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Systematic Review

Toxicity after radiotherapy in patients with historically accepted contraindications to treatment (CONTRAD): An international systematic review and meta-analysis

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ABSTRACT

Background and purpose: To investigate the incidence of radiotherapy-related acute and late toxicities among patients with pro-inflammatory comorbidities.

Material and methods: PICOS/PRISMA/MOOSE methods were used to identify studies on PubMed and MEDLINE, 1970–2018. The following were extracted: location, cancer, sample size, age, follow-up duration, medical contraindication, treatment, and toxicity. A weighted random effects model with the DerSimonian and Laird method was used in the meta-analysis. The primary endpoint was the grade ≥ 3 acute toxicity, and the secondary endpoint was late toxicity.

Results: There were 1137 articles screened and 18 included, assessing 621 patients. Among the 18 articles, 10 had collagen vascular disease ($n = 417$) and 8 had inflammatory bowel disease ($n = 204$). Median follow-up was 52.8 months. 457 patients received radiotherapy alone, and 153 received concurrent chemo-radiotherapy. The random effects estimate for incidence of grade ≥ 3 toxicity in collagen vascular disease patients (95% confidence interval) was 11.7% (5.4–19.6%) and 6.1% (1.4–12.6%) for acute and late toxicities, respectively. Incidence of grade ≥ 3 toxicity in inflammatory bowel disease patients was 14.0% (7.1–22.4%) and 10.2% (3.2–19.7%) for acute and late toxicities, respectively. Average grade 4 toxicity across both diseases was 1.5% and 4.5% for acute and late toxicities, respectively. Average grade 5 toxicity across both diseases was negligible (<1%).

Conclusions: Patients with historically accepted contraindications to radiation therapy have a 10–15% risk of any grade ≥ 3 toxicity, <5% risk of grade 4 toxicity, and <1% risk for grade 5 toxicity, suggesting that collagen vascular disease and inflammatory bowel disease are not absolute contraindications to radiotherapy.

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Radiotherapy (RT) is used in the treatment course of 60% of cancer patients [1]. Current dogma in radiation oncology stipulates that certain autoimmune systemic conditions, including collagen vascular disease (CVD) and inflammatory bowel disease (IBD), are contraindications to RT, predisposing patients to a higher risk of toxicity from RT by triggering a pro-inflammatory cascade.

While case reports published in the 1970s–1980s suggest increased RT-related toxicity in CVD patients [2–11], more recent publications, including several matched control studies, report no increased risk for acute or late complications between CVD and non-CVD patients undergoing RT. A systematic review conducted by Chon and Loeffler in 2002 [12] concluded that the majority of published studies show lower RT tolerance for patients with CVD and IBD. Despite reporting a 12.4–70% and 7–100% risk of significant grade >3 acute toxicity and late toxicity, respectively, they acknowledged their results may have been subjected to publication bias, since the majority of studies found were retrospective case reports with limited sample sizes.

Given that new prospective studies have emerged since the early 2000s, there is a need to re-evaluate relative and absolute contraindications to RT. As such, the aim of this review is to investigate the extent to which CVD and IBD increase the risk of RT-related acute and late toxicities. Prior to beginning our data collection, we hypothesized that the incidence of grade ≥ 3 toxicity would be <20%. The results of this work may be used to support RT as a treatment option for patients with comorbid CVD and IBD.

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Methods and materials

Data sources

The inclusion criteria for the literature search was defined using the Population, Intervention, Control, Outcome, Study Design (PICOS; Table 1) approach. Medical literature including clinical trials, clinical studies, evaluation studies, comparative studies, multicenter studies, and case reports published in English from 1970 up to 2018 was searched in PubMed, MEDLINE, The Cochrane Library, CINAHL, and EMBASE (Search Strategy; Supplementary Text 1). The search was conducted by a medical student (BA) and attending radiation oncologist (MD/MS) with specialization in oncologic meta-analysis. CVD is an overarching categorization of heterogenous systemic autoimmune connective tissue disorders including rheumatoid arthritis (RA), systemic lupus erythematous (SLE), scleroderma, Sjogren's, mixed connective tissue disorder, discoid lupus erythematous, polymyositis or dermatomyositis, CREST Syndrome, or ankylosing spondylitis; thus, the search query aimed to incorporate all historically accepted contraindications to RT [12,13].

