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Original Article

Ongoing prospective studies on reirradiation: A systematic review of a clinical trials database

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ABSTRACT

Introduction: Reirradiation has gained increasing interest, as advances in systemic therapy increase the survival of patients with cancer, and modern radiation techniques allow more precise treatments. However, high-quality prospective evidence on the safety and efficacy of reirradiation to guide clinical practice remains scarce. This systematic review evaluates ongoing prospective studies on reirradiation to identify research gaps and priorities.
Methods: A systematic review of ClinicalTrials.gov was conducted on July 11, 2024, using search terms related to reirradiation. Inclusion criteria were prospective studies that were "recruiting," "not yet recruiting," or "active, not recruiting." Studies with published results, retrospective, and in-silico studies were excluded. The review followed PRISMA 2020 guidelines and recommendations for systematic searches of clinical trial registries.
Results: Among 1026 identified studies, 307 were screened, 99 were included. Fourty (40%) focused on central nervous system (CNS), 23 (23%) head and neck, and 17 (17%) on pelvic reirradiation. Most studies (90%) were interventional, with 32 (32%) phase II and 4 (4%) phase III trials. Sixteen trials were randomized (RCTs), including the 4 phase III trials for recurrent glioblastoma, rectal and nasopharyngeal cancer. Ten dose escalation trials focus on recurrent prostate, rectal, and non-small cell lung cancer as well as glioma. Modern high-precision radiotherapy techniques were frequently used, with 21 (21%) studies using stereotactic radiotherapy and 17 (17%) using particle therapy. Combinations with systemic therapies were investigated in 41 (41%) studies.
Conclusion: Ongoing studies most frequently focus on CNS, head and neck, and pelvic reirradiation. There remains a critical need for RCTs, in particular for lung, breast, and gynecological cancers. Dose escalation trials,

Abbreviations: ATR, Ataxia telangiectasia and Rad3 related; ATM, Ataxia-telangiectasia mutated; DIPG, Diffuse intrinsic pontine glioma; EBRT, External Beam Radiotherapy; EGFR, Epidermal Growth Factor Receptor; IMPT, Intensity-Modulated Proton Therapy; IMRT, Intensity-Modulated Radiotherapy; NPC, Nasopharyngeal carcinoma; NSCLC, Non-small cell lung cancer; PARP, Poly (ADP-Ribose) Polymerase; RCT, Randomized Controlled Trial; SBRT, Stereotactic Body Radiotherapy; SRT, Stereotactic Radiotherapy; TiTE-BOIN, Time-To-Event Bayesian Optimal Interval; TiTE-CRM, Time-To-Event Continual Reassessment method; VEGF, Vascular Endothelial Growth Factor.

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application of precision radiation techniques and combinations with modern systemic therapy may help define the optimal multimodality treatment schedules.

Introduction

Approximately half of all patients with cancer will receive radiotherapy during their course of disease. [1–3] The type of malignancy and the initial curative intent treatment influence the potential patterns of failure: a variable proportion of patients will develop local failure of the primary tumor, regional lymph node failure or distant metastases. [4–10] On the other hand, patients may be cured, but develop second malignancies after an initial treatment. [11–14] Patients with localized recurrent disease or an early stage second primary tumor may still be cured by radical local therapy. Even amongst patients with oligometastatic disease, metastasis-directed local ablative therapy is increasingly offered to achieve long-term disease control. [15] Furthermore, local ablative therapy may be offered to cancer patients under systemic therapy progressing with a limited number of lesions, in order to overcome acquired resistance and delay further disease progression. [16] Besides surgery, radiotherapy is a commonly used local treatment for recurrent, progressing or second primary tumors, which may manifest in the proximity to or even within previously irradiated regions. Reirradiation may be a viable option for patients, who may have limited therapeutic alternatives due to inoperability or dismal response rates to further line systemic treatments. [17] In selected cases, reirradiation may still offer a second chance for cure. However, persisting treatment-related impairments and the prior radiation dose to adjacent organs at risk close to or beyond their commonly accepted tolerance may render reirradiation challenging.

