CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Chest wall toxicity after stereotactic radiation in early lung cancer: a systematic review

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ABSTRACT

Background Radiation-induced chest wall pain (CWP) and rib fracture (RF) are late adverse effects after stereotactic body radiation therapy (SBRT) for stage I non-small-cell lung cancer (NSCLC); however, the literature about their incidence and risk factors shows variability. We performed a systematic review to determine the pooled incidence of CWP and RF in the relevant population.

Methods A literature search using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines considered English publications in MEDLINE and EMBASE from January 1996 to August 2017. Abstracts were screened, followed by full-text review and data extraction.

Results The database searches identified 547 records. Twenty-eight publications comprising 3892 patients met the inclusion criteria. Median reported ages and follow-up durations fell into the ranges 67–82 years and 12–84 months. Prescriptions fell into the range of 40–70 Gy in 3–10 fractions. Despite study heterogeneity, the pooled incidences of CWP and RF were estimated to be 8.94% and 5.27% respectively. Nineteen studies reported CWP grade: 58 of 308 patients (18.8%) experienced grades 3–4 CWP (no grade 5 events reported). Thirteen studies reported RF grade: grades 3–4 RF were observed in 9 of 113 patients (7.96%). A high chest wall V_{30} was an important predictor of CWP and RF.

Conclusions In patients with stage I NSCLC, rates of CWP and RF after SBRT are low; however, tumour location, accurate toxicity reporting, and dose–fractionation schemes might alter those rates. Prospective correlation with dosimetry and quality of life assessment will further improve the understanding of CWP and RF after SBRT.

Key Words Chest wall pain, rib fracture, stereotactic body radiation therapy, non-small-cell lung cancer, systematic reviews

Curr Oncol. 2020 August:27(4)179–189 www.current-oncology.com

INTRODUCTION

Stereotactic body radiation therapy (SBRT) is established as a viable treatment option for patients with stage I non-small-cell lung cancer (NSCLC) and is usually indicated in patients deemed ineligible for surgical resection. Even with extended follow-up (beyond 5 years after therapy), SBRT has been associated with excellent rates of local control[1].

Together with prolonged local control, patients treated with SBRT can, because of the extreme hypofractionation used, experience unique toxicities not usually reported with conventional radiotherapy. The radiation-induced chest wall toxicities (CWTs) of chest wall pain (CWP) and rib fracture (RF) are two examples of unique late adverse effects after hypofractionated SBRT. Chest wall pain can be focal or neuropathic in nature, and mild to moderate in severity; RF can be symptomatic or asymptomatic[2]. Radiation-induced RF is considered a late toxicity of therapy and typically develops after approximately 6–48 months, occurring either transiently or lasting several weeks or longer[3]. The proposed mechanism of CWP is injury to the peripheral nerves, causing any one or more of paresthesia, hypoesthesia, weakness, and pain. Mild-to-moderate CWP can be treated effectively with narcotics or anti-inflammatory medication.

Currently, despite many reports documenting SBRT-induced CWT, the incidence of, and risk factors for, CWP and

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Supplemental material available at http://www.current-oncology.com

RF in this population shows variability. There is also lack of clarity about the dosimetric parameters that might increase the risk of CWP and RF after SBRT. Such information would be useful for clinicians for purposes of patient consent, treatment planning, and follow-up guidelines. We therefore performed a systematic review to determine the pooled incidence of CWP and RF in patients with stage I NSCLC treated with SBRT.

METHODS

Search Strategy

A comprehensive literature search that followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was conducted. The MEDLINE and EMBASE databases were queried to obtain English language studies analyzing CWP and RF after SBRT for early-stage NSCLC for the period January 1996 to 22 August 2017. A health research methodologist (CWD) assisted in the development of the search strategy and executed the search. A grey literature search using the Google and Google Scholar search engines, with key terms, was conducted to find conference abstracts, presentations, proceedings, regulatory data, unpublished trial data, government publications, reports, dissertations or theses, patents, and policies and procedures for review. No additional studies were included after review of pertinent studies from the grey literature search. Details about the search strategy can be found in supplementary Appendix 1.

