Management of vertebral radiotherapy dose in paediatric patients with cancer: consensus recommendations from the SIOPE radiotherapy working group

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Inhomogeneities in radiotherapy dose distributions covering the vertebrae in children can produce long-term spinal problems, including kyphosis, lordosis, scoliosis, and hypoplasia. In the published literature, many often interrelated variables have been reported to affect the extent of potential radiotherapy damage to the spine. Articles published in the 2D and 3D radiotherapy era instructed radiation oncologists to avoid dose inhomogeneity over growing vertebrae. However, in the present era of highly conformal radiotherapy, steep dose gradients over at-risk structures can be generated and thus less harm is caused to patients. In this report, paediatric radiation oncologists from leading centres in 11 European countries have produced recommendations on how to approach dose coverage for target volumes that are adjacent to vertebrae to minimise the risk of long-term spinal problems. Based on available information, it is advised that homogeneous vertebral radiotherapy doses should be delivered in children who have not yet finished the pubertal growth spurt. If dose fall-off within vertebrae cannot be avoided, acceptable dose gradients for different age groups are detailed here. Vertebral delineation should include all primary ossification centres and growth plates, and therefore include at least the vertebral body and arch. For partial spinal radiotherapy, the number of irradiated vertebrae should be restricted as much as achievable, particularly at the thoracic level in young children (<6 years old). There is a need for multicentre research on vertebral radiotherapy dose distributions for children, but until more valid data become available, these recommendations can provide a basis for daily practice for radiation oncologists who have patients that require vertebral radiotherapy.

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Introduction

Approximately one in three children diagnosed with cancer will have radiotherapy with curative intent during their disease course.[1] In contrast to adult patients, a substantial number of target volumes in paediatric patients are close to the growing vertebrae. A major category is patients with CNS tumours undergoing craniospinal irradiation, which includes medulloblastoma, and ependymoma or atypical rhabdoid tumours that have proven dissemination in the cerebrospinal fluid. Often, dose prescriptions are in the range of 20–40 Gy, and peak ages are 10 years or younger.[2] The most common solid tumours that are typically adjacent to the vertebrae include neuroblastoma and renal tumours (peak age of <5 years; radiotherapy doses of 10–36 Gy), as well as rhabdomyosarcoma, Ewing's sarcoma, and other rare soft-tissue sarcomas that present at all ages (radiotherapy doses of 36–60 Gy).[2] As overall 5-year survival outcomes have increased to approximately 80% in recent decades, more attention has been given to long-term detrimental effects associated with treatment. For radiotherapy, the development of highly conformal radiotherapy techniques such as (rotational) intensity-modulated radiotherapy and proton therapy has made it possible to improve dose coverage of tumour target volumes while enabling better sparing of normal tissues.

An important directive that was derived from the 2D and 3D eras of paediatric radiation oncology was to carefully manage doses given to growing vertebrae, as detrimental growth effects resulted in potentially severe functional deficiencies. To harness the full potential of (rotational) intensity-modulated radiotherapy or proton therapy, careful decision making regarding dose constraints over the vertebrae is required. To address this issue, paediatric radiation oncologists from prominent treatment centres throughout Europe met to formulate consensus recommendations. A literature review was done by BAH (with contributions from CC, GOJ, RDK, BT, and HCM) on normal postnatal vertebral development and radiotherapy-related growth deformities and used as a basis for dose recommendations. The review was discussed during a 2-day workshop in April, 2018, at the Istituto Nazionale dei Tumori in Milan, Italy. Factors affecting radiotherapy-related vertebral growth deformities were determined, and they were translated into recommendations for highly conformal radiotherapy techniques when treating target volumes adjacent to the spine in children.

Data collection

Literature review

To provide an evidence base for consensus formation, a review of the available literature was done through a MEDLINE search with use of PubMed and references from relevant articles. We used combinations of the

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search terms "p(a)ediatric", "children", "development", "(ab)normal", "radiotherapy", "irradiation", "radiation", "skeletal", "late effects", "vertebra", "spine", "spinal", "bone", "growth", "abnormalities", "stature loss", "changes", "alterations", "deformity", "scoliosis", "bone mineral density", "osteoporosis", "childhood cancer survivors", "p(a)ediatric cancer survivors", "secondary malignancy", "induced malignancy", "secondary bone tumo(u)rs", "induced bone tumo(u)rs", "osteosarcoma", "pathologic", "bone fracture", "vertebral fracture", and "spinal fracture". Results from the search strategies were evaluated for relevance and the selected articles were scanned for further relevant references. An overview was presented during the 2-day workshop and compiled into a qualitative review to form a basis for the consensus recommendations in this manuscript.

Consensus formation

Recognising the need for guidelines regarding spinal dose distribution in the era of highly conformal radiotherapy techniques, members of the European Society for Paediatric Oncology (SIOPE) radiotherapy working group did a survey of radiation oncologists from 29 connected European centres who had extensive experience. Representatives from these centres responded. The survey recorded local practices in vertebral radiation dose management with regards to various characteristics. It had multiple choice and open questions regarding local approaches to vertebral radiation with regards to different age groups, sexes, radiotherapy to different spinal levels, different radiation doses and effect on vertebral growth, effect of dose gradients, methods of vertebral delineation, and partial or whole spinal radiotherapy. After the survey was completed, respondents and SIOPE members who showed an active interest in the project were invited to participate in a 2-day workshop in April, 2018, at the Istituto Nazionale dei Tumori in Milan, Italy. Representatives of 25 centres attended the meeting. The compiled information from the survey and an extensive overview of the literature were presented by the corresponding author. Radiation oncologists from several large centres presented their local approaches regarding vertebral dose management. After the presentations and an open discussion, an ad hoc survey was done among the group present during the workshop to identify the five most important variables influencing spinal growth effects from radiotherapy. These were presented by GOJ and BAH with a summary of the information gathered from the literature search concerning each variable. The first consensus proposals were then reached through discussion. After the meeting, all participants (and some radiation oncologists who were not able to attend the meeting) received a summary of the minutes from the workshop and the first drafted outline of the guidelines. In total, representatives from 35 centres participated in the project (ie, survey formation, participation in surveys, attendance at the workshop, or participation in guideline formation based on the literature review). Comments and literature suggestions were shared among the group and the proposals were adjusted for broad approval, after which a first draft of this manuscript was prepared. 32 representatives from 27 centres in 11 countries agreed to participate as co-authors. Three versions of the manuscript were shared among co-authors and commented on, until a final agreement on the literature overview and the recommendations for daily practice was reached. A consensus among more than 90% of co-authors (ie, 29 of 32) was reached on every subject.