In clinical practice and research, interest in reirradiation has been rising. [17,18] This is likely due to advances in multimodality cancer treatments and the consequently increasing proportion of long-term survivors with cancer and new lesions requiring local treatment. [19] At the same time, advanced imaging and radiotherapy techniques allow unprecedented precision in targeting the tumor, while mitigating the exposure of adjacent healthy organs and thus reducing the risk of side effects. In combination with developments in treatment planning – including image registration and dose accumulation – high-dose reirradiation with curative intent is therefore becoming a technically feasible option.

The evidence to guide patient selection and treatment planning of reirradiation in clinical practice is scarce and commonly of insufficient quality. A minority of trials is prospective, and reporting standards with regards to reirradiation are limited. [17] Less than twenty randomized controlled trials on reirradiation have been published, many of whom suffer from methodological shortcomings: limited patient numbers, outdated control arms, insufficient reporting of relevant treatment information. [20] Translating these trialś results into clinical practice may therefore be challenging, if not impossible. For many cancer types – lung cancer, rectal and prostate cancer, or pelvic gynecological malignancies – no randomized controlled trials on reirradiation have been published to date. [20] While expert recommendations exist, they commonly failed to find consensus due to the apparent lack of evidence to guide decision. [21–25]

Prospective clinical studies are therefore crucial to address the most pertinent challenges of reirradiation: assessing the safety and efficacy of different reirradiation dose-fractionation schemes, comparing them to alternative treatments, or in combination with novel systemic treatments. In this systematic review, we evaluate ongoing prospective studies on reirradiation to highlight topics of interest and persistent knowledge gaps that warrant increasing efforts.

Materials and methods

A systematic review of the clinical trial registry database ClinicalTrials.gov was conducted to identify ongoing prospective studies on reirradiation. The systematic review adhered to the PRISMA 2020 statement and the recommendations by Hunter et al. for systematic searches of clinical trial registries. [26]

The search and review process was conducted by a single reviewer (JW). The search was performed on July 11, 2024, using the following search terms: “re-irradiation” OR “reirradiation” OR (“recurrent” AND (“radiation” OR “radiotherapy”)). The inclusion criteria for the review were studies on reirradiation that were categorized as “recruiting”, “not yet recruiting”, or “active, not recruiting.” Only prospective studies, either observational or interventional, were considered. Studies that had published results, as well as retrospective and in-silico studies, were excluded. Information available on ClinicalTrials.gov was reviewed to ensure that the studies met the inclusion and exclusion criteria.

Data manually extracted from the registry included the site of treatment, radiotherapy treatment modality, combination treatments (such as systemic therapy, surgery, or other treatments), and the study design. The primary endpoints of the studies were categorized in the following groups: local control-related (including local control and objective response rate of the irradiated lesion), progression-free survival-related (including progression-free survival and endpoints based on progression beyond the irradiated lesion), toxicity-related, quality of life-related, overall survival, feasibility and others (not fitting either of the categories).

Results

A total of 99 ongoing prospective studies were identified (Appendix Table E1 and Figure E1). Of these, 40 (40 %) focus on reirradiation for malignancies in the central nervous system (CNS), 23 (23 %) on the head and neck region, 17 (17 %) on the pelvis, and 6 (6 %) on the thorax. Five (5 %) studies focus on the breast or chest wall, one (1 %) on abdominal and skin reirradiation, and 6 (6 %) include multiple treatment sites. Of these trials, 9 (9 %) allow the inclusion of children. An overview of study designs and interventions per anatomical region and tumor entity is shown in Table 1.

