



Efficacy and safety of sequential versus concurrent administration of immune checkpoint inhibitors with radiotherapy in solid tumors: a systematic review and network meta-analysis

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Abstract

Background Immune checkpoint inhibitors (ICIs) combined with radiotherapy (RT) enhance antitumor efficacy; however, the optimal sequencing of these treatments remains undefined. We conducted a network meta-analysis (NMA) of randomized controlled trials to compare the efficacy and safety of ICIs administered after completion of RT versus those administered concurrently with RT.

Methods A search of PubMed, Embase, Cochrane Library (CENTRAL), and ClinicalTrials.gov identified studies published through February 5, 2025. The primary outcome was overall survival (OS); the secondary outcome was progression-free survival (PFS); safety was assessed by the incidence of grade ≥ 3 adverse events (AEs).

Results This NMA included 24 randomized controlled trials involving 9,480 participants. The sequential ICI arm significantly improved OS (hazard ratio (HR): 0.81 [95% confidence interval (CI) 0.72 to 0.92]) and PFS (HR: 0.73 [95% CI 0.64 to 0.84]) versus the control arm, whereas the concurrent ICI arm showed no significant benefit. Compared with the concurrent ICI arm, the sequential ICI arm showed significantly superior PFS (HR: 0.81 [95% CI 0.67 to 0.97]). Additionally, the sequential ICI arm showed no statistically significant difference in grade ≥ 3 AE rates compared with the concurrent ICI arm (odds ratio (OR): 1.02 [95% CI 0.56 to 1.85]).

Conclusions Compared with concurrent administration of ICI with RT, sequential administration of ICI after RT improves survival outcomes without increasing toxicity. Further studies are needed to define the optimal timing of RT and ICIs to maximize efficacy while minimizing AEs.

Keywords Cancer · Immune checkpoint inhibitors · Immunotherapy · Network meta-analysis · Radiotherapy

Introduction

Immune checkpoint inhibitors (ICIs) are designed to promote antitumor immune responses by blocking inhibitory signals that prevent T-cell activation [1, 2]. However, ICI monotherapy confers prolonged survival and persistent responses only in certain patient subsets due to diverse mechanisms of primary and acquired resistance [3]. In solid tumors, the response rate with ICI monotherapy typically remains around 20% [4]. Accordingly, combination strategies are increasingly pursued to maximize the clinical benefit of ICIs in a wider range of patients. ICIs exhibit greater antitumor activity when combined with radiotherapy (RT) than when used alone, as RT activates immune mechanisms that can enhance the activation, infiltration, and function of T-cells [5].

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Recent randomized trials have suggested that, when RT and ICIs are combined, the sequence of the two treatments may affect efficacy and safety [6, 7]. However, because these were early-phase studies without subsequent confirmatory trials, the optimal timing between the two treatments remains unclear. The National Comprehensive Cancer Network (NCCN) guidelines recommend concurrent pembrolizumab with chemoradiotherapy (CRT) for stage III–IVA cervical cancer, whereas for unresectable stage III non-small cell lung cancer (NSCLC), sequential durvalumab following CRT is advised [8, 9]. These recommendations regarding the sequencing of RT and ICIs are not based on direct head-to-head clinical comparisons of treatment sequencing strategies. To compare the impact of concurrent ICI with RT versus sequential ICI after RT, a previous single-arm meta-analysis was undertaken. However, the lack of direct comparative studies limited definitive conclusions about the relative efficacy and safety of the two sequencing strategies [10]. Because network meta-analysis (NMA) is particularly useful when direct comparative trials are lacking [11], one study conducted an NMA to evaluate the safety of different sequencing strategies of RT and ICI administration in patients with lung cancer [12]. The analysis in this study was limited to pneumonia as the sole outcome, without assessing efficacy or other safety endpoints.

We aimed to evaluate the efficacy and safety of different sequencing strategies between RT and ICI administration across solid tumors, restricting the evidence to randomized controlled trials (RCTs) to ensure higher quality. The two most common approaches for combining RT and ICIs in solid tumors are concurrent therapy, where both are administered simultaneously, and sequential therapy, where ICIs

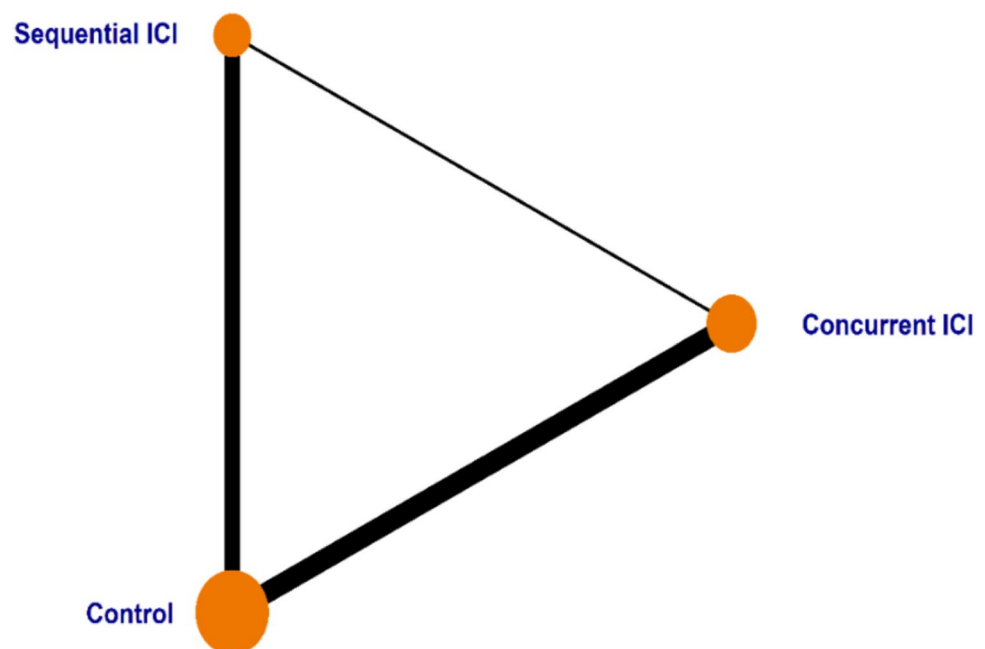
follow completion of RT. Our study systematically reviewed RCTs assessing the efficacy and safety of combining ICIs with RT in patients with solid tumors, and conducted an NMA to compare concurrent versus sequential administration of ICIs alongside RT. Given biological differences across tumor types that could influence treatment effects, we also performed subgroup analyses by tumor type.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and PRISMA for NMA (Supplementary Table 1) [13, 14]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251105771.