Normal development of the spinal column

Development of various components of the spine involves a complex, hierarchical series of events that is influenced by genetic, metabolic, and endocrine signalling pathways.[3–5] The most important growth mechanism in vertebrae is endochondral ossification that occurs at the epiphyseal plates, in which chondrocyte proliferation, hypertrophy, and cartilage matrix secretion result in chondrogenesis. Cartilaginous growth plates in the vertebral arch allow for growth of the vertebral foramen around the developing spinal cord. Ossification occurs in primary ossification centres in the vertebrae; these start to appear at 9 weeks' gestation at the cervicothoracic junction and proceed bidirectionally. At birth, only 30% of the spine is ossified. A typical vertebra has three ossification centres: one centre in the vertebral body and a centre in each dorsal half of the vertebral arch. However, the form and extension of primary ossification centres differ between the vertebral levels (figure 1). The primary ossification centres push the cartilaginous tissue outwards. By the age of 5 years, the ossified portions of the vertebra extend to the lateral margins and the epiphyseal cartilage starts to thin. Between the ages of 13 years and 16 years, secondary ossification centres form at the tip of the spinous and transversal processes, and at the superior and inferior rim of the vertebral body (figure 1). The secondary ossification centres fuse to the vertebral body between the ages of 18 years and 25–30 years.

At birth, sitting height is around 34 cm, and at the end of growth it is around 88 cm for girls and 92 cm for boys.[6] The spine accounts for 60% of total sitting height. Spinal growth is programmed to keep the limbs, spine, and thoracic cage in proportion, and occurs in three periods, with successive acceleration and deceleration phases (table).[6–9] Most growth occurs between the ages of 0 years and 5 years, with an increase in sitting height of 27 cm. From 5 years to 10 years, there is a quiescent steady growth phase. Two-thirds of the pubertal growth occurs during the acceleration phase of 2 years (around the age of 11–13 years for girls and 13–15 for boys), followed by a deceleration phase of approximately 3 years.

The largest increases in sitting height occur in the thoracic and lumbar spine regions, which are

26·0–28·0 cm and 15·5–16·0 cm long at final sitting height, and which form 30% and 18% of the final sitting height, respectively.[10] Most thoracic spine growth and lung development occurs between the ages of 0 years and 8 years. Insufficient or deformed growth will cause inadequate thoracic cage development and potential respiratory insufficiency. A thoracic spine length of 18–22 cm, which is usually reached between 5 years and 10 years of age, is necessary to avoid severe respiratory insufficiency.[11]

At 10 years of age, approximately 90% of the final lumbar spine height is reached, but only 60% of the definitive volume is present. The individual lumbar vertebrae grow at a higher velocity than the thoracic vertebrae (2 mm per year *vs* 1 mm per year).[12] The posterior elements grow more slowly than the anterior components in the lumbar spine, and vice versa in the thoracic spine, resulting in the adult lordotic and kyphotic curves, respectively.

Models to establish bone age, and to predict adult height and the timing of the growth acceleration phase of puberty, are discussed in the appendix. These methods help to establish the risks of radiotherapy for growth interruption.

Effects of radiotherapy on growing vertebrae

Detrimental effects of radiotherapy on bone growth will only manifest in the long term. Therefore, paediatric radiation oncologists must consider late effects when planning radiotherapy of a spinal or paravertebral target volume. However, the severity of treatment-related damage is challenging to predict as the damage can be affected by many factors, including total radiation dose, fractionation schedule, treatment volume, age of the child, symmetry of the delivered dose over vertebrae, developmental status of the irradiated growth plates, and other treatments such as chemotherapy or surgery, as well as inherent factors such as endocrine abnormalities and bone growth aberrations because of tumour location.

Early clinical reports of spinal deformities after radiotherapy described transverse growth disturbance lines on vertebrae, vertebral scalloping, irregular epiphyseal lines, vertebral contour abnormalities, hypoplasia, exostosis, kyphosis, scoliosis, kyphoscoliosis, and soft tissue changes such as skin atrophy, telangiectasia, subcutaneous fibrosis, and muscle atrophy.[13–16] No reliable normal tissue complication models of spinal deformities after radiotherapy have been built. The majority of available literature from the 2D treatment era is mostly based on cohorts assembled over long time periods, which are susceptible to bias (eg, from changes to treatment protocols), and which include patients of different ages who received diverse treatment schedules, often with cobalt machines and therefore with higher bone absorption than linear accelerators. Some mathematical models of bone growth retardation have been described,[17–21] but these models have not been validated on a larger scale.

