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American Radium Society Appropriate Use Criteria Systematic Review and Guidelines on Reirradiation for Non-Small Cell Lung Cancer Executive Summary

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Abstract

Definitive thoracic reirradiation can improve outcomes for select patients with non-small cell lung cancer (NSCLC) with locoregional recurrences. To date, there is a lack of systematic reviews on safety or efficacy of NSCLC reirradiation and dedicated guidelines. This American Radium Society Appropriate Use Criteria Systematic Review and Guidelines provide practical guidance on thoracic reirradiation safety and efficacy and recommends consensus of strategy, techniques, and composite dose constraints to minimize risks of high-grade/fatal toxicities.

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Preferred Reporting Items for Systematic Reviews and Meta-Analyses systematic review assessed all studies published through May 2020 evaluating toxicities, local control and/or survival for NSCLC thoracic reirradiation. Of 251 articles, 52 remained after exclusions (3 prospective) and formed the basis for recommendations on the role of concurrent chemotherapy, factors associated with toxicities, and optimal reirradiation modalities and dose-fractionation schemas.

Stereotactic body radiation therapy improves conformality/dose escalation and is optimal for primary-alone failures, but caution is needed for central lesions. Concurrent chemotherapy with definitive reirradiation improves outcomes in nodal recurrences but adds toxicity and should be individualized. Hyperfractionated reirradiation may reduce long-term toxicities, although data are limited. Intensity modulated reirradiation is recommended over 3D conformal reirradiation. Particle therapy may further reduce toxicities and enable safer dose escalation. Acute esophagitis/pneumonitis and late pulmonary/cardiac/esophageal/brachial plexus toxicities are dose limiting for reirradiation. Recommended reirradiation composite dose constraints (2 Gy equivalents): esophagus V60 <40%, maximum point dose (Dmax) < 100 Gy; lung V20 <40%; heart V40 <50%; aorta/great vessels Dmax < 120 Gy; trachea/proximal bronchial tree Dmax < 110 Gy; spinal cord Dmax < 57 Gy; brachial plexus Dmax < 85 Gy.

Personalized thoracic reirradiation approaches and consensus dose constraints for thoracic reirradiation are recommended and serve as the basis for ongoing Reirradiation Collaborative Group and NRG Oncology initiatives. As very few prospective and small retrospective studies formed the basis for generating the dose constraint recommended in this report, further prospective studies are needed to strengthen and improve these guidelines.

Introduction

As systemic therapy improves, and with increasing utilization of targeted therapy and immunotherapy,¹ local and regional control are increasingly important. Patients with localized non-small cell lung cancer (NSCLC) who receive radiation therapy for early stage NSCLC^{2,3} or as part of bimodality⁴ or trimodality^{5,6} therapy for locally advanced disease, are an inherently heterogeneous group.

Among patients with early stage NSCLC, fewer than 10% develop local failures following stereotactic body radiation therapy (SBRT); however, 10% to 20% will develop nodal metastasis following irradiation.^{7,8} Similarly, among patients with locally advanced NSCLC, local failure rates are as high as 25% to 50% by 2 years,^{4,9} including one-in-four patients developing isolated locoregional recurrences.¹⁰ Even with oligometastatic disease or oligoprogression after definitive radiation therapy, reirradiation could be needed.

Local control for NSCLC directly impacts overall survival (OS). In an analysis of prospective Radiation Therapy Oncology Group trials, locoregional control was association with OS ($P < .0001$, multivariate analyses).¹¹ In a meta-analysis of randomized trials comparing the survival between concurrent versus sequential chemotherapy and radiation therapy, concurrent chemoradiation had a 4.5% improvement in 5-year OS. Concurrent treatment achieved a 6.0% locoregional control benefit at 5 years without improving

distant progression, further indicated local control improvements drive survival gains in nonmetastatic NSCLC.⁹

Despite recognizing the importance of thoracic tumor control and high frequency of local or regional recurrence after radiation therapy, thoracic reirradiation remains particularly challenging because of potential severe toxicities, including catastrophic organ injury or death, and lack of standardized approaches and guidelines. Patients with intrathoracic recurrences after radiation therapy, have historically been treated with palliative systemic alone. However, chemotherapy monotherapy achieves progression free survival (PFS) typically of only 4 to 6 months and does not offer a chance of cure.¹² Immune checkpoint inhibitors are an attractive option to treat recurrences after radiation therapy, but fewer than one-in-four patients respond to these agents.^{13,14} Surgery is often not possible because of perioperative risks with resection following definitive doses of radiation therapy.^{5,6}

Definitive reirradiation for local and/or regional recurrences, defined as “an additional course of radiation which at least partially irradiates the same tissue as a prior course, with a biologically meaningful dose,”¹⁵ is an attractive salvage treatment, providing durable locoregional control, improving PFS and potentially OS. Reirradiation, unlike systemic therapy, can also offer select patients a new chance of cure. Recent improvements in radiation therapy technology and treatment delivery have afforded patients safer thoracic reirradiation. As intensity modulated radiation therapy (IMRT),¹⁶ SBRT,¹⁷ and proton therapy¹⁸ can reduce toxicities or improve survival over conventional radiation therapy, these advanced modalities may hold the key for safer reirradiation.

To date, systematic reviews on the safety and efficacy of reirradiation for NSCLC and dedicated guidelines on reirradiation for patients with locoregionally recurrent NSCLC are lacking. This American Radium Society Appropriate Use Criteria Systematic Review and Guidelines fills a critical void in the literature and provides direct guidance on the safety and efficacy of reirradiation. These guidelines, for the first time, suggest consensus dose constraints for reirradiation to minimize risks of high-grade and potentially fatal toxicities. These guidelines and comprehensive dose constraints serve as the basis for ongoing Reirradiation Collaborative Group initiatives and a planned NRG Oncology NSCLC reirradiation trial (NRG LU2502).

Materials and Methods

A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to ensure all pertinent articles were incorporated into these guidelines.¹⁹ Eligibility criteria included English language publications evaluating toxicities, local control, and/or OS for NSCLC reirradiation. The primary search source was the PubMed database, and publications found from references of selected articles and articles known to the authors were reviewed for inclusion. Unpublished abstracts were excluded.

Search terms included: reirradiation, re-irradiation, second course, third course, repeat radiation, repeat radiotherapy, lung cancer, non-small cell, stereotactic body radiation

therapy, stereotactic body radiotherapy, SBRT, stereotactic ablative radiotherapy, stereotactic ablative radiation therapy, SABR, intensity-modulated radiation therapy, intensity-modulated radiotherapy, IMRT, proton, proton therapy, proton radiation therapy, proton beam therapy, particle therapy, toxicity, toxicities, local control, progression free survival, PFS, survival, and overall survival. These search terms were intentionally left broad to include all potentially pertinent publications and allow for individual screening thereafter rather than missing potentially pertinent articles. No date restrictions were used, and all articles published through May 2020 were included. A meta-analysis proved not possible because of the inherent heterogeneity in studies.