Table 1
Population, intervention, control, outcome, study design (PICOS) inclusion criteria.

Population	Patients receiving radiotherapy for cancer, with comorbid CVD (e.g. SLE, RA, etc.) or IBD
Intervention	RT in the cancer treatment course
Control	Either compared to patients without the disorder or no control group reported
Outcome	Incidence of CTCAE acute and late grade 3, 4, and 5 toxicities. Other grading scales (e.g. RTOG, EORTC) reported by the studies were converted to CTCAE equivalent
Study Design	Prospective or retrospective study, with at least 4 individual patients reported; no minimum time period reported

Abbreviations: CVD: collagen vascular disease; SLE: systemic lupus erythematous; RA: rheumatoid arthritis; IBD: inflammatory bowel disease; RT: radiotherapy; CTCAE: Common Terminology Criteria for Adverse Events; RTOG: Radiation Therapy Oncology Group; EORTC: European Organization for Research and Treatment of Cancer.

Data extraction and synthesis

The systematic search produced 1133 results; four additional studies were found through hand-searching. Terms were screened for eligibility based on publication titles, enabling the exclusion of basic science and non-human studies. After initial screening, 66 studies were further assessed for eligibility, leading to the exclusion of 48 studies due to study type and data evaluation. Specifically, case reports were excluded because of reporting bias, since clinicians may be more likely to report the worst-case scenarios and toxicities. The final 18 studies were selected by two authors based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Fig. 1) literature selection protocol