Inclusion Criteria

Screening of titles and abstracts from the primary search was initially conducted independently by 2 reviewers (ISV, ED), and discrepancies were resolved by a 3rd reviewer (AS). If two or more studies were published using the same cohort of patients, the most recent study that fulfilled the inclusion criteria was kept. Included studies relevant for the review met these criteria:

- An early-stage (stage I) primary NSCLC site of radiation therapy (studies that included patients with lung metastases or in which primary could not be parsed out from metastatic disease were excluded; re-irradiation by SBRT for local recurrence was also excluded)
- The primary modality of treatment being SBRT
- The study type being a randomized controlled trial, a meta-analysis of randomized controlled trials, a prospective study, or a retrospective study (case reports, case series, abstracts, letters, and commentaries were excluded)
- Incidence of CWP or RF (or both) reported
- Inclusion of 20 or more patients
- Publication in the English language
- Toxicities scored using the *Common Terminology Criteria for Adverse Events,* version 3.0 or 4.0[4,5]

Data Abstraction and Analysis

Full-text publication review and data extraction were performed by the primary reviewer (ISV). A weighted analysis of the data was performed by 2 reviewers (ISV, AS). Given the heterogeneity of the studies, a formal meta-analysis could not be performed. Pooled weighted analyses were performed to obtain the incidences of both CWP and RF across all available studies, with the sum of the crude number of RFs (total and totals by grade) and of the crude incidences of CWP (total and totals by grade) divided by the total number of patients included in the analysis who received SBRT for the first time for their lung cancer. The ROBINS-I risk of bias tool was used to assess bias in each study[6].

CWT Reporting

To describe the severity of organ toxicity (adverse events) for patients receiving cancer therapy, toxicity data are reported using standardized definitions *(Common Terminology Criteria for Adverse Events,* version 3.0 or 4.0).

RESULTS

Search Results

A PRISMA 2009 flow diagram (Figure 1) summarizes the review process. The initial database search identified 547 records. After exclusion of abstracts, seventy full-text articles were assessed for eligibility. Of those articles, forty-two were excluded because they did not meet the inclusion criteria. Studies were excluded if they included patients who had previously received radiotherapy for lung cancer, who did not have primary lung cancer, or who received SBRT for lung metastases. Studies were also excluded if toxicity was scored using a scale other than the *Common Terminology Criteria for Adverse Events,* version 3.0 or 4.0.

Study Characteristics

Table I summarizes characteristics of the included studies and patients. Twenty-eight full-text publications met the inclusion criteria, representing 3892 patients treated with

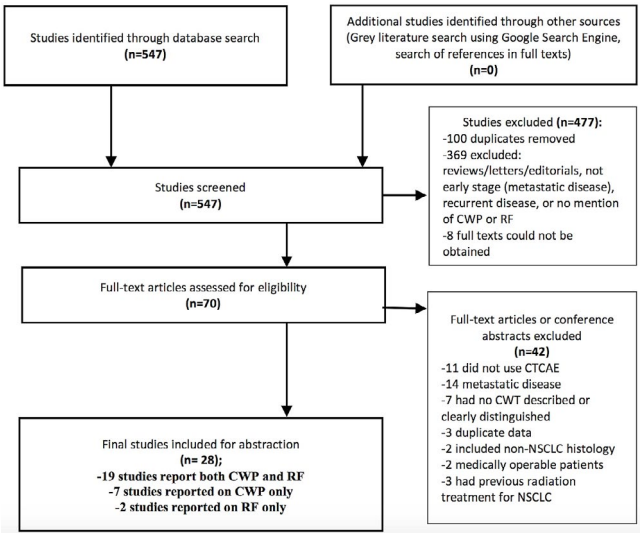

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram outlining the literature search strategy. CWP = chest wall pain; RF = rib fracture; CTCAE = *Common Terminology Criteria for Adverse Events;* NSCLC = non-small-cell lung cancer.

