Review Article

Stereotactic radiotherapy in previously treated lung cancers—what are the risks?

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Abstract: Patients affected by intra-thoracic recurrences of primary or secondary lung malignancies after the first course of definitive radiotherapy (RT) have limited therapeutic options, and they are often treated with palliative intent. Re-irradiation with stereotactic radiotherapy (SRT) represents an appealing approach, due to the optimized dose distribution that allows for high-dose delivery with better sparing of organs at risk; however, toxicity still represents an issue, even with dose-fractionation risk-adapted approaches. This review aims to analyze clinical data and dosimetric parameters related to stereotactic re-irradiation, mainly focusing on the toxicity profile, whose risk often limits the adoption of this technique in clinical practice.

Keywords: Thoracic relapse; lung cancer; re-irradiation; stereotactic ablative radiotherapy (stereotactic ablative RT); stereotactic body radiotherapy (stereotactic body RT)

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Introduction

Radiotherapy (RT) has a crucial role in the clinical management of non-small cell lung cancer (NSCLC) (1), being part of the first line therapeutic strategy for almost two-thirds of the patients (2). The majority of them develop recurrence which can eventually lead to fatal systemic progression; however, a significant number of these patients will experience isolated thoracic relapse, which can involve the previously irradiated site (in-field recurrence) or the remaining parenchyma and/or unirradiated mediastinal lymph nodes (out-field recurrence). This risk of local relapse increases as the prognosis of patients improves (1,3). After a previous course of RT, isolated recurrences can have different clinical presentations, including in-field relapses and/or regional recurrences in patients with locally advanced tumor previously treated with chemo-RT (30–85% of the patients shows recurrence) (1), second primary lung tumors in patients with early-stage disease, or re-treatment for patients presenting different lung metastases after previous stereotactic radiotherapy (SRT). In specific cases of isolated relapse, re-irradiation can be performed with a curative aim (4), despite the possible occurrence of treatment-related toxicity (5). More specifically, new strategies of treatment planning and dose delivery can lead to lower incidence of adverse effects, also for those patients receiving palliative therapies. Major toxic events in the setting of thoracic re-irradiation include toxicity of the lung parenchyma [radiation pneumonitis (RP)], airways and vascular damage (risk of G5 bleeding), development of fibrosis and impaired lung function. Image-guided RT (IGRT), intensity-modulated RT (IMRT) and protons may allow clinicians to deliver higher doses in few fractions safely (6-9). Further improvements of image guidance, respiratory gating and IMRT techniques have further developed the field, increasing the dosimetric performance of SBRT on large tumors, critical localizations and multiple lesions (10-12). In particular, the possibility to verify patients set-up both online and offline with IGRT, and the application

of respiratory gating, has led to a reduction of the applied margin in consideration of the possible inaccuracies in patient positioning and target identification, with a decrease in the onset of side effects for thoracic radiation therapy, especially SBRT (13,14).

Despite its well-established role both for primitive and oligometastatic lung tumors (15), there are still concerns in the setting of lung re-irradiation, due to the different disease presentations and the paucity of prospective data (5,16).

We included in this review 22 published studies in the time interval 2008-2018, using a formal computer-assisted search of the Medline, Scopus and ClinicalKey databases. Keywords used were "re-irradiation", "SBRT", "Stereotactic body radiotherapy", "lung cancer", "toxicity", "radiotherapy". Titles and abstracts were used to screen for initial study inclusion. We included in our analysis cohort studies and case-control studies; editorials and commentaries were excluded. Patients' characteristics, data on previous RT, dose, time interval between first and second RT course of all 22 studies are summarized in *Table 1* (17-38).

Pulmonary toxicity following re-irradiation

In *Table 2*, we describe the incidence and grade of G ≥3 pulmonary toxicity, ranging from 3% to 28% (17-38). The most common adverse event was found to be radiation pneumonitis (RP), which occurred in about 20% of cases, and it was found to be related with cumulative higher doses received by the lungs.

