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Editorial

"Indeed, Cure is Not Enough" – A Reflection on Paediatric Radiation Oncology

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Cancer is the leading cause of death by disease past infancy among children in the Western world. In the United States in 2014, it is estimated that 15,780 children and adolescents from birth to the age of 19 years will be diagnosed with cancer, and 1960 will die of the disease [1]. In 1975, only barely 50% of children diagnosed with cancer before age 20 years survived more than 5 years. Since then results have greatly improved and in 2004–2010 more than 80% of children diagnosed with cancer before age 20 years survived at least 5 years.

Childhood malignancies include a great variety of different tumour types, for most of which multidisciplinary management with a combination of local and systemic treatments is required for optimal outcomes; for many patients, radiation therapy as local treatment is an integral component of the therapeutic strategy. This special issue on Paediatric Radiation Oncology addresses the most recent developments in radiation therapy with respect to the different types of childhood malignancies and the use of modern treatment technologies.

Paediatric malignancies are a challenge for the radiation oncologist due to their rarity, the great variability of histological subtypes, and the complexity of treatment concepts that undergo constant modification. Radiation therapy technologies also undergo a continuous process of optimization and modern technologies (e.g. intensity modulated radiotherapy, proton therapy, inclusion of modern imaging in treatment planning and use of imaging to guide treatment delivery precisely) are rapidly becoming essential in the management of children and teenagers with malignancies. In their article, Steinmeier *et al.* summarise the radiotherapy technical evolution in paediatric practice [2]. While the key principle of radiotherapy for children is to use a tailored technique based on risk-profile which includes molecular genetics, younger age remains the most important factor affecting long-term sequelae. The current approach in numerous cancers is to delay radiotherapy with appropriate systemic therapy until radiotherapy may become an absolute necessity to maintain tumour control or chances of cure. This cut off for initiating radiotherapy has moved from more than 3 years to >8–10 years; but the real impact of delaying radiotherapy is not clear due to the lack of extended long-term follow-up. We also need to understand the best ways to integrate novel agents with radiotherapy to improve clinical outcome.

In the past few years, the use of radiotherapy has been further refined with a wide-spread adoption of high-precision techniques including particle therapy. Despite the fear of increased risk of second cancers, IMRT has been widely adopted in children and results are encouraging [3]. While the number of proton therapy facilities has rapidly increased both in the public and private sectors, the most important question remains: is proton therapy truly clinically superior to photons? Among the public and media, there is a widespread notion that proton therapy is better in terms of local control and cure, but the professional community is divided in their opinion regarding the superiority of one modality over the other. In this context, an international consortium has published consensus guidelines on the clinical use of proton beam therapy in children [4]. Clinical Oncology has also recently published a special issue on proton and particle beam therapy [5,6].

Meanwhile, in the UK, one NHS proton facility (Christie Hospital) has already started treating patients and the second will open in 2020. In keeping with these transitions, the Royal College of Radiologists has updated the 'Good practice guide for Paediatric Radiotherapy' [7]. Approximately 50% or more of all children will be treated with

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proton therapy and organisation of services for the remaining children receiving photon therapy would be challenging. This situation is not unique to the UK, and similar service organisational changes are also happening in other countries. In his editorial, Mark Gaze highlights these modern challenges of clinical paediatric radiotherapy practice [8].

While it is important to offer the best radiotherapy technique to all children needing treatment, it is often difficult to compare techniques in terms of relative reduction in long-term toxicities. The main challenges are the lack of prospective long-term data and resources to capture information on long-term side effects. While planning studies may be a useful surrogate for comparing techniques, they are often inadequate. For example, a recent comparison of different techniques of craniospinal radiotherapy across 15 European centres showed that highly conformal radiotherapy techniques have dosimetric advantages compared with 3D-conformal radiotherapy and that proton therapy often leads to the lowest mean dose to OARs [9]. For most organs, ranges in mean doses were wide and overlapping between techniques, making it difficult to recommend one radiotherapy technique over another. Often randomised controlled trials are neither practical nor the best method to prove the relative effectiveness of different radiotherapy techniques. For proton therapy, the question of clinical equipoise and the challenge of acceptability of a randomisation design by parents of children with cancer may also hinder any future randomised trials. While there are numerous series with limited follow-up duration suggesting equal efficacy of protons to photon therapy, large scale international collaborative data bases are needed to prove the relative efficacy and safety of proton therapy.

