Thoracic reirradiation for lung cancer: a literature review and practical guide

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Introduction: Approximately half of all patients with lung cancer (LC) experience locoregional failure after initial treatment. Historically, thoracic reirradiation (ReRT) has been limited by toxicity concerns and lack of robust evidence. Our objective was to perform a systematic literature review regarding ReRT.
Methods: Search of the English-language literature related to best-practice thoracic ReRT (Medline and Embase) was performed. Clinical practice guidelines and consensus statements were also reviewed. Data was abstracted regarding patient, tumour and radiotherapy characteristics; response rate; overall survival (OS); and toxicity. In addition to descriptive analysis, Spearman's test explored relationships between RT dose and OS.
Results: A total of 379 patients (89% non-small cell; 11% small cell LC) retreated with radical or palliative intent have been described by 13 publications (1982-2014). A total of 86% were symptomatic at the time of ReRT; rate of symptom improvement was 69%. Range of reported median survivals (MS) was 3-15 months. Median initial (59 Gy; range, 12-80 Gy), ReRT (36 Gy; range, 12-70 Gy) and combined dose (86 Gy; range, 58-120 Gy) significantly correlated with OS, with Spearman's rho values of 0.85 (P=0.002), 0.72 (P=0.006), and 0.88 (P=0.001) respectively. Toxicity after ReRT was reported in 17% (esophagitis) and 12% (pneumonitis), with RT complications contributing to 2% of deaths.
Conclusions: Despite heterogeneity of patient cohorts, RT techniques and duration of follow-up, ReRT appears to be a feasible option for recurrent thoracic disease. Treatment guidelines derived from this data will guide clinical decision-making for both radical- and palliative-intent ReRT.

Keywords: Reirradiation (ReRT); lung cancer (LC); radiotherapy; palliative; salvage; review

Introduction

Lung cancer (LC) remains the most common cancer, with approximately 1.8 million cases diagnosed in 2012 worldwide (1). Due to earlier detection, advances in staging, increasing use of combined modality treatment, and advances in radiation therapy (RT), patients with LC are also living longer (2). Unfortunately, approximately 50% will experience locoregional, marginal and/or distant failure post-treatment (3,4). After curative-intent chemoradiotherapy, the five year rate of locoregional recurrence in non-small cell lung cancer (NSCLC) is 30% (5), and in patients with small cell lung cancer (SCLC), local failure occurs in approximately one-third (6). Recurrent LC often causes

significant symptom burden, negatively affecting quality of life and representing the most common cause of death (7-13).

Historically, thoracic reirradiation (ReRT) has been limited by toxicity concerns, the possibility of tumour radioresistance, and lack of robust evidence (14). Consequently, ReRT of recurrent LC in past was primarily palliative, implemented to relieve symptoms and/or delay consequences of tumour growth (11), when no other treatment options were available. However, a small subset of patients presenting with localized recurrence are increasingly being offered ReRT for salvage, albeit on an ad hoc basis and largely at the discretion of the treating radiation oncologist.

Our objective was to systematically review the literature

regarding thoracic ReRT for LC in order to develop practical guidelines for both palliative- and radical-intent ReRT.

Methods

Publications related to repeat fractionated external beam irradiation (ReRT) of the thorax for primary LC were obtained via literature search (*Appendix 1*). Medline and Embase were searched for English language articles published in full between 2000 and 2013. Eligible studies and review articles were also identified from reference lists of retrieved papers. Additional clinical practice guidelines and consensus documents were obtained from searching the online SAGE (Standards and Guidelines Evidence) Directory compiled by the Canadian Partnership Against Cancer (www.cancerview.ca).

Studies investigating fractionated ReRT (EBRT) before or after stereotactic body radiosurgery or which included accelerated EBRT were excluded. Abstracts and studies for which outcomes could not be separated by tumour histology or RT modality were excluded, as were case reports and in silico (treatment planning studies) of single patients. Additionally, one publication (15) described what appeared to be earlier results of the same cohort as an included study (9); determining patient duplication was limited by the data presented, so the earlier paper was excluded.

Spearman's correlation coefficient explored relationships between RT doses and overall survival (OS).

Results

General

Eleven single-centre retrospective reviews (7,9,12-14,16-21), one prospective cohort study (10) and one phase

I/II clinical trial (11) included a total of 379 patients treated with two courses of thoracic EBRT between 1963 and 2013 (*Table 1*). Excluding the clinical trial, fewer than two (12,13,18,19) to a maximum of eight patients per year (16) received ReRT; Wu *et al.* recruited 23 patients over two years.

ReRT was generally defined as a second course of EBRT to an initially radiated volume (9,17), with three reports specifying a minimum interval of three (13) or six (10,11) months after completion of initial treatment. Griffioen required a maximum interval between courses of five years, and two studies stated that the initial EBRT must have delivered a high dose (19) or dose of ≥50 Gy (14). The cohorts of Gressen and Griffioen included new primary lesions (*Table 1*), which was defined by the latter as either a lesion in a new location, a new histology, or recurrence >5 years after initial treatment. Gressen additionally included patients receiving ReRT for lung metastases although did not specify from which primary tumours (19). Kruser *et al.* included 8/48 patients whose initial and repeat RT volumes did not overlap in which the second RT course targeted hilar +/- mediastinal lymph node stations not encompassed in upfront treatment. Remaining studies did not define ReRT or locoregional recurrence.

Main demographic and disease factors along with minimum and median time to ReRT are shown in *Table 1*. Median age ranged from 57 to 71 years, and between 41.2% and 96.4% were male. Between 37.9% and 83.3% of patients had central disease at initial diagnosis (N=4 studies) and just over half had a central recurrence (13). Eight of thirteen studies included SCLC, with only one paper providing separate outcomes (16) (*Table 1*).

Initial RT

Indications for initial RT included definitive therapy

Appendix 1 Search strategy		
Step	String	Results
1	(SCLC or NSCLC).ti,ab. or exp Lung Neoplasms/or [(lung or lungs or alveolar or pulmonary or bronchus or bronchogenic or bronchial or bronchoalveolar) adj3 (cancer or carcinoma or adenocarcinoma or malignan$ or tumor or tumour or neoplasm$)].ti,ab,ot,tw. or [pancoast adj3 (syndrome or tumor or tumour)].ti,ab,ot,tw. or "lung metastases".mp. or "lung mets".ti,ab,ot,tw. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, ps, rs, ui]	419,989
2	(reirradiat$ or re-irradiat$).ti,ab or [(re-treat$ or retreat$) adj3 palliat$].ti,ab. or [(re-treat$ or retreat$) adj3 (radiation or radiotherapy)].ti,ab. or re-radiat$.ti,ab. or [(retreatment/or salvage therapy/) and (exp Radiotherapy/or radiotherapy or radiation or SBRT or IMRT or radiosurgery.ti, ab)]	9,919
3	1 and 2	327
4	Limit to 2000-2013; English; De-dupe	75

