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Radioimmunotherapy as an Immune-Priming Strategy in Cold Solid Tumours: Mechanisms, Preclinical and Clinical Perspectives

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Abstract

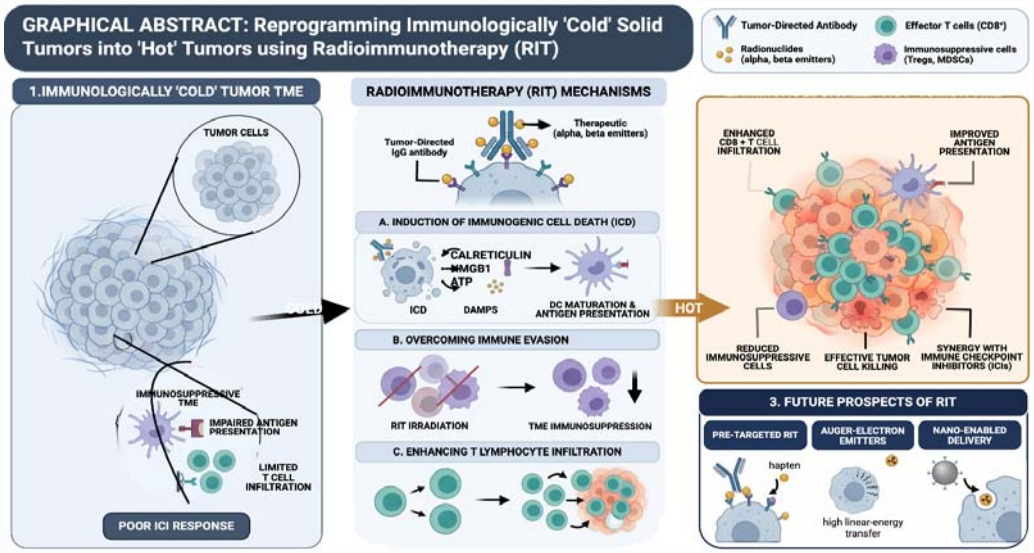
Immunologically “cold” solid tumours are characterised by limited T cell infiltration, impaired antigen presentation, and an immunosuppressive tumour microenvironment (TME), contributing to poor immune checkpoint inhibitors (ICIs) responses. Radioimmunotherapy (RIT) offers a potential remedy to remodel this environment by coupling tumour-directed antibodies with therapeutic radionuclides. This review examines the mechanistic, preclinical, and emerging clinical evidence supporting RIT as an approach for converting immunologically “cold” tumours into more immune-permissive “hot” tumours through interconnected mechanisms which includes the induction of immunogenic cell death, overcoming immune invasion, and enhancing T lymphocytes infiltration. The therapeutic characteristics of α- and β-particle emitters are further discussed herein, in relation to tumour heterogeneity, disease burden, and radiation distribution, while evidence for combining RIT with immune checkpoint blockade and other targeted therapies is critically evaluated. Moreover, the future prospects of RIT are discussed, with emerging approaches including pre-targeted RIT, Auger-electron emitters, and nano-enabled delivery, regarded as promising avenues for further improving tumour selectivity and therapeutic efficacy.

Keywords: Radioimmunotherapy; Cold Tumour Microenvironment; Solid Tumours; T Lymphocytes; Immune Checkpoint Inhibitors

Introduction

Cancer treatment response is heavily dependent on the phenotype of solid tumours, which can be classified as either “hot”, a phenotype associated with T lymphocyte (T cell) infiltration, or “cold” phenotype, which is characterised by the absence of T cells in the tumour parenchyma [1]. Contrary to hot tumours, cold tumours lack T cell infiltration, contain multiple myeloid derived suppressor cells (MDSCs), and possess poor antigen presentation [1], as presented in Figure 1. Interestingly, radioimmunotherapy (RIT) has been known to alter the tumour microenvironment (TME) through a variety of mechanisms, including the induction of immunogenic cell death (ICD), overcoming immune evasion, and the enhancement of immune cell infiltration, resulting in the transformation of immunologically "cold" tumours into "hot" ones, with the latter being more susceptible to immunotherapeutic interventions [2, 3].

ICD induction is a critical approach in which dying tumour cells release damage-associated molecular patterns (DAMPs), which are responsible for activating both innate and adaptive immune responses, therefore, increasing tumour antigenicity and promoting dendritic cell maturation and T cell priming. A growing body of research is dedicated to exploring novel strategies, such as engineered nanoparticles that induce proptosis and ICD simultaneously, which demonstrates potent reversal of immune suppression within the TME, thereby augmenting lymphocyte infiltration and antitumour



Graphical Abstract:

efficacy [3, 4]. Furthermore, combination treatments which include ICD inducers and immune checkpoint inhibitors, have demonstrated synergistic antitumour immunity and have the potential to overcome therapeutic resistance [5].

