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Reirradiation for Locoregionally Recurrent Lung Cancer Outcomes in Small Cell and Non–Small Cell Lung Carcinoma

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Abstract

Objectives—To our knowledge this is the largest report analyzing outcomes for reirradiation (reRT) for locoregionally recurrent lung cancer, and the first to assess thoracic reRT outcomes in patients with small cell lung cancer (SCLC).

Methods—Forty-eight patients (11 SCLC, 37 non–small cell lung cancer [NSCLC]) receiving reRT to the thorax were identified; 44 (92%) received reRT by intensity-modulated radiotherapy. Palliative responses, survival outcomes, and prognostic factors were analyzed.

Results—NSCLC patients received a median of 30 Gy in a median of 10 fractions, whereas SCLC patients received a median of 37.5 Gy in a median of 15 fractions. Median survival for the entire cohort from reRT was 4.2 months. Median survival for NSCLC patients was 5.1 months, versus 3.1 months for the SCLC patients ($P = 0.15$). In NSCLC patients, multivariate analysis demonstrated that Karnofsky performance status 80 and higher radiation dose were associated with improved survival following reRT, and 75% of patients with symptoms experienced palliative benefit. In SCLC, 4 patients treated with the intent of life prolongation for radiographic recurrence had a median survival of 11.7 months. However, acute toxicities and new disease

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symptoms limited the duration of palliative benefit in the 7 symptomatic SCLC patients to 0.5 months.

Conclusions—ReRT to the thorax for locoregionally recurrent NSCLC can provide palliative benefit, and a small subset of patients may experience long-term survival. Select SCLC patients may experience meaningful survival prolongation after reRT, but reRT for patients with symptomatic recurrence and/or extrathoracic disease did not offer meaningful survival or durable symptom benefit.

Keywords

non–small cell lung cancer; small cell lung cancer; recurrent; reirradiation

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Lung cancer is the leading cause of cancer death in the United States, with approximately 220,000 new cases and 157,000 deaths annually.¹ External beam radiation plays an important role in curative management strategies for both small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC). Intrathoracic recurrence of lung cancer after upfront fractionated radiotherapy (RT) remains a challenging clinical scenario.

In NSCLC patients treated with concurrent chemo-radiation to the thorax, 5-year rates of locoregional recurrence approach 30%.² Current National Comprehensive Cancer Network guidelines for locoregionally recurrent NSCLC include the consideration of external beam RT in cases of endobronchial obstruction, mediastinal lymph node recurrence, or symptomatic recurrence (ie, superior vena cava syndrome or hemoptysis).³ Estimates of utilization of reirradiation (reRT) for locoregionally recurrent NSCLC range from 1.5% to 3.7% of patients receiving upfront RT.^{4,5}

Approximately 30% of SCLC patients have limited-stage disease at diagnosis and are treated with curative intent chemo-radiotherapy. Local failure remains problematic in these patients, and occurred in 36% of patients in the landmark study by Turrisi et al.⁶ Patients who have recurrent or progressive SCLC experience enormous symptom burden⁷ and a short life expectancy. Currently, topotecan is the only Food and Drug Administration-approved drug for second-line treatment of SCLC, but response rates in the second-line setting range from 15% to 38%.⁸ Outcomes after reRT to the thorax specific to locoregionally recurrent SCLC have not been described to date.

The existing body of literature of chest reRT for locoregionally recurrent lung cancer was recently reviewed.⁹ The utilization of intensity-modulated RT (IMRT) was either rare or nonexistent in the reviewed publications. Nonetheless, the authors noted that “IMRT appears particularly suited to the setting of retreatment.” We report on a cohort of 48 patients with locoregional lung cancer after upfront fractionated RT undergoing reRT to the thorax, predominantly using IMRT. To our knowledge, this is largest series reported to date, and the first report of reRT outcomes in which IMRT is the dominant method of radiation delivery. In addition, we report outcomes as analyzed by histology, and provide the first results specific to SCLC patients.

