and advised caution when irradiating the spinal cord after Busulfan-melphalan chemotherapy, with a maximum dose of 30 Gy recommended.

5.6.2 Late toxicities

Prescribing radiotherapy necessitates making a balance of the risk of loss of efficacy versus toxicity. The specific effects to be considered for the AYA population include neurocognitive damage, endocrine consequences, incomplete pubertal development, infertility, and stunted growth. It is worth noting that very limited specific radiation toxicity data are available in this group. However, most research that includes children and adolescents has shown trends denoting that the toxicity of conventional RT doses in AYA patients is mitigated due to the protective effect of organ maturation when compared with children. The exception to this is irradiation of sites undergoing maturation, such as breast tissue and gonads, which are at their most vulnerable during adolescence, hence the risk of ovarian radiation and subsequent infertility remains an important consideration. Oophoropexy can be performed to move the ovaries outside the treatment field.

The late effect of radiation vasculopathy is a dynamic, poorly understood process impacting both large and small vessels in long-term survivors. Patients irradiated during paediatric and AYA years may be particularly affected, and certain sub-groups are known to have an enhanced risk, e.g., neurofibromatosis type 1 patients [72]. A careful risk/benefit analysis should be made when planning treatment of susceptible patients.

It is widely documented that the incidence of radiation-induced second malignancy is higher in children than adults. One exception to this general rule is radiation carcinogenesis of breast cancer, where irradiated adolescents and young adults may be at higher risk than younger children [73]. Emerging radiotherapy techniques, especially PBT and carbon-ion therapy, may help reduce such late effects by reducing the integral dose of radiotherapy due to the physical characteristics of the beam. Whilst technologically advanced photon techniques, such as VMAT, can greatly reduce dose to specific OAR, it generally does not reduce integral dose. The incidence of second malignancies in children and AYA treated with IMRT and VMAT therefore remains a concern and the subject of ongoing study.

It is important to address access to long-term surveillance to detect late effects. Screening for all late effects, especially cardiac, endocrine, infertility and second malignancies should occur on an uninterrupted basis (see Section 7). This age group is susceptible to dropping out of care during transition from paediatric to adult health systems. This transition often coincides with social mobility

for education and jobs. Additionally, some may lose healthcare access due to dropping off parent's insurance and as a result, may have gap in care when both tumour recurrence and late effects risks still require careful monitoring.

5.7 PALLIATIVE AND SUPPORTIVE CARE

PC is defined as "an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual" [74]. However, PC integration for AYA cancer patients remains challenging and unsatisfactory compared to that for adults [75]. It is advisable to include the PC team in the multi- disciplinary treatment team from the first day; early PC at time of active treatment and throughout the trajectory of AYA malignant disease can lead to improvement in quality of life by means of prevention and relief of suffering through timely detection, assessment and management of pain and other symptoms.

6. THE PAEDIATRIC RADIOTHERAPY PATHWAY

6.1 DECISION-MAKING

Management of cancer patients requires a multidisciplinary approach where experts from various medical professions collaborate in the diagnosis, staging, treatment, and follow-up of individual cancer patients. Multidisciplinary care of cancer patients plays a pivotal role in the success of cancer treatment, and the MDT is the mainstay of this approach. Usually experts from the same hospital, town or region are the members of a specific MDT which convenes regularly. This group evaluates the individual patient charts, and reviews the radiology, nuclear medicine images, endoscopic findings, laboratory results and pathologic diagnosis. Once the final diagnosis is established and the disease is staged properly, the optimum treatment strategy is agreed according to pre-established treatment protocols.

ROs, paediatric oncologists, paediatric surgeons, radiologists, pathologists, and nuclear medicine specialists are the regular members of a paediatric cancer MDT team. Depending on the diagnosis and condition of the patient, other professionals may join this team including neurosurgeons, gynaecologists, nurses, molecular biologists, or PC specialists. Recently online MDTs have become the norm in many institutes, allowing participation of a wider group of experts from distant regions of a country or even from abroad. MDT working may affect diagnosis, staging, treatment decisions and increase quality of care; therefore, it is recommended as an integral part of paediatric cancer patient management around the world regardless of the country's income level.

6.2 THE INITIAL CONSULTATION

Ideally, the RO and other team members of the MDT should evaluate all cancer patients prior to any diagnostic and treatment procedures including imaging, biopsy, surgery, or chemotherapy. This will prevent unnecessary imaging or procedures and ensure that surgeons adopt the best biopsy site, route, and technique to minimize impact on the radiotherapy fields. Evaluating the tumour *in situ* prior to surgery and chemotherapy allows the RO to visualize and record the exact location of the tumour and relationship to neighbouring structures, so that the pre-treatment volume can be determined, correctly facilitating better TV accuracy and radiotherapy field design. This is especially important for chemo sensitive malignancies such as leukaemias and lymphomas where the tumour may almost disappear after the first chemotherapy administration, or some superficial tumours that cannot be demonstrated with imaging techniques and need to be inspected visually.

Seeing the patient at this stage also allows the RO to meet with the family and explain the radiotherapy process, discuss the expectations from the treatment and inform them regarding possible side effects. The needs of the child and the family such as accommodation, transport, school attendance and possible requirement for daily anaesthesia can be evaluated upfront. If the need for radiotherapy is not yet certain, less detailed information can be given at this stage [41].

Management of paediatric cancer patients usually includes chemotherapy with local therapies (surgery and/or radiotherapy) inserted between the cycles. These complex schedules should be discussed upfront and planned carefully to facilitate seamless continuity of treatment, avoiding undue delays due to logistical issues.

6.3 ASSESSMENT FOR GENERAL ANAESTHESIA

Delivery of safe and effective radiation therapy for paediatric oncology patients younger than 5 years almost always necessitates sedation or general anaesthesia to ensure appropriate immobilization of the patient during radiation therapy. Children older than seven years only occasionally require sedation or anaesthesia [15]. In addition to age, other factors may impact the child's capability of lying alone in the treatment bunker. These include duration and complexity of treatment, the child's ability to be separated from their parent, the child's communication abilities and ability to comprehend instructions [43,76]. The decision to pursue radiation therapy with or without general anaesthesia/intravenous sedation should be made by the RO before initiation of the radiotherapy process in order that appropriate arrangements can be in place. Presence at the new patient paediatric consultation can facilitate this [77]

The addition of anaesthesia or sedation to radiation therapy adds several levels of complexity to the treatment course, conferring significant impact on time scheduling. The anaesthesia team, space, additional instruments, equipment, and medications required are listed in Section 2 [78]. Several simple interventions may greatly assist with radiotherapy in children and even reduce the use of anaesthesia (Section 4) [79-81]. Although anaesthesia and sedation are usually safe, they can be associated with complications. The prevalence of anaesthesia-related complications in children undergoing radiation therapy are similar, if not lower, than rates reported in controlled operating room settings [82-84]. The risk of complications is minimized, although not completely eliminated, by careful pre-procedural evaluation of patients, full monitoring before, during and after the procedure, consistent drug regimens, management by personnel experienced in paediatric anaesthesia, robust procedure documentation and appropriate discharge instructions. It is also vital to have all emergency supplies and medications readily available [83, 84].

6.4 INFORMATION REQUIRED FOR RADIOTHERAPY PLANNING

Initial evaluation of the patient requires a systematic process, especially if care is divided between several hospitals. The RO should ideally have an opportunity to examine the patient before any treatment to record physical findings and request appropriate diagnostic scans that will affect the radiation plan. For example, in patients with head and neck, superficial, or extremity malignancies, the physical examination may detect tumour spread that may not be seen on CT, MRI or PET scans. Full evaluation and/or imaging of the lymph nodes may be overlooked. Abnormal lymph nodes require further evaluation (biopsy, PET scan etc.) since radiation fields and doses would be significantly affected.

Discussion is required with surgical teams and paediatric oncologists about the surgical findings and systemic therapy approach, including agreement on concurrent or subsequent chemotherapy needs. Discussion about OAR concerns, such as mucosal dose, can facilitate mitigation of anticipated acute and late toxicities.

A pre-planning meeting with all members of the radiotherapy team smooths the pathway and ensures the radiotherapy team know what is required of them (see Section 3).

6.5 IMMOBILIZATION AND SIMULATION

Patient positioning and immobilization during simulation are critical to ensure accurate external beam radiotherapy delivery. The goal is to secure the patient and constrain motion in a comfortable reproducible position throughout the course of treatment. To accomplish robust immobilization, prior to simulation, the team require the following information:

(a) the tumour location
(b) the region to be treated
(c) the need for intravenous or other contrast
(d) which normal organs can be displaced away from potential fields to minimize acute and late toxicities
(e) patient age, sedation needs, disabilities, and anxiety

Strategies to help young children accept immobilization and proceed with radiotherapy without anaesthesia are outlined in chapter 4. When sedation is necessary, it is important to be aware of the potential pressure points for the sedated child to avoid injury during prolonged simulation and treatment sessions.

6.5.1 Brain, head, and neck

Typically, when treating above the shoulders, a thermoplastic mask should be used for head/upper neck immobilization for cranial tumours or a head/neck/shoulder immobilization for tumour volumes that extend into the neck. The position of the head for the sedated child is important to allow appropriate airway management and oxygenation. For patients requiring head and neck treatment, intra-oral stents can be effective in moving the tongue, or floor of mouth away from the irradiated area. These stents can be custom made by the dental group when the patient is assessed for dental health prior to treatment. A tongue blade with cork may be effective in opening the mouth and moving the tongue away. If such devices are to be used, the mask should be made with the devices are in place.

Special considerations should be given to set up for CSI since this technique requires comfortable and reproducible patient positioning for the whole body to allow appropriate beam geometry to cover the craniospinal axis. Historically, CSI was delivered in a prone position which was challenging, but the introduction of CT based planning allowed treatment in supine position which is more comfortable for the patient. It is critical that the whole team: physicians, physicists, planners, and therapists are in agreement with the treatment set up, delivery technique and verification.

There are many commercial mask systems available; all have associated neck rests and specific systems to attach the mask to base plates. When selecting a specific system, the cost, availability, reliability, and adaptability for patients with different needs should be considered. The choice of a commercial system should be made in conjunction with the therapy, medical and physics team.

The planning scan should be obtained from the top of the head to below the shoulders to allow for adequate images of the region of interest, and to allow for appropriate digital reconstructed radiographs for treatment setup verification on the machine. If the tumour is visible or palpable, placing a radio-opaque wire around the tumour prior to simulation may help with subsequent tumour delineation. CT acquisition technique should be adjusted for the smaller body habitus for children to minimize unnecessary radiation dose. The slice thickness can be 1.5–3 mm depending on the scan length and need for detail. Occasionally intravenous contrast is required, especially, if a recent

diagnostic CT or MRI scan has not been done, to define tumour details fully. A contrast enhanced CT scan may also facilitate normal organ delineation in the head and neck if MRI is not available.