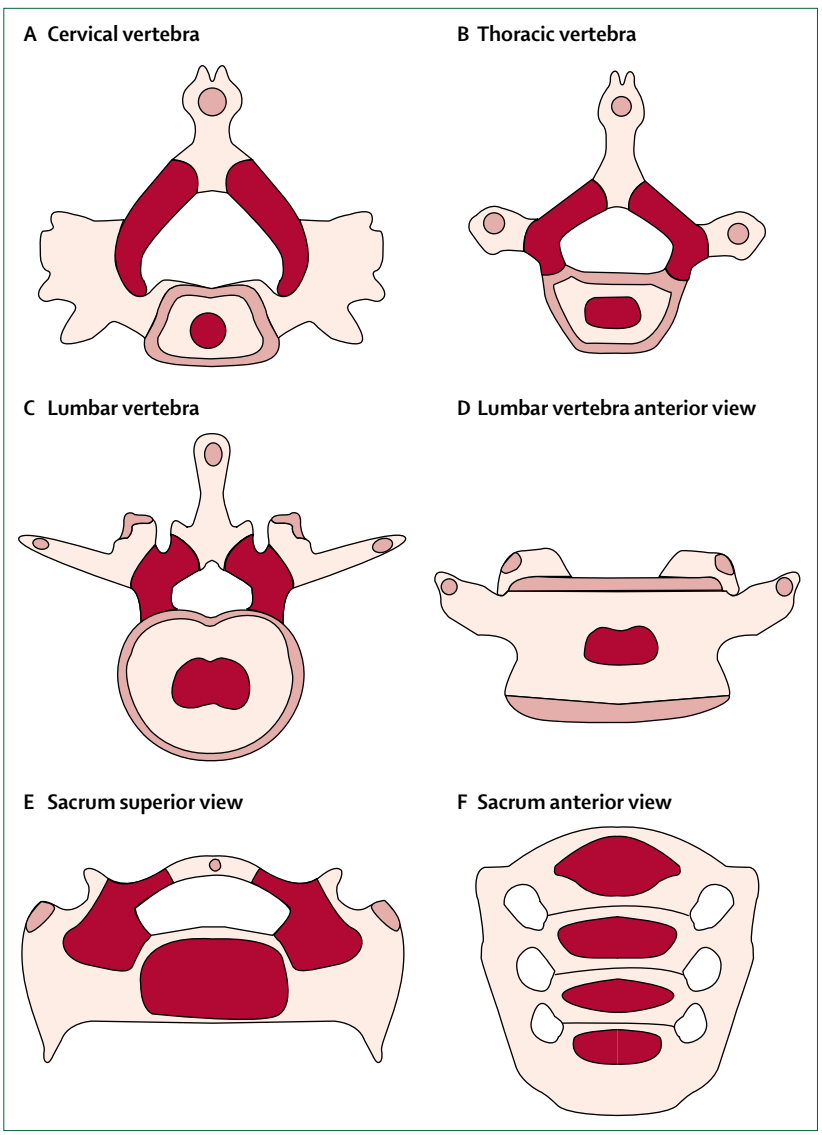

Figure 1: **Localisation of primary and secondary ossification centres**
Primary (red) and secondary (pink) ossification centres of the vertebrae at the cervical (A), thoracic (B), lumbar (C,D), and sacral (E,F) spinal levels. Vertebrae are depicted from an inferior view, unless otherwise specified.

Pathophysiology and fractionation

The pathophysiology of radiotherapy effects on the bone and epiphyseal plates is not completely understood. Most of the available data were gathered from animal studies. In rodent studies, a single dose of less than 5 Gy did not cause detectable epiphyseal growth stunting, but a single dose of 5 Gy did cause growth stunting.[22–25] Very high doses, such as a single dose of 20 Gy, can cause acute bone ossification insult and irreversible growth arrest. The majority of growth reduction seems to be caused by microvascular damage in the proliferative zone of the growth plate.[3] Radiotherapy also has a direct effect on proliferating chondroblasts.[26] Surviving clones eventually repopulate, and the recovery is indirectly proportional to the radiation dose given.[26] Laboratory studies suggest a

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See Online for appendix

	Boys			Girls		
	Sitting height increase (cm)	Lower limb increase (cm)	Proportion of final sitting height (%)	Sitting height increase (cm)	Lower limb increase (cm)	Proportion of final sitting height (%)
1	12·4	9·9	..	12·3	8·9	..
2	5·3	5·3	56%	5·3	5·1	59%
3	3·3	4·0	60%	3·4	4·0	63%
4	3·2	4·2	63%	3·3	4·1	67%
5	2·8	3·9	66%	3·0	3·8	70%
6	2·3	3·2	69%	2·4	3·3	73%
7	2·3	3·2	71%	2·4	3·3	76%
8	2·3	3·2	74%	2·4	3·3	79%
9	2·3	3·2	76%	2·4	3·3	81%
10	2·3	3·2	79%	2·4	3·3	84%
11*	2·3	3·2	81%	2·4	3·3	87%
12*	2·3	3·2	84%	3·4	4·4	91%
13*†	2·3	3·2	86%	4·3	3·0	96%
14†	3·7	4·7	90%	2·5	1·2	98%
15†	4·8	3·3	96%	1·1	0·3	100%
16	2·8	1·2	99%	0·2	0·1	100%
17	1·0	0·6	100%	..	..	100%
18	0·3	0·1	100%	..	..	100%

Data are average values (adapted from Dimeglio and Canavese[7]). *Typical pubertal growth acceleration phase in girls. †Typical pubertal growth acceleration phase in boys.

Table: **Rate of growth by age (years)**

continuous dose-effect relationship from 5 Gy to 35–40 Gy.[3] Eifel and colleagues[27] evaluated the effects of different fractionation schedules on tibial growth plates in weanling rats. The estimated α:β ratio for growing bone from these experiments was 4·5, but given the slow cell cycling time for epiphyseal cells in children (20–30 days) compared with rats (2 days), the α:β ratio of growing human bones might be lower than that of growing rat bones.[28–30] Although the exact fractionation sensitivity remains unclear, most authors concluded that hypofractionation will have larger effects on growing bone than 1·8–2·0 Gy fractionation.[27] Reports are contradictory regarding any further benefit of hyperfractionation.[31–33] In a clinical setting, patients aged 3 years to 20 years with standard-risk medulloblastoma who were treated with hyperfractionated craniospinal irradiation in the randomised PNET4 trial showed greater restriction of spinal growth than children treated with conventional fractionation (hyperfractionation schedule of 36·0 Gy in 36 1·0 Gy fractions given twice a day, 5 days per week, for 3·5 weeks, as compared with a conventional fractionation schedule of 23·4 Gy in 13 1·8 Gy fractions given once a day, 5 days per week, for 2·5 weeks).[34] However, the benefit or disadvantage of hyperfractionation is still unclear, as the hyperfractionation schedule also resulted in a higher biologically effective dose than the conventional fractionation schedule.

Effect of radiotherapy dose on spinal growth restriction

Probert and Parker[35,36] were the first investigators to quantify disproportionate growth in sitting height after whole spinal radiotherapy, which they found was most marked in children receiving doses of more than 35 Gy, as opposed to doses of less than 25 Gy. Since then, numerous studies have reported spinal growth retardation after radiotherapy, with the most important factors being young age at treatment, higher total doses, and larger treatment volumes.[18,19,35–45] Various tolerance doses are described as relevant. The steepest increase in dose-effect relationship is between approximately 15 Gy and 30 Gy, with studies describing total doses of more than 25 Gy or more than 33 Gy as causing significant growth retardation, and measurable growth deficits at doses of 18–20 Gy and higher. In a follow-up study of children treated for Hodgkin lymphoma, Willman and colleagues[44] found that the greatest height impairment was at doses of more than 33 Gy to the entire spine at the age of 11 years or younger for boys and 9 years or younger for girls. These patients had an average sitting height impairment of 8·2%, equating to a sitting height loss of 7·4 cm, or 2 SD scores from US population means. Lower doses, pubertal or postpubertal age, or smaller treatment volumes resulted in growth impairment that was less than one SD from US population means. Hogeboom and colleagues[19] investigated the height deficit of 2778 patients in the long-term follow-up study of the National Wilms Tumour Study Group who had been treated with flank radiation portals, or whole abdominal or lung radiotherapy in doses from 0 Gy to 40 Gy. Hogeboom and colleagues made a prediction model for adult height deficit per Gy of radiation given, as a function of the age at treatment. Patients who received more than 15 Gy were on average 4–7 cm shorter than unirradiated patients, and smaller effects occurred with increasing age at treatment. Infants (≤1 year) were most affected, with height deficits from doses of 10 Gy and higher.