An NMA was conducted to compare the efficacy and safety of ICIs administered sequentially versus concurrently with RT (Fig. 1). We defined the treatment arm in which the ICI was administered during RT as the “concurrent ICI” arm. The arm in which the ICI was administered after completion of RT was defined as the “sequential ICI” arm. Both were compared with the “control” arm, defined as an RT-based therapy without ICIs (e.g., RT with or without chemotherapy).

Fig. 1 Network plot. Network diagram illustrating three treatment arms. The edge width is proportional to the number of direct comparisons for each treatment pair, and the node size is proportional to the number of participants (sample size). Control = radiation-based therapy without immune checkpoint inhibitors; Sequential ICI = immune checkpoint inhibitors administered after radiotherapy; Concurrent ICI = immune checkpoint inhibitors administered during radiotherapy



Data sources and search strategy

A comprehensive search of PubMed, Embase, Cochrane Library (CENTRAL), and ClinicalTrials.gov identified reports published through February 5, 2025. A search was performed using the following keywords: “Immune Checkpoint Inhibitors,” “Radiotherapy,” “Tumor,” and “Randomized Controlled Trial.” Manual searches were conducted in the reference lists of the included studies and relevant systematic reviews. The detailed search strategy is provided in Supplementary Table 2.

Study selection

Two independent investigators screened the titles and abstracts of the searched records, then evaluated the full texts to determine eligibility for inclusion. Any discrepancies were resolved through discussion between the investigators. To mitigate publication bias, conference abstracts were also included following careful review [15]. Studies were included if they met the following inclusion criteria: (1) Population: solid tumor patients; (2) Intervention: ICIs administered either concurrently with RT or after the completion of RT; (3) Comparison: RT-based therapy without ICIs; (4) Outcomes: reporting at least one of overall survival (OS), progression-free survival (PFS), or grade ≥ 3 adverse events (AEs) as defined by the Common Terminology Criteria for Adverse Events (CTCAE); (5) The study design was required to be an RCT.

The exclusion criteria were as follows: (1) Case reports, reviews, editorials, or notes; (2) Studies with fewer than 10 patients per group; (3) Studies not registered in ClinicalTrials.gov or another WHO-certified clinical trial registry; (4) Publications in languages other than English; (5) When multiple sets of results were available for the same clinical trial, the most recently updated data were included in the analysis; (6) Only approved ICIs were included to ensure that the results inform clinical practice and policy decision-making.

Data extraction and quality assessment

Two independent investigators extracted data from the included studies and conducted a quality assessment of the data. Any discrepancies were resolved through discussion. The extracted data included first author/principal investigator, publication year/posted year, type of tumor, sample size, interventions, reported outcomes, clinical trial phase and registration number. Efficacy was evaluated based on OS as the primary efficacy outcome and PFS as the secondary efficacy outcome. Safety was assessed based on the CTCAE grade ≥ 3 AEs, as these represent severe toxicities with a substantial impact on patient care.

The quality of the RCTs was assessed using version 2.0 of the Risk of Bias (RoB) assessment tool developed by the Cochrane Collaboration [16]. The certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, classifying it as high, moderate, low, or very low [17]. Publication bias was evaluated using funnel plots, Egger’s regression test, and Begg’s rank test [18].

Statistical analysis

OS and PFS data were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). When the HRs and 95% CIs for OS and PFS were not reported in the literature, they were estimated from Kaplan–Meier curves using Engauge Digitizer [19]. Grade ≥ 3 AEs were expressed as odds ratios (ORs) with 95% CIs. Direct comparison meta-analysis of the differences in median OS (mOS) and median PFS (mPFS) was also conducted (Supplementary Table 3) [20].

The NMA was performed within a frequentist framework in the R netmeta package. Given the anticipated heterogeneity due to clinical diversity among the included studies, we conducted all analyses using a random-effects model. Intervention rankings were determined by P-score, which ranges from 0 to 1. P-score measures the mean extent of certainty that a treatment is better than the competing treatments [21]. Higher P-score values indicate greater treatment efficacy and lower incidence of grade ≥ 3 AEs. Heterogeneity was assessed using the I^2 statistic and values of $I^2 > 50\%$ were considered heterogeneous across the trials [22]. The transitivity assumption was evaluated by comparing the distributions of potential effect modifiers, including age, Eastern Cooperative Oncology Group performance status, and prior exposure to ICI. The consistency of the NMA was assessed using node-splitting models to determine whether the estimates from direct and indirect comparisons showed statistically significant disagreement [23]. Subgroup analyses were conducted for solid tumor types with a sufficient number of eligible studies. When statistically significant improvements were observed in a subgroup, we converted relative effects into absolute effects according to the Cochrane Handbook to facilitate clinical interpretation [24]. Sensitivity analysis excluded studies at higher risk of bias [25]. After excluding arms that were not aligned with our objective from multi-arm trials, only one comparison per study was included in the analysis. Therefore, correlations arising from multi-arm trials did not need to be accounted for. All statistical analyses for this NMA were performed using R software, version 4.4.3 with significance set at $P < 0.05$.