6.5.2 Chest, abdomen, and pelvis

A large variety of immobilization considerations exist for treatment volumes below the shoulders. For the chest, abdomen and pelvis, the patient can be placed in a moulded device with the arms and lower body placed in a strategic position. Otherwise, the patient may be placed directly on the treatment table with only the lower extremities in a moulded device. Moulded devices include reusable vacuum bags filled with Styrofoam or single patient use moulded pillows made with polyurethane foam. Additional options include generic knee wedges and adjustable wing boards to help to keep the arms above the head for thoracic treatments. Many of these devices are designed for adults; therefore, children may require modifications or alternative positioning devices.

A few considerations should take place for patients with pelvic tumours. In very small children, with low pelvic tumours, a frog leg position may be advantageous to reduce unnecessary upper medial thigh treatment, and this position reduces inguinal skin folds. For boys, an effort to move the testis away from the radiation field should be made; however, this is more feasible in older teenage boys. Scrotal shielding can be considered if the testis lies near, but outside, the irradiation field.

The planning scan should encompass the TV area with an adequate margin to allow for normal tissue delineation and appropriate digital reconstructed radiographs. In cases where there is significant internal organ and tumour motion, i.e., in the chest or the upper abdomen, a 4D CT or MRI scan will allow assessment of tumour and organ motion. Cine-MRI and 4D MRI can be used to determine Clinical Target Volume (CTV) to Internal Target Volume (ITV) margin without the extra radiation dose associated with 4D CT. In older children, breath-hold or gating techniques may be applied to spare normal tissues and whilst treating the tumour effectively. Again, intravenous contrast may be helpful for tumour delineation in the abdomen or for identification of vascular structures.

6.5.3 Extremities

Many children require treatment to the extremities. Immobilization of the extremity to be irradiated should allow separation of the affected part from the body in a way that allows appropriate beam geometries to be achieved without exit dose through the rest of the body. In such cases, it is important to use customized cradles to optimize reproducibility of the limb in its linear and rotational positions. Including the ankle or hand in the immobilization device can reduce rotational uncertainty. The CT scanner bore size should be taken into consideration to make sure that the patient and device will fit through the scanner.

The planning CT scan should be obtained through the tumour volume with adequate margins for normal tissue delineation and adequate digital reconstructed radiographs slice thickness for older children with longer extremities may be 3–5 mm. Occasionally, the patient may need to be scanned in a reversed orientation to achieve the full scan length. If this is necessary, it is important that the patient orientation is recorded appropriately to avoid left to right confusion.

Additional image fusion to the planning scan is highly recommended to optimize tumour and normal tissue delineation. Imaging from before surgery or systemic treatment will often help to guide appropriate CTV delineation. MRI can provide better soft tissue demarcation and definition of tumour extent and PET scans can be valuable to identify lymph nodes or persistent disease that is not enlarged. Fusion quality should be assessed and if there is misalignment or distortion, then the fusion should be done again or optimized to the area of highest importance. Should be there be any

discrepancy in the location of the tumour between the CT and MRI, the CT should be trusted since it is used for planning and targeting.

6.6 TARGET VOLUME, ORGAN AT RISK DELINEATION AND TREATMENT PRESCRIPTION

The most important task for the RO is to determine the TV and identify the OAR. Ideally, volumes should be reviewed and approved by a second experienced clinician (peer review). This is now recommended as standard practise [85, 86], and may be internal within the treating department, or undertaken virtually with colleagues in other centres. Audit tools are available to support systematic and rigorous peer review [87]. External independent review of target and OAR volumes and dosimetry is now available to ensure good quality in clinical trials [88]. TV and OAR delineation will determine the treatment approach and radiation plan, and time and experience are required to appreciate both normal and distorted anatomic relationships. Computer algorithms, including artificial intelligence, are becoming available for OAR delineation and segmentation; however, if using these tools, the final volumes require endorsement by the RO before treatment planning starts.

As noted above, tumour delineation on planning CT scan often necessitates a planning MRI and diagnostic image fusion for better visualization of the tumour and OAR. The final tumour volumes and OAR are generally confirmed on the planning CT, since this image set is the most accurate for patient positioning and geometry, and its underlying information is needed for dose distribution calculation.

TV delineation is approached in a systematic fashion as noted below:

(a) The Gross Tumour Volume (GTV)

This includes any visible tumour(s) that remains after prior interventions and often includes the surgical cavity if surrounding tissue is at risk. Any remaining pathologic lymph nodes that were involved at diagnosis should be included as targets to receive the full radiation dose.

(b)The Clinical Target Volume (CTV)

The CTV encompasses the GTV and tissues that are at risk for subclinical involvement. Evaluation of the anatomic relationships of the OAR, residual and initial disease is needed. The CTV may be a symmetric expansion around a GTV based on estimation of tumour infiltration risk, which can then be adjusted for anatomic boundaries, such as bone or fascial planes. The expansion can range from 0–20 mm depending on the natural history of the tumour type and location. Lymph nodes considered at risk may also be included in the CTV.

(c) An Internal Target Volume (ITV)

The ITV adds a margin on the CTV if this is required to allow for internal motion. It is typically considered for tumours within the thoracic cavity or around the diaphragm. If motion management is required for paediatric patients, a 4D CT or 4D MRI should be used to quantify respiratory motion. Patient specific margins should be applied, because the respiratory motion in children is significantly smaller than that for adults and using standard adult margins will risk unnecessary radiation of OAR.

(d) The Planning Target Volume (PTV)

The PTV is the volume that allows for the uncertainty of daily set up and dose penumbra. It is usually a uniform geometric expansion around the CTV (or ITV) and can be less than for an adult because the smaller body of a child is often easier to immobilize, and setup errors are typically smaller. A margin of 2–5 mm is usually added, based on immobilization, treatment modality and patient factors.

OAR delineation using the planning CT and fused imaging is critical for optimal radiation planning. Adjacent or sensitive nearby structures are identified to facilitate beam orientation, beam weighting and intensity modulation. OAR dose evaluation impacts the final plan approach and dose. A permanent record of final OAR doses is important to predict and monitor risk of toxicity for care providers, the patient and family. Since organs are developing and at higher risk for subsequent injury, growth retardation, and/or second malignancy in children, any normal tissue that is seen within the irradiated volume should be considered for delineation. Functional sub-structures, such as the hippocampi or cardiac substructures, can also be delineated. Some OAR have specific importance in children and significant sequelae may occur even after low or uniform doses. These include the growth plates, vertebral bodies, and thyroid gland.

6.6.1 Dose Prescription

The prescribed dose depends on the tumour type but may also be influenced by prior history, OAR doses, patient age and/or other specific risks. The RO will prescribe and approve the final dose, fractionation, and plan. Prescribed doses in children can be as low as 10 Gray (Gy) for Wilms tumour or as high as 78 Gy for a chordoma, though typically range between 45–54 Gy for many indications. Daily doses generally range from 1.5–2 Gy for most radical cases. Hypofractionated dose regimens, and approaches including stereotactic body radiotherapy may be considered when metastatic sites are treated. Strategic planning approaches for children requiring different doses for different TVs include sequential boosts or simultaneous integrated boosts using IMRT.

The final plan including dose distribution, fractionation and TV and OAR doses should be reviewed and approved by the treating RO and when possible, peer reviewed. The plan and delivery details should be reviewed before the start of treatment by a member of the physics team and the therapy team for verification and preparation in the room.

During treatment delivery, if a significant change in tumour size, patient anatomy or weight is noted, a verification plan should be done to ensure tumour coverage and normal tissue sparing remains adequate. The TVs and OAR can be copied to the verification scan. Occasionally, a re-plan to adapt to new circumstances will be needed. The treatment and planning team should be prepared for re-plans and seek to minimize treatment interruptions if this is required. The new plan should be generated, reviewed, and approved with the same rigor as the initial plan.

6.7 TREATMENT PLANNING

Treatment planning of paediatric patients presents some special challenges and considerations compared to adult tumours. Though the fundamental radiation techniques like 3D-conformal radiotherapy, IMRT, and VMAT are identical, it is important to implement paediatric-specific planning protocols.

Treatment plans for paediatric patients may need to meet OAR constraints which are more restrictive than for adult patients, e.g., for the kidney dose, and the list of OAR to be considered will include more organs. An example is spinal bones; radiation-induced bone growth inhibition may cause kyphosis and scoliosis. Similar structural effects elsewhere in the skeleton may lead to adverse cosmetic results e.g., if facial bones are irradiated.

Secondary cancer is a particular concern when treating children, as survival for many decades after radiotherapy is common. Essentially, the entire body is an OAR and the "as low as reasonably achievable" principle formulated for general radiation protection should be applied to the therapeutic situation. If one compares two different treatment plan suggestions for a patient (e.g., 3D-conformal radiotherapy vs. VMAT, or photons vs. proton), the integral dose to the entire body should be considered in the final decision between the two plans. However, specific organs like the thyroid gland and breast tissue are particularly sensitive to radiation and the risk of developing secondary cancer. These organs should be contoured and spared as much as possible as a priority.

Due to the many sensitive OAR, and the anatomically smaller paediatric body with organs located geometrically close to the tumour, highly conformal techniques like IMRT and VMAT are often used to protect critical organs. When available, PBT is often preferred due to the dosimetric benefit of the Bragg peak.

If the patient is treated under anaesthesia, the choice of field geometry should allow for the presence of anaesthesia equipment, in particular tubes to the airways. These may vary in position from fraction to fraction, and fields should not enter the patient through these mobile tubes.

If the patient is not treated under anaesthesia, it is important to consider total treatment time when designing the field geometry. A treatment plan consisting of a small number of VMAT fields can be much faster to deliver than many non-coplanar IMRT fields.

Since paediatric treatment plans are rarely standard in a radiation centre, they can be more resource heavy in the planning phase. If the centre only treats a small number of children, it is important to have a select group of physicists, who are trained and experienced in the specific procedures and challenges regarding the preparation and possible patient-specific QA of these plans.

6.8 TREATMENT DELIVERY

Once the radiation plan has been generated by the MP and approved by the RO, it should be delivered to the patient in a rigorous manner. This process requires competent, trained RTTs, who understand the treatment plan including the setup and treatment technique and are experienced with the equipment required for positioning, imaging, and dose delivery. Each fraction should be delivered with equal attention and active surveillance to identify changes in the patient or set up.

The modern treatment room includes a variety of different imaging and motion management tools. Imaging systems are embedded within the treatment gantry head and allow for onboard imaging including 2D (portal) and 3D (cone beam CT) verification of patient, target, and normal tissue location. Imaging is done on a regular basis depending on the practice of the facility; this system is typically called Image-Guided Radiotherapy (IGRT). Daily imaging prior to treatment delivery, with consequent reduction in positioning uncertainty, may allow a smaller PTV margin to be employed, potentially reducing toxicities.

