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PENTEC VISIONARY REVIEW

# Radiation Therapy Technology Advances and Mitigation of Subsequent Neoplasms in Childhood Cancer Survivors



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**Purpose:** In this Pediatric Normal Tissue Effects in the Clinic (PENTEC) vision paper, challenges and opportunities in the assessment of subsequent neoplasms (SNs) from radiation therapy (RT) are presented and discussed in the context of technology advancement.

**Methods and Materials:** The paper discusses the current knowledge of SN risks associated with historic, contemporary, and future RT technologies. Opportunities for research and SN mitigation strategies in pediatric patients with cancer are reviewed.

**Results:** Present experience with radiation carcinogenesis is from populations exposed during widely different scenarios. Knowledge gaps exist within clinical cohorts and follow-up; dose-response and volume effects; dose-rate and fractionation effects; radiation quality and proton/particle therapy; age considerations; susceptibility of specific tissues; and risks related to genetic predisposition. The biological mechanisms associated with local and patient-level risks are largely unknown.

**Conclusions:** Future cancer care is expected to involve several available RT technologies, necessitating evidence and strategies to assess the performance of competing treatments. It is essential to maximize the utilization of existing follow-up while planning for prospective data collection, including standardized registration of individual treatment information with linkage across patient databases. © 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

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## Introduction

Ionizing radiation is a well-known carcinogen for most human tissues.<sup>1</sup> This carcinogenic effect is evident across all age groups, yet young patients exhibit heightened susceptibility to developing subsequent neoplasms (SNs) after radiation therapy (RT) alone or in conjunction with cytotoxic- or molecular-targeted agents.<sup>2</sup> This issue is further compounded by the relatively favorable prognosis of many pediatric cancers, putting long-term survivors at risk of developing SNs several decades after initial therapy.<sup>3</sup> Among childhood cancer treatment modalities, RT is the most important contributor to SNs in long-term survivors.<sup>4</sup> Besides the longer life expectancy with extended time for cancer development, children have increased susceptibility because of their growing tissues being more vulnerable to radiation damage. SN poses a significant long-term burden on the lives of children and adolescents treated for cancer. Approximately one-fifth of those treated in recent decades have developed an SN by the age of 50,<sup>5</sup> whereas the general population's cumulative risk of cancer by the same age remains below 1%.<sup>6</sup> Compared with siblings, children and adolescents treated with cranial RT have 10 times higher risk of developing an SN of the central nervous system (CNS).<sup>7</sup> Among girls treated with chest RT, 30% develop breast cancer, a rate comparable to the cumulative incidence among *BRCA* mutation carriers in the general population.<sup>8</sup> The application of RT unavoidably exposes normal tissues but varies considerably depending on patient diagnosis and tumor dose prescription as well as on the applied radiation quality and delivery technique.<sup>9</sup> New RT delivery technologies are being introduced at a historically high rate. Notably, high-conformity photon-based RT and light ion beam therapy have provided hope of enhancing the therapeutic ratio by improving the balance between the effect on the primary malignancy and the risk of inducing toxicities. However, this development has also triggered concern about unknown late effects from the redistribution of dose and secondary stray radiation.<sup>10,11</sup> Additionally, the evolving use of proton therapy is associated with uncertainty in the biological effectiveness, including the occurrence of SNs.<sup>12,13</sup>

For individuals who survived childhood cancers for at least 5 years, the median latent period for the onset of SNs varied, with subsequent leukemia showing a median of 8.9 years (range, 5.0-31.1 years), whereas several solid malignancies exhibit a median latency period of over 20 years<sup>14</sup>; for example, breast cancer,<sup>15,16</sup> non-Hodgkin lymphoma,<sup>17</sup> colorectal cancers,<sup>18,19</sup> lung cancer,<sup>14,20</sup> and thyroid cancer.<sup>14,21</sup> Given the swift advancements in RT planning and delivery, it is a note of caution that the extended latent period for SNs reduces our capacity to quantify effects on SN risks with new technologies. This report examines the evidence concerning the relationship between dose distribution and excess risk of SNs. We pinpoint gaps in our knowledge, explore volume effects across different dose levels, and consider variations in carcinogenicity among tissues.

Additionally, we discuss the effect of radiation modality and the importance of other contributing risk factors. Finally, we highlight future research opportunities and priorities, centering on diminishing SNs in survivors of childhood and adolescent cancers through the utilization of technological advancements in RT and multimodal treatment strategies.

## Evolution of RT and Carcinogenesis in Children

### Early experience

Early experience with radiation carcinogenesis of RT in children came from the treatment of several benign diseases.<sup>22</sup> After x-ray treatment for thymic enlargement during infancy between 1926 and 1951, a significant excess risk of acute leukemia and thyroid carcinoma was observed. This risk was relative to the incidence in untreated siblings and in the general population of the same age distribution.<sup>23</sup> At follow-up exceeding 40 years, thyroid cancer occurred in 3.8% of 1303 irradiated individuals (mean thyroid dose at 1.3 Gy) and in 0.7% of 1768 nonirradiated siblings.<sup>24</sup> Follow-up of 10,834 children treated with single fractions up to 6 Gy for ringworm of the scalp during the 1950s was later found to have a 7-fold higher risk of developing tumors in the CNS compared with matched controls from the general population and untreated siblings.<sup>25</sup> Exposures as low as 1 to 2 Gy were associated with a significant relative risk (RR), approaching 20 at doses of 2.5 Gy. The youngest children had a higher risk compared with exposure after the age of 10 years. Excess risk of leukemia occurred within a few years after exposure, whereas an excess of solid tumors was most pronounced after about 15 years of follow-up.<sup>26</sup>

### Toward conformal RT

Although the carcinogenic effect of radiation exposure has been long known, there were previously no realistic mitigation strategies because of limitations in available technology and alternatives in medicine for cancer treatment. Technology developments throughout past decades have increased the selectivity in irradiated tissues.<sup>27</sup> One prominent example is the involved-node RT in patients with Hodgkin lymphoma and the development of new guidelines with reduced fields.<sup>28,29</sup> Paradoxically, it was the evolving success of RT and improved pediatric cancer survival<sup>30</sup> that actualized the concerns of long-term side effects. Among 14,359 5-year survivors treated from 1970 to 1986 and followed through the Childhood Cancer Survivor Study (CCSS), RT exposure was associated with an RR of SN of 2.7 (95% CI, 2.2-3.3) across all primary cancers and all ages at diagnoses.<sup>14</sup> The considerable improvement in survival rates observed from this era was primarily attributable to reduced mortality from recurrence or progression of the primary