In total, 251 articles were identified and independently screened, with articles excluded for being nonoriginal research (most commonly reviews), single-patient case studies, treatment planning dosimetry studies, not reporting on toxicities/outcomes, and not including NSCLC histology. In total, 52 articles remained after all exclusions and represented the articles for which the American Radium Society Appropriate Use Criteria Thoracic Committee based their recommendations.

Fifteen multidisciplinary expert panels were selected from different institutions based on their thoracic expertise and publication records. Monthly panel conference calls and annual in-person meetings were conducted over the course of ~1.5 years to perform and review the literature search, determine appropriate reirradiation dose constraints, and develop representative clinically relevant cases (Tables). Consensus voting on both Table responses and dose constraints were performed, and then final recommendations were drafted based on the results of the voting. Consensus voting was performed 3 times to quantify agreement in each topic based on reirradiation Tables (Tables 1–5).

Primary recurrence alone after SBRT (Table 1) or definitive chemoradiation therapy (Table 3)

SBRT: SBRT, also called SABR therapy, is standard of care for patients with medically inoperable early stage NSCLC and select patients with limited lung metastases. SBRT provides increased dose conformality and normal tissue sparing compared with conventionally fractionated radiation, while allowing for greater tumor dose escalation than achievable with other techniques to biological equivalent doses (BED_{10}) ≥ 100 Gy, which has been shown to increased tumor sterilization, local control, and OS.²⁰

SBRT has been used for reirradiation to new or recurrent tumors in previously irradiated lung. In a retrospective analysis by Memorial Sloan Kettering Cancer Center investigators, 39 patients were treated with SBRT to a median BED_{10} 70.4 Gy ($\alpha/\beta = 10$) for intrathoracic failures after conventionally fractionated radiation therapy. One- and 2-year local PFS rates were 77% and 64%, respectively, and median recurrence-free survival and OS were 13.8 and 22.0 months, respectively. Four grade 3 (pulmonary, $n = 2$; chest wall, $n = 2$) and one grade 4 (skin) toxicities developed. If reirradiation target volume coverage did not overlap with the primary irradiation plan, patients were more likely to receive BEDs ≥ 100 Gy, which was associated with higher local PFS ($P = .038$) and OS ($P = .04$).²¹

Drexel University investigators reported on 26 patients with 29 tumors treated with SBRT after prior radiation therapy (median 61.2 Gy). The median SBRT dose was 30 Gy in 5 fractions (BED₁₀ 48 Gy). Local tumor control was 78.5% at 1 year and 65.5% at 2 years. No grade ≥ 3 adverse events were seen, possibly attributed to the relatively low irradiation dose used, which also likely contributed to limited local control achieved.²²

University of Pittsburgh investigators reported on their 72-patient thoracic SBRT reirradiation experience to 17 to 60 Gy in 1 to 5 fractions (48 Gy in 4 fractions most commonly) to a median BED₁₀ of 106 Gy. The 2-year local failure was 21.6%, median PFS was 15.2 months, and median OS was 20.8 months. Rates of acute and late grade 3 toxicities were 11.1% and 1.4%, respectively, and no patient developed grade ≥ 4 toxicities.²³

In University of Texas MD Anderson Cancer Center (MDACC) series, 72 patients previously treated with conventionally fractionated radiation therapy (median 63 Gy) received SBRT to 50 Gy in 4 fractions for recurrent or secondary parenchymal lung malignancy. OS and PFS at 2 years were 74.4% and 41.9%, respectively. Only 1 patient (1.4%) developed a recurrence within the SBRT field, whereas 11.1% and 20.8% developed regional nodal and distant recurrences, respectively. Grade ≥ 3 pneumonitis occurred in 20.8% (all were grade 3 toxicities except one grade 5) and was associated with worse pretreatment performance status, forced expiratory Volume in one second (FEV1) $\leq 65\%$, lung V20 $\geq 30\%$ on the composite plan, and prior bilateral mediastinal planning target volumes (PTVs).²⁴

Wake Forest University investigators reported outcomes of 33 reirradiation patients, 30 of whom received SBRT reirradiation to a median of 50 Gy in 10 fractions. Local control at 2 years was only 67% but was 88% when excluding patients receiving a single-fraction regimen. Two-year regional control and distant metastatic-free survival (DMFS) rates were 83% and 58%, respectively. One- and two-year survival rates were 76% and 45%, respectively. One patient developed grade 3 radiation pneumonitis and one suffered grade 5 exsanguination from aorta-esophageal fistula.²⁵ A French series of 46 patients stage III NSCLC treated with SBRT reirradiation reported 4-year PFS and OS of 8.6% and 30.8%, respectively, with 2 grade 5 events (hemoptysis and alveolitis).²⁶

Although many series report on SBRT reirradiation for thoracic recurrences after an initial course of conventionally fractionated radiation therapy, limited data exist using SBRT after primary SBRT failure. Karolinska University investigators assessed 29 patients who received SBRT reirradiation (median dose 30 Gy, most commonly in 2 fractions). LC at 5 months was only 52%, grade 3 to 4 toxicities occurred 14 times, and 3 grade 5 massive bleeding events occurred. Larger clinical target volumes (CTVs) and central tumor location were associated with serious adverse events.²⁷ A Washington University series of 21 patients treated with SBRT reirradiation after prior SBRT reported a 39-month median OS after salvage, with 2-year primary tumor control of 81%. No grade ≥ 3 toxicities were reported despite all courses being BED₁₀ of ≥ 100 Gy.²⁸

Additional series of repeat SBRT following SBRT failure are limited to 10 or fewer patients.^{29,30} The significant rate of high-grade toxicities found by Karolinska investigators²⁷

suggests SBRT reirradiation to central thoracic recurrences after an initial course of SBRT should be approached with caution, and additional data are needed to establish safe dose constraints and ideal dose-fractionation schemas in this setting. Additionally, retreatment with SBRT in the literature to date has generally been limited to peripheral target volumes <5 cm. Caution should be applied when considering SBRT reirradiation to larger target volumes, and these recurrences may be more optimally managed with more modest hypofractionation or conventionally fractionated radiation therapy with concurrent chemotherapy.

In summary, SBRT may improve local control in primary tumor recurrence after conventionally fractionated radiation therapy. SBRT may also have a role in the management of failures following prior SBRT, but more data are needed to define its role in this setting. SBRT reirradiation of centrally located lesions could cause potential severe toxicity, and individualized approach should be considered.

Lymph node recurrence after SBRT (Table 2), lymph node recurrence alone (Table 4) or primary and lymph node recurrence (Table 5) after definitive radiation therapy or chemoradiation therapy

The role of concurrent chemotherapy for definitive reirradiation: Although the use of concurrent chemoradiation therapy (CRT) in the primary setting is standard of care for locally advanced NSCLC to improve local control and OS versus sequential CRT,^{4,9,10} the role of chemotherapy with reirradiation is undefined. This is, in part, related to hesitation of using a regimen that has failed previously, suggesting disease refractory to CRT. Also, concerns that concurrent CRT will increase treated-related toxicities further hesitation, especially in the high-risk scenario of reirradiation.