The majority of the studies (89 %) are interventional, compared to 10 (10 %) observational studies. There are 12 (12 %) phase I trials, 7 (7 %) phase I/II and 32 (32 %) phase II trials. Four (4 %) trials are phase III. Fortyfour trials (44 %) did not specify the respective phase. The median sample size is 40 (interquartile range: 28—69). Primary endpoints are most commonly toxicity-related (47 %), followed by local control- (24 %) and progression-free survival-related primary endpoints (16 %) (Table 2). Thirteen studies have a primary overall survival endpoint. Feasibility and quality of life (QoL) are the primary endpoints in 7 (7 %) and 3 (3 %) studies, respectively. Patient-reported QoL is an outcome measure in about half of the studies (49 %).

Sixteen (16 %) ongoing RCTs were identified (Table 3). Most RCTs (n = 6) investigate head and neck reirradiation. Among them, the randomized phase II KEYSTROKE trial (NCT03546582) includes patients with locally recurrent head and neck cancer who are either treated with stereotactic body radiotherapy (SBRT) reirradiation alone or in combination with pembrolizumab. In another RCT (NCT03164460) patients with recurrent head and neck cancer are randomized to receive either SBRT or intensity modulated radiotherapy/proton therapy (IMRT/IMPT). Five RCTs focus on glioma (glioblastoma or diffuse intrinsic pontine glioma), notably the phase III LEGATO trial (NCT05904119), comparing lomustine chemotherapy alone or in combination with

Table 1
Overview of selected study designs and interventions per anatomical region and tumor entity.

Site (number)	RCT	Dose escalation	+ Systemic therapy	+ Surgery	+ Other combinations
CNS (n = 40)	9	4	24	4	4
- Glioma (n = 36)	7	4	23	4	3
- Other (n = 4)	2	0	1	0	1
Head and neck (n = 23)	6	0	11	0	1
- Mixed (n = 16)	2	0	7	0	1
- NPC (n = 7)	4	0	4	0	0
Thorax (n = 6)	0	1	2	0	0
- NSCLC (n = 5)	0	1	2	0	0
- Other (n = 1)	0	0	0	0	0
Breast (n = 5)	0	0	0	5	1
Abdomen (n = 1)	0	0	0	0	0
Pelvis (n = 17)	2	5	2	3	1
- Prostate (n = 10)	1	4	1	0	1
- Rectum (n = 5)	1	1	1	2	0
- Gynecological (n = 1)	0	0	0	0	0
- Anal (n = 1)	0	0	0	1	0
Skin (n = 1)	0	0	0	0	0
Mixed sites (n = 6)	0	0	2	0	1

Table 2
Primary endpoints in ongoing studies. Thirteen studies had co-primary endpoints or different endpoints for consecutive phases of the study.

n	(%)	Endpoint
47	(47)	Toxicity-related
24	(24)	Local control-related
16	(16)	Progression-free survival-related
13	(13)	Overall survival
7	(7)	Feasibility
3	(3)	Quality of life-related
2	(2)	Other

reirradiation in patients with recurrent glioblastoma. Other RCTs on CNS reirradiation focus on meningioma (NCT03604978) and brain metastases (NCT05124912). Two of the RCTs address the pelvic region, for which no RCTs have been published yet. Importantly, in the phase III GRECCAR15 trial (NCT03879109) patients with resectable locally recurrent rectal cancer are randomized to neoadjuvant chemotherapy alone or in combination with reirradiation, evaluating the R0 resection rate. The RO-PIP trial (NCT05614700) compares reirradiation for locally recurrent prostate cancer using either SBRT or brachytherapy.

Ten (10 %) ongoing dose escalation trials were identified, covering prostate, rectal, and non-small cell lung cancer (NSCLC) as well as glioma (Table 4). The four dose escalation trials for locally recurrent prostate cancer all focus on SBRT reirradiation. One study performs proton therapy dose escalation for locally recurrent rectal cancer (NCT04827732). The NCT04455438 study on SBRT reirradiation for inoperable, peripheral lung lesions (primary NSCLC or lung metastases) uses an innovative time-to-event Bayesian Optimal Interval (TiTE-BION) design, allowing for the continuous accrual of patients despite the late onset of dose-limiting toxicity (≥grade 3 pneumonitis).