Hartley and colleagues[18] measured and modelled spinal growth with use of MRI during follow-up of 61 patients after craniospinal irradiation (23·4 Gy or 36·0–39·6 Gy; mean follow-up of 44·1 months). Slower growth was modelled for patients treated with high dose craniospinal irradiation compared with the standard dose of 23·4 Gy, and the lumbar spine was found to be more affected than the cervical or thoracic spine. Even after a dose of 36 Gy, there was still some discernible growth in the vertebrae. Ng and colleagues[38] performed a vertebral-sparing study with intensity-modulated radiotherapy in 34 patients with neuroblastoma (mean age of 4·3 years). Vertebrae next to the 21·6 Gy target received at least 18 Gy, whereas adjacent-spared vertebrae received a mean dose of 12·9 Gy. Target vertebrae grew slowest on follow-up prepubertal MRI images, but spared vertebrae also grew significantly slower than out-of-field vertebrae (growth measured in cm per vertebral body per year). There was a

larger dose effect in the lumbar spine than in the thoracic spine.

Dörr and colleagues[37] reported on 146 patients who were screened at 18 years of age after radiotherapy to only the spine, trunk, or extremities between 1970–97, at a median age of 8·8 years. Pathological changes in the skeletal system and soft tissues were scored as minor or substantial at the equivalent dose in 2 Gy fractions, recalculated with a tissue α:β value of 3 Gy. The majority of pathological observations were in patients who were less than 6 years old at the time of treatment. There was hypoplasia in more than 50% of patients when doses of more than 20 Gy were given to children who were younger than 6 years old. At a treatment age of 6 years and older, substantial changes were found only after doses of more than 35 Gy, and no substantial changes were found in patients at a treatment age of more than 12 years. The group who had changes that were scored as "substantial" had a mean age at treatment of 4·4 years (SD 3·6) and had received a mean dose of 30 Gy (SD 9). There was a steep rise in the dose-effect curve between approximately 40 Gy and 60 Gy for substantial soft tissue effects.

Effect of treatment age on growth restriction

Probert and Parker[35] reported that growth restriction that affected sitting height after radiation of the vertebrae was most severe in children who were treated at less than 6 years or at 12–13 years. However, Probert and Parker's small cohort study did not have pre-treatment data and had a short follow-up; many children were not followed up through the pubertal growth spurt. Other studies have confirmed the finding that the younger a child is at the time of radiotherapy, the more profound the spinal disproportion.[18–20,37,38,41–43] Studies do not corroborate the finding that radiotherapy during puberty has a disproportionate effect on final attained height, but no radiological evaluations had been done in these studies regarding the timing of the pubertal growth spurt.[18,20,37,41,44]

In animal studies, the correlation between radiation effect and age is thought to be because of the (mostly temporary; only permanent at high doses) stunting effect on the growth plate. It is assumed that after some time, growth restarts at pre-radiotherapy velocities. However, Hogeboom and colleagues[19] found that radiotherapy caused growth deficits that increased over time, indicating that after the first stunting effect, growth resumes at slower velocities than would be expected. This effect is more severe the younger the child is at the time of radiation. In addition, the pubertal growth spurt does not seem to occur for irradiated vertebrae; during puberty, the deficit in sitting height increased compared with the normal population for patients who survived a Wilms' tumour in a study by Wallace and colleagues.[42]

Infants who are less than 1 year old are most affected by spinal radiotherapy compared with other age groups. Children radiated for Wilms' tumours with a dose of 10 Gy or less at younger than 1 year showed height deficits of around 3 cm at the age of 15 years, whereas doses of more than 10 Gy shortened height by 7–8 cm at the age of 15 years.[19]

Effect of sex on growth restriction

Some studies suggest that growth retardation is more severe for boys than for girls after spinal radiotherapy or craniospinal irradiation.[18,43,46] However, most studies have not found sex to have a significant effect on growth restriction.[19,37,44,47] The MRI measurement studies by Hartley and colleagues[18] and Ng and colleagues[38] had contradictory results on whether vertebral body growth was slower in girls or boys after radiotherapy.

The most important reason for differences in spinal radiotherapy effects on sitting height between boys and girls might be the greater percentage of attainable height remaining for boys at any age. In addition, girls have an earlier adolescent growth spurt than boys. Therefore, radiotherapy between the ages of 12 years and 15 years will have a larger effect for boys.

Effects of other treatment modalities on growth restriction

Other therapies for paediatric malignancies can influence growth impairment. Surgery, especially laminectomy, has been established as a frequent cause of scoliosis.[47,48] In addition to the effects of spinal irradiation, which only affects sitting height, growth can be disrupted by hypothalamic–pituitary dysfunction as a result of cranial irradiation.[40,41,49] Sulmont and colleagues[50] compared children who received cranial or craniospinal radiotherapy with or without subsequent growth hormone deficiency, and found that craniospinal irradiation disrupted growth more than cranial radiotherapy alone. Standard growth hormone treatment for the children who received irradiation and had growth hormone deficiency only had a minor effect on height gain because of small bone age retardation at the onset of supplementation and an earlier onset of puberty compared with children with idiopathic growth hormone deficiency. Furthermore, hormone substitution had a significantly reduced effect after craniospinal irradiation because of the direct effect of radiotherapy on spinal growth.