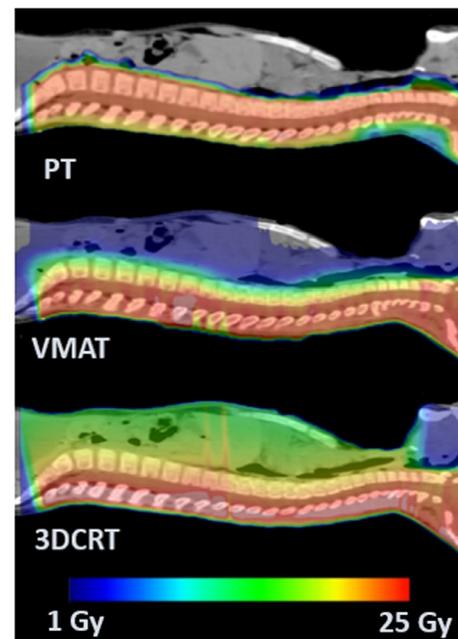
cancer.<sup>31</sup> Certain initial cancer types, such as leukemia, Hodgkin lymphoma, astrocytoma, and Wilms tumor, showed a reduction in treatment-related mortality with decreased exposure to RT and chemotherapy. However, despite more advanced RT techniques and lower chemotherapy doses, no or very little reduction in treatment-related mortality was reported for tumors such as medulloblastoma, non-Hodgkin lymphoma, rhabdomyosarcoma, and bone tumors. For certain tumor types, primarily neuroblastoma, there was even an increase in all-cause and treatment-related mortality, presumably due to increased therapeutic intensity. Noticeably, apart from Hodgkin lymphoma survivors, the cumulative incidence of SNs remained unchanged in patients treated in the 1990s compared with those treated earlier.<sup>32</sup>

### Intensity modulated RT, volumetric modulated arc therapy, and image guidance

There have been high expectations regarding the ability of intensity modulated RT (IMRT) and volumetric modulated arc therapy (VMAT) to reduce late sequelae.<sup>33</sup> Advances in medical imaging (computed tomography [CT], magnetic resonance imaging, positron emission tomography) have been integral to this process, with better visualization of the gross tumor volume and organs at risk. Despite improved dose conformity from modern RT and image guidance, the use of IMRT and VMAT in children<sup>34,35</sup> has remained controversial because of increased volumes of nontarget tissues receiving low doses of radiation (the “low-dose bath”), as well as longer beam-on times increasing normal-tissue exposure to scatter and leakage radiation. Although secondary neutrons are of concern from high-energy photon-based therapy (>10 MV), these energies are rarely used in pediatric RT.<sup>34,36</sup> IMRT has now been used routinely for almost 2 decades, but little evidence from clinical studies has been accumulated so far on associated SN risk, especially in pediatric cancer survivors. Published series<sup>37</sup> on late toxicities after IMRT in children involve small patient numbers with median follow-up times less than 10 years, mostly with no or inadequate comparator groups in terms of indication, selection biases, and nonstandardized methods of follow-up, and therefore poor capability to assess SN risk.

### Proton therapy

Compared with photon-based therapy, proton therapy generally reduces the integral radiation dose to nontarget tissues. This, in turn, reduces the estimated risk of SNs in children compared with IMRT and VMAT.<sup>35,38</sup> Avoiding the low-dose bath associated with IMRT and VMAT became a strong rationale for protons being the RT modality of choice in pediatric radiation oncology (Fig. 1). Whereas passive collimation of the proton beams was the previous standard to shape and modulate treatment fields, new proton facilities have implemented pencil beam scanning (PBS)

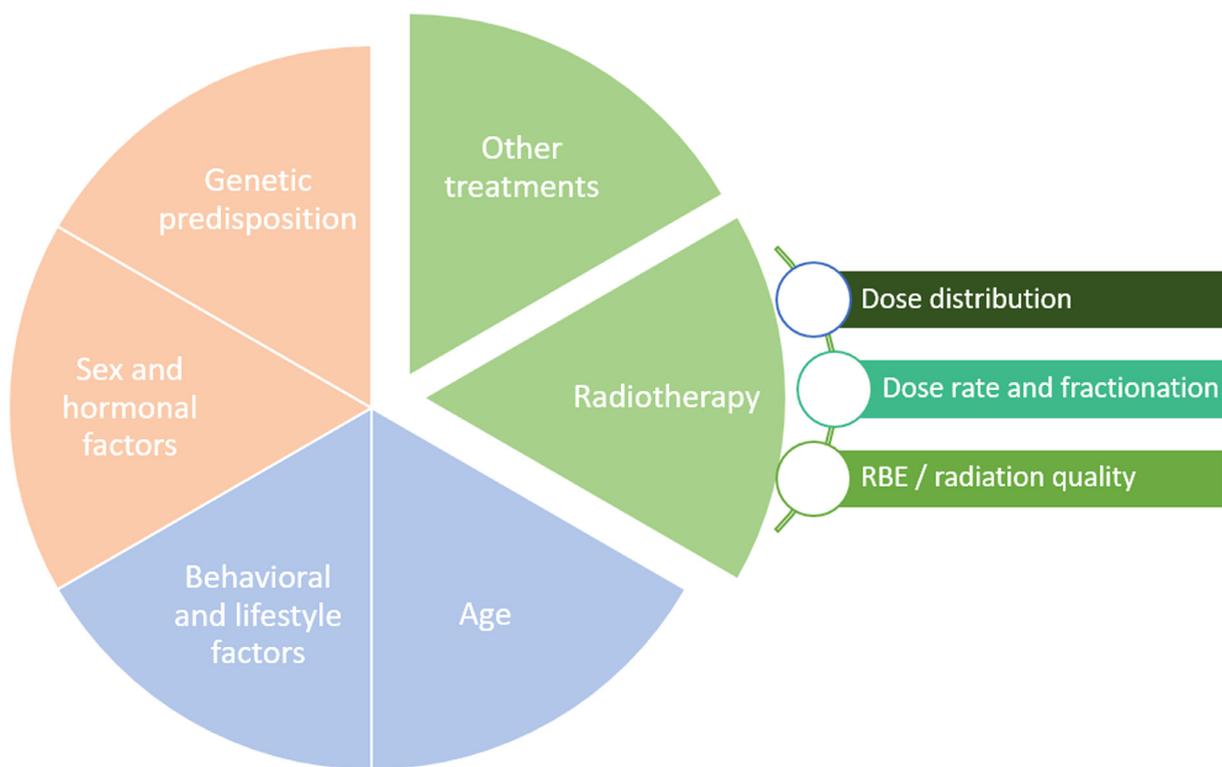


**Fig. 1.** Developments in techniques for craniospinal radiation therapy, from 3-dimensional conformal photon-based radiation therapy (3DCRT) and volumetric modulated arc therapy (VMAT) to proton therapy (PT), have gradually reduced the dose to non-target tissues over time.

