

## REVIEW

# The impact of radiotherapy on the hypothalamo-pituitary axis: old vs new radiotherapy techniques

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## Abstract

Multimodality cancer therapy has led to remarkable improvements in survival of childhood and young adult cancer, with survival rates exceeding 85%. Such remission rates come with their own adverse sequelae or 'late effects'. Although the cause of these late effects is multifactorial, radiation-related adverse effects are one of the most prevalent. Hypopituitarism is a recognised complication of irradiation of brain tumours distant to the hypothalamo-pituitary (HP) axis when the axis is included within the exposed field. Much of the data concerning the development of hypopituitarism, however, relate to early forms of photon-based radiotherapy. In this narrative review, we discuss advances in individual radiotherapy techniques currently used in treating brain tumours and their theoretical benefits based primarily on dosimetric studies. Increasingly precise radiation techniques, including advances in the delivery of photons (i.e. intensity-modulated radiotherapy) and proton beam therapy, are now available options. The premise behind these newer techniques is to reduce the dose and volume of normal tissue irradiated whilst maintaining an effective radiation dose to target tissue. When treating brain tumours distant to the HP axis the expectation, based upon dosimetric studies, is that newer forms of radiotherapy will less frequently involve the HP axis in the exposed field, and where incorporated within the field it will be exposed to a lower radiotherapy dosage. Intuitively the dosimetric studies should translate into significant reductions in the prevalence of HP dysfunction. These data are promising; however, to date there are minimal robust clinical data to determine if the theoretical benefits of these newer techniques on HP dysfunction is to be realised.

### Key Words

- ▶ radiotherapy
- ▶ hypopituitarism
- ▶ photon
- ▶ proton
- ▶ hypothalamo-pituitary dysfunction

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## Background

Improvements in childhood and young adult (CAYA; 0–24 years) cancer therapy have led to dramatic improvements in survival in the last few decades of the 20th century; however, recent improvements in survival rates have been more measured. Overall, 5-year survival of CAYA cancer survivors now exceeds 85% (1). Currently, there are estimated to be around half a million CAYA cancer survivors in Europe (2) who have undergone multimodality therapy including combinations of

surgery, radiotherapy (RT), chemotherapy, and immunotherapy. Although potentially lifesaving, these interventions often come with their own adverse sequelae that occur both acutely and after a variable duration of time, in some cases decades, following completion of treatment. Over 40% of the population of CAYA cancer survivors suffer from severe, disabling, or life-threatening complications in the 30 years following diagnosis (3). Although the cause of these complications is

multi-factorial, radiation-induced adverse effects are considered as one of the most important factors and not infrequently occur many decades after the original cancer diagnosis (4). As such, CAYA cancer survivors necessitate regular long-term follow-up and monitoring to allow early identification and intervention to prevent treatment-associated morbidity.

Over the last few decades, chemotherapy regimens have enabled delaying and de-intensification of RT schedules in terms of delivered dose and/or volume of tissue exposed to minimise impact on young developing brains, particularly in children under the age of 3 years. Exposure of healthy brain tissue to radiation, however, continues to occur during treatment of most central nervous system tumours, skull base, parameningeal, selective head and neck tumours, acute leukaemia with CNS involvement, as well as during total body irradiation (TBI) utilised as preconditioning before bone or stem cell transplantation. Cranial RT treatment volumes may be localised to the tumour's original site (focal irradiation), or the entire cranial contents may be intentionally irradiated, such as in whole-brain RT, craniospinal RT (CSRT), or TBI.

Early side effects of irradiation to the CNS are in part the consequence of cerebral oedema, which can lead to acute neurological symptoms such as weakness, speech, and sensory disturbance. In more severe cases, this can result in nausea, vomiting, and additional sequelae of raised intracranial pressure including seizures. Additional early sequelae of cranial RT can include hair loss, fatigue, skin, and scalp changes. Patients not infrequently develop somnolence syndrome in the intermediate weeks after completion of cranial irradiation. In the long-term, CNS irradiation is associated with hearing loss, cataracts, endocrinopathies, stroke, neurocognitive impairment, secondary tumours, worse socioeconomic outcomes, and excess mortality (5, 6). The excess mortality of CAYA cancer survivors predominantly relates to recurrence or progression of the primary disease; however, an increase in cardiovascular mortality (5) and risk of early- and late-occurring stroke (6, 7) are also observed. As a consequence, survivors are more likely to be hospitalised compared with the general population.