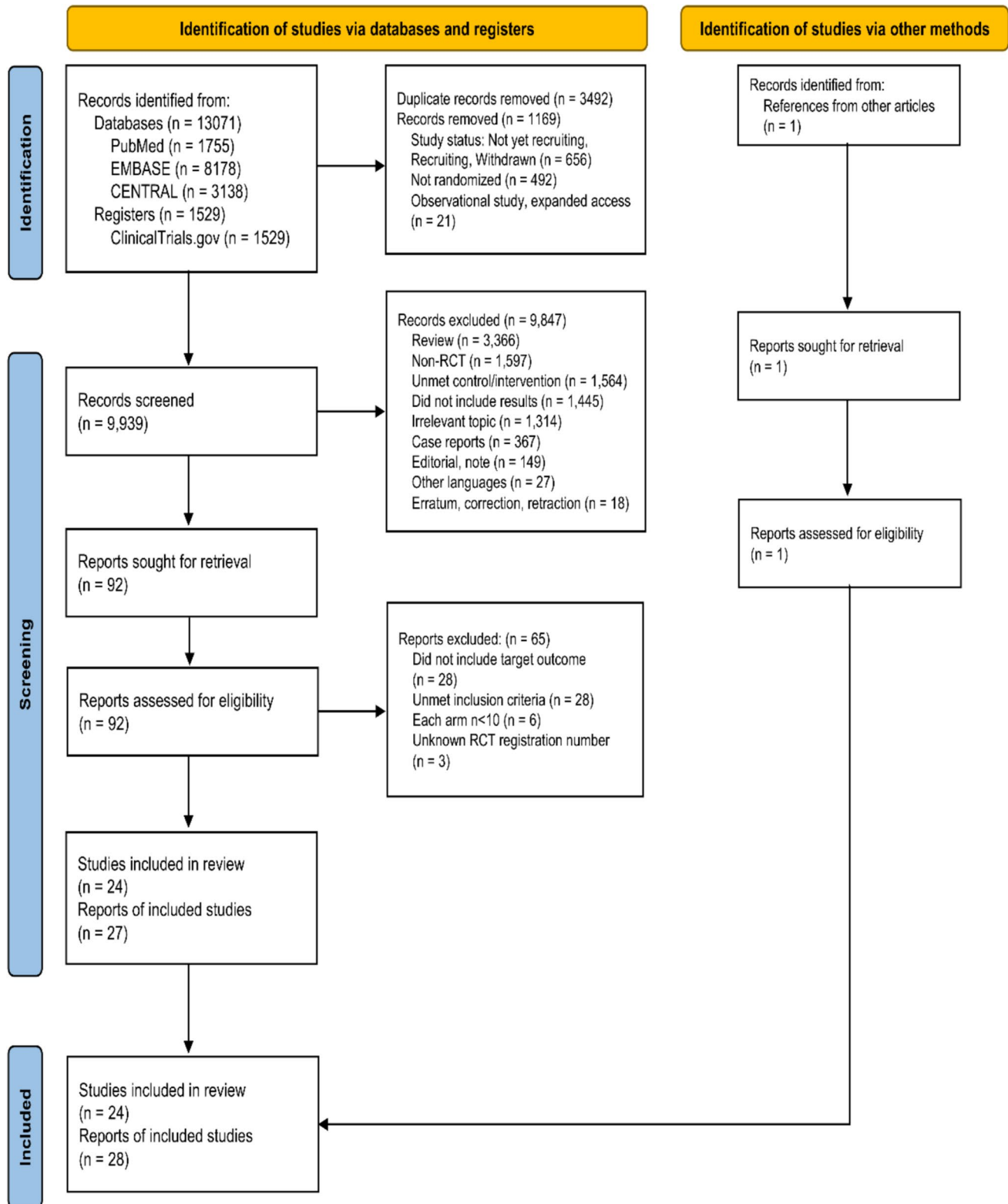


Fig. 2 PRISMA flowchart

Results

Study selection

A total of 14,600 records were identified through database and registry searches. After removing duplicates and screening titles and abstracts, 92 reports remained. Full-text review led to the exclusion of 65 reports, leaving 27 reports for inclusion. A subsequent manual search yielded 1 additional report, resulting in 24 studies presented in 28 reports included in the NMA (Fig. 2) [6, 7, 26–51].

Study characteristics

The characteristics of the studies included in the NMA are summarized in Table 1 and Supplementary Table 4. A total of 24 studies involving 9,480 patients with solid tumors were included. Notably, 10 trials (41.7%) were conducted in patients with lung cancer, 4 trials (16.7%) were conducted in patients with head and neck squamous cell carcinoma (HNSCC), and 3 trials (12.5%) were conducted in patients with glioblastoma. The ICIs included atezolizumab, avelumab, camrelizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, sugemalimab, tislelizumab, and toripalimab. In most studies, RT was used in combination with chemotherapy.

Overall survival

OS was assessed in 21 RCTs. The sequential ICI arm showed a significant OS benefit over the control arm (HR: 0.81 [95% CI 0.72 to 0.92]). In contrast, there was no statistically significant difference in OS between the concurrent ICI arm and the control arm (HR: 0.96 [95% CI 0.85 to 1.07]). The sequential ICI arm showed a trend toward improved OS compared with the concurrent ICI arm, although the result was not significant (HR: 0.85 [95% CI 0.72 to 1.00]; Fig. 3a and Supplementary Fig. 1a). The I^2 statistic did not identify any heterogeneity across the studies ($I^2=28.5\%$, Supplementary Table 5). The sequential ICI arm ranked highest (P-score=0.99), followed by the concurrent ICI arm (P-score=0.40), with the control arm ranking lowest (P-score=0.12) (Fig. 4 and Supplementary Table 6).