to reduce the amount of secondary radiation. Today, thousands of children have received proton RT, but the data available from controlled clinical trials and from prospective cohort studies are still limited.<sup>39-41</sup> Most studies to date originated from single institutions with small sample sizes, featuring limitations in terms of standardized and robust follow-up methods, lack of relevant comparator group receiving photon RT, and a too short follow-up for assessing SN risk. In the most recent and largest study of pediatric proton therapy, reporting from the first decade following a retrospective cohort of 1700 children with a median follow-up of 3.3 years (range, 0.1-12.8), the 5-year cumulative incidence of SNs was 0.8%,<sup>42</sup> with most located within the high-dose region. Compared with SN risk after IMRT,<sup>43</sup> the authors concluded with caution that “at least within the first decade following treatment, the stray dose from passive modulation [of protons] and heavy particle RBE [relative biological effectiveness] is not associated with an increased risk of second neoplasms relative to IMRT in children.” A new cohort with record linkage in the United States and Canada has been established to perform the first large-scale systematic comparison of SNs from protons compared with photon-based RT.<sup>44</sup>

### Dose-Distributional Effects

The biological effects related to the absorbed radiation dose depend on the volume distribution in tissue, dose rate and



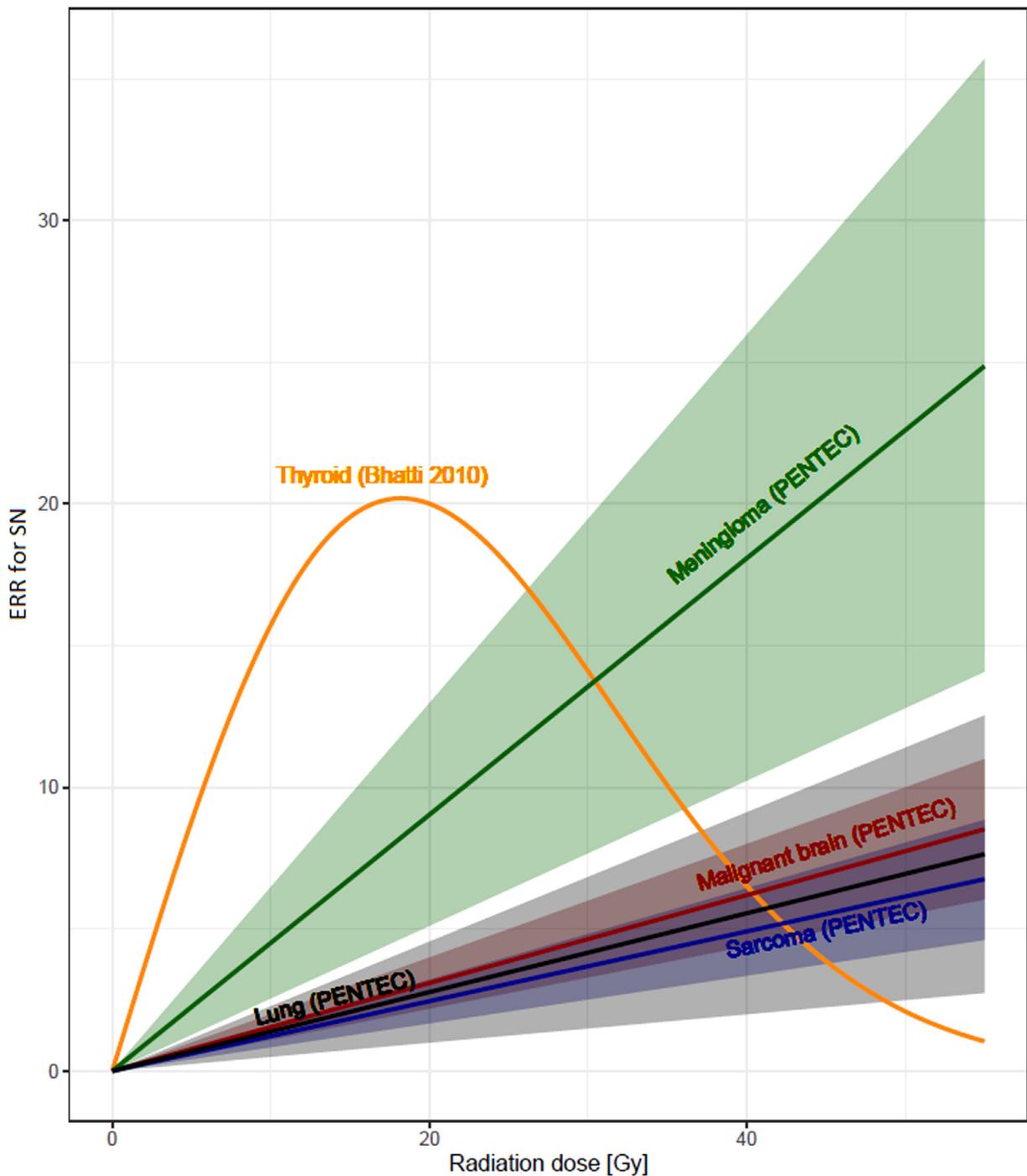
**Fig. 2.** Factors affecting the risks of subsequent neoplasms. The influence of radiation therapy depends on the total dose, dose distribution, fractionation and type of radiation, and other treatments. At the patient-level, age, sex, hormonal factors, and genetic predispositions are nonmodifiable, whereas lifestyle factors may be considered. Radiation therapy and systemic, targeted cancer treatments are changing with technology, with a direct effect on the overall risk of subsequent neoplasms.

fractionation scheme, radiation quality, type of exposed tissue, and endpoint. Other contributors that affect the SN risk include combined treatments and lifestyle, as well as host-specific factors such as age and genetic susceptibility (Fig. 2).

### Dose-response relationship of subsequent neoplasms

Cancer risks after radiation exposures to low and moderate doses are relatively well documented, mainly through the lifelong follow-up in the life span study (LSS) of atomic bomb survivors in Japan (approximately <math>2.5\text{ Gy}</math>). Considering RT, not many children have been followed after the age of 50 years when the cancer risks of the general population increase sharply. There is subsequently uncertainty related to the overall SN burden from RT, including the shape of the dose-response relationship over the very wide dose range of in-field and out-of-field exposures as well as potential volume effects and influence of dose fractionation. The combined effect of cell inactivation, mutation rate, and repopulation effects<sup>34,45</sup> potentially introduces a downturn of the dose-response curve at higher doses.<sup>46-49</sup> However, such a deviation from the linear dose-risk relationship at high doses has only been consistently documented for thyroid cancer,<sup>50</sup> whereas for other SN histologies, a linear dose-risk relationship has been observed in the vast majority