## Effects of conventional radiotherapy on hypothalamo-pituitary axis function

It is estimated that around 40–50% of CAYA cancer survivors develop an endocrinopathy requiring

long-term surveillance and follow-up (8). Growth disorders, hypopituitarism, central precocious puberty, primary hypothyroidism, primary gonadal insufficiency, hyperparathyroidism, and low bone mass occur at increased prevalence in CAYA cancer survivors. Hypothalamo-pituitary (HP) dysfunction is one of the most frequent endocrinopathies resulting directly from tumours in the hypothalamus and suprasellar cistern, surgery in the region of the HP axis, RT and putatively from raised intracranial pressure from hydrocephalus. Hypopituitarism is however most commonly a sequelae of irradiation therapy when the HP axis lies within the exposed field. Robust data to support the occurrence of hypopituitarism following the use of chemotherapy in CAYA cancer survivors remain elusive (9). The pathological mechanism leading to radiation-induced pituitary hormone deficiencies is not fully understood but may result from a combination of damage to hypothalamic nuclei, portal vasculopathy, pituitary fibrosis, or the development of pituitary atrophy secondary to hypothalamic damage.

HP dysfunction can present as central precocious puberty (CPP) and/or pituitary hormone deficiencies. CPP is believed to result from the release of the pre-pubertal inhibitory effects of higher centres on the gonadotrophin-releasing hormone pump, leading to the onset of gonadotrophin secretion. Pituitary hormone deficits can involve one or multiple anterior pituitary hormone axes. The risk of developing HP dysfunction is dependent on a number of variables, including total radiation dose at the HP axis, dose per fraction, volume of the HP axis exposed to radiation, time since irradiation, and age at radiation. It is unsurprising therefore that the development of radiation-induced HP dysfunction, following radiation delivered during childhood, can present either during childhood itself or following the completion of growth and puberty. Higher radiation doses lead to greater damage to the HP axes, with both earlier onset and a greater number of pituitary hormone deficits (10).

Following exposure of the HP axis to RT pituitary hormone deficits generally occur in a relatively predictable order. The growth hormone axis is almost exclusively the first to be impaired, followed by gonadotrophins, adrenocorticotrophic hormone (ACTH), and lastly thyroid-stimulating hormone (TSH). With increasing recognition that TSH deficiency can be reflected by a fall in free thyroxine levels of >20% (11), it is becoming clear that TSH deficiency likely occurs earlier and in parallel with the development

of gonadotrophin and ACTH deficiency. A causative effect of irradiation to impair posterior pituitary function is yet to be shown. The prevalence of pituitary hormone deficits in a large single-centre cohort of childhood cancer survivors followed for a median of 24 years and in whom the HP axis was exposed to RT, estimated the prevalence of deficiencies to be 40.2% for growth hormone, 11.1% for TSH, 10.6% for luteinizing hormone (LH)/follicle-stimulating hormone, and 3.2% for ACTH. CPP was present in 0.9% (12). The largest study performed in adult survivors of non-pituitary brain tumours showed a comparatively higher prevalence of pituitary dysfunction of 88.8% after a median follow-up of 8 years. For individual axes, growth hormone deficiency (GHD) was the most frequent (86.9%), followed by luteinizing hormone/ follicle stimulating hormone deficiency (LH/FSHD) (34.6%), adrenocorticotrophic hormone deficiency (ACTHD) (23.4%), and thyroid stimulating hormone deficiency (TSHD) (11.2%), with hyperprolactinemia reported in 15% of patients (13). The cohort was however, in part, selected for surveillance based on the dose and distribution of the RT delivered (13).