In a study of 38 prepubertal children (mean age of 6·78 years) with medulloblastoma, patients who received chemotherapy with craniospinal irradiation showed lower growth velocities than patients who received only craniospinal irradiation.[39] A study by Ogilvy-Stuart and colleagues[49] found that chemotherapy had a restrictive effect on growth that was additive to the effect of cranial radiotherapy or craniospinal irradiation in children with brain tumours. Several other radiotherapy studies have looked for a confounding effect of chemotherapy but have found no significant effect in multivariate analyses.[19,40,44,47] Mostly, these cohort studies cannot

evaluate the confounding effect of chemotherapy, either because statistical power is too low when different chemotherapy schedules are given to several small groups,[40,44,47] or because the entire study population receives a uniform chemotherapy regimen.[19]

Radiation-induced kyphoscoliosis

After early clinical and preclinical observations that asymmetrical irradiation of growing vertebral bodies resulted in scoliosis,[51–53] it became established protocol to include entire vertebral bodies in radiation fields (eg, in the treatment of Wilms' tumours). However, scoliosis was still reported in patients who were irradiated for Wilms' tumours and neuroblastomas.[13,15] Subsequently, most studies on radiation-induced kyphoscoliosis focused on the partially irradiated spine. Scoliosis typically developed several years after irradiation and occurred in up to 70–80% of patients; it was mostly to an angle of less than 25° and occurred more frequently in children receiving doses of more than 30 Gy. Only a minority of patients needed intervention in the form of a brace or rod correction.[54–56] Kyphosis occurred less frequently and, in the absence of associated scoliosis, was usually mild.

Radiation-induced scoliosis only shows ongoing deterioration, in a similar manner to idiopathic scoliosis, when it occurs shortly after radiation (ie, within 1 year). When this deterioration occurs, it is usually in very young children (typically <2 years). More frequently, radiation-induced scoliosis occurs after several years (typically 5 years after treatment) and progresses minimally. It progresses most markedly during the adolescent growth spurt, and then plateaus. However, kyphotic curves can progress after the adolescent growth spurt.

Studies of partial spinal radiotherapy report more frequent and more severe scoliosis after long follow-up (at least 5–10 years) and high radiation doses (doses of >18 Gy or vertebral dose gradients of >10 Gy).[37,47,57,58] In a study of 58 patients with stage I–IV neuroblastoma, Paulino and Fowler[47] found that the percentage of patients who developed scoliosis after radiotherapy was 37%. Radiation doses of 17·5–36·0 Gy were associated with a 50–60% incidence of scoliosis, whereas doses of 17·5 Gy or less were associated with a 10% incidence of scoliosis. After radiotherapy and laminectomy, the percentage of patients who developed scoliosis was 80%. Dörr and colleagues[37] found a significant inverse relationship between age at radiotherapy treatment and the development of scoliosis. For vertebral body dose gradients of less than 35 Gy, a significant effect of dose, with a steep increase in incidence of scoliosis between 5 Gy and 20 Gy gradients, was observed in children aged 6 years or younger at treatment, but not in older age groups. For gradients of more than 35 Gy, no further effect of dose was found; the effect of radiation on increasing the risk of scoliosis was already maximal at a gradient of 35 Gy.

In contrast to partial spinal radiotherapy, only a few papers have reported on scoliosis risk for patients receiving craniospinal irradiation. Probert and Parker[35] found a 14% incidence of scoliosis after whole spine irradiation of more than 25 Gy. Gaspar and colleagues[59] reported low rates of scoliosis (one of 37 patients) with electron treatment of the entire spine. In 2015, Paulino and colleagues[60] described long-term x-ray follow-up of 22 patients who received craniospinal irradiation with a 3D technique; 15 of the 22 patients had developed scoliosis, and 12 of the 15 patients with scoliosis had an angle of less than 20°.

The majority of published retrospective clinical studies on scoliosis after spinal radiotherapy have not included detailed analysis of dose distributions, making it difficult to correlate late effects with the degree of dose inhomogeneity.[13,15,37,47,51–59]

Late effects of skeletal radiotherapy unrelated to growth

In the long term, people who survive paediatric malignancies can exhibit deficits in bone mineral density.[61,62] Risk factors include increased age at the time of diagnosis and treatment, oestrogen deficiency, female sex, corticosteroid use and type, growth hormone deficiency, and cranial or craniospinal radiation. In patients who survived childhood brain tumours, Remes and colleagues[63] and Cohen and colleagues[64] found no significant difference in bone mineral density between people who received craniospinal irradiation and people who were irradiated to the cranium only.

Insufficient bone mass development can increase the risk for early onset osteoporosis and risk of fracture later in life. In the St Jude Lifetime Cohort Study, among 1713 childhood cancer survivors with a median age of 32 years, 9·6% were diagnosed with osteoporosis.[65] Osteoporosis can lead to wedge-shaped, biconcave or crush compaction fractures in the spinal column, of which wedge-shaped fractures are the most common and induce the most physical complaints.[66] In a report from the Childhood Cancer Survivor Study, the prevalence of self-reported fractures was not found to be significantly higher for people who had survived childhood cancer than for their siblings after a median follow-up of 22 years.[67]

The risk of induction of secondary bone sarcomas after treatment of childhood cancers and the dose-dependent effects of radiotherapy and chemotherapy on this risk are well described in the literature.[68–74] The estimated 20-year cumulative risk of a bone sarcoma is 2·8% for people who survive childhood cancer and up to 5·0% for people who have been treated for Ewing's sarcoma.[70,72] Bone sarcomas can occur after radiotherapy doses of less than 45 Gy,[71] but the risk increases sharply after doses of more than 40–50 Gy.[68,70–72] Although the relative risk is between nine times and 133 times that of the general population, the excess absolute risk of induced sarcomas is low, at 3·3 cases per 10 000 person-years.[70]

Considerations and recommendations for daily practice

Modern treatment techniques, such as (rotational) intensity-modulated radiotherapy and proton therapy, give more dosimetric freedom, but also add complexity to the planning of treatment, because dose-gradient definitions are required for any prescription volume, as well as for any organs at risk. For spinal or paravertebral target volumes, the paediatric radiation oncologist treating a young child has to balance reducing dose inhomogeneity, to avoid serious growth issues, against avoiding additional exposure to paravertebral organs at risk. For bony structures, the high risk of scoliosis that is associated with a steep vertebral gradient, with resulting early-onset functional problems, has to be balanced against the potential and small increase in risk of future osteoporosis, compaction fractures, or induction of bone sarcoma that is associated with homogeneous dose distributions.

