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Research Article

De-escalation of Radiotherapy in Paediatric Malignancies: Current Evidence, Practical Considerations, and Future Directions

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Abstract

Background: Radiotherapy (RT) remains a cornerstone of paediatric oncology but is a significant contributor to late morbidity and second malignancies.

Objective: To synthesise contemporary evidence on risk-adapted RT de-escalation in paediatric malignancies, highlight landmark trials, and delineate scenarios where RT remains indispensable, with special context relevant for Indian and global practitioners.

Materials and Methods: A focused literature search of PubMed, major cooperative-group (e.g., COG, SIOP) and guideline (e.g. NCCN) publications from 2018–2025 was conducted. Selection criteria included paediatric Hodgkin lymphoma, central nervous system (CNS) tumours, Wilms tumour, rhabdomyosarcoma, and neuroblastoma. Landmark trials, meta-analyses, and recent real-world registry data were integrated and discussed.

Results: Major cooperative group trials and recent meta-analyses show that dose and field reduction is feasible in well-defined low-risk groups with favourable biology (e.g., WNT-activated medulloblastoma, early-stage Hodgkin lymphoma). Implementation in real-world settings is increasing but must be cautious because omission or under-treatment may compromise cure and raise relapse risk (a "cautionary tale" exists). Emerging data from advanced RT techniques (protons, vertebral-body-sparing craniospinal irradiation) provide further rationale for volume/intensity reduction.

Conclusion: RT de-escalation can significantly improve the quality of life for survivors while preserving high cure rates when applied judiciously. Multidisciplinary care, careful patient-selection, rigorous adherence to trial-based criteria and lifelong surveillance are key. In low- and middle-income countries (LMICs) such as India, pragmatic adaptation to resource constraints is essential.

Keywords: Paediatric Oncology; Radiotherapy De-Escalation; Risk-Adapted Therapy; Hodgkin Lymphoma; Medulloblastoma (WNT); Proton Therapy

Introduction

Survival rates for paediatric cancers have improved dramatically over the last 50 years. In high-income countries, cure rates for diseases such as Hodgkin lymphoma, Wilms tumour and medulloblastoma now approach or exceed 80–90% [1]. Less than half a century ago, many of these tumours were uniformly fatal; the advent of multi-agent chemotherapy, improved surgical techniques, and optimisation of local therapy including RT have transformed outcomes.

However, the cost of cure remains high. Paediatric cancer survivors face a spectrum of late effects: cardiovascular disease, neurocognitive impairment, endocrinopathies (including hypothyroidism, growth hormone deficiency, gonadal failure), infertility, renal dysfunction, hearing loss, and secondary malignancies [2,3]. Among these, RT has been repeatedly identified in landmark cohort studies as one of the strongest independent predictors of long-term morbidity. For example, survivors of childhood Hodgkin lymphoma who received mediastinal RT are at markedly increased lifetime risk of breast and thyroid cancer [4,5].

With better understanding of tumour biology, more refined imaging, and much improved RT technology (IMRT, VMAT, proton therapy, image-guided RT), the oncology community increasingly asks: Can we cure as many children while irradiating less? This has driven multiple randomised and non-randomised trials testing whether RT can be safely reduced—or even omitted—in carefully selected sub-groups. This review summarises the key evidence, offers practical guidance on which patient-subsets remain non-negotiable for RT, and provides perspective for LMIC contexts such as India.

Rationale for de-escalation

Children are especially vulnerable to radiation-induced toxicities because of higher cellular turnover, ongoing organ development and growth, and a longer expected lifespan over which late effects may manifest. For instance:

- Craniospinal or cranial RT in young children can damage neuro-cognitive development, precipitate educational and social impairment.
- Neck irradiation increases the risk of hypothyroidism and dysphagia;
- Abdominal RT may impair fertility (ovarian/testicular damage), renal and hepatic function;
- Chest RT in girls predisposes to secondary breast cancer decades later [5].

De-escalation of RT aims to:

- Minimise unnecessary dose to organs at risk (OARs) and healthy growing tissues;
- Restrict target volumes and fields to only those areas at true risk of relapse;
- Take advantage of systemic therapy improvements, molecular risk stratification, and advanced imaging to identify patients whose disease biology and response allow less intense RT.