In childhood cancer survivors, a radiation dose threshold below which deficiency of an individual axis rarely occurs has been described. A dose of  $\geq 18$  Gy to the HP axis is required to increase the risk of GHD and CPP, but higher doses of  $\geq 30$  Gy significantly increase the risk of LH/FSHD, ACTHD, and TSHD (14). It has however been suggested that radiation doses of  $< 30$  Gy may cause LH/FSHD and TSHD but at a much later time period, indicating the importance of ongoing surveillance (12). Not dissimilar data regarding dose thresholds for individual anterior pituitary hormone deficits have been reported for adult survivors of gliomas (15). In CAYA cancer survivors, the time from RT exposure to HP dysfunction varies for each individual hormone axis, with GHD occurring earliest at  $< 1.0$ – $4.4$  years, followed by TSHD  $1.8$ – $5.1$  years, ACTHD  $2.5$ – $7.0$  years, LH/FSHD  $4.5$ – $10.2$  years; and  $3.1$ – $3.8$  years for CPP (16).

Clinically, the presentation of hypopituitarism occurring following HP axis irradiation is not different from other causes of HP disease, though it may be more insidious and difficult to recognise symptomatically within the milieu of symptoms relating directly to the previous tumour, treatment thereof, and additional late sequelae. Growth hormone deficiency presents in childhood with reduced height velocity and in adults with adult growth hormone deficiency syndrome.

When considering growth, other treatment-related factors including the direct impact of previous CSRT and chemotherapy on vertebral growth plates need to be considered. Gonadotrophin dysfunction during childhood presents either with CPP or alternately with failure of pubertal progression and in adults with symptoms of sex steroid deficiency and subfertility. ACTH deficiency presents similarly in children and adults, though hypoglycaemia generally only occurs in children. The presentation of TSH deficiency is indistinguishable from primary hypothyroidism.

Without intervention, deficiencies in these hormones during childhood can contribute to a reduction in final adult height, failure of pubertal development, gynaecomastia, osteoporosis, subfertility, adverse body composition and vascular risk profile, and impaired quality of life (QoL). Importantly, untreated ACTH deficiency can result in life-threatening adrenal crises. Diabetes insipidus when present is unrelated to irradiation and should stimulate investigation for an alternate cause of posterior pituitary dysfunction. CAYA cancer survivors with one or more endocrine or metabolic disorders are more likely to report poorer health-related QoL and sub-optimal physical activity levels (17).

## Evolution of conventional XRT

The paediatric population, due to their growth and development potential, is particularly sensitive to radiation-induced side effects. Competing objectives to maximise cure and minimise toxicity including late effects are pivotal in younger vulnerable patients. This has led to innumerable efforts in the past few decades for the development of increasingly precise radiation techniques to reduce the dose and volume of normal tissue irradiated (18, 19). The use of modern imaging equipment for planning; co-registration of planning CT and diagnostic MRI sequences to optimise accurate RT targets and organs at risk (OAR) delineation; evolution of RT from conventional to intensity-modulated RT (IMRT) and volumetric-modulated arc therapy (VMAT) to further improve conformality; and modern irradiation techniques like proton beam therapy (PBT) and stereotactic RT (SRT) have enabled better sparing of normal tissues in this population. These in turn have resulted in reduced long-term side effects, improved QoL, and have allowed dose escalation in radio-resistant tumours (20).

## Two- and three-dimensional radiotherapy

The interaction of high-energy electromagnetic waves with the tumour cells is the basis of photon-based RT. Photons, while traversing through the body, interact with the electrons and deposit energy, thereby causing DNA damage. Due to their unique properties, maximum dose deposition occurs shortly after entering the body and thereafter continuously decreases until they exit. As such, conventional RT is not the ideal modality to treat tumours situated at a depth, especially paediatric tumours, where the intervening and surrounding developing normal tissues will receive a significant RT dose, thereby increasing side effects.