Despite therapeutic advancements, significant obstacles remain. The immunosuppressive environment generated by regulatory T cells, MDSCs, and tumour associated macrophages prevent effective immune activation [2, 6]. Consequently, clinical translation becomes a challenge owing to limitations in targeted administration, tumour heterogeneity, inefficient dosage regimens, and the possibility of adverse immunological responses [2, 6]. Therefore, in order to overcome these obstacles, interdisciplinary efforts need to play a role. This includes optimised radiopharmaceutical design, accurate immunomonitoring, and sensible combination tactics based on breakthroughs within a single cell [2, 6].

The research landscape on RIT has considerably broadened, with alpha (α)-particle-emitting drugs exhibiting highly localised powerful therapeutic and immunostimulatory effects in preclinical models [2]. These radionuclide therapies, whether used alone or in conjunction with other therapies such as oncolytic viruses, nanoparticle-based formulations, or chemotherapy, have shown exceptional tumour control and immune activation properties. Presented in Figure 2 is the schematic representation of the typical RIT strategy. Particularly, oncolytic viruses can stimulate ICD and activate pathways such as cGAS-STING, transforming the TME and increasing $CD8^+$ T cell infiltration [2, 7]. Additionally, nanotechnology can aid RIT accurate delivery as ICD inducers, leading to improved treatment outcomes and immune responses [8].

Clinically, RIT has shown significant promise in the induction of abscopal effects, notably in non-small cell lung cancer (NSCLC), where localised irradiation elicits systemic immune responses that aid in the regression of distant metastases. Emerging clinical trends include identifying new tumour-associated antigens, such as strategically combining radiopharmaceuticals with immune checkpoint inhibition or other immunomodulatory drugs to improve long-term patient responses [2, 6]. These translational breakthroughs highlight the changing paradigm that combines targeted radiotherapy and systemic immunotherapy to improve patient prognosis. Accordingly, this review explores the preclinical and clinical advancements, mechanical insights, and future prospects on the application of RIT to prime the cold TME, for better treatment response.

Key Mechanisms of Action for Priming the Cold TME by RIT

Cold tumours are characterised by an immunosuppressive TME, which is defined by the scarcity or complete absence of tumour-infiltrating $CD8^+$ T cells, the accumulation of immunosuppressive cellular populations including MDSCs, regulatory T cells (Tregs), and M2-polarised macrophages and defective antigen presentation arising from the downregulation of major histocompatibility complex class I (MHC-I) molecules on the tumour cell surface [2]. This immunologically inactive environment renders cold tumours intrinsically resistant to immune checkpoint inhibitors (ICIs), as these agents require a preexisting, albeit exhausted, immune response to augment a prerequisite that is absent in the cold TME [9]. RIT offers a unique approach to this problem.

Unlike conventional antitumour strategies, RIT exerts a dual function; it delivers targeted radiation to the tumour whilst simultaneously triggering immunological cascades capable of fundamentally remodelling the TME [10]. Specifically, RIT primes the cold microenvironment through three interconnected and sequentially acting mechanisms; (i) the induction of ICD, (ii) the dismantling of immune evasion machinery, and (iii) the enhancement of cytotoxic T lymphocyte infiltration into the tumour [11]. Together, these processes converge to shift the TME from an immunosuppressive to a pro-inflammatory state, converting cold tumours into immunologically active, therapeutically accessible entities [12].

Induction of Immunogenic Cell Death (ICD)

A foundational principle underpinning RIT-mediated immune activation is that not all modalities of cell death are immunologically equivalent [13]. Conventional apoptosis, the predominant cause of cancer cell death induced by many systemic therapies, is immunologically silent; the orderly packaging and phagocytic