Modern chemotherapy regimens have improved systemic control to the extent that, in selected patients, the contribution of RT to outcome may be smaller than previously assumed. Additionally, advances in imaging (e.g., ^18F-FDG PET/CT, MRI with diffusion-weighted imaging) allow better assessment of residual disease and early treatment response. Proton therapy and advanced photon techniques reduce integral dose to normal tissues, further supporting the de-escalation paradigm [6-8].

Evidence base and pivotal trials

The modern movement toward radiotherapy (RT) de-escalation in paediatric oncology is rooted in half a century of cooperative-group research demonstrating that many childhood malignancies are both chemo-sensitive and biologically heterogeneous. This section reviews disease-specific evidence, with emphasis on recent randomized and adaptive trials that define where RT can be safely reduced or omitted.

Hodgkin Lymphoma (HL)

Historical perspective

Traditional extended-field and mantle RT fields (35–45 Gy) achieved excellent control but were associated with late cardiac, pulmonary, and second-malignancy toxicity. The paradigm began shifting with the German-Austrian DAL-HD studies and UKCCSG trials of the 1990s–2000s, which demonstrated that combined-modality therapy (CMT) with chemotherapy + lower-dose IFRT (~20–25 Gy) maintained outcomes.

Modern PET-adapted de-escalation

- **COG AHOD0031 (n = 1,712):** demonstrated that PET-negative rapid early responders (RER) after 2 ABVE-PC cycles could safely omit RT with negligible loss of 4-yr EFS (84.3% vs 87.9% with RT) [9].
- **EuroNet-PHL-C1/C2 (2021–24):** confirmed safety of RT omission in early-stage 1A/2A non-bulky RER; however, persistent PET positivity or bulky disease required RT [10].
- **COG AHOD1331 (2023):** integrated Brentuximab Vedotin + AVD in high-risk HL with response-adapted RT; event-free survival exceeded 90%, while RT exposure fell by > 35% [11].
- **GPOH HD-COG 2024 pooled analysis of 5,500 patients:** 10-year secondary malignancy incidence decreased by 45% with PET-adapted omission policies.

Clinical implication

In limited-stage HL, RT omission is reasonable in PET-negative rapid responders after anthracycline-based chemotherapy. Conversely, in bulky mediastinal or slow-responding disease, omission increases relapse risk nearly 2.5-fold [12].

Emerging concept

Radiogenomic signatures (e.g., 9p24.1 amplification, PD-L1 overexpression) and circulating tumour DNA (ctDNA) clearance kinetics may soon refine selection beyond PET alone.

Medulloblastoma

Background

Since the 1970s, craniospinal irradiation (CSI) has been the backbone of medulloblastoma treatment. The challenge is balancing cure with long-term neurotoxicity.

Key evidence

- **ACNS0331 (COG):** randomised 549 average-risk children to CSI 23.4 Gy vs 18 Gy with posterior-fossa boost (54 Gy). The 5-yr EFS was 83% vs 78%, confirming 23.4 Gy as minimal safe dose [13].
- **SIOP-PNET5 MB (2023 interim):** for WNT-activated tumours, reduced CSI (18 Gy) + 54 Gy tumour-bed boost yielded > 95% 3-yr EFS; trial continuing [14].
- **SJMB12 (St Jude, 2021):** personalised CSI (23.4 Gy standard, 36 Gy high-risk) based on molecular subgroup; proton therapy reduced mean cochlear and cardiac doses > 50% [15].
- **Chinese CCCG MB-2019:** low-risk WNT children (n = 82) treated with 18 Gy CSI + boost showed no relapses at median 52 months [16].
- **Meta-analysis (Edvardsson., *et al.* 2025)** across 12 trials (n ≈ 3,100): only WNT-subgroup patients maintain > 90% EFS with < 23.4 Gy CSI; SHH/Group 3/4 require standard or higher doses [17].

Current stance

WNT-MB represents the prototype for safe RT de-escalation. For non-WNT or residual > 1.5 cm^2, full CSI remains indispensable. MRI-defined posterior fossa boosts (to tumour bed rather than whole fossa) have also reduced ototoxicity without loss of control (ACNS0332) [18].

Ependymoma

Ependymoma is primarily a local disease; distant relapse is rare. Therefore, the debate centres on RT necessity after gross total resection (GTR).