MATERIALS AND METHODS

Records of patients undergoing RT for lung cancer from 2004 to 2010 were reviewed in an institutional review board-approved database, and 53 patients with NSCLC and 11 patients with SCLC who received reRT to the thorax were identified. Patients receiving stereotactic body RT as either the upfront radiation course or for recurrent disease ($n = 16$) were excluded from this analysis, leaving 37 NSCLC patients for analysis. Thirty-four patients (71%) underwent their primary RT at our institution, whereas 14 patients were treated at our institution only upon recurrence. Although split-course radiation for bulky disease^{10,11} was occasionally used at our institution during this timeframe, such patients were not included in this analysis; only 1 patient in this series was retreated to the thorax within 4 months of original thoracic radiation.

Thoracic recurrence was defined as documented radiographic findings within the thorax deemed to represent recurrence by interpreting radiologists, with or without pathologic confirmation of recurrence. Recurrence was documented pathologically in 12 cases (25%). ReRT was primarily delivered by IMRT using helical tomotherapy (44 patients; 92%). Thin-slice treatment planning computed tomographies (CTs) with 4-dimensional CT were used for treatment planning. No elective nodal irradiation was utilized in the reRT setting in any patient. For reRT, in patients treated to doses of 40 Gy, our institutional practice has been to utilize a 6-mm margin added to the motion envelope to form the clinical target volume (CTV) and to expand the CTV by 5 mm in all directions to form the planning target volume (PTV). In palliative cases, a direct gross tumor volume (GTV) to PTV expansion of 5 mm was typically utilized.

The best palliative response at any time after reRT was assessed as per the system proposed by Kramer et al,¹² with the following definitions: vanished (complete symptom resolution), diminished (any improvement without complete resolution), stabilized (no change), or progressive. Duration of palliative benefit was defined as time from completion of reRT to symptomatic recurrence or symptomatic progression, cancer-related hospitalization, or death. Acute (within 30 d of ending radiation) and late toxicities were scored by National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. Median overall survival from initial diagnosis and from completion of reRT, time to local progression after reRT, and time to hospice (decision not to pursue further oncologic treatment) from reRT were determined by the Kaplan-Meier method, while 6-month and 1-year survival rates were reported crudely. Normalized tumor doses in 2 Gy fractions using α/β ratio of 10 ($\text{NTD}(2)_{10}$) were calculated for all radiation courses (upfront, reRT, and cumulative). Univariate analysis examining relationships between prognostic variables and survival after reRT was performed using pairwise log-rank associations. The Cox proportional hazards model with stepwise variable selection and a univariate significance level of $P < 0.10$ for determining the entry and retention of predictors was used. All statistical tests were 2-tailed, and P was considered statistically significant when < 0.05 .

RESULTS

Patients and Initial Treatment

Forty-eight patients who received reRT to the thorax were identified. Patient characteristics are reported in Table 1. Eleven patients (23%) had SCLC, while the remainder had NSCLC. The majority of NSCLC patients (54%) had stage III disease at diagnosis, whereas a quarter of all patients (12/48) had metastatic disease at diagnosis.

Upfront treatment details are detailed in Table 2. In NSCLC patients, the most common (and median) upfront radiation dose/fractionation schedule was 57 Gy delivered in 25 fractions. This regimen represented the first “bin” of a prospective institutional hypofractionated, dose per fraction escalation protocol.¹³ Concurrent chemotherapy was delivered with initial RT in 13 patients (35%), and 30 patients (81%) had either neoadjuvant or adjuvant/consolidative chemotherapy followed upfront RT; 7 patients (19%) received no chemotherapy as part of their upfront treatment approach.

In the 11 SCLC patients, all had mediastinal involvement at diagnosis. Initially, 9 had limited-stage disease and were treated with definitive chemoradiotherapy, most commonly with the twice-daily radiation *a la* Turrisi.⁶ Two extensive stage patients received upfront palliative radiation for superior vena cava syndrome without concurrent chemotherapy, followed by carboplatin and etoposide chemotherapy.