Data exploring potential benefits of concurrent CRT for reirradiation are limited and are predominantly in the setting of small, heterogeneous institutional series. Furthermore, at the time of local or regional recurrence, patients are commonly first started on systemic therapy before being reevaluating for possible reirradiation, so they usually receive some form of sequential chemotherapy and radiation therapy, with or without subsequent concurrent CRT.

Two prospective studies testing the safety and efficacy of reirradiation have not mandated consistent use and sequencing of chemotherapy. Wu et al³¹ reported a phase 1/2 trial with 3-dimensional conventional radiation therapy (3DCRT) for reirradiation, with chemotherapy delivered before and after reirradiation but not concurrently. Survival was limited, with 1- and 2-year survival rates of 59% and 21%, respectively, but no acute grade ≥ 3 esophageal or lung toxicities were described. In a 57-patient multi-institutional prospective study at 3 proton centers, concurrent CRT was delivered in 67% of patients and was associated with increased grade ≥ 3 acute toxicity (53% vs 16%; $P = .003$). Concurrent CRT did result in a non-significant improvement in 1-year OS (66% vs 43%; $P = .3$), likely from delayed separation of the survival curves after 6 to 8 months.³² This delayed potential survival benefit may be related to sustained tumor control with concurrent chemotherapy.

A prospective registry experience from Proton Collaborative Group (PCG) and University of Florida Proton Therapy Institute reported on 79 patients reirradiated with conventionally

(58%), hyper- (3%), or hypofractionated (39%) proton therapy at 8 institutions. Concurrent CRT was used in 30% patients, although nearly 80% received chemotherapy before reirradiation. On univariate analysis, concurrent CRT was associated with improved median survival (23.4 vs 12.9 months; $P = .04$). Performance status was the only factor associated with improved OS on multivariate analysis, suggesting concurrent CRT was likely offered to patients with better performance status.³³

With limited prospective data, further assessment of the utility of concurrent CRT in the reirradiation setting is guided by institutional experiences. University of Texas MDACC investigators reported on proton beam reirradiation for recurrent NSCLC. Of 31 patients (94%) who completed treatment, 45% received prior chemotherapy. Concurrent chemotherapy was used in only 8 patients. No local control, OS or toxicity differences were noted with CRT.³⁴ A subsequent reirradiation report of 99 patients reirradiated with protons or IMRT, 45% received prior and 33% received concurrent chemotherapy. Concurrent CRT and definitive radiation doses were associated with an increase in acute grade ≥ 2 esophageal toxicity ($P = .029$), but also improved local control (hazard ratio [HR], 6.48; $P = .0004$), DMFS (HR, 0.464; $P = .027$), and OS (HR, 2.613; $P = .0045$).³⁵ In a third University of Texas MDACC report of 27 patients reirradiated with intensity modulated proton therapy, definitive radiation dose was again associated with improved locoregional recurrences, PFS and OS, but the 48% who received concurrent CRT did not appear to achieve significant improvements in outcome.³⁶

VU University Medical Center investigators did not find a significant impact of chemotherapy use on survival.^{37,38} Stanford University investigators reported on 38 patients receiving 44 retreatment courses. Concurrent CRT was used in 26% of courses and was not associated with toxicity or outcomes,³⁹ similar to findings by a Japanese reirradiation series in patients who failed prior SBRT.⁴⁰ In a 31-patient thoracic reirradiation series in Korea, concurrent CRT was used in just under 10% of patients. Systemic therapy after reirradiation, performed in 61%, was associated with improved DMFS ($P = .020$).⁴¹ A 67-patient Chinese study of thoracic reirradiation showed chemotherapy did not impact likelihood of grade ≥ 3 radiation pneumonitis (26.9% for their cohort).⁴²

In summary, definitive reirradiation doses are associated with improved disease control and potentially survival if able to be tolerated. There is considerable variation in the use of chemotherapy with reirradiation. Although the available data suggest a potential benefit in clinical outcomes with concurrent CRT, it comes at the cost of potentially exaggerated serious toxicities, and sequential chemotherapy or potentially no chemotherapy may also be appropriate in different clinical situations. A definitive recommendation across all patients is not possible, and a shared decision guided by patient performance status, tolerance to prior systemic therapy, and other factors should be made. Recognizing that some radiation oncologists may limit total radiation dose and/or planning margins because of concerns of toxicity from reirradiation, there is rationale and prospective data to support concurrent CRT to compensate for any such limitations in reirradiation delivery. Failure of concurrent CRT in primary setting should not justify deferring concurrent CRT for reirradiation, the purpose of which is to act as a radiosensitizer independent of direct systemic effect. This is underscored

by the low 16% local failure rate seen in the multicenter prospective study reported by Chao et al.³²

Finally, there are little data to guide use of concurrent immunotherapy or targeted therapy with reirradiation. Until such use is established, caution should be taken when considering concurrent immunotherapy or targeted therapy with reirradiation, and enrollment on clinical trials in this setting is recommended. Recognizing high distant failure rates seen in patients who develop locoregional recurrences, patients could benefit from consideration of induction systemic therapy followed by reirradiation with or without concurrent systemic therapy in patients who continue to have locoregional disease limited to the thorax.

Factors associated with toxicity from reirradiation

When considering reirradiation for lung cancer, the goals of treatment need to be defined—palliative or definitive. When the intent is definitive, higher doses are generally considered to maximize local control. With higher doses, however, comes increased risk of high-grade and even fatal toxicities. Acute esophagitis and pneumonitis and late pulmonary fibrosis, esophageal stricture/fistulae, and cardiac toxicities are dose limited even with an initial course of thoracic radiation therapy for NSCLC.⁴³ When considering high-dose definitive reirradiation, therefore, the potential benefits and the risks of toxicities need to be clearly estimated and discussed with patients within a shared decision-making model.

Toxicities: The main toxicities to consider with thoracic reirradiation include damage to the esophagus, lungs, airway/bronchi, great vessels, heart, chest wall, and brachial plexus. Data on toxicity incidence and predictive factors from reirradiation are generated from retrospective reviews, systematic reviews and 3 prospective studies.^{24,31–35,39,42,44–46}

Esophageal toxicities include acute esophagitis, late esophageal stricture, and fistula. The incidence range of grades ≥ 2 , ≥ 3 , and ≥ 4 esophageal toxicities with definitive reirradiation are 7.9 to 17.6%, 0% to 9%, and 0% to 2%, respectively.^{31,33–35,39,44}

Life-threatening pulmonary, airway, and vascular damage can develop from thoracic reirradiation. Pulmonary injury from radiation therapy can result in acute/subacute pneumonitis and late pulmonary fibrosis. The incidence range of grades ≥ 2 , ≥ 3 , ≥ 4 , and 5 pulmonary toxicities with definitive reirradiation are 5% to 26.5%, 0% to 21%, 0% to 2.9%, and 0% to 3.6%, respectively.^{24,31–35,39,44} Airway toxicity, such as tracheal/bronchial necrosis, tracheoesophageal fistula, and bronchopleural fistula,^{34,35} need to be seriously considered and stressed when discussing reirradiation with patients, as these can be fatal. Prospective data from Chao et al³² detailed these grade 5 toxicity risks. Of 57 patients in that study, one patient each developed grade 5 bronchopulmonary hemorrhage, pneumonitis, hypoxic respiratory failure/pleural effusion, and tracheoesophageal fistula. Reirradiation-induced great vessel injury can lead to a delayed presentation of a rapidly fatal hemorrhage in 0% to 12%.^{33,39,44,45}

The incidence of grade ≥ 2 chest wall toxicities is estimated at 10.5%.³⁹ Brachial plexopathy incidence is estimated at 2.6%.³⁹ The incidence of cardiac toxicities has not been commonly described in reirradiation papers.