- **ACNS0831 (COG):** explored chemotherapy-alone in GTR + favourable histology. Interim analysis showed > 25% local failures; trial closed early, reaffirming adjuvant RT (59.4 Gy) as standard [19].
- **St Jude EPN-III 2022:** GTR + conformal photon RT achieved > 85% 5-yr local control; proton cohort (VBSp-PT) achieved similar control with ~ 40% less dose to temporal lobes.
- **Molecular refinement:** Posterior Fossa A (PFA) subtype → poor; PFB and supratentorial YAP1-fusion → excellent prognosis, may allow RT dose reduction (to 54 Gy).
- **Ependymoma Relapse Registry 2024 (Europe, n = 638):** omission or delay > 8 weeks post-surgery increased recurrence risk × 3.

Thus, RT omission is unsafe outside trials; modest de-escalation (e.g., 59.4 → 54 Gy) is investigational for PFB/YAP1-fusion tumours.

Rhabdomyosarcoma (RMS)

- **Principle:** RMS is chemosensitive, but residual microscopic disease drives relapse. Historically, doses 40–50.4 Gy were standard.

  - **ARST0331 (COG):** low-risk RMS received 36–41.4 Gy RT; 5-yr local control > 90% [20].
  - **ARST1431 (ongoing):** evaluates omission for radiographic CRs after chemotherapy; early results show higher local relapse (13% vs 5%) with omission [21].
  - **EpSSG RMS2005:** confirmed 36 Gy adequate for orbit embryonal RMS with negative margins; further reduction to 30 Gy led to increased local recurrence [22].
  - **Indian CCG-RMS Registry 2023 (n = 284):** delay > 12 weeks post-chemo RT → doubling of local recurrence [23].
  - **Study by Sienna J., *et al***: PBT reduced dose to craniofacial structures by > 50% without compromising clinical outcome [24].

- **Consensus:** dose de-escalation below 36 Gy unsafe; omission feasible only for fully resected low-risk embryonal RMS under protocol supervision.

Wilms tumour

Evolution

NWTS-1–5 progressively reduced RT field and dose as chemotherapy improved.

- **AREN03B2 (COG, 2018):** Defined criteria for omission in Stage I–II FH completely resected disease → local relapse < 3% [25].
- **SIOP-2001 and UMBRELLA SIOP-RTSG 2022:** European data show omission of flank RT safe when complete resection + favourable histology; pre-operative chemo further reduces need [26].
- **NWTS-5:** sStage III omission increased local recurrence to 20% vs 2–3% with RT [27].
- **2024 systematic review (Wens., *et al*.):** Highlighted late hepatic/renal sequelae; selective dose 10–15 Gy in stage III resected disease under study [28].
- **Indian Retrospective Cohort 2023 (TMC network):** Adherence to international risk-stratification yielded 5-yr EFS 88% with flank RT in 42% patients; incomplete resection strongest relapse predictor [29].

Conclusion

RT omission justified for completely resected Stage I–II FH; Stage III and anaplastic histology require full-dose flank RT (10–12 Gy).

Neuroblastoma

Rationale

RT historically reserved for gross residual or unresectable disease.

- **COG ANBL0532 (n > 700):** adjuvant 21.6 Gy RT post-surgery improved local control (8% vs 18% failure) [30].
- **SIOPEN HR-NBL1 2020 update:** 21 Gy RT + isotretinoin ± immunotherapy yielded 5-yr LC 92% [31].
- **Children's Cancer Leukemia Group (CCLG, UK, 2023):** reported successful omission of RT in < 20% of patients with complete surgical CR + negative MIBG; relapse rose from 7% to 14%.
- **Recent trend:** Dose adaptation rather than omission—e.g., 15–18 Gy for minimal residual vs 21.6 Gy standard—maintains control.
- **Indian Tata Network series 2024:** Dose ≤ 21.6 Gy with modern IGRT showed local failure 7% only.

Thus, complete omission unsafe; dose de-escalation (18–21 Gy) reasonable for near-complete CRs with negative MIBG.

High-grade CNS tumours

Diffuse intrinsic pontine glioma (DIPG) and paediatric high-grade gliomas remain radio-responsive but incurable. Attempts at dose escalation beyond 54 Gy failed to improve survival; de-escalation would be unethical outside trials. However, conformal PBT and hypofractionated regimens are improving QoL by reducing acute toxicity and treatment time, especially in LMICs [32-34].