Liu *et al.* reported the occurrence of severe RP in 15 patients (20.8%) at a median follow-up of 4 months (range: 1–15 months), including a G5 (22). The authors demonstrated a statistically significant association between the incidence of G ≥3 RP ($P<0.05$) and several factors, including pre-SRT ECOG performance status ≥2, a FEV1 ≤65% before SRT, previous PTV involving bilateral mediastinum, previous V10 ≥33% and mean lung dose (MLD) ≥12.4 Gy, together with a V10 ≥43%, a V40 ≥15% and MLD ≥16.5 Gy in the plan sum.

The time interval between the two RT courses, the V_{30Gy} and V_{40Gy} of the first RT plans and the V_{10Gy}–V_{40Gy} and MLD of the SRT plans seemed to be associated with the onset of G3–5 RP, even if the association does not reach statistical significance. Trovò *et al.* described four patients (23%) with G3 RP (needing oxygen therapy), while one patient developed G5 RP 4 months after SRT (26). Fatal G5 toxicity (bleeding) was also reported following salvage SRT for recurrent central tumors (33). More specifically, Trovò and co-authors described the case of a patient having a recurrent disease at the hilum who experienced fatal, and more likely iatrogenic, hemoptysis following SRT (26). One patient from the series by Kilburn *et al.* experienced grade 3 RP (28). Of note, one patient developed fatal (G5) fistula involving aorta and esophagus, after being re-irradiated for a central tumor. Kelly *et al.* hypothesized different adverse events between patients who received additional radiation treatment for an in-field recurrence (11 patients) and those re-irradiated after an out-of-field recurrence (13 patients) (18). The authors demonstrated a diverse pattern of side effects in these two subgroups, with chest wall pain being significantly more common in those presenting an in-field relapse (31%) and on the contrary G3 pneumonitis associated more frequently with out-field recurrence (28%). Peulen *et al.* described eight patients who developed G3–4 toxicity (30%), while three patients (13%) died of massive hemorrhage (G5) (20).

Liu *et al.* reported one case of fatal G5 RP (22). However, this patient was known for having presented chronic infectious pulmonary disease of different etiology occurring before SRT. Median MLD and V_{20Gy} for the composite plans were 16.5 Gy and 30%, respectively; no information is available about the time interval between the two RT courses; this interval could potentially relate to the toxicity, assuming that long-lasting chronic obstructive pulmonary disease (COPD) might be responsible for a poorer pulmonary function.

Unexpectedly, Trovò *et al.* demonstrated a significant correlation between the risk of developing severe pneumonitis and the maximum heart dose (D_{max}) and the minimum dose to at least 5% and 10% of the heart volume ($D5_{Gy}$ and $D10_{Gy}$, respectively) (26). More specifically, patients with severe pulmonary toxicity showed higher values of D_{max} (mean value of 27 *vs.* 13.3 Gy in patients without toxicity), $D5_{vol}$ (mean value of 10.2 *vs.* 3.9 Gy), and $D10_{vol}$ (mean value of 7.1 *vs.* 2.8 Gy) to the heart. *Table 3*, derived from the study by Liu *et al.* (22), provides a predictive score for RP on the basis of few clinical-dosimetric parameters.

Cardiac toxicity

While we still do not have mature data concerning the impact of SBRT re-irradiation on heart toxicity, plenty of studies have been evaluating heart dose in lung cancer patients. RTOG 0617 is a landmark study published in 2015 which showed a significant relationship between high heart