It should be noted, however, that given the relatively short life expectancy of patients with recurrent NSCLC, many may not live long enough to develop late toxicities, as well as the relatively short median follow-up reported in many of the studies included in this systematic review, the above toxicity estimates may underestimate the true risks associated with reirradiation. Future reirradiation experiences are encouraged to report actuarial incidence of toxicities, which were rarely available in the literature to date.

Factors associated with toxicity from reirradiation: Factors like target volume size, location, time interval from previous radiation course, toxicity during previous radiation course, pulmonary function, use of concurrent chemotherapy, and dosimetric factors should be considered when assessing risks of toxicities for definitive reirradiation.

Larger target volumes can increase reirradiation risk. In University of Texas MDACC reirradiation experience, larger PTV size was not associated with toxicity but was with poorer OS.^{34,35} PTV size was significantly associated with grade ≥ 2 toxicities in the Stanford series.³⁹ Additionally, the multicentered prospective proton study stratified by CTV size (<250 or ≥ 250 cc). The high-volume cohort was deemed infeasible because of toxicities.³² Large target volumes should be reirradiated with caution as volumes ≥ 250 cc may result in increased toxicities, including grade 5 events. Although larger target volumes are recognized as a factor impacting the risk of high-grade complications from reirradiation, there are currently insufficient data to recommend different composite dose constraints based on reirradiation target volume.

Target volume location should also be considered. Centrally located targets can especially put patients at higher risk for esophageal and airway/great vessel toxicities. Initial reirradiation data from University of Texas MDACC investigators demonstrated that peripheral lesions have fewer cardiac toxicities ($P = .002$), a trend toward fewer pulmonary/airway toxicities ($P = .08$), but no impact on esophageal toxicities.³⁴ Their updated data, however, did not find an association between toxicity and tumor location.³⁵ Investigators from Stanford demonstrated central target volume location was associated with grade ≥ 2 toxicities (50% vs 8%). University of Texas MDACC SBRT reirradiation data demonstrated prior course radiation volume also impacts the development of radiation pneumonitis with reirradiation. Chao et al³² found target volume overlap with the central “no fly zone” significantly correlated with acute toxicities. The rate of grade ≥ 3 toxicity was 14% for low volume overlap (<41 cc) versus 64% for high-volume overlap (≥ 41 cc) ($P < .001$). French investigators similarly found central location was associated with grade ≥ 2 toxicities.²⁶

The time interval between prior radiation therapy and reirradiation has not been clearly demonstrated to correlate with toxicity.^{32,34,35,39} Investigators from University of Texas MDACC found that a time interval of >6 months between radiation courses resulted in improved local control.³⁵ The median time to reirradiation in most studies has been greater than 1 year.^{32,34,35,39} There remains considerable heterogeneity in how the field applies, if at all, dose “discounts” or forgiveness for normal tissue recovery between treatment courses,⁴⁷ and given thoracic reirradiation courses in general occur in closer temporal proximity to each other than reirradiation from other diseases sites like breast, head and neck, and pelvic malignancies, the panel did not endorse provided dose forgiveness when determining

recommended dose constraints. Particularly longer intervals between treatment courses, however, should be considered during treatment planning.

Lung function and sensitivity to prior radiation therapy should be considered. In the Stanford series, 30% of patients who developed grade ≥ 2 toxicities during their initial course of radiation developed grade ≥ 2 toxicities with reirradiation.³⁹ In University of Texas MDACC series, pre-reirradiation lung function (FEV1 <65%) predicted for grade ≥ 3 radiation pneumonitis with SBRT reirradiating.²⁴

Dosimetric factors and recommended dose constraints: Multiple dosimetric factors should be considered when planning definitive reirradiation. The patient's previous treatment course(s) should be evaluated or recreated on the reirradiation computed tomography simulation scan when not available to generate composite doses to organs at risk (OARs). Esophagus, lungs, heart, chest wall, brachial plexus, aorta/great vessels, trachea/proximal bronchial tree, and spinal cord should be contoured.

For the esophagus, maximum composite dose, mean dose, and volume receiving 60 Gy (V60) should be evaluated. Investigators from University of Texas MDACC reported the maximum dose ($P = .001$) and V60 ($P < .001$) associated with grade ≥ 2 esophageal toxicities, and a tracheoesophageal fistula developed when the composite esophageal maximum dose was 135.7 Gy. Patients with grade ≥ 3 esophageal toxicities had average composite esophageal V60s of $\sim 36.5\%$.^{34,35} Stanford investigators reported patients with grade ≥ 2 esophageal toxicities had a composite (EQD2 [dose delivered in 2Gy fractions that is biologically equivalent to a total dose]) dose of 41 to 100.6 Gy to 1 cc of esophagus (D1cc).³⁹ Chao et al³² found composite mean esophageal dose below versus above the cohort mean (12.45 Gy) correlated with acute grade ≥ 3 toxicities (22% vs 64%; $P = .003$). Based on these data, composite maximum esophageal doses >100 Gy (EQD2) should be minimized in volume, composite doses >110 Gy should be avoided and >120 Gy strongly discouraged. Efforts should be taken to keep the composite esophageal V60 <40%.

For the lung, V20 and mean lung dose (MLD) should be considered and evaluated. In University of Texas MDACC series, V10 ($P = .025$), V20 ($P = .025$), MLD ($P = .032$), and composite MLD ($P = .024$) all associated with grade ≥ 2 pulmonary toxicities. Patients with grade ≥ 3 pulmonary toxicities had an average composite lung V5 of 52%, V10 of 44%, V20 of 34%, and MLD of 22.5 Gy.^{34,35} In the Stanford series, patients with grade ≥ 2 pulmonary toxicities had a composite lung V20 of 4.7% to 21.7%.³⁹ In University of Texas MDACC experience, a composite V20 >30% with SBRT reirradiation was associated with grade ≥ 3 pneumonitis.²⁴ Based on these data, the reirradiation goal composite lung V20 should be similar to lung V20 constraints for an initial course of definitive radiation therapy. We recommend a composite (EQD2) lung V20 <40%. Beam arrangements should be designed to intentionally treat through previously irradiated lung, when feasible. When doing so, however, the MLD calculated in treatment planning systems is likely often higher than what is physiologically perceived given the damage sustained by that same lung volume during the initial radiation therapy course. Composite lung V20 >50% is discouraged, particularly if the patient has limited pulmonary function or history of prior pulmonary toxicity. Composite lung V5 constraints should similarly mirror those for an initial

radiation therapy course ($\leq 65\%$). A composite lung V5 $> 75\%$ is discouraged, although high-dose conformity should not be sacrificed to limit composite lung V5.