Direct meta-analysis comparing each treatment arm with the control arm showed that, although not statistically significant, the sequential ICI arm showed an increase in mOS, unlike the concurrent ICI arm (differences in mOS [months]: 5.25 [95% CI –7.90 to 18.39] vs –2.74 [95% CI –11.08 to 5.59]; Supplementary Fig. 2a, b).

Progression-free survival

PFS was evaluated across 20 RCTs. The sequential ICI arm demonstrated a significant PFS benefit compared with the control arm (HR: 0.73 [95% CI 0.64 to 0.84]). No statistically significant difference in PFS was observed between the concurrent ICI arm and the control arm (HR: 0.90 [95% CI 0.79 to 1.03]). The sequential ICI arm showed a statistically significant improvement in PFS compared with the concurrent ICI arm (HR: 0.81 [95% CI 0.67 to 0.97]; Fig. 3b and Supplementary Fig. 1b). The analysis revealed substantial heterogeneity across the included studies ($I^2=51.1\%$, Supplementary Table 5). The sequential ICI arm ranked highest (P-score=0.99), followed by the concurrent ICI arm (P-score=0.48), with the control arm ranking lowest (P-score=0.03) (Fig. 4 and Supplementary Table 6).

Direct meta-analyses indicated that, although not statistically significant, the sequential ICI arm showed a greater increase in mPFS than the concurrent ICI arm (differences in mPFS [months]: 4.72 [95% CI –1.05 to 10.49] vs 0.76 [95% CI –1.72 to 3.24]; Supplementary Fig. 2c, d).

Grade ≥ 3 adverse events

Grade ≥ 3 AEs were assessed in 10 RCTs. Both the sequential and concurrent ICI arms showed significantly higher risks of grade ≥ 3 AEs compared with the control arm (OR: 2.09 [95% CI 1.34 to 3.27] vs 2.06 [95% CI 1.30 to 3.27]). There was no statistically significant difference in the incidence of grade ≥ 3 AEs between the sequential and concurrent ICI arms (OR: 1.02 [95% CI 0.56 to 1.85]; Fig. 3c and Supplementary Fig. 1c). The I^2 statistic indicated substantial heterogeneity ($I^2=76.2\%$, Supplementary Table 5). The control arm ranked highest (P-score=1.00), followed by the concurrent ICI arm (P-score=0.26), with the sequential ICI arm ranking lowest (P-score=0.24) (Fig. 4 and Supplementary Table 6).

Subgroup analysis and sensitivity analysis

Subgroup analyses of OS and PFS by solid tumor type were performed for lung cancer, HNSCC, and glioblastoma. For other solid tumor types, subgroup analyses were not feasible because the number of eligible studies was insufficient. In the lung cancer subgroup, the sequential ICI arm demonstrated statistically significant improvements in both OS and PFS compared with the control arm (HR: 0.76 [95% CI 0.68 to 0.86] and HR: 0.69 [95% CI 0.60 to 0.80]). Additionally, the sequential ICI arm showed a statistically significant OS benefit over the concurrent ICI arm (HR: 0.75 [95% CI 0.60 to 0.93]; Supplementary Table 7). The converted absolute effects are presented in Supplementary Table 8.

Table 1 Characteristics of included studies

Study	Patients		Intervention arm/control arm (n)	Intervention	Control	Treatment details		Outcomes	Phase	Registration number
	Type of tumor					ICI treatment	Total dose of RT [Gy]			
Sequential ICI arm versus control arm										
Spigel 2022 ^a	NSCLC	476/237	Sequential ICI after RT	RT-based therapy	Durvalumab (10 mg/kg Q2W)	60–66	Platinum-based chemotherapy	OS, PFS, grade ≥ 3 AEs	III	NCT02125461
Wu 2025	NSCLC	272/135	Sequential ICI after RT	RT-based therapy	Durvalumab (1500 mg Q4W)	54–66	Platinum-based chemotherapy	OS, PFS	III	NCT03706690
Wu 2022 ^b	NSCLC	255/126	Sequential ICI after RT	RT-based therapy	Sugemalimab (1200 mg Q3W)	54–66	Platinum-based chemotherapy	OS, PFS	III	NCT03728556
Cheng 2024	SCLC	264/266	Sequential ICI after RT	RT-based therapy	Durvalumab (1500 mg Q4W)	45 or 60–66	Platinum and etoposide	OS, PFS	III	NCT03703297
Peters 2022	SCLC	78/75	Sequential ICI after RT	RT-based therapy	Nivolumab (1 mg/kg Q3W) + ipilimumab (3 mg/kg Q3W)	45 or 56	Cisplatin or carboplatin + etoposide	OS, PFS, grade ≥ 3 AEs	II	NCT02046733
Zhang 2024	SCLC	31/33	Sequential ICI after RT	RT-based therapy	Toripalimab (240 mg Q3W)	45 or 60–66	Cisplatin + etoposide	PFS	II	NCT04418648
Mulholland 2023	GBM	79/40	Sequential ICI after RT	RT-based therapy	Ipilimumab (3 mg/kg Q3W)	NR	Temozolomide	OS, PFS	II	ISRCTN84434175
Sim 2023	GBM	69/34	Sequential ICI after RT	RT-based therapy	Nivolumab (240 mg Q4W in 1–4 cycles, 480 mg Q4W in 5–6 cycles)	40	Temozolomide	OS, PFS, grade ≥ 3 AEs	II	NCT04195139
Ma 2024	NPC	226/224	Sequential ICI after RT	RT-based therapy	Camrelizumab (200 mg Q3W)	NR	Cisplatin	grade ≥ 3 AEs	III	NCT03427827
Fizazi 2021 ^a	PCa	399/400	Sequential ICI after RT	RT-based therapy	ipilimumab (10 mg/kg Q3W)	8	None	OS, PFS, grade ≥ 3 AEs	III	NCT00861614
Concurrent ICI arm versus control arm										
Machiels 2024	HNSCC	402/402	Concurrent ICI with RT	RT-based therapy	Pembrolizumab (200 mg Q3W)	70	Cisplatin	OS, grade ≥ 3 AEs	III	NCT03040999