Table 1 Patients' characteristics of selected studies

1st author [year] (reference)	Years of enrollment	N of pts (lesions)	Tumor histology [N]	IF/OF relapse (N)	Median target volume [cc, range]	Dose of primary RT [Gy, range]	Time interval primary-salvage RT [median, months]	Salvage SBRT schedule Gy [N of fr]
Coon [2008] (17)	2005–2007	12	LC [NA]	NA	14 [3.4–128]	NA	NA	60 [3]
Kelly [2010] (18)	2004–2008	36	LC [36]	11/25	NA	Median 61.5 [30–79]	22	50 [4], 40 [5]
Seung [2011] (19)	2009–2010	8	LC[8]	NA	NA	50–68 [1.8–2.5 Gy per fr]	36	40 [5], 48 [4], 50 [5], 60 [3]
Peulen [2011] (20)	1994–2004	29	Primary [6], lung mets [23]	NA	76 [16–355]	30–45 [2–3 fr]; 40 [4 fr]	14	30–45 [2–3], 40 [5]
Trakul [2012] (21)	2004–2010	15 [17]	Primary [12], lung mets [5]	17/0	31.6 [7.4–119.7]	Not specified	16	20 [1], 40 [5]
Liu [2012] (22)	2004–2010	72	Primary [10], lung mets [62]	19/53	NA	Median 63 [30–79]	21	50 [4]
Valakh [2013] (23)	2006–2011	9	Primary [8], lung mets [1]	6/3	22.2	Median 60 [30–60]	NA	30–60 [3–5]
Meijneke [2013] (24)	2005–2012	20	Primary [17], lung mets [3]	0/20	NA	60 [3 fr] 60–50 [20–25fr]	11	60 [5], 50 [5]
Reyngold [2013] (25)	2004–2011	39	Primary [17], lung mets [22]	22/17	67 [17–463]	Median 61 [30–79]	37	48 [4]
Trovò [2014] (26)	Not specified	17	Primary LC [17]	17/0	NA	50–70 [20/30 fr]	18	30 [5–6]
Hearn [2014] (27)	2004–2012	10	Primary LC [10]	NA	NA	50 [5 fr] 30 or 34 [1fr]	15	50 [5], 60 [3]
Kilburn [2014] (28)	2001–2012	33	Primary [29], lung mets [4]	NA	NA	Median 66 [45–80]	18	50 [5], 20 [1]
Patel [2014] (29)	2008–2011	26 [29]	Primary LC [26]	27/2	17.2 [0.9–448.7]	Median 61.2 [30–74]	8	15–50 [3–5]
Maranzano [2015] (30)	2003–2013	18 [29]	Primary [4], lung mets [14]	23/6	18 [8–55]	Multiple regimens	18	20–50 [5]
Owen [2015] (31)	2006–2012	18 [27]	Primary [15], lung mets [3]	4/23	19.2 [6.4–79.6]	Median 60 [39–70]	18	40–60 [3–10]
Parks [2016] (32)	2009–2012	27 [29]	Primary LC [27]	13/12 (4 marginal)	29 [6.5–448]	Median 64.8 [45–74]	13	30–54 [3–5]
Repka [2017] (33)	2004–2014	20	Primary LC	20/0	79.6 [6–318]	Median 63 [69.4–75]	23	25–45 [5]
Horne [2017] (34)	NA	72	Primary LC	NA	2.5 [0.8–7.8], T size [cm]	69 in 33 fr 60 in 30 fr [new primary]	13	17–60 [1–5]
Ceylan [2017] (35)	2005–2015	28 [34]	Primary LC	21/13	24.2 [2.3–156.3]	Median 59.4 [47.5–66]	15	20–60 [3–9]

Table 1 *(continued)*

Table 1 *(continued)*

1st author [year] (reference)	Years of enrollment	N of pts (lesions)	Tumor histology [N]	IF/OF relapse (N)	Median target volume [cc, range]	Dose of primary RT [Gy, range]	Time interval primary-salvage RT [median, months]	Salvage SBRT schedule Gy [N of fr]
Sun [2017] (36)	2005–2013	59*	Primary LC	Mostly OF	38.47 [4.71–147]	66 [49–88]*	28	40–50 [4]
Ogawa [2018] (37)	2004–2017	31	Primary [23], lung mets [8]	23	69.8 [10.2–149]	50 [36–60]**	NA	48–60
Caivano [2018] (38)	2011–2016	22 [27]	Primary [12], lung mets [15]	21/6	30.8 [2.7–260.7]	NA	18	30–54 [1–6]