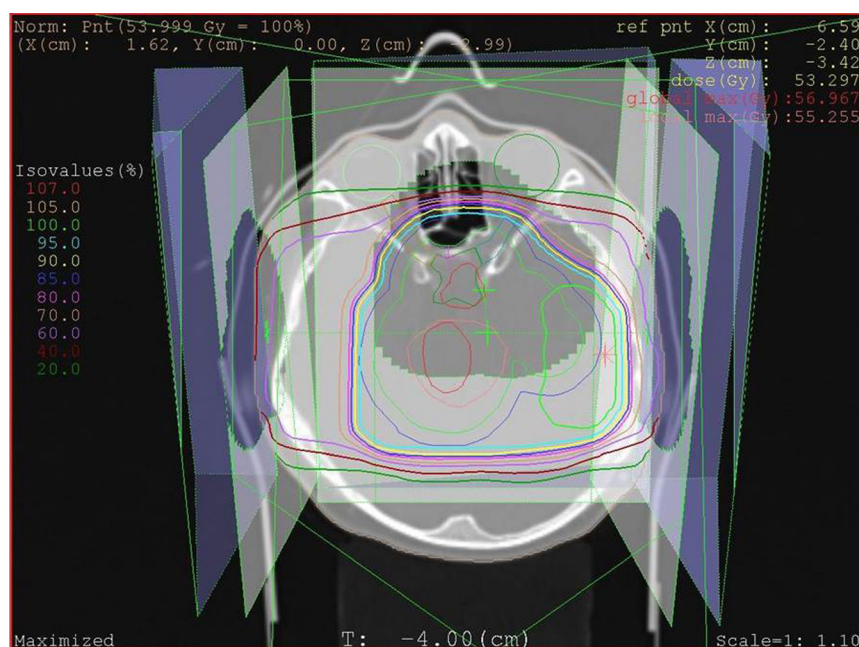
Historically, RT treatment comprised 2D techniques relying on bony anatomy and hand-drawn shielding blocks for treatment planning. The earliest use of RT in paediatric malignancies dates back to 1919 when Harvey Cushing innovated its use in the treatment of medulloblastoma (21). In the 1930s, orthovoltage and cobalt therapy were the main RT modalities in treating childhood tumours (22). During the 2D era, the adjustment of fields to the actual tumour volume was difficult. By the end of the last millennium, sophisticated 3D imaging was incorporated into planning software, which along with the introduction of multileaf collimation, allowed accurate delivery of radiation to mirror the shape of the tumour (conformal; Fig. 1). As a consequence of these advancements during the last few decades, two 2D RT has been superseded by 3D conformal techniques and, more latterly, by IMRT (23, 24).

Parallel to these improvements in photon-based techniques, during the period 1970–2000, emerging concerns regarding radiation-induced life altering, often irreversible and at times devastating late effects, dampened enthusiasm in the use of RT in the management of paediatric brain tumours (23). The interest in systemic chemotherapy use surged to defer or minimise the use of RT, especially in extremely young children with cancer. However, RT remains an essential component of current contemporary multimodality treatment regimes for CAYA cancers.

## IMRT, VMAT, and IGRT

A landmark development in the evolution of RT techniques is the introduction of IMRT, which is an advanced method of delivering conventional RT. The availability of better imaging modalities, modern linear accelerators, and advanced treatment planning software has made IMRT more clinically relevant. This has enabled the optimisation of RT fields to the actual tumour volume and clear delineation of normal tissues that need to be protected from radiation (OAR). IMRT has allowed dose escalation to the target tissue and dose constraints to OAR. IMRT techniques are now the standard of care for the majority of paediatric photon treatments (23, 24, 25). Dosimetric studies comparing conformality and dose homogeneity have established the superiority of IMRT over conventional RT (26).

The techniques for photon therapy have further evolved over the past few decades with the introduction



**Figure 1**

Conventional radiotherapy planning scan for a low-grade glioma showing isodose lines representative of percentage of the tumoural dose.

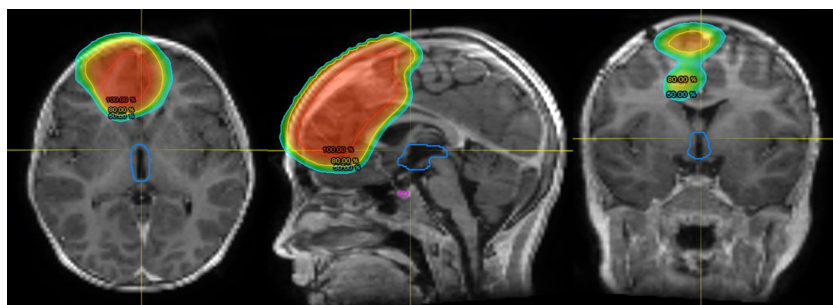


**Figure 2** Planning dosimetric scans for delivery of craniospinal radiotherapy using volumetric-modulated arc therapy (VMAT) for a metastatic ependymoma. Isodose The colour scale represents the percentage of the tumoural dose.