The importance of radiotherapy quality increases in parallel with the technical complexity and precision of treatment delivery. Field-based photon treatment approaches generally avoid marginal misses even if there are subtle variations in clinical target volume delineation, but using high-precision techniques, any inadequacy in clinical target volume (CTV) delineation would become much more significant [10]. Fortunately, expert consensus guidelines have recently been developed to address variations in CTV in different situations; but there is still a need for more consensus guidelines to improve the quality and consistency of radiotherapy target volume delineation [11]. Importantly, future studies should prospectively evaluate patterns of failure, especially failures in and around the previously treated CTV using high-precision radiotherapy [3]. The issues of movement and target volume delineation while using high-precision radiotherapy for extracranial malignancies have been recently reviewed in Clinical Oncology [12].

Primary central nervous system (CNS) tumours constitute the second largest group of paediatric tumours and radiotherapy has a pivotal role in the majority of these tumours. Gliomas are the most common (53%) with approximately 70% tumours being low-grade gliomas (LGGs) and 10% ependymal tumours [13]. Radiotherapy principles for treatment of low-grade gliomas and ependymomas differ. The majority of low-grade gliomas in children are pilocytic astrocytomas which are well-defined tumours amenable to gross tumour resection followed by surveillance. Radiotherapy for LGGs is indicated when there are no further surgical options in children aged >5–8 years. Surgery is also the most effective treatment for ependymoma, even for metastatic disease. In the adjuvant setting, radiotherapy has an established role while systemic treatment has so far been ineffective. The current role of radiotherapy for paediatric LGGs and ependymoma is reviewed in this special issue [14,15].

Approximately 15% of primary CNS tumours are embryonal tumours of which more than 60% are medulloblastomas [13]. The current standard treatment approach is based on risk group (average vs. high-risk) and age at diagnosis (infant vs. children). Molecular stratification may allow for de-escalation of treatment including avoidance or reduction in the radiotherapy dose or volume. For example, WNT type medulloblastoma in children less than 16 years is treated with a CSI of 18 Gy in the SIOP PNET5 and SJMB12 study. In their article, Padovani *et al.* review the current role of radiotherapy in paediatric and infant medulloblastoma [16].

The role of radiotherapy in the management of intracranial germ cell tumours has been the subject of a recent review in Clinical Oncology [17]. More recently, the SIOPE GCT II trial has successfully completed recruitment and the interim results should be available after July 2020. Surprisingly, the ACNS 1123, which has evaluated the role of whole ventricular irradiation with focal boost in localised non-germinomatous tumours has been closed prematurely due to an unexpectedly higher incidence of recurrences outside the radiotherapy volume [18].

Radiotherapy also plays a significant role in extracranial malignancies. In their meta-analysis, Arumugam *et al.* illustrate the paucity of evidence for optimal use of radiotherapy for children with neuroblastoma and highlights the importance of the ongoing IMAT trial [19]. We have also commissioned reviews on paediatric lymphomas, rhabdomyosarcoma, and Wilm's tumour, which will be published in the future issues of Clinical Oncology.

Despite multimodality treatment, childhood cancers recur. With advances in radiotherapy techniques, there is currently more enthusiasm for further courses of radiotherapy to achieve local control or long-term disease remission. In this issue, Tsang and Laperriere review the current evidence for re-irradiation in various childhood tumours [20].

In 2010, the international QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) consortium recommended radiation dose constraints for normal tissues in adults and illustrated the uncertainties in those constraints [21]. In their article, Constine *et al.* outline the methodological approach of the international collaboration on Paediatric Normal Tissue Effects in the Clinic (PENTEC) [22].

This special issue aims not only to provide a comprehensive overview of current and future treatment concepts for common paediatric tumours but also addresses specific issues in palliative radiation therapy, radiotherapy quality assurance, and survivorship and quality of life.

In 2018, we said good-bye to Dr Giulio J D'Angio, one of the best-known and well-loved experts in Paediatric

Fig. 1. Dr Giulio J. D'Angio (May 2, 1922-September 14, 2018).

Radiation Oncology (Figure 1). Along with other notable achievements, he made a significant contribution to the evolution of multidisciplinary management of paediatric cancers in collaboration with Sydney Farber (the father of chemotherapy). In a visionary article in 1975, he concluded that in paediatric cancer 'Cure is not enough' [23]. In the same issue of *Cancer*, in a poetic obituary to his collaborator, Sidney Farber, he wrote, "*This, then, is the best way to eulogize and pay tribute to Dr. Farber: by turning, as he did, to boys and girls with cancer, making their problems our own; and striving, as he did, to dispel this dark cloud from the sunny skies of childhood*" [24]. We could not find better words to pay tribute to Dr D'Angio other than to borrow his own!

We dedicate this special issue in memory of Dr Giulio J D'Angio, the father of Paediatric Radiation Oncology.

Conflict of interest

None.

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