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Scientific Article

# Meta-analysis and Critical Review: Association Between Radio-induced Lymphopenia and Overall Survival in Solid Cancers

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**Abstract**

**Purpose:** Immune system modulation, with the use of immune checkpoint inhibitors, has drastically changed the field of oncology. Strong preclinical data indicate that radiation therapy (RT) may enhance the response rate to such drugs via in situ vaccination, although these data do not consider immune radiotoxicity. This meta-analysis investigates whether radio-induced lymphopenia (RIL) is associated with overall survival (OS).

**Methods and Materials:** A systematic literature search and quantitative analysis were planned, conducted, and reported per the Preferred Reporting Items for Systematic Reviews and Meta-analyses and Quality of Reporting of Meta-analyses checklists. The literature from January 1990 to March 2021 was searched to identify clinical studies with OS data in patients treated with RT and presenting with lymphopenia. A random-effect model was employed for the meta-analysis. Heterogeneity was assessed using the $I^2$ statistic. Publication bias was estimated using a *P*-curve analysis.

**Results:** A total of 56 studies with 13 223 patients and 11 types of cancers were selected. The mean follow-up time was 35.9 months. Over a third of patients had RIL (37.25%). After removing outlying studies (n = 14), the between-study heterogeneity variance was estimated at $t^2 = 0.018$ ($P = .01$) with an $I^2$ value of 36.0% (95% confidence interval, 6%-56%). The results showed that RIL was significantly associated with worse OS (hazard ratio: 1.70; 95% confidence interval, 1.55-1.86; $P < .01$; 95% prediction interval, 1.27-2.26). A subgroup analysis was performed based on the type of primary tumor, and a difference between the subgroups was found ($P < .01$). Based on the *P*-curve analysis, a significant evidential value was found, and no significant publication bias was identified among the studies.

**Conclusions:** RIL is a significant prognostic factor for mortality in virtually all solid cancers. Pooled-effect estimates indicate a significantly reduced risk of death in patients without RIL. Tailoring RT regimens to spare the immune system and updating dosimetric constraints for new organs at risk, such as major blood vessels, organs with rich blood supplies, bones, and all lymph node areas, may improve prognoses.



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## Introduction

Since the 1950s, oncologists have described the abscopal effect, which refers to the systemic effects of radiation

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on out-of-field tumor deposits.[1] Later, through the use of murine models, the abscopal effect was found to be mediated by immune mechanisms.[2,3] Historically, our comprehension of radio-induced cell death was DNA-centered; however, new molecular biology techniques challenge the ubiquity of this model.[4,5] Radiation has an effect on virtually all cellular organelles, and can cause apoptosis, autophagy, or senescence without direct DNA damage.[5] These cellular effects have molecular consequences that mobilize the immune system. This phenomenon is known as immunogenic cell death or in situ vaccination.

Exploration of the immune antitumor response has revealed concrete clinical repercussions with the use of drugs, such as the checkpoint inhibitors (CPIs).[6] CPIs target, for example, programmed cell death protein 1 (PD-1), which belongs to the superfamily of B7 immunoglobulins. These molecules are expressed on the T-cell membrane, and either amplify or diminish the immune response.[7] Programmed death-ligand 1 (PD-L1) can be upregulated in certain tumor cells; thus, transmitting an antiapoptotic signal and protecting tumor cells from T-cell attack.[8,9] Antibodies against PD-1 or PD-L1 have shown major therapeutic success in melanoma, kidney cancer, and lung cancer, because they permit a T-cell-mediated immune response.[10] Strong preclinical data suggest that radiation therapy (RT) may enhance the response rate to CPIs via in situ vaccination,[11] although these data do not consider radio-induced lymphopenia (RIL).

Indeed, immune cells (specifically lymphocytes) are described as one of the most radiosensitive cells in the body, which can be counterintuitive considering that lymphocytes are well-differentiated and nondividing cells. In the 1950s, Trowell[12] showed that the dose required to produce 50% pyknotic nuclei in circulating lymphocytes within 5 hours ranged from 1.6 Gy to 0.4 Gy. More recent studies[13,14] corroborated the very high radiosensitivity of lymphocytes demonstrated by Trowell using modern techniques. Overall, the authors concurred that immune cells die at doses >2 Gy per fraction.

If the balance between immunotoxicity and immune stimulation seems uncertain, RIL may have a clear clinical effect. RIL was described first when x-rays were discovered. Indeed, after exposing virtually any body part through x-rays, a decline in circulating lymphocytes was observed,[15] and then most noticeably studied in cerebral irradiation in the early 1980s. The skull contains hardly any bone marrow and has no lymph nodes; however, several children undergoing prophylactic cranial radiation for lymphoblastic acute leukemia developed lymphopenia. Lymphocyte drops were correlated with the number of fractions administered.[16] Later, other studies showed a trend toward inferior clinical outcomes (overall survival [OS] and progression-free survival) in patients treated for solid cancers and presenting with RIL. Moreover, several published studies found that RIL's association with OS was independent of pretreatment prognostic factors, tumor histology, chemotherapy regimen, or corticosteroid use.[17-19]

The aim of this study was to formally determine whether RIL is correlated with OS in solid cancers. All available clinical data were systematically reviewed and processed in this meta-analysis.