Table 1 Patient populations

	%, squamous/ adeno	SCLC	Initial stage III/IV	Distant metastases present at ReRT	%, new primary	%, without pathologic confirmation at ReRT	PS at ReRT	Minimum/ median time to ReRT (months)
Green	65.5/13.8	2/29	NR	NR	0	72.4 (21/29)	14/29 good, 11/29 poor, 4/29 NE	3*/10
Jackson	47.8/34.8	0/22	NR	NR	0	47.8 (11/23)	NR	5.7/15
Montebello	53.3/26.7	1/30	76.7%/0	NR	0	73.3 (22/30)	Median KPS 60 [40-100]	8.1/NR
Gressen	34.8/30.4	2/23	NR/NR	NR	Not specified	NR	NR	3/15
Okamoto	50.0/17.6	6/34	82.4%/8.8%	38.2%	0	NR	WHO 0-3/34; 1-11/34; 2-10/34; 3-7/34; 4-3/34	5/23
Wu	39.1/30.4	7/23	69.6%/0	Not permitted	0	34.8 (8/23)	KPS ≥70-23/23	6*/13
Kramer	NR/NR	0/28	NR/NR	NR	0	32.1 (9/28)	Median KPS 80 [40-90]	6*/17
Tada	73.7/21.1	0/19	100%/0	Not permitted	0	0	ECOG 0-1-8/19; 2-6/19; 3-5/19	5/16
Poltinnikov	35.3/58.8	0/17	NR/NR	NR	0	NR	Median KPS 80 [60-90]	2/13
Ebara	43.2/25.0	9/44	NR/NR	NR	0	81.8 (36/44)	ECOG 0-1-38/44	5.8/12.6
Cetingoz	60.5/13.2	0/38	94.7%/0	15.8%	0	5.3** (2/38)	NR	1/8.8
Kruser	35.4/NR	11/48	41.7%/25.0%^	37.5%	0	75 (36/48)	NR	4/19.1
Griffioen	41.7/20.8	4/24	62.5%/8.3%	16.7%	54.2 (11/24)	16.7 (4/24)	Median ECOG 1 [0-2]	5/51

*, minimum time to recurrence required; **, initial diagnosis; ^, includes two extensive stage small cell lung cancer patients. Abbreviations: adeno, adenocarcinoma; NE, not evaluable; NR, not reported; PS, performance status; ReRT, reirradiation; SCLC, small cell lung cancer.

(N=8 studies), neoadjuvant/adjuvant (N=5), to salvage a postoperative recurrence (N=4), or palliative (N=4) (*Table 2*). From studies reporting intent, greater than half of each cohort was treated with radical, and approximately ¼ with palliative intent, with the exception of one in which 81.6% were treated palliatively (9). EBRT techniques, energies, field sizes (FS), doses and volumes varied significantly as can be expected from these differing treatment indications (*Tables 2-4*). Some patients were simulated two-dimensionally (2D) under flurosocopy [12/23 (21); 44/44 (17)]. Generally, volumes included the tumour and adjacent mediastinum/regional LN, with some series reporting elective nodal irradiation (ENI). For all cohorts published before 2008, initial RT was delivered 2D, consisting of an anterior-posterior/posterior-anterior (APPA) parallel opposed pair (POP), followed by an off-spinal cord boost with custom blocking. The use of 3D conformal RT (66.7%) and intensity-modulated RT (IMRT) (33.3%) was reported in only one study (16). Half of the Griffioen cohort had their initial RT at another centre, of which 8/12 plans were not available for review (7). A varying number of patients received chemotherapy [sequential (3.3-45.8%), concurrent (7.9-81.8%), or timing not specified] (*Table 2*). Reported median dose, fraction number and spinal cord doses are shown in *Table 4*. Biologically equivalent dose was calculated from available reported data.

Reporting of outcomes was limited. Between 6.7% and 21.1% had a complete response (CR) and 40-63.2% a partial response (PR) to initial RT in two studies (18,20). Of 25 patients symptomatic at the time of initial RT, 22 had improvement of at least one symptom, with 100% of those with hemoptysis, superior vena cava obstruction (SVCO), hoarseness and dysphagia responding in one study (20). Toxicity included rates of 12-53% with esophagitis, 47% dry desquamation, up to 32% with pneumonitis and 7% moist desquamation (12,14,20). Authors disagreed on whether patients had to have had a favourable (12,13) response to initial RT to be considered for ReRT, or at least the absence of progression (21); two series retreated patients who did not have a radiographic response after upfront treatment, or progressed during initial RT (18,20).

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Table 2 Initial RT

	Indication for initial RT				Median FS [range]	Energy	Technique	Received Chemo	Volume
	Definitive	Neo/adjuvant	Postoperative recurrence	Palliative					
Green	15/29	3/29	11/29	0	200 cm²** [NR]	60 Co or 4 MV	NR	7/29 after	T + LN
Jackson	19/23	4/23	NS	0	NR	4-6 MV	POP then off-cord boost	NR	T + M +20 mm
Montebello	NR	NR	2/30	NR	255 cm²^ [NR]	60 Co or 4-21 MV	APPA then cone down	1/30 before; 3/30 conc; 1/30 after	T + LN
Gressen	NR	NR	NR	NR	NR	60 Co or Linac	APPA then off-cord obliques	NR	NR
Okamoto	24/34	6/34	4/34	0	150 [30-355] cm²	10 MV	POP	26/34*	T + LN
Wu	13/23	4/23	0	6/23	NR	NR	POP then oblique boost	NR	T +/- LN
Kramer	25/28	1/28	2/28	0	NR	10-18 MV	NR	NR	T + M + 10-20 mm
Tada	NR	NR	NR	NR	NR	10 MV	NR	17/19 conc or sequential	NR
Poltinnikov	NR	NR	NR	NR	NR	NR	NR	17/17*	NR
Ebara	NR	NR	NR	NR	104 [26-288] cm²	NR	44/44 APPA POP	25/44*	T + LN
Cetingoz	NR	NR	NR	31/38	162.5 [36-405] cm²	NR	NR	10/38 sequential*; 3/38 conc	T + LN
Kruser-NSCLC	24/37	4/37	0	9/37	NR	NR	25/37 3DCRT; 12/37 IMRT	13/37 conc; 30/37 before or after	NR
Kruser-SCLC	9/11	0	0	2/11	NR	NR	7/11 3DCRT; 4/11 IMRT	9/11 conc; 2/11 after	NR
Griffioen	23/24	1/24	NS	0	539§ [114-950] cc	NR	NR	8/24 conc; 11/24 sequential; 1/24 CRT + surg	NR

*, timing with respect to RT not specified; **, average; ^, initial field size before cone down; §, PTV volume. Abbreviations: 60 Co, cobalt; 3DCRT, three-dimensional conformal radiotherapy; APPA, anterior-posterior/posterior-anterior; conc, concurrent; CRT, chemoradiotherapy; FS, field size; IMRT, intensity-modulated radiotherapy; LN, regional lymph nodes; M, mediastinum; NR, not reported; NS, not specified; NSCLC, non-small cell lung cancer; POP, parallel opposed pair; SCLC, small cell lung cancer; surg, surgery; T, tumour.