Motion management tools are also available for treatment delivery. With these techniques, which are typically adopted from experience in adult patients, internal patient movement associated with breathing can be monitored. This process allows techniques such as breath hold or phase gating that can improve treatment accuracy and minimize normal tissue irradiation.

The RTT team should have access to dosimetry, physics and medical personnel for questions that arise. If the patient set up or treatment delivery appears incorrect, then the treatment should not be delivered, and the question should be resolved by the team. IGRT processes should be reviewed by the treating physician on a regular basis to ensure appropriate delivery of the planned dose.

In special situations such as high dose stereotactic radiotherapy (fewer than five fractions, with a high dose per fraction) the physician and physics team should be present to verify the patient's setup and supervise delivery of the treatment. This ensures appropriate and precise delivery since each fraction is critical to the overall treatment plan.

Active management of the patient's weight and nutritional status is important since significant changes in weight can affect immobilization devices and the radiation plan. Re-planning may be required during the treatment course when significant changes in the tumour volume or surrounding tissues occur. These changes are commonest with radiosensitive tumours that shrink or tumour cysts that enlarge during treatment.

During the treatment course, the patient should be seen by their treating physician every week to monitor treatment tolerance and consider if adjustments to the plan are needed.

6.9 ON TREATMENT REVIEW

Children receiving radiation therapy may experience acute toxicity during treatment. This may limit the delivery of safe, therapeutically optimal radiotherapy doses and negatively impact treatment outcome. Therefore, it is essential that the paediatric radiotherapy team monitor children at least weekly for acute toxicities during treatment. Input from staff such as dietitians, physiotherapists, social workers, speech therapists and occupational therapists may be appropriate.

6.10 COMPLETION OF TREATMENT SUMMARY

The treatment summary provides a description of what has been done and why, with doses to target and OAR. Reasons should be given if there was a decision to modify treatment from the standard protocol.

Most cancer care is provided in a multidisciplinary environment which includes personnel who will not have access to, or do not fully understand, radiotherapy plan details. In addition, once the patient has completed cancer therapy, they will probably be seen in a primary care environment or intermittently by specialists providing late effects care or monitoring. In both circumstances, it is important that a precise summary of the radiation therapy is available in the patient's medical record. This information will provide valuable information for future care, including both late effects monitoring and decisions for any further cancer care if required (including further radiotherapy). Ideally, this summary document should include at least the following:

(a) A summary of the patient's medical history and indication for radiation therapy
(b) Intent of treatment: curative, adjuvant, pre-operative, palliative
(c) The protocol which was followed or any on which the patient was enrolled
(d) Concurrent chemotherapy: specific agents should be named
(e) Area(s) of the body treated. Each site should be separated to avoid confusion
(f) Start and end dates of treatment, which can include elapsed days
(g) Radiotherapy treatment plan details:

(i) Modality: electrons, photons, protons, brachytherapy.
(ii) Energy, e.g. 6MV, 9MeV, Iridium.
(iii) Technique: 2D, 3D-conformal radiotherapy, stereotactic body radiotherapy, IMRT, VMAT, intensity modulated PBT, interstitial
(iv) Fractionation: daily, bid, etc.
(v) Dose details: dose per fraction, number of fractions, boost dose and total dose for each site treated

(h) Treatment breaks: intended and unexpected. Give causes and document change (if any) which was made in the plan to adjust for this.

(i) Treatment tolerance: acute toxicities expected and unexpected. When possible, attribution of toxicity to specific treatment may be added.

(j) Follow up recommendations: timing of next visit, confirmation of who will follow up the patient.

7. LONG TERM SURVEILLANCE OF LATE EFFECTS

7.1 INTRODUCTION

As cancer therapies evolve, and therapeutic ratios and outcomes improve, health providers should continually evaluate and modify their management programmes in terms of survivorship. While late effects related to historic cytotoxic chemotherapy agents and radiotherapy are well-characterized, the impact of novel targeted agents and advanced radiation techniques, including proton therapy, on long-term health outcomes has not been systematically described. In this section, one review the fundamental relationships between treatment exposures and acute and late health complications following treatment for childhood cancer and examine current recommendations for surveillance in an organ and system specific fashion. Finally, one discusses the limitations of present data and the need for continued study.

7.2 ORGAN & SYSTEM SPECIFIC CONSIDERATIONS

7.2.1 CNS late effects

7.2.1.1 Neurocognitive late effects

Critical factors are the location of the tumour, the age of the child, the dose and extent of radiotherapy and the damage caused by the tumour [89]. Female gender [90], concomitant chemotherapy (e.g., high dose and intrathecal methotrexate) and hereditary factors may increase the therapy related risk. Factors such as hydrocephalus and post-surgical cerebellar mutism and other therapy related insults to the visual and auditory system may also contribute to cognitive decline [91].

Intelligence quotient is affected including attention, concentration, processing, and memory [92]. The result is an inability to attain new skills rather than neuroregression, hence the effect is age dependent [93]. CSI is discouraged in children under three years and radiotherapy to the hippocampus is avoided whenever possible because it is critical to spatial and relational memory, and thereby behaviour [94]. Limiting the radiotherapy dose to the brain preserves neurocognitive function but should be evaluated in randomized controlled trials since underdosing may worsen outcomes [95]. The use of proton therapy to decrease the dose to the normal brain carries potential to limit neurocognitive sequelae and early data are encouraging.

7.2.1.2 Neurological sequelae

Tumour or therapy (radiation and surgery) related vasculopathy can lead to stroke [96], and direct damage to white matter in the form of leukoencephalopathy can yield a constellation of symptoms including seizures, spasticity, and ataxia, especially in the setting of concomitant treatment with high dose methotrexate [97].

Myelitis is a significant risk for children receiving radical thoracic or abdominal radiotherapy for solid tumours, especially after exposure to alkylating agents as part of conditioning for autologous stem cell rescue following high dose chemotherapy [98].

Hearing loss may be caused by direct damage to the VII/VIII nerve complex by the tumour or may occur following exposure to radiotherapy and/or systemic therapy (e.g., cisplatin) [99] via insult to the cochlea.

Visual impairment after radiotherapy may result from cataracts, keratoconjunctivitis or direct insult to the optic apparatus [100].

7.2.1.3 Neuroendocrine late effects

Neuroendocrine late effects may be caused by the tumour itself (e.g., Diabetes Insipidus in craniopharyngioma), surgery or radiotherapy. Radiotherapy can cause growth failure (growth hormone deficiency), secondary hypothyroidism (thyroid stimulating hormone deficiency), Addisonianism (adrenocorticotropic deficiency) or precocious or delayed puberty [101]. The risk for anterior hypopituitarism correlates with radiotherapy dose, with growth failure and precocious puberty occurring at doses as low as 18 Gy, while hypothyroidism and pubertal failure tend to occur at doses exceeding 40 Gy [102].

Post-treatment obesity may develop, especially in patients receiving cranial radiotherapy and total body irradiation for Acute Lymphoblastic Leukaemia or Hodgkin lymphoma, where steroids are a component of treatment [103].

7.2.1.4 Summary

All these sequelae may have a profound impact on the social and academic functioning of paediatric cancer survivors. They may require special education and living assistance [104], leading many childhood survivors to struggle to access higher education, form relationships, and/or gain employment [105].

Neurocognitive rehabilitation emerges as a viable and effective strategy after completion of therapy and is a focus of research. There is good evidence for the efficacy of modafinil [106], memantine [107], methylphenidate [108] and metformin [109].

7.2.1.5 Surveillance

All patients should undergo a baseline neurocognitive evaluation following treatment completion, as well as an annual history and physical evaluation, growth monitoring and endocrine assessment with growth hormone, thyroid function, and IGF-1. Where there is precocious or delayed puberty, luteinising hormone, follicle-stimulating hormone and oestradiol should be checked. Further neurocognitive assessment is considered mandatory in high-risk cases at the time of school entry or following evidence of poor school performance.

The Children's Oncology Group of North America (COG) LTFU guidelines [110] may help in organising post-radiotherapy surveillance.

7.2.2 Cervicofacial Late Effects

7.2.2.1 Thyroid dysfunction

Radiotherapy to the cervical region can result in hypothyroidism at doses as low as 4.5 Gy with an early onset (<5 years), with a higher risk in females and children over the age of 15 years

[102]. This is a common late effect approaching an incidence of 50% at 20 years [111]. While chemotherapy can cause hypothyroidism, this is uncommon. Thyroid nodules occur in more than 10% of patients receiving head or neck radiation [112], with the risk of thyroid cancer increasing in patients treated under the age of 10 years with an increased incidence in the dose range of 20–29 Gy [102]. Hyperthyroidism following combined modality therapy is unusual.

7.2.2.2 Xerostomia

A dry mouth resulting from irradiation of the salivary glands is an unpleasant complication for patients and can accelerate dental caries. It is recommended that the mean parotid dose should be ≤26 Gy [113]. IMRT facilitates parotid gland sparing [114]. Trials are in progress evaluating the potential benefits of PBT and adaptive radiotherapy at reducing this complication in adult cancers [115, 116].

7.2.2.3 Dental complications

Oral health and masticatory function can be compromised in many ways. Radiation to facial bones can result in asymmetry [117] and dose to the pterygoid and masseter muscles can result in loss of jaw functions. Low doses of radiotherapy (>2.5 Gy) especially in younger children <5 years [102] to the oral cavity can result in defective dentition, increased risk of caries, and periodontal disease. The latter can be exacerbated by concomitant chemotherapy, graft-versus-host disease, post autologous stem cell transplant, and xerostomia from salivary gland dysfunction [101].

7.2.2.4 Surveillance

Annual history and physical evaluation together with thyroid function testing and investigation of thyroid nodules where necessary. Referral to a dentistry service at diagnosis and annual evaluation and cleaning is recommended.

7.2.3 Abdominopelvic Late Effects

7.2.3.1Fertility and sexual function

The Childhood Cancer Survivor Study and St. Jude LIFE Study cohorts have documented gonadal and hypothalamic radiotherapy dose as key predictors of abnormal gamete production (azoospermia) [118], sexual maturation [119], gonadotropic production [120-123], decreased birth weight [124], increased spontaneous abortion rate [125], increased pregnancy complications [126, 127], and overall impaired fertility in survivors of childhood cancer [128]. The contribution of alkylators to adverse fertility outcomes cannot be overestimated as revealed by Green et al. [129]. The advent of novel fertility preservation options which allow the storage, retrieval, and use of gametes or other reproductive tissues, necessitates close communication with onco-fertility specialists and the formation of MDTs specializing in assessing risk, prevention, and interventional approaches to maximize fertility.