Recurrence and Retreatment Details

Median time to recurrence after upfront radiation for all patients was 10.4 months (NSCLC = 11.2 mo, SCLC = 9.6 mo; $P = 0.63$). Before thoracic reRT, 14 NSCLC patients (38%) and all 11 (100%) of SCLC had received chemotherapy for recurrent disease and had shown subsequent progression.

Median time to reRT for all patients from initial RT was 19.1 months (NSCLC = 18.6 mo, SCLC = 24.0 mo; $P = 0.79$). For patients with metastatic disease at initial presentation, median time to reRT was 12.6 months. The majority of NSCLC patients (78%) and all (100%) of the SCLC patients had at least partial overlap between the recurrent tumor volume and the previous radiation target volume. ReRT without overlapping target volumes ($n = 8$) in general targeted hilar and/or mediastinal lymph node stations not encompassed within radiation target volumes in upfront radiation courses. Thirteen NSCLC patients (35%) and 5 (45%) SCLC patients had known extrathoracic metastatic disease before reRT.

NSCLC reRT

Median reRT dose was 30 Gy in a median of 10 fractions (Table 3). Nine patients without extrathoracic disease received radical reRT with doses of at least 50 Gy (1 patient receiving 40 Gy in 10 fractions was included in this group); none received concurrent chemotherapy. The median dose for radical reRT was 56 Gy, in a median of 25 fractions, with a median NTD(2)₁₀ of 57.1 Gy. The median cumulative NTD(2)₁₀ received by these 9 patients was 116.7 Gy. An additional 9 patients with radiographic progression but without symptoms were treated in an effort to prevent impending airway collapse or other locoregional

sequelae of projected disease progression, with doses ranging from 20 to 40 Gy. Nineteen patients with symptoms were treated with palliative intent with prescribed doses ranging from 20 to 40 Gy (1 patient proceeded to hospice after receiving only 12 Gy). Dose-volume histogram data for reRT plans are summarized in Table 3. Median GTV reRT volume was 43.1 cm³, limiting the median dose to organs at risk. The median PTV for patients undergoing radical reRT (58.3 cm³) was much smaller than the median PTV (208 cm³) for those patients receiving palliative or prophylactic reRT ($P = 0.01$).

SCLC reRT

Median reRT dose was 37.5 Gy in a median of 15 fractions (Table 3). Four patients without symptoms or extra-thoracic disease were treated with radical intent, with doses of 40 to 45 Gy in 20 to 25 fractions. Median cumulative NTD(2)₁₀ received for these 4 patients was 87.4 Gy. Seven patients with symptomatic recurrence (with or without extrathoracic disease) were treated with palliative intent to doses of 25 to 37.5 Gy in 9 to 15 fractions. Dose-volume histograms for reRT plans were available in 10 patients, and are summarized in Table 3. The median PTV for patients undergoing radical reRT (169 cm³) was much smaller than the median PTV (648 cm³) for those patients receiving palliative or prophylactic reRT ($P = 0.02$).

Patient Outcomes

At time of last review, 42 patients (87%) are deceased, including all SCLC patients and all patients treated with palliative intent. Median survival for the entire cohort after reRT was 4.2 months. Median survival for the 37 NSCLC patients was 5.1 months (range, 0.5 to 42.0 mo), versus 3.1 months (range, 1.0 to 22.7 mo) for the 11 SCLC patients ($P = 0.15$) (Fig. 1) (Table 4).

NSCLC Outcomes

Of 9 patients treated with radical intent, 5 remained alive with follow-up ranging from 11 to 42 months. Despite documented progression or death in 35 patients (95%), only 14 patients received further oncologic treatment (chemotherapy and/or RT). For the 24 patients who enrolled in hospice, subsequent median time to death was 1.3 months.