Table 3 Reirradiation

	Indication for ReRT		Median FS [range]	PTV volume	Energy	Technique	Volume	Inhomo correct	Received chemotherapy
	Curative/ salvage/ prophylactic	Palliative							
Green	NR	NR	80 cm²* [NR]	NR	NR	29/29 angled portals to avoid cord	T +/– ENI	NR	6/29 after RT
Jackson	0	23/23	NR	NR	4-6 MV	Usually oblique fields	T	NR	NR
Montebello	NR	NR	96 cm²** [NR]	NR	60 Co or 4-25 MV	NR	T +/– ENI	No	1/30 before ReRT; 2/30 conc
Gressen	NR	NR	81 [30-315] cm²	NR	Linac	17/23 opposed oblique; 2/23 opposed lateral; 2/23 POP then oblique; 2/23 noncoplanar oblique; 2/23 also got brachy	T +10-20 mm	NR	4/23 before; 7/23 conc; 8/23 after; 1/23 BMT
Okamoto	18/34	16/34	65 [20-238] cm²	NR	10 MV	34/34 POP and off-cord obliques	T	NR	11/34 before RT; 5/34 conc
Wu	0	23/23	NR	80^ [30-128] cm²	6 MV	6/23 noncoplanar fields; 6/23 coplanar fields; 8/23 dynamic arc; 3/23 combo	T +15-20 mm	No	Before or after RT; median 1 cycle (range 1-3)
Kramer	0	28/28	104 cm²* [NR]	NR	6-18 MV	28/28 opposed obliques off-cord	NR	NR	Not permitted
Tada	19/19	0	64 [30-204] cm²	NR	10 MV	NR	T	No	1/19 concurrent
Poltinnikov	0	17/17	95 [30-189] cm²	NR	6 MV	17/17 multiple noncoplanar fields	GTV +5 mm	No	5/17 conc
Ebara	NR	NR	48 [16-100] cm²	NR	NR	44/44 APPA POP	T +5-10 mm	NR	16/44 conc
Cetingoz	0	38/38	88.7 [25-244.5] cm² NR	NR	60 Co, 6 or 23 MV	38/38 opposed off-cord obliques	T +10-20 mm	No	9/38 before; 1/38 conc
Kruser-NSCLC	18/37	19/37	NR	149 [26-585] cc	NR	2/37 3DCRT; 35/37 tomotherapy	ITV +6 mm = CTV +5 mm = PTV§;	NR	14/37 before; 12/37 after
Kruser-SCLC	4/11	7/11	NR	456 [64-456] cc	NR	1/11 POP; 1/11 IMRT; 9/11 tomotherapy	GTV +5 mm = PTV€	NR	11/11 before; 3/11 after
Griffioen	NR	NR	NR	248 [59-1,140] cc	NR	NR	NR	NR	13/24 sequential; 2/24 conc

*, average; **, initial field size before cone down; ^, GTV; €, patients treated with palliative intent; §, patients treated with radical intent. Abbreviations: 60 Co, cobalt; 3DCRT, three-dimensional conformal radiotherapy; APPA, anterior-posterior/posterior-anterior; BMT, bone marrow transplant; brachy, low dose rate brachytherapy; conc, concurrent; correct, correction; CTV, clinical target volume; ENI, elective nodal irradiation; FS, field size; GTV, gross tumour volume; IMRT, intensity-modulated radiotherapy; inhomo, inhomogeneity; ITV, internal target volume; linac, linear accelerator; NR, not reported; NSCLC, non-small cell lung cancer; POP, parallel opposed pair; PTV, planning target volume; ReRT, reirradiation; SCLC, small cell lung cancer; T, tumour.

Table 4 Initial and reirradiation doses

| | Initial RT | | | | ReRT | | | | Median combined | |
	Median total dose (range)	Median fraction# [range]	BED	Median cord dose (range)	Median total dose (range)	Median frac# [range]	BED	Median cord dose	tumour dose (range)	Median survival from start of ReRT
Green	53 Gy (40-65 Gy)	NR	--	NR	35 Gy (6-54 Gy)	NR	--	NR	82 Gy (60-166 Gy)	5 mos (1-54 mos)
Jackson	NR (50-61 Gy)	NR	--	45 Gy¶	NR (20-60 Gy)	NR	--	NR	NR (70-120 Gy)	5.4 mos (NR)
Montebello	NR (28-66.6 Gy)	NR [10-30]	--	NR	30.3 Gy (19.8-56 Gy)	NR [10-20]	--	NR	NR	5 mos (NR)
Gressen	59 Gy (32-66 Gy)	NR	--	NR	30 Gy (6-38 Gy)	NR*	--	NR	86 Gy (61-101 Gy)	4.9 mos^Σ (NR)
Okamoto	60 Gy (30-80 Gy)	NR	--	46 Gy (0-60 Gy)	50 Gy (10-70 Gy)	NR	--	8 Gy (0-50 Gy)	120 Gy (56.5-150 Gy)	8 mos (NR)
Wu	66 Gy (30-78 Gy)	NR	--	42-44 Gy§	51 Gy (46-60 Gy)	NR	--	≤25 Gy¶	NR	14 mos (2-37 mos)
Kramer	NR (36-60 Gy)**	NR [12-30]**	--	50 Gy¶	16 Gy	2 fract in 8 days	28.8 Gy$_{10}$	NR	NR	5.6 mos (95% CI 4.4-8.8 mos)
Tada	NR (50-69.6 Gy)	NR	--	NR	50 Gy (50-60 Gy)	25 [25-30]	60.0 Gy$_{10}$	NR	NR	7.1 mos (NR)
Poltinnikov	52 Gy (50-66 Gy)	NR	--	NR	32 Gy (17.5-42 Gy)	NR	--	NR	84 Gy^ (67.5-108 Gy)	5.5 mos (2.5-30 mos)
Ebara	60 Gy (50-70 Gy)	NR	--	NR	40 Gy (30-60 Gy)	NR	--	NR	102 Gy (80-130 Gy)	6.5 mos (NR)
Cetingoz	30 Gy (28.8-67.2 Gy)	10 [9-33]	39.0 Gy$_{10}$	NR	25 Gy (5-30 Gy)	10 [1-10]	31.3 Gy$_{10}$	NR	57.5 Gy (35-96 Gy)	3 mos (0-55 mos)
Kruser-NSCLC	57 Gy (30-80.5 Gy)	25 [10-37]	70.7 Gy$_{10}$	NR	30 Gy (12-60 Gy)	10 [4-30]	39.0 Gy$_{10}$	10.2 Gy (2.2-28.1 Gy)	87 Gy^ (42-140.5 Gy)	5.1 mos (0.5-42 mos)
Kruser-SCLC	45 Gy (12-54 Gy)	30 BID [4-30]	51.8 Gy$_{10}$	NR	37.5 Gy (25-45 Gy)	15 [9-25]	46.9 Gy$_{10}$	12.2 Gy (4.1-24.1 Gy)	82.5 Gy^ (37-99 Gy)	3.1 mos (1-22.7 mos)
Griffioen	59.8 Gy (24-70 Gy)	25 [3-35]	74.4 Gy$_{10}$	NR	60 Gy (39-66 Gy)	30 [13-33]	72.0 Gy$_{10}$	NR	120 Gy$_{10}$*** (84-138 Gy$_{10}$)	13.5 mos (95% CI 5.7-21.2 mos)

*, unspecified number of patients treated BID; **, radical RT only; ***, BED reported by study, obtained by arithmetic addition of reported doses; Σ, measured from time to diagnosis of progression/recurrence; §, dose to cord limited to 42-44 Gy for patients receiving definitive RT; ¶, cord generally limited to this dose. Abbreviations: BID, twice per day; fract, fraction; NR, not reported; ReRT, reirradiation.