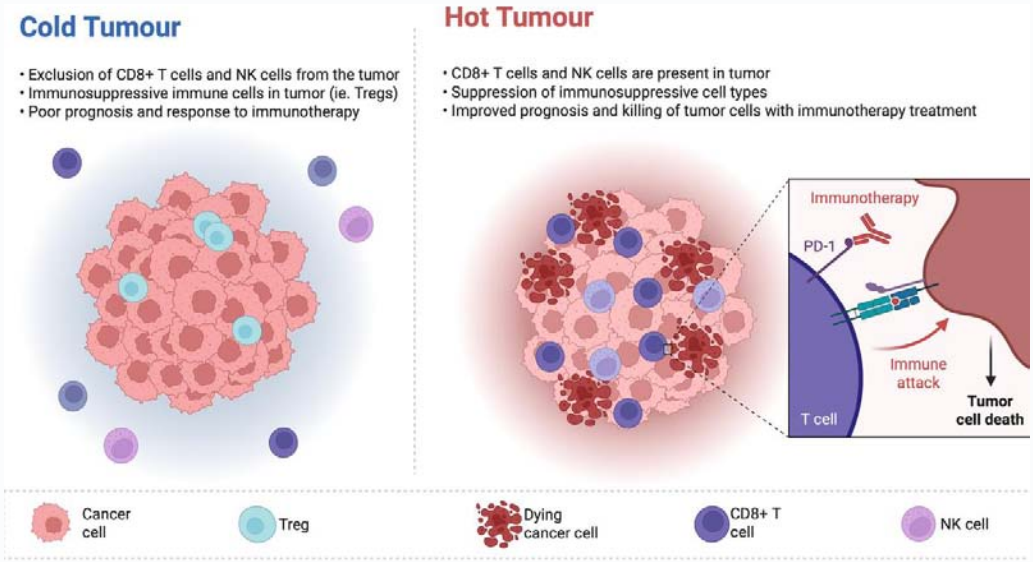


Figure 1: Tumour microenvironment (TME) in "cold" versus "hot" tumours and the immunotherapy response mechanism are compared in this schematic diagram. An immunosuppressive or "immune-desert" microenvironment is a characteristic of cold tumours (left). The core tumour mass is physically isolated from effector lymphocytes, such as cytotoxic $CD8^+$ T cells and Natural Killer (NK) cells. Immunosuppressive cell types such regulatory T cells (Tregs) predominate in the TME, worsening the prognosis and reducing the response to traditional immune checkpoint inhibition. Hot tumours (right), show an abundance of $CD8^+$ T cells, $CD4^+$ T cells, and NK cells actively infiltrating the tumour core, that drives apoptotic tumour cell death.
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clearance of apoptotic bodies proceeds without the release of inflammatory signals, rendering the immune system a passive bystander [13]. ICD, in contrast, is a functionally distinct form of regulated cell death characterised by the precise and coordinated release of DAMPs internal danger signals that initiate and sustain a productive antitumour immune response [14]. Targeted radiation, as delivered by RIT, preferentially induces ICD over apoptosis, positioning it as an immune-priming modality rather than a purely cytotoxic one [12].

The mechanistic basis of ICD resides in three canonical DAMPs, each fulfilling a non-redundant role in immune activation. Calreticulin (CRT), an endoplasmic reticulum-resident protein, undergoes translocation to the outer leaflet of the plasma membrane during ICD, where its ectopic surface exposure functions as a potent *"eat-me"* signal, which is recognised by pattern recognition receptors on dendritic cells (DCs) [13]. This interaction drives DC-mediated phagocytosis of dying tumour cells, and initiates the processing of tumour-associated and radiation-induced neo-antigens. Concurrently, extracellular adenosine triphosphate (ATP), which is released through lysosomal exocytosis, acts as a chemotactic *"find-me"* signal, recruiting immature DCs and other innate immune effectors to the site of ICD by binding to ATP-sensing receptors on nearby immune cells [13]. High-mobility group box 1 protein (HMGB1), released from the nucleus upon loss of plasma membrane integrity, engages Toll-like receptor 4 (TLR4) on DCs, promoting their maturation and enhancing their capacity to cross-present tumour antigens to $CD8^+$ T lymphocytes [15]. Critically, the immunogenic potency of ICD is contingent upon the coordinated emission of all three DAMP signals (attenuation of any single component compromises the downstream immune response) [13].

The downstream consequence of this DAMP-driven cascade, though, is the initiation of adaptive immunity. Antigen-loaded, matured DCs migrate to tumour-draining lymph nodes where they prime and expand tumour-specific $CD8^+$ cytotoxic T lymphocytes (CTLs) against both pre-existing tumour antigens and radiation-induced neo-antigens [11, 16]. Neo-antigens are novel protein fragments which appear on the surface of malignant cells as a direct result of radiation-induced DNA-damage. Since they are new and unrecognisable by the body, they can provoke a particularly strong and targeted immune response, making them valuable targets for CTL-mediated killing [17]. This process effectively transforms RIT from a localised cytoreductive intervention into a systemic immunisation event, generating a trained, antigen-specific lymphocytic population primed to seek and destroy malignant cells. However, the efficacy of this response is contingent upon the receptivity of the TME. In the cold tumour, the immunosuppressive network remains intact and actively counteracts the immune response that is just beginning to build, necessitating the concurrent dismantling of immune evasion mechanisms.

Overcoming Immune Evasion

The immunosuppressive architecture of the cold TME is not a passive state but rather, an actively maintained network sustained by the cooperative interactions of multiple cellular and molecular actors. Tregs, recruited and expanded within the TME, suppresses effector T cell function through the secretion of immunoinhibitory cytokines, interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), and through direct cell-contact-dependent mechanisms that attenuate CTL proliferation and cytotoxicity [2, 18]. MDSCs compound this suppression through a mechanistically distinct but complementary set of mechanisms; the depletion of the amino acids arginine and cysteine renders T cells metabolically anergic, the generation of reactive oxygen species (ROS) induces direct T cell damage, and the upregulation of programmed death-ligand 1 (PD-L1) on MDSC surfaces engages the PD-1 checkpoint on T cells, enforcing their functional exhaustion [9, 18].