of clinical studies.<sup>4,51</sup> Inskip et al<sup>4</sup> provided a comprehensive review of SNs reported by the CCSS in long-term survivors followed for 20 years, with linear dose-risk relationships for all SNs including sarcoma, skin, meningioma, salivary glands, glioma, and breast, again, with the exception of thyroid cancer. Berrington de Gonzalez et al<sup>51</sup> found that in 26 of the 28 studies published up to 2013, there was no evidence of a decrease or even a plateau in risk at high doses (absorbed organ doses >5 Gy) from RT. It is, however, important to note that the number of SN cases detected at doses >30 Gy has in general been too low to demonstrate any departure from linearity at such dose levels. Results from the French CCSS indicated a possible downturn in the curvature of the dose-response >25 to 30 Gy in risk of meningioma after childhood cancer,<sup>52</sup> whereas a larger pooled case-control analysis could not confirm this.<sup>53</sup> The newly conducted pediatric normal tissue effects in the clinic (PENTEC) analysis supports a linear dose response for the investigated SNs (Fig. 3). This is intriguing, particularly because it suggests that optimizing conformality around the target volume to restrict the high-dose volume emerges as a promising strategy for mitigating the risk of SNs after RT. The excess relative risk (ERR) of subsequent meningioma was found to have the steepest dose-response, with ERR/Gy at 0.44 (95% CI, 0.19-0.68) for all ages combined, whereas sarcomas and SN of the lung and malignant CNS neoplasms resulted in shallower dose-responses. The ERR/Gy was

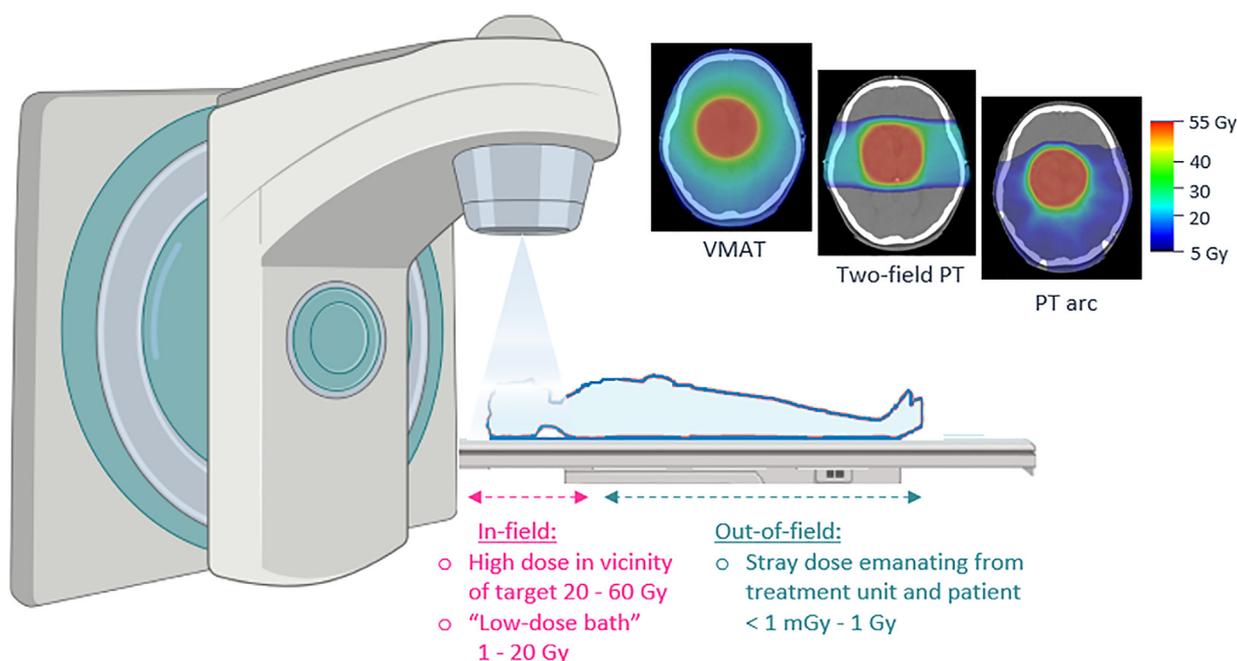


**Fig. 3.** Radiation dose-response of the excess relative risk of subsequent neoplasms from the PENTEC analysis of radiation-induced meningiomas, malignant brain tumors, lung cancers, and sarcomas, including 95% CIs. Dose-response of secondary thyroid cancer as reported by Bhatti et al.<sup>50</sup>

0.045 (0.023-0.067) for sarcomas, 0.068 (0.03-0.11) for SN of the lung, and 0.15 (0.11-0.18) for malignant CNS neoplasms.<sup>54</sup> The meninges are thus considered highly susceptible to SNs, notably with significantly steeper dose-response for young individuals treated before the age of 10 years.<sup>53</sup>

**Low-to-moderate dose exposures**

Cohorts of pediatric patients treated with nonconformal or conformal RT have demonstrated that, in addition to the increased risks observed close to the treated volume, SN can



**Fig. 4.** In-field radiation exposure includes a high-dose region with the target volume and surrounding dose gradients and low-to-moderate doses to surrounding normal tissues, hereunder the “low-dose bath” associated with multiple beam angles. Dose distributions include photon-based arc (volumetric modulated arc therapy; VMAT) and proton therapy (PT) delivered by 2 fields and through arc.

develop in the low-to-moderate dose regions, especially when highly radiosensitive tissues are involved, for example, leukemia, sarcoma, meningioma, and thyroid cancer. In a cohort of 4600 patients treated in the past decades, Diallo et al<sup>55</sup> found 1 of 4 SNs in the low-to-moderate dose regions (median dose, 0.3 Gy; median follow-up, 15 years). With modern RT techniques, particularly IMRT and VMAT, we can expect a reduction in SN risk for critical tissues located near the treated volume but an increased proportion of SN developing in tissues distant to the tumor because of larger low-to-moderate dose volumes from using an extended number of beams. Now, epidemiologic data on SN risk after IMRT or proton RT remain very limited to confirm or invalidate this hypothesis because of insufficient population sizes and/or too short follow-up times to detect SN. Although IMRT is associated with improved dose gradients and larger low-to-moderate dose volumes than past RT techniques, very few studies have assessed the effect of the dose-volume distributions on SN risk.<sup>56-58</sup> These past studies found little evidence of volume effects, but this could be a result of limited individual variability of the highly standardized (mostly nonconformal) treatment plans. With the rapidly evolving RT delivery techniques, an expanding number of beams, including proton arcs, will likely become commonplace shortly.<sup>59</sup> The increased flexibility, particularly in proton beam delivery, will provide improved selectivity across tissues receiving low-to-moderate doses.<sup>60</sup> To enable meaningful optimization concerning SNs, reliable dose responses are prerequisites, and the updated PENTEC data

come with opportunities toward incorporating SN in treatment planning objectives.

