European Journal of Cancer 242 (2026) 116820

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original research

The survival impact of combining radiotherapy and immune checkpoint inhibitors in patients with solid tumors: A systematic review and living meta-analysis of randomized controlled trials☆

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ARTICLE INFO

Keywords:
Immune checkpoint inhibitors
Radiotherapy
Solid tumors
Meta-analysis
Survival

ABSTRACT

Background: Preclinical studies indicate synergistic effects of radiotherapy and immune checkpoint inhibitors (ICIs), yet randomized trials have yielded inconsistent results. We conducted a living systematic review and meta-analysis to evaluate the survival impact of combining radiotherapy with ICIs versus radiotherapy or ICIs alone in solid tumors.

Methods: PubMed and EMBASE were searched for randomized trials (January 2010-January 2026), evaluating two strategies: (1) addition of ICIs to a radiotherapy backbone (immunotherapy trials), and (2) addition of radiotherapy to an ICI backbone (radiotherapy trials). Risk of bias was assessed with RoB-2. Hazard ratios (HRs) for overall survival (OS), progression-free survival (PFS), and event-free survival (EFS) were pooled using random-effects models. Meta-regression explored subgroup effects.

Results: Of 4447 unique records, 41 trials (15,049 patients) were included: 35 ICIs versus no ICIs and 6 radiotherapy versus no radiotherapy trials. Methodological quality was high. Across ICI trials, the pooled HR for OS was 0.88 (95%CI 0.75–1.02; n = 28), reaching statistical significance after exclusion of glioblastoma trials (pooled HR 0.83, 95%CI 0.70–0.99; n = 23). For PFS and EFS, pooled HRs were 0.80 (95%CI 0.68–0.93; n = 27) and 0.73 (95%CI 0.55–0.99; n = 7), respectively. Adjuvant ICIs conferred greater benefit than concurrent/induction for OS (pooled HR 0.81 versus 0.98; interaction p = 0.045) and PFS (pooled HR 0.69 versus 0.94; interaction p = 0.013).

Conclusions: This meta-analysis provides a field-wide overview of randomized trials on combining radiotherapy and ICIs. Addition of ICIs to a radiotherapy backbone improves PFS/EFS and yields an OS benefit after exclusion of glioblastoma trials, highlighting tumor-specific heterogeneity. Sequencing appears critical, with greatest benefit observed for adjuvant ICIs. The living meta-analysis is available at https://www.immunorad.org/clinical-evidence.

☆ Manuscript type: Systematic review and meta-analysis. A living version of this meta-analysis has been developed to enable periodic updates of the evidence base. The results will be systematically updated every six months and made publicly available online at: https://immunorad.org/clinical-evidence

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https://doi.org/10.1016/j.ejca.2026.116820
Received 17 March 2026; Received in revised form 13 May 2026; Accepted 14 May 2026
Available online 25 May 2026
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1. Introduction

Over the past decade, there has been increasing interest in combining radiotherapy with immune checkpoint inhibitors (ICIs), as a strategy to potentiate anti-tumor immunity [1,2]. Radiotherapy not only induces DNA damage and tumor cell death, but also exerts immunomodulatory effects by activating the cGAS–STING–type I interferon axis, enhancing tumor antigen presentation and dendritic cell maturation, and promoting T-cell recruitment and infiltration into the tumor microenvironment, thereby initiating or amplifying anti-tumor immune responses [3,4].

Preclinical studies across multiple tumor models have demonstrated robust synergy between radiotherapy and ICIs [5–10], providing the rationale for numerous clinical trials. In pivotal phase III trials such as PACIFIC and CheckMate-577 [11,12], the addition of ICIs following chemoradiotherapy (CRT) improved survival outcomes in non-small cell lung cancer (NSCLC) and esophageal cancer, respectively. However, clinical results have not been uniformly positive. Although Checkmate-577 reported substantial improvement in disease free survival (DFS), OS improvement was modest and not significant for the overall patient population [12]. Negative outcomes from trials such as CheckMate-548 in glioblastoma and JAVELIN Head and Neck 100 in locally advanced head and neck squamous cell carcinoma (HNSCC) highlight potential limitations related to tumor-intrinsic resistance, suboptimal treatment sequencing, and the immunosuppressive effects of radiotherapy itself [13,14]. Emerging data further suggest that radiotherapy can both stimulate and suppress anti-tumor immune responses, with its net effect depending on dose, fractionation, treatment sequencing, irradiated volume and field design, and the underlying tumor immune microenvironment, thereby influencing the systemic efficacy of ICIs [15,16].

Despite these advances, the overall clinical value of combining radiotherapy with ICIs remains uncertain and appears to vary according to tumor type, treatment intent, and sequencing strategy. Previous reviews have primarily focused on mechanistic rationales or individual tumor types, and a comprehensive quantitative synthesis of randomized trial data across all solid tumors is lacking [17–20]. To address this evidence gap, we conducted a living systematic review and meta-analysis of completed randomized controlled trials (RCTs) in patients with solid tumors to evaluate the survival impact of combining radiotherapy with ICIs, compared with radiotherapy alone or ICIs alone.

2. Methods

This living systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. The study protocol was prospectively registered in the PROSPERO international database (CRD42024596888, http://www.crd.york.ac.uk/prospero). Future updates of the present living systematic review will remain focused on ICIs to preserve methodological consistency over time. If randomized evidence on other immunotherapeutic strategies in combination with radiotherapy becomes sufficiently mature, the same methodology could be applied in a separate review or in an explicitly expanded review scope.

2.1. Living systematic review and meta-analysis

Given the rapidly evolving nature of this research field, this study was designed as a living systematic review [22]. The literature search will be updated every six months using the same predefined search strategy and eligibility criteria, with newly eligible studies incorporated into the meta-analysis and updated results made publicly available on a dedicated website (https://immunorad.org/clinical-evidence).

2.2. Search strategy

PubMed (MEDLINE) and EMBASE were systematically searched from January 1, 2010, to January 15, 2026, using Medical Subject Headings (MeSH) and title/abstract keywords related to “cancer”, “radiotherapy”, and “immunotherapy” or “radioimmunotherapy”, and synonyms combined with terms for “randomized trial”. Searches were limited to human trials, written in English or Dutch, and published after 2010, which corresponds to the year when ICIs began entering prospective clinical testing [22]. Broad immunotherapy-related search terms were used to maximize sensitivity, but eligibility was restricted to trials evaluating ICIs. The full search strategy is provided in Supplementary Material 1. Reference lists of all included articles and relevant reviews were additionally screened to identify further eligible trials (i.e., cross-referencing).

2.3. Trial selection

After deduplication in Rayyan (Qatar Computing Research Institute), two investigators (CP and MT) independently screened titles and abstracts. Eligible records described RCTs in adult patients with cancer and involving both radiotherapy and immunotherapy. Full-text review was restricted to phase II-III RCTs in adults with solid tumors, directly comparing a combination of radiotherapy and immunotherapy with radiotherapy alone or immunotherapy alone. Only trials using ICIs were included. This restriction was chosen because ICIs represent the immunotherapeutic class for which randomized evidence in combination with radiotherapy is currently sufficiently mature and clinically comparable. Immunotherapy studies investigating vaccines or targeted therapies were excluded. Trials in which patients had already received neoadjuvant ICIs before randomization were excluded to ensure that the control group had not already been exposed to ICIs.

Included trials were required to report a hazard ratio (HR) with 95% confidence interval (CI) for overall survival (OS), progression-free survival (PFS), DFS and/or event-free survival (EFS). DFS was considered equivalent to PFS when defined as time to disease progression or death. When multiple reports from the same trial were available, the most complete and recent version was used. Disagreements were resolved through discussion with a third investigator (PR).

2.4. Data extraction

From each included trial, data were extracted on trial characteristics (e.g. first author, year, trial acronym, primary trial determinant, follow-up duration), patient demographics (e.g. sample size, age, tumor type, disease stage), and treatment details (e.g. type of radiotherapy, type of ICIs, treatment sequence). HRs with 95%CIs were collected for OS, PFS, DFS and EFS, preferentially from intention-to-treat analyses. In three-arm randomized trials with two experimental arms sharing one control group, HRs were pooled using inverse variance weighting with a correlation adjustment ($\rho = 0.5$) to avoid double-counting. All HRs were oriented in the same direction, with combined radiotherapy-ICIs as the experimental group and radiotherapy or ICIs alone as the reference group. CIs were converted to 95%CIs when reported at other levels.