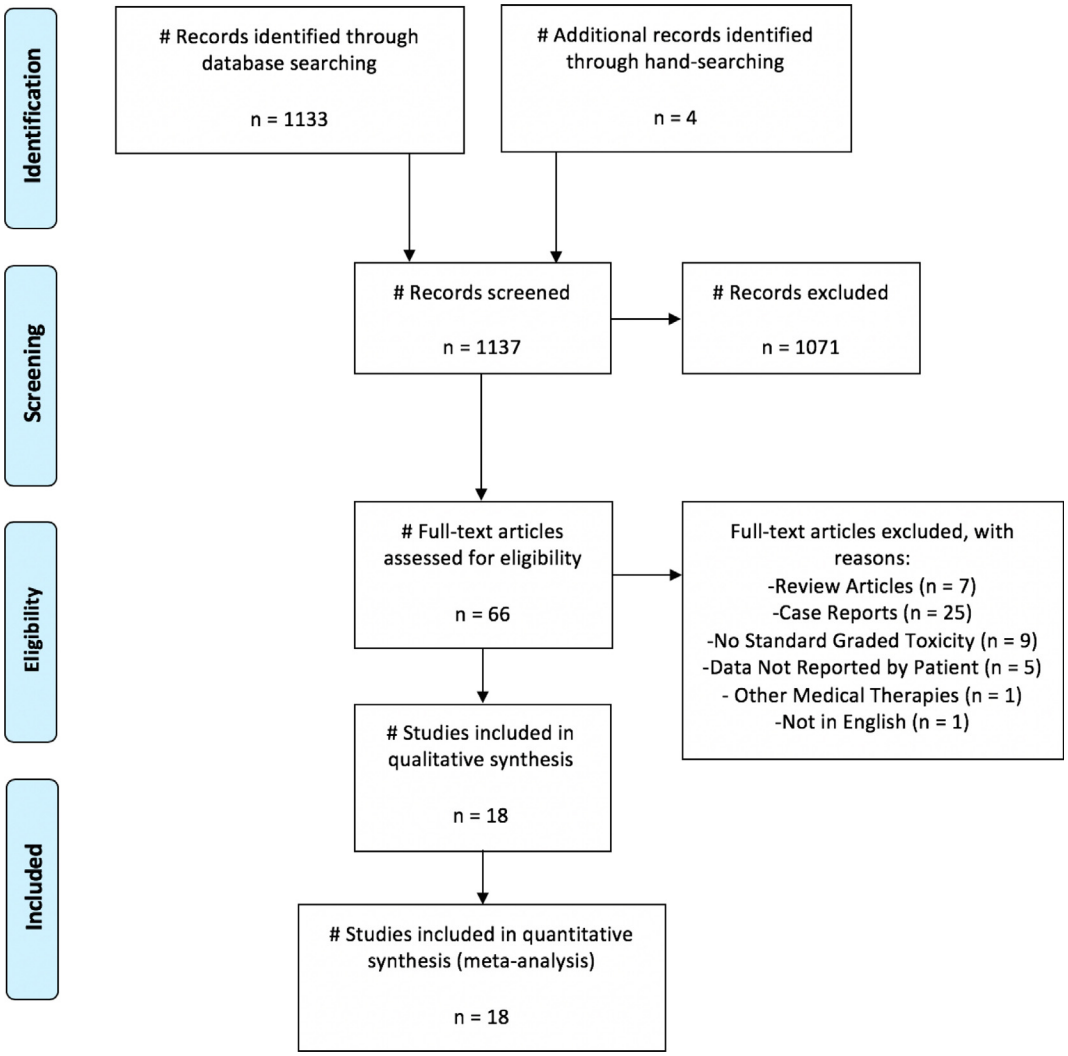

Fig. 1. PRISMA diagram flow diagram describing the data collection process following the PRISMA convention.

[14]. Given the date range of articles found, authors of the manuscripts were not contacted, since their contact credentials were no longer valid; moreover, we were able to extract all necessary data from the works.

Extracted data include population size, median patient age, median follow-up duration, contraindication, study location, treatment modality, intervention technique, acute toxicities (grade 1–5), and late toxicities (grade 1–5). Due to a common lack of patient-level data reported in the studies, it was not possible to extract incidence of grade ≥ 3 toxicity by irradiation site or cancer subtype.

Endpoints

The primary endpoint was the rate of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 acute toxicity. Toxicities rated as grade 3 are severe or medically significant but not immediately life-threatening; grade 4 include life-threatening consequences; and grade 5 pertain to death due to RT-related adverse events. The secondary endpoint was CTCAE grade ≥ 3 late toxicity.

Statistical analysis

Statistical analyses were conducted using R Studio Version 1.1.383 (Boston, MA) via the Meta-Analysis Package for R (metafor) package. Weighted random-effects meta-analyses, using the DerSimonian and Laird method [15] to calculate between study variances, were utilized in order to evaluate toxicity with respect to contraindication. A random effects approach was chosen over its fixed effect counterpart for two reasons: (1) random effects models have been shown to be superior when the meta-analysis is designed to aid in clinical decision making [16,17]; (2) the presence of heterogeneity among the outcomes. Heterogeneity was assessed using the I^2 statistic and the Cochran Q-Test [17,18]. Significant heterogeneity was considered to be present if the I^2 statistic was > 50% and the p-value of the Q-test was < 0.10. Sensitivity analyses included assessment of publication bias for each outcome, which was assessed via funnel plots and the Egger test (Supplementary Fig. 1) [19]. Publication bias was considered to be present if the *p*-value of the Egger Test was <0.05.

Results

Study characteristics

The meta-analysis included a total of 621 patients across 18 studies published from the year 1993 to 2017, across the United States [20–33], Canada [34,35], the Netherlands [36], and France [37]. Of the 18 studies, 10 included CVD patients and 8 included IBD patients, with 417 and 204 patients, respectively. Of the CVD patients, 245 had RA, 55 had SLE, 7 had Sjogren's or mixed connective tissue disease, 29 had discoid lupus erythematous, 22 had polymyositis or dermatomyositis, 5 had juvenile RA, 44 had scleroderma or CREST syndrome, and 8 had ankylosing spondylitis.

