Supplementary Table II. Challenges in radioprotector use in cancer radiotherapy and strategies to address them

Sr. No.	Issue	Clinical evidence	Means to fill the gap	Additional research and evidence	References
1	Adverse side effects and toxicity	Amifostine causes nausea, vomiting, and hypotension in >50% of patients; severe dermatologic reactions (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) reported in head & neck cancer patients receiving radiotherapy, with incidence rates up to 5-10% in some cohorts	Develop safer radioprotectors *via* R&D	Tempol (phase I): topical application prevented alopecia in brain tumour patients (n=20) with no significant toxicity; Melatonin (phase II): oral 20 mg reduced oral mucositis (grade 3/4 incidence dropped from 40% to 15%) in head and neck cancer patients (n=39), mild drowsiness only side effect	101
2	Lack of tissue specificity	WR-2721, WR-3689, and WR-77913 offer radioprotection to both normal and tumour tissues in animal models, as their uptake is not tissue-specific. One study showed similar dose-modifying factors across tissues, despite differing drug accumulation	Targeted delivery/ selective agents	CBLB502, a TLR5 agonist, activates NF-κB-mediated protective pathways primarily in normal tissues, such as the gastrointestinal tract, without shielding tumours, as demonstrated in multiple preclinical studies	102
3	Complex regulatory requirements	Stringent FDA and EMA approval processes demand multi-phase trials; only 50% of radioprotector candidates advanced to clinical trials between 2010-2013 due to regulatory hurdles	Regulatory guidance and support	FDA requires extensive multi-phase trials with over five years of safety data for radioprotectors, & resources like Radioprotectors.org aid in navigating these regulatory demands	103
4	High cost of development	Development costs exceed $100 M per agent due to extensive preclinical/ clinical testing; low perceived ROI deters investment in niche markets	Market incentives, public-private funding	SBIR-funded BIO 300 (genistein-based) is undergoing phase I/II trials for lung cancer radioprotection (n=50), with federal support helping to offset high development costs	104
5	Limited efficacy in severe toxicities	Ineffective against grade 4 toxicities in critical organs (*e.g.*, brain, spinal cord); trials (NCT00274937, NCT00158691) showed no significant protection in CNS radiotherapy patients	Evidence generation via clinical trials	In a phase III trial, palifermin reduced severe (grade 3/4) mucositis by 40% in patients (n=212) undergoing chemoradiotherapy	105
6	Narrow therapeutic window	Variability in patient metabolism leads to dosing challenges; *e.g.*, Amifostine's narrow window increases toxicity risk in 20-30% of patients	Develop oral/topical formulations	Development of novel agents like UTS-1401 and P7C3, as well as targeted delivery systems, are expanding the therapeutic window of radioprotectors by improving efficacy & reducing toxicity.	106
7	Inconvenient administration	Intravenous delivery (*e.g.*, Amifostine requires 15-30 min infusions pre-radiotherapy) reduces compliance, especially in outpatient settings	Develop oral/topical formulations	Oral BIO 300 (genistein) phase I/II trials and topical Tempol phase I study show improved compliance & effective radioprotection	107
8	Uncertainty in advanced radiotherapy	Most available data on amifostine are from conventional radiotherapy settings, and its role in modern modalities remains poorly defined. For example, while one phase II study suggested that amifostine may augment salivary gland sparing during IMRT, comprehensive data on its dose-sparing effects in stereotactic settings like SBRT are lacking	Research integration with IMRT/SBRT	Amifostine with IMRT reduced acute toxicities (*e.g.*, mucositis grade 3+ from 35 to 20%) in head & neck cancer patients (n=54)	108
9	Lack of robust clinical evidence	Preclinical success rarely translates to phase III success; *e.g.*, only 2 of 10 agents tested from 2000-2020 reached approval due to insufficient human data	Large-scale, well-designed trials	Amifostine (phase III): reduced xerostomia (grade 2+ from 78 to 51%) but no mucositis benefit in head & neck cancer patients (n=315)	109
10	Clinician reluctance	Hesitancy to adopt new radioprotectors persists due to limited clinical experience & concerns about safety or efficacy.	Education campaigns & awareness	Radioprotection Campaign: multi-centre workshops increased clinician acceptance by 25% in pilot studies (2018-2020)	110
	Pharmaceutical industry inertia	Slow industry investment & commercialization hinder the clinical translation of promising radioprotective agents.	Market incentives (*e.g.*, orphan drug status)	Palifermin: orphan drug designation accelerated approval for mucositis prevention, boosting investment	111