Patient status prior to ReRT

Various restaging studies prior to ReRT were required by four studies (7,9,11,18). Stringent eligibility criteria in the clinical trial required: minimum performance status (PS), FEV1 >1 L, no severe cardiovascular disease, and normal major organ function (11). Restaging was not required in Green or Kramer and was not specified by remaining. Neither Wu nor Tada permitted distant metastases, and only Tada required pathologic confirmation of disease. In patients without pathologic confirmation, eligibility in the Wu study required recurrence to be confirmed by a group of physicians, while radiographic findings in the Kruser study had to be diagnosed as recurrence by interpreting radiologists. For the remaining, pathologic confirmation was desirable but not essential.

Reirradiation (ReRT)

Indications for repeat irradiation can be divided into four categories: emergent symptomatic, such as SVCO; symptomatic but not emergent, such as dyspnea; asymptomatic but impending serious event, such as airway obstruction; or asymptomatic but with radiological disease progression. Specific indications for ReRT were decided on a case-by-case basis at the discretion of the attending radiation oncologist in each retrospective study. At retreatment, the proportion of symptomatic patients ranged from 42.1% to 100%. In Jackson, Kramer, and Cetingoz, at least 95% of patients were symptomatic, while in Poltinnikov, the figure was just over three-quarters; all patients in these four studies were treated with palliative intent (*Table 4*).

In the majority of series, ReRT included gross tumour plus a margin (7,9,11,12,14,17-19,21). Significant efforts were made to increase precision of treatment and exclude critical normal organs with maneuvers such as 4D CT simulation (7,16), localized portals (10,13,18), absence of ENI (11,16), immobilization devices (14), consensus gross tumour volume (GTV) determination (11), oblique field arrangements (9,17), use of lesion motion to determine margins (9,11,16), and blocking/multileaf collimation (9,17).

The selection of ReRT dose was at the discretion of the attending physician. It was limited to that sufficient to relieve symptoms in many series (12,17,20), but it was not clear how this was determined. Prescribed doses appeared to be influenced by ReRT intent, initial dose, normal tissue dose and expected lifespan (11,19). For example, Kruser delivered a higher median dose when treating with radical

intent (56 Gy/25), compared to those with asymptomatic radiographic progression (20-40 Gy), and those being treated with palliative intent (12-40 Gy). In the phase I/II clinical trial, if the intial RT dose had been <50 Gy, 60 Gy was given at ReRT, and if >50 Gy upfront, 46-50 Gy was delivered (11). Kramer chose a high dose per fraction schedule (16 Gy/2/8 days) to minimize the number of fractions, while Tada used a small dose per fraction to minimize late toxicity. In addition, a handful of patients were reirradiated twice (ie three courses of EBRT total), with cumulative (arithmetic) dose up to 180 Gy.

Ideally, the ReRT planning target volume (PTV) should be covered with the 95% isodose with none of the PTV receiving more than 107% of prescribed dose (11,22). While doses to organs at risk (OARs) were limited to "within tolerance" (not further specified) (4,11), no specific dose limitations were described for the volume of lung, esophagus or heart, other than to spare these as much as possible (10,12). Wu *et al.* avoided the same beam pathway as the initial RT field arrangement for this reason. High spinal cord doses were accepted by two series if: the patient's life expectancy was limited; and a high tumour dose was required to control symptoms or prevent a catastrophic outcome such as spinal cord compression (12,21). Spinal cord dose contributed by ReRT was limited to <25-50 Gy by three series (*Table 4*), although Wu *et al.* admitted that the constraint lacked firm evidence.

Composite plans were constructed (7,16) when possible and efforts were made to retrieve the original plans for patients treated at an outside institution (Kruser: 14/48). Cumulative dose was estimated with the aid of rigid +/– deformable coregistration (7). Median PTV overlap was 34% (range, 0-96%; N=16) in one study (7). The median degree of overlap of the 50% isodose volumes was 62% (range, 0-95%), and that of the 90% isodose volumes was 44% (range, 0-100%; N=22); however, these dosimetric parameters did not correlate with outcomes (7). Cumulative spinal cord doses were reported by two studies, with Jackson *et al.* reporting between 30 and 79 Gy received, and Okamoto *et al.* reporting a median combined dose of 52 Gy and maximum dose of 103 Gy. Most authors mathematically added initial and repeat doses, despite changing dose-fractionation schedules (*Table 4*). The exceptions to this were Kruser and Griffioen, who calculated equivalent doses in 2 Gy fractions using α/β =10. In the patients conventionally simulated at the time of the second course (9,17,21), little information is available on ReRT or cumulative tumour or OAR doses and composite plans could not be constructed.

Systemic therapy

The rationale for delivery of chemotherapy before, after or concurrent with ReRT was not stated but presumably was at the discretion of the treating oncology team. It is not clear whether the patients who received chemotherapy at the time of ReRT were also those treated with radical intent ReRT, as would be expected. In the prospective Kramer study, all patients were treated with palliative intent and chemotherapy was not permitted, whereas in the Poltinnikov series, all patients were treated with palliative intent, and almost one-third received concurrent chemotherapy. One of thirty-eight patients treated palliatively by Cetingoz also received concurrent chemotherapy and explanation was not provided. In the clinical trial, patients in good condition received one cycle prior to ReRT, although an eligibility criterion was a minimum PS of 70 for all patients (11). Additional sequential cycles were given subsequently if the patient could tolerate. No paper reported use of targeted therapy.

Follow-up

Median follow-up from completion of ReRT ranged from 3.2 to 19.3 months (7,12,17,19,21) although this was variously measured from the start or the completion of repeat RT, or not specified. The majority were followed at the cancer centre until death (7,13,14,21); intensity of follow-up investigations varied, even for patients treated with palliative intent. Most underwent examination every one to three months (11,12,21) by a radiation oncologist and/or respiratory physician, together with CT scan every 3-6 months (12). CT scans were performed 4-6 weeks after the completion of ReRT and then every 8 weeks in another series in which all patients were palliatively treated (14). All patients were seen at 6 and 12 weeks and then every 3 months with exam and CXR after palliative ReRT (10). CT chest was required at 3, 6, and 12 months after ReRT, and after that either CT chest or chest X-ray in the clinical trial (11).

Outcomes: radiologic response

Of patients evaluable for radiographic response, 0-11% had a CR and 7-44% a PR (13,14,20). Of 18 patients given radical-intent ReRT, 6 (33%) had a CR and 8 (44%) had a PR (12). In another study, 5/6 patients receiving chemotherapy after ReRT responded, but neither histology nor FS correlated with radiologic response (13).