*, 26 pt did not receive RT as primary treatment, 5 pts received SBRT; **, primary SBRT. N, number; IF, in-field; OF, out-field; cc, cubic centimeter; Gy, Gray; RT, radiotherapy; SBRT, stereotactic body radiotherapy; fr, fractions; LC, lung cancer; mets, metastases; NA, not available.

dose and survival decrease (39). A prospective trial from Lee *et al.* (40) demonstrated an association between increased RT prescription dose and increased late toxicity (myocardial infarction, pericarditis, pericardial effusion) in patients with stage III NSCLC undergoing high-dose thoracic radiation in combination with chemotherapy. In their analysis on 125 patients included in prospective trials at Ann Arbor University (41), Dess *et al.* found a relative 7% increase in G3–5 cardiac toxicity per Gy in mean heart dose (MHD); this subgroup of patients had decreased overall survival. Specific constraints on cumulative heart dose given with hypofractionated RT after a first fractionated RT course are not available, but the LQ formalism might be used to estimate the dose according to widely used dose limits. In general, patients receiving high MHD or high cumulative doses to a portion of the heart may benefit from long-term cardiologic follow-up and should minimize cardiovascular risk factors.

Dose-volume parameters

A careful dosimetric analysis of the analyzed publications could be useful to define dose limits for organs at risk in the RT planning. However, only a few studies provide a definition of planning target volume (PTV) and add information about the used dosimetric constraints. *Table 4* give detailed information concerning volumes and planning. We report a few cases of G5 fatal toxicities; dose values obtained with the Linear-Quadratic formalism are used, when available, to gather cumulative doses to organs at risk (42). Peulen *et al.* reported on three iatrogenic deaths for massive hemorrhage. One of them received 30 Gy in 3 fractions (CTV =114 cm^3, EQD2 =78 Gy) and was re-irradiated with SRT receiving 45 Gy in 3 fractions (CTV =77 cm^3, EQD2 =162 Gy), with a time interval of 12 months between the two RT courses. The total EQD2 value was 240 Gy (alpha/beta for lung =3 Gy), and fatal bleeding was reported at 11 months from re-treatment (20). A schedule of 40 Gy in 4 fractions (CTV right hilar region =12 cm^3, EQD2 =104 Gy) was delivered to a patient diagnosed with metastatic renal cell carcinoma and presenting with metastases at both right and left hilum. After three years, a re-treatment with five fractions of 8 Gy (CTV =37 cm^3, EQD2 =88 Gy) was given for a tumor recurrence in the proximity of the right hilus. The patient developed different G3 adverse events (pneumonitis, cough, dyspnoea, and pain) at three months after re-treatment, and later he developed a stenosis of the right and left lower lobe bronchus after 9 months, and ultimately he died from acute hemoptysis