Univariate analysis revealed lack of extrathoracic disease, longer interval to disease recurrence, higher original radiation dose, Karnofsky performance status (KPS) 80, reRT intent, and higher dose of reRT to be associated with longer survival after reRT for NSCLC (Table 5). ReRT intent was associated with survival after thoracic reRT whether considered as a bimodal variable (radical vs. nonradical, data not shown) or a trimodal variable (radical vs. prophylactic vs. palliative). In addition, squamous cell histology showed a trend toward improved survival after reRT ($P = 0.07$). On multivariate Cox regression analysis, higher dose at reRT ($P = 0.007$), and KPS 80 ($P = 0.01$) remained significantly associated with improved survival.

All 19 patients undergoing NSCLC reRT with palliative intent had symptoms attributable to intrathoracic disease at the time of reRT, as did 3 patients treated with radical intent. Of these 22 patients, 20 were assessable for palliative relief. Symptoms vanished in 3 and were

diminished in 12 patients, for an overall symptomatic response rate of 75% (Table 4). In patients with symptoms, the median time to symptomatic thoracic progression, cancer-related hospitalization, or death was 1.8 months (range, 0 to 15 mo).

SCLC Outcomes

Three patients (27%), all with no known extrathoracic disease or symptoms at time of reRT, subsequently received additional chemotherapy for later relapses (Table 4). Five patients (45%) received subsequent radiation (whole brain radiation therapy and/or stereotactic radiosurgery), all for failure in the central nervous system. The decision to not pursue further oncologic treatment (hospice only) was reached at a median of 1.6 months (range, 0.5 to 21.6 mo) after reRT, and patients lived a median of 0.7 months (range, 0.5 to 2.0 mo) once this decision was reached.

In univariate analysis, the 4 patients treated with intent of life prolongation through durable local control in the setting of isolated intrathoracic failures (all receiving 40 Gy) had a median survival of 11.7 months (range, 3.1 to 22.7 mo) after reRT, whereas patients treated with palliative intent (all receiving 37.5 Gy) had a median survival of 1.7 months (range, 1.0 to 4.0 mo) ($P = 0.01$) (Table 6). Further chemotherapy after reRT was also associated with improved survival. In addition, the absence of known extrathoracic disease showed a trend toward improved survival after thoracic reRT ($P = 0.09$). Because of small sample number, multivariate analysis was unable to be performed.

Seven patients had symptoms attributable to intrathoracic disease at the time of reRT, most commonly cough and dyspnea. Symptoms prompting reRT vanished in 1 patient (14%) and were diminished in 6 patients (86%). However, median duration of palliative benefit in these 7 patients was 0.5 months after reRT secondary to the development of acute pulmonary toxicities or new disease symptoms (0 to 1.4 mo). All 7 patients went on to hospice at a median of 1.2 months (range, 0.5 to 3.2 mo) after reRT.

Toxicity

Esophageal toxicity from reRT was minimal, with 5 patients (10%) manifesting grade 2 acute esophagitis; no grade 3 to 4 acute or any late esophageal toxicities were noted. The rate of grade 2 acute pulmonary toxicity was 15% overall, involving 3 of 37 (8.1%) of NSCLC patients and 4 of 11 (36%) of SCLC patients. Two NSCLC patients (5.4%) developed grade 3 acute pulmonary toxicities, including 1 patient with grade 3 dyspnea (questionable pneumonia) who improved with antibiotics, and 1 case of grade 3 pneumonitis that required oxygen and steroids at 1 month after radiation and subsequently resolved. Among the SCLC patients, 1 patient's (9.1%) progressive extrathoracic disease developed acute grade 3 dyspnea during her radiation course, with hospice enrollment 3 weeks after treatment; 2 patients developed grade 2 dyspnea. A fourth patient had asymptomatic hydropneumothorax noted on daily megavoltage CT image localization during the radiation course, treated with chest tube (grade 2).