There was a clear preference for high-precision radiotherapy techniques in current studies on reirradiation (Table 5). Stereotactic radiotherapy (extracranial or intracranial) and hypofractionated external beam radiotherapy (EBRT) are applied in 21 (21 %) and 8 (8 %) instances, respectively. Particle therapy (proton or carbon ion therapy) is used in 17 (17 %) studies. In six (6 %) studies reirradiation is delivered using brachytherapy.

Table 3
Ongoing randomized controlled trials on reirradiation.

NCT number	Acronym	Site	Phase	Treatment arms
NCT05124912	REMASTer	CNS: Metastasis	NA	Surgical resection of recurrent brain metastases followed by Laser Interstitial Thermal Therapy (LITT) + reirradiation *vs.* LITT alone
NCT05614700	RO-PIP	Pelvis: Prostate	NA	Brachytherapy reirradiation *vs.* SBRT reirradiation
NCT03604978	–	CNS: Meningioma	I/II	Nivolumab + SRT reirradiation *vs.* Ipilimumab + Nivolumab + SRS reirradiation
NCT02866747	STERIMGLI	CNS: Glioblastoma	I/II	Durvalumab + reirradiation *vs.* reirradiation alone
NCT01464177	GBM Hypo RT	CNS: Glioblastoma	II	Two SRT reirradiation schedules
NCT06160206	–	CNS: Glioblastoma	II	Retifanlimab + Bevacizumab + reirradiation *vs.* Bevacizumab + reirradiation
NCT05653635	ReciDOPA	CNS: Glioblastoma	II	FDOPA-PET-guided boost reirradiation *vs.* reirradiation
NCT03620032	DIPG	CNS: DIPG	II	Two reirradiation schedules
NCT04533620	–	Head/neck: NPC	II	Carbon-ion reirradiation standard *vs.* individualized prescription based on normal tissue complication model
NCT04143984	–	Head/neck: NPC	II	Camrelizumab + Carbon-ion reirradiation *vs.* Carbon-ion reirradiation alone
NCT03546582	KEYSTROKE	Head/neck: mixed	II	Pembrolizumab + SBRT reirradiation *vs.* SBRT reirradiation
NCT03164460	–	Head/neck: mixed	II	SBRT reirradiation *vs.* IMRT/IMPT reirradiation
NCT04215510	–	Head/neck: NPC	III	IMRT reirradiation *vs.* endonasal endoscopic surgery
NCT04453813	–	Head/neck: NPC	III	Toripalimab + reirradiation + concurrent chemotherapy *vs.* reirradiation + concurrent chemotherapy
NCT03879109	GRECCAR15	Pelvis: Rectum	III	Neoadjuvant chemotherapy + reirradiation *vs.* neoadjuvant chemotherapy alone
NCT05904119	LEGATO	CNS: Glioblastoma	III	Lomustine + reirradiation *vs.* lomustine alone

Table 4
Ongoing reirradiation dose escalation trials.

NCT number	Site	Modality	Dose escalation mode
NCT03073278	Pelvis: Prostate	SBRT	Three dose levels: 6 x 6 Gy; 6 x 6.33 Gy; 6 x 6.66 Gy
NCT04536805	Pelvis: Prostate	SBRT	Three dose levels in the first phase: 5 x 5 Gy; 5 x 6 Gy; 6 x 6 Gy. Combined with metformin
NCT03253744	Pelvis: Prostate	SBRT	Four dose levels: to the tumor 5 x 8 Gy; 5 x 8.5 Gy; with and without 5 x 6 Gy to the whole prostate
NCT03438552	Pelvis: Prostate	SBRT	Three dose levels: 5 x 5 Gy; 5 x 6 Gy; 6 x 6 Gy
NCT04827732	Pelvis: Rectum	Protons	Three dose levels
NCT04455438	Thorax: NSCLC	SBRT	Three dose levels: 5 x 6 Gy; 5 x 8 Gy; 5 x 10 Gy. Time-To-Event Bayesian Optimal Interval (TITE-BOIN)
NCT06344130	CNS: Glioblastoma	EBRT, hypofractionated	Three dose levels, 3 + 3 design
NCT05284643	CNS: Glioblastoma	Protons	Two dose levels: 10 x 3.5 Gy; 10 x 4 Gy
NCT01464177	CNS: Glioblastoma	SRT	Randomization between to doses: 5 x 5 Gy; 5 x 7 Gy
NCT05737212	CNS: Glioma	Neutrons (Boron Neutron Capture Therapy)	Three dose levels, 3 + 3 design