Table 2 Clinical outcomes reported by selected studies

1st author [year] (reference)	FUP after salvage treatment (months)	Local control	Overall survival	Acute and late toxicity (≥ G3)
Coon [2008] (17)	12	1 yr: 92%	1 yr: 81%	NA
Kelly [2010] (18)	15	2 yr: 92%	2 yr: 59%	G3 pneumonitis: 28%/G3 esophagitis: 4%/ chest wall pain: 31%
Seung [2011] (19)	18	18 months: 86%	18 months: 87.5%	None
Peulen [2011] (20)	12	1 yr: 52%	1 yr: 59%, 2 yr: 43%	G3 pneumonitis: 30%/G5 bleeding 13% (central lesions)
Trakul [2012] (21)	15	1 yr: 65%	1 yr: 80%	None
Liu [2012] (22)	16	1 yr: 95%	2 yr: 74%	G3 pneumonitis: 19%, 1pt presenting G5 pneumonitis
Valakh [2013] (23)	22	2 yr: 75%	2 yr: 69%	(Late) G3 pneumonitis: 22%, (late) G3 chest wall pain: 11%
Meijneke [2013] (24)	12	1 yr: 75%, 2 yr: 50%	1 yr: 67%, 2 yr: 33%	None
Reyngold [2013] (25)	12	1 yr: 77% 2 yr: 64%	22 months (median)	G3 pneumonitis: 5%, G4 dermatitis: 25%
Trovò [2014] (26)	18	1 yr: 86%	1 yr: 59%, 2 yr: 29%	G3 pneumonitis: 17%, 1/17 pts presenting G5 pneumonitis, 1/17 pts presenting G5 bleeding
Hearn [2014] (27)	14	Not specified	Not specified	None
Kilburn [2014] (28)	11	2 yr: 67%	21 months (median)	(Late) G3 pneumonitis: 3%, 1/33 pts presenting G5 aorto-esophageal fistula
Patel [2014] (29)	14	1 yr: 78%, 2 yr: 65.5%	1 yr: 52.3%, 2 yr: 37%	None
Maranzano [2015] (30)	57	1 yr: 82%, 2 yr: 66%	40 months (median)	None
Owen [2015] (31)	21.2	2 yr: 90%	1 yr: 88%	None
Parks [2016] (32)	22	2 yr: 72%	2 yr: 79%	(Late) G3 pneumonitis: 22%, G3 chest wall pain: 3.7%, G4 chest wall pain: 3.7%
Repka [2017] (33)	12	1 yr: 30% (66.7% in those receiving >40 Gy)	1 yr: 45% (77.8% in those receiving >40 Gy)	1/20 pts presenting (late) G5 hemoptysis, 1/20 pts presenting (late) G3 recurrent laryngeal nerve paralysis
Horne [2017] (34)	17.9	2 yr: 78.4%	1 yr: 63.4%, 2 yr: 46.3%	(Acute) G3 pneumonitis: 11% ; (late) G3 esophagitis: 1.4%
Ceylan [2017] (35)	9	1 yr: 69%, 2 yr: 37%	1 yr: 71%, 2 yr: 42%	None
Sun [2017] (36)	58.3	Local relapse at 3 yrs: 5.2%	1 yr: 93.1%, 2 yr: 63.5%, 5 yr: 56.5%	(Acute) G3 dermatitis: 2%, (acute) G3 pneumonitis: 3%
Ogawa [2018] (37)	26	3 yrs: 53%	3 yr: 36%	None
Caivano [2018] (38)	N/A	1 yr: 67%, 2 yr: 54%	1 yr: 81%, 2 yr: 63%	1/22 pts presenting (acute) G3 dyspnea, 1/22 pts presenting (late) G3 dyspnea, 1/22 pts presenting (late) G3 chest pain, 2/22 pts presenting (late) G3 fibrosis

FUP, follow-up; yr, year(s).

Table 3 A predictive scoring system for grade 3-5 radiation pneumonitis [from Liu et al. (22)]

Score*	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
≥1	100.0	11.5	24.2	100.0
≥2	93.3	54.4	35.0	96.9
≥3	93.3	91.2	73.7	98.1
≥4	26.7	98.2	80.0	83.6

*Assigned scores: ECOG performance status 2–3 before SBRT =1 point; FEV1 ≤65% before SBRT =1 point; V20 ≥30% (composite plan) =1 point; previous bilateral mediastinal PTV =1 point. ECOG, Eastern Cooperative Oncology Group; SBRT, stereotactic body radiotherapy; FEV1, forced expiratory volume in 1 second; V20, percentage of volume receiving more than 20 Gy; PTV, planning target volume.

