**American Radium Society™ Appropriate Use Criteria Systematic Review and Guidelines on Reirradiation for Non-small Cell Lung Cancer**

Charles B. Simone, II, M.D.,1,2 Arya Amini, M.D.,3 Indrin J. Chetty, Ph.D.,4 J. Isabelle Choi, M.D.,1,2 Stephen G. Chun, M.D.,5 Jessica Donington, M.D.,6 Martin J. Edelman, M.D.,7 Kristin A. Higgins, M.D.,8 Larry L. Kestin, M.D.,9 Pranshu Mohindra, M.D., M.B.B.S.,10 Benjamin Movsas, M.D.,4 George B. Rodrigues, M.D.,11 Kenneth E. Rosenzweig, M.D.,12 Igor I. Rybkin, M.D., Ph.D.,4 Annemarie F. Shepherd, M.D.,1,2 Benjamin J. Slotman, M.D., Ph.D.,13 Andrea Wolf, M.D.,12 Joe Y. Chang, M.D., Ph.D.5

1New York Proton Center, New York, NY.

2Memorial Sloan Kettering Cancer Center, New York, NY.

3City of Hope Comprehensive Cancer Center, Duarte, CA.

4Henry Ford Health System, Detroit, MI.

5The University of Texas, M.D. Anderson Cancer Center, Houston, TX.

6The University of Chicago, Chicago, IL.

7Fox Chase Comprehensive Cancer Center, Philadelphia, PA.

8Emory University Winship Cancer Institute, Atlanta, GA.

9MHP Cancer Institute, Pontiac, MI.

10University of Maryland, Baltimore, MD.

11London Health Sciences Centre, London, ON.

12Mount Sinai School of Medicine, New York, NY.

13Amsterdam University Medical Center, De Boelelaan, Amsterdam, The Netherlands

**Conflicts of Interest Statement:** All panelists were required to declare all conflicts of interest for the previous 36 months prior to initiating work on this document. These complete disclosure forms are retained by the American Radium Society™ in perpetuity. The ARS Appropriate Use Criteria Steering Committee reviewed these disclosures with the chair and co-chair of this document and approved participation of the panelists prior to starting development of this work. Disclosures potentially relevant to the content of this guideline are provided: C.B.S.: Varian Medical Systems, Inc A.A.: AstraZeneca, PLC; RefleXion Medical, Inc. S.G.C.: AstraZeneca, PLC M.J.E.: WindMIL Therapeutics, Inc; Syndax Pharmaceuticals, Inc; GlaxoSmithKline, PLC; AstraZeneca, PLC; Takeda Pharmaceutical Company, Inc; Andarix Pharmaceuticals, Inc; BioMarker Strategies, LLC. K.A.H.: AstraZeneca, PLC; Genentech, Inc; RefleXion Medical, Inc. B.M.: ViewRay, Inc; Varian Medical Systems, Inc; Philips, NV. A.F.S.: American Society of Clinical Oncology B.J.S.: ViewRay, Inc; Varian Medical Systems, Inc. J.Y.C.: BMS-MD Anderson Cancer Center; AstraZeneca, PLC; Varian Medical Systems, Inc; Global Oncology One, Inc.

**Shortened Running Title:** ARS Guidelines on NSCLC Reirradiation

**Abstract**

**Background:** Definitive thoracic reirradiation can improve outcomes for select non-small cell lung cancer (NSCLC) patients with locoregional recurrences. To date, no systematic review on safety or efficacy of NSCLC reirradiation exists, and no dedicated guidelines are available. This ARS Appropriate Use Criteria Systematic Review and Guidelines provides 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.

**Methods:** PRISMA systematic review assessed all studies published through 3/2020 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 these recommendations on: 1) the role of concurrent chemotherapy, 2) factors associated with toxicities, and 3) optimal reirradiation modalities and dose-fractionation schemas.