Table 5
Treatment modalities applied to deliver reirradiation in ongoing studies.

n	(%)	Modality
21	(21)	Stereotactic radiotherapy, cranial or extracranial
17	(17)	Particle therapy
8	(8)	Hypofractionated EBRT
6	(6)	IMRT
6	(6)	Brachytherapy
2	(2)	Comparing different modalities
2	(2)	Pulsed low-dose-rate EBRT
2	(2)	Diffusing Alpha-Emitters Radiation Therapy
35	(35)	Not specified

Forty-one (41 %) studies combine reirradiation with systemic therapy, of which 13 (32 %) use a combination of drugs (Table 6). Immune checkpoint inhibitors are most commonly used (46 %), known for their potential to provide long-term distant disease control and potentially local radiosensitization. Chemotherapy is used in 10 (24 %) studies. Multiple types of targeted therapy – including VEGF, ATM, ATR, EGFR and PARP inhibitors – are also tested in combination with reirradiation.

Table 6
Types of systemic therapy used in combination with reirradiation in 41 ongoing studies, of which 13 studies apply multiple systemic therapy agents.

n	(%)	Systemic therapy
19	(46)	Immunotherapy
10	(24)	Chemotherapy
7	(17)	VEGF-inhibition
3	(7)	ATM/ATR-inhibition
2	(5)	EGFR-inhibition
2	(5)	Nanoparticles
1	(2)	PARP-inhibition
1	(2)	Multitarget-tyrosine-kinase-inhibition
9	(22)	Other

Notably, two studies (NCT04784221 and NCT04505267) combine reirradiation with novel nanoparticles, which serve as radio-enhancers to increase the radiotherapy energy dose deposition inside tumor cells.

A combination of reirradiation and surgery is utilized in 11 (11 %) studies. Other medical devices – including hyperthermia, focused ultrasound, hyperbaric oxygenation and laser interstitial thermal therapy – are tested in 8 (%) studies.

Discussion

In this systematic review, we analyzed ongoing prospective studies on reirradiation to identify key areas of interest and gaps requiring further investigation. Reirradiation for glioma and head and neck cancers stands out as the most frequently studied tumor sites, while prostate cancer dominates reirradiation studies in the pelvic region. However, lung, breast, and gynecological malignancies exhibit notably less research activity, highlighting the need for enhanced efforts in these areas. Additionally, while research on rectal cancer reirradiation remains sparse, a large, randomized controlled phase III trial offers potential to shape future clinical practice in this domain.

To change clinical practice, randomized controlled phase III trials are generally preferred. In the reirradiation setting, conducting such trials presents unique challenges: patient populations are usually smaller and certainly more heterogeneous than for primary radiotherapy trials, necessitating multicenter or even multinational collaboration. This complicates efforts to standardize workflows, dose constraints, and prescription doses due to the variability in global practices. [18] Moreover, defining a sufficiently homogeneous patient population is hindered by the wide range of prior treatments, dosages, and residual toxicities or organ dysfunctions present in reirradiated patients.