## Methods and Materials

A systematic literature search and quantitative analysis were planned, conducted, and reported per the Preferred Reporting Items for Systematic Reviews and Meta-analyses and Quality of Reporting of Meta-analyses checklists (Appendix Tables 1 and 2). The search was performed on February 2021, and articles published from 1990 to this date were retrieved. We reviewed all papers published since 1990, because nearly 90% of articles related to our subject were issued after 1989, but we decided to process only articles dated after 2010 to have more up-to-date RT techniques and chemotherapy regimens. The PubMed (National Institutes of Health), Cochrane Central (Cochrane collaboration), Embase (Elsevier), and Web of Science databases were queried with the search terms "radiotherapy", "radiation therapy", "lymphopenia", and "cancer."

Furthermore, conference proceedings from the American Society of Radiation Oncology, European Society of Therapeutic Radiation Oncology, European Society of

**Table 1 Description of patients, intervention, comparison, and outcome strategy**

| CRITERION | DESCRIPTION |
|---|---|
| PATIENTS | Patients treated with RT for malignant disease, with at least 6 mo follow up who had lymphocyte count monitoring during or after RT |
| INTERVENTION | Quantitative analysis of absolute lymphocyte count or lymphocyte count relative to neutrophil count during or after RT |
| COMPARISON | Predictive value of lymphocyte count during or after RT |
| OUTCOME | Prognosis: Overall survival |

*Abbreviation*: RT, radiation therapy.

**Table 2 Characteristics of studies included in meta-analysis**

| First author | Year | Cancer | Number (n = 13,223) | RT technique | Radiation regimen, median, Gy | Follow-up time, median, mo | Biomarker | Threshold for lymphopenia | OCEBM score |
|---|---|---|---|---|---|---|---|---|---|
| Grossman[44,*] | 2011 | GBM | 96 | CFRT | 60 | 12 | TLC at 2 mo | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 2 |
| Mendez[18] | 2016 | GBM | 76 | CFRT | 45 | ND | TLC at 2 mo | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 3 |
| Rudra[45,*] | 2018 | GBM | 210 | CFRT | 57 | 15.4 | TLC at week 12 | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 2 |
| Ye[46] | 2019 | GBM | 148 | CFRT | 57 | 32.8 | TLC <1 G/L during treatment | TLC <1 G/L during treatment | 3 |
| Campian[50] | 2014 | H&N | 56 | CFRT | 57 | 12 | TLC 2 mo after treatment initiation | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 3 |
| Li[51,*] | 2017 | H&N | 249 | CFRT | 69 | ND | PLR 3 mo after end of treatment | Optimum cutoff values determined by ROC curve; PLR >2.5 | 2 |
| Liu[52,*] | 2018 | H&N | 181 | CFRT | 69 | 60 | TLC 3 mo after treatment | Optimum cutoff values determined by ROC curve; lymphocytes <390/$\mu$L | 2 |
| Lin[53] | 2019 | H&N | 108 | CFRT | 67.5 | 37 | TLC and NLR 3 mo after treatment initiation | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 3 |
| Ng[54] | 2020 | H&N | 850 | CFRT | 70 | 59 | TLC during treatment | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 3 |
| Liu[55] | 2020 | H&N | 207 | CFRT | 69 | 82 | NLR 3 mo after treatment minus NLR before treatment | Optimum cutoff values determined by ROC curve | 3 |
| Hyder[59] | 2016 | Esophagus | 83 | CFRT | 53.4 | 29.3 | NLR after treatment | Relative NLR change from diagnosis to after surgery | 3 |
| Davuluri[60] | 2017 | Esophagus | 504 | CFRT | 50.4 | 32.1 | Nadir TLC during treatment | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | |
| Deng[61] | 2019 | Esophagus | 325 | CFRT | 50.4 | 65.5 | TLC up to 3 mo after treatment | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 3 |
| Chen[67,*] | 2019 | Esophagus | 64 | CFRT | 60 | 11.8 | TLC and lymphocyte subtypes after treatment | Optimum cutoff values determined by ROC curve | 2 |
| Wang[62] | 2020 | Esophagus | 189 | CFRT | 59 | 46 | Nadir TLC during treatment | Optimum cutoff values determined by ROC curve | 3 |

(*continued on next page*)