of image-guided RT (IGRT) and arc-based therapies like VMAT (Fig. 2) and helical tomotherapy. In IGRT, imaging techniques like CT and MRI are incorporated to increase precision in planning and daily treatment. Arc therapy allows patients to be treated from a full 360° beam angle thereby reducing treatment time. Tomotherapy (slice therapy) machines are a combination of a CT scanner and linear accelerator, where radiation is delivered in a fan-shaped distribution with the help of a continuous rotating gantry. This innovative technique provides

daily 3D imaging of the tumour, achieving precision and decreased toxicity (27).

There are however potential disadvantages of IMRT. IMRT could expand the volume of non-target tissue receiving low-dose radiation while trying to limit the volume exposed to high-dose irradiation. This increase in the total region exposed to low-dose radiation may increase the risk of secondary cancers developing through a higher ‘integral dose’. However, the true incidence of secondary cancers can be quantified only



**Figure 3** Dosimetric planning study for delivery of proton therapy to a high-grade glioma showing 100, 80, and 50% isodose lines. The hypothalamus is outlined in blue and the pituitary in purple.

through long-term follow-up data, which is as yet unavailable. When compared to conventional planning, IMRT and VMAT involve more complex treatment planning (Fig. 2) and are more labour-intensive for the RT multidisciplinary team (28).

## Newer forms of radiotherapy

Much of the data suggesting advantages of newer forms of radiation are derived from a comparison of modelled dose distributions which take into account properties of the RT (i.e. photons or protons); delivery of the radiation (i.e. beams, arc therapy), and target volume which allow prediction of both effects on the tumour and OAR. These dosimetric models estimate the distribution of the RT and dosage delivered to the tumour, surrounding tissue, and OAR (Figs. 1, 2 and 3).

### Proton beam therapy

PBT involves the delivery of proton particles in place of X-rays (photons) for radiation treatment. The potential therapeutic benefit of protons was first reported as early as 1946 by physicist Robert Wilson (29), with the first patient being treated at the University of California in 1954 (30). Protons travel through tissue in a straight line with increasing energy loss and decreasing pace,

resulting in a steep dose fall off (Bragg peak) distal to the target tissue. Due to these unique physical properties, protons can deliver a characteristic dose distribution of minimal dose to surrounding uninvolved organs, while maintaining dose and efficacy against the tumour (Fig. 3). Comparison of modelled dose distributions of PBT with advanced photon-based techniques demonstrates that the dose received by the surrounding normal tissues is lower with PBT (31, 32). Intuitively therefore PBT offers similar chances of cure with a theoretical reduction in long-term side effects. Based on the dosimetry, PBT, when used to treat brain tumours distant to the HP axis, can potentially reduce the risks of growth and developmental disorders, endocrine dysfunction, and incidence of second cancers, while maintaining equivalent efficacy to photons (33). Side effects and toxicities still ensue with PBT, as tissues within and in close proximity to the target treatment volume receive a comparable high dose of radiation. Variance in the radiobiologic effect between photon and proton therapy on brain parenchyma and vasculature may give rise to different spectrums of toxicities, for example brain stem toxicity.

PBT is internationally considered as the treatment modality of choice for the CAYA population in view of its dosimetric advantage over conventional photon RT, resulting in significantly less radiation exposure to vulnerable healthy developing tissues, in turn translating into a lower risk of developing some RT-related acute and long-term toxicities. An additional benefit is anticipated in radio-resistant tumours where higher doses are required to optimise the chance of cure. In the absence of robust clinical outcome data, both Holland and Denmark have adopted the dosimetric model-based approach as the basis for their proton programmes (34). Similarly, based on a review of the dosimetry modelling and early treatment outcomes, NHS England has published a commissioning policy for the use of PBT in CAYA with malignant and non-malignant tumours (Table 1) (35). When compared with other RT modalities, the availability and distribution of proton centres are currently limited; however, the last decade has witnessed a global expansion in PBT centres, which is likely to continue into the future.