SBRT for primary lung cancer for the first time[2,3,7–32]. Dates for the extracted studies reached up to August 2017. Median patient age in the included studies ranged from 67 to 82 years, and median follow-up varied from 12 to 84 months. Studies were mostly retrospective in nature. The number of patients evaluated in each study ranged from 20 to 772. Doses ranged from 40 Gy to 70 Gy in 3–10 fractions.

Patient characteristics summarized in Table I include sex, T stage, and tumour location and histology. Results across studies were heterogeneous because of differences in grading, tumour location, and the observational nature of the studies. As a result, a formal meta-analysis of the data was not performed, and a weighted pooled analysis of the data was undertaken as described in the Methods section. The ROBINS-I risk of bias tool noted a significantly high risk of bias in most studies because of nonrandomized populations.

CWT Results Across Studies

Table II summarizes the CWP and RF toxicity grading. The weighted pooled incidence of reported CWP, including all grades, was estimated to be 8.94%, and the pooled incidence of reported RF, including all grades, was estimated to be 5.27%. Across studies, the median time to CWP fell into the range of 3–13 months, and the median time to RF fell into the range of 3–34.8 months. Nineteen studies reported the grade of CWP toxicity[2,7-12,14-17,19,20,23,25-28,31] (summarized in Table III), with 58 of 308 patients who had graded CWP (18.8%) experiencing grades 3–4 pain (no grade 5 events reported). Thirteen studies reported the grade of RF toxicity[2,7,8,10-12,15,20,21,24,26,27,32] (summarized in Table III), with 9 of 113 patients who had graded RF (7.96%) experiencing grades 3–4 toxicity[2,10,11,20,24,26].

SBRT Dosimetry Across Studies

Table IV summarizes the SBRT dosimetry analysis for twenty-eight included studies. Four studies reported specifically on chest wall dosimetry, with the most common parameter being the volume receiving 30 Gy or more (V_{30}) in cubic centimetres[19,24,28,31]. Within those studies, a high chest wall V_{30} was found to be an important common predictor of both CWP and RF.

DISCUSSION

Individual studies have reported the incidence of CWT after SBRT for early-stage NSCLC[33]; however, to our knowledge, the present comprehensive systematic review is the first to examine the pooled incidence of CWP and RF across studies in patients specifically with early-stage NSCLC (excluding patients with lung metastases) treated with SBRT. Because SBRT-related toxicities typically occur late (after 6 months) and can be severe, knowledge about the potential incidence of late side effects is important for guiding the consent process with patients and for ensuring appropriate SBRT planning to minimize the toxicity risk. Based on our review, the overall rates of RF and CWP across studies appear reassuringly low; however, a small but significant proportion of patients with RF and CWP experience significant morbidity, with 7.96% (RF) and 18.8% (CWP) reporting grade 3 or greater toxicity. In patients undergoing surgery (the standard of care for stage I NSCLC), post-thoracotomy pain can occur in approximately 50% of patients[34], with 30% of patients reporting pain after 4–5 years[35]. Up to 10% of postsurgical patients experience severe, disabling pain[36]. Thus, in a valid comparison between treatments, the risks

TABLE I Characteristics of 28 studies analyzed

Variable	Value
Study characteristics	
Location (*n* studies)	United States (14) Netherlands (5) Sweden (2) Japan (2) Canada (2) Korea (1) Multicentre (2)
Type (*n* studies)	Retrospective (22) Prospective (4) Randomized controlled trials (2)[a]
Patient characteristics	
Enrolled *(n)*	3892
Per-study range	20–772
Median age range [years (21 studies)]	67–82
Sex *(n)*	
Men (21 studies)	1790
Women (22 studies)	1580
Tumour characteristics	
T Stage *(n)*	
T1 (20 studies)	2128
T2 (16 studies)	607
Histology *(n)*	
Adenocarcinoma (16 studies)	968
Squamous cell carcinoma (16 studies)	625
NOS or other (16 studies)	151
Location *(n)*	
Central (11 studies[7–17])	454
Peripheral (17 studies[3,7–10,12–23])	2059
Treatment characteristics	
Total dose (Gy)	40–70
Total fractions *(n)*	3–10
Dose per fraction (Gy)	5–22
Most common Rx (total Gy/*n* fractions)	60/3 and 60/5
Median follow-up (months)	12–84
Studies stating tumour distance from chest wall *(n)*	4[2,24,25]

[a] Pooled analysis of 2 randomized controlled trials (RCTs).
NOS = not otherwise specified.