**Table 2** (*Continued*)

| First author | Year | Cancer | Number (n = 13,223) | RT technique | Radiation regimen, median, Gy | Follow-up time, median, mo | Biomarker | Threshold for lymphopenia | OCEBM score |
|---|---|---|---|---|---|---|---|---|---|
| So[63] | 2020 | Esophagus | 92 | CFRT | 41.4 | 16.9 | Nadir TLC during treatment | Optimum cutoff values determined by ROC curve | 3 |
| Campian[17] | 2013 | NSCLC | 47 | CFRT | 60 | ND | TLC at 2 mo after treatment | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 3 |
| Tang[35] | 2014 | NSCLC | 711 | CFRT | 66 | 51 | TLC after treatment | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 3 |
| Deng[36] | 2017 | SCLC | 320 | ND | NA | 39.1 | NLR during and after treatment | Optimum cutoff values determined by ROC curve | 4 |
| Luo[27] | 2018 | NSCLC | 63 | SBRT | 48 | 29.5 | NLR 1-3 d before treatment | Optimum cutoff values determined by ROC curve | 3 |
| Cho[37] | 2016 | SCLC | 73 | CFRT | 59 | 22 | TLC after treatment | Optimum cutoff values determined by ROC curve; lymphocytes <297/$\mu$L | 3 |
| Contreras[22] | 2018 | NSCLC | 290 | CFRT | 66 | 17 | NLR at 4 mo after treatment | Optimum cutoff values determined by ROC curve | 3 |
| Zhao[38,*] | 2020 | NSCLCL | 76 | CFRT | 64 | ND | Nadir TLC during treatment | Optimum cutoff values determined by ROC curve and lymphocytes <500/$\mu$L | 2 |
| Wang[39] | 2019 | SCLC | 226 | ND | NA | 23 | TLC directly after treatment and at 3 mo after treatment | Optimum cutoff values determined by ROC curve | 3 |
| Zhao[40] | 2019 | NSCLC | 107 | SBRT | 50-60 | 22 | 1 wk afer treatment TLC | Lymphocytes <800/$\mu$L | 3 |
| Xia[34] | 2020 | NSCLC | 244 | CFRT | >60 | 15.5 | 1 mo after treatment NLR | Optimum cutoff values determined by ROC curve | 3 |
| Shaverdian[41] | 2016 | NSCLC | 83 | SBRT | 61 | 28.9 | NLR within 2 mo before treatment | Optimum cutoff values determined by ROC curve and lymphocytes <1000/$\mu$L | 3 |
| Matiello[33,*] | 2020 | NSCLC | 46 | CFRT | 72.3 | 13 | Baseline TLC minus TLC at 6 mo | No definition of immunosuppression | 2 |
| Balmanoukian[48] | 2012 | Pancreas | 53 | CFRT | 50.4 | 16 | TLC 2 mo after treatment | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 3 |

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**Table 2** (*Continued*)

| First author | Year | Cancer | Number (n = 13,223) | RT technique | Radiation regimen, median, Gy | Follow-up time, median, mo | Biomarker | Threshold for lymphopenia | OCEBM score |
|---|---|---|---|---|---|---|---|---|---|
| Wild[19] | 2015 | Pancreas | 101 | CFRT | 50.4 | 10.1 | TLC at 2 mo after treatment | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 3 |
| Chadha[49] | 2017 | Pancreas | 162 | CFRT | 59.5 | 12 | TLC after treatment | Lymphocytes <200/$\mu$L | 3 |
| Zhao[71] | 2017 | HCC | 69 | CFRT | 54 | 30 | Nadir TLC during treatment | Lymphocytes <450/$\mu$L | 3 |
| Zhuang[72] | 2019 | HCC | 78 | SBRT | 48 | 32 | 2 mo posttreatment TLC | Lymphocytes <450/$\mu$L | 3 |
| Onal[29] | 2018 | Cervix uteri | 95 | CFRT; BRT | 50.4 | 68 | TLC at least 3 mo after treatment | CTCAE, version 4.0, threshold; lymphocytes <500/$\mu$L | 3 |
| Taguchi[68] | 2020 | Cervix uteri | 131 | CFRT; BRT | 50.4 | 44 | 6 mo posttreatment TCL | Optimum cutoff values determined by ROC curve | 3 |
| Moon[56,*] | 2016 | H&N | 153 | CFRT | 70 | 39.5 | 2 mo posttreatment NLR | Optimum cutoff values determined by ROC curve | 2 |
| Wu[69] | 2016 | Cervix uteri | 47 | CFRT; BRT | NA | 25 | 2 mo posttreatment TLC | CTCAE, version 4.03, threshold; TLC <500/$\mu$L | 3 |
| Jensen[57] | 2017 | H&N | 114 | CFRT | 70 | 50 | TLC during treatment | CTCAE, version 4.03, threshold | 3 |
| Lin[25] | 2018 | H&N | 57 | CFRT | 66 | 69.6 | From 16-56 wk after start RT initiation | CTCAE, version 4.03, threshold and optimum cutoff values determined by ROC curve | 3 |
| Byun[73] | 2019 | HCC | 920 | CFRT; SBRT | 60 | 15.8 | 3 mo after RT initiation | CTCAE, version 4.03, threshold | 3 |
| Byun[32] | 2019 | Glioblastoma | 336 | CFRT | 60 | 19.3 | Within 3 mo after RT initiation | CTCAE, version 4.03, threshold | 3 |
| Nuradh[42] | 2019 | Lung | 216 | CFRT | 55.4 | 36 | Earliest TLC after RT completion | CTCAE, version 4.03, threshold | 3 |
| Sherry[30] | 2019 | Esophagus | 93 | CFRT | 50.4 | 19.2 | At least 1 wk after treatment completion | Optimum cutoff values determined by ROC curve | 3 |
| Zhang[74] | 2019 | HCC | 184 | CFRT or SBRT | 75 | 21.9 | TLC during RT and 1 mo after RT completion | Optimum cutoff values determined by ROC curve | 3 |
| Abravan[43] | 2020 | Lung and esophageal | 584 | CFRT | 54.6 | 17.4 | TLC during RT | CTCAE, version 4.03, threshold | 3 |