7.2.3.2 Renal

Advanced radiotherapy techniques such as IMRT can successfully limit renal injury. However, nephrotoxic agents frequently cause acute renal tubular injury leading to persistently low glomerular filtration rates and, rarely, severe chronic kidney disease [130].

7.2.3.3 Spleen

Patients who have undergone surgical splenectomy are known to be at risk of potentially fatal overwhelming post-splenectomy sepsis, and prophylaxis against infection by encapsulated bacterial organisms such as pneumococcus, meningococcus and Haemophilus influenzae B with vaccination and prophylactic antibiotics is recommended. Radiotherapy to the upper abdomen or left lower thorax may cause incidental splenic irradiation, which, even at low doses, may also result in similar splenic dysfunction. The spleen should be contoured for dosimetry as an OAR, and prophylaxis against overwhelming post-splenectomy sepsis should be considered in the mean spleen dose exceeds 10 Gy [131].

7.2.3.4 Liver

Abdominal radiation carries a well-known risk for hepatotoxicity and can result in acute and chronic hepatic injury, benign or malignant post-treatment parenchymal tumours, or limited function [132-134]. Radiation-induced liver injury may be potentiated by commonly used systemic therapies, used either concurrently or adjacent to radiotherapy, e.g., dactinomycin [135], doxorubicin [136], carmustine [137], busulfan [138, 139], melphalan [140], methotrexate [141, 142, 143], mercaptopurine [144] and asparaginase [145]. Use of these agents alone or in combination with radiotherapy can lead to elevations in transaminases, synthetic dysfunction (elevated international normalized ratio, decreased bilirubin conjugation) or intrahepatic vascular injury (sinusoidal obstruction syndrome). Although the liver is rarely a direct target of radiotherapy, it is frequently a bystander in whole- abdomen, flank, or even focal radiotherapy. Low-dose exposures remain common following photon radiotherapy, even with modern conformal techniques.

Treatment-related imaging findings are seen in paediatric cancer survivors receiving abdominal cancer–directed therapies and systemic therapies [146]. Optimal evaluation and workup of these abnormalities have not been assessed systematically. Concerning findings identified on ultrasound or MRI screening include, but are not limited to, steatosis, iron deposition, focal liver lesions and/or fibrosis [147]. The preceding list may or may not modify the patient's risk of chronic health conditions depending on the constellation of additional exposures and/or severity and extent of findings.

7.2.3.5 Metabolic

Subsets of childhood cancer survivors are at an increased risk of metabolic syndrome. Specifically, primary CNS tumours, lymphomas, sarcomas, neuroblastomas, acute lymphocytic leukaemia, Wilms tumours, testicular tumours, and post–bone marrow transplant survivors appear to be at increased risk of developing metabolic syndromes and other complications related to high-morbidity conditions such as cardiovascular compromise. Thus, the American Heart Association and the Council on Lifelong Congenital Heart Disease and Heart Health in the Young have recognized their heightened risk status and categorized survivors of childhood cancer as having tier III risk status[148, 149].

Screening and counselling for modifiable risk factors are warranted, given the known association of site-specific radiotherapy with increased incidence of cardiovascular disease and metabolic syndromes.

7.2.3.6 Surveillance

An evaluation of fertility, endocrine screening panels (follicle-stimulating hormone, oestrogen), sperm quality testing, serial AMH, inhibin, and pelvic ultrasounds may be warranted. Routine chemistries are recommended by most groups at least annually for monitoring renal function [110].

Objective measures of metabolic dysfunction (HgbA1c, fasting glucose, insulin) as well as other readily used clinical metrics (body mass index, weight) to screen serially for the development of metabolic syndrome are recommended in COG LTFU guidelines for patients treated with proton radiotherapy.

7.2.4 Bone and Soft Tissue Late Effects

It has been established that radiation therapy can cause a constellation of varying degrees of soft tissue and bone growth abnormalities. The severity of these abnormalities is largely contingent upon the radiation dose and volume used for the radiotherapy plan as well as patient-specific features such as age and presence of pre-existing conditions [150]. The aetiology of these abnormalities varies by tissue type, location, and degree of damage. One means of evaluating the degree of potential insult has been to stratify patients based on their bone age prior to radiotherapy [151] and limit the corresponding extent of dose uniformity across bone or other soft tissues based on the patient's risk for subsequent growth asymmetry [152].

Bone mineral density CT studies are recommended in patients over five years old and should be completed again five years following radiotherapy. Asymmetric growth and/or abnormal curvature should be quantified during evaluation. If abnormal curvature or other growth abnormalities are detected, it is recommended that the patient be referred to Orthopaedics for X-ray and/or CT scan. If abnormal bone density findings are detected, discussion with Endocrinology is recommended.

7.2.5 Thoracic Late Effects

7.2.5.1 Cardiac

The cumulative mortality from cardiac toxicity at 25–30 years has been shown to continue to increase despite significant changes in technique over many years and results in standardized mortality ratios of 11.7 [153, 154].

Historical experience with anthracyclines [155] and more recent data suggesting comparative dose effects with other non-anthracycline cardiotoxic drugs [155-157] have improved the understanding of the primary contributors to decreased cardiac function, but radiotherapy remains a clear contributor in patients requiring chest radiotherapy [158, 159]. The COG LTFU Guidelines suggest surveillance echocardiogram evaluations based on anthracycline and radiation dose exposures. These recommendations are aligned with the International Late Effects of Childhood Cancer Guideline Harmonization Group, where the differences are subtle, especially for individuals at lowest risk for cardiomyopathy. A recent cost-effectiveness analysis of screening according to the International Late Effects of Childhood Cancer Guideline Harmonization Group risk groups suggests that screening those at lowest risk, i.e., those exposed to only <100 mg/m^2 anthracycline or only <15 Gy chest radiotherapy, may not be clinically- or cost- effective [160]. one anticipates that these findings will lead to modification of the existing COG guidelines shortly.

Patients should undergo cardiac screening if they meet the criteria specified above. Echocardiogram evaluations should include measurements taken in the 2D, M-mode, spectral, colour-flow, and tissue

Doppler imaging mode. Concurrent measurements of height, weight, body mass index, body surface area, blood pressure, and heart rate should be recorded. Details of heart anatomy, cardiac position, valve function and pressure differentials, wall thickness, and systolic and diastolic function should be specified. A coincident electrocardiogram should be completed as indicated in the specific contexts below. If the patient received neck radiotherapy, a colour doppler ultrasound of the carotid arteries should be considered at year 10 or earlier if clinically indicated.

7.2.5.2 Lung

Patients receiving chest radiotherapy should undergo pulmonary function tests at baseline and annually following radiotherapy. These pulmonary function tests should include forced vital capacity, forced expiratory volume, forced expiratory flow 25–75%, quantification of total lung capacity and diffusing capacity for carbon monoxide.

7.2.5.3 Breast

Prior chest radiotherapy has a strong association with increased risk for subsequent breast cancer. Most of this evidence is derived from the Hodgkin literature, although other survivorship populations are known to be at risk. While risk for subsequent cancers is a stochastic effect, many providers limit breast tissue to <8 Gy when photon radiotherapy is employed. Patients with chest radiotherapy exposure are advised to undergo annual screening mammograms and breast MRI starting eight years following chest radiotherapy or at the age of 25 years, whichever is later. Clinical breast examinations should start at puberty until age 25 years and be completed every six months thereafter.

7.3 LATE EFFECT CLINIC STRUCTURE AND ORGANIZATION

A joint clinic for LTFU of the side effects of treatment should be considered. As far as possible all members of the core team (radiation oncology, paediatric oncology, the surgical disciplines (as appropriate), endocrinology, educational psychology, and occupational therapy) should be the members of the follow-up clinic.

There are many options of follow-up dependent on the structure of health services and the available resources [161, 162]:

(a) A multidisciplinary “one stop shop” based in a paediatric or radiation oncology service (with a transitional step where necessary)
(b) Clinic attendances at either of those services with a single provider utilising targeted referrals

(c) Follow up by a family practitioner, paediatrician, or

(d) Physician in the community with the option to refer

(e) No formal follow-up with referral as required

The advent of the Survivorship Passport [163] which contains all the details of the patient's diagnosis and treatment has been championed in HICs and could prove to be a critical default step to protect survivors in LMICs. In the absence of capacity for formal follow up, when one relies on symptoms only, it may be lifesaving.

7.4 FUTURE DIRECTIONS

7.4.1 Cost effectiveness in late effect follow up

The burden of late effect follow-up, both to the health services and to families, is considerable and may limit the scope of surveillance programmes in LMIC settings. Research into cost effectiveness is critical. The incremental cost-effectiveness ratio calculates the risk benefit comparing cost per capita gross domestic product to the gain in quality-adjusted life-years [164, 165]. This methodology can be used to estimate the value of late effect follow up as demonstrated in the study by Wong et al. of the effectiveness of the COG guidelines [www.survivorshipguidelines.org/] to avert treatment related heart failure [166].

New technologies may help to limit costs. The use of a mobile phone application to screen for neurocognitive impairment has been established in some patient cohorts [167] and may help to select paediatric brain tumour survivors for formal evaluation by educational psychologists. The use of new technologies such as proton therapy may offer potential to limit endocrinopathies, cardiomyopathy, cognitive decline and infertility thus lessening the utilization of interventions and diagnostic procedures to mitigate late effects and maximizing the productivity and potential of survivors of childhood cancer.

7.4.2 Second malignancies and predisposition syndromes

It is well established that childhood cancer survivors are at high risk of second malignancies because of exposure to radiation and/or chemotherapy. Leukaemias are usually the result of exposure to topoisomerase inhibitors or alkylating agents, but most solid tumours are strongly linked to radiotherapy exposure. These include skin cancers, meningiomas, and other solid tumours such as breast, thyroid, and osteogenic and soft tissue sarcomas [168].

What is of emerging importance to the practicing oncologist (whether paediatric or radiation) is the lengthening shadow of the cancer predisposition syndromes [169]. Clinical suspicion should prompt genetic testing and specific surveillance regimens, with emerging evidence demonstrating improved outcomes [170] and cost effectiveness [171].

7.5 PROTON SPECIFIC GUIDELINES

The current application of proton therapy is driven by a combination of geographic and provider bias, reimbursement limitations and patient preference such that efforts at quantifying the differential effects of protons over photons in childhood cancer survivors have been confounded by socioeconomic factors or lack of relevant explanatory variables [172]. Studies have largely taken the form of historical, descriptive matched comparisons as more formal matching strategies are not possible with single or even select multi-institutional cohorts [173, 174].