### Out-of-field dose and imaging

Beyond the in-field low-to-moderate dose exposures arising from contemporary techniques delivered by multiple fields or arcs, there is an additional low-dose region of stray radiation, including secondary produced and scattered particles in the patient as well as leakage radiation from the treatment machine (Fig. 4). During passively scattered proton RT this is typically below 500 mSv for an entire treatment of cranio-spinal irradiation.<sup>61</sup> In passively scattered proton therapy, neutron dose to the patient arises from interactions of the protons with high-Z materials in the beam line (external neutrons) and in the patients' low-Z tissues (internal neutrons). The PBS techniques avoid most of the materials in the beamline, virtually eliminating external neutrons and thereby greatly reducing the overall dose from secondary neutrons.<sup>62,63</sup> In the case of low energy photon-based therapy (<10 MV) there are no neutrons; however, there is a significant exit dose, which can be orders of magnitude greater than the secondary neutron dose even from passive scatter proton therapy.<sup>64</sup>

Low-dose concerns also extend to the growing use of radiologic imaging.<sup>65</sup> Despite a slight reduction over time in number of CT procedures in pediatric patients, up to 7% of CT examinations in high-income countries are performed

in children.<sup>66,67</sup> Recently, a large-scale multicenter study (EPI-CT) investigated the risk of hematological malignancies after exposure from CT examinations in childhood and young adulthood.<sup>67</sup> The results revealed a clear dose-response relationship, indicating an increased risk of hematological malignancies at doses as low as 10 to 15 mGy. In terms of absolute risk, if 10,000 children undergo a typical CT examination (with an average dose of 8 mGy to the active bone marrow), it is anticipated that 1.4 cases of CT radiation-induced malignancy would occur in the 12 years after the examination.<sup>67</sup> Pediatric patients with cancer, because of numerous diagnostic, treatment, and follow-up examinations, represent a vulnerable group exposed to additional risks, potentially extending throughout lifelong surveillance. Given that certain pediatric patients with cancer may be more susceptible to radiation carcinogenesis, it is crucial to actively monitor and assess the associated risk with follow-up examinations, and to implement measures to minimize such risk.

Daily imaging is a prerequisite of high-conformity radiation techniques, in which the use of kV energies is preferred in children rather than MV modalities.<sup>68</sup> Cone beam CT for position verification can be achieved at 0.5 to 1 mGy, which for a full treatment would be well below expected out-of-field treatment exposure.<sup>69</sup> Ultimately, the desire to keep added exposure from imaging as low as possible must be weighed against the considerable benefit of high-conformity RT. It is furthermore important to note that pediatric patients should have adapted imaging protocols distinguished from adult patients. The default imaging protocols as set by manufacturers are primarily tailored for adults, and their application in children can result in doses 2 to 3 times higher than those in adults.<sup>69</sup> This becomes especially crucial in settings where pediatric patients receive treatment within a larger department predominantly serving adults.

### Dose-time fractionation effects

Variations in the period over which the exposure occurs have been widely used to optimize the therapeutic ratio but have also been shown to have a clear effect on carcinogenic potential.<sup>70,71</sup> Berrington de Gonzalez et al<sup>51</sup> demonstrated that ERR/Gy after fractionated high-dose RT (maximum absorbed dose in the cohorts >5 Gy) was 5- to 10-fold lower for most SNs compared with the acute lower-dose exposure experienced by the Japanese atomic bomb survivors (absorbed dose <2 Gy). This varied according to the second cancer site, and even by cancer subtype, such as across meningiomas and gliomas. The occurrence of SNs in patients treated for rectal cancer (7% in 1599 patients followed at a median 6.5 years after therapy; range, 1-18 years) tended toward a lower rate of SNs in a group receiving conventional fractionation (30 × 2 Gy) versus short-term RT with higher dose fractions (5 × 5 Gy).<sup>72</sup> These findings are somewhat in contradiction to a concern of cellular

repopulation adversely affecting SN risk.<sup>73,74</sup> Given the limited SN data related to fractionation, this topic clearly represents a considerable knowledge gap.

## Risk Modifiers and Risk Mitigation

### Age at exposure

Elevated risks associated with decreasing age at exposure have been observed within a broad range of RT doses,<sup>7,25</sup> as well as in the LSS cohort.<sup>75</sup> In a pooled cohort of 28,000 infants who received radium treatment for hemangiomas, the ERR/Gy of brain cancer was 4.5 for exposure before the age of 5 months<sup>76</sup> compared with 0.4 if the treatment was administered later than age 7 months.<sup>77</sup> Among various cohorts, a particularly striking influence of age at exposure has been found for the thyroid and may be explained by an increased radiosensitivity during rapid cell proliferation in the developing thyroid gland in young individuals.<sup>76</sup> There is also clear evidence for age-dependent ERR of meningioma.<sup>53</sup> In the pooled case-control analysis, the excess odds ratios per gray were 2.20 (0.87-6.31) for RT before the age of 10 years and 0.57 (0.18-1.91) if treated after the age of 10. For second primary glioma, an effect of age at exposure was not demonstrated. Although the LSS indicated no significant effect of age at exposure for glioma, it reported a decreasing ERR with increasing age at exposure for schwannoma.<sup>78</sup> For SN of the breast, the LSS showed an increasing ERR with increasing age at exposure before menarche and then a decreasing risk with increasing age at exposure after menarche.<sup>79</sup> However, this result was not confirmed by the CCSS.<sup>15</sup> Interpretation of these variations across studies and SN histologies is challenging because of differing follow-up times and the prevalence of genetic predisposing factors among patient subgroups.<sup>7,52</sup>

### Effect of RT in combined treatments

Several chemotherapy drugs are recognized for elevating the risk of subsequent leukemia and solid tumors.<sup>80</sup> The use of RT to treat childhood cancers has declined over time, accompanied by changes in both the types and dosages of prescribed chemotherapies.<sup>81</sup> In the CCSS, chemotherapy-only survivors had almost a threefold risk of SNs compared with the general population.<sup>81</sup> The RR of leukemia was 1.4 to 2.2 after use of alkylating agents in the CCSS cohort, whereas the National Health Service Central Register in England and Wales reported the risk increasing 7-fold after the use of anthracycline-based chemotherapy. A Dutch cohort of 6165 5-year survivors of childhood cancers found a cumulative incidence of all SN at 3.9% by 25 years after chemotherapy.<sup>82</sup> In this cohort, the excess absolute risk (EAR) for subsequent solid cancers increased with time since childhood cancer, while the hematologic malignancies peaked at 5 to 9 years. After adjusting for RT use, treatment

with alkylating agents and anthracyclines was associated with SNs of the breast, sarcoma, lung, stomach, and pancreas.<sup>82</sup> Although the declining use of chest RT in female patients with childhood cancer has contributed to reducing the occurrence of SN in the breast, there is a growing concern related to the risk from chemotherapy agents.<sup>83</sup> In particular, the contribution of anthracycline exposure is a concern.<sup>84</sup> Furthermore, methotrexate has been found to increase the risk of meningioma, although no clear dose-response relationship has been found and there is no reported interaction with RT.<sup>53</sup> An increased risk of thyroid cancer was reported among patients in the CCSS cohort treated with a combination of chemotherapy and RT (RR was 1.8-2.4) but not if chemotherapy was administered alone.<sup>80</sup> A French study including 4338 5-year survivors with an average follow-up of 27 years concluded that the risk of SN of the thyroid should be assessed in combination with chemotherapy, splenectomy, RT dose to the pituitary gland, and body mass index.<sup>85</sup>