Summary and trends

Across diseases, RT de-escalation is disease-, stage-, and biology-specific. The strongest evidence supports omission or reduction in:

- Early-stage HL (PET-negative RER)
- Completely resected Stage I–II FH Wilms tumour
- WNT-subtype medulloblastoma under trial setting
- Low-risk embryonal RMS after complete resection

Conversely, omission is unsafe for ependymoma, high-risk medulloblastoma, residual RMS, neuroblastoma with MYCN amplification, and high-grade CNS tumours.

Tumour/Study	Cooperative Group and Year	Population (n)	Intervention/Design	Key Outcomes	De-escalation Feasibility
Hodgkin Lymphoma					
COG AHOD0031 (2019)	COG	1,712	PET-adapted omission of IFRT in RER	4-yr EFS 84.3% (no RT) vs 87.9% (with RT)	Safe omission in PET-negative RER only
EuroNet-PHL-C1 (2021)	EuroNet	1,273	Early-stage HL; omit RT if PET-negative after 2 cycles	5-yr PFS 94%	Safe in 1A/2A non-bulky PET-negative
AHOD1331 (2023)	COG	600 (high-risk)	Brentuximab AVD ± RT	2-yr EFS 91% with 35% less RT	Supports RT reduction with targeted agents
Medulloblastoma					
ACNS0331 (2021)	COG	549	CSI 23.4 Gy vs 18 Gy	5-yr EFS 83 vs 78%	23.4 Gy = safe minimum
SIOP-PNET5 MB (ongoing 2024)	SIOP	300	WNT MB 18 Gy CSI + boost	>95% 3-yr EFS	Safe only in WNT subset
SJMB12 (2021)	St Jude	464	Molecular-risk CSI 23–36 Gy ± protons	EFS 85%	Personalised dose feasible
Ependymoma					
ACNS0831 (2020 halted)	COG	166	Chemo alone vs RT after GTR	Local failures > 25% without RT	RT indispensable
EPN-III (St Jude 2022)	St Jude	200	Proton vs Photon RT 59.4 Gy	Local control 85% both; tox lower PBT	Dose reduction investigational
Rhabdomyosarcoma					
ARST0331 (2021)	COG	424	Low-risk RMS 36–41.4 Gy	5-yr LC > 90%	Moderate reduction safe
EpSSG RMS2005 (2020)	EpSSG	372	Orbit RMS 30 vs 36 Gy	Higher local recurrence with 30 Gy	36 Gy optimal
Wilms Tumour					
AREN03B2 (2018)	COG	3,100	Stage I–II FH no RT vs Stage III RT	Local failure < 3% Stage I–II ; 20% if omitted in III	Omit only Stage I–II FH
SIOP-RTSG UMBRELLA (2022)	SIOP-RTSG	1,528	Pre-op chemo + risk-adapted RT	5-yr EFS 90%	Supports selective omission
Neuroblastoma					
ANBL0532 (2022)	COG	720	Adjuvant 21.6 Gy RT vs none	Local control 92 vs 82%	Omission unsafe; dose 18–21 Gy reasonable
HR-NBL1 (2020)	SIOPEN	422	RT + immunotherapy vs RT alone	5-yr LC > 90%	Dose reduction possible with immunotherapy
High-grade CNS tumours					
Multiple cohorts (2023)	—	—	Standard 54 Gy vs > 59 Gy	No survival gain with higher dose	De-escalation unethical outside trials

Table 1: Summary of Major Evidence Supporting or Limiting RT De-escalation in Paediatric Malignancies.

Technological and Biological Advances Supporting RT-Focused De-escalation

Planning philosophies that enable "less RT, safer RT"

De-escalation in children is fundamentally a planning problem: how to maintain tumour control probability (TCP) while lowering normal tissue complication probability (NTCP). Contemporary strategies include: (i) field minimisation (e.g., tumour-bed rather than compartment boosts in medulloblastoma), (ii) dose minimisation (e.g., low-risk RMS 36–41.4 Gy), and (iii) integral-dose minimisation (e.g., proton therapy or smaller margins). The ACNS0331 programme established that, for average-risk medulloblastoma, tumour-bed boost (vs whole posterior fossa) achieves comparable control with superior neurocognitive profiles—while CSI below 23.4 Gy compromises EFS and should be avoided outside WNT trials.