Ongoing efforts evaluating the differential cost/benefit ratio expected from the use of proton therapy suffer from a host of issues. The most prominent is identifying mechanisms for garnering lifetime data on healthcare expenditures and then successfully attributing therapy related insult in a modality and organ specific manner [175]. Specialized means of assessing organ and substructure doses are becoming increasingly relevant and many centres performing large scale substructure level dose and function evaluations are employing artificial intelligence-based methods [176, 177].

Cross sectional studies such as St. Jude LIFE study and Childhood Cancer Survivor Study will likely have sufficient power to identify a differential total toxicity burden after considering various exposures, genetic backgrounds, and patient specific radiotherapy parameters (target and anatomic variations).

The application of proton therapy will need to consider cost-effectiveness in select populations to maximize the therapeutic ratio while allowing for individualized decision making to be influenced by multiple evidence-based resources and patient specific factors, including individual anatomic variations, comorbidities, and genetic background.

8. EDUCATION, TRAINING AND ACCREDITATION

While ROs, MPs and RTTs have unique training requirements to attain their core professional skills, all need additional training to manage the care of children. Common educational elements for the specialized care of children can help a local MDT develop and function cohesively when undertaken together, or learnings shared between team members. This section describes the training recommended for each of the professional groups, ongoing education recommended for continuing professional development and proposes credentialing and accreditation as a way of ensuring a minimum standard of care for children is maintained by facilities over time.

8.1 TRAINING

8.1.1 Radiation oncologists

Most ROs who treat children have completed a residency in radiation oncology. Radiation oncology residency training varies from three to five years and usually leads to a pathway for board certification [178]. Board certification in radiation oncology in different countries may include requirements for paediatric training, but this is highly variable [179-181]. In the USA, for example, residents are supposed to participate in the radiotherapy planning of 12 patients under 18 years of age during the entire four-year residency [179]. The American Board of Radiology does give instruction on what paediatric tumours are part of the radiation oncology curriculum (Table 7), but it is not necessary to see a patient with each of type of tumour [182].

Because of the limited number of paediatric cases available for training and the lack of faculty sub-specialization in many radiation oncology programmes, many trainees have ranked their paediatric oncology knowledge base far below their adult oncology experience [183, 184]. Approximately 89% of respondents in one survey of paediatric ROs reported that there should be a formal training programme beyond the general radiation oncology residency to treat children [178]. To increase knowledge in the management of children with cancer, the Royal Australian, and New Zealand College of Radiologists and the Paediatric Special Interest Group have devised a paediatric radiation oncology teaching programme incorporating a structured, clinical, objective, referenced, problem-based, integrated and organized model of medical teaching into the traditional based course for trainees in radiation oncology [185]. Others have adopted a traditional classroom style teaching course incorporating various topics in paediatric radiation oncology. At the MD Anderson Cancer Center, a one- to two-day paediatric radiation oncology course has been given in the past 5 years to approximately 50 to 60 radiation oncology residents in Texas.

Few trainees subspecialize after a general radiation oncology residency by doing a fellowship in paediatric radiation oncology. In a 2019 survey of ROs who treat childhood cancer, only 12% reported that they completed a fellowship for paediatric sub-specialization. The fellowship training programmes were primarily located in North America, Europe, and India [178].

TABLE 7. TUMOURS INCLUDED IN THE AMERICAN BOARD OF RADIOLOGY RADIATION ONCOLOGY CURRICULUM STUDY GUIDE

General paediatric	**Paediatric CNS**
Retinoblastoma	Medulloblastoma
Wilms tumour	
Neuroblastoma	Astrocytoma (glioma), low-grade and high-grade
Rhabdomyosarcoma	
Lymphomas – Hodgkin and non-Hodgkin	Brain stem glioma
Leukaemias	
Histiocytosis X	Ependymoma
Ewing sarcoma and other bone tumours	
Osteosarcoma	Pineal / germ cell
Soft tissue sarcoma	
Germ cell tumour	Craniopharyngioma
Hepatic tumour	
Other solid tumours	Optic tract glioma

8.1.2 Medical physicists

MPs are healthcare professionals dedicated to the safe and effective use of radiation in the medical environment. They are responsible for the establishment and continued implementation of QA programmes, but also take part in the clinical decision-making team to ensure that an optimal balance is maintained between the beneficial and detrimental effects of radiation [34]. Training includes aspects relating to general radiation physics and safety, as well as specialized training in the fields of radiation therapy and medical imaging, including diagnostic radiology and nuclear medicine. The current requirements for registration and practise as a MP vary greatly throughout the world, both in terms of minimum qualification as well as clinical timeframe and scope of training. Most countries require a combination of academic education and clinical residency in one or more of the fields of specialization [41,186]. Even though the role of the MP is acknowledged as part of good practise for paediatric radiotherapy [15,41], many curricula only focus on paediatric dose issues associated with imaging of children, with little or no mention of radiotherapy considerations [187, 188]. As a result, exposure to good paediatric radiotherapy practises may vary greatly, even among clinically qualified MPs. In the LMIC settings, departments face additional challenges in terms of actual number of trained MPs available with reported deficits of 68.4%. A gradual increase in staffing numbers as well as exposure to new complex paediatric radiotherapy techniques is therefore critical in the

establishment of paediatric departments [15, 187-189], where the MP may need to acquire expertise in dosimetry, radiation treatment and QA techniques more commonly used in the childhood setting such as CSI and total body irradiation.

8.1.3 Radiotherapy Technologists

RTTs typically complete a three- or four- year degree at an accredited university. This can be followed by an additional year of hospital practise, the successful completion of which allows registration with the professional board [190].

Advanced Practise RTT positions and the pathways to achieve these have been implemented in countries such as Australia, Canada, and the United Kingdom [191]. These positions are achieved through further training and education in a specific scope of radiation therapy with the intent being that an expert level of treatment delivery and patient care is administered [192, 193].

A recommendation for advanced practise in paediatric radiation therapy is inclusion of the following further training or education elements, which could be assessed by a national credentialing committee:

(a) Paediatric anatomy, growth, and development
(b) Paediatric malignancies [41]
(c) Paediatric specific planning including a range of technologies and techniques.
(d) Psychosocial development in AYA [41]
(e) Age-appropriate communication
(f) Paediatric basic life support for allied health [41]
(g) Proton treatment and planning.

8.2 CONTINUING EDUCATION

Once trained, continuing education in paediatric radiation oncology is essential to ensure maintenance of competency in the sub-specialty and continual improvement in the care and treatment of children. The Royal College of Radiologists stipulate that all members of the paediatric radiation oncology team ‘should have an appropriate programme of continuing professional development’ and that those attending meetings and courses should disseminate their knowledge of their peer group [41].

Many international organizations now provide education programmes linked to conferences. These include the Paediatric Radiation Oncology Society which holds a congress every two years, and education sessions affiliated annually with the International Society of Paediatric Oncology. Paediatric Radiation Oncology Society was founded in 2006 as a not-for-profit association and is the only international operating society that brings together ROs and allied health professionals involved in paediatric oncology, providing a platform for education and teaching resources including resources specifically applicable for LMICs [194]. European Society for Radiotherapy and Oncology runs a three-day Paediatric Radiotherapy Course annually.

The IAEA supports educational activities on paediatric radiotherapy for its Member States including fellowships, meetings, courses, and workshops. In the last decade national and regional educational

events were organized by the IAEA in Tunisia, Egypt, Costa Rica, Indonesia, Georgia, Kazakhstan and Bangladesh, and several fellowships for radiotherapy staff from LMICs were provided.

St. Jude Children's Research Hospital in Memphis, USA provides several training programmes for professionals dealing with paediatric cancers including fellowships, seminars, symposia, and distant learning activities through its St. Jude Global programme. Recently IAEA, WHO and St. Jude combined their forces to enhance the capacity of paediatric radiotherapy globally.

Other groups that provide educational opportunities for the team caring for children include The Children's Cancer and Leukaemia Group in the United Kingdom and the COG.

Institutional support for members of the radiation oncology team who care for children to travel abroad for short-term observerships allows concentrated learning and reflection without competing clinical demands, provides the opportunity for new skill acquisition and promotes enduring connections with other facilities and professional teams.

In addition to external learning opportunities, an in-house education programme is fundamental to the ability to disseminate knowledge to all relevant professionals, with the opportunity to participate available to all.

8.3 CREDENTIALING

Assessment of the competencies of an individual practitioner is known as credentialing. Typically, this process occurs at the time of appointment to a facility, and a scope of practice is allocated to the practitioner. Credentialing is the right time to ensure that members of the radiation oncology team appointed to treat children have the right training even if they have good general skills, knowledge, and experience. The scope of practice to include the care of children can be extended as additional skills and experience are acquired. For many practitioners, meeting Continuing Professional Development requirements is necessary for ongoing registration to practice. Re-credentialing at the facility level, for example every five years, is one way of ensuring the team caring for children maintain currency of knowledge and experience in the care of children. A professional development plan relevant to the care of children which includes clinical practice, research, teaching, and administration components is one way of guaranteeing successful re-credentialing [195].

Specifying a minimum caseload of paediatric patients to manage each year to maintain credentialing is challenging although 20 children per RO could be a reasonable threshold. This minimum number may force the concentration of the care of children in one or a few facilities nationally as has occurred in The Netherlands [196]. The concentration of expertise should lead to better outcomes [197, 198]. However, having only one or two facilities managing children by radiation treatment is not relevant when the caseload is high and is not practical when travel to a facility may cause family dis-cohesion or lead to treatment abandonment due financial limitations or challenges with travel.

A minimum attendance and participation in a regular paediatric radiation oncology tumour board with peer review of radiation treatment plans could be a mandatory requirement for ongoing practice in paediatric radiation oncology for all members of the team [199, 200]. Depending on caseload, the tumour board could include several hospitals managing paediatric cancer patients to provide more robust peer review of treatment plans including contours of TVs and OAR.

Participation in an international paediatric radiation oncology conference at least once every two years is achievable now that many large organisations provide virtual attendance options.

8.4 ACCREDITATION

Accreditation is the formal independent process of external peer assessment of performance that can be applied to a training programme as well as a facility's capability to deliver an agreed standard of care. This can be implemented at a national level with standards relevant to the nation.

Institutional membership of a research organisation, for example, COG can involve meeting specified criteria regarding the facility and staff, essentially an accreditation process. In addition, COG membership includes credentialing of an institution or individuals through the Imaging and Radiation Oncology Core which involves radiation treatment planning of one or more test cases.

A proposal for the *additional* training, ongoing education and re-credentialing of a radiation treatment team caring for paediatric patients is summarized in Table 8.