Outcomes: symptom response

Symptom improvement rates ranged from just under half (48.3%) to 100% of those assessable, with an overall average of 69.2% either improved or resolved (*Table 5*). Data on response rates after initial palliative RT and second line systemic therapy are included in the table for comparison. Median duration of symptom response, reported by three series, ranged from 1.8 to 4 months for NSCLC +/– SCLC, and was 0.5 months (range, 0-1.4 months) for SCLC analyzed separately (N=1). As a result of symptom improvement in assessable patients in one study, PS of 9/20 improved and 8/20 stabilized (10). Specific symptom improvement rates were not reported by Wu, Okamoto, Poltinnikov, Kruser, or Griffioen, despite the palliative intent of treatment in most (16), if not all (11,14) of their patients. In at least one series, rates were considered low because of concomitant development of acute pulmonary toxicity and/or symptomatic progressive disease (16). The following did not appear to significantly impact the likelihood of symptomatic benefit from ReRT: histology (21), dose (12,21), specific symptom (12), tumour size (9), or previous RT aim (9).

Outcomes: overall survival (OS)

The majority of patients died of lung cancer (LC) (9,10,12,17,19). Median survival (MS), usually measured from the start of repeat RT, is shown in *Table 4*. Reported MS in series in which all patients were treated palliatively was approximately 5 months (9,10,14,21). In one study, MS after radical versus palliative-intent ReRT was 15 months (range, 3-58 months) versus 3 months (range, 1-14 months) respectively (12). One year OS ranged from 9-59% (7,9,11,12,16-18) for the NSCLC +/– SCLC populations and 18% for SCLC analyzed separately (16). Median initial, ReRT and combined dose significantly correlated with OS, with Spearman's rho values of 0.85 (P=0.002), 0.72 (P=0.006), and 0.88 (P=0.001) respectively (*Figure 1*). Relationships between BED and MS could not be investigated due to insufficient data.

The following factors did not appear to significantly influence OS: improvement in dyspnea (19), age (7,9,19), new primary *vs*. recurrence (7), initial stage ≥ III *vs*. < III (7), use of chemotherapy at the time of ReRT in a mixed NSCLC/SCLC population (7), comorbidities (7), degree of initial and repeat PTV overlap (7), dosimetric overlap (7), tumour size <6 or >6 cm (9), or tumour location (central *vs*. peripheral) (9).

Table 5 Rates of symptom improvement

	Hemoptysis	SVCO	Pain	Cough	Bronchial obstruction/ dyspnea	Dysphagia	Hoarseness	Total [%]	Median duration of response (range)
Green	1/3	2/4	NR	5/9	4/9	1/2	0/2	14/29 [48.3]	NR** (1-23 mos)
Jackson	5/6	0/1	4/11	1/2	2/3	NR	NR	12/23§ [52.2]	NR (NR)
Montebello	8/9	3/4	10/13	7/11	8/15	NR	0/2	36/54# [66.7]	2.8 mos (NR)
Gressen	6/6	NR	4/5	9/15	11/15	NR	1/2	31/43# [72.1]	NR (NR)
Okamoto	NR/3	NR	NR/8	NR	NR/8	NR/2	NR	12/16 [75.0]	NR (NR)
Wu	NR	NR	NR	NR	NR	NR	NR	NR	NR (NR)
Kramer	13/13	4/4€	NR	4/6€	6/17€	NR	NR	27/40# [67.5]	4 mos (1-19 mos)
Tada	NR	2/2£	4/5£	NR	1/1£	NR	NR	7/8 [87.5]	NR (NR)
Poltinnikov	NR	NR	NR	NR	NR	NR	NR	11/13 [84.6]	NR (NR)
Ebara	8/8	NR	9/11	3/6€	3/6	NR	NR	23/31#€ [71.9]	NR (NR)
Cetingoz	6/7	1/1	6/10	10/13	9/13	NR	NR	32/44#€ [72.7]	NR (NR)
Kruser-NSCLC	NR	NR	NR	NR	NR	NR	NR	15/20€ [75]	1.8 mos (0-15 mos)
Kruser-SCLC	NR	NR	NR	NR	NR	NR	NR	7/7€ [100]	0.5 mos (0-1.4 mos)
Griffoen	NR	NR	NR	NR	NR	NR	NR	NR	NR (NR)
Total	47/52 (90.4%)	12/16 (75.0%)	37/55 (67.3%)	39/62 (62.9%)	44/79 (55.7%)	1/2 (50.0%)	1/6 (16.7%)	227/328 [69.2]	n/a
First line palliative RT*	636/792 (80.3%)	NR	616/958 (64.3%)	822/1614 (50.9%)	NR	NR	NR	2,074/3,364 [61.6]	n/a
Second line erlotinib^	24/298 (8.1%)	NR	235/643 (36.5%)	131/298 (44.0%)	225/650 (34.6%)	36/296 (12.2%)	NR	651/2,185 [29.8]	4.9 mos (cough); 2.9 mos (dyspnea); 2.8 mos (pain)

*, from ref (23); ^, from ref (24); **, duration of response in 'most' patients ≤5 months; #, number of symptoms; §, one main symptom reported per treatment course; €, assessable patients; £, symptom assessment performed in patients completing prescribed RT only. Abbreviations: mos, months; NR, not reported; NSCLC, non-small cell lung cancer; pall, palliative; PRT, palliative radiotherapy; SCLC, small cell lung cancer; SVCO, superior vena cava obstruction.
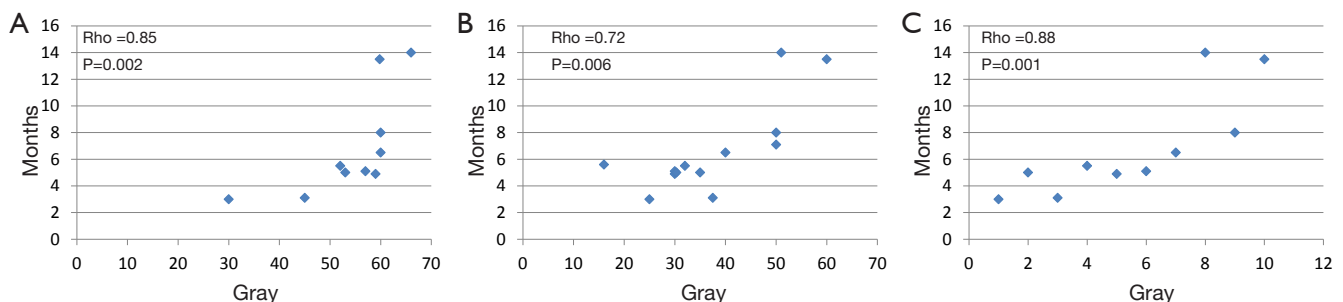

Figure 1 (A) Median initial RT dose versus median overall survival measured from repeat RT; (B) median repeat RT dose versus median overall survival measured from repeat RT; (C) median combined RT dose versus median overall survival measured from repeat RT. Combined doses not reported were obtained by arithmetic addition (Wu, Poltinnikov, Kruser).