Late grade 2 pulmonary toxicity was noted in 4 patients (11%) including 2 NSCLC patients (5.5%) and 2 SCLC patients (18%). These included 1 case of grade 2 dyspnea that

persisted in an NSCLC patient. Another NSCLC patient developed a grade 4 bronchostenosis requiring repeated operations starting 7 months after radiation. An episode of grade 2 pneumonitis was noted in a SCLC patient 6 weeks after treatment that never required treatment and ultimately subsided. One SCLC patient who developed bronchostenosis and fibrosis requiring bronchoplasty 4 months after 45 Gy of reRT (with no local recurrence noted). A second patient developed grade 2 pneumonitis requiring steroids 6 weeks after 45 Gy of reRT. One NSCLC patient had a rapid decline in performance status, stopping RT after 4 fractions (12 Gy) and enrolling on hospice; all other patients completed the prescribed RT course.

As detailed above, 9 patients (18.8%) had grade 2 pulmonary toxicity (either acute and/or late) associated with thoracic reRT. The total doses (NTD(2)₁₀) were not higher in patients who experienced pulmonary toxicities (median NTD(2)₁₀ = 87.4 Gy) as compared with those not experiencing pulmonary toxicity (median NTD(2)₁₀ = 90.0 Gy) ($P = 0.96$). However, 5 of 13 patients (38.5%) treated with radical intent at reRT experienced grade 2 pulmonary toxicity (either acute and/or late), which was a significantly higher rate than those treated with either palliative or prophylactic intent (4 of 35; 11.4%) ($P = 0.047$).

DISCUSSION

We report on the use of thoracic reRT in a series of 48 patients with locoregionally recurrent lung cancer. To our knowledge, this is the largest experience reported to date, the first to report outcomes in patients treated predominantly with IMRT, and the first to report on differences in outcomes between NSCLC and SCLC patients receiving thoracic reRT. The outcomes reported here in NSCLC patients are consistent with previous reports, with 75% of NSCLC patients presenting with symptomatic disease recurrence deriving palliative benefit from thoracic reRT. However, the results presented in recurrent SCLC redemonstrate the aggressive, systemic nature of this disease, with a dismal prognosis and few therapeutic options available for life prolongation and symptom control.

In NSCLC, median survival was 5.1 months for the cohort, and the rates of palliative benefit in this study utilizing IMRT are consistent with previously published palliative responses. Overall, studies of palliative reRT for locoregionally recurrent lung cancer suggest that 70% to 80% of patients with symptoms can be expected to benefit from treatment.⁹ The majority of patients in this series treated palliatively received doses of 25 to 37.5 Gy in 2.5 to 3 Gy fractions by IMRT. Although median survival of NSCLC patients treated with palliative intent in this series was a disappointing 3.3 months, 7 of 19 patients treated in this manner lived 6 months. Hence, the decision to significantly hypofractionate should be made with caution, as late toxicities may be unexpectedly troublesome in an individual patient with prolonged survival after reRT. Limited rates of acute and late toxicities may be partially attributable to the use of IMRT technique; however, it is worth noting that the median GTV volume for the NSCLC patients was diminutive and this allowed for more limited dose to organs at risk, also likely impacting treatment-associated toxicity.

In addition to palliation, thoracic reRT may also be considered with the goal of life prolongation and/or cure for recurrent disease. Although median survival in most reported