**Results:** Stereotactic body radiotherapy 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 lymph node recurrence 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 (2Gy equivalents): esophagus V60<40%, 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; and brachial plexus DMax<85 Gy.

**Conclusions:** Personalized thoracic reirradiation approaches and consensus dose constraints for thoracic reirradiation are recommended. Further prospective studies are needed to strength and improve these guidelines.

**Key words:** reirradiation; lung cancer; toxicity; dose constraints; guidelines

**Introduction**

Among the >40% of patients who present with localized non-small cell lung cancer (NSCLC),1 many will receive radiotherapy, either for medically operable2 or even operable3 early stage NSCLC, or as part of bimodality4 or trimodality5-6 therapy for locally advanced disease.

As systemic therapy improves, and with increasing utilization of immunotherapy,7 local and regional control are increasingly important. However, among early stage NSCLC patients, while fewer than 10% develop local failures following stereotactic body radiation therapy (SBRT), 10-20% of patients will develop nodal metastasis following irradiation.8-9 Similarly, among locally advanced NSCLC patients, local failure rates are as high as 25-50% by 2 years,4,10 including one-in-four patients developing isolated locoregional recurrences.11 Even with oligometastatic disease or oligoprogression after definitive radiotherapy, 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<0.0001, multivariate analyses).12 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 non-metastatic NSCLC.10

Despite recognizing the importance of thoracic tumor control and high frequency of local or regional recurrence after radiotherapy, thoracic re-irradiation remains particularly challenging due to potential severe toxicities, including catastrophic organ injury or death, and lack of standardized approaches and guidelines. Patients with intrathoracic recurrences after radiotherapy, therefore, have historically been treated with palliative systemic alone. However, chemotherapy monotherapy achieves progression-free survival (PFS) typically of only 4-6 months and does not offer a chance of cure.13 Immune checkpoint inhibitors are an attractive option to treat recurrences after radiotherapy, but fewer than one-in-four patients respond to these agents.14-15 Surgery is often not possible due to perioperative risks with resection following definitive doses of radiotherapy.5-6

Definitive reirradiation for local and/or regional recurrences 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 radiotherapy 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 radiotherapy, these advanced modalities may hold the key for safer reirradiation.

To date, no systematic review on the safety and efficacy of reirradiation for NSCLC exists, and no dedicated guidelines on reirradiation for patients with locoregionally recurrent NSCLC are available. 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, suggests consensus dose constraints for reirradiation to minimize risks of high grade and potentially fatal toxicities.

**Materials and Methods:**

A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 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, intensity-modulated radiation therapy, intensity-modulated radiotherapy, IMRT, stereotactic body radiation therapy, stereotactic body radiotherapy, SBRT, stereotactic ablative radiotherapy, stereotactic ablative radiation therapy, SABR, 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 March 2020 were included. A meta-analysis proved not possible due to 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.

Fourteen multidisciplinary expert panel were selected from different institutions based on their thoracic expertise and publication records. Monthly panel conference call and annual in-person meetings were conducted for more than 2 year to review and discuss thoracic AUC projects. Consensus voting was allowed a maximum of three times to decide whether agreement was achieved in each topic based on reirradiation variants (Variant 1 to 5).

**Primary recurrence alone after SBRT (Variant 1) or definitive chemoradiotherapy (Variant 3)**

Stereotactic Body Radiotherapy (SBRT)

SBRT, also called SABR (Stereotactic Ablative Radiotherapy), 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 (BED10) ≥100Gy, 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 (MSKCC) investigators, 39 patients were treated with SBRT to a median BED10 70.4Gy (α/β=10) for intrathoracic failures after conventionally fractionated radiotherapy. One- and 2-year local progression-free survival (LPFS) rates were 77% and 64%, respectively, and median recurrence-free (RFS) 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 ≥100Gy, which was associated with higher LPFS (p=0.038) and OS (p=0.04).21