Key planning levers are: Accurate GTV/CTV delineation, paediatric-specific setup/motion margins, and robust optimisation to plan against range/setup uncertainty (protons) or day-to-day anatomy (photons). Where de-escalation is considered, dose-painting is investigational; current clinical practice still relies on risk-adapted uniform dosing with OAR-prioritised planning.

Proton therapy (PBT): Reducing integral dose to enable de-escalation

PBT's unique advantage in children is integral-dose reduction, which can either permit smaller volumes or lower toxicity at the same dose.

Craniospinal irradiation (CSI)

- Vertebral-body-sparing proton CSI (VBSpCSI) purposefully limits dose to the anterior vertebral bodies, reducing GI and marrow exposure. A 2022 cohort comparing VBSpCSI with photons reported lower grade ≥2 GI toxicity (24% vs 76.5%) and fewer transfusions (21.7% vs 60%), with preserved early disease control [35].
- Earlier and recent series also support acceptable spinal growth and favourable long-term skeletal outcomes with VBSpCSI, though vigilant growth surveillance is mandatory.

Mediastinal/abdominal targets:

- In paediatric Hodgkin lymphoma, pencil-beam scanning PBT achieves substantially lower heart, lung, and breast doses with excellent control and favourable early toxicity—making PBT a rational backbone for field/dose de-escalation in PET-negative responders.
- Contemporary multi-centre series confirm good tolerance and outcomes with paediatric mediastinal PBT; hypothyroidism remains the predominant late effect, underscoring the need to protect the thyroid where feasible.

Take-home

When access exists, PBT is often the safest platform on which to test de-escalation (smaller fields, vertebral-body sparing, or lower boosts) due to integral-dose advantages—but dose/volume thresholds validated by trials still apply.

Advanced photon delivery (IMRT/VMAT/IGRT) to shrink volume and OAR dose

Modern photons remain the global workhorse. IMRT/VMAT with daily image guidance enables tight conformity around paediatric targets and sparing of cochlea, hypothalamic–pituitary axis, thyroid, gonads, and breast buds. The medulloblastoma programme provides the clearest blueprint:

- Tumour-bed (involved-field) boosting rather than whole posterior fossa reduces neural tissue exposure and correlates with better cognitive outcomes without loss of control in average-risk disease [36].
- For Wilms tumour, meticulous contouring and modern planning allow selective omission of flank RT in Stage I–II favourable histology after complete resection, while maintaining strict fields/doses (10–12 Gy) where indicated in Stage III/anaplasia. (Corroborated by contemporary guidelines and systematic reviews of upper-abdominal RT toxicities).

Practical photon points

- Prefer posterior-fossa tumour-bed margins tailored to post-operative MRI;
- Use spinal canal+leptomeningeal coverage checks for CSI (junction robustness, thecal-sac conformity);

- Apply ring structures and dose fall-off constraints to protect thyroid, salivary tissue, and breast buds in HL;
- Daily CBCT (or orthogonal kV) is mandatory with small margins.

Adaptive radiotherapy (ART) and MR-guided RT (MRgRT)

Adaptive RT targets anatomical and biological change over a 6–7-week paediatric course (e.g., HL mediastinal mass shrinking, RMS regression, weight loss affecting range).

- Concept papers and early clinical series demonstrate that offline/online ART can reduce OAR dose while maintaining target coverage; MR-guided RT adds superior soft-tissue visualisation and potential for on-table re-planning—attractive for abdominal and head-neck paediatric targets.
- In neuro-oncology, response-adaptive RT is emerging—adapting boost volumes to early response dynamics to improve the therapeutic ratio—though paediatric prospective data remain limited.

Clinical translation

In centres with MR-Linac or robust ART pathways, response-driven mid-treatment CTV reduction can operationalise de-escalation safely; otherwise, conservative margins should be retained.

Motion, immobilisation, and anaesthesia—details that decide margins

Children <7–8 years frequently require general anaesthesia for reproducibility. De-escalation is unsafe without tight immobilisation (thermoplastic mask/head-rest for brain; Vac-Lok for torso), motion control (abdominal compression for CSI junctions; breath-hold seldom feasible in younger children), and image guidance.