Tregs and MDSCs further sustain one another through reciprocal

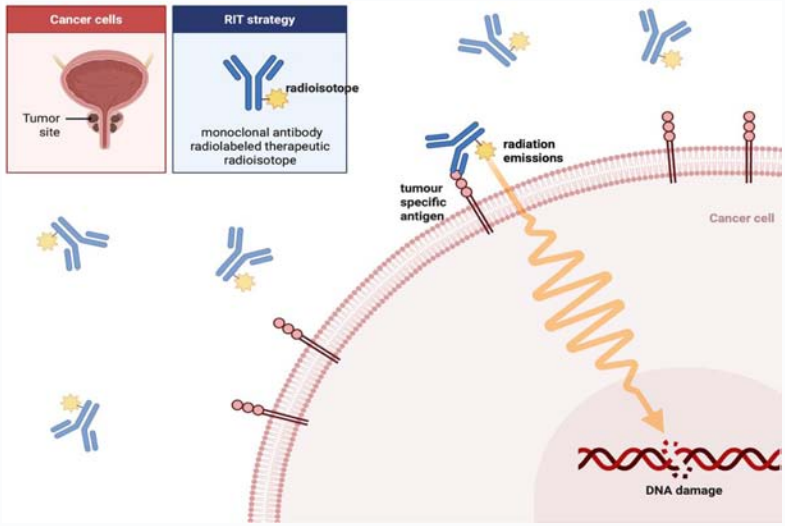


Figure 2: Schematic representation of how RIT targets solid tumours. A typical therapeutic radiopharmaceutical modality comprising a monoclonal antibody (mAb) chemically coupled to a cytotoxic therapeutic radioisotope is used in the RIT approach. The mAb binds to the tumour specific antigen overexpressed on the cancer cell membrane, and the radioisotope subsequently undergoes radioactive decay upon targeted binding sites, creating localised radiation emissions such as α or beta (β) particles.
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signalling loops, creating a self-reinforcing immunosuppressive circuit. The M2-polarised tumour-associated macrophages (TAMs) complete this triad, secreting TGF-β and IL-10, remodelling the extracellular matrix (ECM) in ways that impede T cell trafficking, and failing to perform the antigen-presenting functions expected of their lineage [2]. RIT disrupts this suppressive network across all three cellular compartments simultaneously. Essentially, Tregs are preferentially depleted by targeted radiation owing to their heightened radiosensitivity relative to effector $CD8^+$ T cells, a differential that, at appropriate dosing regimens, tips the intratumoral lymphocyte balance towards immune activation [12, 16].

Accordingly, MDSC populations are destabilised as the radiation dismantles the tumour-derived cytokine signalling environment, particularly granulocyte-macrophage colony-stimulating factor (GM-CSF) and vascular endothelial growth factor (VEGF) signalling, that sustains their recruitment and immunosuppressive programming [11]. Ideally, the most significant shift is the RIT-driven repolarisation of M2 TAMs to the pro-inflammatory M1 phenotype, which is mediated by IFN-γ and TNF-α, cytokines produced by newly activated CTLs and NK cells in response to ICD-initiated immune priming which overrides the M2-sustaining signals in the TME and redirect macrophage effector function towards tumour cytotoxicity [11, 16].

The net immunological consequence is a significant shift in the intratumoral cytokine profile. In essence, elevated IFN-γ exerts wide-ranging pro-immunogenic effects, which include the up-regulation of MHC-I expression on tumour cells, the reversal of the antigen-presentation deficiency (rendering them immunologically invisible to CTLs), the activation of M1 macrophages, and the direct impair of tumour cell proliferation [12, 16]. Furthermore, TNF-α augments direct tumour cytotoxicity, enhances vascular permeability within the TME, and synergises with IFN-γ to sustain the pro-inflammatory state.

Enhancing T cell Infiltration

Even in the context of a trained CTL population and a dismantled immunosuppressive network, the physical architecture of cold solid tumours imposes formidable barriers into the T cell entry. Tumour-associated vasculature, which is generated through pathological angiogenesis driven principally by VEGF, is structurally disorganised and characterised by the low surface expression of adhesion molecules, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), which are required for T cell extravasation from the circulation into the tumour parenchyma [16, 18]. Beyond the vascular barrier, cancer-associated fibroblasts (CAFs) deposit dense collagen networks within the tumour stroma, generating a fibrous physical barrier reinforced by elevated interstitial pressure that actively excludes infiltrating lymphocytes [2].

This challenge is a distinguishing feature of solid tumours relative to haematologic malignancies, where no such stromal architecture exists. A chemokine mismatch further compounds T cell exclusion, as the cold TME is deficient in CXCL9 and CXCL10 (the cognate chemokines that direct CXCR3-expressing CTLs towards the tumour), while simultaneously enriched in chemokines that preferentially recruit immunosuppressive MDSCs and Tregs [9, 18]. Interestingly, RIT resolves each of these barriers through mechanistically distinct but temporarily coordinated processes. At the vascular level, radiation upregulates ICAM-1 and VCAM-1 on the tumour endothelium, restoring the adhesion molecules required for CTL docking and migration out of the bloodstream into the tumour tissue.