TABLE II Overview of the 28 analyzed studies

Reference	Study type	Treatment with SBRT (*n*)		Dose (Gy/fractions)	EQD2 with alpha/beta of 3 (Gy)	Tumour location, if reported	Reported rate (%) of ...	
		Pts	Tumours				CWP	RF
Baumann *et al.*, 2009[26]	Retrospective	57	57	45/3, 66/3	162, 330	Mixed (not specific)	22.8	10.5
Collins *et al.*, 2009[18]	Retrospective	20	20	42/3, 60/3	142.80, 276	Close (5 mm) to pleura: 12	40	NR
Stephans *et al.*, 2009[30]	Retrospective	86	94	50/5, 60/3	130, 276	Mixed (not specific)	11.6	NR
van der Voort van Zyp *et al.*, 2009[23]	Retrospective	70	70	45/3, 60/3	162, 276	Peripheral: 70	7.14	1.43
Dunlap *et al.*, 2010[3]	Retrospective	40	40	60/3–5	276, 180	Peripheral: 40	22.5	NR
van der Voort van Zyp *et al.*, 2010[16]	Retrospective	39	39	60/3	276	Central: 6; peripheral: 33	7.69	NR
Videtic *et al.*, 2010[17]	Retrospective	26	28	50/5	130	Central: 3; peripheral: 25	3.85	NR
Bongers *et al.*, 2011[25]	Prospective	500	530	60/3, 60/5, 60/8	276, 180, 126	Mixed (not specific)	11.4	1.60
Haasbeek *et al.*, 2011[11]	Retrospective	63	63	60/8	126	Central: 63	19.0	1.59
Taremi *et al.*, 2012[2]	Retrospective	46	46	50/10 or 60/8 central, 48/4 or 54–60/3 peripheral	80 or 126, 144 or 226.80–276	Mixed (not specific)	45.7	37.0
Asai *et al.*, 2012[24]	Retrospective	116	116	48/5	120.96	Mixed (not specific)	NR	24.1
Mutter *et al.*, 2012[28]	Prospective	126	126	40–60/3–5	130.40, 88, 276, 180	R-Superior: 41; R-inferior: 26 R-middle: 11; L-superior: 26; L-inferior: 22	42.9	3.97
Woody *et al.*, 2012[31]	Retrospective	102	102	60/3, 50/5, 48/4, and 50/10	276, 130, 144, 80	Not reported	19.6	NR
Chang *et al.*, 2014[9]	Retrospective	101	101	50/4, 70/10	155, 140	Central: 82; peripheral: 19	30.7	0
Lucas Jr *et al.*, 2014[13]	Retrospective	81	81	54/3	226.80	Central: 15; peripheral: 66; unknown: 4	6.17	0
Rosen *et al.*, 2014[29]	Retrospective	79	79	48/4, 60/5	144, 180	Not reported	7.59	2.53
Chang *et al.*, 2015[10]	Pooled RCTs	31	31	54/3 peripheral, 50/4 central	130, 155	Central: 2; peripheral: 29	9.68	3.23
Jung *et al.*, 2015[12]	Retrospective	44	44	48–60/3–4	182.40, 144, 276, 216	Central: 3; apical: 3; chest wall abutting: 22; peripheral: 16	4.55	6.82
Lindberg *et al.*, 2015[20]	Prospective phase II	57	57	45/3	162	Peripheral: 57	7.02	14.0
Yoshitake *et al.*, 2015[32]	Retrospective	88	88	48/4	144	Not reported	NR	6.82
Alite *et al.*, 2016[7]	Retrospective	107	117	50/5, 60/5	130, 180	Central: 34; peripheral: 83	2.80	0.93
Bhandari *et al.*, 2016[27]	Retrospective	55	59	48/5, 50/5, 54/3, 60/3, 62.5/10	120.96, 130, 226.80, 276, 115.63	Not reported	5.45	3.64
Mancini *et al.*, 2016[14]	Retrospective	251	251	54/3	226.80	Central: 111; peripheral: 10	0.80	NR
Nyman *et al.*, 2016[21]	RCT	48	48	66/3	330	Peripheral: 48	4.17	16.7
Brooks *et al.*, 2017[8]	Retrospective	772	772	50/4, 70/10	155, 140	Central: 127; peripheral: 645	4.02	2.07
Jumeau *et al.*, 2017[19]	Retrospective	356	361	60/3–5	276, 180	Peripheral: 361	5.62	3.37
Stam *et al.*, 2017[22]	Retrospective	466	466	45/3, 54/3	162, 226.80	Peripheral: 466	NR	13.7
Sun *et al.*, 2017[15]	Prospective	65	65	50/4	155	Central: 8; peripheral: 57	35.4	24.6
							Pooled incidence:	
TOTAL		3892	3951				8.94%	5.27%