2.5. Risk of bias assessment

Two investigators (CP and MT) independently assessed the risk of bias using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [23]. Five domains of bias were evaluated and scored as low risk, some concerns or high risk. Authors were contacted when key methodological details were unclear. A full description of the quality assessment is provided in Supplementary Material 2.

2.6. Statistical analysis

Meta-analyses were conducted using random-effects models to calculate pooled HRs comparing combined radiotherapy-ICIs versus radiotherapy or ICIs alone. Log HRs and their standard errors were used as effect measures. Analyses were performed separately for trials comparing ICIs versus no ICIs (in patients receiving radiotherapy as standard of care), or radiotherapy versus no radiotherapy (in patients receiving ICIs as standard of care), as these trial types differ fundamentally in objectives and comparator arms. Between-trial heterogeneity was quantified using the I^2 statistic, with values of 30–60% considered moderate, and values of 50–90% considered substantial, in accordance with the Cochrane Handbook for Systematic Reviews [24].

Subgroup analyses were performed using meta-regression to explore the impact of trial-level characteristics on survival outcomes. Nineteen predefined covariates were examined, including publication format (abstract-only trials versus peer-reviewed manuscripts), age (>60 versus ≤60), chemotherapy (CRT versus radiotherapy), design (phase II versus III, open-label versus blinded), elective nodal irradiation, follow-up (<30 months versus ≥30 months), geographic region (Western, Eastern, or global), publication year, surgical intervention (no, post-radiotherapy and pre-radiotherapy), sample-size, sex (male percentage <70% and ≥70%), tumor type, type of ICI (anti-PD-L1, anti-PD-1, or anti-CTLA-4), timing of first ICI administration (induction, concurrent, adjuvant), and type of radiotherapy (CRT, SABR, and radiotherapy alone). Patients receiving ICIs across multiple phases (e.g. induction, concurrent, and adjuvant) were classified under the induction category, reflecting the timing of first ICI administration. In addition, a four-category analysis was performed combining (chemo)radiotherapy with ICI timing: CRT with non-adjuvant ICI, CRT with adjuvant ICI, RT with non-adjuvant ICI, and RT with adjuvant ICI.

Cutoffs for subgroup comparisons were determined to ensure balanced sample sizes. For each subgroup analysis, the R^2 statistic and interaction p-value for heterogeneity were calculated to estimate the proportion of total heterogeneity explained by the subgroups. A stratified pooled HR was calculated per subgroup, using the category with the highest number of trials as the reference. Glioblastoma trials were included in the primary overall evidence synthesis. Because subgroup exploration indicated that glioblastoma trials differed from other tumor types and materially influenced the pooled estimate, we performed an

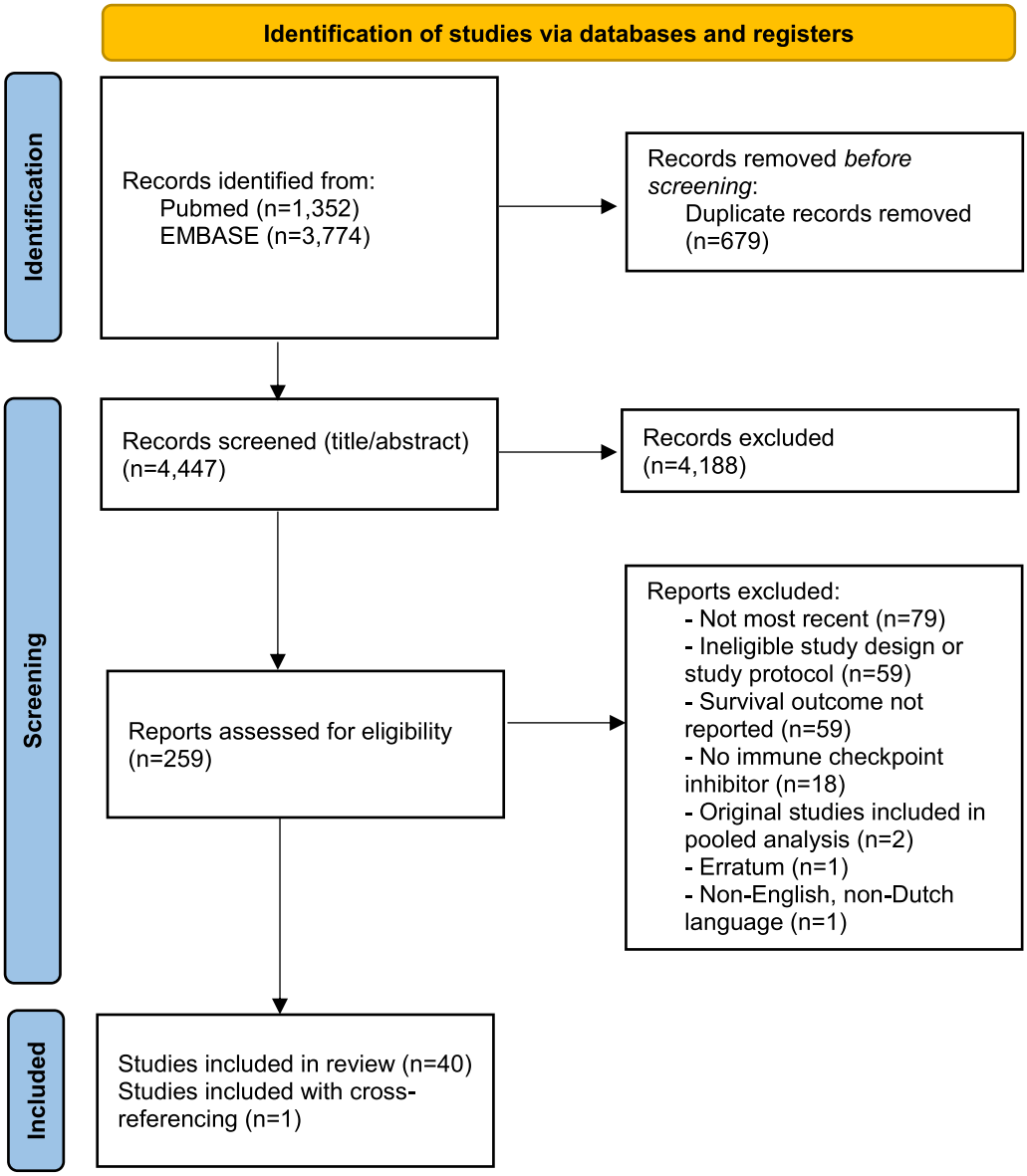

Fig. 1. Flowchart summarizing search results and trial selection.

exploratory post-hoc sensitivity analysis excluding these trials. Results are reported both including and excluding glioblastoma, and this approach will be maintained in future updates when sufficient data are available.

Analyses were performed using R software (version 2025.05.1 +513; R Foundation for Statistical Computing, Vienna, Austria) with the 'metafor' package. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Trial selection

A total of 5126 records were identified through the systematic search. After the removal of 679 duplicates, titles and abstracts of 4447 unique records were screened. Of these, 4188 records were excluded based on predefined eligibility criteria. The remaining 259 articles were assessed by full-text review. Reasons for exclusion were: not the most recent report (n = 79), ineligible study design or study protocol (n = 59), no reported survival outcomes (n = 59), no ICIs (n = 18), original trials included in pooled analysis (n = 2), erratum (n = 1) and non-English or non-Dutch language (n = 1). One additional trial was identified through cross-referencing [25]. In total, 41 randomized trials met all inclusion criteria and were included in the quantitative synthesis (Fig. 1)

3.2. Included trial and patient characteristics

Of the 41 included trials, summarized trial characteristics are provided in Table 1. These trials included a total of 15,049 patients of which 7990 received combined radiotherapy and ICIs, while 7059 received radiotherapy alone (n = 6793) or ICIs alone (n = 266). Disease stage varied substantially across the included trials and is reported for each trial in Table 1. Briefly, the evidence base included trials in locally advanced, postoperative/adjuvant, recurrent, and metastatic disease settings, reflecting important clinical heterogeneity in treatment intent and ICI sequencing.