TNF-α concurrently increases local vascular permeability, facilitating T cell transendothelial migration [12, 16]. Meanwhile, within the stroma, IFN-γ suppresses CAF activation and ECM deposition, whilst radiation-induced structural disruption and M1 macrophage-derived matrix metalloproteinases (MMPs) collectively degrade collagen barriers, creating physical conduits through which T cells can navigate [11]. Critically, radiation induces the intratumoral production of CXCL9 and CXCL10, establishing the chemokine gradients necessary to direct CXCR3+ CTLs into the tumour core, whilst the pro-inflammatory cytokine shift simultaneously suppresses

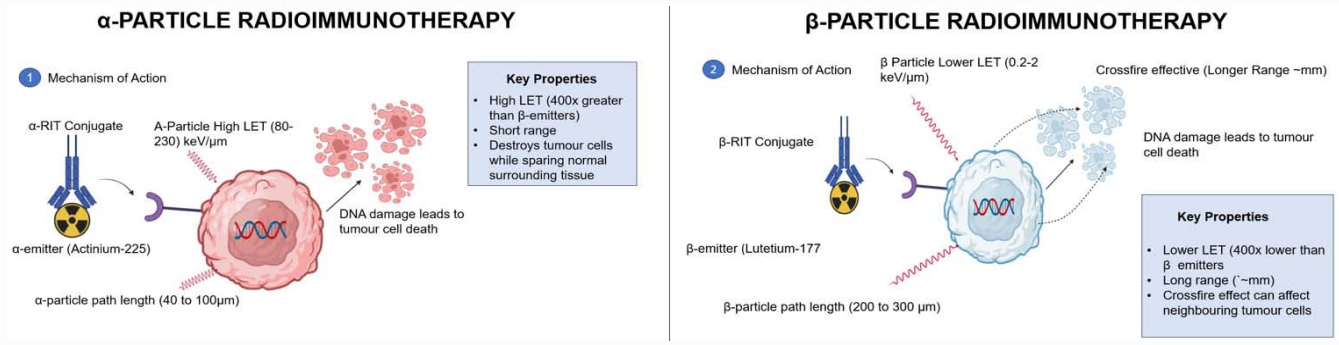


Figure 3: A comparison of α-particle and β-particle RIT. The schematic depiction highlights the key properties and mechanism of action of each RIT approach in causing tumour cell DNA damage.

the chemokine gradients sustaining MDSC and Treg recruitment [11, 16]. The cumulative outcome of these processes is a measurable increase in $CD8^+$ T cell density specifically within the tumour core, the defining histological criterion distinguishing a "hot", immunologically active tumour from its "cold" counterpart [2, 12].

Overall, all three mechanisms discussed in this section constitute a sequential, self-reinforcing cascade through which RIT fundamentally remodels the cold TME, with the induction of ICD raising the immunological alarm and generating a trained antitumour army, the dismantling of immune evasion neutralising the suppressive defences that would otherwise silence that response, and the enhancement of infiltration that opens the structural and chemical gates that have excluded cytotoxic T cells from the tumour core. Accordingly, this mechanistic framework provides the biological rationale for the preclinical and clinical investigations explored in subsequent sections.

Preclinical Investigations on Priming Cold Solid Tumours by RIT

Understanding the dosage effect on TME Remodelling

Previous preclinical studies have highlighted that priming the TME relies heavily in the dose administered, which is highly effective when administered in conjunction with other therapeutic agents [10, 19-23]. Contrary to external beam therapy, RIT involves the administration of low-dose irradiation, which maintains sustained pressure on the TME, whilst preserving systemic immune competence [24], allowing for prolonged antigen release, gradual vascular normalisation and stepwise repolarisation of immunosuppressive myeloid populations [24], which is sensitive to cumulative dose and the pattern of dose delivery. The dose dependency of RIT-induced tumour microenvironment priming is demonstrated across multicellular compartments. RIT of administered doses less than 12 Gy have been shown to reshape immunological landscape without inducing any toxicities, including severe lymphodepletion [21].

According to Demaria et al [22], the key element of RIT's capability to prime local antitumuor $CD8^+$ T cell responses is the radiation dose per fraction (DPF), rather than total biologically effective dose. Preclinical studies using orthotopic mammary carcinoma models have concluded that radiation doses of ≤8 Gy per fraction demonstrate a greater recovery of cytotoxic $CD8^+$ T cells when compared to single high fraction doses of 20 Gy. This was demonstrated in a study performed by Zhao et al [23]. This DPF-dependent effect is mediated in part by the differential impact of fractionation on regulatory T cell dynamics within irradiated tumours. High-DPF schedules induce sustained regulatory T cell dynamics accumulation that actively suppresses T cell reconstitution. In contrast, fractionated low dose per fraction treatment plans allow for temporary regulatory T cell dynamics expansion [22], resulting the development of a therapeutic window which allows for immune activation.

Alpha (α)-Particle and Beta (β)-Particle RIT

RIT using α-particles is an effective way of treating solid tumours due to their high linear energy transfer (LET) and short range which allows for the destruction of malignant tumours whilst sparing normal surround tissue [25]. The α-emitters also induce irreparable DNA double-strand breaks which can destroy tumours up to 2–10 cell diameters. The LET of α-emitters such as actinium-225 (^{225}Ac), bismuth-213 (^{213}Bi), and astatine-211 (^{211}At) is 400 times greater than that of β-emitters such as lutetium-177 (^{177}Lu) and rhenium-188 (^{188}Re) [26]. Nonetheless, RIT using β-emitting radionuclides has also demonstrated the upregulation of major histocompatibility complex (MHC) class I expression on metastatic cells, the enhancement of cell maturation, and the increase of overall intratumoral density of $CD8^+$ T cells and NK cells. This has resulted in the conversion of "cold" lesions into "hot" microenvironments [10]. A schematic comparison between α-particle and β-particle RIT is presented in Figure 3, with relevant preclinical studies highlighted in Table 1.