The use of growth hormone therapy has in some studies shown an increased risk in SNs but with diminishing incidence for increasing follow-up time. The risk of meningioma was not found to increase in children receiving recombinant human growth hormones alongside brain RT.<sup>86</sup> Moreover, immunotherapy has not been applied in the first-line treatment of pediatric cancer, although several types have been approved for clinical use in children. Heudel et al<sup>87</sup> investigated the effect of immune checkpoint inhibitors on SNs and found that immunotherapy alone or in combination with chemotherapies was associated with a reduced SN incidence across all ages and cancer types. Given the considerable observed effects on SN from RT and combined treatments, approaches integrating the mutual effects of these risk contributors have substantial potential from the standpoint of optimizing and reducing the risk of SNs.

## Mitigation strategies

Beyond minimizing SN risk from treatments, there is a strong rationale for managing the overall risk of SNs. The myriad of contributing causes at play in cancer development provides an opportunity to reduce the background risk by adjusting modifiable behavioral and lifestyle factors.<sup>88</sup> Leading risk factors for attributable cancer deaths are currently smoking, followed by alcohol use and high body mass index.<sup>89</sup> Moreover, as an example, smoking interacts multiplicatively with RT related to the risk of developing lung cancer.<sup>90</sup> Considering that environmental and lifestyle factors could be a contributor in as many as 90% of all cancers in the general population, the potential of adjusting this background risk is extensive.<sup>91</sup> Patient awareness of risk and mitigation strategies is therefore crucial. This is within the scope of the International Late Effects of Childhood Cancer Guideline Harmonization Group, a worldwide collaboration developing common guidelines for long-term follow-up and

surveillance of chronic health problems and subsequent cancers in young cancer survivors.<sup>92</sup>

Cancer screening has contributed to decreasing the morbidity and mortality of cancer.<sup>93</sup> With 8.5% of pediatric cancers caused by genetic susceptibility,<sup>94</sup> it is crucial to identify individuals who may benefit from early screening programs. Well-known examples are carriers with *BRCA* mutations at elevated risk of having breast cancer.<sup>93</sup> With the relatively high mortality rate of SN of the breast,<sup>8</sup> early detection in this group is associated with favorable outcomes. Recently, female childhood cancer survivors were shown to have more than 2-fold increased risk of SN of the breast after anthracycline-based chemotherapy (doxorubicin cumulative dose  $\geq 200$  mg/m<sup>2</sup>),<sup>84</sup> suggesting a potential for including these patients in forthcoming surveillance guidelines. Furthermore, young women treated with chest RT have an increased risk of breast cancer with incidence 13% to 20% by age 40 to 45.<sup>95</sup> Significant gaps persist in our understanding of the interplay between genetic susceptibility and treatment factors related to SN risks.<sup>96</sup> Although this combined information holds great promise for enhancing future precision screening strategies, further research is warranted to determine the treatment dose levels and host-specific factors that should prompt the initiation of surveillance programs. In addition, such investigations should be supplemented by an assessment of potential harms and benefits related to life-long surveillance.

Because of the effect of age at exposure, postponed RT is sometimes considered in very young patients. For instance, the risk of breast cancer is higher when exposed at an age younger than 5 years.<sup>97</sup> It is, however, unknown to what degree systematic implementation of RT delay to avoid exposure during particularly critical ages would influence the incidence of SN.

## Retrospective and Prospective Registry Studies

Cancer therapy is constantly changing and poses challenges in obtaining robust predictive methods to evaluate new technology and exposure scenarios. Although achieving solid clinical evidence requires sufficient cohort sizes, there is a trade-off in generalizing and controlling for treatment and patient factors. Variations within different radiation settings, such as response depending on dose rate (across RT and LSS cohorts)<sup>51</sup> or across RT fractionation regimens,<sup>72</sup> highlight the complexity. Furthermore, there are research opportunities related to retrospective, detailed whole-body dosimetry. Dose estimates used in most studies are subject to several uncertainties, causing information loss in the dose distribution because of the heterogeneity of organ doses in RT. This particularly influences organs in the vicinity of the target volume and field edges, where the steepest dose gradients occur.<sup>98</sup> Methods for dose reconstruction accounting for dose uncertainties and heterogeneities in organs should

be explored and developed to increase the accuracy of predictive dose-response models.

In addition to data collected during the past decades, there are ongoing efforts to register SNs and late effects in children treated with modern techniques. They include the United States Pediatric Proton/Photon Consortium Registry (ClinicalTrials.gov identifier: NCT01696721), which includes 25 centers and has registered close to 4800 patients.<sup>99</sup> In Europe, the HARMONIC-RT project (NCT04746729) is currently piloting a similar registry in 4 European countries and is expected to include 2300 patients by the end of 2023.<sup>100</sup> To enable the evaluation of advances in pediatric RT in terms of SN, it is necessary to have multicenter and multicountry registration of patient-level outcome and treatment data. Prospective registration is ideal because it usually allows standardized, and probably more complete, data collection across centers. Still, prospective data collection faces many challenges. The most important ones are to set up a sustainable information technology infrastructure, governance, and incentives to convince individual RT centers and investigators to collaborate. This also requires the allocation of resources locally for registration (ie, staff and time), which can be particularly challenging in countries where the hospital staff is already under pressure. Moreover, low- and middle-income countries lack resources and essential infrastructure in cancer care, not at least related to follow-up and research. Pediatric cancer survival rates in low- and middle-income countries are considerably lower (5-year overall survival range, 5%-60%) compared with high-income countries.<sup>101,102</sup> More than 80% of pediatric patients with cancer reside in low- and middle-income countries,<sup>103</sup> but over 90% of global cancer research is conducted in high-income countries.<sup>103,104</sup> Optimized treatment protocols from high-income countries are not adapted to the local conditions and patient demographics of low- and middle-income countries, and directly transferring such protocols may result in inferior survival or increased toxicity in low- and middle-income countries.<sup>105</sup> Whereas available technology for cancer treatment is dramatically different across the world,<sup>101</sup> low- and middle-income countries will likely follow a different path of implementation of developments and tools to optimize care. The research priorities are different, but rather than a limitation, this should be viewed as an opportunity to fill research gaps not attainable otherwise (eg, genetic variability, diversity in combined treatments).