Mean heart dose (MHD) is typically evaluated in an initial radiation plan and is increasingly being recognized to correlated with radiation-induced cardiac events and survival.^{4,48,49} Although MHD < 20 Gy is commonly recommended in the definitive setting, no established reirradiation MHD constraints exist. Cardiac toxicities associated with reirradiation are not well reported. Chao et al³² reported that reirradiation MHD below versus above the cohort mean (394 cGy) correlated with acute grade ≥ 3 toxicity (26% vs 60%; $P = .02$).³² Therefore, keeping MHD as low as reasonably achievable (ALARA) is advised, and heart V40 $< 50\%$ is recommended.

For chest wall, dose delivered to 30 cc should be considered as is done in initial SBRT plans. Stanford investigators reported patients with grade ≥ 2 chest wall toxicities had composite D30cc to the chest wall of 35 to 117.2 Gy.³⁹ Because chest wall toxicity is rarely life threatening, keeping the chest wall dose ALARA is advised with appropriate counseling of chest wall toxicity risks.

For brachial plexus, aorta/great vessels, airway/trachea/proximal bronchial tree, and spinal cord, maximum point doses (Dmax) should be considered. The 1 patient in the Stanford series with brachial plexopathy had a composite brachial plexus maximum dose of 242.5 Gy.³⁹ Evans et al⁴⁵ reported an association between maximum dose received by 1 cc volume (D1cc) to the aorta of 120 Gy and risk of aortic rupture, although 5 patients in Stanford series received 1 cc > 120 Gy to the aorta without toxicity.³⁹ A grade 5 exsanguination from aorta-esophageal fistula occurred in a patient with composite aorta maximum EQD2 of 200 Gy.²⁵ Badiyan et al³³ reported 2 patients develop hemorrhage after cumulative doses to right pulmonary arteries of 132.3 and 135.1 Gy (EQD2 ~ 207). University of Texas MDACC investigators reported tracheal necrosis after trachea composite maximum dose of 147.37 Gy (BED of 220 Gy).^{34,35} Spinal cord toxicity was not reported in any reirradiation series included in this systematic review. The multicenter prospective proton protocol required a composite maximum dose < 75 Gy, although most patients had a composite maximum < 50 Gy.³²

To achieve definitive doses to target volumes while respecting OAR constraints, individualized/asymmetric CTV expansions and PTV coverage should be considered. Because maximum doses to aorta, great vessels, trachea, and proximal bronchial tree can result in fatal toxicities, composite maximum doses should be conservative and limited to 120 Gy for aorta/great vessels and 110 Gy for trachea/proximal bronchial tree. Although not enough data exist to recommend strict maximum composite doses to spinal cord or brachial plexus, as these OARs are in series and can have dramatic quality of life significance, Dmax should be kept ALARA, with spinal cord Dmax < 57 Gy and brachial plexus Dmax < 85 Gy recommended.

The recommended composite plan sum EQD2 dose constraints for each critical organ, generally derived from conventionally fractionation thoracic reirradiation experiences, are depicted in Table 6. These constraints were devised to minimize the risks for grade 3 or

higher acute or late toxicities from reirradiation. Where a Dmax constraint was used, Dmax was selected over the maximum dose to a fraction of a cubic centimeter since: (1) Dmax was most commonly used in the existing reirradiation literature and (2) the panel felt Dmax would best facilitate conservative treatments that could otherwise allow for discrete point doses far in excess of what are supported by the literature.

In all cases, however, clinical assessment of the treating physician should be used, and many individualized factors go into individual patient dose constraints. Many scenarios may lend themselves to being clinically appropriate to exceed Table 6 dose constraints, and this should be performed with shared decision-making and patient informed consent.

Dose-fractionation schemas and radiation modalities

Fractionation: In the era of 3DCRT, the ability to deliver a second course of definitive doses to the thorax was limited by the excess cumulative doses delivered to surrounding OARs that resulted in unacceptable rates of severe toxicities.⁵⁰ Reports of 3DCRT reirradiation were generally using doses of 30 to 60 Gy in 1.8 to 3 Gy fractions, with most experiences limited to 30 Gy and palliative intent.^{51–54} Even with moderately higher, more definitive doses, the persistent limitation of conventional fractionation was the inability to deliver tumoricidal doses of radiation required for optimal local control. The advent of IMRT and its increased conformality, along with advancements in immobilization and image guidance,⁵⁵ have allowed for greater ability to explore altered radiation dose-fractionation schemas such as hypofractionation and hyperfractionation to potentially improve outcomes and reduce toxicities compared with 3DCRT reirradiation experiences.

Although conventional fractionation, more mild hypofractionation, and SBRT have been discussed throughout the manuscript to date, hyperfractionation is an alternative strategy that may reduce risks of high-grade late radiation-induced toxicities from reirradiation by allowing normal tissues to better repair between fractions when the dose per fraction is reduced. Hyperfractionated reirradiation has been used for rectal cancer^{56–58} and head and neck cancer⁵⁹ recurrence, with tumor response rates ranging from 45% to 75% and few reported grades 4 to 5 adverse events. To date, very limited data exist regarding the clinical use of hyperfractionation for lung cancer reirradiation. Binkley et al³⁹ delivered hyperfractionated radiation therapy in 3 of 44 thoracic reirradiation course, but hyperfractionation was not associated with toxicity rate. There have been no reports exclusively utilizing hyperfractionation for NSCLC reirradiation to date, and there are insufficient data to make recommendations for its use.

Particle therapy: Heavy particle therapy has been explored to reduce dose delivered to normal tissues and potentially reduce serious toxicities associated with thoracic reirradiation.^{60–64} Proton and carbon ion therapy possess innate physical properties that allow radiation dose to be deposited at specified depths, beyond which little/no further energy is transferred. In proton therapy, the development of pencil-beam scanning (PBS) technology further improves the ability to achieve dose conformality compared with older passive-scatter (PSPT) or uniform scanning (USPT) proton therapy.^{65–67} Experience with

this technology in the setting of thoracic irradiation is yet limited, although results are promising.