SBRT = stereotactic body radiation therapy; Pts = patients; EQD2 = equivalent total dose in 2 Gy fractions; CWP = chest wall pain; RF = rib fracture; NR = not reported; RCT = randomized controlled trial.

TABLE III Studies describing the grade of adverse effects

Reference	Total pts *(n)*	CWP or RF with reported toxicity grade	Grade			
			1	2	3	4
*Studies (*n*=19) describing grade of CWP*						
Baumann *et al.*, 2009[26]	57	13	11 (9 early, 2 late)		2 (early)	—
van der Voort van Zyp *et al.*, 2009[23]	70	5	—	—	5 (1 acute, 4 late)	—
van der Voort van Zyp *et al.*, 2010[16]	39	3	—	—	3 (late)	—
Videtic *et al.*, 2010[17]	26	1	—	1 (late)	—	—
Bongers *et al.*, 2011[25]	500	57 (28 acute, 29 late)	47	10	—	4
Haasbeek *et al.*, 2011[11]	63	12	7 (3 acute, 4 late)	3 (1 acute, 2 late)	2 (1 acute, 1 late)	—
Taremi *et al.*, 2012[2]	46	7 without RF, 14 with RF	4 without RF, 5 with RF	3 without RF, 6 with RF	0 without RF, 3 with RF	—
Mutter *et al.*, 2012[28]	126	54	19	16 (late)	19 (late)	—
Woody *et al.*, 2012[31]	102	20	6	13	1	—
Chang *et al.*, 2014[9]	101	31	18	13	—	—
Chang *et al.*, 2015[10]	31	3	—	—	3	—
Jung *et al.*, 2015[12]	44	2	2 (acute)	—	—	—
Lindberg *et al.*, 2015[20]	91	4	—	2 (early)	2 (early)	
Alite *et al.*, 2016[7]	107	3	3	—	—	—
Bhandari *et al.*, 2016[27]	55	3	—	3 (late)	—	—
Mancini *et al.*, 2016[14]	251	2	—	—	2 (late)	
Brooks *et al.*, 2017[8]	772	31	—	28	3	—
Jumeau *et al.*, 2017[19]	356	11 without RF, 9 with RF	—	18	2	—
Sun *et al.*, 2017[15]	65	23	15 (late)	7 (late)	1 (late)	—
TOTAL	2902	308	Grades 1–2 CWP: 250 (81.2%)		Grades 3–4 CWP: 58 (18.8%)	
*Studies (*n*=13) describing grade of RF*						
Baumann *et al.*, 2009[26]	57	6	4 (late)		2 (1 early, 1, late)	
Haasbeek *et al.*, 2011[11]	63	1	0	0	1 (late)	0
Taremi *et al.*, 2012[2]	46	17	8	6	3	—
Asai *et al.*, 2012[24]	116	28	20	7	1	—
Chang *et al.*, 2015[10]	31	1	—	—	1	0
Jung *et al.*, 2015[12]	44	3	3 (chronic)	0	0	0
Lindberg *et al.*, 2015[20]	57	8	0	7 (2 early, 5 late)	1 (late)	
Yoshitake *et al.*, 2015[32]	88	6	0	6	0	—
Alite *et al.*, 2016[7]	107	1	1	0	0	0
Bhandari *et al.*, 2016[27]	55	2	2	—	—	—
Nyman *et al.*, 2016[21]	48	8	6	2	0	—
Brooks *et al.*, 2017[8]	772	16	—	16	0	0
Sun *et al.*, 2017[15]	65	16	13 (late)	3 (late)	0	0
TOTAL	1549	113	Grades 1–2 RF: 104 (92.04%)		Grades 3–4 RF: 9 (7.96%)	