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**Table 2** (*Continued*)

| First author | Year | Cancer | Number (n = 13,223) | RT technique | Radiation regimen, median, Gy | Follow-up time, median, mo | Biomarker | Threshold for lymphopenia | OCEBM score |
|---|---|---|---|---|---|---|---|---|---|
| Ahn[47] | 2020 | Glioblastoma | 97 | CFRT | 60 | ND | TLC 1 mo after treatment | Cutoff value based on previous studies | 3 |
| Gutkin[23] | 2020 | Breast | 99 | ND | ND | 44 | 1 y after RT completion | TLC <1000/$\mu$L | 3 |
| Holub[70] | 2020 | Endometrial & cervix uteri | 139 | CFRT; BRT | 52 | 40.5 | TLC within 3 mo of treatment completion | TLC <1000/$\mu$L | 3 |
| Lee[24] | 2020 | Pancreas | 285 | CFRT | 49.56 | 12 | 1-3 mo after treatment | CTCAE, version 5.0, threshold | 3 |
| Lee[75] | 2020 | Anal canal | 140 | CFRT | 43 | 55 | 2 mo after treatment | CTCAE, version 5.0, threshold | 3 |
| McLaughlin[28] | 2020 | NSCLC | 40 | SBRT | 50 | ND | Within 6 mo after treatment | CTCAE, version 5.0, threshold | 3 |
| Patil[58] | 2020 | H&N | 532 | CFRT | 70 | 39.13 | TLC from treatment initiation to 6 wk of treatment | CTCAE, version 4.0, threshold | 3 |
| Sun[31] | 2020 | Breast | 598 | CFRT | 50 | 57.6 | During and 1 mo after RT completion | CTCAE, version 4.0, threshold | 3 |
| Wu[64] | 2019 | Esophagus | 105 | CFRT | 50 | 19.2 | After RT completion | CTCAE, version 4.0, threshold | 4 |
| Xu[65] | 2020 | Esophagus | 488 | CFRT | 50.4 | 29.6 | During RT and 1 mo after treatment | CTCAE, version 4.0, threshold | 3 |
| Peter[66] | 2020 | Esophagus | 860 | CFRT | 50.4 | 49 | During RT | CTCAE, version 4.0, threshold; TLC <200/$\mu$L | 3 |

*Abbreviations*: BRT, brachytherapy; CFRT, conventionally fractionated radiation therapy; CTCAE, Common Terminology Criteria for Adverse Events; GBM, glioblastoma; H&N, head and neck; HCC, hepatocellular carcinoma; NA, not available; ND, no data; NLR, neutrophil-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; OCEBM, Oxford Center for Evidence Based Medicine; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic; RT, radiation therapy; SBRT= stereotactic body radiation therapy; SCLC, small cell lung cancer; TLC, total lymphocyte count.

* Prospective study.

Therapeutic Radiation Oncology, and American Society of Clinical Oncology were probed for any additional articles. The articles retrieved from the initial search were imported into reference manager software (EndNote X9, version 3.3). Duplicates were excluded, and the titles of articles were assessed. Papers found to be relevant to the topic were shortlisted, and the selected full-length papers were reviewed according to the eligibility criteria. The references of the included studies were manually searched for additional studies. References from review articles were assessed for cross-references. Abstracts and other unfinished works were excluded. All selected articles were reviewed by YEH and JC.

## Eligibility criteria

The patients, intervention, comparison, and outcome criteria for the review are shown in Table 1. Any prospective clinical trial, retrospective study, or cohort study on solid malignancies in humans was eligible. RT had to be part of the treatment, and the intent was curative in either a neoadjuvant, definitive, or adjuvant setting. The study was required to have data on OS and lymphocyte count measurements, whether absolute or relative to the polynuclear neutrophil or platelet count. Studies without clinical information, preclinical models, and studies on lymphopenia in patients undergoing immunotherapy, chemotherapy, or surgery alone were excluded. Studies reporting outcomes in patients infected with the human immunodeficiency virus or those with immunodeficient states were also rejected. No limit was set for the minimum follow-up time. Articles focusing on advanced disease stages or palliative therapy were excluded. Studies reporting only pre-RT lymphocyte counts were excluded.

The selected studies were assessed for risk of bias on the basis of the following 5 variables: Retrospective versus prospective study design, sufficient descriptions of lymphocyte count data collection and treatment modality, uniform inclusion criteria, incomplete outcome data, and number of patients included (studies with <40 patients were automatically excluded). The risk of bias was classified as high if no was the response for ≥3 criteria. The level of evidence was scored according to the Oxford Center for Evidence-Based Medicine (OCEBM) 2011 level of evidence guide[20], as follows: Systematic review of inception cohort studies, inception cohort studies, cohort study or control arm of a randomized trial, and case series or case-control studies or poor-quality prognostic cohort studies.

## Statistical analysis

Categorical variables are presented as percentages, and continuous variables are presented as medians. When not available, confidence intervals (CIs) of hazard ratios (HRs) were calculated with the *P* value and the population number for each group. HRs and mean differences were plotted with the generic inverse variance method, and depicted in forest plots comparing patients with and without RIL. When neither the population number nor the HR was published, the study was excluded from the final analysis. $P < .05$ was considered statistically significant.