Despite the clear dosimetric advantages of proton therapy when treating brain tumours, there are as yet few robust studies comparing the clinical outcome, short- and long-term adverse effects of PBT vs photon-based therapies. The results of available studies are as yet inconclusive, due to biases or incorrect analysis (35). The sparsity of comparative evidence, particularly with the

**Table 1** NHS England criteria for commissioning proton beam therapy (PBT) for children, teenagers, and young adults in the treatment of malignant and non-malignant tumours.

- (1) A clear indication for radiotherapy; defined as curable; and with a reasonable disease-specific 5-year survival expectation.
- (2) Confirmation by a Children's Principal Treatment Centre (PTC) or TYA PTC multi-disciplinary team (MDT) that treatment with PBT is an option.
- (3) Age from birth up to about 25 years of age.
- (4) No evidence of distant metastases, with the exception of tumours which remain curable when metastatic (i.e. metastatic intracranial germinomas).
- (5) Adequate performance status and medically sufficiently stable to undergo PBT without delay, which may lead to increased risk of recurrence or compromise cure rates.
- (6) Exclusion of patients requiring radiotherapy for indications where there is no dosimetric advantage for protons over photons (i.e. TBI, WBRT).
- (7) Shared Decision-Making Tool: To be utilised as a framework for discussing radiotherapy with patients and their guardians, including knowns and unknowns regarding benefits and risks for PRT vs PBT.

PRT, photon radiotherapy; TBI, total body irradiation; WBRT, whole-brain radiotherapy.

most advanced photon techniques, remains a challenge in quantifying the efficacy and putative safety advantages of PBT over photons. Furthermore, the difference in relative biological effectiveness also ideally needs to be taken into consideration. A particularly difficult challenge is the ethical and social concerns of carrying out RCTs in paediatric populations given the theoretical benefits of PBT.

Clinical data regarding efficacy and adverse effects are increasingly becoming available as PBT is utilised for a more expansive range of CAYA brain tumours including medulloblastomas, ependymomas, germinomas, low-grade gliomas, selective meningiomas, and CNS embryonal tumours, craniopharyngiomas, and head and neck tumours. Accepting that current data are limited due to a small sample size, limited follow-up duration, and lack of randomisation, the available data are in keeping with the dose distribution data that adverse sequelae of radiation are less with PBT compared with photon-based RT. Compared with photon-based RT, PBT has been shown to maintain a higher level of QoL (36) in survivors of childhood-onset brain tumours; similar rates of ototoxicity in those treated for medulloblastomas (37) and equivalence in progression-free and overall survival in children treated for standard-risk medulloblastomas and ependymomas (38, 39, 40). In contrast to the data in childhood-onset tumours, recent data have demonstrated a benefit in overall survival for proton-based vs photon-based RT in adult-onset low-grade gliomas; however, selection bias may have contributed to this outcome (41). Alongside this, cognitive function and QoL have been shown to be preserved 5 years out from treatment of adult-onset grade 2 gliomas (42). These results are promising but require more detailed mapping with hippocampal and temporal lobe RT dose-volume histogram parameters to inform whether there is a benefit over those who have received photon treatments.

Acute toxicity from PBT when treating childhood brain tumours is generally low grade; predominantly fatigue, alopecia, and dermatitis; and manageable with supportive care (43). In a prospective study of 174 paediatric low-grade gliomas, only 22 experienced nausea or vomiting requiring anti-emetics during treatment with PBT, and only two required glucocorticoids (44). After a median follow-up of 4.4 years, 4% experienced severe toxicity (brain stem necrosis, symptomatic vasculopathy, epilepsy, retinopathy) (44). In a further study, CAYA who received proton therapy >50.4 Gy involving the brain stem, the cumulative incidence

of brain stem toxicity at two years was 3.8%, with the incidence of grade 3+ toxicity (severe interference with activities of daily life through to grade 5, death) of 2.1% (45).