TABLE 8. A PROPOSAL FOR ADDITIONAL TRAINING, ONGOING PROFESSIONAL EDUCATION AND RE-CREDENTIALING OF THE PAEDIATRIC RADIOTHERAPY TREATMENT TEAM

	Training	**On-going education**	**Re-credentialing**
Radiation oncologist	Fellowship of at least 6 months to become a local lead in paediatric radiotherapy *or* Observership at a different facility or jurisdiction of at least 3 months if commencing practise in an existing paediatric radiotherapy practise Attendance at a training course of at least 3 days	Attendance at one relevant conference at least every two years Develop in-house training and education opportunities for medical physicists and radiation therapists involved in the care of paediatric patients Actively participate in a multi-disciplinary paediatric oncology tumour board meeting held at least fortnightly	An average of 20 children are treated each year At least 70% of all radiation treatment plans are peer-reviewed Attend a multi-disciplinary radiation chart round held at least fortnightly on at least 70% of occasions
Medical physicist	Participate in in-house training and education sessions over the course of 12 months Observership at a different facility of at least 10 total body irradiation or CSI cases, if specific expertise needs to be acquired	Attendance at one relevant conference at least every two years Actively participate in in-house teaching and education	Attend a multi-disciplinary radiation chart round held at least fortnightly on at least 70% of occasions Manage the radiation treatment planning or verification and eventual patient-specific QA of least 20 children annually
Radiotherapy technologists	Participate in in-house training and education sessions over the course of 12 months Learning portfolio demonstrating an understanding of paediatric malignancies, paediatric anatomy and growth, and ability to plan and deliver total body irradiation and CSI.	Attendance at one relevant conference at least every two years Actively participate in in-house teaching and education	Attend a multi-disciplinary radiation chart round held at least fortnightly on at least 70% of occasions Manage the radiation treatment (planning and / or delivery) of least 20 children annually

Abbreviations: CSI: craniospinal irradiation; QA: quality assurance

9. QUALITY ASSURANCE AND SAFETY SYSTEMS FOR PAEDIATRIC RADIOTHERAPY

9.1 INTRODUCTION

The aim of radiotherapy is to achieve the highest chance of tumour control while not exceeding normal tissue radiation tolerance. This requires dose delivery within 5% of the prescribed dose [201]. Delivery of an incorrect dose to the tumour or the surrounding tissues may impact negatively on quality of life for children, for whom survival rates have increased from 10% to nearly 85% in HICs over the last 40 years [202]. Radiotherapy is a complex treatment involving sequential steps with multiple levels of responsibility between staff. Despite automation of some steps and a greater reliance on record-and-verify systems, data should still be checked and verified by humans.

Quality management and improvement systems fulfil a crucial role in achieving these goals [203]. Both the WHO and the IAEA provide a detailed guide on commissioning, setting up a radiotherapy programme and QA and safety programmes [29,203-206].

Periodic and preventive maintenance of radiotherapy equipment is pivotal in the continuity of any radiotherapy service. Machine breakdown causes treatment gaps which may compromise the chance of local control. Clinical engineer availability and maintenance contracts, machine downtime reporting and root cause analyses help avoid disruption of radiotherapy services [207 - 212].

9.2 QUALITY MANAGEMENT SYSTEM

A QMS should include all aspects relating to process, design, capital and human resources, quality improvement, independent audit and error/incident management. Inclusion of a comprehensive QA component ensures ongoing training and professional development of all staff, initial commissioning of new radiotherapy and ancillary equipment, and QC processes to maintain equipment functioning at the required standard [204]. There are well-established methods in radiation oncology to prevent errors or to mitigate their effects. Examples include daily, weekly, and monthly machine calibration and QA, independent checks of delivered dose, weekly review of patient charts and standard QA measures designed to uncover more systematic errors. The QMS for paediatric radiotherapy should also consider the local resource constraints, demand for radiotherapy services and experience of the local staff [30, 34, 213, 214].

9.3 INCIDENT REPORTING

The WHO World Alliance for Patient Safety has taken the initiative to address risk areas in the radiotherapy process of care; this is complementary to the IAEA-developed safety measures and other previously developed standards. Frequent formal and informal staff communication, competency-based training, and regular audits to assess adherence to the protocols are the top three focus areas to improve safety in the radiotherapy processes [201].

There are many stages throughout the patient's journey where incidents might occur. Although major clinical radiotherapy incidents are usually recognized and reported, it is believed that many errors and deviations have remained unrecognized and unreported, especially in developing countries [215]. Even with potential under-reporting, adverse events from radiotherapy are much less common than adverse drug reactions [216] and the reported death rate from adverse events in radiotherapy (1%) is lower than the reported rates of death from population-based adverse event studies (about 5–14%) [217]. With increasing requirements and regulations to report medical errors and better recording systems, these data may change [218, 219]. The discipline of radiation oncology has developed many methods to uncover, report and prevent errors or to mitigate their effects. Voluntary, confidential, and non-punitive incident reporting promotes a departmental safety culture that strives for continuous improvement.

A QMS system designed to the specific service level will ensure that safe and efficient radiotherapy is delivered [23]. Where quality and safety requirements are set out in national and international quality and accreditation standards, they should be strictly followed. To find a selection of references related to quality and accreditation standards in radiation therapy, see Refs. [29,220 - 228].

9.4 UNIQUE ASPECTS FOR SAFETY AND QUALITY PROGRAMMES FOR PAEDIATRIC RADIOTHERAPY

Children should be treated in a centre with well-established QMS and quality protocols and policies in place. All the general principles of quality are directly applicable to paediatric practise with additional steps needed to ensure the safest outcome [15].

There are multiple and complex steps in the clinical care of children undergoing radiotherapy and each carries potential for errors. However, paediatric radiotherapy can be delivered safely even in the context of treatments carried out under general anaesthesia for very young children [229-231].

9.4.1 Access to modern techniques

Modern radiotherapy equipment can provide precise and highly conformal therapy, supported by essential equipment that allow image guidance of the treatment delivery. Even if it should ideally be available to all children, for many children with cancer it is not accessible due to the significant shortage of radiotherapy facilities in LMICs where most children live [12,189,232-236]. Careful planning for allocation of resources for children who need radiotherapy is essential to ensure the best achievable care.

9.4.2 Protocols and paediatric training

In addition to technical quality standards, radiotherapy centres treating children should develop paediatric specific clinical protocols and processes to ensure safe delivery of radiotherapy [15]. ROs treating children should have the required training and skills to provide high-quality treatment, including precise delineation and dosing of TVs and dose constraints to the OAR. Clinical trials experience has shown that deviations from TVs and prescribed dose can negatively affect the outcome of children [237,238].

9.4.3 Peer review

The peer review process is an effective mechanism for capturing contouring and dose errors in a radiotherapy department. This includes intra and inter-disciplinary discussion amongst ROs, MPs, and RTTs for different components of planning such as image acquisition, prescribed dose, contouring, planning technique, dose optimisation and periodic QA of treatment plans [239, 240, 241]. Peer review provides opportunities for continuous education, communication and collaboration within a department besides ensuring safety and enhancing quality of treatment planning and delivery for the patient [242 - 246]. Peer review of radiotherapy planning of all paediatric cases can be achieved and should be considered essential [15, 41, 200,243,246, 247]. The importance of peer review and its usefulness for minimizing deviation from recommendations, improving compliance and safe practises is emphasized by various paediatric radiation therapy studies from Europe & North America [237,238,248 - 251].

9.4.4 Co-ordination of care

The provision of safe daily radiotherapy for children in both the inpatient and outpatient setting requires coordination and regular communication amongst teams. There is a shared responsibility to provide reliable access to treatment facilities and schedule appointments so that families can comply with challenging treatment protocols. Regular clinical review as described is required. Documentation of radiotherapy is essential with careful evaluation of any previous plans and the ability to register them with a new radiotherapy plan to appreciate potential toxicity from cumulative doses fully.

Specific safety and quality measures associated with each episode of clinical care for children undergoing radiotherapy are listed in Figure 7 (adapted from [201]).

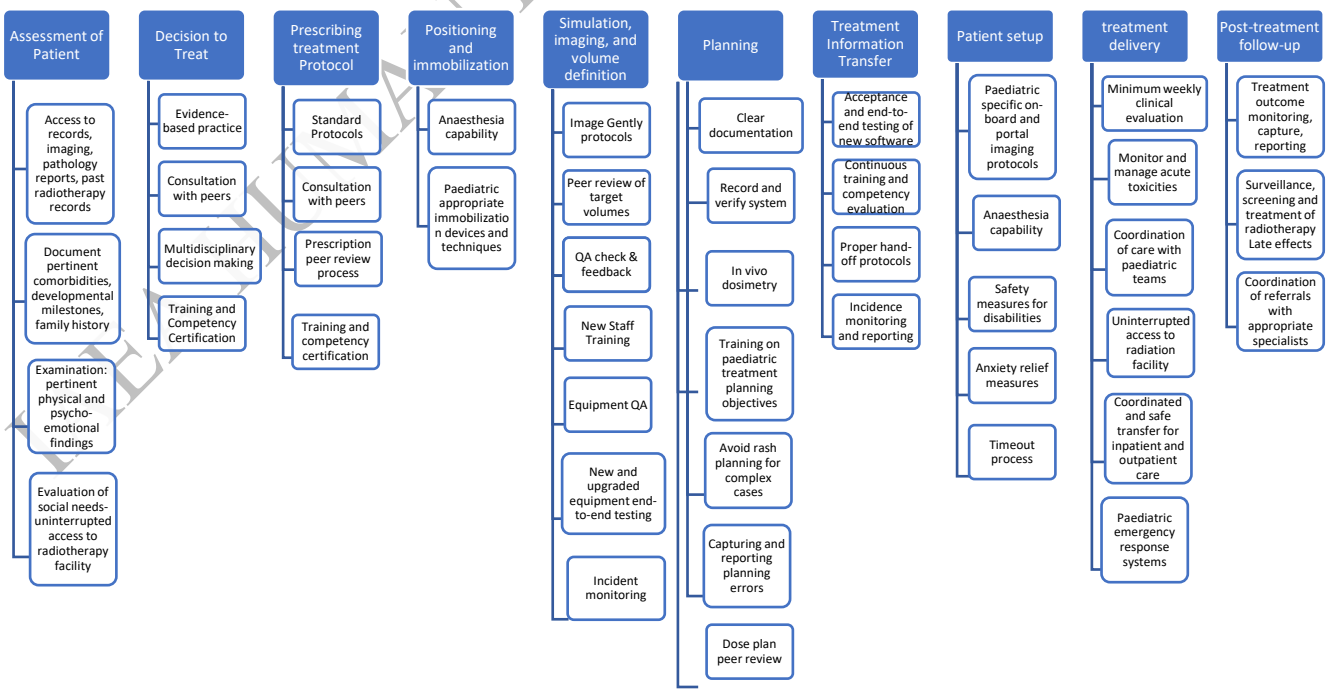

FIG. 7. Safety and quality measures required for each aspect of paediatric radiotherapy (adapted from the WHO Radiotherapy Risk Profile technical manual) **[201].**

10. THE IMPORTANCE OF RESEARCH IN PAEDIATRIC RADIATION ONCOLOGY

It is only through carefully designed, prospective clinical trials that remarkable improvements in survival for AYA with cancer have been achieved over the last few decades [252 – 256]. Most paediatric tumours are uncommon or rare, so meaningful clinical trial results can only be achieved by enrolling patients on national or international studies capable of recruiting sufficient patients [257].