Across all trials, the median sample size was 381 patients (interquartile range [IQR]: 103–560) and the median age was 62 years (IQR: 59–66). The median follow-up duration was 32 months (IQR: 21–38). Most trials focused on lung or brain malignancies, with ten trials (25%) investigating NSCLC [26–35] and six (15%) investigating small-cell lung cancer (SCLC) [25,36–40]. There were five trials (12%) in glioblastoma [13,41–44], and five (12%) in head and neck cancer [14,45–48]. Other tumor types included nasopharyngeal cancer (n = 3; 8%) [49–51], cervical cancer (n = 3; 8%) [52–54], esophageal or gastroesophageal junction cancer (n = 2; 5%) [12,55], cutaneous squamous-cell carcinoma (n = 2; 5%) [56,57] and one trial each (2%) focusing on sarcoma [58], kidney [59], pancreatic [60], or prostate cancer [61]. One trial included patients with various advanced solid tumors, such as melanoma, renal cell carcinoma, urothelial carcinoma, head and neck squamous cell carcinoma, or NSCLC [62].

Twenty-two (54%) trials were conducted across multiple countries, and 33 (81%) were multicenter. Nineteen trials (46%) were phase II trials, and 22 (54%) were phase III. Twenty-two trials (54%) employed an open-label design, while 19 (46%) were blinded. Sixteen trials (39%) were conducted in Western countries, 15 (37%) globally, and ten (24%) in Eastern countries. Thirty-five trials (85%) assessed the addition of ICIs to standard-of-care radiotherapy, whereas six trials (15%) assessed the addition of radiotherapy to standard-of-care ICIs. Of the 35 trials evaluating ICIs versus no ICIs, 28 trials (80%) reported HRs for OS, 27 (77%) for PFS, and 7 (20%) for EFS. Of the six trials comparing radiotherapy with no radiotherapy, five trials (83%) reported HRs for OS, all six (100%) reported HRs for PFS, and none reported EFS.

3.3. Risk of bias

A detailed overview of the risk-of-bias assessment is provided in Supplementary Material 2. Overall, 25 trials (62%) were judged low risk, eight (19%) raised some concerns, and eight (19%) were high risk, including three abstract-only studies. Overall methodological quality was high, with limitations mainly related to outcome measurement and deviations from intended interventions.

3.4. ICIs added to radiotherapy

Across trials evaluating the addition of ICIs to radiotherapy, pooled analyses of all trials showed no significant OS benefit (HR 0.88, 95% CI 0.75–1.02; n = 28; p = 0.083), whereas OS became significant after excluding glioblastoma trials (HR 0.83, 95% CI 0.70–0.99; n = 23; p = 0.034; Fig. 2). PFS was significantly improved in all trials (HR 0.80, 95% CI 0.68–0.93; n = 27; p = 0.003), with greater effect after excluding glioblastoma trials (HR 0.72, 95% CI 0.61–0.86; p < 0.001; Fig. 3). Similarly, EFS, reported in seven trials, was also improved (HR 0.73, 95% CI 0.55–0.99; p = 0.041; Supplementary Figure 1).

None of the five glioblastoma trials (CheckMate-498 [41], Ipi-Glio [42], NUTMEG [43], STERIMGLI [44], and CheckMate-548 [13]) demonstrated a statistically significant OS benefit (pooled HR OS 1.06 95%CI 0.76–1.46). For PFS, CheckMate-498 [41] showed a statistically significant adverse effect, whereas Ipi-Glio [42], NUTMEG [43], STERIMGLI [44], and CheckMate-548 [13], did not show significant effects (pooled PFS HR 1.13, 95%CI 0.80–1.58).

In head and neck cancer, KEYNOTE-689 [47] demonstrated a significant OS benefit, while KEYNOTE-412 [45], IMvoke010 [48], and JAVELIN [14] did not (pooled HR 0.93, 95%CI 0.64–1.34). For PFS, NIVOPOST-OP [46] showed a significant benefit, whereas JAVELIN [14] did not (pooled HR 0.95,95%CI 0.58–1.57). EFS analyses indicated a significant benefit in KEYNOTE-689 [47] and KEYNOTE-412 [45], but not in IMvoke010 [48] (pooled HR 0.81, 95%CI 0.55–1.19).

In nasopharyngeal carcinoma, neither DIPPER [49] nor CONTINUUM [51] showed significant OS advantage (pooled HR 0.84, 95%CI, 0.37–1.86). PFS was reported in a single trial (B2019–014–01) [50], which demonstrated a significant reduction in risk (HR 0.40, 95%CI, 0.18–0.89). Although both DIPPER [49] and CONTINUUM [51] showed significant effects for EFS individually, the pooled estimate was not significant (pooled HR 0.57, 95%CI 0.30–1.11).

Within NSCLC, GEMSTONE-301 [26] and PACIFIC [27] demonstrated significant OS benefit, whereas PACIFIC-5 [29] and PACIFIC-2 [35] did not(pooled HR 0.77, 95%CI, 0.53–1.12). For PFS, Intrist [30], PACIFIC [27], GEMSTONE-301 [26], and PACIFIC-5 [29] were significant, while PACIFIC-2 [35] was not, resulting in a significant pooled HR of 0.65 (95%CI, 0.46–0.91). For EFS, I-SABR [34] was significant, KEYNOTE-867 was not [28](pooled HR 0.70, 95%CI 0.33–1.45). In SCLC, ADRIATIC [36] demonstrated a significant OS benefit, whereas AdvanTIG-204 [39], STIMULI [38], and NRG/Alliance LU005 [25] were not significant (pooled OS HR 0.89, 95%CI 0.60–1.31). For PFS, only ADRIATIC [36] showed significant benefit, while 2019-FXY-243 [37], AdvanTIG-204 [39], STIMULI [38], and NRG/Alliance LU005 [25] did not (pooled HR 0.83, 95%CI 0.57–1.21).

In esophageal cancer, neither CheckMate-577 [12] nor ESR-14–10737 [55] demonstrated a statistically significant OS benefit (pooled HR 0.89, 95%CI 0.51–1.55). For PFS, CheckMate-577 showed significant improvement [12], whereas ESR-14–10737 [55] did not (pooled HR 0.84, 95%CI 0.49–1.42). The single pancreatic cancer trial (Zhu et al. [60]) demonstrated significant benefit for both OS (HR 0.69, 95%CI, 0.51–0.94) and PFS (HR 0.60, 95%CI, 0.44–0.81). In cervical cancer, neither KEYNOTE-A18 [52] nor CALLA [53] showed a statistically significant OS benefit (pooled HR was 0.72, 95%CI 0.41–1.26). For PFS, KEYNOTE-A18 [52] was significant, whereas ATEZOLACC [54] and CALLA [53] were not (pooled HR 0.75, 95%CI 0.49–1.15). In prostate cancer, a single trial (CA184–043) [61] demonstrated

Table 1
Trial and patient characteristics. Due to the large size, the table starts at the next page.