As there are no established radiotherapy dose constraints for the developing spinal column, recommendations are needed to reduce asymmetrical growth as much as possible. The SIOPE radiotherapy working group proposes several elementary recommendations for dose prescriptions for vertebrae adjacent to the target volume, to provide more uniformity in daily practice.

There is a pressing need for multi-institutional research on this important subject. Future studies could focus on several aspects of vertebral growth development. In a retrospective multicentre setting, big data from patients who were irradiated on the spinal axis and who had high-quality imaging during follow-up, should be analysed to develop prediction models. In parallel, new data from patients treated with (rotational) intensity-modulated radiotherapy or intensity-modulated proton therapy, using the recommendations in this Policy Review, can be used to validate and refine the prediction model, and correct the guidelines, if required. In addition, the relationship between vertebral growth disturbances and functional outcomes needs to be identified. Functional outcomes could be monitored via multidisciplinary late-effect or scoliosis outpatient clinics, and the monitoring could involve orthopaedic surgeons and rehabilitation specialists.

During the consensus meeting of the SIOPE radiotherapy working group in April, 2018, five variables, which are partially interrelated, were defined as being most relevant for the guidelines: age, radiotherapy dose, radiotherapy dose inhomogeneities, the location of the primary ossification centres and growth plates, and the number of irradiated vertebrae (figure 2). The elementary recommendations might not be applicable to exceptional cases, and these can be discussed with the national paediatric radiotherapy coordinator or the study coordinator involved.

Age and radiotherapy dose

According to the literature and expert opinions, higher doses have more detrimental effects than lower doses, and all doses have a more pronounced effect at a younger treatment age than at an older treatment age. In general, there is a dose effect per Gy given, with the steepest increase of the dose-effect curve between the doses of 10–15 Gy and 35 Gy. As each child develops at an

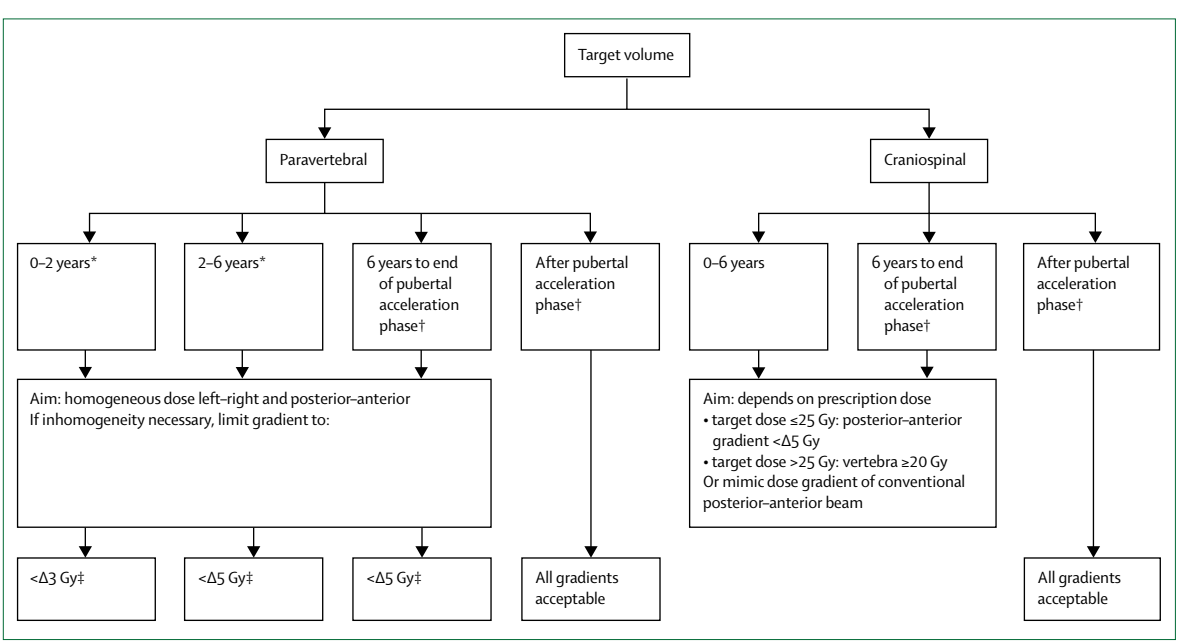

Figure 2: **Flow chart of consensus recommendations for vertebral dose gradients for radiotherapy on paravertebral and craniospinal targets**
*If possible, avoid giving a dose of more than 20 Gy to seven or more thoracic vertebrae. †Establish the end of the pubertal acceleration phase with use of the Risser and Sauvegrain methods. ‡For a target dose of more than 40 Gy, higher gradients might be allowed, with a minimum vertebral dose of 36 Gy.

individual rate, only approximations of the effect of each dose on growth can be given per age group. Between the ages of 0 years and around 2 years, there is a substantial effect of radiotherapy, even at doses of less than 10 Gy. Between the ages of approximately 2 years and 6 years, there is a substantial effect of radiotherapy at doses of more than 15 Gy. Between the age of approximately 6 years and the end of the pubertal growth acceleration phase, there are substantial effects at doses of more than 35 Gy, and discernible but less substantial effects with doses between 15 Gy and 35 Gy. After the pubertal growth acceleration phase, insignificant growth effects are expected, despite a dose-response relationship. We recommend that for children between the ages of around 10 years and 16 years, an evaluation should be done to decide whether they have reached the end of the pubertal growth acceleration phase before radiotherapy planning, and age alone should not be used as the cutoff criterion to determine the constraints of the radiotherapy plan. The optimal evaluation to make this decision is based on a combination of the Risser (ossification of iliac apophysis) and Sauvegrain (closure of olecranon) criteria, with the end of the growth acceleration phase corresponding to Risser stage 1 and Sauvegrain olecranon closure. Hand maturation methods might be less reliable for establishing the stages of the pubertal growth spurt, but they can assist in correlating bone age with calendar age (see appendix).