TABLE IV Chest wall or rib dosimetry characteristics in 28 studies

Reference	CW V_{30} (cm^3)	D_{max} to ribs or chest wall	$D_{0.5–5cm3}$ to small volume	Notes
Baumann *et al.*, 2009[26]		No dosimetric data		—
Collins *et al.*, 2009[18]		No dosimetric data		—
Stephans *et al.*, 2009[30]		No dosimetric data		—
van der Voort van Zyp *et al.*, 2009[23]		No dosimetric data		CWP, RF not reported separately
Dunlap *et al.*, 2010[3]		No dosimetric data		—
van der Voort van Zyp *et al.*, 2010[16]		No dosimetric data		—
Videtic *et al.*, 2010[17]		No dosimetric data		—
Bongers *et al.*, 2011[25]		No dosimetric data		60 Gy in 3 fractions for T1 lesions not adjacent to CW; 60 Gy in 5 fractions for T1 lesions showing broad contact with CW and for all T2 lesions; 60 Gy in 8 fractions for central lesions. CW was defined by an expansion of the lungs with 2 cm in lateral, posterior, and anterior directions, except in the direction of the mediastinum
Haasbeek *et al.*, 2011[11]		No dosimetric data		—
Taremi *et al.*, 2012[2]	—	—	$D_{0.5cm3}$ > 60 Gy: 50% RF risk	$D_{0.5cm3}$ and V_{25} cross-correlated for RF incidence
Asai *et al.*, 2012[24]	≥1.35 cm^3: 45.8% RF; <1.35 cm^3: 2.16% RF	≥42.4 Gy: 45.8% RF; <42.4 Gy: 1.43% RF	—	D_{max} and V_{10}, V_{20}, V_{30}, and V_{40}— median rib–tumour distance: 2.0 cm (range: 0.3–6.2 cm)
Mutter *et al.*, 2012[28]	V_{30}≥70 cm^3	—	—	A CW volume ≥70 cm^3 receiving 30 Gy was significantly correlated with grade 2 or greater CWP
Woody *et al.*, 2012[31]	Modified equivalent uniform dose, V_{30} = 29 cm^3 (0–170 cm^3), and maximum point dose as predictors	—	—	In the modified equivalent uniform dose models, V_{30} and maximum point dose were significant predictors of CWP (p<0.0005)
Chang *et al.*, 2014[9]		No dosimetric data		—
Lucas Jr *et al.*, 2014[13]		No dosimetric data		—
Rosen *et al.*, 2014[29]		No dosimetric data		—
Chang *et al.*, 2015[10]		No dosimetric data		—
Jung *et al.*, 2015[12]		No dosimetric data		—
Lindberg *et al.*, 2015[20]		No dosimetric data		—
Yoshitake *et al.*, 2015[32]		No dosimetric data		—
Alite *et al.*, 2016[7]		No dosimetric data		—
Bhandari *et al.*, 2016[27]		No dosimetric data		—
Mancini *et al.*, 2016[14]		No dosimetric data		—
Nyman *et al.*, 2016[21]		No dosimetric data		—
Brooks *et al.*, 2017[8]		No dosimetric data		—
Jumeau *et al.*, 2017[19]	V_{30}<30 cm^3 (3 fractions) vs. V_{30}>30 cm^3 (5 fractions)	BED_3: 522 Gy (CWT) vs. 401 Gy (no CWT)	D_{1cm3}: 411 Gy (CWT) vs. 388 Gy (no CWT) (BED_3)	—
Stam *et al.*, 2017[22]	—	<207 Gy vs. >452 Gy: TD5% vs. TD50% RF	$D_{0.5cm3}$, D_{2cm3} were predictors of RF	D_{max} EQD2 <225 Gy and <475 Gy correlated with RF of <5% and <50% respectively at 26 months
Sun *et al.*, 2017[15]		No dosimetric data		CWP, RF, plexopathy proportions mentioned, but no dose–volume correlation given