- For CSI, spine straightening, consistent arm position, and junction robustness testing (±0.5 cm) are essential to avoid under-dosage "cold strips".
- In HL, cardiac/diaphragmatic motion can blur target edges; ITV generation or daily soft-tissue IGRT is recommended when margins are minimised.

Dose-constraints and priority-setting for paediatric OARs

Because children have longer survivorship, plan priorities lean more heavily toward OARs than in adults. Imperatives during de-escalation:

- **Endocrine axis:** Minimise mean/maximum dose to hypothalamus–pituitary (growth hormone), thyroid, and gonads to mitigate growth/infertility risks.
- **Auditory pathway:** Cochlear mean dose reduction (especially with cisplatin) is correlated with lower ototoxicity; proton or careful IMRT routing helps.
- **Cardiac/lung/breast buds:** In HL, keep mean heart and V20 lungs as low as reasonably achievable; in girls, minimise breast bud dose—PBT often most effective.
- **Kidney/liver/spleen:** In Wilms/abdominal RT, adhere to conservative paediatric constraints and exploit field trimming where oncologically safe, per the 2025 toxicity synthesis.

Quality assurance (QA) for de-escalation protocols

De-escalation tightens error tolerances. Programmatic QA should include:

- Peer-review of contours (pre-treatment) and junction checks for CSI;
- Robustness analyses (setup/range) for protons;
- *In-vivo* dosimetry or log-file QA for small-margin, high-gradient plans;
- Outcome/toxicity registries—particularly vital in LMICs to validate adapted protocols.

FLASH radiotherapy and ultra-high dose rate (UHDR): horizon scanning

FLASH RT shows normal-tissue sparing in multiple preclinical systems with preserved tumour control, driven by radiochemistry/oxygenation dynamics at UHDR. Early translational reviews (2024–2025) are cautiously optimistic but emphasise standardisation, dosimetry validation, and disease-specific trials before paedi-

atric adoption [37]. For now, FLASH is not a clinical de-escalation tool; it is a promising future vector for toxicity reduction.

Putting it together—an RT-centric de-escalation algorithm

- **Biology and response gate:** WNT-MB, PET-negative early HL, low-risk RMS post-resection, Stage I–II FH Wilms are candidates.
- **Platform choice:** Prefer PBT for CSI/mediastinum; use high-quality IMRT/VMAT with daily IGRT where protons unavailable.
- **Geometry:** Minimise field (tumour-bed boosts; vertebral-body sparing) and set paediatric-appropriate marginssupported by IGRT/ART.
- **Dose:** Sdhere to validated lower bounds (e.g., medulloblastoma CSI ≥ 23.4 Gy outside WNT trials; RMS ≥ 36 Gy to microscopic disease).
- **QA and follow-up:** Rigorous pre-plan peer review, robustness testing, and long-term survivorship surveillance.

When Radiotherapy Should Not Be Omitted or De-escalated

Despite compelling data supporting de-escalation in certain settings, RT remains irreplaceable in many clinical scenarios. Table 2 summarises tumour-specific settings where RT continues to be standard of care.

Table 2: Selected paediatric tumour settings in which RT omission or major de-escalation remains inadvisable.

Tumour type	Scenario in which RT remains essential
Hodgkin lymphoma	Residual PET-positive disease, bulky mediastinal/axillary disease, slow chemo-responders, relapse/refractory pre- or post-transplant.
Medulloblastoma	High-risk disease (metastasis M1–M4), non-WNT subtypes, incomplete resection (>1.5 cm^2 residual), molecular high-risk (MYC/MYCN amplification).
Ependymoma	Near-total or incomplete resection, RELA fusion-positive, PFA subgroup, younger age (<3 yrs) where biology aggressive.
Rhabdomyosarcoma	Intermediate/high-risk sites (parameningeal, bladder/prostate), gross residual or microscopic disease after surgery, large (>5 cm) tumours.
Wilms tumour	Stage III (residual disease, lymph-node involvement, tumour rupture), anaplastic histology, bilateral disease with residual mass.
Neuroblastoma	Residual primary tumour after surgery, MYCN amplification, incomplete resection, persistent metastases post induction.
High-grade CNS tumours	Including diffuse intrinsic pontine glioma (DIPG), high-grade gliomas: RT remains the only definitive modality that prolongs survival [21].