The extensive evidence supporting the dosimetric advantages of PBT with lesser dose to normal tissue and the theoretical advantage of the reduction in long-term side effects leads to PBT to be considered the treatment of choice internationally. However, taking into consideration the sparsity of robust comparative evidence, clinicians should discuss the pros and cons of the different treatment modalities with patients and their parents before deciding on the best treatment for an individual as per the NHSE Clinical Commissioning Policy (35).

### Stereotactic radiotherapy (SRS or SRT)

Precise immobilisation technique, CT/MRI, and use of multiple intersecting beams are the central features of stereotactic radiosurgery (SRS). This has the potential to deliver a single large dose of radiation to a very discrete tumour volume to ablate it, thereby reducing the dose to particularly sensitive developing brain tissues (46). The fact that treatment can be delivered in a single visit or fewer number of visits makes it favourable in the paediatric age group. But on the reverse, SRT often involves invasive immobilisation techniques such as frames fixed to the skull with metal pins. To overcome this hurdle, frameless options have evolved utilising a mask-based approach. Children often require sedation for this procedure.

SRS has been established in the treatment of both primary and metastatic adult brain tumours. Equivalent data with respect to the use of SRT for the treatment of paediatric brain tumours have not been well studied to date. Currently, its role in paediatric tumours is limited to palliative scenarios after fractionated photon treatments have been thoroughly explored (47). Within the adult population, SRT has been used in a variety of clinical scenarios; for example, in high-risk ependymoma patients treated with adjuvant RT, SRS can be incorporated as a boost to the tumour site. The use of single-fraction high-dose SRT in palliative approaches to ablate oligometastatic disease has been tried with promising results (48). Recurrent or residual disease is another area where SRS can be utilised. As this population might have received radiation in the primary setting, risks and complications related to re-radiation like radiation necrosis are higher (49). SRS may be helpful in these cases as it causes minimal re-radiation of critical normal structures that have previously been exposed to radiation. This is however

dependent on the OAR, as after prior RT, SRS would not be suitable if the recurrence was considered too proximate to the optic chiasm or brainstem.

SRS is a technically feasible method of treatment delivery with minimal adverse effects to date. However, multicentric prospective trials are needed to examine the impact of SRS on late endocrine effects and to assess the risks/benefits with minimal bias. In the majority of the retrospective studies, previous irradiation is a significant confounding factor.

### Evolution of hypopituitarism with newer forms of radiation

The radiation dose received at the HP axis is arguably the most important determinant of HP dysfunction. RT technological advances aim to limit the dose of radiation to surrounding critical normal tissues, including the HP axis. Newer techniques achieve this through a significant reduction of the volume of normal tissue within the field such that the HP axis is not exposed, or alternatively, where the axis is within the field, ensuring it is exposed to a significantly lower radiation dosage. It can therefore be theorised that when treating brain tumours distant to the HP axis, modern RT modalities and techniques will reduce the incidence of subsequent hypopituitarism.

Data comparing contemporary RT with conventional options are beginning to emerge; however, there remains a lack of robust data. Proton RT has the potential for reducing radiation exposure of the HP region during irradiation of tumours distant to the axis as a consequence of the more rapid fall-off of radiation with distance from the tumour (Bragg peak effect). These properties, based on dosimetry studies, may in turn limit the occurrence of late-onset endocrinopathies. Standard radiation schedules for medulloblastoma place the child at significant long-term risk of developing hypopituitarism (50). A number of small studies have shown that the use of proton therapy for the treatment of medulloblastoma has reduced the incidence of primary hypothyroidism, sex hormone deficiency, and the need for any hormone replacement therapy (51, 52). One study reported that those treated with protons had improved height outcomes; however, this may primarily reflect the lesser impact of protons on the growth plates in the spine due to the Bragg peak effect, which minimises exposure of the vertebral bodies (51). Differences in the incidence of GHD, central hypothyroidism, and adrenal insufficiency have not been conclusively shown (51,