Table 4 Definition of clinical target volume (CTV) and planning target volume (PTV) in selected studies

1st author [year] (reference)	CTV and PTV definition
Kelly [2010] (18); Liu [2012] (22)	CTV = gross disease delineated on 4DCT scan +8 mm in all directions; PTV = CTV +3 mm in all directions
Peulen [2011] (20)	CTV = GTV +1/2 mm; PTV = CTV +5/10 mm (mobility evaluated with fluoroscopy)
Kilburn [2014] (28)	PTV = gross disease delineated on 4DCT scan +5/10 mm (in the pre 4DCT era, PTV = gross disease +10 mm in all directions)
Reyngold [2013] (25)	CTV = GTV +3 mm; PTV = CTV +5 mm
Trovò [2014](26); Ceylan [2017] (35)	PTV = GTV +5 mm (no CTV delineated)
Valakh [2013] (23)	PTV = GTV +3 mm
Seung [2011] (19)	PTV = gross disease delineated on 4DCT scan +3/5 mm
Repka [2017] (33)	Recurrent GTV (no CTV/PTV expansion)
Patel [2014] (29)	CTV = delineated considering inspiration and expiration CT movements of GTV; PTV = CTV +5 mm
Parks [2016] (32)	GTV/ITV = defined on 4DCT and PET/CT; PTV = ITV +5 mm
Owen [2015] (31)	ITV = defined on 4DCTPTV = ITV +5 mm
Ogawa [2018] (37)	GTV = defined on PET/CT = CTV; CTV → ITV; PTV = ITV +5 mm in lateral and anteroposterior/10 mm in craniocaudal
Maranzano [2015] (30)	GTV =CTV; PTV =CTV +8–10 mm in craniocaudal/4–5 mm in axial
Horne [2017] (34)	GTV = involved node on 4DCT-maximal expiration phase; PTV = GTV +5 mm
Sun [2018] (36)	IGTV = defined on 4DCT MIP
Caivano [2018] (38)	PTV = GTV + ITV +4 mm in all directions

CTV, clinical target volume; PTV, planning target volume; ITV, internal target volume; rITV, recurrent internal target volume; 4DCT, 4 dimension computed tomography; MIP, maximal intensity projection; PET/CT, positron emission tomography/computed tomography.

(cumulated EQD2 to the right hilus 192 Gy with alfa/beta 3 Gy). The last patients received 40 Gy in four fractions for stage III NSCLC of the left hilus (EQD2 =104 Gy). After 13 months, the hilar lesion received re-irradiation with 33 Gy in 3 fractions (CTV =58 cm^3, EQD2 =92 Gy), followed by death six weeks later for massive bleeding in the upper pulmonary area (cumulated EQD2 196 Gy with alfa/beta =3).

Concerning oesophageal toxicity, Kilburn *et al.* described one case of G5 aorta-oesophageal fistula occurring six months after re-irradiation of a central tumor (28) with 54 Gy in 3 fractions in a patient who had previously received radio-chemotherapy (74 Gy, 2 Gy/fraction, one year before). As reported by the Authors, a rough estimation of the composite doses: D_{max} to esophagus was 66 Gy from the fractionated

Table 5 Dose constraints

Structure	Dose constraints	Ref.
PTV	Dose prescribed at about the 67% isodose at the periphery of the PTV	(20)
	Dose prescribed at the 69% isodose line	(29)
	Dose prescribed at about the 70–85% isodose, covering at least 95% of the PTV	(24)
	Dose prescribed to the isodose line covering the PTV (generally 100% isodose line)	(25)
	95% of the prescribed dose covers 95% of the PTV	(26)
	80% of the prescribed dose covers 95% of the PTV	(37)
	90% of the PTV had to be covered by 99% of the prescribed dose	(19)
	Isodose line covers 95% of the PTV and 100% of the IGTV	(36)
	Dose prescribed to the isocenter. Minimal coverage accepted dose: 90%	(30)
	Dose prescribed directly to the rGTV	(33)
	95% of the prescribed dose covers PTV	(34)
Spinal chord	Dmax (1 cc) <20 Gy ; Dmax (10 cc) <15 Gy	(18,22)
Brachial plexus	Dmax (any point) <40 Gy, Dmax (1 cc) <35 Gy, Dmax (10 cc) <30 Gy	(18,22)
Trachea	Dmax (1 cc) <35 Gy, Dmax (10 cc) <30 Gy	(18,22)
Main bronchus and bronchial tree	Dmax (1 cc) <40 Gy, Dmax(10 cc) <35 Gy	(18,22)
Heart	Dmax (1 cc) <40 Gy, Dmax (10 cc) <35 Gy	(18,22)
Esophagus	Dmax (1 cc) <35 Gy ; Dmax (10 cc) <30 Gy	(18,22)
Whole lung (-GTV)	V20 <20%, V10 < 30%, V5 <40%	(18,22)
Major vessels	Dmax (1 cc) <40 Gy, Dmax (10 cc) <35 Gy	(18,22)
Skin	To 5 mm: Dmax (1 cc) <40 Gy, Dmax (10 cc) <35 Gy	(18,22)