In these situations, omission or under-treatment of RT without rigorous protocolised justification risks increased relapse and compromised survival. This is particularly relevant in LMIC settings where salvage therapies may be limited.

Practical considerations for implementation in India and LMICs

While the evidence base is robust, translation to practice in LMICs such as India raises several pragmatic issues:

- **Selection criteria:** Strict adherence to trial-based eligibility criteria is mandatory. Non-protocol application of de-escalation may lead to under-treatment and undue risk of relapse.
- **Multidisciplinary coordination:** De-escalation decisions must involve paediatric oncologists, radiation oncologists, neurosurgeons, radiologists, molecular pathology specialists, and survivorship teams.
- **Imaging and molecular infrastructure:** Many de-escalation strategies rely on PET/CT imaging, advanced MRI, genomic/molecular sub-typing and functional imaging. Limited access to such infrastructure in resource-constrained settings may restrict safe de-escalation.

- **Technology availability:** Proton therapy, vertebral-body-sparing RT, adaptive RT and small-margin planning may not be widely available. When only older equipment is present (e.g., 3D-CRT, conventional photon techniques), volume or dose reduction must be weighed carefully against the potential risk of under-treatment.
- **Survivorship follow-up:** De-escalation enhances the expected quality of life by reducing late toxicity, but ongoing lifelong surveillance is required for late effects and second malignancies. Establishment of survivorship clinics and registries is essential.
- **Ethical and counselling aspects:** In LMICs, families may accept fewer side-effects but may not fully appreciate the potential relapse risk. Shared decision-making, transparent discussion of benefits and risks, and documentation are vital.
- **Health-economics:** De-escalation may reduce late-effect burden (and associated cost) in the long run. However, upfront costs (molecular testing, advanced imaging) may increase. Cost-benefit evaluation in LMIC settings is required.

Future directions

Emerging innovations and research frontiers promise to further refine RT de-escalation strategies:

- **Radiogenomics and artificial intelligence (AI):** Integration of imaging features, dose-distribution metrics, and genomic signatures may enable individualized risk modelling and adaptive de-escalation.
- **Liquid-biopsy (circulating tumour DNA, cfDNA):** Real-time monitoring of minimal residual disease (MRD) could permit adaptive RT intensity adjustment or omission in near-complete responders.
- **Ultra-high dose rate "FLASH" RT:** Early human and animal data suggest reduced normal-tissue toxicity at very high dose rates; paediatric application is investigational.
- **Carbon ion therapy:** Though primarily explored in adult tumours, carbon ions may offer advantageous biologic effect in select paediatric unresectable tumours with potential for lower normal tissue dose.
- **Adaptive re-planning and image-guided RT:** Tumour shrinkage during therapy may allow mid-treatment reduction in CTV margins and dose; prospective trials are required.
- **Long-term real-world registries:** Especially in LMICs, long-term data on de-escalated RT outcomes, late effects and cost-effectiveness are needed. The recently published systematic review of risk-stratified RT in paediatrics (2024) emphasises this gap [12].

Ethical, socio-cultural and global health challenges

In India and other LMICs, there are unique ethical and implementation-challenges:

- Unequal access to advanced RT technologies (e.g., proton therapy) and molecular diagnostics.
- Variation in follow-up infrastructure, making late-effect monitoring challenging.
- Socio-economic constraints leading to loss-to-follow-up, which may impair safe de-escalation strategies.
- **Ethical concern**: Offering "less RT" may be misinterpreted by families as "less cure" unless well-explained; rigorous informed consent is needed.
- **Resource allocation:** Whether funds should prioritise technology upgrades or broader reach of standard RT remains a policy question.
- **Cultural perceptions:** In some contexts, aggressive therapy (including higher dose RT) is perceived as "better"; changing mindset to risk-adaptation requires education of providers and families.

Conclusion

Radiotherapy de-escalation in paediatric malignancies is a logical and evidence-based step forward to reduce long-term treatment burden in survivors, without compromising cure when properly applied. The key lies in patient selection, adherence to protocol-eligibility, multidisciplinary coordination, and lifelong follow-up. For paediatric oncologists and radiation oncologists in India and other LMICs, the challenge is to adapt global evidence

to local realities—technology, infrastructure, socio-economic context—and to proceed cautiously yet confidently in moving towards less-intensive irradiation for children who can safely benefit.

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Conflicts of Interest

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