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Table 6 Prognostic factors. Refers to NSCLC or mixed NSCLC/SCLC unless otherwise specified

Outcome	Parameter	P value	Reference
Longer OS			
Dose	Original RT dose ≥58.3 Gy$_2$	0.03	Kruser
	Repeat RT dose >32.5 Gy$_2$*	0.007	Kruser
	Higher repeat RT dose for SCLC	0.01	Kruser
KPS	KPS ≥80 at time of ReRT*	0.01	Kruser
	ECOG 0-1 versus 2 versus 3*	<0.05	Tada
	Good *vs.* poor performance status	NR	Green
Chemotherapy	Further chemo given after ReRT for SCLC	<0.001	Kruser
Disease extent	Absence of extrathoracic disease	0.002	Kruser
	Absence of distant metastases	0.02	Ebara
	PTV <300 versus ≥300 cc	0.02	Griffioen
Time to recurrence	Interval to disease recurrence ≥1 yr	0.05	Kruser
	Interval to recurrence >1 yr	NR	Kramer
Intent of repeat RT	ReRT given with radical intent	0.001	Kruser
	ReRT given with radical intent for SCLC	0.013	Kruser
Interval between RT courses	>18 months versus 12-18 months versus <12 months*	<0.05	Tada
	≥35 weeks versus <35 weeks*	<0.001	Cetingoz
Radiologic response	Favourable radiologic response	NR	Green
Longer EFS			
PTV size	PTV <300 versus ≥300 cc	0.03	Griffioen
More frequent symptomatic improvement			
Tumour location	Central versus peripheral	0.01	Cetingoz
Increased frequency of radiologic response			
Chemotherapy	Adjuvant after ReRT	NR	Green
Increased rates of pulmonary toxicity			
Intent of repeat RT	Radical intent	0.05	Kruser
Increased rates of esophageal toxicity			
Esophageal dose	Any volume receiving ≥100% of prescribed dose	0.004	Poltinnikov

*, multivariate analysis. Abbreviations: EFS, event-free survival; KPS, Karnofsky performance status; NR, not reported; OS, overall survival; PTV, planning target volume; ReRT, reirradiation; RT, radiotherapy; SCLC, small cell lung cancer.

Two studies reported that interval from completion of initial RT to recurrence did not significantly influence OS (7,19), but two studies did (*Table 6*). Griffioen *et al.* did not find that PS influenced OS, but three studies did. Griffioen *et al.* reported that dose did not influence OS but one study did (*Table 6*).

Outcomes: progression-free survival

One year event-free survival (EFS) was 37% (7) and one year locoregional progression-free survival was 51% (11). Median relapse-free interval after ReRT ranged from 5

to 8.4 months (7,13). In Griffieon, the following did not appear to significantly influence EFS: PS, new primary *vs.* recurrence, stage ≥III *vs.* <III, ReRT alone versus chemoRT, age, comorbidities, degree of PTV overlap between initial and ReRT, dosimetric overlap, dose, and interval between RT courses (7).

Outcomes: toxicity

RT-related toxicity and adverse outcomes are seen in *Table 7*. RT pneumonitis was more frequent after ReRT than after initial EBRT in one study, while the frequency and severity

Table 7 RT-related toxicity and adverse outcomes

	Esophagitis	Pneumonitis	Desquamation (dry +/– moist)	Fracture	Myelopathy	% not completing ReRT	ReRT-related death**
Green	0/29	1/29	0/29	1/29 (rib)	0/29	5/29	0/29
Jackson	0/22	0/22	0/22	0/22	1/22*	0/22	0/22
Montebello	6/30	1/30	4/30^	0/30	0/30	0/30	0/30
Gressen	0/23	1/23§	0/23	0/23	0/23	0/23	1/23§
Okamoto	6/34 (4 gr II, 2 gr III)	19/34 (12 gr II, 7 gr III)	0/34	0/34	1/34*	0/34	0/34
Wu	2/23 (gr I/II)	5/23 (gr I/II)	2/23 (gr I/II)	0/23	0/23	0/23	0/23
Kramer	1/28 (gr II)	1/28	0/28	0/28	0/28	0/28	1/28¶
Tada	3/19 (gr II)	1/19 (gr III)	0/19	0/19	0/19	5/19	0/19
Poltinnikov	7/17 (gr I/II)	1/17 (gr II)*	0/17	0/17	0/17	1/17	0/17
Ebara	0/44	6/44 (3 gr II, 3 gr III)	0/44	0/44	0/44	0/44	0/44
Cetingoz***	21/26 (20 gr I/II, 1 gr III)	0/26	0/26	0/26	0/26	5/38^	0/26
Kruser-Combined	5/48 (gr II)	7/48 (gr ≥ II)	0/48	0/48	0/48	1/48	0/48
Griffoen	12/24 (11 gr I/II, 1 gr III)	2/24	9/24	1/24 (spine)	0/24	0/24	4/24£
Total	63/367 (17.2%)	45/367 (12.3%)	15/367 (4.1%)	2/367 (0.5%)	2/367 (0.5%)	17/379 (4.5%)	6/367 (1.6%)

*, likely related to initial rather than repeat RT according to study; **, death due to RT complication; ***, evaluable patients; §, grade III or higher; patient's death due either to disease progression or ReRT with chemotherapy; £, hemoptysis, hematemesis or lung-related sepsis; *, post-pneumonectomy; ^, two additional patients died within two days of completing ReRT; ¶, received two courses of RT and laser, then died of bronchoesophagheal fistula. Abbreviations: gr, grade; ReRT, reirradiation.

of other RT side effects were similar to those after initial RT (12). In addition to the data in the Table, 6/23 had pulmonary fibrosis on CT chest, of whom four had no symptoms and two were symptomatic (grade three) in one series (11). In another, 6/24 had grade I/II fatigue and 10/24 grade I/II cough (7). In the Kruser series, 2/48 developed bronchostenosis requiring surgery. No publication reported fistula solely as a complication of repeat EBRT.

The following did not appear to influence the rate of pulmonary toxicity: cumulative dose (16), previous or repeat RT dose (17), previous or repeat RT field size (17), interval between courses (17), PS (17), age (17), cumulative FS (17), concurrent chemotherapy (17), or tumour location (17). The length of esophagus within the treatment portal did not influence the likelihood of esophagitis (14). In one series, the single patient who had RT pneumonitis after initial RT did not have a recurrence after repeat RT, and the one patient who developed this after ReRT did not after initial treatment (20).

Due to the development of new symptoms, general deterioration in clinical or PS or death, approximately 5% of patients could not complete the prescribed ReRT

(13,14,16,18) (*Table 7*). In Tada, 4/5 of these patients had PS 3. In Cetingoz, two of the patients abandoned treatment, both dying within the next two months (9). Generally, no descriptors of these patients were reported to help guide patient selection.

One treatment-related death was due to bronchoesophageal fistula following laser treatment two months after ReRT (10), although another patient who underwent laser 8 months after ReRT did not develop fistula. Five over thirteen patients retreated primarily for bleeding died 3-11 months after ReRT from fatal hemoptysis (10). However, because FS were comparable to the rest of the population and none of the patients without hemoptysis at the time of ReRT died of hemoptysis, the authors considered these events tumour-and not treatment-related (10). In Griffioen, three patients were scored as having possible grade 5 toxicity due to either hematemesis or hemoptysis (7). They did not score a fourth fatal event as RT-related (lung-related sepsis after irradiation of a pre-existing cavity); however, without RT it is much less likely that this would have been fatal, so this has been included as a treatment-related death

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(*Table* 7). Significant prognostic factors for clinical outcomes are summarized in *Table 6*.