It is imperative to distinguish clinical research from evidence-based and best clinical practice. Patients should not be subjected to treatment which is still under investigation except in the context of a clinical trial. This can cause potential harm and adverse outcomes, including worse tumour control and unanticipated toxicities. International consensus guidelines for radiation treatment in AYA practice are a valuable resource for guiding the treatment of patients who are not enrolled in a clinical trial.

10.1 INFRASTRUCTURE

Clinical trials are complex and may be costly, especially when conducted across several jurisdictions. Countries equipped with sufficient resources have succeeded in conducting them. However, research infrastructure may not exist in some jurisdictions and local resources should be considered before committing to implementation of a clinical trial. Regulatory bodies, overseeing proper and ethical study design and conduct of research need to be established and supported by an entity without conflicts of interest. In many instances, governmental agencies have some oversight, but institutions should also provide both initial approval and monitoring of a research study. Additionally, there should be a fully equipped research team responsible for the conduct and reporting of every step of the study.

10.2 PROTOCOL DEVELOPMENT

The concept and protocol development phases of a clinical trial need multi-disciplinary involvement, including pathologists, radiologists, surgeons, paediatric and ROs, and nurses. Increasingly advocacy groups with input from parents and survivors are also part of the clinical study design team. Engaging all members of the team from the beginning will ensure the quality and robustness of the trial as well as feasibility and engagement. The provision of standard templates and review processes for clinical trials by groups such as COG and the Trans-Tasman Radiation Oncology Group Cancer Research that cover the steps from concept development to study reporting can streamline study initiation and completion. A clinical trial should allow representation from all ethnic and socio-economic groups to ensure trial results are widely applicable.

10.3 INSTITUTIONAL REVIEW BOARD

A Human Research & Ethics Committee should approve any clinical trial to ensure it meets ethical standards and guidelines. The purpose of this is to protect the rights of patients as well as to consider the potential risks and benefits for the community where the research will take place [259]. All investigators should undergo training in Good Clinical Practice, an internationally accepted standard for the design, conduct, recording and reporting of clinical trials.

10.4 STAFFING

Paediatric clinical trials with a radiation treatment component may include RTTs, MPs and nurses as well as ROs. An appendix to a clinical trial dedicated to the planning and delivery of radiation treatment is essential for consistency of treatment, even when the study question is not related directly to radiation treatment. When designing protocols involving delivery of radiation treatment, the planning systems and treatment machines available in the areas where the trial will be conducted should be considered.

10.5 QUALITY CONTROL

When designing a randomized trial of a systemic therapy intervention in a combined modality treatment programme, it may be assumed that any variation in the quality of radiation treatment is accounted for by the randomisation process. However, the impact of inadequate radiation therapy can offset any benefit from systemic therapy [260]. Real-time peer review and feedback as part of the trial protocol is an important way of ensuring the quality of the radiation treatment and the most robust outcome. Before enrolment of the first patient from each centre, a dummy run can guide the need for clearer instruction or a training session [251].

Cooperative groups for clinical trials may have a designated body for the QA of radiotherapy plans. For instance, the Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials is a European Society for Paediatric Oncology project for quality and excellence in radiotherapy and imaging for children and adolescents with cancer [261].

Similarly, Imaging and Radiation Oncology Core, provides radiotherapy QA for several cooperative clinical trial groups including COG conducting research for AYA in Northern America, Australia, and New Zealand [262].

The rates of deviations in clinical trials have been reported for several clinical trials involving children and AYA. These are summarized in Table 9.

10.6 MONITORING

Monitoring the quality of data submitted during recruitment provides the opportunity for improvement, for example through establishment of educative review panel meetings [263].

As the greatest burden of cancer in children occurs in LMICs, the local resources available both to deliver treatment and to manage acute and longer-term toxicity should be considered.

TABLE 9. RATES OF DEVIATIONS IN PAEDIATRIC CLINICAL TRIALS

Reference	Trials Group	Tumour	Deviation	Timing of Radiation treatment Review
Gaze [237]	SIOPE	Neuroblastoma	29% justifiable deviations with no adverse effect; 17% unjustifiable deviation with risk of adverse outcome	Retrospective for first 100 patients
Schiff [264]	COG	Medulloblastoma	7% major target deviations	Retrospective, although all patients underwent pre-treatment review of boost plan and on-treatment review of CSI treatment plans
Coles [248]	HIT-SIOP	Medulloblastoma	'demonstrated several ambiguities in the draft protocol and highlighted particular areas of inter-clinician variation'	Prospective for some national groups, retrospective for others
Dharmarajan [249]	COG	Hodgkin Lymphoma	Minor deviations in 12%, major in 6%	Interventional review of 88%, final review for 98%
Coskun [250]	EORTC	Meningioma	Major deviations in 22% and minor in 10%*	Prospective
Taylor [265]	PNET-3	Medulloblastoma	44% had one or more deviations	Retrospective

*All centres completed a "dummy run" exercise

Abbreviations: CSI: craniospinal irradiation; SIOPE: European Society for Paediatric Oncology; COG: Children's Oncology Group; HIT-SIOP: German Brain Tumor - International Society of Paediatric Oncology; EORTC: European Organisation for Research and Treatment of Cancer; PNET-3: primitive neuroectodermal tumour

10.7 STUDIES IN LMICS

Clinical trials developed in HICs are not immediately transferable to LMICs. In addition to the different availability of treatment and supportive resources, children present with more advanced

disease and may have significant co-morbidities such as malnutrition [266]. Studies specifically designed for LMIC population, many of which are led by the IAEA, are limited primarily to adults [267 – 271]. Paediatric trials have been limited but have made a measurable difference to the adoption of treatment approaches for children in resource limited settings [256,272] and a meaningful reduction of the burden caused by lengthy treatments for both healthcare services and families.

De-escalation of radiation dose and reduced treatment volumes are now being investigated in some trials. The aim is to maintain high rates of local control and survival, whilst reducing longer term morbidity and improving quality of life for survivors [273].

Clinical research in LMICs also needs to include investigation of genetic and environmental differences that can impact outcomes when compared to HICs [274]. One successful way of conducting high quality research in LMICs is to develop research partnerships with international centres of excellence not only to develop the research capability of the team, but to design robust studies [275]. Research capacity can be built by linking to higher education degrees, including using nurses and RTTs as part of the research team [265]. There are several examples where collaborative training between centres in LMICs and HICs has resulted in research success [256]. Research related to children should extend beyond clinical trials and include epidemiology and health service provision amongst other fields [12].

11. ECONOMIC ASSESSMENT OF THE USE OF RADIOTHERAPY IN CHILDHOOD CANCER MANAGEMENT IN LMIC

11.1 INTRODUCTION

With the growing interest in childhood cancer due to the Global Initiative for Childhood Cancer, governments in LMICs are under pressure to increase health investment to scale-up services and meet the needs of the population [276,277]. The practice of paediatric oncology is a complex multi-disciplinary process involving laboratory services, diagnostic imaging, pathology, surgery, radiotherapy, chemotherapy, and supportive care. This requires investment in facilities and technologies, and a highly specialized workforce operating in an enabled organisational environment.

The decision to invest and to include radiotherapy in the management of childhood cancer should take multiple criteria into consideration. Radiotherapy equipment is a technology asset that can be used to treat many different tumour types in both adults and children. The required investment for optimal paediatric radiotherapy services relates to the need for specific service delivery arrangements (centralized services vs. regionalization), specialized personnel (ROs, anaesthesiologists, and oncology nurses with sub-specialist expertise) and expensive technologies (such as particle therapy) which are preferred in paediatric oncology to reduce long-term toxicity (see Section 7).

Multiple competing priorities and scarce resources in LMICs necessitate a systematic evidence-based approach to assess the impact of the introduction of new technologies or services and guide policy-making bodies in efficient allocation of limited resources. In this section one will analyse the tools available for economic assessment of the use of radiotherapy in the treatment of childhood cancer.

11.2 HEALTH TECHNOLOGY ASSESSMENT

Health Technology Assessment (HTA) is a structured approach to guide policy-making decisions and to ensure that available resources are efficiently allocated. HTA has been defined as "A multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making to promote an equitable, efficient, and high-quality health system" [278,279].

Ideally, HTA is a patient-centred, value-based, comprehensive, and integrative assessment of all the relevant dimensions (safety, effectiveness, economic, ethical, sociocultural, and legal) in the introduction of health technologies, considering the local context and the implementation factors, and is a unique tool to manage the opportunities and uncertainties, and guide and optimize decision-making for the introduction of health technologies [280].

With the growing international commitment to universal health coverage, HTA has been advocated as an objective tool to help countries improve allocation of finite resources while maximizing the health impact [281]. A recent scoping review found that LMICs across regions worldwide are using HTA systematically to help policymaking in priority setting, purchasing and quality improvement [282]. In 2014, the resolution on Health Intervention and Technology Assessment in Support of universal health coverage called on the WHO to develop global guidance on methods and processes for HTA [283].

11.2.1 Methodology for HTA

There are several methodologies and toolkits described to conduct HTA [284 - 290]. A common workflow for conducting HTA is described [291]. In a simplified form, this workflow has five phases: scope definition, assessment, appraisal, decision-making and implementation.

Experience with HTA in radiotherapy (and particularly in paediatric radiotherapy) is very limited [292,293]. Published reports usually focus on clinical interventions [294 - 298], but more efforts are needed to adopt this methodology to the analysis of service delivery interventions.

11.3 HEALTH ECONOMIC EVALUATION AND RADIOTHERAPY

In the absence of robust HTA for paediatric radiotherapy, other approaches such as health economic evaluation (HEE) can be used. HEE is defined as a comparative analysis of alternative courses of action in terms of both their costs and consequences [299]. For service delivery this involves a comparative analysis of at least two scenarios or interventions or courses of action, in terms of costs and consequences. In some cases, one of the scenarios is the 'status quo' (doing nothing). The goal of HEE is to inform decision makers on how to use resources more efficiently, or to prioritize interventions to maximize value-for-money [300]. HEE considers only economic factors, leaving out contextual, societal, and ethical factors that are included in HTA.