A multicenter prospective study from Chao et al³² evaluated 57 patients with recurrent NSCLC located within/near their initial radiation field (mean 65 Gy) treated with proton reirradiation to a mean dose of 66.6 Gy. From the time of reirradiation completion, 1-year OS and PFS were 59% and 58%, respectively. Median OS from reirradiation completion was 14.9 months, with the mean survival of nearly 2 years from recurrence diagnosis, a survival approximating newly diagnosed patients with locally advanced NSCLC. Grade ≥ 3 acute and/or late toxicities developed in 42% of patients, and 6 grade 5 toxicities were reported. Only one-quarter of patients developed local or regional recurrences. Factors associated with grade ≥ 3 toxicities included central airway overlap, mean esophagus dose, MHD, and use of concurrent chemotherapy. Higher mean esophagus dose was associated with decreased OS ($P = .007$). Of note, only 10.6% of patients were treated with PBS, whereas 59.6% were treated with PSPT and 29.8% with USPT.³² This may have implications on the toxicities reported, as studies have shown PBS results in superior normal tissue sparing than photon radiation therapy, PSPT, or USPT.^{66,68–71} In addition, 67% of patients received concurrent chemotherapy, which likely magnified reported toxicities.³² High-volume CTV sizes of $\geq 250 \text{ cm}^3$ were initially allowed in this study, but because of excess grade 5 events, the study was amended to only allow CTVs $< 250 \text{ cm}^3$.³²

University of Texas MDACC investigators evaluated 27 patients who exclusively received intensity-modulated proton therapy for the definitive thoracic reirradiation to a median of 66 Gy (EQD2) ($\alpha/\beta = 3$).³⁶ At 11.2-month median follow-up, 1-year survival was 54%. One-year freedom from locoregional failure was 61%, and 15% developed in-field local failures. Local control, locoregional control, and PFS were improved with EQD2 doses ≥ 66 Gy. Toxicities were minimal, with only 7% developing late grade 3 pulmonary toxicities, with no grade ≥ 3 esophagitis or any grade ≥ 4 events despite 81% having centrally located tumors. These findings further support difference in proton modalities (PBS vs PSPT/USPT) significantly affecting safety of thoracic reirradiation. Other factors likely contributed to the excellent outcomes of this study, including small median CTV (98 mL), implementation of strict dose volume constraints (similar to the current manuscripts), particularly long median time between radiation courses (29.5 months), and only 48% of patients receiving concurrent chemotherapy.

In the aforementioned PCG/University of Florida registry study, 79 patients from 8 institutions received thoracic proton reirradiation to a median dose of 60 Gy at a median of 19.9 months from prior radiation therapy. Median OS was 15.2 months, 1-year OS and PFS rates were 59.9% and 42.5%, respectively, and the predominant patterns of progression were regional and distant. Poorer baseline Eastern Cooperative Oncology Group performance status was associated with worse survival, whereas receipt of concurrent chemotherapy was associated with significantly longer OS. Grade 3 adverse events occurred acutely in only 6% and late in only 1% of patients, although 3 grade 5 toxicities occurred. In this study, few (5%) received PBS, and only 30% received concurrent chemotherapy, potentially impacting observed toxicity rates.³³

Carbon ion radiation therapy has physical properties similar to protons, permitting more conformal treatment than achieved with photon radiation therapy, while also having biological advantages that may improve NSCLC local control.⁷² Japan investigators reported their experience of 95 patients who receive carbon ion reirradiation (median 66 Gy [Relative Biological Effectiveness]) after a previous intrathoracic carbon ion course (median 52.8 Gy [Relative Biological Effectiveness]). All retreated was hypofractionated, with the primary tumor receiving 52.8 to 72 Gy in 12 to 16 fractions and nodal metastases receiving 48 Gy in 12 fractions. No patient received concurrent chemotherapy. The rates of adverse events were only 2% grade 3, 1% grade 4, and 1% grade 5. Local control and OS at 2 years were 54% and 62%, respectively. On multivariate analysis, female sex ($P = .008$) and interval between radiation courses ≥ 24 months ($P = .048$) were predictors for superior local control, whereas CTV size < 80 cc predicted for improved OS ($P = .001$).⁷³

In summary, in the setting of recurrent thoracic disease, particle therapy may have a significant role in reducing toxicities to surrounding OAR and enabling higher dose delivery to target volumes, making reirradiation safer and more effective.⁷⁴ As proton therapy becomes more widely available, use of PBS is increased, and there is more widespread availability of cone beam computed tomography and deformable registration for adaptive proton therapy for lung cancer,^{75,76} the potential benefits of this modality for reirradiation may be even more optimally realized. The role of proton therapy in the reirradiation setting may be further informed based on findings in the de novo setting that are being assessed in a randomized comparison with photon therapy (NRG Oncology RTOG 1308).⁷⁷

Future research directions

Most available data on thoracic reirradiation are based on small retrospective studies, some of which have not required pathologic confirmation of recurrence before initiating retreatment. Furthermore, the definitions of reirradiation varied or were not always defined in the studies included in this analysis, particularly for retrospective studies, underscoring a need for standardization and improved reporting of future reirradiation reports. This is particularly important, as the prognosis, as well as the risk for toxicity, are inherently different in a patient with a direct in-field recurrence receiving reirradiation relatively to a patient with a second primary tumor arising in an area adjacent or in close proximity to a prior radiation field. More data are needed on thoracic reirradiation in the era of molecular targeted therapy and immunotherapy, such as the recently reported phase 2 trial of consolidation pembrolizumab after proton reirradiation for thoracic recurrences of NSCLC that showed promising results.⁷⁸

Investigators are also encouraged to report their reirradiation experiences and to correlate toxicities with cumulative OAR doses. As the cumulative dose constraints developed in this report were generated based off of relatively limited data, such addition reports will serve to strengthen and refine those constraints. These constraints, however, serve as a critical current step toward standardization and improving the safety of reirradiation, and they have been adopted as the cumulative dose constraints of the planned NRG Oncology NSCLC reirradiation phase 2 randomized trial LU2502. Additionally, as reirradiation has emerged as a more common clinical practice,⁷⁸ it is critical to have well designed prospective

studies. Furthermore, although outside the scope of this study, the authors acknowledge the importance of methods for operationalizing thoracic reirradiation, including image registration and dose accumulation. Such efforts are critical to standardize and make reirradiation safer and are ongoing through Reirradiation Collaborative Group.

Different fractionations (from 1.5 Gy/fraction to 34 Gy/fraction) of radiation therapy deliver different BEDs to each pixel of normal tissue, and adding accumulative physical dose is inadequate and underestimates BED when large fraction sizes from SBRT are used. To assess composite BED calculation across different radiation therapy regimens, investigators from University of Texas MDACC reported pixel-by-pixel BED calculation using a computer software algorithm based on deformable image registration of previous and current radiation therapy planning.⁷⁹ With such novel tools, adhering to dose constraint recommendations outlined above, and more precise radiation therapy such as volumetric image-guided intensity-modulated proton therapy, thoracic reirradiation is poised to be delivered more safely in near future, further allowing reirradiation to help more patients with locoregional recurrences achieve better clinical outcomes.

Pulsed low-dose-rate radiation therapy which harnesses benefits of dose rates low enough to capture tumor cells in a hypersensitive state in which repair cannot occur but at which normal tissue repair is increased,^{80–82} may allow for safer reirradiation. Pulsed low-dose-rate radiation therapy dosimetric and delivery feasibilities studies have been reported,^{81,82} but clinical data are lacking.

On the opposite end of the spectrum, as in vivo data suggest FLASH ultrahigh dose rate delivery can substantially enhance the therapeutic window and more optimally protect normal tissues,^{83,84} and with early investigations into lung cancer dose rate models^{85–87} and the first thoracic human FLASH trial ongoing,⁸⁸ this may be an attractive option for reirradiation. However, no clinical data exist using FLASH for thoracic reirradiation.