(18): for the majority (91%) of patients, composite plans were generated, and adjustments were made to limit the radiation dose to critical structures on an individual basis to account for any prior EBRT, at the discretion of treating physicians. (22): authors declared to have followed the normal tissue constraint guidelines for RTOG 0813 (available online at: http://www.rtog.org/members/protocols/0813/0813.pdf. Other available studies do not describe details of planning dosimetric constraints for organs at risk, and it should be assumed that doses to nearest organs have been maintained as low as possible. PTV, planning target volume.

radiation given with concurrent chemotherapy and 20.5 Gy in 3 fractions for salvage SABR plan (EQD2: 40.3 Gy, alpha/beta =3 Gy). Finally, re-treatment of the primary centrally located tumor resulted in a total combined maximum oesophageal dose of approximately 106 Gy. *Table 5* provides details on the dose constraints used among the 22 studies included in the analysis, when available.

Discussion

In this article, we review literature data on thoracic re-irradiation with SRT for recurrent lung cancer and/or lung metastases following a previous thoracic RT course. We analyzed 22 full-text articles published over the last decade. The number of patients per study is often limited, with a small number of enrolled patients and typical biases of retrospective studies are present. Schedules of salvage SRT largely vary between different studies, with treatment fractions ranging from one to five, and total doses between 20 and 60 Gy. Heterogeneous criteria were used to define treatment volumes (*Table 4*).

Furthermore, cumulative doses are reported only in some studies. These limitations and the need for a clear definition of the cumulative biologically equivalent doses (usually EQD2) should be taken into account when interpreting the results. Information about PTV volumes is scarce: this lack of data is detrimental in the evaluation of toxicity rates and, consequently, for the selection of patients who would

most benefit from re-irradiation. Overall, re-irradiation with fractionated SRT was shown to be relatively safe in terms of RP risk. However, severe RP was commonly reported (nearly 20% of the cases, more than after palliative conventional RT) and showed association with dosimetric and patient-related risk factors (ECOG PS 2–3, FEV1 <65%, tumor location) (22). The reported incidence is widely variable between different reports, but generally, particular caution should be paid before re-irradiate patients at higher risk of developing side effects. Toxic deaths after high-dose re-irradiation to the structures included in the mediastinum (central airways, great vessels) are reported, with cases of fatal bronchial bleeding and/or fistulae (26,28) as well as occasionally fatal lung hemorrhage after high-dose irradiation to non-central lesions. These events seem to be related to very high prescription doses. Given the current acknowledgment on radiation dose constraints to central structures when high-dose hypo-fractionation is adopted (43), the occurrence of G5 events should now be sporadic. Feddock *et al.* have reported an unusually high rate of toxicity in a prospective study analyzing SRT as a boost after standard chemoradiation in stage II–III NSCLC (not true re-irradiation) (44). Such boost consisted of 10 Gy in 2 fractions (20 Gy total). After having enrolled 16 patients, the protocol was amended for the risk of inducing significant side effects in patients with central tumors, with two patients having developed fatal pulmonary hemorrhage after being treated for a medial tumor.

In conclusion, in the setting of lung re-irradiation, a careful evaluation of patients at higher risk for RP is mandatory and, as long as central re-irradiation carries substantial risks of high-grade toxicity, special attention should be paid.

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Footnote

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