Recommendations

Consideration of many factors is required when determining whether repeat palliative or radical thoracic RT is warranted (*Tables 8,9*). In both settings, the following should be reviewed, on a case-by-case basis, by a multidisciplinary tumor board: comorbidities, PS, extent of locoregional recurrence, current symptomatology, distant metastases, expected survival, degree of benefit from the first course, likely incremental benefit from and ability to tolerate a second course. Recurrent SCLC should be considered separately, as it is typically aggressive and systemic with a dismal prognosis, especially when symptomatic (16). Tissue sampling to confirm disease recurrence would rule out a non-malignant cause and is highly recommended when considering curative-intent ReRT. Histological diagnosis is also important as the implications, potential treatment options and prognosis for a new primary are significantly different.

Patient and disease characteristics will determine the intent of ReRT, which should be clear to clinician, patient and family. For example, implementation of salvage ReRT should be limited to those who are minimally symptomatic or asymptomatic, with limited local tumour volume, no uncontrolled extrathoracic disease and good PS (20). For palliative ReRT, especially if there are no other treatment options, a potentially effective modality such as ReRT should not be withheld (19). A clear and thorough discussion of the pros and cons should take place and informed consent obtained.

With respect to treatment planning, ReRT intent will determine the reasonable complexity of the plan. Highly conformal EBRT would allow for maximum normal tissue sparing and is advised for radical-intent ReRT. For both radical- and palliative-intent, treatment planning should entail every effort to review previous RT volumes, beam arrangement and number, isodose distribution, and tumor dose. Doses already received by critical normal structures such as the spinal cord and estimation of risk of significant side effects such as RT myelitis will determine the ReRT dose prescription. Composite isodose distribution and dose-volume histograms should be reviewed with attention directed towards minimizing cumulative spinal cord dose, volume of combined normal lung receiving 20 Gy or more, and mean lung dose. For those patients radiated initially

with two-dimensional treatment plans, caution is advised due to lack of information about previous doses received.

Conclusive recommendations for follow-up after ReRT have not been established. Many patients treated with palliative intent do not have routine post-RT imaging performed (4). In those who do, distinguishing fibrosis from atelectasis, pneumonic infiltrate, or progression can be difficult (19,20). Follow-up post radical-intent ReRT should adhere to current applicable guidelines for newly diagnosed patients regarding toxicity assessment and options for systemic therapy.

Discussion

To date, the use of ReRT, especially radical-intent, has been controversial. The complexity of implementing ReRT is primarily related to the possibility of causing radiation injury; choosing an appropriate dose in the context of the initial dose and field arrangement; limiting further dose to normal structures which have already received maximum or near-tolerance doses; lack of availability of specific guidelines and data proving efficacy; and a dearth of radiation oncologist experience, with few patients treated per year per institution. The evidence-based recommendations in this report can inform treatment of locoregional recurrence in the palliative and salvage settings, acknowledging the significant heterogeneity in the patient populations, RT, and follow-up practices, and the inherent limitations of retrospective data. Previously published LC treatment guidelines typically recommend RT at the time of recurrence for those who have not previously received it, with skant guidance for ReRT.

The limitations of the data reviewed should be acknowledged. Patients included were highly selected; only 1.5-8.1% of all patients receiving one course of RT were considered eligible for a second course (10,12,13,19,21). Only 11% of patients reviewed had SCLC, and not all series distinguished outcomes separately. The studies describe patients treated over three decades, with outcomes confounded by evolution in diagnosis and imaging.

In the majority of studies published to date, patients were retreated on an ad hoc basis at the discretion of their radiation oncologist without a reported rationale for the choice of dose fractionation, minimum interval between courses, allowed cumulative doses to critical normal structures, or use of chemotherapy. Most studies report the arithmetic cumulative dose (rather than biologically equivalent dose), which does not take into account

Table 8 Recommendations for instituting palliative-intent reirradiation

Patient selection	(I).	Patients should be reviewed at multidisciplinary tumour board;
General	(II).	informed consent must be obtained;
Patient factors	(III).	patients should have persistent, recurrent or progressive locoregional disease which is symptomatic, or with a radiological impending catastrophic event such as SVCO or tracheobronchial obstruction;
Disease factors	(IV).	rule out non-malignant causes;
Treatment factors	(V).	consider obtaining histopathological confirmation of the presence of malignancy, depending on disease-free interval and extent of disease;
	(VI).	address non-malignant contributions to symptoms, if present, prior to initiating ReRT;
	(VII).	patients whose disease progressed during initial RT should not receive ReRT;
	(VIII).	offer ReRT with caution to a patient whose initial RT was planned and delivered two-dimensionally, as minimal information will be available regarding tumour and critical normal structure doses received, and it is unlikely an accurate composite plan could be constructed;
	(IX).	institute non-radiotherapeutic and supportive measures concurrently, including referral to specialists or allied health professionals, to optimize symptom control and quality of life
Interval between courses		A long interval between initial RT and ReRT is preferable, which indicates the natural history of the malignancy and may decrease the risk of toxicity related to the repeat course. Patients should not be considered for palliative ReRT until a minimum of three months have elapsed since the initial course
Treatment planning	(I).	Review previous treatment volumes, beam arrangement and number, isodose distribution, tumour dose and dose to normal structures;
	(II).	perform CT simulation with appropriate immobilization, such as a wing board, preferably in the same position as the previous RT course;
	(III).	utilize information from available diagnostic imaging (CT, PET, MRI) for target delineation; consider image fusion;
	(IV).	attempt to re-establish the previous isocentre coordinates in the patient's current geometry;
	(V).	construct a composite plan;
	(VI).	simple field arrangements, especially for symptomatic SCLC or poor PS patients, are preferred
Dose	(I).	Determine the incidental dose delivered by the initial RT course to the new gross tumour by delineating it on the initial CT simulation scan after image registration. Taking that into consideration, as well as the initial normal structure doses, determine the ReRT dose;
	(II).	review the composite dose distribution and dose-volume histograms;
	(III).	consider hypofractionated dosing to decrease overall treatment time, depending on estimated risk of late toxicity;
	(IV).	keep the contribution of dose to critical normal structures from the second course of RT as low as possible;
	(V).	minimize cumulative spinal cord dose, lung volume receiving 20 Gy or more, and mean lung dose
Treatment verification		Consider employing portal films, electronic portal verification and/or *in vivo* dosimetry as necessary
Systemic therapy		There is no current level I evidence supporting concurrent chemotherapy
Follow-up	(I).	Assess patients during and at the completion of ReRT for acute toxicity;
	(II).	the first follow-up appointment should be at six weeks after completion of ReRT for early assessment of symptom status and to screen for RT pneumonitis. Follow-up thereafter may be at the discretion of the radiation oncologist, or with the referring physician

Abbreviations: CT, computed tomography; KPS, Karnofsky performance status; MRI, magnetic resonance imaging; PET, positron emission tomography; PS, performance status; ReRT, reirradiation; RT, radiotherapy; SCLC, small cell lung cancer; SVCO, superior vena cava obstruction.