Among the ongoing trials, we identified four phase III RCTs focusing on glioblastoma, rectal, and nasopharyngeal cancers. Previously, two notable multicenter RCTs on recurrent nasopharyngeal cancer from China demonstrated the feasibility of large-scale reirradiation trials. [27,28] Still, challenges persist, as exemplified by the phase II RCT NRG Oncology/RTOG1205 trial on recurrent glioblastoma, where slow patient accrual necessitated to broadened inclusion criteria, highlighting the difficulties in conducting large trials in this domain. [29] Another significant challenge is the choice of control groups; for example, the inclusion of bevacizumab as a control arm in NRG Oncology/RTOG1205, despite its limited use in Europe, contrasts with the more common use of lomustine. The EU-funded phase III RCT LEGATO seeks to explore reirradiation combined with lomustine, with overall survival and QoL endpoints providing crucial insights to define clinical practice.

Phase II or earlier phase RCTs also play an important role in refining the role of reirradiation, particularly for glioma and head and neck cancers, where numerous questions remain about the optimal approaches, despite previously published RCTs. [20] The effective translation of trial results into clinical practice hinges on the standardization of reporting for radiotherapy techniques and dose constraints. As this has been inconsistent in many previous studies, reporting guidelines proposed by EORTC and ESTRO aim to facilitate cross-study comparison and practical applicability. [17] An additional concern is the relatively small size of many trials, with a median enrollment of only 40 patients, underscoring the need for larger, impactful studies with practice-changing consequences.

The safety and efficacy of reirradiation are critical concerns, as reflected by the choice of endpoints in ongoing trials, where toxicity and local control are the most common. Yet, focusing on local control overlooks the high risk of distant failure and systemic disease progression, which is common among many patients with recurrent disease who may be candidates for reirradiation. Additionally, improvements of local control may or may not translate into an overall survival benefit, as has been observed in a RCT on postoperative reirradiation for head and neck cancer. [30] It is well known that certain surrogate endpoints may have a low correlation with survival. [31] This should be considered when

designing reirradiation trials as well. In the phase III GRECCAR15 trial, assessing reirradiation in rectal cancer, the primary endpoint of R0 resection rate illustrates an objective, early-readout endpoint, which may at least facilitate the swift completion of larger trials.

Not only the duration, but also the quality of life after reirradiation is a relevant concern for cancer patients. Nonetheless, quality of life remains underexplored, and is only included as an endpoint in about half of the ongoing trials. More emphasis is needed on patient-reported outcomes to assess the real-world burden of these treatments. Future studies should prioritize quality of life and decision-regret metrics [32], as these data are invaluable for patients making treatment decisions, particularly when multiple options exist, each carrying a significant—and often uncertain—risk of side effects.

Designing early-phase reirradiation trials around late toxicity endpoints presents significant challenges. Long follow-up periods are required to capture late toxicities, which may lead to higher dropout rates and increased costs. Innovative trial designs, such as time-to-event Bayesian Optimal Interval (TiTE-BOIN) [33] or continual reassessment (TiTE-CRM) methods [34], may – at least to a certain degree – help overcome these barriers by allowing continuous patient enrollment despite the late onset of toxicities. These methodologies require sophisticated infrastructure and real-time data analysis, which many clinical trial teams may lack, thus hampering widespread adoption. A French dose-escalation trial for prostate cancer reirradiation successfully implemented such advanced designs, underscoring their potential to guide future phase II or III studies on optimal treatment strategies. [35]

A broad spectrum of innovative trial designs may improve the feasibility of trials on reirradiation, particularly in the context of rare or heterogeneous patient populations, and combinations with novel systemic therapies. These include adaptations of umbrella, basket and platform trials. [36] Umbrella trials test multiple treatment types for a single disease, stratified by tumor or patient characteristics. In basket trials, a common treatment is used aginst different disease entities. The multi-arm platform studies compare different interventions with a common control arm. This design can improve patient enrolment and facilitate simultaneous or sequential assessments of various experimental therapies.