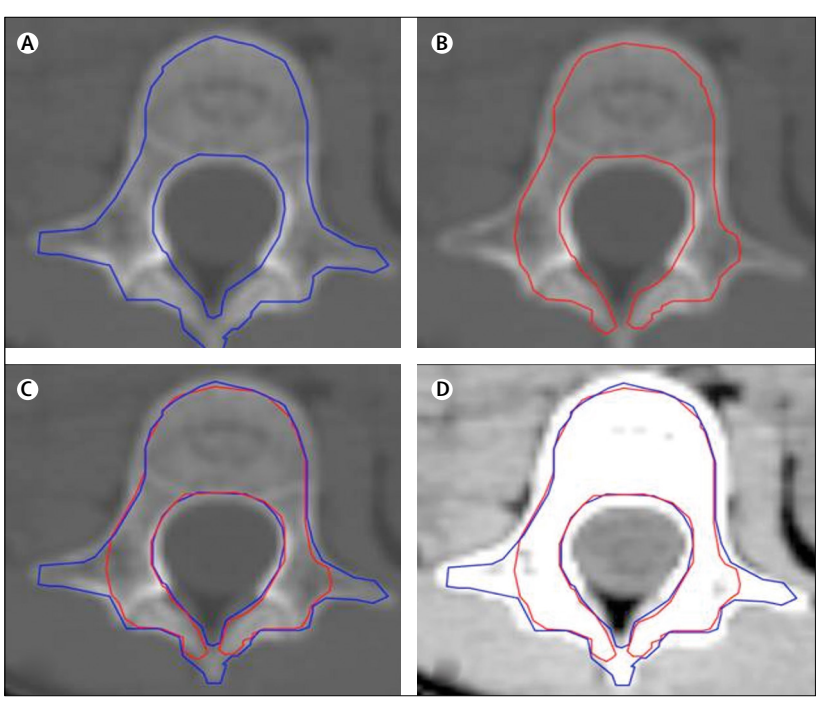

Figure 3: **Examples of vertebral contouring methods encompassing the primary ossification centres at the lumbar level, which could be used to plan radiotherapy treatment**
Two different examples are shown in red and blue. (A) Contouring of the entire vertebra. (B) Contouring of the vertebral body and arch. The two methods are combined in bony (C) and soft tissue (D) settings (CT window/level settings of 1500/350 and 200/20, respectively).

Dose homogeneity

To avoid asymmetrical growth, literature reports and experts recommend homogeneous dose irradiation in all vertebral dimensions, in particular for paravertebral target volumes. However, when the radiosensitivity of adjacent organs at risk is deemed to be more consequential than the consideration of maintaining homogeneous vertebral growth, dose gradients within the vertebrae can be considered according to the following recommendations. The need to maximally spare a critical organ at risk might be more important than adhering to these recommendations on an individual basis. At older treatment ages, especially after the end of the pubertal growth spurt, more vertebral dose heterogeneity is acceptable (figure 2). Left-right dose asymmetry can cause vertebral body wedging and scoliosis, whereas posterior-anterior gradients can affect the kyphotic and lordotic curves of the vertebral column. Cranio-caudal gradients, which are applicable to partial spinal irradiation, should be accepted to be steep, as a slow tapering of radiotherapy dose would greatly increase the number of irradiated and affected vertebrae. The effects of left-right gradients are considered to be more clinically relevant than posterior-anterior or cranio-caudal gradients. A posterior-anterior radiotherapy dose fall-off was inherent to the posterior beam characteristics of conventional craniospinal irradiation techniques.

We recommend that the primary aim for radiotherapy planning is to establish a homogeneous dose in the left-right and posterior-anterior vertebral dimensions if possible, whereas cranio-caudal gradients are acceptable. If left-right or posterior-anterior homogeneity over the vertebral volume cannot be achieved, we recommend the following gradients (on the basis of daily fractions of 1·8–2 Gy) for paravertebral target volumes (eg, renal tumours, neuroblastoma, or soft-tissue sarcoma). Between 0 years and approximately 2 years, the left-right and posterior-anterior dose gradients should be less than 3 Gy for (tumour) prescription doses of 40 Gy or less; for (tumour) prescription doses of more than 40 Gy, higher gradients can be allowed, with a minimum dose of 36 Gy covering the primary ossification centres of the vertebrae. Between around 2 years and the end of the pubertal growth acceleration phase, the left-right and posterior-anterior dose gradients should be less than 5 Gy for (tumour) prescription doses of 40 Gy or less; for (tumour) prescription doses of more than 40 Gy, higher gradients can be allowed, with a minimum dose of 36 Gy covering the primary ossification centres of the vertebrae. For spinal axis target volumes with homogeneous left-right gradients (eg, craniospinal irradiation for medulloblastoma, ependymoma, or germ cell tumours), we recommend the following gradients (on the basis of daily fractions of 1·8–2 Gy). For dose prescriptions of 25 Gy or less, posterior-anterior gradients should be less than 5 Gy; for dose prescriptions of more than 25 Gy, 20 Gy or more should cover the primary ossification centres of the