Table 9 Recommendations for instituting radical-intent reirradiation

Patient selection		
General	(I).	Patients must be reviewed at multidisciplinary tumour board;
Patient factors	(II).	good performance status (i.e., KPS ≥80 or ECOG ≤2);
Disease factors	(III).	informed consent must be obtained;
	(IV).	aggressive ReRT should be limited to patients with a low to moderate volume of recurrent tumour and no extrathoracic metastases. Consequently, complete restaging should be performed in this population;
Treatment factors	(V).	obtain histopathological confirmation of the presence of malignancy;
	(VI).	address non-malignant contributions to symptoms, if present, prior to initiating ReRT;
	(VII).	patients whose disease progressed during initial RT should not receive radical-ReRT. Patients should have had at least a partial response to initial RT;
	(VIII).	offer ReRT with caution to a patient whose initial RT was planned and delivered two-dimensionally, as minimal information will be available regarding tumour and critical normal structure doses received, thereby impeding the ability to construct an accurate composite plan
Interval between courses		A long interval between initial RT and ReRT is preferable, which indicates the natural history of the malignancy and may decrease the risk of toxicity related to the repeat course. Patients should not be considered for radical ReRT until a minimum of three, and preferably 6-8 months, have elapsed
Treatment planning	(I).	Review previous treatment volumes, beam arrangement and number, isodose distribution, tumour dose and dose to normal structures;
	(II).	perform CT simulation with 1.5-5 mm slices in the target region. Consider appropriate immobilization, respiratory motion management and/or intravenous contrast, and attempt to reproduce the previous treatment position;
	(III).	utilize information from available diagnostic imaging (CT, PET, MRI) for target delineation; consider image fusion;
	(IV).	attempt to re-establish the previous isocentre coordinates in the patient's current geometry;
	(V).	construct a composite plan;
	(VI).	three-dimensional conformal or intensity-modulated RT should be considered to limit the volume of normal tissue irradiated
Dose	(I).	Determine the incidental dose delivered by the initial RT course to the new gross tumour by delineating it on the initial CT simulation scan after image registration. Taking that into consideration, as well as the initial normal structure doses, determine the ReRT dose;
	(II).	review the composite dose distribution and dose-volume histograms;
	(III).	keep the contribution of dose to critical normal structures from the second course of RT as low as possible;
	(IV).	minimize cumulative spinal cord dose, lung volume receiving 20 Gy or more, and mean lung dose;
Treatment verification		Consider employing portal films, electronic portal verification and/or *in vivo* dosimetry as necessary
Systemic therapy		There is no current level I evidence supporting concurrent chemotherapy
Follow-up	(I).	Assess patients weekly for acute toxicity;
	(II).	the first follow-up appointment should be at six weeks after completion of ReRT for early assessment of symptom status and to screen for RT pneumonitis;
	(III).	thereafter, patients should be followed in a specialist lung cancer RT outpatient clinic so that RT-related complications can be readily recognized and treated

Abbreviations: CT, computed tomography; KPS, Karnofsky performance status; MRI, magnetic resonance imaging; PET, positron emission tomography; PS, performance status; ReRT, reirradiation; RT, radiotherapy.

differences in dose-fractionation or overall treatment time between courses. Treatment techniques, FS, dose calculation procedures and prescription points either vary considerably or are not specified. Complicating the interpretation of results in the palliative ReRT setting is the relatively high dose applied for symptom control (>40 Gy) in some papers and the treatment of asymptomatic patients.

Symptomatic and radiologic response rates may be underrepresented due to the lack of specific definitions and the absence of prospective assessment (10,19,21). There is limited information available about the important parameter of duration of symptom response in relation to survival. In addition, two studies with symptom palliation as the intent of ReRT did not actually report this endpoint (7,11), and response rates of specific symptoms were not provided in others (12,14). It is often difficult to differentiate between symptoms caused by persistent or progressive disease versus those caused by RT-induced parenchymal damage, such as cough and dyspnea (15,25). The rates of specific toxicity in relation to ReRT dose are unclear in the setting of the unknown contribution of the first course to parenchmyal fibrosis. Finally, the often short MS following retreatment does not allow sufficient time for the full extent of late toxicity to manifest (12,20,21); therefore, the degree of risk for the few long-term survivors is unknown.

However, on balance, ReRT should be considered for thoracic recurrence that is currently or imminently symptomatic, if it can be delivered without unacceptable side effects, particularly for those who are expected to achieve a favourable reponse based on results of the previous course (11,13). Radiation oncologists must critically evaluate whether patients are likely to survive long enough to be at risk of late toxicity. A straightforward and thorough discussion must then take place with patients about their options, including an honest appraisal of the potential benefits and potential risks. Only once fully informed patient consent has been obtained should ReRT be delivered.

Recent advances in RT delivery capabilities reduce the volume of normal tissue within treatment fields without compromising tumour coverage. Higher doses may be required to overcome radio-resistance possibly secondary to the presence of chronically hypoxic cells (14,18). Application of 3D conformal or IMRT is essential since these higher initial, repeat and combined doses appear to correlate with improved survival (*Figure 1*). Since most trials did not analyze outcomes by dose or calculate BED, derivation of robust normal tissue tolerances and correlation of dosimetric parameters with acute and late side effects is not yet possible.

At the time of locoregional recurrence, other treatment options may include stereotactic RT, proton therapy, brachytherapy, boron neutron capture therapy, laser ablation, high linear energy transfer RT, hyperthermia, photodynamic therapy, image-guided ablation, re-resection or systemic therapy (26-35). However, these options are not universally available; each has different and often stringent eligibility criteria; strength of supporting evidence varies; and in some, proof of long-term efficacy is lacking. *Table 5* includes comparative data on second line targeted therapy, but further comparison of these modalities is beyond the scope of this review. Finally, the option of best supportive care should not be overlooked.

Our recommendations must be interpreted in the context of the following additional limitations: the type of data available; the likely presence of selection and referral bias; small patient numbers and in some, high attrition rates; short and varying follow-up which affects the incidence of late toxicity; outcomes of patients with SCLC not reported separately in most studies; lack of available quality of life outcomes; and heterogenous baseline characteristics (7,8,14,16). Many studies did not include all radiation details, with the lack of information often due to treatment planning software system changes and evolution of RT delivery techniques (8,17) such as the change from fluoroscopy (2D) to CT-based 3D simulation (16). BED was not reported and data sufficient to calculate it could not be found in most studies, so conclusions regarding dose are limited and confounded by different dose per fraction and overall treatment time.

Conclusions

Despite heterogeneity of patient cohorts, RT techniques and duration of follow-up, ReRT appears to be a feasible option for recurrent thoracic disease, with a small proportion of patients cured by radical-intent ReRT. Treatment guidelines described should guide clinical decision-making. These represent the best evidence-based recommendations which can be derived until further prospective data on modern delivery and planning techniques, and further response, symptom improvement and quality of life data, are available.

Acknowledgements

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