The median age was 60 years, median follow-up was 53 months, and median RT dose was 49.75 Gy. Radiation sites for CVD patients varied, while sites for IBD patients were more localized to the pelvis, prostate, and colon/rectum areas [30,31,33,35–37]. Of the total 621 cancer patients receiving RT as part of their treatment course, 270 patients received RT alone; 151 received concurrent chemo-RT; 187 received post-operative RT; and 2 received post-operative chemo-RT. Study characteristics were outlined in (Study Characteristics; Table 2).

Within each of the 18 studies, the majority of the patients experienced either no toxicity or grade 1–2 toxicity. A distribution of acute and late toxicities across each individual study (Acute and

Table 2
Study characteristics.

Study	Contraindication	*n*	Median age (yr)	Median follow-up (mo)	Treatment				Acute toxicity (%)			Late toxicity (%)		
					RT only	RT + Chemo	RT + Surgery	RT + Chemo + Surgery	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Benk, 2005 [34]	CVD (SLE)	4	56	44	3	1	0	0	0	0	0	0	0	0
Diao, 2017 [20]	CVD (RA, SLE, Scleroderma, etc.)	31	64	55	6	25	0	0	23	0	3	0	0	0
Dong, 2017 [21]	CVD (RA)	40	60	94	25	15	0	0	3	0	0	0	0	0
Felefly, 2017 [37]	CVD (RA)	8	NR	56	1	7	0	0	13	0	0	13	0	0
Gold, 2007 [22]	CVD (Scleroderma)	20	65	56	14	6	0	0	10	5	0	10	0	5
Lowell, 2011 [23]	CVD (RA, SLE)	14	63	16	14	0	0	0	NR	NR	NR	0	0	0
Morris, 1997 [24]	CVD (RA, SLE, Scleroderma, etc.)	209	63	192	85	53	71	0	NR	NR	NR	6	5	0
Patel, 2012 [25]	CVD (DLE)	13	69	31	12	3	3	0	8	8	0	23	0	0
Pinn, 2008 [26]	CVD (SLE)	17	57	67	NR	NR	NR	NR	24	0	0	12	12	0
Ross, 1993 [27]	CVD (RA, DLE, Scleroderma, etc.)	61	61	78	31	6	23	1	11	0	0	3	3	3
Song, 2001 [28]	IBD	24	50	11	9	15	0	0	13	8	0	0	8	0
White, 2015 [29]	IBD	19	64	33	11	8	0	0	11	0	0	5	0	0
Willett, 2000 [30]	IBD	28	58	32	4	0	24	0	21	0	0	4	25	0
Bosch, 2017 [36]	IBD	66	58	NR	0	0	66	0	8	3	0	0	0	0
Chang, 2015 [31]	IBD	15	57	55	15	0	0	0	20	7	0	0	13	0
Green, 1999 [32]	IBD	15	48	24	2	12	0	1	13	7	0	0	13	0
Pai, 2013 [35]	IBD	13	67	50.4	13	0	0	0	15	8	0	8	8	0
Peters, 2006 [33]	IBD	24	NR	48.5	25	0	0	0	0	0	0	0	0	0

Abbreviations: RT: radiotherapy; Chemo: chemotherapy; CVD: collagen vascular disease; SLE: systemic lupus erythematous; RA: rheumatoid arthritis; DLE: discoid lupus erythematous; IBD: inflammatory bowel disease; NR: not reported.