Vn = absolute volume receiving ≥*n* Gy; D_{max} = maximum dose; $D_{0.5–5cm3}$ = dose to 0.5–5 cm^3; CWP = chest wall pain; RF = rib fracture; CW = chest wall; BED_3 = biologically effective dose to normal tissue expressed for an alpha/beta ratio of 3 Gy; CWT = chest wall toxicity; TD5% = dose with 5% complications; TD50% = dose with 50% complications; EQD2 = equivalent total dose in 2 Gy fractions.

of CWP and RF after radiation appear fairly modest compared with post-thoracotomy pain after surgery; however, further prospective comparisons between those modalities will be required to validate our findings.

Despite the observed low rates of CWP and RF, our analysis also demonstrated significant variability across studies in terms of dose–fractionation regimens, tumour location, and accurate reporting of toxicities and dosimetry. The definitions of "acute" and "late" toxicity with respect to RF and CWP were also variable across studies. Specific to dosimetry, we found that the V_{30} (and perhaps maximum dose avoidance within the chest wall) might be an important parameter to evaluate, but the exact constraints that would lead to increased risk are still unclear. Further, the variation in dose–fractionation across studies is not accounted for.

In addition to the total dose delivered, the dose per fraction contributes to the biologic effect of radiation on both tumour and normal tissue. According to Bongers *et al.*[25], it might be argued that doses should be converted to a linear quadratic model, and yet most studies did not limit their prescriptions to one common scheme[37]. Furthermore, it was difficult to parse out the proportion of patients with peripheral compared with central tumours in each study, and many centres used adapted dose–fractionation schedules for tumours abutting the chest wall. Generally, it has been suggested that the planning target volume and the distance from tumour to chest wall correlate with post-SBRT CWT[33]. As a result, it could be argued that the rates of CWP and RF are underestimated because of those variables.

Another factor affecting dosimetry could be the method of chest wall delineation. Whether only the ribs or the entire chest wall (including intercostal musculature) was delineated was not clear across studies; that uncertainty might influence the dosimetric analysis of CWP and RF, and might provide different results across studies with respect to relevant values when evaluating chest wall dose constraints.

Finally, older studies using less-conformal techniques tended to use SBRT to treat larger tumour volumes[38–47]. Newer approaches using conformal techniques such as volumetric modulated arc therapy and intensity-modulated radiotherapy—and more modern radiotherapy planning algorithms—might be able to further reduce the dose to organs at risk, such as the chest wall[48] and cannot be accounted for in this review.

Despite the foregoing issues, we believe that, based on this review, some minimum standards for chest wall dosimetry can be applied, including V_{30} and ensuring that the maximum dose within the planning target volume is outside the rib or chest wall contour. However, those factors will have to be prospectively evaluated to establish their relationship with late CWP and RF, especially with variation in dose–fractionation regimens. Two currently open randomized trials in lung SBRT, the Ontario Clinical Oncology Group LUSTRE trial[49] and the VALOR study (see NCT02984761 at https://ClinicalTrials.gov/) both have chest wall dosimetry limits. The LUSTRE trial (SBRT doses of 48 Gy in 4 fractions or 60 Gy in 8 fractions) mandates that the ribs be contoured (not the entire chest wall) and suggests dose–volume limits for $V_{40–50}$ of less than 5 cm^3 and a maximum point dose of 50–60 Gy (depending on the fractionation chosen). In the VALOR trial, which is comparing SBRT (54 Gy in 3 fractions, 56 Gy in 4 fractions, or 57.5 Gy in 5 fractions) with surgical resection, ribs and chest wall (including musculature) are both to be contoured. Rib dose–volume limits are D_{5cm3} less than 40–45 Gy and a maximum point dose of 50–57 Gy; and chest wall limits are D_{30cm3} less than 30 Gy and a maximum point dose of 56.7–60.4 Gy, again depending on the fractionation chosen [Moghanaki D (VALOR principal investigator). Personal communication, 2019]. The toxicity outcomes of those trials with respect to late CWP and RF (particularly in the VALOR trial's comparison with surgery) will provide greater knowledge about the dose–toxicity relationship in a prospective fashion.