The short range of α-emitters make α-particle RIT effective against microscopic disease and micro-metastases, whilst sparing normal surrounding tissue. Particularly, ^{225}Ac-labeled antibodies have been used in the treatment of ovarian cancer, prostate cancer and glioma models in preclinical studies and have demonstrated complete irradiation of the tumour cells at micro-doses [26, 27]. In a study performed by Green et al [28], At-labeled anti-CD20 antibodies used in the treatment of lymphoma cells achieved complete irradiation of the tumour, with no disease regression at 3 months post-therapy, demonstrating superior therapeutic efficacy compared to their iodine-131 (^{131}I)-labelled counterparts. This study also demonstrated prolonged survival of at least 150 days post therapy in more than 60% of mice which myeloma [28]. Another study by Cheal et al [29] reported that an α-based PRIT using ^{225}Ac-tumor-targeting DOTA-hapten system demonstrated high tumour accumulation, with complete responses, and prolonged survival observed in three solid human cancer xenograft models of neuroblastoma, breast cancer, and colorectal cancer following intravenous administration.

A study by Ertveldt et al [30] demonstrated that using ^{225}Ac-radiolabelled CD20 single-domain antibody modulated the cold TME to a more hospitable and hot habitat for antitumoral immune cells. Essentially, α-particle RIT is beneficial in the treatment of

Table 1: Preclinical alpha (α)-RIT and beta (β)-RIT studies in solid tumour models, with promising prospects.

RIT Type (Emitter/ Agent)	Tumour Model	Key Findings	Ref.
α (^{211}At-labeled anti-CD20 mAb)	Lymphoma xenograft	Complete eradication of tumour, and prolonged survival	[28]
α (^{225}Ac-proteus-DOTA)	Breast cancer, colorectal cancer, neuroblastoma xenografts	Rapid renal clearance, minimal normal tissue retention, histological remission, prolonged overall survival	[29]
α (^{225}Ac-labeled anti-CD20 mAb)	Melanoma xenograft	Delayed tumour growth, with peripheral antitumoral T cell responses detected. Increased percentage of PD-L1^{pos} immune cells in the TME	[30]
β (^{90}Y-NM600)	Breast cancer, melanoma, neuroblastoma xenografts	Marked increase in the production of pro-inflammatory cytokines in the TME and enhanced tumour infiltration by effector T cell lineages	[39]
β (^{177}Lu-labeled N297A mAb)	Orthotopic breast tumour-bearing mice	Supressed tumour growth with improved tumour accumulation.	[40]

mAb: monoclonal antibody, T cell: T lymphocytes, PD-L1^{pos}: programmed death-ligand 1 (PD-L1)-positive, TME: tumour microenvironment.

solid tumours where the inability to treat micro metastases remains the primary cause of disease progression. Additionally, α-particle RIT has been shown to induce immunogenic cell death, providing a mechanistic basis for its synergy with immunomodulatory agents [31]. Moreso, when compared to chemotherapy ICD, α-particle RIT remains superior due to minimal bystander effects, preserving the structural integrity of the TME, which is necessary for productive immune priming [31].

Meanwhile, β-particle RIT involves the use of β-emitting radionuclides to deliver cytotoxic radiation to cancer cells, whilst also employing antitumour immunity through ICD and crossfire effects within the TME [32]. These β emissions induce DNA damage which is cytotoxic to cancer cells and promotes antigen release, resulting in the enhancement of DC activation and T cell priming, therefore synergising with concurrent immunotherapies such as ICIs or chimeric antigen receptor (CAR)-T approaches [32-34]. This approach capitalises on the crossfire effect of β-radiation, allowing neighbouring malignant cells to be irradiated [33]. The integration of β-radionuclide therapy with immunotherapy is favourable because it allows for real-time imaging of the target site to monitor biodistribution, assess response to treatment, allows for personalised dosimetry, and aligns with immunotherapy's personalised medicine purposes [32, 34, 35].

Some preclinical studies have further demonstrated the importance of combining β-RIT with immunomodulatory strategies to overcome immune evasion and promote positive patient responses, whilst also recognising challenging factors such as dose optimising, haematological toxicity, and TME context dependence [32, 34, 36]. Li et al [37], further expressed that combining RIT with immune checkpoint inhibitors (ICI) has been shown to reverse immunotherapy resistance, especially in triple-negative breast cancer (TNBC) [37]. It shoule be noted that RIT-induced cell death results in antigen cross-presentation by CD103+ DCs and reduced intratumorally regulatory T cells, allowing for the immunosuppressive brakes on T cell function and restoration of responsiveness to checkpoint blockage [38].