First Author, year	Acronym	Tumor type	Type of RT	Type of ICI	ICI timing	TNM stage	Disease stage	First Therapy	RIT < 30 days	n	Age*	FU
Trials comparing immune checkpoint inhibitors versus no immune checkpoint inhibitors in patients receiving radiotherapy as standard of care												
Bourhis, 2025 [46]	NIVOPOST-OP	HNSCC	CRT	Nivolumab	Concurrent + Adjuvant	I-IV	All	ICI	Yes	666	59	30.3
Bradley, 2024 [35]	PACIFIC-2	NSCLC	CRT	Durvalumab	Concurrent + Adjuvant	III	LA	ICI	Yes	327	NR	30.5
Brown, 2025 [42]	Ipi-Glio	Glioblastoma	CRT	Ipilimumab	Adjuvant	NR	NR	RT	NR	119	54	NR
Cabarrou, 2025 [44]	STERIMGLI	Glioblastoma	SABR	Durvalumab	Concurrent + Adjuvant	NR	NR	RT	Yes	102	61.5	34.1
Chargari, 2025 [54]	ATEZOLACC	Cervical	CRT	Atezolizumab	Concurrent + Adjuvant	IB2-IVB	All	ICI	Yes	189	NR	33.6
Chang, 2023 [34]	I-SABR	NSCLC	SABR	Nivolumab	Concurrent + Adjuvant	I-II	ES	RT	Yes	156	72	33
Cheng, 2024 [36]	ADRIATIC	SCLC	CRT	Durvalumab or tremelimumab	Adjuvant	I-III	ES-LA	RT	Yes	530	62	37.2
Fizazi, 2020 [61]	CA184–043	Prostate	Conventional	Ipilimumab	Adjuvant	IV	MS	RT	Yes	799	68.3	28.8
Gong, 2025 [39]	AdvanTIG-204	SCLC	CRT	Tislelizumab or ociperlimab	Concurrent + Adjuvant	I-III	ES-LA	ICI	Yes	85	61.5	18.5
Haddad, 2025 [48]	IMvoke010	HNSCC	CRT	Atezolizumab	Adjuvant	III-IV	LA-MS	RT	No	406	59.4	46.5
Higgins, 2026 [25]	NRG/Alliance LU005	SCLC	CRT	Atezolizumab	Concurrent + Adjuvant	I-III	ES-LA	RT	Yes	544	66	23.8
Kelly, 2025 [12]	CheckMate 577	Esophageal	CRT	Nivolumab	Adjuvant	II-III	LA	RT	No	794	61.7	24.4
Koyfman, 2025 [57]	Keynote-630	Cutaneous SCC	Conventional	Pembrolizumab	Adjuvant	NR	NR	RT	No	450	NR	28.6
Lee, 2021 [14]	JAVELIN	HNSCC	CRT	Avelumab	Concurrent + Adjuvant	III-IVB	LA-MS	ICI	Yes	697	59.5	14.6
Liang, 2025 [49]	DIPPER	Nasopharyngeal	CRT	Camrelizumab	Adjuvant	III-IVA	LA-MS	RT	No	450	NR	37
Lim, 2022 [13]	CheckMate 548	Glioblastoma	CRT	Nivolumab	Concurrent + Adjuvant	NR	NR	SD	Yes	709	60	16
Liu, 2024 [51]	CONTINUUM	Nasopharyngeal	CRT	Sintilimab	Induction + Concurrent + Adjuvant	III-IVA	LA-MS	ICI	Yes	425	46	50.6
Liu, 2024 [50]	B2019–014–01	Nasopharyngeal	CRT	Toripalimab	Induction + Adjuvant	III-IVA	LA-MS	ICI	Yes	150	46.8	37.7
Lorusso, 2024 [52]	KEYNOTE-A18	Cervical	CRT	Pembrolizumab	Concurrent + Adjuvant	III-IVA	LA-MS	SD	Yes	1060	49.5	29.9
Monk, 2023 [53]	CALLA	Cervical	CRT	Durvalumab	Concurrent + Adjuvant	III-IVA	LA-MS	SD	Yes	770	49	18.5
Mowery, 2024 [58]	SU2C-SARC032	Sarcoma	Conventional	Pembrolizumab	Concurrent + Adjuvant	III	LA	ICI	Yes	143	59.5	43.1
Omuro, 2022 [41]	CheckMate 498	Glioblastoma	CRT	Nivolumab	Concurrent + Adjuvant	NR	NR	SD	Yes	560	57.8	13.0
Park, 2022 [55]	ESR-14–10737	Esophageal	CRT	Durvalumab	Adjuvant	II-III	LA	RT	No	86	65	38.7
Peters, 2021 [38]	STIMULI	SCLC	CRT	Nivolumab + Ipilimumab	Adjuvant	I-III	ES-LA	RT	No	153	61.6	35
Pircher, 2024 [28]	KEYNOTE-867	NSCLC	SABR	Pembrolizumab	Concurrent + Adjuvant	I-II	ES	SD	Yes	448	73	20.6
Rischin, 2025 [56]	-	Cutaneous SCC	Conventional	Cemiplimab	Adjuvant	NR	NR	RT	Yes	415	61.5	24
Sim, 2023 [43]	NUTMEG	Glioblastoma	CRT	Nivolumab	Adjuvant	NR	NR	RT	No	103	73	37
Spigel, 2022 [27]	PACIFIC	NSCLC	CRT	Durvalumab	Adjuvant	III	LA	RT	Yes	713	64	34.2
Tao, 2025 [45]	KEYNOTE-412	HNSCC	CRT	Pembrolizumab	Induction + Concurrent + Adjuvant	III-IV	LA-MS	ICI	Yes	804	58.7	74.4
Uppaluri, 2025 [47]	KEYNOTE-689	HNSCC	CRT	Pembrolizumab	Induction + Concurrent + Adjuvant	III-IV	LA-MS	ICI	Yes	714	60	38.3
Wang, 2025 [30]	InTRist	NSCLC	CRT	Toripalimab	Induction + Adjuvant	III	LA	ICI	Yes	52	NR	13.1
Wu, 2025 [29]	PACIFIC-5	NSCLC	CRT	Durvalumab	Adjuvant	III	LA	RT	Yes	381	63	36.5
Zhang, 2024 [37]	2019-FXY-243	SCLC	CRT	Toripalimab	Adjuvant	I-III	ES-LA	RT	NR	64	59	25
Zhou, 2022 [26]	GEMSTONE 301	NSCLC	CRT	Sugemalimab	Adjuvant	III	LA	RT	Yes	381	60.5	14.0

(*continued on next page*)

Table 1 (*continued*)

First Author, year	Acronym	Tumor type	Type of RT	Type of ICI	ICI timing	TNM stage	Disease stage	First Therapy	RIT < 30 days	n	Age*	FU
Zhu, 2022 [60]	-	Pancreatic	SABR	Pembrolizumab + Trametinib	Adjuvant	III	LA	RT	Yes	170	65.5	13.1
Trials comparing radiotherapy versus no radiotherapy in patients receiving immune checkpoint inhibitors as standard of care												
Li, 2022 [59]	-	Kidney	SABR	Nivolumab + Ipilimumab	Concurrent + Adjuvant	IV	MS	SD	Yes	44	61.6	NR
Kothari, 2025 [32]	NIVORAD	NSCLC	SABR	Nivolumab	Concurrent + Adjuvant	IV	MS	ICI	Yes	50	66	26
Owonikoko, 2019 [40]	NCI-2016–00026	SCLC	SABR	Durvalumab + Tremelimumab	Adjuvant	IV	MS	RT	Yes	15	70	NR
Schoenfeld, 2022 [31]	NCI-2016–01325	NSCLC	Conventional	Durvalumab + Tremelimumab	Concurrent + Adjuvant	IV	MS	SD	Yes	78	66	12.4
Spaas, 2023 [62]	CHEERS	Advanced solid	SABR	Nivolumab + Atezolizumab + Pembrolizumab	Concurrent + Adjuvant	III-IV	LA-MS	ICI	Yes	99	67	12.5
Theelen, 2021 [33]	PEMBRO-RT & MDACC	NSCLC	SABR	Pembrolizumab	Concurrent + Adjuvant	IV	MS	RT	Yes	148	64.5	33

ES = early-stage. FT = First Therapy. ICI = immune checkpoint inhibitor. LA= locally advanced. MS = metastatic. PO = postoperative. RT = Radiotherapy. RIT = radioimmunotherapy. NR = not reported. NSCLC = Non-Small-Cell Lung Cancer. SCLC = Small-Cell Lung Cancer. CRT = chemoradiotherapy. SABR = Stereotactic Ablative Radiation Therapy. SCC = squamous cell carcinoma. SD= Same day.
* Age in median years.
** Follow-up in median months.

significant OS benefit (HR 0.66, 95%CI 0.52–0.84). In sarcoma, SU2C-SARC032 [58] did not demonstrate significant benefit for OS (HR 0.67, 95%CI 0.33–1.38) or PFS (HR 0.61, 95%CI 0.36–1.04). In cutaneous squamous-cell carcinoma, neither the trial from Rischin et al. [56] nor KEYNOTE-630 [57] demonstrated significant OS benefit (pooled HR 1.19, 95%CI 0.54–2.61). For PFS, Rischin et al. [56] showed significant reduction in risk, whereas KEYNOTE-630 [57] did not (pooled HR 0.51, 95%CI, 0.22–1.18).