Drexel University investigators reported on 26 patients with 29 tumors treated with SBRT after prior radiotherapy (median 61.2Gy). The median SBRT dose was 30Gy in 5 fractions (BED10 48Gy). Local tumor control was 78.5% at 1 year and 65.5% at 2 years. No grade ≥3 adverse events were seen, possible 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 17-60Gy in 1-5 fractions (48Gy in 4 fractions most commonly) to a median BED10 of 106Gy. 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 an MDACC series, 72 patients previously treated with conventionally fractionated radiotherapy (median 63Gy) received SBRT to 50Gy in 4 fractions for recurrent or secondary parenchymal lung malignancy. OS and PFS at 2 years were 74.4% and 41.9%, respectively. Only one 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 pre-treatment performance status, FEV1 ≤65%, lung V20 ≥30% on the composite plan, and prior bilateral mediastinal PTVs.24

Wake Forest University investigators reported outcomes of 33 reirradiation patients, 30 of whom received SBRT reirradiation to a median of 50Gy 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 2-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 stage III NSCLC patients treated with SBRT reirradiation reported 4-year PFS and OS of 8.6% and 30.8%, respectively, with 2 grade 5 events (hemoptysis, alveolitis).26

While many series report on SBRT reirradiation for thoracic recurrences after an initial course of conventionally-fractionated radiotherapy, limited data exist using SBRT after primary SBRT failure. Karolinska University investigators assessed 29 patients who received SBRT reirradiation (median dose 30Gy, most commonly in two fractions). LC at 5 months was only 52%, grade 3-4 toxicities occurred 14 times, and three grade 5 massive bleeding events occurred. Larger 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 overall survival after salvage, with 2-year primary tumor control of 81%. No grade ≥3 toxicities were reported despite all courses being BED10 of ≥100Gy.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 investgators27 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.

In summary, SBRT or SABR may improve local control in primary tumor recurrence after radiotherapy. However, centrally-located lesions could cause potential severe toxicity and individualized approach should be considered.

**Lymph node recurrence after SBRT (Varian 2), lymph node recurrence alone (Variant 4) or primary and lymph node recurrence (Variant 5) after definitive radiotherapy or chemoradiotherapy**

The role of concurrent chemotherapy for definitive reirradiation

While the use of concurrent chemoradiotherapy in the primary setting is standard of care for locally advanced NSCLC to improve local control and OS versus sequential chemoradiotherapy (CRT),4,10-11 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 radiotherapy, 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 al. reported a phase 1/2 trial with 3-dimensional conventional radiation therapy (3DCRT) for re-irradiation,31 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 three proton centers, concurrent CRT was delivered in 67% of patients and was associated with increased grade ≥3 acute toxicity (53% vs. 16%, p=0.003). Concurrent CRT did result in a non-significant improvement in 1-year OS (66% vs. 43%, p=0.3), likely from delayed separation of the survival curves after 6-8 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 prior to reirradiation. On univariate analysis, concurrent CRT was associated with improved median survival (23.4 vs. 12.9 months, p=0.04). 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. MD Anderson Cancer Center (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=0.029), but also improved local control (HR =6.48; p=0.0004), distant metastasis-free survival (HR=0.464; p=0.027), and OS (HR =2.613; p=0.0045).35 In a third MDACC report of 27 patients reirradiated with intensity-modulated proton therapy, definitive radiation dose was again associated with improved loco-regional 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 distant metastases-free survival (p=0.020).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. While the available data suggest a potential benefit in clinical outcomes with concurrent CRT, it comes at the cost of potentially exaggerated series 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 due to 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 multi-center 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, come 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 radiotherapy 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 7.9-17.6%, 0-9%, and 0-2%, respectively.31,33-35,39,44

Life-threatening pulmonary, airway, and vascular damage can develop from thoracic reirradiation. Pulmonary injury from radiotherapy 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 5-26.5%, 0-21%, 0-2.9% and 0-3.6%, 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 al. 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.32 Reirradiation-induced great vessel injury can lead to a delayed presentation of a rapidly fatal hemorrhage in 0-12%.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.