In a study by Patel et al [39], it was observed that using yttrium-90 (^{90}Y) chelated with an alkylphosphocholine analogue (NM600) in conjuction with ICI rendered immunologically cold tumours responsive to immune checkpoint blockade, in breast cancer, melanoma, and neuroblastoma xenograft models. Likewise, Yamaguchi et al [40], developed a ^{177}Lu-labeled aglycosylated N297 mAb, targeting trophoblast cell-surface antigen 2 (TROP2), which showed enhanced radioactivity accumulation in the tumour and supressed tumour growth for over 50 days in orthotopic breast tumour-bearing mice.

Clinical Investigations on Priming Cold Solid Tumours by RIT

Clinically, RIT has demonstrated the potential to induce tumour-specific immune responses and promote abscopal effects, which has led to an increasing number of clinical investigations exploring the abscopal effect together with potential RIT targets to sensitise immunologically cold tumours [12, 41]. Accordingly, NSCLC has become a useful clinical model for the abscopal concept because focal radiation can provide local cytotoxicity while also functioning as an *in situ* vaccine [42, 43]. Recent clinical NSCLC evidence comes from external beam RIT, particularly stereotactic body radiotherapy (SBRT) plus PD-1/PD-L1 blockade, pembrolizumab. In the PEMBRO-RT trial, SBRT to a single lesion before pembrolizumab increased the 12-week objective response rate in non-irradiated disease from 18% to 36%, without increased treatment-related toxicity [41].

A pooled analysis of PEMBRO-RT and the MD Anderson randomised trial reported higher out-of-field response and improved outcomes when radiotherapy was added to pembrolizumab, including a median progression-free survival of 9.0 versus 4.4 months and median overall survival of 19.2 versus 8.7 months, without any new safety concerns [41]. A 2025 multitopic analysis of serial PEMBRO-RT specimens strengthened the biological signal, after SBRT, non-irradiated tumours showed enrichment of interferon-gamma, interferon-alpha, chemokine, antigen-processing, NK-cell and adaptive immune programmes, together with expansion of new and pre-existing T cell clones in tumour and blood compartments [12]. This data supports the premise that spatially confined radiation can help convert distant cold disease towards a more inflamed state, while preserving measurable out-of-field lesions for systemic-response assessment [12, 43, 44].

Although, prostate-specific membrane antigen (PSMA) and somatostatin-receptor theranostics continue to dominate radiotheranostics, as seen in the phase II trial of ^{177}Lu labelled anti-PSMA monoclonal antibody J591 validated PSMA as an excellent target [45], newer targets are expanding into the field, particularly where tumour cell antigen expression is heterogeneous or the stroma contributes to immune exclusion [46]. Fibroblast activation protein (FAP) is compelling, owing to its predominant expression by cancer-associated fibroblasts in epithelial malignancies, and can target the stromal compartment rather than malignant cells alone. FAP-targeted positron emission tomography/ computed tomography (PET/CT) imaging also provides a non-invasive route for patient selection [47].

Likewise, integrins, particularly $\alpha_v\beta_3$, remain attractive because they are expressed in tumour angiogenesis and in some tumour cells. The first in human ^{177}Lu-AB-3PRGD2 study in integrin- $\alpha_v\beta_3$

advanced tumours reported acceptable early safety, pharmacokinetics and dosimetry, supporting further dose-escalation and multi-cycle evaluation rather than established efficacy [48]. Gastrin-releasing peptide receptor (GRPR) is another multicancer theranostic target overexpressed in the prostate, breast, small-cell, NSCLC, and other tumours, and can be labelled with ^{68}Ga for imaging or ^{177}Lu or ^{225}Ac for therapy [49, 50]. Overall, FAP, integrins and GRPR should be framed as precision selectable expansions of RIT. Their value in cold solid tumours will depend on companion PET/CT uptake, inter-lesional heterogeneity, radiation dosimetry, immune-contexture readouts and rational sequencing with SBRT and ICIs [44, 46, 47].

Current Challenges with RIT

Despite the momentum, consistent clinical benefits in solid tumours remain elusive, and the contrast with haematologic malignancies is concerning. RIT has demonstrated clear clinical efficacy in non-Hodgkin's lymphoma, where combination regimens yield superior outcomes. However, in solid tumours, the evidence remains inconclusive, with a meta-analysis of randomised clinical trials (20 trials; 3,562 patients) finding that while RIT consistently reduced disease progression, overall survival benefit was highly variable and did not reach statistical significance, with heterogeneity exceeding 50% [51]. This gap is structural as much as biological, as solid tumours present physical barriers including abnormal vasculature, highly fibrotic or desmoplastic stroma, absent functional lymphatics, and elevated interstitial fluid pressure, all of which impair antibody delivery to the target site [52]. High intra-tumoral pressure and suppressive myeloid and stromal cells create a microenvironment resistant to immune activation, with particularly severe consequences in desmoplastic cancers such as pancreatic and prostate cancer [53].