3.5. Radiotherapy added to ICIs

Six trials evaluated radiotherapy versus no radiotherapy. Five studies delivered radiotherapy to metastatic lesions, whereas the NCI-2016–00026 trial [40] targeted recurrent disease. Radiotherapy target volumes were not reported in detail. Radiotherapy dose-fractionation schedules varied across trials, including NCI-2016–01325 [31] (2 Gy in 4 bidaily fractions or 24 Gy in 3 fractions), NIVORAD [32] (18–20 Gy in 1 fraction), PEMBRO-RT and MDACC [33] (24 Gy in 3 fractions, 50 Gy in 4 fractions, or 45 Gy in 15 fractions), Li et al. [59] (50 Gy in 5 fractions), CHEERS [62] (24 Gy in 3 fractions), and NCI-2016–00026 [40] (27 Gy in 3 fractions). In NSCLC, PEMBRO-RT & MDACC [33] demonstrated significant benefit for both OS and PFS, whereas NIVORAD [32] and NCI-2016–01325 [31] were not significant for either endpoint. The pooled HR was 0.84 (95%CI, 0.51–1.40) for OS and 0.84 (95%CI, 0.48–1.45) for PFS. In SCLC, evidence was restricted to a single trial (NCI-2016–00026) [40], showing no significant effect on OS (HR 0.67, 95%CI 0.20–2.22), or on PFS (HR 0.41, 95%CI 0.1–1.33). In kidney cancer, single-trial evidence (Li et al. [59]) showed a potential benefit for OS (HR 0.39, 95%CI 0.17–0.93), while the effect on PFS was non-significant (HR 0.53, 95%CI 0.25–1.14). In advanced solid tumors, a single trial (CHEERS [62]) showed no significant effect on OS (HR 0.82, 95%CI 0.48–1.41), or on PFS (HR 0.95, 95%CI 0.58–1.53). When pooling all tumor types combined, radiotherapy was not associated with a statistically significant improvement in outcomes (pooled HR 0.76 for OS (95%CI 0.50–1.15; p = 0.198) and a pooled HR of 0.77 for PFS (95% CI 0.50–1.18; p = 0.224) (Supplementary Figures 2 and 3).

3.6. Subgroup analyses

Subgroup analyses for ICI versus no ICI trials are presented in Table 2 (OS) and Table 3 (PFS). Adjuvant administration, defined as ICIs administered in the adjuvant phase as the timing of first ICI after radiotherapy (as opposed to induction or concurrent ICI as the timing of first administration), emerged as a key determinant. The pooled HR for OS was 0.81 (95%CI 0.64–1.01, n = 14) versus a pooled HR of 0.98 (95%CI 0.77–1.25, n = 10, interaction p = 0.045). For PFS, the pooled HR for adjuvant timing was 0.69 (95%CI 0.55–0.87, n = 13) versus a pooled HR of 0.94 (95%CI 0.76–1.18, n = 11) for concurrent timing (interaction p = 0.013). In the four-level analysis combining (C)RT modality and timing of ICI, CRT with non-adjuvant ICI served as the reference category. A statistically significant PFS benefit was observed for RT combined with adjuvant ICI (pooled HR 0.55, 95%CI 0.34–0.90; n = 3), compared with CRT and non-adjuvant ICI (pooled HR 0.90, 95% CI 0.72–1.13; n = 11; interaction p = 0.008). In contrast, CRT with adjuvant ICI (pooled HR 0.74, 95%CI 0.57–0.95; n = 10; interaction p = 0.141) and RT with non-adjuvant ICI (pooled HR 0.76, 95%CI 0.43–1.35; n = 3; interaction p = 0.427) were not statistically different from the reference category.

The subgroup analyses for radiotherapy versus no radiotherapy trials were only possible for PFS (Table 4). The pooled effect estimates differed significantly between trials evaluating anti-PD-L1 ICIs and those evaluating other types of ICIs (HR 0.64, 95%CI 0.35–1.16 versus HR 0.93, 95%CI 0.51–1.71, interaction p = 0.038).

4. Discussion

This living systematic review and meta-analysis of completed randomized trials demonstrates a significant overall improvement in PFS and EFS with the addition of ICIs to standard-of-care radiotherapy in patients with solid tumors. This benefit was more pronounced in a post-hoc sensitivity analysis after exclusion of glioblastoma trials, at which point an OS advantage also emerged, suggesting that the efficacy of the combination of radiotherapy and ICIs may be tumor-type dependent. In contrast, trials evaluating the addition of radiotherapy to ICIs showed favorable trends in survival outcomes, but these did not reach statistical significance, possibly owing to the limited number of trials and between-study heterogeneity. Overall, our findings support the use of combined radiotherapy and ICIs in selected clinical contexts and provide a meta-level overview of where these strategies currently deliver the greatest survival gains.

The timing of immune checkpoint inhibition appears to influence therapeutic synergy with radiotherapy. At the meta-regression level, greater benefit was observed when ICIs were administered after (i.e. adjuvant to) radiotherapy rather than before or during treatment, and

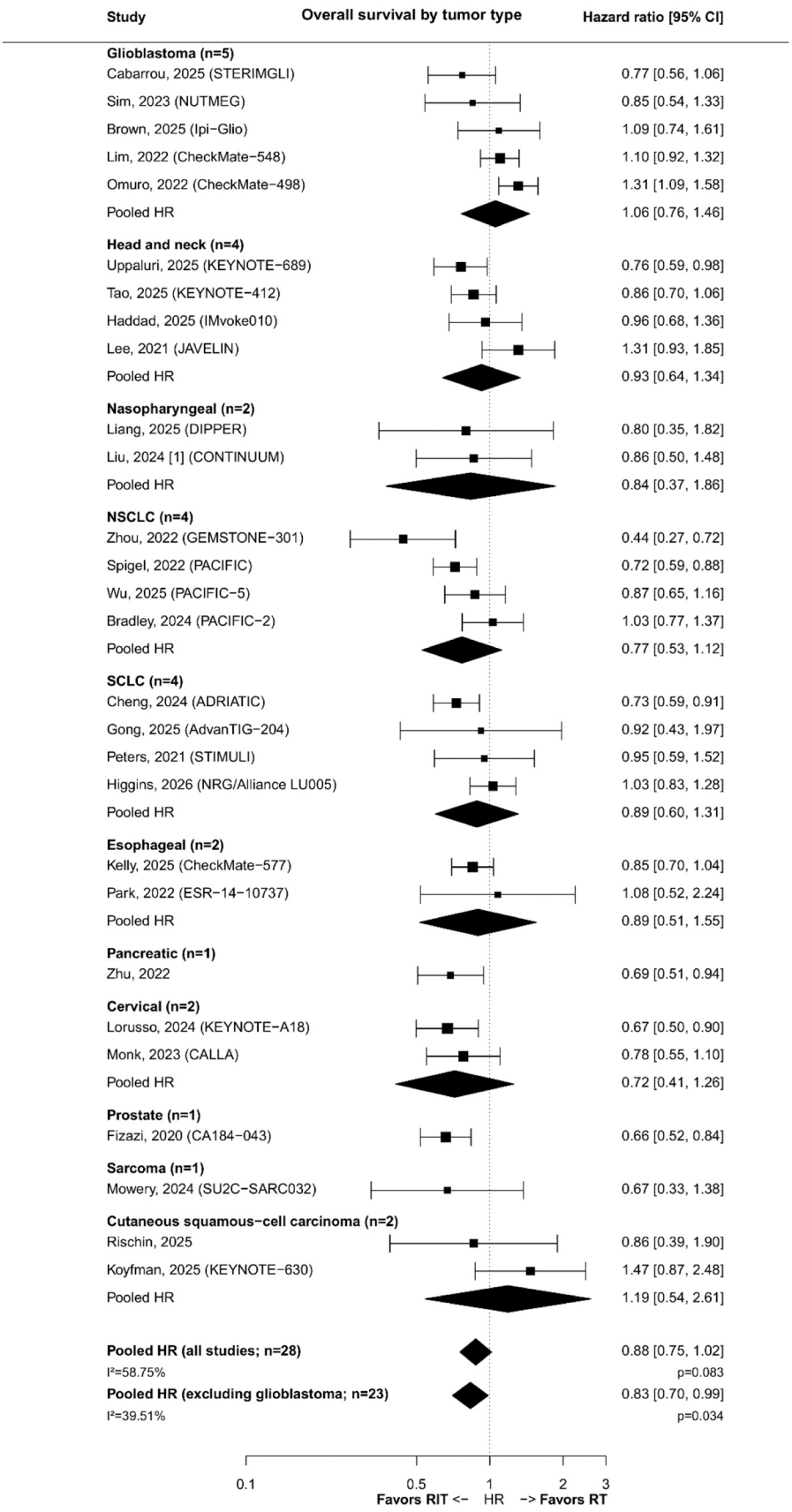

Fig. 2. Forest plots of pooled hazard ratios for overall survival per tumor type and of all trials in- and excluding glioblastoma.