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 the MDACC reirradiation experience, larger planning target volume (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 multi-centered prospective proton study stratified by clinical target volume (CTV) size (<250 or ≥250 cc). The high-volume cohort was deemed infeasible due to toxicities.32 Large target volumes should be reirradiated with caution as volumes ≥250 cc may result in increased toxicities, including grade 5 events.

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 MDACC investigators demonstrated that peripheral lesions have fewer cardiac toxicities (p=0.002), a trend towards fewer pulmonary/airway toxicities (p=0.08), 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%). MDACC SBRT reirradiation data demonstrated prior course radiation volume also impacts the development of radiation pneumonitis with reirradiation. Chao et al. 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) vs. 64% for high volume overlap (≥41 cc) (p<0.001).32 French investigators similarly found central location was associated with grade ≥2 toxicities.26

The time interval between prior radiotherapy and reirradiation has not been clearly demonstrated to correlate with toxicity.32,34-35,39 Investigators from 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

Lung function and sensitivity to prior radiotherapy 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 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 CT 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 60Gy (V60) should be evaluated. Investigators from MDACC reported the maximum dose (p=0.001) and V60 (p<0.001) associated with grade ≥2 esophageal toxicities, and a tracheoesophageal fistula developed when the composite esophageal maximum dose was 135.7Gy. Patients with grade ≥3 esophageal toxicities had average composite esophageal V60s of approximately 36.5% .34-35 Stanford investigators reported patients with grade ≥2 esophageal toxicities had a composite (EQD2) dose of 41-100.6Gy to 1cc of esophagus (D1cc).39 Chao et al. found composite mean esophageal dose below versus above the cohort mean (12.45Gy) correlated with acute grade ≥3 toxicities (22% vs. 64%, p=0.003).32 Based on these data, composite maximum esophageal doses >100Gy (EQD2) should be minimized in volume, composite doses >110Gy should be avoided and >120Gy 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 the MDACC series, V10 (p=0.025), V20 (p=0.025), MLD (p=0.032), and composite MLD (p=0.024) 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 mean lung dose of 22.5Gy.34-35 In the Stanford series, patients with grade ≥2 pulmonary toxicities had a composite lung V20 of 4.7-21.7%.39 In the 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 radiotherapy. 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 radiotherapy course. Composite lung V20 >50% is discouraged, particularly if the patient has limited pulmonary function or history of prior pulmonary toxicity. Compositive lung V5 constraints should similarly mirror those for an initial radiotherapy course (≤65%). A compositive 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.4,47-48 While MHD <26Gy is commonly recommended in the definitive setting, no established reirradiation MHD constraints exist. Cardiac toxicities associated with reirradiation are not well reported. Chao et al. reported that reirradiation MHD below versus above the cohort mean (394cGy) correlated with acute grade ≥3 toxicity (26% vs. 60%, p= 0.02).32 Therefore, keeping MHD as low as reasonably achievable (ALARA) is advised, and heart V40 <50% is recommended.