Table 1 (continued)

Study	Patients	Intervention arm/control arm (n)		Intervention	Control	Treatment details		Outcomes	Phase	Registration number
		Type of tumor				ICI treatment	Total dose of RT [Gy]			
Lee 2021	HNSCC	350/347	Concurrent ICI with RT	RT-based therapy	Avelumab (10 mg/kg Q2W)	70	Cisplatin	OS, PFS, grade ≥ 3 AEs	III	NCT02952586
Tao 2024	HNSCC	275	Concurrent ICI with RT	RT-based therapy	Avelumab (10 mg/kg Q2W)	70	None	OS, PFS	III	NCT02999087
Lorusso 2024	CC	529/531	Concurrent ICI with RT	RT-based therapy	Pembrolizumab (200 mg Q3W in 1–5 cycles, 400 mg Q6W in 6–20 cycles)	75 or 80	Cisplatin	OS, PFS, grade ≥ 3 AEs	III	NCT04221945
Monk 2023	CC	385/385	Concurrent ICI with RT	RT-based therapy	Durvalumab (1500 mg Q4W)	45	Cisplatin or carboplatin	OS, PFS	III	NCT03830866
Higgins 2025	SCLC	274/270	Concurrent ICI with RT	RT-based therapy	Atezolizumab (1200 mg Q3W)	45 or 66	Platin-um + etopo-side	OS, PFS	III	NCT03811002
Gong 2024	SCLC	42/43	Concurrent ICI with RT	RT-based therapy	Tislelizumab (200 mg Q3W)	60–70	Cisplatin or carbopl-atin + etopo-side	PFS	II	NCT04952597
Lim 2022	GBM	358/358	Concurrent ICI with RT	RT-based therapy	Nivolumab (240 mg Q2W for 8 cycles, 480 mg Q4W after 8 cycles)	60	Temozolomide	OS, PFS	III	NCT02667587
Bradley 2025	NSCLC	219/109	Concurrent ICI with RT	RT-based therapy	Durvalumab (1500 mg Q4W)	60	Platinum-based chemotherapy	OS, PFS	III	NCT03519971
Katz 2023	PDAC	24/13	Concurrent ICI with RT	RT-based therapy	Pembrolizumab (200 mg Q3W)	50.4	Capecitabine	OS, PFS	I/II	NCT02305186
George 2023 ^b	RC	90/95	Concurrent ICI with RT	RT-based therapy	Pembrolizumab (200 mg Q3W)	50.4	Capecitabine	OS	II	NCT02921256
Mowery 2024	STS	71/72	Concurrent ICI with RT	RT-based therapy	Pembrolizumab (200 mg Q3W)	50	None	OS, grade ≥ 3 AEs	II	NCT03092323
Sequential ICI arm versus concurrent ICI arm										
Zandberg 2023	HNSCC	39/41	Sequential ICI after RT	Concurrent ICI with RT	Pembrolizumab (200 mg Q3W)	70	Cisplatin	OS, PFS, grade ≥ 3 AEs	II	NCT02777385

Table 1 (continued)

Study	Patients		Intervention arm/control arm (n)	Intervention	Control	Treatment details		Outcomes	Phase	Registration number
	Type of tumor					ICI treatment	Total dose of RT [Gy]			
Bestvina 2022	NSCLC	19/18		Sequential ICI after RT	Concurrent ICI with RT	Nivolumab (3 mg/kg Q2W) + ipilimumab (1 mg/kg Q6W)	30, 45 or 50	None	OS, PFS	I NCT03223155

Abbreviations: AEs, adverse events; CC, cervical cancer; GBM, glioblastoma; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; NPC, nasopharyngeal carcinoma; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival; PCa, prostate cancer; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; RC, rectal cancer; RT, radiotherapy; SCLC, small cell lung cancer; STS, soft tissue sarcoma

^aFor a single RCT, two articles were available; because both reported the required outcomes, both were included in the analysis

^bAlthough the latest outcomes were all extracted from conference abstracts, earlier published articles were used for the risk of bias assessment due to insufficient information in the conference abstracts

No statistically significant findings were observed in the HNSCC or glioblastoma subgroups.

Sensitivity analysis was performed to assess the robustness of the results by including and excluding studies at higher risk of bias. This analysis showed no substantial changes in overall effect sizes, 95% CIs, or heterogeneity (Supplementary Table 9).

Transitivity, inconsistency and quality assessment

The distribution of potential effect modifiers was balanced across the included studies, indicating that the transitivity assumption was essentially met (Table 1 and Supplementary Table 4). Node-splitting analysis revealed no significant inconsistency between direct and indirect evidence (Supplementary Table 10). The RoB assessment indicated that most included studies were of low risk or some concerns, with only 3 of 24 studies classified as high risk (Supplementary Figs. 3 and 4). Certainty of evidence, as assessed using the GRADE method, is summarized in Table 2. In the comparison between the sequential ICI arm and the concurrent ICI arm, OS and PFS had moderate and high certainty of evidence, respectively, whereas the safety outcome had low certainty of evidence. The funnel plot exhibited no asymmetry, and results from both Egger's regression and Begg's rank correlation tests showed no significant publication bias (Supplementary Fig. 5).