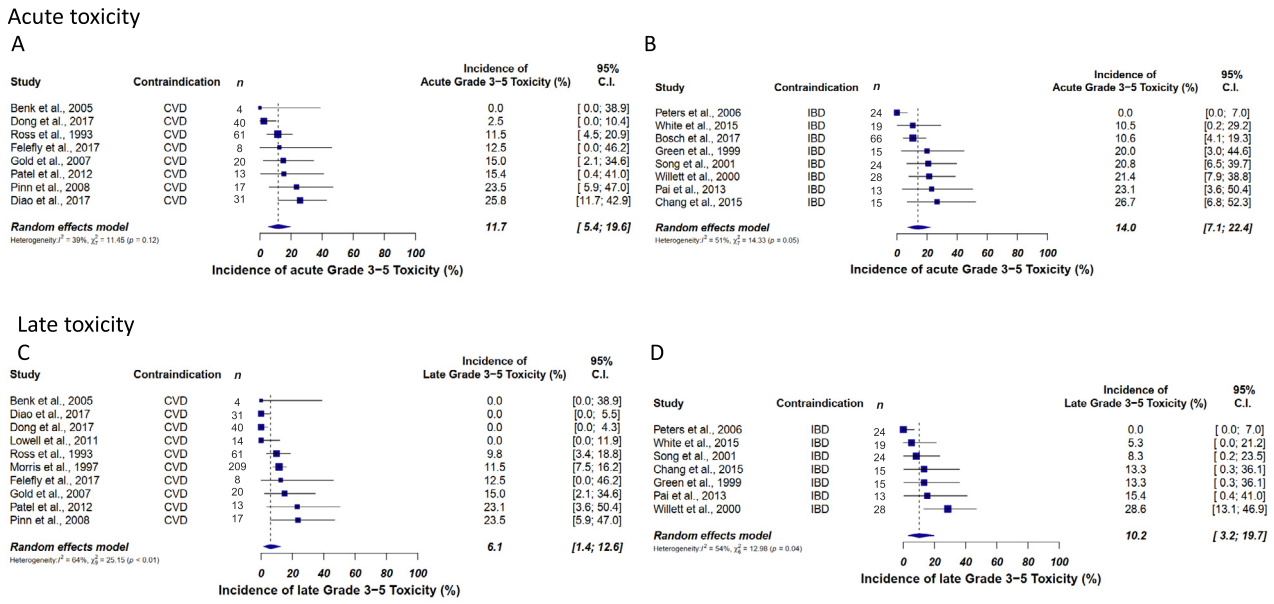

Fig. 2. Acute and late toxicity after RT. Forest diagrams depicting each study, contraindication, and incidence of acute and late grade 3–5 toxicities with 95% CI. Summary effect sizes under the random-effects model are depicted along with heterogeneity tests. These results indicate that incidence of grade 3–5 toxicity is low across CVD (panels A, C) and IBD (B, D) patients. The random effects estimate for incidence of grade 3–5 toxicity in CVD patients was 11.7% (A) and 6.1% (C) for acute and late toxicities, respectively. Incidence of grade 3–5 toxicity in IBD patients was 14.0% (B) and 10.2% (D) for acute and late toxicities, respectively. (Abbreviations: CI: confidence interval, CVD: collagen vascular diseases, IBD: inflammatory bowel disease).

Late Toxicity After RT; Fig. 2) revealed the negligible incidence of grade 5 toxicity and a relatively low (ranging from 0 to 25%) incidence of grade 3 or 4 toxicity, regardless of contraindication or the sample size within each study.

Endpoints

The endpoints for this meta-analysis were grade $\geq$ 3 toxicity, which represent clinically significant adverse events. Overall, grade $\geq$ 3 acute and late toxicity occurred in <15% of patients. Average grade 4 toxicity across CVD and IBD patients was 1.5% and 4.5% for acute and late toxicities, respectively. Average grade 5 toxicity was negligible (<1%) for both CVD and IBD patients.

Results of the meta-analysis of acute and late toxicities after RT, grouped by contraindication is depicted in (Fig. 2). The random effects estimate for incidence of grade $\geq$ 3 toxicity in CVD patients was 11.7% (95% CI: 5.4–19.6%) and 6.1% (95% CI: 1.4–12.6%) for acute and late toxicities, respectively. Incidence of grade $\geq$ 3 toxicity in IBD patients was 14.0% (95% CI: 7.1–22.4%) and 10.2% (95% CI: 3.2–19.7%) for acute and late toxicities, respectively.

Subgroup analysis

A CVD subgroup analysis for grade $\geq$ 3 toxicity was conducted for RA and SLE, which were among the most frequently reported CVDs by different studies (Subgroup Analysis of Late Toxicity for RA and SLE; Fig. 3). The analysis included 6 studies for RA and 4 for SLE. Of the total 296 patients, the 245 RA patients and 51 SLE patients all shared similar irradiation sites including, head and neck, CNS, intrathorax, breast, abdomen, and pelvis [20,21,23,24,26,27,37]. The incidence of grade $\geq$ 3 toxicity for RA was 8.7% (95% CI: 1.4–19.7%) and for SLE was 12.5% (95% CI: 0.0–39.5%).