53), and not all studies have shown a clear reduction in overall neuroendocrine deficits (39). The benefit, in terms of reduced endocrine late effects, has not been at the expense of treatment efficacy thus far (38) and seems to be in keeping with expected outcomes from dosimetric and toxicity modelling in childhood-onset medulloblastoma patients (54). In a study of 70 patients treated with PBT for paediatric CNS ependymoma and followed for 42 months, 1 of 32 developed central hypothyroidism, 2 of 25 tested had developed GHD, with a further 7 patients having a new low insulin-like growth factor 1 value but had not received a diagnosis of GHD (55). Height data were available in 57 patients after a median of 41 months from PBT and showed a decline in median height from the 54th percentile at baseline to the 36th percentile (55). In a cohort of adult-onset grade 2 glioma, new endocrine dysfunction was detected in 6 of 20 patients treated with PBT after 5.1 years of surveillance (42).

There are however significant limitations to the current data, which are based on relatively small numbers of patients, limited duration of follow-up, absence of control groups, lack of randomised prospective studies, and data directly comparing proton therapy with modern photon techniques such as IMRT.

Comparison of stereotactic conformal RT with conventional photon RT in CAYA with residual or progressive low-grade brain tumours has been undertaken in a randomised clinical trial (56). The study showed SRT to achieve superior neurocognitive and neuroendocrine functional outcomes at 5 years. Pituitary hormone deficits were recorded in only 29% of the individuals who received SRT vs 52% in the group who received conventional RT while maintaining comparable overall survival rates (56). Findings in adults can be conferred from prospective data using fractionated stereotactic radiation therapy for craniopharyngiomas, resulting in no new endocrinopathy in 16 patients, while providing good tumour control (57).

### Summary

Survival of CAYA cancer survivors has improved markedly over the last few decades, with 5-year survival now exceeding 85%. The long-term sequelae of multimodality cancer therapy however remains a concern. Although RT is recognised as central to many of the adverse long-term sequelae experienced by CAYA cancer survivors, it remains an essential part of the



treatment regimes for a number of brain tumours, head and neck soft tissue sarcomas, and bone tumours. This is unlikely to change in the foreseeable future given how effective radiation therapy is for certain tumour subtypes. Over the last decade, it has also become clear that individuals with adult-onset brain tumours experience similar levels of pituitary hormone deficits following irradiation compared with CAYA brain tumour survivors. If we are to use radiation therapy safely and avoid the adverse late sequelae associated with this modality, a reduction in exposure of normal tissue to radiation is required.

When considering the data characterising the adverse late effects from RT that we are observing currently in our patients with multiple organ systems, it has to be recognised that many of these are a reflection of the conventional RT in use 20–30 years ago. RT techniques have been transformed over the last few decades to improve the targeting of the tumoural tissue with greater sparing of the normal healthy tissue from radiation exposure. As such, it is hoped that we will start to observe fewer radiation-related late effects in both children and adults. Based on dosimetric modelling, state-of-the-art photon systems such as IMRT, in addition to PBT, should bring this closer to reality. As a consequence of the sharp fall-off in radiation dose around the target organ with PBT and the susceptibility of growing brain tissue to radiation-induced damage, PBT is likely to become the treatment of choice for many childhood cancers requiring radiation therapy to induce remission. Current data support at least the equivalence of PBT to photon-based therapies in terms of recurrence-free survival and overall survival.

Although the dosimetric studies are reassuring, as clinicians we wish to see robust clinical data that show the theoretical advantages of state-of-the-art photon and PBT have translated into better long-term health outcomes for our patients, particularly late effects. Currently, this is lacking. Specifically, in relation to HP dysfunction, irradiation of tumours distant to the HP axis with either state-of-the-art photon and PBT intuitively should result in fewer pituitary hormone deficits. To date, however, robust clinical outcome data regarding the reduction in late effects of PBT are not available. Studies have been small, of short duration, and often compare protons to older photons rather than state-of-the-art techniques. There may also be unconscious bias of the patients included, as the proton is more likely to be utilised if the target tissue is adjacent to critical structures such as the HP axis. Both larger observational

and randomised studies are required; however, given the difficulties of undertaking randomised studies in children, data are likely to be derived from the adult population and large databases of ‘real-world’ data. We await the outcome of these studies with trepidation and in the hope that newer techniques will significantly reduce the risk of the observed late effects associated with conventional 2D and 3D RT.

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