Discussion

This study is the first NMA comparing the efficacy and safety of ICIs administered sequentially versus concurrently with RT in patients with solid tumors using evidence from RCTs. Our NMA demonstrated that sequential administration of ICIs after RT improved OS and PFS in patients with solid tumors compared with concurrent administration of ICIs with RT. This finding is consistent with previous studies that have demonstrated the efficacy of sequential ICI after RT [7, 52, 53]. Subgroup analyses demonstrated that the sequential ICI arm showed significantly improved OS compared with the concurrent ICI arm in lung cancer, with low heterogeneity (Supplementary Table 7). In fact, the PACIFIC trial evaluating sequential durvalumab after CRT in stage III NSCLC demonstrated improved OS and PFS, whereas PACIFIC-2 assessing concurrent durvalumab with CRT in the same population showed no improvement in survival outcomes [47, 54]. However, while statistically significant, some of these improvements may be modest (Supplementary Table 8).

Administering ICIs after RT may yield superior anti-tumor efficacy compared with concurrent administration because radiation reprograms the tumor microenvironment.

(a)

Sequential ICI		
0.849 (0.719; 1.001)	Concurrent ICI	
0.813 (0.719; 0.918)	0.958 (0.854; 1.074)	Control

(b)

Sequential ICI		
0.809 (0.673; 0.973)	Concurrent ICI	
0.729 (0.636; 0.835)	0.900 (0.789; 1.028)	Control

(c)

Sequential ICI		
1.016 (0.557; 1.854)	Concurrent ICI	
2.092 (1.341; 3.265)	2.059 (1.295; 3.274)	Control

Fig. 3 League tables comparing treatments for overall survival, progression-free survival, and grade ≥ 3 adverse events. **a** HR with 95% CI for overall survival, **b** HR with 95% CI for progression-free survival, **c** OR with 95% CI for grade ≥ 3 adverse events. CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; OR, odds ratio

Responses to ICIs are preferentially observed in “hot” tumors that already exhibit a robust T-cell infiltrate [55]. In contrast, “cold” tumors with almost no infiltrating T-cells have low responsiveness to immunotherapy [56]. As the cold phenotype is commonly observed in solid tumors, additional strategies are needed to transform the tumor microenvironment from “cold” to “hot”. RT can serve as such a strategy. Radiation induces cancer cell death and the release of danger signals, activating dendritic cells that migrate to tumor-draining lymph nodes to prime tumor-specific T-cells [57]. The activated effector T-cells subsequently return to the tumor, kill cancer cells, and secrete cytokines that further activate dendritic cells and drive the polarization of tumor-associated macrophages toward the antitumor M1 phenotype, turning “cold” tumors into “hot” ones [58, 59]. In a preclinical study, ablative irradiation increased tumor-infiltrating CD8⁺ T-cells as well as activated natural killer cells and M1 macrophages from day 3 through day

14 after irradiation [60]. Radiation of the tumor induced a hot microenvironment with activation of both the innate and adaptive immune systems within two weeks, followed by a subsequent shift toward a cold microenvironment [60, 61]. These observations were also suggested in an exploratory subgroup analysis of the double-blind, placebo-controlled, phase III PACIFIC trial in patients with unresectable stage III NSCLC. A subgroup analysis of the PACIFIC trial indicated that ICIs administered within 14 days of RT conferred greater improvements in OS and PFS than ICIs administered after 14 days [47]. Initiating ICI therapy within 14 days after RT may represent an optimal strategy for improving prognosis in patients with solid tumors. However, the 14-day window should be considered exploratory and not be generalized as a clinical recommendation until it is confirmed in prospective studies.

ICIs administered after RT may induce a stronger abscopal effect than concurrent administration. The abscopal