For chest wall, dose delivered to 30cc 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 35-117.2Gy.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 should be considered. The one patient in the Stanford series with brachial plexopathy had a composite brachial plexus maximum dose of 242.5Gy.39 Evans et al. reported an association between D1cc to the aorta of 120Gy and risk of aortic rupture,45 although 5 patients in Stanford series received 1cc >120Gy to the aorta without toxicity.39 A grade 5 exsanguination from aorta-esophageal fistula occurred in a patient with composite aorta maximum EQD2 of 200Gy.25 Badiyan et al. reported 2 patients develop hemorrhage after cumulative doses to right pulmonary arteries of 132.3Gy and 135.1Gy (EQD2 ~207).33 MDACC investigators reported tracheal necrosis after trachea composite maximum dose of 147.37Gy (BED of 220Gy).34-35 Spinal cord toxicity was not reported in any reirradiation series included in this systematic review. The multi-center prospective proton protocol required a composite maximum dose <75Gy, although most patients had a composite maximum <50Gy.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 120Gy for aorta/great vessels and 110Gy for trachea/proximal bronchial tree. While 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, maximum point dose should be kept ALARA, with spinal cord DMax <57Gy and brachial plexus DMax <85Gy 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 1**. 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 1 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.49 Reports of 3DCRT reirradiation were generally using doses of 30-60Gy in 1.8-3Gy fractions, with most experiences limited to 30Gy and palliative intent.50-53 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,54 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.

Hyperfractionation 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 cancer55-57 and head and neck cancer58 recurrence, with tumor response rates ranging from 45-75% and few reported grade 4-5 adverse events. To date, very limited data exist regarding the clinical use of hyperfractionation for lung cancer reirradiation. Binkley and colleagues delivered hyperfractionated radiotherapy in 3 of 44 thoracic reirradiation course, but hyperfractionation was not associated with toxicity rate.39 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.59-63 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.64-66 Experience with this technology in the setting of thoracic irradiation is yet limited, although results are promising.

A multi-center prospective study from Chao and colleagues evaluated 57 patients with recurrent NSCLC located within/near their initial radiation field (mean 65Gy) treated with proton reirradiation to a mean dose of 66.6Gy. 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 locally advanced NSCLC patients. 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, mean heart dose, and use of concurrent chemotherapy. Higher mean esophagus dose was associated with decreased OS (p=0.007). 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 radiotherapy, PSPT, or USPT.65,67-70 In addition, 67% of patients received concurrent chemotherapy, which likely magnified reported toxicities.32 High-volume CTV sizes of ≥250cm3 were initially allowed in this study, but due to excess grade 5 events, the study was amended to only allow CTVs <250cm3.32

MDACC investigators evaluated 27 patients who exclusively received IMPT for the definitive thoracic reirradiation to a median of 66Gy (EQD2) (α/β=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 ≥66Gy. Toxicities were minimal, with only 7% experiencing late grade 3 pulmonary toxicities, and no grade ≥3 esophagitis or any grade ≥4 events despite 81% having centrally located tumors. These findings further support difference in proton modalities (PBS versus PSPT/USPT) significantly affecting safety of thoracic reirradiation. Other factors likely contributed to the excellent outcomes of this study, including small median CTV (98mL), 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 60Gy at a median of 19.9 months from prior radiotherapy. 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 ECOG 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 radiotherapy has physical properties similar to protons, permitting more conformal treatment than achieved with photon radiotherapy, while also having biological advantages that may improve NSCLC local control.71 Japan investigators reported their experience of 95 patients who receive carbon ion reirradiation (median 66Gy(RBE)) after a previous intrathoracic carbon ion course (median 52.8Gy(RBE)). All retreated was hypofractionated, with the primary tumor receiving 52.8-72Gy in 12-16 fractions and nodal metastases receiving 48Gy 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=0.008) and interval between radiation courses ≥24 months (p=0.048) were predictors for superior local control, whereas CTV size <80 cc predicted for improved OS (p=0.001).72

In summary, in the setting of recurrent thoracic disease, particle therapy may have a significant role in reducing toxicities to surrounding organs at risk and enabling higher dose delivery to target volumes, making reirradiation safer and more effective.73 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,74 the potential benefits of this modality for reirradiation may be even more optimally realized.

**Future research directions**

Most available data on thoracic reirradiation are based on retrospective studies. More data on thoracic reirradiation in the era of molecular targeted therapy and immunotherapy are needed. Investigators are also encouraged to report their reirradiation experience and correlated toxicities with cumulative OAR doses. Additionally, as reirradiation has emerged as a more common clinical practice, it is critical to have well designed prospective studies.