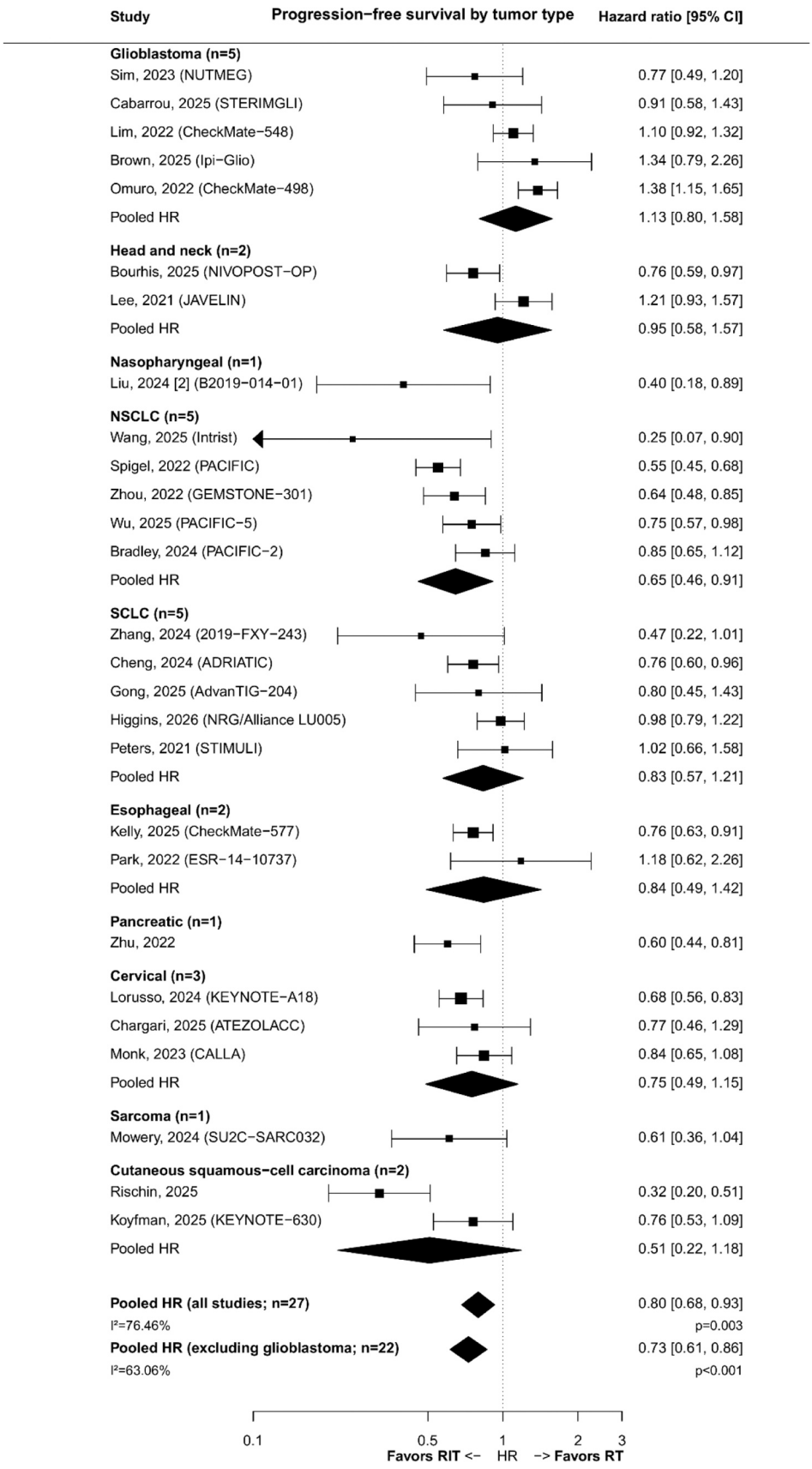

Fig. 3. Forest plots of pooled hazard ratios for progression-free survival per tumor type and of all trials in- and excluding glioblastoma.

Table 2
Results from trial-level subgroup analyses for trials comparing immune checkpoint inhibitors versus no immune checkpoint inhibitors in patients receiving radiotherapy on overall survival.

Factor	n	Stratified HR (95%CI)	*p*-value	I^2 (%)	R^2 (%)
Abstract only			0.359	60.0	0.0
No	24	0.86 (0.73–1.02)			
Yes	3	1.00 (0.62–1.62)			
Age			0.317	55.7	7.4
> 60	13	0.82 (0.66–1.03)			
≤ 60	13	0.91 (0.73–1.14)			
	1	Not reported			
Chemotherapy addition			0.256	56.7	8.1
Chemoradiotherapy	21	0.90 (0.76–1.07)			
Radiotherapy	6	0.78 (0.54–1.12)			
(C)RT and timing ICI				53.3	17.9
CRT and non-adjuvant ICI	11	0.97 (0.78–1.21)	Ref		
CRT and adjuvant ICI	10	0.81 (0.62–1.06)	0.116		
RT and adjuvant ICI	4	0.80 (0.52–1.23)	0.185		
RT and non-adjuvant ICI	2	0.74 (0.38–1.42)	0.227		
Design			0.761	60.1	0.0
phase II	8	0.85 (0.61–1.19)			
phase III	19	0.89 (0.74–1.05)			
Elective nodal irradiation			0.894	60.1	0.0
No	21	0.88 (0.74–1.05)			
Yes	6	0.86 (0.61–1.21)			
Follow-up			0.337	57.3	3.9
< 30 months	13	0.93 (0.75–1.15)			
≥ 30 months	14	0.83 (0.67–1.03)			
Glioblastoma trial			**0.029***	47.6	34.1
No	22	0.83 (0.70–0.99)			
Yes	5	1.06 (0.76–1.46)			
Global location				58.0	2.6
Global	13	0.90 (0.74–1.10)	Ref		
Eastern	6	0.73 (0.48–1.12)	0.145		
Western	8	0.90 (0.67–1.21)	0.991		
Male percentage treatment group			0.517	61.4	0.0
< 70%	8	0.95 (0.73–1.23)			
≥ 70%	11	0.85 (0.65–1.11)			
	8	Not reported			
Sample size			0.761	60.1	0.0
< 300	8	0.85 (0.61–1.19)			
≥ 300	19	0.89 (0.74–1.05)			
Type of ICI					
anti CTLA4			0.787	59.8	0.0
No	24	0.88 (0.75–1.04)			
Yes	3	0.83 (0.52–1.33)			
anti PD1			0.524	58.7	0.0
No	13	0.85 (0.68–1.05)			
Yes	14	0.91 (0.73–1.14)			
anti PDL1			0.714	59.7	0.0
No	16	0.90 (0.73–1.10)			
Yes	11	0.85 (0.68–1.08)			
Open or blind design			0.563	58.7	0.0
Blind	15	0.85 (0.70–1.04)			
Open	12	0.91 (0.72–1.17)			
Publication before 2025			0.449	59.8	0.0
No	11	0.92 (0.71–1.18)			
Yes	16	0.85 (0.70–1.04)			
Radiotherapy type			0.256	58.4	1.0
Chemoradiotherapy	21	0.90 (0.76–1.07)			
Radiotherapy (SABR or conventional)	6	0.78 (0.54–1.12)			
Surgery timing				56.2	15.9
No	16	0.82 (0.67–0.99)	Ref		
Post radiotherapy	2	0.85 (0.37–1.97)	0.902		
Pre radiotherapy	8	1.00 (0.76–1.32)	0.070		
	1	Partly surgery			
Timing of first given ICI				49.1	29.0
Adjuvant	14	0.81 (0.64–1.01)	Ref		
Concurrent	10	0.98 (0.77–1.25)	**0.045***		
Induction	3	0.82 (0.53–1.26)	0.903		