These observations have driven three interconnected priorities. Firstly, improved patient selection; a greater-than-additive clinical response to radiotherapy and immunotherapy combinations is limited to a subset of patients, and how these modalities can best be combined remains unresolved [54], demanding biomarker-driven stratification beyond PD-L1 scoring. Secondly, optimal sequencing of radiation and immunotherapy, where the timing of each modality, relative to the other meaningfully shapes the immune response elicited. And lastly, overcoming stromal barriers; stromal fibroblast programs and ECM remodelling have been identified as actionable levers for overcoming immune exclusion [55], and effective regimens will need to target not only malignant cells and checkpoints but also the non-malignant compartments shaping the TME. Taken together, the field is moving from single agent optimisation towards ecosystem-aware combination design, with patient selection, sequencing, and stroma-directed strategies as the defining challenges of the coming trial generation.

Future Perspectives

The combination of RIT, antibody-drug conjugates (ADCs), and ICIs is becoming a primary area of clinical research for patients with advanced solid tumours that have shown resistance to previous treatments [56]. The biological basis for these methods lies in their complementary nature, i.e., blocking PD-1/PD-L1 boosts T cell activation and immune responses, allowing the immune system to identify and destroy tumour cells targeted by ADC payloads more efficiently [57]. These payloads are able to trigger immunogenic cell death, promoting the development of antigen-presenting cells and enhancing T cell infiltration, with these effects being further intensified by checkpoint inhibition [58]. Clinical trials have confirmed this synergy, with combinations like enfortumab vedotin, with pembrolizumab showing a significant improvement in objective response rate (ORR), overall survival (OS), and progression-free survival (PFS) in urothelial carcinoma.

Similar research is currently being conducted for lung, cervical, and other resistant solid tumour types [59]. As of 2026, it is anticipated that established ADC targets such as HER2, TROP2, and Nectin-4 will have approved treatments in the near future, while newer targets like B7H3 and CEACAM5 are under active investigation, with combination immunotherapy strategies showing promising synergistic effects [51, 60]. Progress in the development of next-generation ADCs is also moving towards bispecific and tri-specific platforms that simultaneously tackle antigen diversity and immune co-stimulation, such as constructs that target both HER2 and PD-L1 [61, 62]. Similarly, the NADiR trial (NCT04837209) was investigating the use of niraparib, dostarlimab in conjunction with radiotherapy in metastatic PD-L1–negative or immunotherapy-refractory triple-negative breast cancer, especially in patients where RIT-mediated TME could potentially result in the reversal of ICI-resistance [63].

Several pre-targeting platforms, including bispecific antibody-hapten systems and bio-orthogonal chemistry, have progressed from experimental models into early clinical investigation, although optimal scheduling, immunogenicity, manufacturing complexity, and reliable tumour accumulation remain important barriers to wider translation [29, 64]. Future studies should therefore evaluate PRIT not only according to tumour response, but also according to whether it provides a reproducible improvement in tumour-to-background absorbed dose and creates sufficient radiation exposure to initiate immune priming. Meanwhile, radionuclide selection is also likely to become increasingly phenotype and disease-stage dependent, beyond the conventional α- and β-emitters. Auger-electron emitters provide a further opportunity, particularly for minimal residual disease and micrometastases [65].

Nanotechnology may also provide an additional strategy for overcoming the pharmacokinetic and intratumoral delivery limitations of conventional RIT, particularly in solid tumours where heterogeneous target expression, abnormal vasculature, and poor penetration can restrict the distribution of radiolabelled antibodies. Nanocarriers such as liposomes and polymeric nanoparticles can be functionalised with tumour-targeting ligands and loaded with RIT cargos thereby enhancing tumour accumulation and radionuclide retention. More recent work has extended this concept towards radionuclide nanomedicines designed to improve isotope stability, tumour exposure and pharmacokinetic behaviour, although the majority of these approaches remain at preclinical level [66-68].

Conclusion

RIT is a viable therapeutic modality that incorporates a tumour-targeting antibody with a radionuclide to deliver radiation doses to tumours and stimulate immune responses. This approach significantly improves tumour absorption whilst limiting radiation exposure to non-target organs. The work done so far shows that RIT can do more than directly eradicate tumour cells, but can generate ICD, increase tumour antigen visibility, and alter suppressive immune populations, which all support the biological rationale that RIT can convert immunologically cold solid tumours into more immune-responsive environments. However, the positive preclinical observations do

not yet translate into consistent clinical benefit in solid tumours, with treatment sequencing, dose, and patient selection still needing to be addressed. Accordingly, the future work on RIT should aim to improve targeting and immune stimulation by employing novel strategies that promote tumour selectivity, reduce systemic toxicity, and boost antitumor immune responses.

Pre-targeting approaches may improve the therapeutic efficacy, while emerging radionuclides may provide new opportunities for highly localised radiation. PRIT has the potential to greatly improve therapeutic efficacy in solid tumours, particularly metastatic, castration-resistant, and treatment-resistant cancers. Furthermore, nanotechnology may offer alternative strategies for improving tumour delivery. These approaches will be most valuable when integrated with quantitative dosimetry, molecular imaging, and biomarkers capable of identifying both radionuclide delivery and the immune state of individual tumours. Similarly, combining RIT with ICIs or other immunomodulatory agents should be guided by the biological sequence of tumour killing, antigen presentation, T cell recruitment, and checkpoint activation rather than by empirical combination alone.

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