thoracic reRT series are from 5 to 7 months,^{4,5,12,14-18} 2 studies examining high-dose reRT in carefully selected patients have demonstrated median survivals of 14 to 15 months.^{19,20} Wu et al²⁰ prospectively evaluated high-dose thoracic reRT (46 to 60 Gy) in select patients; patients were eligible only if their KPS was ≥ 70 , had no extrathoracic disease, possessed adequate lung function (forced expiratory volume in 1 s of >1 L) and at least 6 months between original radiation and recurrence. Nine NSCLC patients in our series were treated in a radical manner, all of whom had received >50 Gy of upfront thoracic radiation. Although pulmonary function testing data was not uniformly available in these 9 patients, they otherwise met the above criteria, and median survival was estimated at 12.6 months for this subset of patients. At last follow-up, 5 were alive at times ranging from 11 to 42 months after reRT, although only 1 patient was without evidence of disease. It should be noted that the NSCLC patients selected for radical reRT had a low volume of recurrent disease (median PTV of 58.3 cm³), whereas those treated with lower doses had a significantly higher volume necessitating reRT. We feel, in addition to the above noted selection criteria noted by Wu and colleagues, aggressive reRT should likely be limited to patients with a low to moderate volume of recurrent tumor. Taken together, these data provide evidence that in properly selected patients with locoregionally recurrent NSCLC, high-dose reRT should be considered as meaningful survival that can be achieved in select patients.

Reports of thoracic reRT have largely focused on NSCLC, but a small number of studies^{4,5,14,16,19,20} have included limited numbers (< 10) of SCLC cases without reporting on this histology as a prognostic variable or reporting palliative responses and/or survival data separately; therefore no published literature is available for comparison with our results. In patients with progressive SCLC after second-line chemotherapy who presented with disease-related thoracic symptoms, we found that symptoms that prompted the reRT for SCLC were palliated. However, given that these patients were progressing, and all had recently received at least a second-line chemotherapy regimen, their performance status was low (median KPS = 70) before reRT. Decline generally occurred rapidly after palliative thoracic reRT, with a median survival of 1.7 months and short intervals to subsequent hospitalization and hospice enrollment. We would advocate that if palliative reRT is entertained in these patients, hypofractionated approaches be considered, as well as consideration for simple 3 dimensional-conformal field design, as the likelihood of late radiation toxicity is low given the short anticipated overall survival.

In contrast, thoracic reRT with the intent of life prolongation, may have a role for those few SCLC patients with radiographic progression limited to the chest. Four patients with asymptomatic, low to moderate volume recurrent disease in the thorax underwent reRT and had a median survival after reRT of 11.7 months. reRT to 40 to 45 Gy in 20 to 25 fractions by IMRT in these patients was well tolerated acutely (no acute grade 2 toxicities) although 2 late pulmonary toxicities (bronchostenosis requiring bronchoplasty and grade 2 pneumonitis) developed.

Limitations of this study include the heterogeneous patient population with regard to upfront stage, treatment intent, and radiation technique. Furthermore, a significant portion of patients were treated at our institution only upon recurrence. In addition, plans generated for helical tomotherapy (TomoTherapy Hi-Art treatment planning system; Madison, WI) were

unable to be fused with nontomotherapy plans given the different planning software; thus composite plans were unable to be generated for the majority of patients. Robust composite dose-volume histogram analysis would be useful for identifying parameters for pulmonary toxicity upon reRT in future studies of thoracic reRT.

In conclusion, reRT to the thorax for locoregionally recurrent NSCLC can provide palliative benefit to the majority of properly selected patients, and a small subset of patients may experience long-term survival. KPS 80 and dose >30 Gy in 10 fractions appear associated with improved outcomes. Nonetheless, median overall survival remains limited and appropriate patient selection is essential. Locoregionally recurrent SCLC confers a dismal prognosis. Select patients without symptoms or extrathoracic disease may experience meaningful survival prolongation after reRT at doses of 40 to 45 Gy, but are at risk for treatment-associated toxicity. reRT for SCLC patients with symptomatic recurrence and/or extra-thoracic disease did not offer meaningful survival or durable symptom benefit; if reRT is to be utilized in this setting, hypofractionated approaches with simple 3 dimensional-conformal techniques may be more appropriate. Alternatively, such patients may be better served by enrollment in hospice care and end of life preparation.

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FIGURE 1.
Actuarial survival of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) patients after thoracic reirradiation.