We anticipated considerable between-study heterogeneity; thus, a random-effect model was used to pool effect sizes. The restricted maximum likelihood estimator was used to calculate the heterogeneity variance $t^2$ for analysis. We used Knapp–Hartung adjustments to calculate the CI around the pooled effect. Study heterogeneity was assessed using the inconsistency index ($I^2$), and prediction intervals were used to calculate the estimated between-study heterogeneity variance $t^2$. The presence of outlying cases within the selected studies was assessed using a generic outlier removal process that excluded every study with a CI that did not overlap with the CI of the pooled effect.

Publication bias was appraised with funnel plots, tested for asymmetry through Egger's test, and adjusted with the trim-and-fill method. Due to the limitation of the trim-and-fill method when the between-study heterogeneity is large,[21] publication bias was also assessed using the *P*-curve method to test for right-skewness and flatness. All statistical analyses were performed using R, version 4.0.5 (Shake and Throw) using the Meta Package.

## Results

We reviewed 195 papers reporting studies published between 2005 and 2021. Of these 195 papers, we selected 56 studies, 8 of which were prospective. The review process is depicted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses chart in Fig. 1. The 56 studies reported outcomes for 13,223 patients. Eight articles addressed stereotactic RT. Most papers studied lung cancer (n = 15), esophageal cancer (n = 10), head and neck cancer (n = 10), and pancreatic cancer (n = 4). The mean follow-up time was 32.9 months (range, 10.1-82 months) for the 50 studies reporting these data. The number of patients with RIL was 4926 (37.25% of entire population).

The mean radiation dose, biomarkers used to analyze RIL, and thresholds to define lymphopenia are shown in Table 2. Most articles used the lymphocyte count at 2 to 3 months after treatment to characterize the relationship between RIL and survival. The results for all studies showed that RIL was significantly associated with worse OS with an HR of 1.74 (95% CI, 1.54-1.97; $P < .01$) and a nonsignificant predicted interval (95% CI, 0.85-3.6). The between-study heterogeneity variance was estimated at

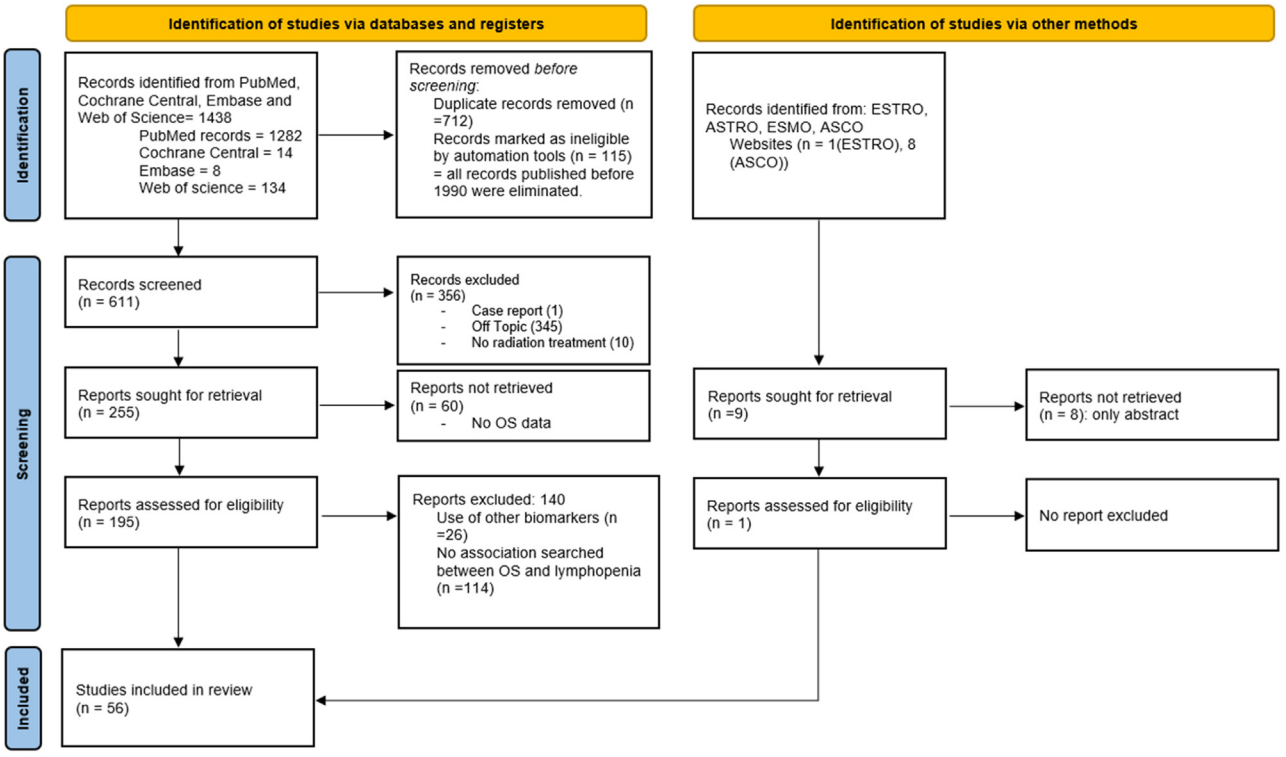


**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of retrieved studies OS, overall survival.

$t^2 = 0.12$ ($P < .01$), with an $I^2$ value of 88% (95% CI, 85%-90%; Appendix Fig. 1).