The increasing application of advanced radiotherapy techniques, including stereotactic radiotherapy and particle therapy, reflects a belief that these methods may reduce toxicity and improve outcomes. While modern radiotherapy techniques may improve outcomes in certain scenarios [37,38], proving the clinical benefit of these technologies in reirradiation remains a challenge. Real-world data (RWD) from observational studies may complement interventional trials by providing insights into the effects of novel technologies, as well as in underrepresented subgroups and rare events. Our review identified six ongoing observational studies on reirradiation. The inherent biases and confounders of RWD should be considered, which limit their utility for comparative effectiveness research. [38]

The role of reirradiation in combination with systemic therapies, including targeted therapies, and immunotherapies, is a major area of interest. Over half of the ongoing studies involve reirradiation combined with systemic agents, which may improve systemic and local control but also increase the risk of toxicities. Therefore, the risk of long-term toxicities of combination treatments of reirradiation with targeted and immunotherapy warrants critical appraisal in future studies. To the best of our knowledge, comprehensive analyses on the safety of combining reirradiation with novel drugs, as recently published for SBRT [39], are currently lacking but would be of great value to guide clinical practice.

When publishing results of the ongoing and future trials on reirradiation, adherence to ESTRO/EORTC guidelines on reporting technical aspects of reirradiation studies is encouraged for cross-study comparison and implementation in clinical practice. [17] Technical elements, such as deformable registration and dose accumulation, may affect treatment outcomes and should be standardized to ensure safety and reproducibility. [40–42] To facilitate the safe translation of reirradiation treatments from clinical trials into clinical practice, expert consensus guidelines are desirable. While different disease- and technique-specific guidelines on reirradiation have been published, they share a common lack of consensus among participants – due to the scarcity of prospective, high-quality evidence. Measures to allow for regular adaptation of guidelines should be adopted, as in the so-called living guidelines, which receive updates once new trial results are published.

Several limitations should be considered when interpreting the results of this systematic review. While the largest clinical trials registry globally (ClinicalTrials.gov) was searched, additional trials on reirradiation may be ongoing and registered elsewhere. Regardless, the results of this review highlight current trends in reirradiation research and areas where increased efforts are needed to address the lack of evidence. Also, trials incorporating reirradiation as one of several treatment modalities may not have been captured in the search. Moreover, some studies may not explicitly mention reirradiation in their descriptions despite using it, though the number of such trials is considered negligible.

Conclusion

In conclusion, this systematic review highlights both the progress and challenges in reirradiation research across various tumor types. While glioma, head and neck, and prostate cancers dominate ongoing studies, underrepresented areas such as lung, breast, and gynecological malignancies warrant further investigation. The complexity of conducting large RCTs in this domain, due to small patient populations and variability in global practices, underscores the need for innovative trial designs and international collaboration. Moreover, improving quality of life assessments and addressing the long-term safety of combining reirradiation with systemic therapies are critical for future research. Standardized reporting and adherence to guidelines will be essential to advance clinical practice and optimize patient outcomes.

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CRediT authorship contribution statement

Jonas Willmann: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Panagiotis Balermpas:** Writing – review & editing, Conceptualization. **Andreas Rimner:** Writing – review & editing. **Ane L Appelt:** Writing – review & editing. **Eliana Maria Vasquez Osorio:** Writing – review & editing. **Heidi S. Rønde:** Writing – review & editing. **Madalyne Day:** Writing – review & editing. **Anna Embring:** Writing – review & editing. **Dorota Gabryś:** Writing – review & editing. **Marianne G. Guren:** Writing – review & editing. **Peter Hoskin:** Writing – review & editing. **Mariangela Massaccesi:** Writing – review & editing. **Charles Mayo:** Writing – review & editing. **Louise Murray:** Writing – review & editing. **Carsten Nieder:** Writing – review & editing. **Matthias Guckenberger:** Writing – review & editing. **Nicolaus Andratschke:** Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

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