TABLE 1**Patient Characteristics**

Variables	N
Sex	
Male	29
Female	19
Age at diagnosis	
Median	61
Range	40–81
Histology	
SCLC	11
NSCLC	37
Squamous	17
Nonsquamous	15
NSCLC NOS	5
Initial stage	
I	2
II	5
III	20
IV	10
Limited-SCLC	9
Extensive-SCLC	2
Metastatic sites	
Adrenal only	2
Lung only *	5
Other	5

* Distant pulmonary recurrence, outside of the initial lobe (AJCC Sixth edition definition of M1 disease).

NSCLC indicates non–small cell lung cancer; NOS, not otherwise specified; SCLC, small cell lung cancer.

TABLE 2

Initial Radiation Characteristics

Variables	NSCLC Patients (n = 37)		SCLC Patients (n = 11)	
	Median	Range	Median	Range
Radiation dose (Gy)	57	30–80.5	45	12–54*
No. fractions	25	10–37	30 (bid)	4–30
	N	%	N	%
Initial radiation intent				
Definitive	24	65	9	82
Preoperative/adjuvant	4	11	0	—
Palliative	9	24	2	18
Initial radiation delivery				
3 dimensional-CRT	25	68	7	64
IMRT	12	32	4	36
Concurrent chemotherapy				
Yes	13	35	9	82
No	34	65	2	18

* Palliative radiation (12 Gy) for superior vena cava syndrome, no concurrent chemotherapy.

CRT indicates conformal radiotherapy; IMRT, intensity-modulated radiotherapy; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer.

TABLE 3

Retreatment Characteristics

Variables	NSCLC Patients (n = 37)		SCLC Patients (n = 11)	
	Median	Range	Median	Range
Reirradiation dose (Gy)	30	12–60	37.5	25–45
Reirradiation fractions	10	4–30	15	9–25
	N	%	N	%
Radiation technique				
Opposed AP-PA fields	—	—	1	9
7-field IMRT	—	—	1	9
3 dimensional-CRT	2	5	—	—
Helical tomotherapy	35	95	9	82
Intent				
Radical	9	24	4	36
Prophylactic	9	24	—	—
Palliative	19	51	7	64
GTV (cm ³)	43.1	5.6–775	162	20–330
PTV (cm ³)	149	26–585	456	64–456
Lung V5 (%)	35.4	4.4–92.9	49.4	22–76
Lung V20 (%)	3.4	0–16.7	9.9	0.8–16.7
Lung mean dose (Gy)	5.1	0.2–12.2	7.3	4.6–10.2
Esophageal maximum dose (Gy)	30.6	9.7–61.1	39.1	25.6–48
Esophageal mean dose (Gy)	7.9	1.8–17.9	11.9	2.5–20.8
Heart maximum dose (Gy)	21	0–41.1	28.2	20.6–39.6
Heart mean dose (Gy)	2.8	0–14.3	3.9	1.2–18
Spinal cord maximum dose (Gy)	10.2	2.2–28.1	12.2	4.1–24.1

CRT indicates conformal radiotherapy; GTV, gross tumor volume; IMRT, intensity-modulated radiotherapy; NSCLC, non-small cell lung cancer; PTV, planning target volume; SCLC, small cell lung cancer; V20, volume lung receiving 20 Gy; V5, volume lung receiving 5 Gy.

TABLE 4**Patient Outcomes and Management After Repeat Thoracic Radiation**

Endpoints	NSCLC (n = 37)	SCLC (n = 11)
Management after reirradiation		
Further chemotherapy	12/37 (32%)	3/11 (27%)
Further radiotherapy*	6/37 (16%)	5/11 (45%)
Survival and disease progression		
Interval to hospice (median) (mo)	2.6	1.6
Median survival from hospice decision (median) (mo)	1.3 (n = 24)	0.7
Median survival from reRT (range) (mo)	5.1	3.1
6 mo survival	17/37 (46%)	3/11 (27%)
1 y survival	8/36 (22%)	2/11 (18%)
Palliation		
Symptoms vanished	3/20 (15%)	1/7 (14%) [†]
Symptoms diminished	12/20 (60%)	6/7 (86%) [†]
Stable	1/20 (5%)	— [†]
Progressive symptoms	4/20 (20%)	— [†]
Median duration of palliation (mo)	1.8	0.5

* No further thoracic radiation was delivered; these represent extrathoracic (ie, bone, whole-brain) palliative radiation courses only.