Using a generic outlier removal process, we identified 14 outlying studies because their CI did not overlap with the CI of the pooled effect.[18,22-34] Without outliers, the between-study heterogeneity was significantly less important, with a variance of $t^2 = 0.018$ (95% CI, 0.002-1.13) and a $I^2$ value of 36% (95% CI, 6%-56%). The HR for OS was 1.70 (95% CI, 1.55-1.86; $P < .01$), with a predicted interval of 2.13 (95% CI, 1.27-2.26), showing that RIL is a prognostic factor for poor OS (Fig. 2). The results for all studies with and without outliers are compared in Table 3. Due to the high between-study heterogeneity, a funnel plot was computed without outlying studies (Appendix Fig. 2). Funnel plot asymmetry was tested with Egger's test (Suppl. Table 1). The Egger's test indicated the presence of funnel plot asymmetry. The trim-and-fill method added 14 studies, and the HR was still significant (HR: 1.56; 95% CI, 1.40-1.74; $P < .0001$; Appendix Fig. 3).

The *P*-curve analysis showed the presence of evidential value for the main analysis (Suppl. Fig. 1A) and the analysis without outliers (Suppl. Fig. 1B). From the group of studies without outliers, a subgroup analysis was performed based on the type of primary tumor. The studies were divided into 6 groups: Lung cancer,[17,35-43] glioblastoma,[44-47] pancreatic cancer,[19,48,49] head and neck cancer,[50-58] esophageal cancer,[30,43,59-67] and various. The various group included studies on cervical and endometrial cancer[68-70] hepatocellular carcinoma[71-74] and anal cancer[75] because each entity was represented <3 articles. A forest plot of studies without outliers, stratified by the 6 subgroups, is depicted in Fig. 2. A forest plot of all studies (with outliers) divided into the 6 subgroups is depicted in Appendix Fig. 4.

When dividing the studies into cancer subtypes, the analysis showed a significant HR of 1.57 (95% CI, 1.36-1.82; 95% prediction interval [PI], 1.36-1.82) for lung cancer and a low between-study heterogeneity of 20% (Fig. 2). The analysis processed 1026 patients who showed RIL and 1036 patients without RIL. Of note, of the 15 studies on lung cancer, 3 exclusively analyzed small cell lung cancer (SCLC),[36,37,39] and 1 investigated both SCLC and non-small cell lung cancer (NSCLC).[42] Among the SCLC studies, only 2 reported treatment with no chemotherapy.[36,42] For NSCLC, 4 studies did not select patients treated with chemotherapy.[27,28,41,76] Among the 15 articles, 2 were prospective.[33,76] For esophageal cancer, the analysis showed significantly poorer OS for the 801 patients showing RIL, with an HR of 1.44 (95% CI, 1.25-1.66; 95% PI, 1.25-1.67) and low between-study heterogeneity ($I^2$ = 25%; Fig. 2). Among the 9 remaining studies without outliers, only 1 did not determine precisely whether patients received chemotherapy.[59] One article was a prospective study.[67]

For head and neck cancer, 10 studies reported outcomes for 1167 patients presenting with RIL. The analysis