(C)RT: (chemo)radiotherapy. HR: hazard ratio, *p* value significance of difference between stratified HR as compared to reference (*Ref*) subgroup. I^2: residual heterogeneity / unaccounted variability in the meta-regression model. ICI: immune checkpoint inhibitor. Partly surgery: 1 trial reported 40% of the patients had surgery, therefore the trial was excluded for surgery subgroup analysis. R^2: amount of heterogeneity accounted for by including the factor in the meta-regression model. 95%CI: 95% confidence interval. RIT = radioimmunotherapy. * = statistically significant.

this difference largely explained the between-trial heterogeneity in OS and PFS. By contrast, no survival advantage was observed with induction or concurrent ICIs, suggesting that sequencing may be critical for optimizing the efficacy of radiotherapy-immunotherapy combinations. Mechanistically, ionizing radiation can function as an *in situ* vaccine by inducing immunogenic cell death, releasing tumor antigens and danger-associated molecular patterns (DAMPs), enhancing dendritic-cell uptake and cross-presentation of tumor antigens, and engaging cGAS–STING-dependent type I interferon signaling to promote antitumor immune priming [20,63]. Radiotherapy may therefore convert immunologically 'cold' tumors into 'hot' tumors when appropriately integrated with checkpoint blockade, as supported by preclinical evidence and early clinical studies [2,64]. However, these immunostimulatory effects may be counterbalanced by treatment-related immunosuppression, most notably radiation-induced lymphopenia which can be exacerbated by larger field sizes or target volumes, elective nodal irradiation (ENI), low-dose bath, and concomitant chemotherapy [2]. Such factors may partly explain why non-adjuvant strategies did not consistently outperform adjuvant-only strategies in the pooled RCT data.

In our trial-level analysis, ENI was not associated with treatment-related outcomes, possibly due to inconsistent reporting and

Table 3
Results from trial-level subgroup analyses for trials comparing immune checkpoint inhibitors versus no immune checkpoint inhibitors in patients receiving radiotherapy on progression free survival.

Factor	n	Stratified HR (95%CI)	*p*-value	I^2 (%)	R^2 (%)
Abstract only			0.630	76.4	0
No	21	0.81 (0.68–0.95)			
Yes	6	0.72 (0.49–1.07)			
Age			0.248	76.2	7.9
> 60	13	0.74 (0.59–0.92)			
≤ 60	11	0.88 (0.70–1.11)			
	3	Not reported			
Chemotherapy addition			0.074	72.8	12.9
Chemoradiotherapy	21	0.83 (0.70–0.98)			
Radiotherapy	6	0.63 (0.44–0.92)			
(C)RT and timing ICI				68.1	30.1
CRT and non-adjuvant ICI	11	0.90 (0.72–1.13)	Ref		
CRT and adjuvant ICI	10	0.74 (0.57–0.95)	0.141		
RT and adjuvant ICI	3	0.55 (0.34–0.90)	**0.008***		
RT and non-adjuvant ICI	3	0.76 (0.43–1.35)	0.427		
Design			0.728	76.4	0.0
phase II	12	0.74 (0.55–1.00)			
phase III	15	0.81 (0.68–0.97)			
Elective nodal irradiation			0.846	75.9	0.0
No	23	0.79 (0.67–0.93)			
Yes	4	0.81 (0.55–1.17)			
Follow-up			0.640	75.4	0.0
< 30 months	15	0.82 (0.68–1.00)			
≥ 30 months	12	0.75 (0.59–0.95)			
Glioblastoma trial			**0.001***	62.5	42.8
No	22	0.72 (0.61–0.86)			
Yes	5	1.13 (0.80–1.58)			
Global location				74.7	2.4
Global	11	0.85 (0.69–1.04)	Ref		
Eastern	7	0.61 (0.42–0.90)	0.082		
Western	9	0.80 (0.60–1.07)	0.645		
Male percentage treatment group			0.155	79.6	9.6
< 70%	8	0.93 (0.72–1.20)			
≥ 70%	12	0.71 (0.56–0.90)			
	7	Not reported			
Sample size			0.728	76.4	0.0
< 300	12	0.74 (0.55–1.00)			
≥ 300	15	0.81 (0.68–0.97)			
anti PD1 ICI			0.243	76.2	0.0
No	12	0.83 (0.67–1.04)			
Yes	15	0.75 (0.61–0.93)			
anti PDL1 ICI			0.488	76.2	0.0
No	16	0.77 (0.63–0.95)			
Yes	11	0.81 (0.65–1.02)			
Open or blind design			0.326	74.4	2.3
Blind	14	0.75 (0.62–0.91)			
Open	13	0.86 (0.67–1.09)			
Publication before 2025			0.722	76.0	0.0
No	10	0.76 (0.58–1.00)			
Yes	17	0.81 (0.67–0.97)			
Radiotherapy type			0.074	73.9	9.4
Chemoradiotherapy	21	0.83 (0.70–0.98)			
Radiotherapy (conventional or SABR)	6	0.63 (0.44–0.92)			
Single or multicenter trial			0.100	74.6	4.5
Multi	22	0.82 (0.70–0.96)			
Single	5	0.57 (0.35–0.92)			
Surgery timing				75.8	0.0
No	16	0.76 (0.62–0.93)	Ref		
Post radiotherapy	3	0.74 (0.46–1.21)	0.958		
Pre radiotherapy	8	0.86 (0.63–1.16)	0.560		
Timing of first given immunotherapy				67.0	30.7
Adjuvant	13	0.69 (0.55–0.87)	Ref		
Concurrent	11	0.94 (0.76–1.18)	**0.013***		
Induction	3	0.55 (0.29–1.05)	0.495		

(C)RT: (chemo)radiotherapy. HR: hazard ratio, *p* value significance of difference between stratified HR as compared to reference (*Ref*) subgroup. I^2: residual heterogeneity / unaccounted variability in the meta-regression model. ICI: immune checkpoint inhibitor. R^2: amount of heterogeneity accounted for by including the factor in the meta-regression model. 95%CI: 95% confidence interval. RIT = radioimmunotherapy. * = statistically significant.

confounding by concurrent chemotherapy [65]. Nevertheless, preclinical data suggest that ENI may attenuate antitumor immunity by impairing effective immune priming in tumor-draining lymph nodes (TDLN) [66], although translational data suggest that TDLN may retain type I immune responses despite high dose radiation exposure when (chemo)radiotherapy is combined with concurrent dual ICIs [67]. Systemic treatment-related immunosuppression, including radiation-induced lymphopenia, may therefore represent a more relevant constraint on effective immune synergy [68,69]. When oncologically feasible, immune-sparing radiotherapy strategies (such as minimizing elective volumes, avoiding unnecessary low-dose bath, and limiting dose to lymphocyte relevant organs) may help preserve immune function. Future RCTs should incorporate immune-relevant dosimetric parameters and lymphocyte kinetics as stratification factors for biomarker variables [2,64]. These considerations support the concept that administering ICIs after radiotherapy may more effectively consolidate radiation-induced immune priming before adaptive immune resistance mechanisms, including recruitment of myeloid regulatory cells, PD-L1 upregulation and Treg accumulation, gain the upper hand [70]. Clinically, this treatment sequencing effect is tentatively reflected in stage III NSCLC, where adjuvant durvalumab improved survival in PACIFIC [11], whereas concurrent durvalumab did not in PACIFIC-2 [35].

Table 4
Results from trial-level subgroup analyses for trials comparing radiotherapy versus no radiotherapy in patients receiving immune checkpoint inhibitors on progression free survival.