[†] Response of presenting symptom only; see text for discussion of competing acute toxicities and other developing symptoms.

NSCLC indicates non-small cell lung cancer; reRT, reradiation; SCLC, small cell lung cancer.

TABLE 5

Univariate Analysis of Categorical Variables: Impact on Survival After Reirradiation for NSCLC

Variables	N	Median Survival	P
Sex			
Male	23	4.9	0.84
Female	14	5.0	
Initial stage			
I	2	2.0	0.46
II	5	12.4	
III	20	3.8	
IV	10	5.0	
Histology			
Squamous	17	9.6	0.07
Nonsquamous	15	3.2	
Original RT intent			
Palliative	9	5.0	0.13
Nonpalliative *	28	4.9	
NTD(2) ₁₀ of initial RT			
58.3 Gy(2)	23	9.2	0.03
< 58.3 Gy(2)	14	2.6	
Infield component to failure			
Yes	28	5.0	0.49
No	8	4.0	
Hilar/mediastinal involvement at recurrence			
Yes	30	4.3	0.17
No	7	10.8	
Interval to recurrence (y)			
< 1	19	4.3	0.05
1	18	5.8	
Chemotherapy at recurrence [†]			
Yes	14	3.3	0.23
No	23	8.1	
Extrathoracic disease at or before reRT			
Yes	13	2.6	0.002
No	24	9.6	
ReRT intent			
Radical	9	12.6	0.001
Prophylactic	9	5.0	
Palliative	19	3.3	
Age at reRT (y)			
< 65	20	3.3	0.17
65	17	9.6	

Variables	N	Median Survival	P
Interval from prior thoracic radiation (mo)			
18	18	4.0	0.29
> 18	19	2.5	
KPS at time of reRT			
70	7	1.5	< 0.001
80	27	9.2	
Dose (NTD(2) ₁₀) of reRT			
32.5 Gy(2)	23	4.3	< 0.001
> 32.5 Gy(2)	14	5.8	
Further chemotherapy after reRT			
Yes	12	6.6	0.71
No	25	4.9	

* Nonpalliative includes definitive radiation and upfront postoperative radiation.

† Chemotherapy administered at recurrence, before reirradiation.

Bold values represent statistically significant factors.

KPS indicates Karnofsky performance status; NSCLC, non-small cell lung cancer; NTD(2)₁₀, normalized tumor doses in 2 Gy fractions, calculated using an α/β of 10; ReRT, reirradiation; RT, radiotherapy.

TABLE 6

Univariate Analysis of Continuous Variables: Impact on Survival After Reirradiation for SCLC

Variables	N	Median Survival	P
Sex			
Male	6	2.8	0.85
Female	5	5.1	
Initial stage			
Limited	9	3.1	0.49
Extensive	2	2.5	
Extrathoracic disease at reirradiation			
Yes	4	1.8	0.09
No	7	3.7	
Intent of reirradiation			
Palliative	7	1.7	0.013
Radical	4	11.7	
Interval to recurrence (mo)			
9.6	6	2.9	0.79
> 9.6	5	3.1	
No. courses of chemotherapy at recurrence *			
1	7	4.0	0.20
> 1	4	1.6	
Radiation dose received upon reirradiation (Gy)			
37.5	6	5.1	0.15
< 37.5	5	1.7	
Further chemotherapy after reirradiation			
Yes	3	16.3	< 0.001
No	8	1.8	
Interval from prior thoracic radiation (mo)			
< 24	5	4.0	0.22
24	6	2.5	

* Second-line chemotherapy administered after recurrence, before reirradiation.

Bold values represent statistically significant factors.

SCLC indicates small cell lung cancer.