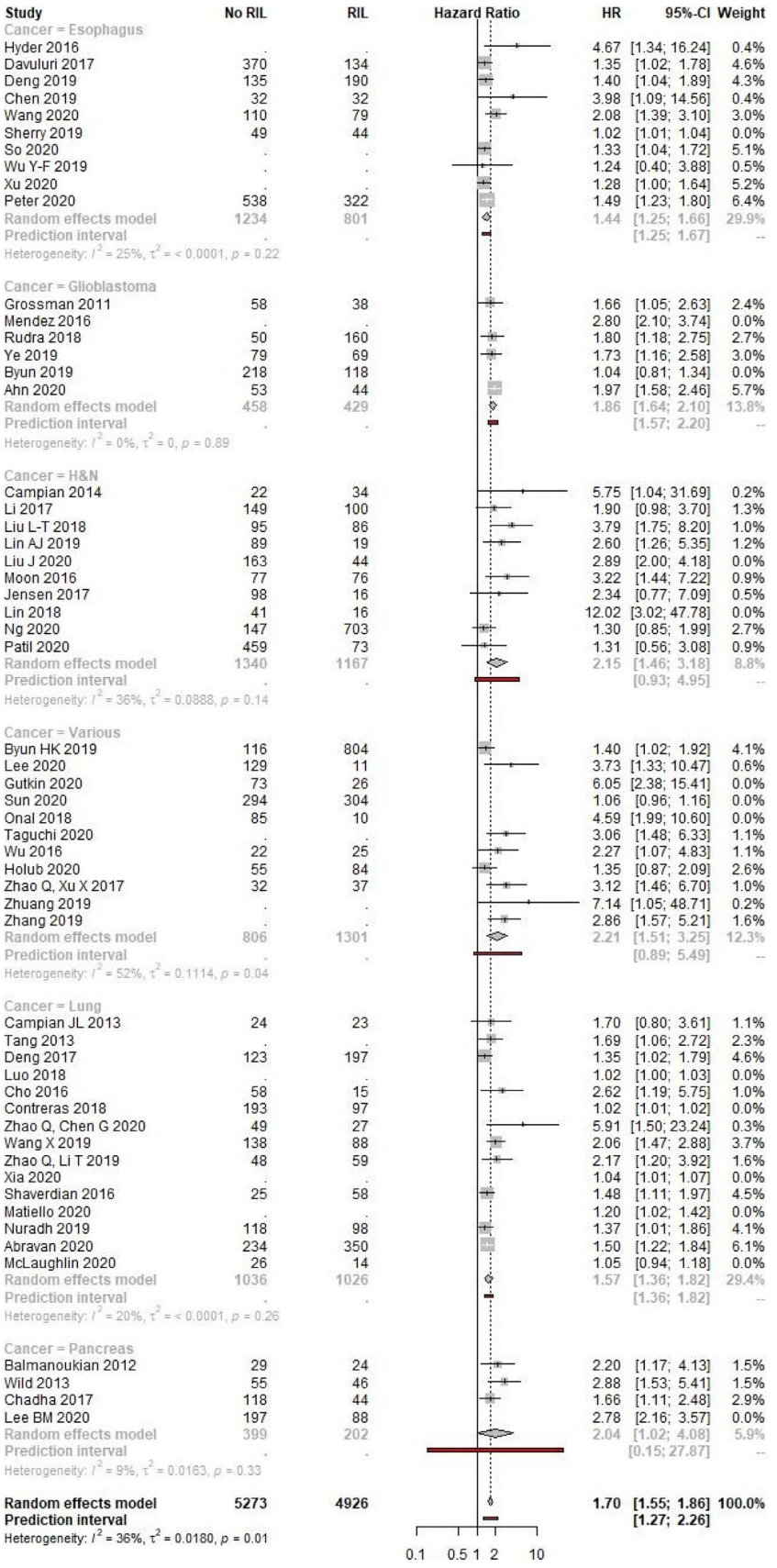


**Figure 2** Forest plot of subgroup analysis for overall survival in patients presenting with radio-induced lymphopenia compared with patients without lymphopenia, stratified by cancer groups, without outlying studies.

**Table 3 Results from analysis with and without outlying studies**

| Analysis | Hazard ratio | 95% confidence interval | *P*-value | 95% prediction interval | $I^2$, % | I2 95% confidence |
|---|---|---|---|---|---|---|
| Main analysis | 1.74 | 1.54-1.97 | < .01 | 0.85-3.6 | 88 | 85-90 |
| Analysis without outliers | 1.70 | 1.55-1.86 | < .01 | 1.27-2.26 | 36 | 6-56 |
| Removed as outliers.[18,22-34] | | | | | | |

showed that RIL was associated with worse OS, with an HR of 2.15 (95% IC, 1.46-3.18; 95% PI, 0.93-4.95) and moderate between-study heterogeneity of 36% (Fig. 2). Only 1 study did not report whether the selected patients received chemoradiotherapy or not;[57] otherwise, all other data were collected from patients receiving chemoradiotherapy. Three papers were prospective in nature.[51,52,56] The 4 pancreatic cancer studies included 202 patients with RIL among a population of 601 patients. RIL was significantly associated with worse OS, with an HR of 2.04 (95% CI, 1.02-4.08; 95% PI, 0.15-27.87) and very low between-study heterogeneity ($I^2$ = 9%; Fig. 2). All patients presenting with RIL also received systemic treatment.

Six studies investigated glioblastoma, with a population of 429 patients presenting with RIL among 887 patients. RIL was significantly associated with death, with an HR of 1.86 (95% CI, 1.64-2.10; 95% PI, 1.57-2.20; Fig. 2). The $I^2$ and $t^2$ in the glioblastoma group were too low to be generated. The 429 patients presenting with RIL were also treated with concomitant systemic therapy. Two glioblastoma papers were prospective in nature.[44,45] Finally, the last group of patients presented outcomes for hepatocellular carcinoma,[32,71,72,74] cervical[29,68,69] and endometrial cancer,[70] breast cancer,[23,31] and anal cancer.[75] In this group, only 3 papers reported data for patients treated with RT alone.[71,72,74] The analysis shows that RIL is associated with poor OS in this group (HR: 2.21; 95% CI, 1.51-3.25; 95% PI, 0.89-5.49) and, as expected, moderate between-study heterogeneity of 52% (Fig. 2). A difference between the subgroups was found ($P < .01$; Fig. 2).

## Discussion

According to our study, RIL seem to have an effect on survival outcomes, regardless of the localization of the radiation. All 6 subgroups of cancer showed that lymphopenia was a significant prognostic factor for poor OS. Three of the subgroups (head and neck, pancreas, and mixed pathologies group), although showing an association between RIL and death, had a statistically nonsignificant prediction interval, probably due to a lack of power in the analysis. After removing outlying studies, the low between-study heterogeneity and absence of publication bias support the robustness of these results.