Furthermore, the infrastructure and resources must be sustainable to enable long-term follow-up during the decades after treatment. For doing so, a passive follow-up by linkage with other databases, such as disease registries and health insurance databases, is the most efficient option to assess SNs and most late effects and to avoid selection bias due to follow-up rates and times depending on the health status and/or treatment-related factors. Registers should ideally also include biological information to further our knowledge of genetic variability related to radiosensitivity and radiosusceptibility.

## Mechanisms and Risk Modeling

### Risk measures

The EAR provides the additional absolute risk above the background risk, whereas the ERR is the increase in relative risk over the background risk. This is further discussed in the PENTEC state of science article by Bentzen et al in this issue. These measures can be represented for different attained ages and vary depending on SN histology. The lifetime risk is often used (eg, lifetime attributable risk), but whether an SN presents early or later in life, it clearly has an effect on the overall consequence for the childhood cancer survivor. Secondary leukemia may appear 5 to 10 years post-RT, whereas an increased risk of solid tumors typically presents later and persists throughout life.<sup>75</sup> In addition, the endpoints of incidence versus fatality risk should be considered. A more comprehensive perspective could be achieved by using more integrated measures, such as quality of life and life years lost.<sup>106</sup>

### Mechanistic modeling approaches

The available epidemiologic data limit our capabilities to precisely model the risk of SNs on a personal level for the various scenarios of RT. There are, however, several approaches in use for predicting risks for individual patients based on the delivered dose distribution and to compare treatment plans across delivery techniques. To account for the complete dose exposure, the dose from both the primary treatment fields and the out-of-field scatter and neutron contributions should be considered. Standard radioprotection models have been extensively applied to low-dose levels from scattered radiation and neutrons.<sup>70,107,108</sup> These models are primarily based on the LSS cohort and are valid up to about 2.5 Gy,<sup>70</sup> wherein a dose and dose-rate effectiveness factor is applied to adapt for different exposure scenarios. For the higher doses from the primary fields, semiempirical models have been generated by fitting mechanistically founded mathematical functions to follow-up data of radiation-exposed groups. A commonly used base function is the adaptation of the linear quadratic model for cell survival, replaced by tumor induction from malignant cell transformation.<sup>109</sup> Another approach assumes cellular DNA damage results in carcinogenic cell mutations or cell killing, promoting competition between these 2 components.<sup>110</sup> Further advanced models adjust for fractionation effects and cell repopulation<sup>48</sup> or include more complex dynamics of cancer formation with short- and long-term cellular processes.<sup>47,111</sup> The initial slope of the derived semi-mechanistic models is then typically fitted to follow-up data from the appropriate dose span and RT cohort. Schneider<sup>46,112</sup> fitted a model to the observed risk of organ-specific cancer after chest RT as the only treatment of 32,591 patients with Hodgkin cancer with reconstructed treatment plans and dose distributions. Several models for absolute risks, albeit

omitting background risks, were generated including linear dose responses, as well as models reaching a plateau or fall-off at higher doses. Furthermore, the organ-equivalent dose concept has been a much-applied approach for comparing SN risk across different dose distributions,<sup>113,114</sup> and it provides risk ranking independent of knowledge of the absolute risk. Nevertheless, there are uncertainties associated with retrospective dose reconstruction and SN location<sup>98</sup> that may be improved using new modeling strategies addressing dose heterogeneity. In addition to considering RT characteristics, semi-mechanistic models incorporate risk factors such as age at exposure, attained age, and sex. Other known contributors such as genetic predisposition, hormonal status, lifestyle factors, and other therapies remain to be integrated in the SN models but could provide important input to clinical practice and an opportunity to guide technology developments.

### Genetic predisposition and individual radiation response

The diversity in responses to ionizing radiation within a population suggests that future treatment planning could potentially leverage personalized tolerance doses based on biological markers.<sup>115</sup> Patients with cancer predisposition, such as those with genetic mutations in the critical tumor suppressor gene *T53*, are often approached with caution regarding diagnostic and therapy-related use of ionizing radiation.<sup>116,117</sup> A recent review examined the risks linked to radiation exposure in individuals with pathogenic variants of DNA damage response genes.<sup>118</sup> The authors concluded that for carriers of germline variants of *T53* there was clinical evidence indicating a high risk from RT and recommended contraindicating RT for this group. For other common germline mutations including *BRCA1/BRCA2*, *ATM*, and *CHEK2*, there was either no direct evidence or only limited evidence of risk related to RT, and avoidance of RT was not recommended except for a few specific variants among these.

Historically, the term “radiation sensitivity” has been applied in describing both acute tissue effects and radiation-related cancers.<sup>119</sup> Britel et al<sup>120</sup> proposed using this term only when referring to the endpoint of tissue toxicity related to noncancer events and using “radiation susceptibility” for SNs. Furthermore, different normal-tissue effects are likely not clustered within individuals,<sup>121,122</sup> implying that individuals are not inherently radiosensitive but may be predisposed to specific types of adverse events. This predisposition could be attributed to various host factors and may not necessarily reflect intrinsic cellular radiosensitivity. Similarly, individuals may be susceptible to developing a specific type of SN without being universally at an elevated risk for all SNs. Despite evidence for variation across both radiation sensitivity and susceptibility, there is currently no standard clinical testing available.<sup>123</sup> Access to such biological information would open new avenues for selection among

available technologies and likely influence the development of RT delivery techniques.

### Modeling of local versus patient-level risks

The relationship between local cellular effects and global, patient-level risk represents one of the widest knowledge gaps related to SNs from competing technologies. The local nature of mutagenesis and the linear relationship between dose and risk could suggest that it is the total energy deposited (dose x volume) that drives the risk of SNs. However, it is conceivable that the wound-healing response induced by radiation<sup>124</sup> could promote malignant progression on one hand and suppress tumor regrowth on the other. Likewise, the immune effects seen in survivors after RT<sup>125</sup> may influence carcinogenesis. The interplay between these properties will likely only be sorted from actual analysis of long-term human data, supported by biologically motivated multiscale models considering the body as a set of interconnected systems.

### Proton therapy and relative biological effectiveness

Protons deposit energy as a function of the distance traveled in tissue, which causes an increase in linear energy transfer (LET) toward the end of the Bragg peak. In general, more densely ionizing radiation increases the biological effect and has clinically been set to a generic factor of 1.1 relative to the biological effectiveness of photon-based therapies. This spatially invariant RBE of 1.1 was originally chosen as a conservative scalar to maintain tumor control probability throughout the tumor and disregards effects in normal tissues.<sup>126</sup> In particular, the potential contribution to brain stem injury related to increased LET near the target has been a concern.<sup>127–129</sup> The clinical significance and RBE for SNs are unknown<sup>130</sup>; however, data from preclinical studies<sup>126,131</sup> do not indicate deviation in RBE for cell kill and mutation frequencies, and should, given transferability to the tissue level, have similar carcinogenic impact per unit of delivered biologically equivalent dose.