Summary of evidence (Tables 1–5)

- Definitive thoracic reirradiation can improve outcomes for select patients with NSCLC who develop locoregional recurrences after prior radiation therapy.
- SBRT is an effective modality for thoracic reirradiation, particularly after prior conventionally fractionated radiation therapy, but its safe delivery is more challenging for centrally located lesions and should not be used for nodal target volumes.
- Concurrent chemotherapy with reirradiation may allow for improved tumor control, particularly for nodal involvement, but adds toxicity to retreatment, and its use should be individualized.
- Image-guided intensity modulated reirradiation with photons or protons is recommended over 3D conformal photon reirradiation for central lesions or nodal disease.
- Acute esophagitis and pneumonitis and late pulmonary/airway, cardiac, esophageal, brachial plexus toxicities are dose limiting for thoracic reirradiation,

and newly recommended composite dose constraints should be followed to reduce the risk of high-grade toxicities.

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Table 1

An 82-year old male with a recent myocardial infarction was found on cardiac workup to have a peripheral 1.9 cm right lower lobe lung nodule. Biopsy confirmed non-small cell lung cancer for the primary tumor, and mediastinal sampling was not performed. Metastatic imaging workup was negative, and he was staged as cT1N0M0 early stage non-small cell lung cancer. He was determined by a thoracic surgeon to be medical inoperable due to comorbidities and was treated with definitive stereotactic body radiation therapy to 48 Gy in 4 fractions. Imaging 12 months after treatment reveals an increase in size of the primary tumor to 4.3 cm. Positron emission tomography/computed tomography confirms significant (SUV 7.5) avidity of the primary tumor without evidence of nodal or distant metastases. Biopsy of the primary tumor site confirms recurrence. Mediastinal sampling is performed and negative, and magnetic resonance imaging brain is negative. His ECOG performance status is 1. He is planned to undergo reirradiation to his primary tumor.

Treatment	Variant	Rating category *	Final tabulations									Group median rating	References	Comment
			1	2	3	4	5	6	7	8	9			
Fractionation														
	Once daily conventional (1.8-3.0 Gy)	M			1		4	4	1			5.5	#32, 33, 34, 38, 40	
	Twice daily hyperfractionation (1.0-1.8 Gy)	U			9	1						3	#39	
	Stereotactic body radiation therapy (≥6 Gy)	A					2	8				7	#21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 39	Stereotactic body radiation therapy can be delivered with any of the 3 techniques listed below
Technique														
	3-dimensional conformal radiation therapy	U		2	1	5	1	1				3	#31, 41	
	Intensity modulated radiation therapy	A							6	1	1	7	#35, 36	
	Intensity modulated proton therapy	M					1	7	1	1		6	#32, 33, 34, 35, 36	

Rating categories: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Final tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc).

References: Lists the references associated with the recommendation.

Non-small cell lung cancer reirradiation—Local recurrence after stereotactic body radiation therapy.

ECOG = Eastern Cooperative Oncology Group; SUV = standard uptake value.

* Includes a) concurrent chemoradiation alone, b) concurrent chemoradiation followed by additional systemic therapy, and c) systemic therapy followed by concurrent chemoradiation.

Table 2

A 62-year old male with a recent motor vehicle accident was found on trauma workup to have a peripheral 1.9 cm right lower lobe lung nodule. Biopsy confirmed non-small cell lung cancer for the primary tumor, and mediastinal sampling was not performed. Metastatic imaging workup was negative, and he was staged as cT1N0M0 early stage non-small cell lung cancer. He refused surgery and was treated with definitive stereotactic body radiation therapy to 48 Gy in 4 fractions. Imaging 12 months after treatment reveals an excellent response of the primary tumor but new right lower paratracheal and subcarinal lymphadenopathy. Positron emission tomography/computed tomography demonstrates lack of avidity in the primary tumor but avid paratracheal and subcarinal nodes (SUV 5.3 and 6.7) without evidence of other nodal or distant metastases. Mediastinal sampling confirms nodal recurrence, and magnetic resonance imaging brain is negative. His ECOG performance status is 0. He is planned to undergo reirradiation to his multi-station nodal recurrence.

Treatment	Variant	Rating category	Final tabulations									Group median rating	References	Comment
			1	2	3	4	5	6	7	8	9			
Fractionation	Once daily conventional (1.8–3.0 Gy)	A					1		4	3	2	7.5	#32, 33, 34, 38, 40	Stereotactic body radiation therapy will not be given concurrent with chemotherapy
	Twice daily hyperfractionation (1.0–1.8 Gy)	U			1	7	2					3	#39	
	Stereotactic body radiation therapy (≥6 Gy)	U			1	6	1					3	#21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 39	
Technique	3-dimensional conformal radiation therapy	U			1	7	2					3	#31, 41	Stereotactic body radiation therapy will not be given concurrent with chemotherapy
	Intensity modulated radiation therapy	A						1	5	4	1	7	#35, 36	
	Intensity modulated proton therapy	A						1	6	1		7	#32, 33, 34, 35, 36	
Chemotherapy	Radiation alone	U			1	7				1		3	#42	Stereotactic body radiation therapy will not be given concurrent with chemotherapy
	Sequential chemotherapy followed by radiation therapy	M			2	1	5	1				5	#31, 32, 33, 34, 35, 36, 37, 41, 42	
	Concurrent chemoradiation +/- immunotherapy*	A							3	3	3	2	7	

Rating categories: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Final tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc).

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Non-small cell lung cancer reirradiation—Local recurrence after stereotactic body radiation therapy.

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ECOG = Eastern Cooperative Oncology Group; SUV = standard uptake value.

* Includes a) concurrent chemoradiation alone, b) concurrent chemoradiation followed by additional systemic therapy, and c) systemic therapy followed by concurrent chemoradiation.

Table 3

A 72-year old female with a history of cT3N2M0 (peripheral right lower lobe primary tumor, right lower paratracheal and subcarinal nodal metastases) locally advanced stage III non-small cell lung cancer. She was treated with definitive chemoradiation to 60 Gy in 2 Gy daily fractions. Imaging 12 months after treatment reveals an increase in size of the primary tumor to 5.3 cm. Positron emission tomography/computed tomography confirms significant (SUV 8.7) avidity of the primary tumor without evidence of nodal or distant metastases. Mediastinal sampling is performed and is negative, and magnetic resonance imaging brain is negative. Her ECOG performance status is 1. She is planned to undergo reirradiation to her primary tumor.

Treatment	Variant	Rating category	Final tabulations									Group median rating	References	Comment
			1	2	3	4	5	6	7	8	9			
Fractionation														
	Once daily conventional (1.8–3.0 Gy)	A						2	8		7	-		
	Twice daily hyperfractionation (1.0–1.8 Gy)	M			2	7	1				5		#32, 33, 34, 38, 40	
													#39	
	Stereotactic body radiation therapy (≥6 Gy)	M				1	9				6		#21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 39	Stereotactic body radiation therapy will not be given concurrent with chemotherapy
Technique														
	3-dimensional conformal radiation therapy	U	2		6	1	1				3		#31, 41	
	Intensity modulated radiation therapy	A						1	5	3	1	7	#35, 36	
	Intensity modulated proton therapy	M						6	2		6		#32, 33, 34, 35, 36	
Chemotherapy														
	Radiation alone	A						1	7		7		-	
													#42	Stereotactic body radiation therapy is preferred if radiation is used alone without chemotherapy
	Sequential chemotherapy followed by radiation therapy	M				1	1	6	1		6		#31, 32, 33, 34, 35, 36, 37, 41, 42	
	Concurrent chemoradiation +/- immunotherapy *	M			1	1	8		1		6		#32, 33, 34, 35, 36, 39, 40	

Rating categories: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Final tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc).