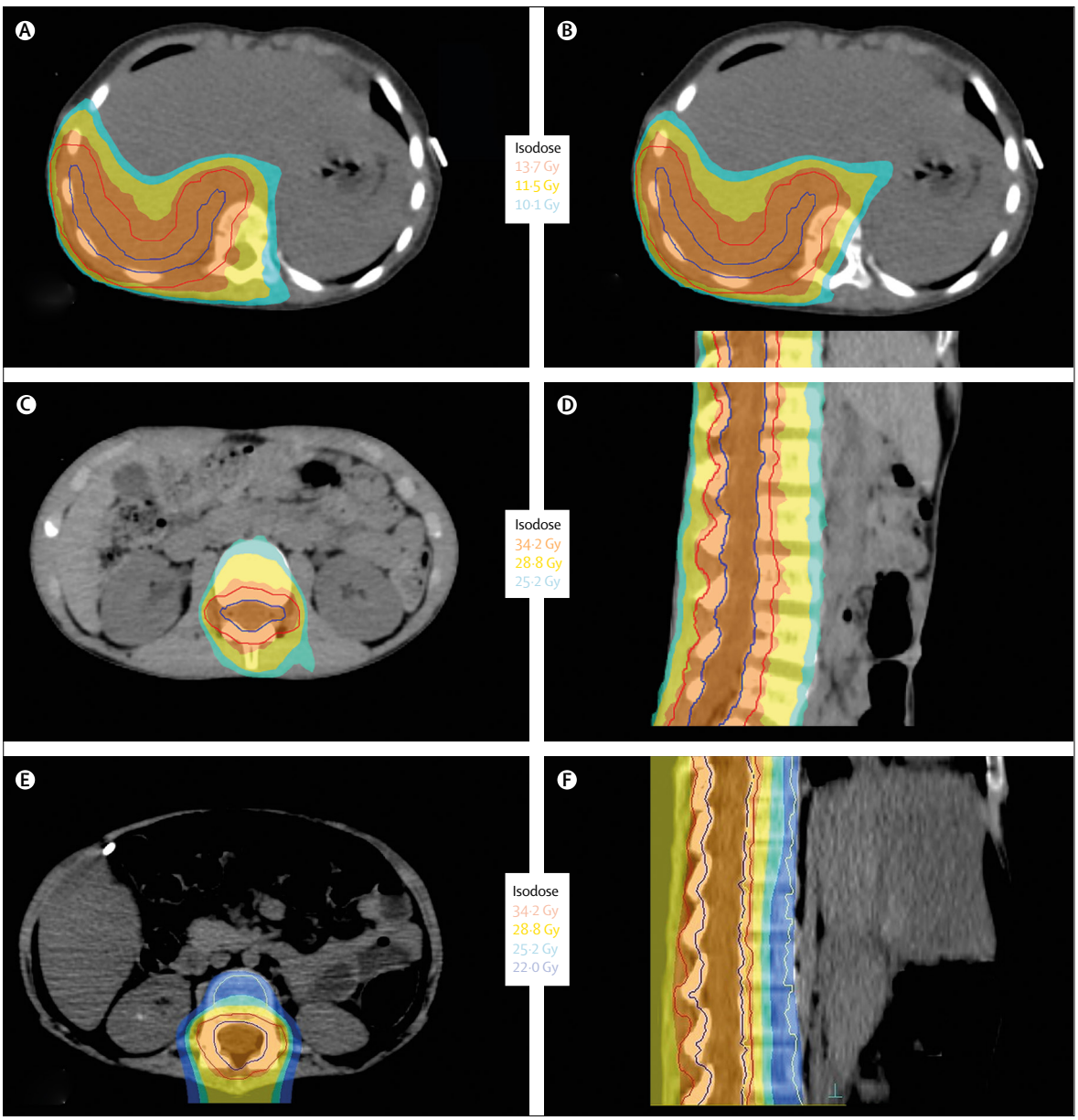

Figure 4: **Radiotherapy dose distributions for paravertebral and craniospinal targets**
Examples of acceptable (A,C–F) and undesirable (with a dose gradient that is too high) (B) radiotherapy dose distributions for paravertebral (A,B) and craniospinal (C–F) targets, generated with volumetric-modulated arc photon therapy (A–D) or intensity-modulated proton therapy (E,F). The prescription dose to the paravertebral and craniospinal targets is 14·4 Gy and 36·0 Gy, respectively. The clinical target volumes are contoured in blue and the planning target volumes are contoured in red.

vertebrae. Alternatively, the posterior-anterior dose gradient can mimic that which was given with a conventional craniospinal irradiation photon beam technique (a minimum of approximately 70% of the target dose).

Location of primary ossification centres and growth plates

Ossification of the vertebrae occurs in primary ossification centres. The primary ossification centres, located in the vertebral bodies and arches, push the cartilaginous tissue outwards. At the age of 13 years to 16 years, secondary ossification centres form at the tip of the spinous process, at each transversal process, and at the superior and inferior rim of the vertebral body. The secondary ossification centres fuse with the vertebral body by the age of 25–30 years.

We recommend that delineation of the vertebrae should include at least the primary ossification centres and growth plates. Therefore, the vertebral body and the vertebral arch should be included (figure 3). There is no

need to include secondary ossification centres, as they form after the pubertal growth spurt and induce no substantial growth.

Number of irradiated vertebrae

Radiation of extensive thoracic spinal segments can cause thoracic cage and lung underdevelopment, which considerably increases the risk of future respiratory insufficiency. Severe respiratory insufficiency is observed with adult thoracic spine lengths of less than 18–22 cm, which are usually achieved between the ages of 5 years and 10 years.[11] Extrapolating from thoracic growth curves and potential growth inhibition by radiotherapy at a young age, especially at doses of more than 20 Gy, it is sensible to limit the number and dose of irradiated thoracic vertebrae as much as is possible without compromising the per protocol target volume. Radiation over the entire lumbar spine might cause lower back problems due to underdeveloped vertebrae and muscular atrophy. These issues are particularly applicable to children irradiated at the age of 6 years or younger.

We recommend that between the ages of 0 years and around 6 years, partial irradiation of the spinal column should be limited to approximately seven thoracic vertebrae, particularly for doses of more than 20 Gy, if it is possible to do so without compromising target volume coverage. Figure 4 shows an acceptable and, considering the dose gradient, an undesirable vertebral dose distribution for a paravertebral target with use of volumetric modulated arc photon therapy. Acceptable dose distributions are also shown over the lumbar spine for a craniospinal radiotherapy plan, with either volumetric modulated arc photon therapy or proton therapy.

Conclusion

In the era of highly conformal radiotherapy, practical guidelines are needed for children receiving radiotherapy to the vertebrae before the end of the pubertal growth spurt. As previous studies do not provide clear guidance, the recommendations in this review have been made by expert paediatric radiation oncologists who have reached a consensus on relevant variables on the basis of the available literature and discussion among peers. The guidelines provide a framework, and they can be re-evaluated and updated in the future as more reliable data become available.

Contributors

BAH did the literature search. CC, BT, HCM, and GOJ made suggestions for the literature review. BAH prepared the figures. BAH, MMvdH-E, and GOJ wrote the survey for the consensus meeting. CC, BT, HCM, LG, KD, MRA, HM, YL-R, BO, TA, CA, BVB, SB, ALC, RDF, SD, DDL, RDK, AL, PM, LP, BR, GS, RS, KS, ES, NT, GAW, and TB took the initial survey and/or the survey during the workshop. BAH, CC, BT, and GOJ did presentations at the consensus meeting. BAH, CC, BT, HCM, LG, KD, MRA, HM, YL-R, BO, TA, CA, BVB, SB, ALC, RDF, SD, DDL, RDK, AL, PM, LP, BR, GS, RS, NT, GAW, TB, and GOJ took part in discussions during and after the consensus meeting. BAH and GOJ collected and processed co-author suggestions. BAH and GOJ wrote the manuscript. All authors made editing suggestions, and approved the final version of the manuscript.

Declaration of interests

The authors declare no competing interests.

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