Over the last twenty years, multiple HEE of healthcare clinical interventions have been reported [301]. In radiotherapy, several domains of clinical interventions have been analyzed recently using an economic evaluation framework [302 - 307]. However, economic evaluation of service delivery interventions is scarcer, especially in LMICs. In addition, a systematic review conducted in 2014 found a dearth of up to date, robust evidence on the cost-effectiveness of radiotherapy in cancer suitable to support decision making [308]. This scarcity of results should encourage researchers to produce more and better evidence to support the investment case for radiotherapy.

11.3.1 Methodology for HEE

There are multiple initiatives, at national and international level, to guide the process of conducting HEE [285,287,309,310]. In a simplified form, HEE has four stages:

- Framing the evaluation (defining the decision problem and scope of the analysis)
- Assessing the resources needed (identify, quantify and value [299])
- Estimating the health consequences (identify, quantify and value)
- Presenting and interpreting the evidence for decision-making. This includes management of the uncertainties (e.g. how will variations in the input values impact on the final results of the analysis.)

In radiotherapy, there is a complex interplay of factors influencing the costs of services; this includes the case-mix and presentation of the cancer cases, the technologies, and techniques to be implemented, the existing treatment modalities available (surgery and chemotherapy) and the broad local context.

Various methods for costing radiotherapy have been developed and applied in various geographic and income settings [311 - 316]. Also, several attempts to review the available literature on radiotherapy costs systematically have been published recently [317 - 319]. Almost 60% of the reported studies developed their own costing methodologies. The IAEA uses Time-Driven Activity-Based Costing methodology for costing a radiotherapy programme. It can be applied either to the set-up of a new radiotherapy centre or to estimate the needs and costs for a country-wide radiotherapy service delivery programme [312,315,320].

The assessment of health consequences is very dependent on the scope of the analysis (which includes the perspective employed) and the type of economic evaluation that is being undertaken. For curative interventions, benefit can be measured as increase in survival as 'life-years gained'. However, survival does not account for other health outcomes, such as quality of life or monetary return of investment. Morbidity measures are used in chronic diseases, and in this regard, cancer can be considered a chronic condition, as it may transition from a remission state to a progression state (and to death). Generic health measures such as quality-adjusted life-years or disability-adjusted life-years (DALY) are used to summarize these outcomes and include dimensions other than just survival to express the health outcomes. The advantage of these indices is that they allow for inter-comparability across disease types and interventions. Once valuation of the resources and consequences is finished, the actual analysis is performed (in the form of a cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, cost-minimisation analysis, or cost-consequences analysis); and the results are presented and interpreted [321]. Defining a communication framework to highlight the key elements of the analysis and adapt the language to the audiences is essential.

11.3.2 HEE of paediatric radiotherapy

There are few articles reporting full economic evaluation examining the difference in costs and consequences between competing treatment methods in paediatric oncology service delivery in LMICs [2,322,323]. Of these, one study presented a form of return on investment or cost-benefit analysis whereby expected lives saved/life-years gained were translated into monetary returns for society balanced against investment costs [2] and two studies reported cost-utility analysis [322,323]. In all these studies the comparator was the status quo, or 'doing nothing'. In none of the papers was the radiotherapy service delivery costed, and consequences analyzed explicitly. Instead, radiotherapy was analyzed bundled with other interventions in treatment packages. The scale of analysis was global in one study [277], regional to four countries in Sub-Saharan Africa in one [322] and country-level (El Salvador) in one [323]. The perspective used was societal in the first [277], the healthcare system in the second [322] and the hospital in the third [323].

The global (including HIC) investment case and cost-benefit analysis for comprehensive scale-up of interventions for the treatment of childhood cancer (including radiotherapy) used a modelling approach and estimated a cost of $594 billion for a global lifetime productivity return of $2580 billion; hence giving a net return on investment of $3 for every $1 invested in the period 2020–50 [277]. The methodology follows the recommendations of the Lancet Commission on global health in 2035 using Net-Present-Value as a measure of economic return [324]. The authors also calculated the cost per DALY averted through cancer treatment varying between $1034 and $3039 depending on the centre analyzed. The authors estimated the operating costs per year and concluded that radiotherapy accounted for 1% of costs in each of the three centres studied.

The other two studies were cost-utility analysis and gave incremental cost-utility ratios in cost per

DALY. These studies collected real world data from hospitals that provided specialized, integrated childhood care, and served as national referral centres. The comparator for these studies was the status quo, and the assumption in both cases was that without the service, all patients would have died, and no costs would have been incurred.

Githang'a et al. reported an economic evaluation (using the same standardized methodology for data collection and validation) of current childhood treatment compared with the alternative of no treatment in four centres in Kenya, Nigeria, Tanzania, and Zimbabwe [322]. The cost per DALY varied from $323 to $5783. Radiotherapy represented less than 2% of the annual operating costs.

Fuentes-Alabi et al. reported results from the Hospital Nacional de Niños Benjamin Bloom in El Salvador, Central America [323]. The incremental cost-utility ratios for providing integrated cancer care for childhood cancer compared to a 'null' scenario without any service provision was $1624/DALY. Radiotherapy accounted for only 1% of the total operating costs per year.

Thresholds for incremental cost-utility ratios were discussed in the context of WHO-Choosing Interventions that are Cost-Effective recommendations [325]. Accordingly, in El Salvador, childhood cancer treatment strategies are very cost effective (less than 1x gross domestic product per capita); and in Sub-Saharan Africa are between cost-effective (less than 3x gross domestic product per capita) and very cost-effective (less than 1x gross domestic product per capita).

11.4 BUDGET IMPACT ANALYSIS

Budget impact analysis (BIA) is a type of financial analysis used to estimate the financial consequences of adoption and diffusion of a new healthcare intervention. BIA takes context and resource availability into consideration to analyze the short to medium term financial impact of the adoption of a healthcare intervention.

While HEE focuses on the value (defined as costs relative to health outcomes) of the proposed intervention on the overall healthcare system, BIA evaluates whether a high-value intervention is affordable. More concretely, BIA estimates how the introduction of a new intervention, given an epidemiological projection of the condition to be treated and an adoption rate of this intervention, will impact on the health expenditure for this condition (i.e., paediatric cancer). Usually BIA calculates annual cash-flows and is matched to the financing cycles (2 to 5 years) at a governmental (or payer) level.

A BIA can be used for budget or resource planning, and for forecasting health expenditure. The full potential to inform policymaking is obtained when BIA and HEE are used together [326,327].

11.4.1 Methodology for calculating BIA

The International Society for Pharmacoeconomics and Outcomes Research has developed a framework to conduct BIA [328]. The framework requires a series of inputs to produce a BIA estimate: the epidemiology of the affected population (current and projected number of cases), the mix and costs of the current intervention strategy, the proposed intervention mix (proportion of old versus new intervention) and projected adoption rate of the new intervention, the cost of the new intervention mix (old and new intervention) and the use and cost of other resources. Data should be

country-specific, if possible, particularly reflecting epidemiology and costing of the interventions.

Finally, the total costs of the transitioned scenario (from baseline to the final mix) are calculated and projected over the decided time horizon. Then the budget impact of adoption of the new treatment strategy can be estimated. BIA informs policy makers about the affordability of cost-effective interventions.

11.4.2 Affordability of childhood cancer treatment

The results of the HEE of paediatric cancer interventions described above should be put in the context of affordability for the healthcare system. That an intervention is cost-beneficial or cost-effective does not mean that it is affordable for the system. For example, the cost per year per newly diagnosed case is $28 707 in El Salvador, value that compares to a per capita health expenditure of only $280 [323]. Similarly, in the four countries studied in Sub-Saharan Africa the cost per newly diagnosed patient ranged from $2 338 in Zimbabwe to $31 344 in Kenya, for a health expenditure per capita of $69 and $83 respectively [322]. However, no country study reported a budget impact analysis of the cost-effective interventions, nor the equity implications of non-cost-effective interventions or scale-up strategies. In radiotherapy, a recent assessment by the Ontario Health (Quality) Agency did include conducting a BIA for proton therapy (4 treatment rooms) in adult and paediatric populations and found an additional expenditure of $125 million over a time horizon of 5 years. This expenditure translated into an average cost per patient of around $48 000 (including the initial capital costs) for local treatment, compared to about $327 000 per patient when referred for treatment to the USA [298].

11.5 CONCLUSION

For successful financing of paediatric cancer services which include radiotherapy, countries should develop an economic assessment that considers all the elements discussed in this section. Paediatric cancer management necessitates a complex combination of services provided by a highly specialized team in dedicated facilities. For this reason, economic assessment of paediatric cancer treatment should necessarily consider multiple modalities bundled into one package. But at the same time, an explicit assessment for radiotherapy is required for better planning of the facilities and equipment, organisational arrangements, and training of professionals.

The radiotherapy community should seek to develop the methodology and generate data to support the technical assessments required to make the case for investment in paediatric radiotherapy and improved planning of services. This assessment can be done in coordination with the other components of integrated childhood cancer management. Only in this way will the target of the WHO initiative for childhood cancer to achieve at least 60% survival rate for childhood cancer globally be attained.

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APPENDIX

BIBLIOGRAPHY OF GUIDELINES ON PAEDIATRIC ANAESTHESIA

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GLOSSARY

Service Delivery Terms

Multidisciplinary management: Cancer care delivered through multiple specialists, including doctors with different specialisms, such as radiology, surgery and oncology, and professional staff in other disciplines such as nurses and dieticians.

Multidisciplinary Team (MDT) Meeting or Tumour Board: Formal meetings where the MDTs discuss the diagnosis, staging and treatment plan for each patient.

Radiotherapy Terms

Radical Radiotherapy Treatment: Treatment given when the primary aim is to cure the patient or to extend life significantly

Palliative Radiotherapy Treatment: Treatment given when the primary aim is to alleviate symptoms

External Beam Radiotherapy (Teletherapy): Radiotherapy delivered from a source outside the patient, usually by beams of high energy X rays, gamma rays or protons.

Brachytherapy: Radiotherapy delivered from a source close to the target area, which often necessitates a radioactive source being placed internally for a prescribed duration.

Radiotherapy Treatment Planning: The process by which ROs identify the target area to be treated, and work with MPs and RTTs to calculate how best to deliver the necessary radiation dose to this area whilst sparing healthy adjacent tissues.

Radiotherapy Treatment Delivery: Most radical radiotherapy courses necessitate daily treatment for several weeks. The treatment is delivered in multiple small doses, termed 'fractions', to reduce side effects.

Radiation Oncologist: A doctor with specialist training in prescribing, planning and supervising radiotherapy. A paediatric RO has further sub-specialist training in the treatment of children with radiotherapy.

Clinically Qualified Medical Physicist: A physics graduate with academic and clinical post graduate qualifications to work in the radiotherapy department.

Radiotherapy Technologist: Sometimes termed ‘therapy radiographer’ or manipulator, these staff work in radiotherapy planning, deliver radiotherapy on the treatment machines, and participate in QA processes.

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