Preclinical data have shown that the abscopal effect is, in fact, mediated by immune mechanisms.[2,3] However, RT can be a double-edged sword. Even if numerous molecular and cellular effects of RT lead to immune stimulation, radiation has been described also to be immunosuppressive. For example, radiation can upregulate PD-L1 expression in tumor and T cells, preventing an adequate antitumor response.[77] Lymphopenia, has been shown to be a prognostic factor for poor survival for patients receiving immunotherapy. A few papers showed that patients with lymphopenia before and during treatment with immunotherapy demonstrated significantly poorer outcomes.[78-80] However, whether a decline in the number and function of lymphocytes decreases the efficacy of immunotherapeutic agents or if lymphopenia is mainly a good biologic surrogate for performance status as shown in previous papers remains uncertain.[30,56]

The mechanisms of interaction between the immune stimulatory and suppressive effects of RT remain to be fully understood. We hypothesize that RIL could tilt the balance toward immune suppression and significantly diminish any hope of potentializing immunotherapy with RT; however, the results of this meta-analysis need to be interpreted with caution. Indeed, these results do not imply that a better OS was obtained by abscopal effect in the group of patients not showing RIL, but only indicate that patients showing RIL during treatment seem to have poorer OS than those not having lymphopenia. Nevertheless, the preclinical data mentioned previously and the results of this analysis hint that a better understanding of the mechanisms of RIL and protecting the antitumor immune response during radiation could help us understand the process by which RT may potentiate immunotherapy or create an out-of-field response.

Arguably, RIL is first a function of field size,[81] fractionation,[82] and overall treatment time.[38] Second, RIL could be explained also by the radiation dose received by hematopoietic and lymphopoietic organs. For example, the heart, lungs, liver, prominent blood vessels, and body, represent structures with abundant blood circulation, and the spleen, bone marrow, thymus, and lymph nodes are the proper lymphoid and hematopoietic organs.

For the first set of organs, the literature already alludes to a significant association between radiation to the heart,[22,34,40] lungs,[34,40] and body and lymphopenia.[34] The effect of radiation on proper lymphoid structures was evaluated in a study comparing leukocyte counts before, during, and 3 months after the beginning of treatment for 23 patients receiving pelvic radiation (70-78 Gy to the

prostate and seminal vesicles, with or without 50.4 Gy to pelvic lymph node areas) with a control group not receiving RT.[83] The study showed a significantly lower lymphocyte count associated with lymph node irradiation. The same question was asked for Berg lymph node radiation, with the same results.[84] Furthermore, radiation to the spleen was also assessed and showed that in some cohorts, the median cumulative spleen dose of patients with grade ≥3 lymphopenia was only 9.8 Gy,[49] and that a mean spleen dose >2.27 Gy had an approximate 14-fold increase in the risk of severe lymphopenia.[85] The dose to the bone marrow was also linked significantly to lymphopenia in a study of patients with esophageal cancer.[86]

A few authors have tried to combine the different plausible components of RIL into 1 mathematical model to estimate the effective dose to circulating immune cells (EDIC) to help risk-stratify patients and predict disease outcomes. In esophageal cancer, a study of 488 patients treated with concurrent chemoradiotherapy concurred that the EDIC was strongly associated with severe lymphopenia, especially when >4 Gy.[65] A similar paper, of 464 NSCLCs reported that EDIC >7.3 Gy was significantly associated with a greater reduction in local tumor control.[87] Considering EDIC instead of dose constraints to organs at risk of the immune system might be a more rounded approach to RIL, even if EDIC does not consider all alleged contributors of RIL, such as field size and overall treatment time.

This analysis has several limitations. First, because we colligated >11 types of cancers and >13,000 patients, the population we analyzed had mixed histologic data and mixed stages of disease. However, after removing outlying studies, the between-study heterogeneity was acceptable at 35%, and a significant effect of RIL on OS was found in all cancer subtypes. The included studies were published between 1991 and 2020, resulting in the inclusion of outdated RT techniques and old chemotherapy regimens, which is why we did not analyze the role of RT doses and techniques or chemotherapy on RIL. Treatment modality and dose–volume histogram constraints might differ between studies, which can influence the occurrence of lymphopenia, but because this is not an individual patient data meta-analysis, their input is impossible to assess.

Additionally, considering that the effect of RIL on survival was our main focus, the means by which lymphopenia may occur is beyond the scope of this paper. We focused only on OS without considering other important clinical endpoints (eg, local control or disease-free survival), because OS might be the least subject to bias, especially considering the primarily retrospective data. Furthermore, the studies did not all use the same definition of lymphopenia. Some used lymphocyte count relative to the neutrophil count, others used a selected cutoff value for the absolute lymphocyte count or neutrophil to lymphocyte ratio that was optimal for survival prediction based on receiver operating characteristic curves and the most used the Common Terminology Criteria for Adverse Events, version 4.0 or 5.0, thresholds. When determining the most discriminating biomarker for survival prediction, most studies used lymphocyte count (relative or absolute) 2 to 3 months after the end of RT, but no consensus regarding when blood sampling would be the most relevant was established.

Finally, this meta-analysis did not employ an individual patient data approach; therefore, we were not able to pool the raw data from each participant from each included study, which might be considered the ideal approach in meta-analysis statistical models.

## Conclusions

This meta-analysis confirms that RIL is a significant prognostic factor for survival in virtually all solid cancers. Pooled-effect estimates indicate a significantly reduced risk of death in patients without RIL. Tailoring RT regimens to spare the immune system and updating dosimetric constraints for new organs at risk, such as major blood vessels, organs with rich blood supplies, bones, and all lymph node areas, may be important to improve prognoses.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101038.

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