Discussion

CVD and IBD have historically been considered contraindications to RT due to concerns of causing higher rates of post-RT acute and late toxicities, yet have been poorly understood, given the heterogeneity in CVD subtypes, diversity of graded toxicity guidelines, and variation in RT treatment sites. This work represents the most comprehensive systematic review and meta-analysis studying the impact that historically accepted contraindications have on the tolerance of irradiation in cancer patients. Contrary to historical dogma, we report relatively low incidence of severe toxicities among these patients: a 10–15% risk of grade $\geq$ 3 toxicity, <5% risk of grade 4 toxicity, and <1% risk for grade 5 toxicity.

Although within expected range, it is important to note that the incidence for grade $\geq$ 3 toxicity in the current work supports results from other reviews, matched control group studies, and large retrospective trials [13,20,27,31]. These studies, all of which provide a higher level of evidence than the case reports excluded in our selection strategy, have reported that acute grade $\geq$ 3 toxicity occurred in 7–14%, and late grade $\geq$ 3 toxicity occurred in 7–23% of CVD patients [13,24,27,38]. Similarly, acute grade $\geq$ 3 toxicity occurred in 7–20%, and late grade $\geq$ 3 toxicity occurred in 5–15% of IBD patients [39]. Taken together, these findings suggest RT is generally well-tolerated in these patients and that other factors, such as multiple sites of irradiation, RT dose, or the use of concurrent chemotherapy, may explain the variation in adverse events following RT.

Our data showing <5% risk of grade 4 toxicity and <1% risk for grade 5 toxicity indicate that life-threatening consequences (grade 4 toxicity) and death (grade 5 toxicity) as direct results of RT are minimal in this patient population. As such, these findings provide additional evidence that CVD and IBD are not absolute contraindications to RT. This implication is of particular importance for the treatment of certain neoplasms, such as prostate cancer, where clinicians may be concerned about increased toxicity from RT with comorbid IBD when compared to definitive surgery. In this case, evidence found through this research, suggesting that CVD and IBD should not preclude RT in the course of a patient's cancer treatment, has direct clinical significance and application.

Several limitations exist in our analysis. To develop our search criteria for the systematic review, we identified specific CVD subtypes based on the most frequently studied diseases; however,