Another factor potentially influencing rates of CWP and RF is the accurate reporting of those toxicities after SBRT. Given that most of the studies included in the present review were retrospective, it is difficult to know if the CWP and RF reporting is correct, especially if the aim of the particular study was not specifically evaluating those endpoints. In retrospective studies, grading toxicity is also very difficult unless events were documented clearly as they arose. Nonetheless, it is reassuring that most patients reported only minimal-grade (1 or 2) CWP after SBRT. Still, it is important not to dismiss the more severe toxicity experienced by some patients and also the risk factors—including age, sex, body mass index, comorbidities, smoking, and osteoporosis—that might increase a patient's risk of post-SBRT CWP and RF. Those risk factors should be considered in conjunction with dosimetric parameters during the SBRT planning process.

Despite the fact that we were evaluating a relatively homogeneous population (patients with stage I NSCLC, excluding patients with lung metastases), we were unfortunately unable to perform a meta-analysis of the available literature. First, the present work is a systematic review and pooled analysis based on observational studies. When combining such studies, heterogeneity of populations, designs, and outcomes can occur and influence the pooled estimates. However, when no studies with adequately large sample sizes are available, a systematic review and pooled analysis of observational studies might still be a valid method of assessment, providing useful evidence to inform the decision about whether more evidence is needed. Second, our analysis is limited by accuracy in the reporting of patient characteristics, tumour location, dose–fractionation schemes, and toxicity reporting as already described, which can affect the pooled toxicity rate. Third, lack of consensus with respect to dose–fractionation regimens across the studies makes it challenging to interpret the findings and thus perform a meta-analysis or pooled analysis of the data. Furthermore, most studies were deemed to have a significantly high risk of bias because of nonrandomized populations, and thus overall evaluation of studies was heavily biased, further limiting our ability to conduct a formal meta-analysis.

Future directions beyond this review would include careful prospective documentation and reporting of patient and dosimetric factors influencing CWP and RF after SBRT. Such documentation would facilitate data pooling such that robust multivariable normal-tissue complication probability models could be developed. Quality of life in patients affected by CWP and RF must also be assessed, as must the use of medications and narcotics and the duration of their use. In turn, clinicians might be better equipped

to inform patients of the risk of SBRT-induced CWTs and to adapt treatments to minimize the risks.

CONCLUSIONS

Results from the present review demonstrate low rates of CWP and RF after SBRT in a large variety of patients with stage I NSCLC. However, significant heterogeneity was evident in tumour location, accurate reporting of toxicity, and dose–fractionation schemes, which could relatively increase or decrease those rates. Thus, it is important that authors fully document the characteristics of study populations. Consistency in toxicity grading scales should also be maintained, and the grade of toxicity should be clearly documented, including distinguishing between symptomatic clinically relevant and asymptomatic radiation-induced RF. Differences in organs-at-risk delineation might also have contributed to different outcomes. Nonetheless, despite the limitations of the present systematic review and pooled analysis inherent to the included literature, this report provides a valuable estimate of the incidence of CWP and RF toxicity after SBRT, identifies potential high-risk dosimetric factors, and increases knowledge about this topic that can be further validated in future prospective and comparative trials.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: AS, ISV, and CWD have no known conflicts of interest associated with this publication. ED is funded by an Accuray Incorporated grant, with no relation to the present research.

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