The energy deposition in microscopic structures (cell/nucleus/DNA) is likely biologically relevant and may be studied through so-called microdosimetric quantities, representing stochastic analogs of dose and LET.<sup>132</sup> Recent dedicated Monte Carlo packages can be applied for this purpose, such as Geant4-DNA,<sup>133</sup> which in combination with preclinical model experiments may help our understanding of damage patterns and radiation-induced mechanisms in cells and the relation to biological outcomes.

### Emerging and Future Technologies

#### Proton arc therapy

State-of-the-art PBS typically delivers 2 to 5 treatment fields. The use of proton arc therapy is emerging, analogous to the

**Table 1 Research topics with opportunities related to RT technology advances**

Maturing of retrospective outcome data	Opportunities exist with increasing follow-up time in cohorts treated decades ago with nonconformal or 3DCRT techniques. This includes dose-response modeling using retrospective dosimetry, related to dose fractionation and combined treatments.
Documentation of RT treatment in studies	Standardized registration and follow-up of patients treated with current RT techniques and emerging and future technologies. Reporting should include both diagnostic and therapeutic radiation exposures.
Dose-response relationship	Estimation of the SN risk attributable to low-dose bath versus high-dose volumes. Potential for risk mitigation related to dose conformity surrounding the target volume and the integral dose volumes of the body.
Characterization of patient and treatment factors	Better characterize the combined effect of radiation factors (ie, total dose, dose fractionation, volume, beam quality), systemic cancer treatments, patient's genetic background, and other potential modifying factors such as comorbidities, noncancer medications, smoking, and hormonal factors.
SN risk modeling	Risk projection models provide guidance to what data are needed to obtain new knowledge. Providing input of projected SN risk of emerging and future RT modalities can maximize the potential of risk reduction when technology matures. Models should include dose-volume data for various organs at risk, and include RBE of protons and secondary neutrons.
Decision support tools	Develop efficient decision-aid tools to explore contemporary and developing RT techniques. Opportunities to optimize personalized treatment for current patients, as well as influence technology development.
Mechanisms of radiation carcinogenesis	Improved understanding of the microscopic dose distribution to increase knowledge of mechanisms involved in cancer induction (Monte Carlo, microdosimetry, radiobiological experiments, and theoretical modeling from basic principles). Relationship between local cellular effects and global patient-level risk.
Emerging RT planning and delivery	Explore future treatment planning and delivery techniques, including proton arcs, multi-ion schemes, and FLASH RT, and improve modeling of biological effectiveness in mixed radiation fields. Selective SN constraints on dose to organs at risk.
<i>Abbreviations:</i> 3DCRT = 3-dimensional conformal photon-based RT; RBE = relative biological effectiveness; RT = radiation therapy; SN = subsequent neoplasm.	

evolution of photon-based RT. In silico studies have demonstrated the feasibility of proton arc therapy delivery and its potential to reduce normal tissue complication probability (NTCP) in brain tumors.<sup>134–136</sup> This reduction is achieved by decreasing high-dose volumes, albeit at the expense of increasing volumes at doses below approximately 2 Gy. For pediatric craniopharyngioma, Toussaint et al<sup>137</sup> found that increasing the number of proton beams in total achieved lower integral dose and estimated risks of SNs compared with standard intensity modulated proton therapy (IMPT) and VMAT. The reduced integral dose with increased dose conformity around the target holds promise, in particular related to the linear dose response as presented in the current PENTEC data.

### Carbon ions and multi-ion therapy

Carbon ions have so far been applied with great caution in children,<sup>138</sup> mainly in highly aggressive and radio-resistant

tumors difficult to treat with conventional photons or protons.<sup>139,140</sup> The radiation field is more complex compared with protons, with increasing uncertainties in RBE of normal tissues, including uncertainties in carcinogenic potential.<sup>141,142</sup> From in vitro experiments, the carcinogenic patterns of the entrance channel of carbon ion beams have, however, been found comparable to those of photon-based RT, whereas for decreasing energies relevant for the tumor volume, the transformation per surviving cell was significantly higher with carbon ions.<sup>143</sup> Nevertheless, a clinical study of SNs after treatment of prostate cancer in adults<sup>144</sup> found a lower risk from carbon ions compared with photons.<sup>145</sup> Helium is another promising candidate for RT,<sup>146</sup> offering improved dose characteristics with a reduced lateral penumbra compared with protons, but with less uncertainty in RBE compared to carbon ions.<sup>147</sup> It is conceivable that future personalized RT will involve selection and combination across multiple ions.<sup>148</sup> Expanding our knowledge of SNs seems crucial for a wider adaptation of carbon and other ions in children.

## FLASH RT

In preclinical models, the sparing of normal tissue toxicity has been observed after FLASH RT.<sup>149</sup> FLASH delivers radiation at a single ultrahigh dose rate ( $\geq 40$  Gy/s), approximately 400-fold higher than contemporary RT. Compared with conventional dose rates, FLASH has been found to reduce brain injury and radiation-induced cognitive dysfunction in the radiosensitive juvenile mouse brain.<sup>150</sup> Although the carcinogenic effects of using ultrahigh dose rates in normal tissues are unknown, the potential to reduce late morbidity, for instance from whole-brain RT of pediatric medulloblastoma, could represent long-awaited relief for this patient group.

## Advanced computing and artificial intelligence

Software and hardware developments are paving the way for new possibilities in the delivery of treatment, multicriteria optimization, and in the domain of data collection, analysis, and follow-up. Artificial intelligence can offer comprehensive risk assessment in guidance of therapeutic strategies, by combining RT dose optimization with other patient-specific risk factors with the scalability to large patient cohorts.<sup>151</sup> Radiomics and radiogenomics are promising fields in conjunction with developments in data management and sharing across institutions.<sup>152,153</sup> The future of routine health care after childhood cancer should ideally include efficient decision support tools<sup>154,155</sup> as well as personalized surveillance combined with management and prevention of late effects based on individual risks.<sup>156</sup> Although multiscale modeling and optimization are computationally demanding, quantum computing stands out as a promising technological advancement that could propel progress in this field.

## Summary and Conclusions

The rapid pace of technological advancements in hardware and software development is not likely to slow down, presenting a landscape where numerous evolving RT modalities will become available in the coming years. To enhance our knowledge of SNs in various scenarios involving RT alone or in combination with other therapies and host-specific risk factors, more clinical data and analyses are needed, as outlined in Table 1. When setting research priorities, it is crucial to maintain perspectives on patients treated with currently available technology while considering implications with novel RT techniques and other treatment modalities. Furthermore, supporting and prioritizing research in low- and middle-income countries holds significance not only from an ethical viewpoint but also in gathering data from children of diverse genetic backgrounds and different geographic locations. Future treatments are unlikely to converge into a single technology; rather, we will have several alternatives to choose from. This in turn means that we

need tools and evidence to assess the relative merits of competing treatments tailored to each child with cancer.

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