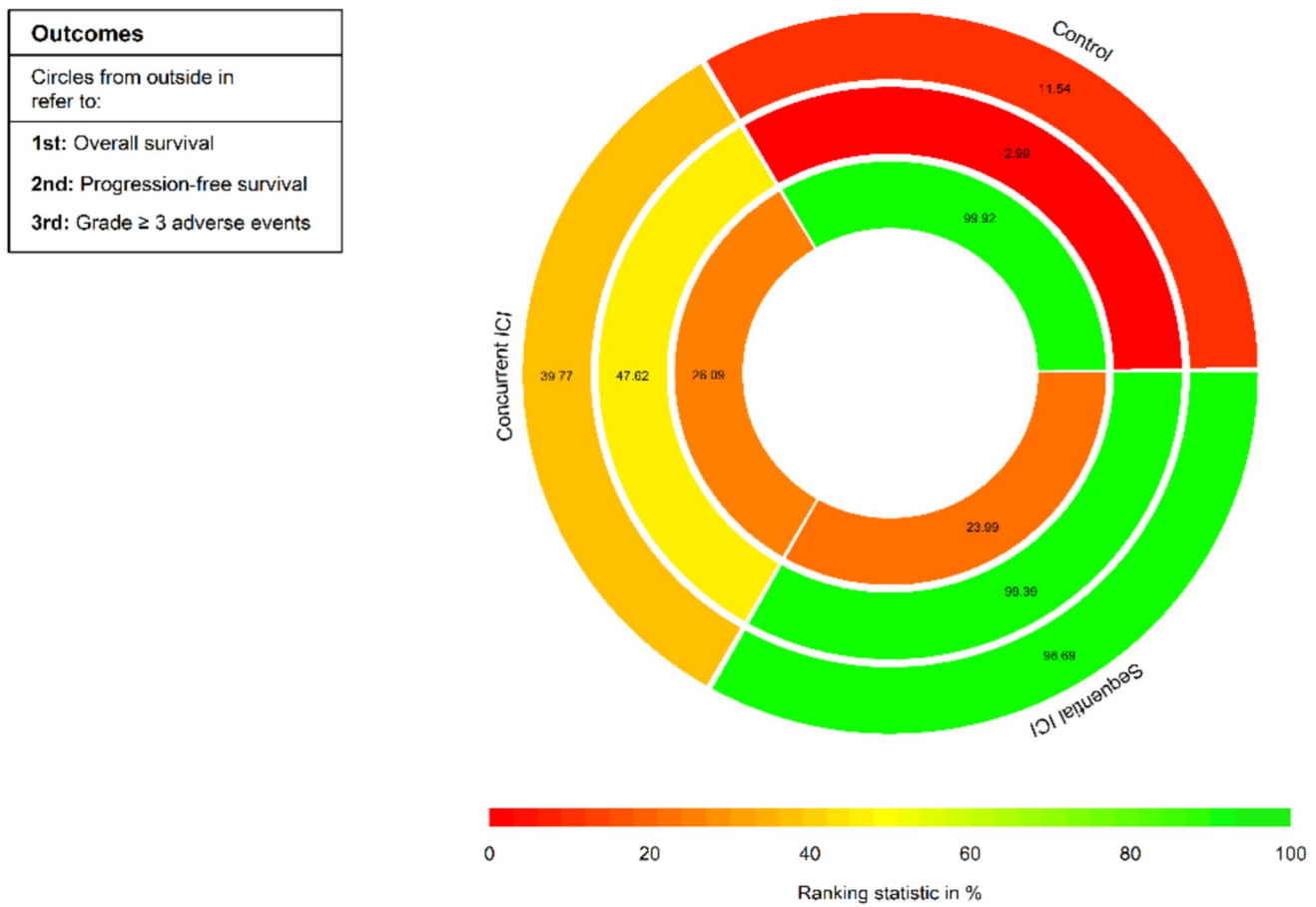


Fig. 4 Rank-heat plot. Each concentric circle represents a different outcome: the outermost circle represents overall survival, the middle circle represents progression-free survival, and the innermost circle represents grade ≥ 3 adverse events. The intervention corresponding to each sector is indicated by the label outside the outer-

most circle. Each sector is colored according to the rank of the corresponding intervention for that outcome, and the detailed ranking statistic (P-score) is shown as a number within each sector. A value of 0% (red) indicates the lowest rank (lower efficacy or safety), whereas 100% (green) indicates the highest rank (higher efficacy or safety)

effect describes tumor regression outside the irradiated region [62]. RT induces immunogenic cell death, which triggers systemic antitumor immune responses and enables CD8⁺ T-cells to eliminate distant, non-irradiated tumors [63]. In this context, ICIs administered after RT may enhance the immune elimination of distant tumor cells [64]. A preclinical study showed that sequential administration of a PD-1 inhibitor after RT induced a greater abscopal effect than concurrent ICI with RT [65]. In mouse tumor models, administration of anti-PD-1 after local tumor irradiation elicited a potent abscopal response, with an expansion of polyfunctional CD8⁺ T-cells and a reduction in the terminally dysfunctional CD8⁺ T-cells at non-irradiated tumors [66]. Consistent with the observation, in the PEMBRO-RT trial in patients with metastatic NSCLC, analysis of non-irradiated tumors showed significant on-therapy expansion of new and pre-existing T-cell clones and upregulation of inflammatory response gene expression programs in the cohort that received pembrolizumab after RT [67, 68].

Therefore, sequential administration of ICIs after RT may be a more appropriate treatment strategy than concurrent administration for patients with metastatic solid tumors.

It is also possible that RT techniques influence the anti-tumor efficacy of ICIs. Stereotactic body RT (SBRT), an RT approach that delivers higher doses to smaller target lesions [69], may be particularly suitable for combination with ICIs. Because lymphocytes are highly sensitive to RT, cancer patients receiving RT are at increased risk of developing radiation-induced lymphopenia [5]. Combining hypofractionated treatment plans with smaller target volumes could reduce radiation exposure to circulating blood cells, thereby reducing radiation-induced lymphopenia compared with conventional RT [70, 71]. In patients with locally advanced pancreatic cancer, SBRT (6.6 Gy $\times$ 5) preserved post-treatment lymphocyte counts more effectively than conventional CRT (1.8 Gy $\times$ 28) [72]. SBRT yields significantly less radiation-induced lymphopenia, potentially leading to better outcomes when ICIs are administered after SBRT.

Table 2 Certainty of evidence evaluated with GRADE framework

Comparisons	K ^a	Risk of bias	Inconsistency	Indirectness	Publication bias	Imprecision	Other considerations	NMA Effect Size (95% CI)	Certainty of evidence
<i>OS</i>									
Sequential ICI versus Concurrent ICI	2	Not serious	Not serious	Not serious	Not serious	Serious	None	0.85 (0.72 to 1.00)	⊕⊕⊕○ Moderate
Sequential ICI versus Control	8	Not serious	Not serious	Not serious	Not serious	Not serious	None	0.81 (0.72 to 0.92)	⊕⊕⊕⊕ High
Concurrent ICI versus Control	11	Not serious	Not serious	Not serious	Not serious	Serious	None	0.96 (0.85 to 1.07)	⊕⊕⊕○ Moderate
<i>PFS</i>									
Sequential ICI versus Concurrent ICI	2	Not serious	Not serious	Not serious	Not serious	Not serious	None	0.81 (0.67 to 0.97)	⊕⊕⊕⊕ High
Sequential ICI versus Control	9	Not serious	Not serious	Not serious	Not serious	Not serious	None	0.73 (0.64 to 0.84)	⊕⊕⊕⊕ High
Concurrent ICI versus Control	9	Not serious	Not serious	Not serious	Not serious	Serious	None	0.90 (0.79 to 1.03)	⊕⊕⊕○ Moderate
<i>Grade ≥ 3 AEs</i>									
Sequential ICI versus Concurrent ICI	1	Not serious	Not serious	Not serious	Serious	Serious	None	1.02 (0.56 to 1.85)	⊕⊕○○ Low
Sequential ICI versus Control	5	Not serious	Serious	Not serious	Not serious	Not serious	None	2.09 (1.34 to 3.27)	⊕⊕⊕○ Moderate
Concurrent ICI versus Control	4	Not serious	Not serious	Not serious	Not serious	Not serious	None	2.06 (1.30 to 3.27)	⊕⊕⊕⊕ High