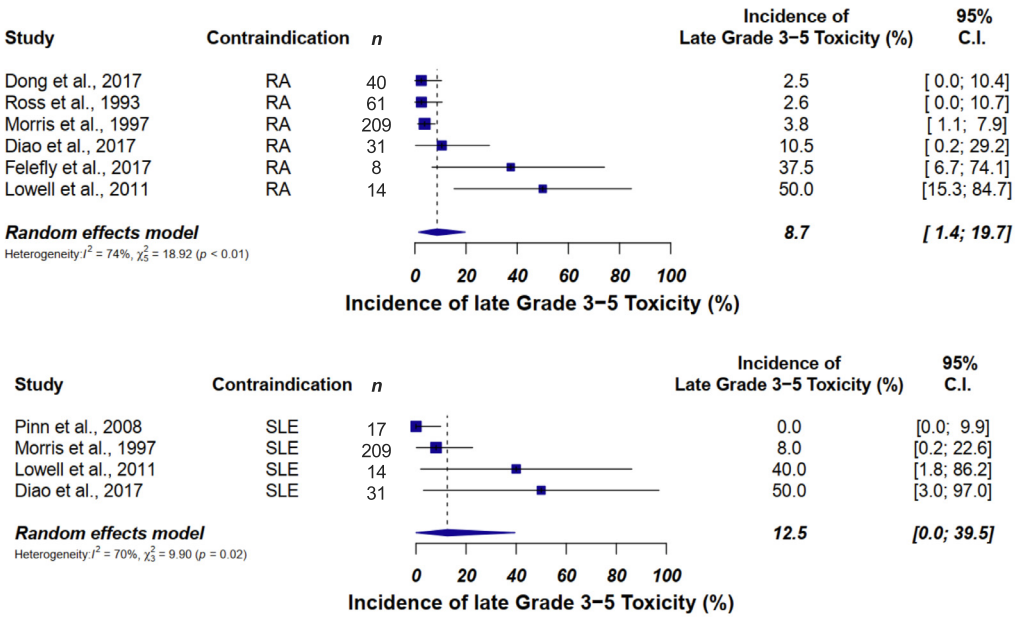

Fig. 3. Subgroup analyses of late toxicity for RA and SLE Forest diagrams depicting late grade 3–5 toxicity in CVD subgroups, RA and SLE, with 95% CI. Summary effect sizes under the random-effects model are depicted along with heterogeneity tests. Results indicate the incidence of grade 3–5 toxicity for RA was 8.7% and for SLE was 12.5%. Not all subgroups of CVD were included; because Sjogren's, mixed connective tissue disorder, discoid lupus erythematous, polymyositis or dermatomyositis, CREST Syndrome, and ankylosing spondylitis did not have sufficient studies (n < 5), they were excluded from the subgroup meta-analysis.

there may be other unique conditions or biomarkers that predispose patients to toxicity (e.g. IL-6, TGF-B, PD-1 in lung cancer patients) [40,41]. Our work may have excluded certain populations of patients for analysis and limited the number of patients analyzed for each subtype.

Based on the studies identified, our analysis was most likely limited to patients of European/Caucasian descent. In attempts to address heterogeneity and publication bias, funnel plots with the Egger tests were included (Supplementary Fig. 1).

Extensive analysis of potential cofounding variables was limited given that many publications were retrospective, did not select for radiation site or cancer subtype in their participants, or reported contraindications in subgroups rather than individually (e.g. non-RA vs. RA). Additionally, some studies reported toxicities per treatment or toxicity type rather than by patients. As such, we were unable to account for factors such as CVD or IBD severity at the time of RT, or incidence of grade ≥ 3 toxicity by irradiation site or cancer subtype. Moreover, toxicity grading guidelines utilized by studies varied. To standardize the criteria, we favored the conversion of all other grading systems (e.g. RTOG or EORTC) to CTCAE, especially since RTOG has been previously criticized for its lack of sensitivity in comparison to CTCAE [42]. Since various studies defined acute and late toxicities differently, or did not provide specific time frames, we were limited in our ability to standardize this definition for the meta-analysis. Due to a lack of comprehensive patient-level data and inconsistency among studies, it was necessary for us to extrapolate, estimate, or exclude some data from our analysis, which could have compromised accuracy.

Most importantly, these studies included patients treated in the 1960s and 1970s, predating the availability of modern RT and imaging modalities, such as intensity-modulated radiation therapy (IMRT), which was not introduced until the mid-to-late 2000s [43–45] but have significant implications on RT toxicity. Similarly, intra-prostatic fiducial markers and tissue spacing agents have been reported to reduce radiation exposure of surrounding tissue [46]. As a result, RT toxicity is even lower in the current era than it was in the 1990s or early 2000s [47,48].

In our work, we noted statistical heterogeneity due to clinical and methodological variabilities among the studies. Select factors affecting heterogeneity include setting (e.g. definitive, post-op), time period, duration of follow-up, diagnostic criteria (e.g. of cancer, comorbidity, toxicity), and RT modality. To address heterogeneity in our meta-analysis, we utilized a random effects model over a fixed effects model, which accounts for inherent heterogeneity present among studies.

Conclusions

In summary, although CVD and IBD have previously been thought to predispose patients to an increased risk of RT toxicity, our analysis indicates a10–15% risk of any grade ≥ 3 toxicity, <5% risk of grade 4 toxicity, and <1% risk for grade 5 toxicity. As such, CVD and IBD are not absolute contraindications to RT and should not preclude RT for curable cancer therapy.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.03.006.

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