References: Lists the references associated with the recommendation.

Non-small cell lung cancer reirradiation—Local recurrence after stereotactic body radiation therapy.

ECOG = Eastern Cooperative Oncology Group; SUV = standard uptake value.

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* Includes a) concurrent chemoradiation alone, b) concurrent chemoradiation followed by additional systemic therapy, and c) systemic therapy followed by concurrent chemoradiation.

Table 4

A 72-year old female heavy smoker with a history of cT3N2M0 (peripheral right lower lobe primary tumor, right lower paratracheal and subcarinal nodal metastases) locally advanced stage III non-small cell lung cancer. She was treated with definitive chemoradiation to 60 Gy in 2 Gy daily fractions. Imaging 12 months after treatment reveals an excellent response of the primary tumor but progression in a new right upper paratracheal lymph node and recurrence in the right lower paratracheal region. Positron emission tomography/computed tomography demonstrates lack of avidity in the primary tumor and subcarinal node but avid upper and lower paratracheal nodes (SUV 5.6 and 4.9) without evidence of other nodal or distant metastases. Mediastinal sampling confirms nodal recurrence, and magnetic resonance imaging brain is negative. Her ECOG performance status is 1. She is planned to undergo reirradiation to her multi-station nodal recurrence.

Treatment	Variant	Rating category	Final tabulations									Group median rating	References	Comment
			1	2	3	4	5	6	7	8	9			
Fractionation	Once daily conventional (1.8–3.0 Gy)	A						1	1	6	2	8	- #32, 33, 34, 38, 40	Stereotactic body radiation therapy will not be given concurrent with chemotherapy
	Twice daily hyperfractionation (1.0–1.8 Gy)	M					1	1	5	2	1	5	#39	
	Stereotactic body radiation therapy (≥6 Gy)	U				1	6	1				3	#21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 39	
Technique	3-dimensional conformal radiation therapy	U		2		6	1	1				3	- #31, 41	For never smokers or those with a high index of suspicion for targetable mutations, molecular profiling could be considered, and targeted therapy with radiation therapy could be considered if targetable gene mutations are detected
	Intensity modulated radiation therapy	A							2	6	2	7	#35, 36	
	Intensity modulated proton therapy	A							2	6		7	#32, 33, 34, 35, 36	
Chemotherapy	Radiation alone	U			8							3	#42	
	Sequential chemotherapy followed by radiation therapy	M			1		5	3	2			5	#31, 32, 33, 34, 35, 36, 37, 41, 42	
	Concurrent chemoradiation +/- immunotherapy*	A					1	1	5	4		7	#32, 33, 34, 35, 36, 39, 40	

Rating categories: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Final tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc).

References: Lists the references associated with the recommendation.

Non-small cell lung cancer reirradiation—Local recurrence after stereotactic body radiation therapy.

ECOG = Eastern Cooperative Oncology Group; SUV = standard uptake value.

* Includes a) concurrent chemoradiation alone, b) concurrent chemoradiation followed by additional systemic therapy, and c) systemic therapy followed by concurrent chemoradiation.

Table 5

A 72-year old female with a history of cT3N2M0 (peripheral right lower lobe primary tumor, right lower paratracheal and subcarinal nodal metastases) locally advanced stage III non-small cell lung cancer. She was treated with definitive chemoradiation to 60 Gy in 2 Gy daily fractions. Imaging 12 months after treatment reveals an increase in size of the primary tumor to 5.3 cm and recurrence in the subcarinal region. Positron emission tomography/computed tomography confirms significant avidity of the primary tumor (SUV 8.7) and subcarinal node (SUV 6.5) without evidence of other nodal or distant metastases. Bronchoscopy confirms primary tumor and subcarinal nodal recurrences, and magnetic resonance imaging brain is negative. Her ECOG performance status is 1. She is planned to undergo reirradiation to her primary tumor and nodal recurrences.

Treatment	Variant	Rating category	Final tabulations							References	Comment		
			1	2	3	4	5	6	7			8	9
Fractionation	Once daily conventional (1.8–3.0 Gy)	A				1		5	3	1	7	#32, 33, 34, 38, 40	
	Twice daily hyperfractionation (1.0–1.8 Gy)	M				2	8				5	#39	
	Stereotactic body radiation therapy (≥6 Gy)	U		1	9						3	#21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 39	Stereotactic body radiation therapy will not be given concurrent with chemotherapy
Technique	3-dimensional conformal radiation therapy	U		2	7	1					3	#31, 41	
	Intensity modulated radiation therapy	A					1	4	4	1	7.5	#35, 36	
	Intensity modulated proton therapy	A					1	6	1		7	#32, 33, 34, 35, 36	
Chemotherapy	Radiation alone	M		2	3	3	3				5	#42	
	Sequential chemotherapy followed by radiation therapy	M		1		1	7	1	1		6	#31, 32, 33, 34, 35, 36, 37, 41, 42	
	Concurrent chemoradiation +/- immunotherapy*	A					3	3	5		7	#32, 33, 34, 35, 36, 39, 40	

Rating categories: A = usually appropriate; M = may be appropriate; U = usually not appropriate.

Final tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc).

References: Lists the references associated with the recommendation.

Non-small cell lung cancer reirradiation—Local recurrence after stereotactic body radiation therapy.

ECOG = Eastern Cooperative Oncology Group; SUV = standard uptake value.

* Includes a) concurrent chemoradiation alone, b) concurrent chemoradiation followed by additional systemic therapy, and c) systemic therapy followed by concurrent chemoradiation.

Table 6
Recommended reirradiation composite dose constraints (in 2 Gy equivalent dose)

Organ	Dose constraint	Toxicity endpoint
Esophagus	V60 <40%, Dmax < 100 Gy	Acute grade ≥3 esophagitis, late esophageal stricture and fistula
Lung	V20 <40%	Symptomatic pneumonitis, late pulmonary fibrosis
Heart	Mean dose ALARA, V40 <50%	Major cardiac events
Aorta and great vessels	DMax < 120 Gy	Hemorrhage, fistula
Trachea and proximal bronchial tree	DMax < 110 Gy	Tracheal/bronchial necrosis, tracheoesophageal fistula, bronchopleural fistula
Spinal cord	DMax < 57 Gy	Myelopathy
Brachial plexus	DMax < 85 Gy	Brachial plexopathy

Abbreviations: ALARA = as low as reasonably achievable; Dmax = maximum point dose; V60/V20/V5/V40 = volume receiving 60 Gy/20 Gy/5 Gy/40 Gy.