Factor	n	Stratified HR (95% CI)	*p*-value	I^2 (%)	R^2 (%)
Publication before 2022			0.059	0.0	100.0
No	3	0.92 (0.52–1.65)			
Yes	3	0.62 (0.33–1.16)			
Sample size			0.128	30.3	27.3
n ≥ 75 patients	3	0.91 (0.54–1.55)			
n < 75 patients	3	0.56 (0.27–1.15)			
Type of ICI					
antiCTLA4			0.814	42.9	0.0
No	3	0.76 (0.37–1.55)			
Yes	3	0.76 (0.43–1.33)			
antiPD1			0.096	0.0	100.0
No	2	0.84 (0.31–2.32)			
Yes	4	0.71 (0.43–1.19)			
antiPDL1			**0.038***	0.0	99.9
No	3	0.93 (0.51–1.71)			
Yes	3	0.64 (0.35–1.16)			

HR: hazard ratio. *p* value significance of difference between stratified HR as compared to reference subgroup. I^2: residual heterogeneity / unaccounted variability in the meta-regression model. ICI: immune checkpoint inhibitor. R^2: amount of heterogeneity accounted for by including the factor in the meta-regression model. 95%CI: 95% confidence interval.

Beyond PD-(L)1 and CTLA-4 blockade, next-generation radiotherapy-immunotherapy strategies are increasingly aimed at eliminating additional immunosuppressive pathways within the tumor microenvironment. These include the adenosine pathway, for example through CD73 or A2A receptor blockade to counteract adenosine-mediated suppression of cytotoxic T-cell activity [71], and targeting TGF-β signaling, a key driver of stromal exclusion and immune evasion [72]. In parallel, additional activation of innate immune sensing pathways, including STING and Toll-like receptor signaling, has been proposed to further amplify radiation-induced immune priming [19]. Biomarker-informed trials may further refine these strategies by evaluating translational markers of response and resistance, such as ctDNA-based minimal residual disease [73], interferon-response signatures [74], myeloid inflammatory markers [75], and T-cell receptor repertoire features including clonality or treatment-induced expansion [76]. However, the current randomized evidence base remains overwhelmingly dominated by PD-(L)1 inhibitors, and the findings of the present meta-analysis should therefore not be extrapolated directly to these newer immunotherapeutic classes.

The divergent results observed in glioblastoma highlight the importance of tumor microenvironmental context. The central nervous system has a distinct immune landscape, and glioblastoma typically exhibits heterogeneous immune trafficking across the blood-brain and blood–tumor barriers, frequent corticosteroid exposure, and a profoundly immunosuppressive, myeloid-rich tumor microenvironment [77]. These factors may attenuate the synergy between radiotherapy and immune checkpoint blockade and may partly explain unfavorable outcomes observed in glioblastoma trials in subgroup analyses. Rather than indicating a universal lack of efficacy, these findings suggest that effective radioimmunotherapy combinations in glioblastoma may require strategies capable of overcoming the profound local immunosuppression characteristic of this disease. Targeting myeloid-driven immune suppression, enhancing tumor-specific immune priming through vaccination or neoantigen-directed strategies, and developing rational combination therapies may help convert the relatively immunologically cold GBM microenvironment into a more inflamed state [78].

This systematic review and meta-analysis has several limitations, with heterogeneity representing the principal constraint. Only a limited number of trials were available per subgroup, restricting the ability to perform granular subgroup analyses. Heterogeneity in radiotherapy dose, fractionation schedules, and target-volume definitions likely contributed to outcome variability across trials. In the absence of standardization, these parameters may influence the immunomodulatory effects of radiotherapy and confound interpretation of treatment effects. Only six trials comparing radiotherapy versus no radiotherapy, with ICIs as standard of care in both groups, were eligible for inclusion, reflecting the methodological, logistical, and biological challenges of trial design in this setting, including uncertainty regarding optimal dose, fractionation, and target volumes. Although substantial heterogeneity was observed for EFS, this endpoint was reported in only seven trials, precluding meaningful subgroup analyses.

Another limitation was the inclusion of conference abstracts when full-text publications were not yet available, as these often-provided limited methodological detail and introduce potential bias. Of the eight trials judged to be at high risk of bias, three were available only as abstracts, contributing to incomplete reporting. Additional bias arose from open-label designs without blinded independent central review, which could influence PFS assessment. Inconsistent reporting of biomarkers, including PD-L1 status and tumor mutational burden limited stratified analyses and identification of patients most likely to benefit from radioimmunotherapy. Finally, toxicity was beyond the scope of this survival-focused meta-analysis, although combined treatment may increase the risk of immune-related or radiation-associated adverse events, such as pneumonitis or radionecrosis [79]. However, toxicity was not systematically evaluated because reporting, grading, attribution, and definitions varied substantially across trials. Distinguishing radiotherapy-related, ICI-related, and potentially synergistic toxicities would require a dedicated safety-focused methodology. Therefore, treatment-related toxicity is better suited to a separate future systematic review than to routine updates of the present living survival meta-analysis. A strength of this study is its living design, enabling regular updates as new randomized evidence emerges.

In conclusion, this meta-analysis indicates that adding immune checkpoint inhibition to radiotherapy improves time-to-event outcomes across solid tumors and yields an OS signal after exclusion of glioblastoma trials, highlighting clinically meaningful tumor-type heterogeneity. The most consistent benefit was observed when ICIs were delivered adjuvantly after radiotherapy, supporting post-radiotherapy checkpoint blockade as the preferred sequence when combined-modality therapy is pursued. By contrast, evidence for adding radiotherapy to ICIs remains inconclusive, underscoring the need for adequately powered trials in settings where ICIs are standard of care. Clinically, these findings encourage prioritizing radiotherapy-immunotherapy integration in indications with demonstrated efficacy, while tempering expectations in glioblastoma, where benefit appears limited. Future trial design should therefore (i) embed treatment sequencing as a core design principle, particularly adjuvant versus induction or concurrent approaches, (ii) incorporate lymphocyte-sparing, field-size-minimizing radiotherapy to mitigate treatment-related immunosuppression, and (iii) prospectively enrich or stratify according to biological and immune biomarkers to better match patients and tumor types to the most effective radiotherapy-immunotherapy strategy. This meta-analysis will be maintained as a living evidence synthesis with periodic updates as new randomized trials emerge.

CRediT authorship contribution statement

Hanneke W.M. van Laarhoven: Writing – review & editing. **Idris Bahce:** Writing – review & editing. **Abrahim Al-Mamgani:** Writing – review & editing. **Suresh Senan:** Writing – review & editing. **Famke L. Schneiders:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation, Conceptualization. **Peter S.N. van Rossum:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation,

Conceptualization. **Mathijs L. Tomassen:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tanja D. de Gruijl:** Validation, Writing – review & editing. **Claudia E. Pronk:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Eric Deutsch:** Writing – review & editing. **Joost J.C. Verhoeff:** Writing – review & editing. **Ben J. Slotman:** Writing – review & editing.

Funding

No external funding was involved in this study.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

MT: no COI

CP: no COI

BSL: no COI

IBA: no COI

JV: no COI

AA: no COI.

SS has received fees paid to his institution for consulting from AstraZeneca, MSD Oncology, and Lilly, and institutional research funding from AstraZeneca.

HvL: Research funding and/or medication/material supply from: AMGEN, Auristone, BMS, Incyte, Merck, MyeloidTx, ORCA, Servier. Consultant/advisory role: AMGEN, Amphera, Astellas, AstraZeneca, Beigene, BMS, Boehringer, Daiichy, MSD, MyeloidTx. Speaker role: AstraZeneca, BMS, Congress Care, Daiichy, Medtalks, MSD, Uitgeverij JAAP, Travel Congress Management

PvR reports speaker honoraria from Congress Care, Benecke, and AstraZeneca, paid to his institution.

FS reports research funding from ViewRay and speaker honoraria from AstraZeneca paid to her institution.

TDdG received speaker fees from BMS and consulting fees from Mendus and GE Health, all paid to her institution.

ED reports grants and personal fees from Roche Genentech, grants from Boehringer Ingelheim, grants from Astrazeneca, grants and personal fees from Merck Serono, grants from BMS, and grants from MSD.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116820.

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