Abbreviations: AEs, adverse events; ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; RT, radiotherapy

^aTrials with direct comparisons

The efficacy of ICIs administered after RT may differ based on the ICI subclass. A preclinical study has shown that RT upregulates PD-L1 expression on tumor cells and PD-1 expression on tumor-infiltrating CD4⁺ and CD8⁺ T-cells [73]. Although these changes may facilitate immune evasion, they also increase the responsiveness of tumor cells to PD-1/PD-L1 inhibitors, thereby making PD-1/PD-L1 blockade after RT more effective [74]. In mouse models, the combination of RT and CTLA-4 inhibitors induced PD-L1 upregulation on melanoma cells and T-cell exhaustion [75]. These findings support the hypothesis that blockade of the PD-1/PD-L1 axis after RT is required to sustain antitumor effects. In our NMA, apart from two studies that assessed CTLA-4 inhibitors, all included trials evaluated the combination of RT and PD-1/PD-L1 inhibitors. Accordingly, direct extrapolation of our results to CTLA-4 inhibitors or to other ICI subclasses should be undertaken with caution.

Our NMA suggests that a sequential ICI after RT may provide greater efficacy than a concurrent strategy. Consistent with our findings, the current NCCN guidelines for stage III NSCLC recommend sequential administration of

durvalumab after CRT [9]. The negative results of the recent PACIFIC-2 trial, which tested concurrent durvalumab with CRT in patients with stage III NSCLC, support both our findings and the NCCN guidelines [54]. However, the NCCN guidelines recommend concurrent pembrolizumab with CRT in stage III–IVA cervical cancer [8]. Although it was not included in our study, a recent exploratory small phase II trial for locally advanced cervical cancer reported no significant differences in secondary survival endpoints between the concurrent and sequential arms [76]. As both strategies demonstrated acceptable safety and feasibility, an ongoing study is examining the efficacy of the two sequencing strategies in cervical cancer (NCT03833479 and NCT03612791). In cervical cancer, the optimal sequencing of RT and ICIs remains uncertain due to the lack of confirmatory studies.

To support clinical decision-making, our safety analysis focused on the incidence of CTCAE grade ≥ 3 AEs, which have a substantial impact on patient care. Importantly, in our NMA, there was no statistically significant difference in the incidence of grade ≥ 3 AEs between the sequential and concurrent ICI strategies. This finding was consistent with the results of a previously conducted NMA on safety [12],

suggesting that sequential ICI after RT showed no apparent increase in grade ≥ 3 AEs compared with concurrent administration. However, because our safety analysis included a limited number of studies and showed high heterogeneity ($I^2 = 76\%$), the results should be interpreted with caution. Additional studies are required to more fully define the safety of sequential and concurrent ICI strategies.

This study has several limitations. First, most outcomes in our NMA exhibited substantial heterogeneity. This issue was largely resolved through subgroup analyses by tumor type, which were conducted to reduce heterogeneity. Second, subgroup analyses based on RT fractionation and dose, ICI type, or whether chemotherapy was administered could not be conducted due to limited data. Third, the safety comparison between the sequential ICI arm and the concurrent ICI arm was rated as having low certainty of evidence. However, all other outcomes were graded as having moderate to high certainty of evidence, supporting the reliability of our findings. Fourth, because we conducted the analysis using reported aggregate data rather than individual patient data, we were limited in our ability to assess effect modification by clinical factors. For example, although patient-level PD-L1 expression is an important predictor of responsiveness to immunotherapy [77], the absence of individual participant data prevented a detailed exploration of the potential relationship between PD-L1 expression and treatment outcomes. Finally, although our assessment of transitivity indicated that the distribution of effect modifiers was balanced, the possibility of unmeasured confounding cannot be excluded.

Despite these limitations, our analysis is the first NMA to compare the efficacy and safety of ICIs administered after RT versus concurrently with RT in solid tumors, helping to fill the gap created by the lack of head-to-head evidence. In this study, safety was not apparently influenced by the sequence of RT and ICIs. Importantly, sequential administration of ICIs after RT was associated with improved efficacy compared with concurrent administration. This finding was particularly evident in subgroup analyses of patients with lung cancer. However, due to the limited number of included studies, the efficacy outcomes were not statistically significant in the subgroup analyses for HNSCC and glioblastoma. These results support the need for confirmatory, tumor-specific trials to evaluate the optimal sequencing of RT and ICIs.

Conclusion

In this NMA, sequential administration of ICIs after RT was an effective strategy for improving OS and PFS in patients with solid tumors, compared with the concurrent strategy. Additionally, there was no statistically significant difference

in rates of grade ≥ 3 AEs between administering ICIs after RT and administering ICIs concurrently with RT. These findings suggest that, in clinical practice, treatment sequencing should be considered when combining RT and ICIs for maximal clinical benefit. Our results could improve the design of future clinical trials to define the optimal sequencing of RT and ICIs.

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Author contributions All authors read and approved the final version of the manuscript. The corresponding author (EY) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. JW: conceptualization, data curation, formal analysis, investigation, validation, writing—original draft, writing—review and editing; SE: writing—review and editing; DR: writing—review and editing; HK: investigation, writing—review and editing; EY: supervision, writing—review and editing.

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Data availability All data used in this analysis were obtained from publicly available sources. A complete list of references for all included studies is provided in the manuscript. The datasets generated during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval Not applicable.

Consent to participate/publish Not applicable.

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