Different fractionations (from 1.5Gy/fraction to 34Gy/fraction) of radiotherapy 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 radiotherapy regimens, investigators from MD Anderson reported pixel-by-pixel BED calculation using a computer software algorithm based on deformable image registration of previous and current radiotherapy planning.75 With such novel tools, adhering to dose constraint recommendations outlined above, and more precise radiotherapy such as volumetric image-guided IMPT, 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 radiotherapy (PLDR), 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,76-78 may allow for safer reirradiation. PLDR dosimetric and delivery feasibilities studies have been reported,77-78 but clinical data are lacking.

On the opposite end of the spectrum, as *in vivo* data suggest FLASH ultra-high dose rate delivery can substantially enhance the therapeutic window and more optimally protect normal tissues, this may be an attractive option for reirradiation.79-80 However, no clinical data exist using FLASH for thoracic reirradiation.

**Summary of Evidence (Variant 1-5)**

• Definitive thoracic reirradiation can improve outcomes for select patients with NSCLC who develop locoregional recurrences after prior radiotherapy.

• SBRT is an effective modality for thoracic reirradiation, 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.

**Acknowledgements**

The panel would like to acknowledge Ms. Andrea Taylor and the ARS Appropriate Use Criteria Steering Committee for assistance in generation of this document.

**References**

1. Noone AM, Howlader N, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975\_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.
2. Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol*. 2017;7(5):295-301.
3. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol*. 2015;16(6):630-7.
4. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015;16(2):187-99.
5. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374(9687):379-86.
6. Vyfhuis MA, Bhooshan N, Burrows WM, et al. Oncological Outcomes from Trimodality Therapy Receiving Definitive Doses of Neoadjuvant Chemoradiation (≥60 Gy) and Factors Influencing Consideration for Surgery in Stage III Non-Small Cell Lung Cancer. *Adv Radiat Oncol*. 2017;2:259-269.
7. Antonia SJ, Villegas A, Daniel D, et al; PACIFIC Investigators. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350.
8. Timmerman RD, Hu C, Michalski JM, et al. Long-term Results of Stereotactic Body Radiation Therapy in Medically Inoperable Stage I Non-Small Cell Lung Cancer. *JAMA Oncol*. 2018;4(9):1287-1288.
9. Simone CB 2nd, Wildt B, Haas AR, et al. Stereotactic body radiation therapy for lung cancer. *Chest*. 2013;143(6):1784-90.
10. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2010;28(13):2181-90.
11. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst*. 2011;103(19):1452-60.
12. Machtay M, Paulus R, Moughan J, et al. Defining local-regional control and its importance in locally advanced non-small cell lung carcinoma. *J Thorac Oncol*. 2012;7(4):716-22.
13. Noble J, Ellis PM, Mackay JA, et al; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: a systematic review and practice guideline. *J Thorac Oncol*. 2006;1(9):1042-58.
14. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(17):1627-39.
15. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(2):123-35.
16. Chun SG, Hu C, Choy H, et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. *J Clin Oncol*. 2017;35(1):56-62.
17. Nyman J, Hallqvist A, Lund JÅ, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol*. 2016;121(1):1-8.
18. Higgins KA, O'Connell K, Liu Y, et al. National Cancer Database Analysis of Proton Versus Photon Radiation Therapy in Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys*. 2017;97(1):128-137.
19. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8(5):336–341.
20. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer*. 2004;101(7):1623-31.
21. Reyngold M, Wu AJ, McLane A, et al. Toxicity and outcomes of thoracic re-irradiation using stereotactic body radiation therapy (SBRT). *Radiat Oncol*. 2013;8:99
22. Patel NR, Lanciano R, Sura K. et al. Stereotactic body radiotherapy for re-irradiation of lung cancer recurrence with lower biological effective does. *J Radiat Oncol*. 2015;4(1):65-70.
23. Horne ZD, Dohopolski MJ, Clump DA, et al. Thoracic re-irradiation with SBRT for residual/recurrent and new primary NSCLC within or immediately adjacent to a prior high0dose radiation field. *Pract Radiat Oncol*. 2018;8(3):e117-e123.
24. Liu H, Zhang X, Vinogradskiy YY, et al. Predicting radiation pneumonitis after stereotactic ablative radiation therapy in patients previously treated with conventional thoracic radiation therapy. *Int J Radiat Oncol Biol Phys*. 2012;84(4):1017-1023.
25. Kilburn JM, Kuremsky JG, Blackstock AW, et al. Thoracic re-irradiation using stereotactic body radiotherapy (SBRT) techniques as first or second course of treatment. *Radiother Oncol*. 2014;110(3):505-510.
26. Sumodhee S, Bondiau PY, Poudenx M, et al. Long term efficacy and toxicity after stereotactic ablative reirradiation in locally relapsed stage III non-small cell lung cancer. *BMC Cancer*. 2019;19(1):305.
27. Peulen H, Karlsson K, Lindberg K, et al. Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy. *Radiother Oncol*. 2011;101(2):260-6.
28. Kennedy WR, Gabani P, Nikitas J, Robinson CG, Bradley JD, Roach MC. Repeat stereotactic body radiation therapy (SBRT) for salvage of isolated local recurrence after definitive lung SBRT. *Radiother Oncol*. 2020;142:230-235.
29. Valakh V, Miyamoto C, Micaily B, et al. Repeat stereotactic body radiation therapy for patients with pulmonary malignancies who had previously received SBRT to the same or an adjacent tumor site. *J Cancer Res Ther*. 2013;9(4):680-5.
30. Hearn JW, Videtic GM, Djemil T, et al. Salvage stereotactic body radiation therapy (SBRT) for local failure after primary lung SBRT. *Int J Radiat Oncol Biol Phys*. 2014;90(2):402-6.
31. Wu KL, Jiang GL, Qian H, et al. Three-dimensional conformal radiotherapy for locoregionally recurrent lung carcinoma after external beam irradiation: a prospective phase I-II clinical trial. *Int J Radiat Oncol Biol Phys*. 2003;57(5):1345-50.
32. Chao HH, Berman AT, Simone CB 2nd, et al. Multi-Institutional Prospective Study of Reirradiation with Proton Beam Radiotherapy for Locoregionally Recurrent Non-Small Cell Lung Cancer. *J Thorac Oncol*. 2017;12(2):281-292.

Badiyan SN, Rutenberg MS, Hoppe BS, et al. Clinical Outcomes of Patients with Recurrent Lung Cancer Reirradiated with Proton Therapy on the Proton Collaborative Group and University of Florida Proton Therapy Institute Prospective Registry Studies. *Pract Radiat Oncol*. 2019;9(4):280-288.

1. McAvoy SA, Ciura KT, Rineer JM, et al. Feasibility of proton beam therapy for reirradiation of locoregionally recurrent non-small cell lung cancer. *Radiother Oncol*. 2013;109(1):38-44.

McAvoy S, Ciura K, Wei C, et al. Definitive reirradiation for locoregionally recurrent non-small cell lung cancer with proton beam therapy or intensity modulated radiation therapy: predictors of high-grade toxicity and survival outcomes. *Int J Radiat Oncol Biol Phys*. 2014;90(4):819-827.

1. Ho JC, Nguyen QN, Li H, et al. Reirradiation of thoracic cancers with intensity modulated proton therapy. *Pract Radiat Oncol*. 2018;8(1):58-65.
2. Tetar S, Dahele M, Griffioen G, Slotman B, Senan S. High-dose conventional thoracic re-irradiation for lung cancer: updated results. *Lung Cancer*. 2015;88(2):235-6.
3. Griffioen GH, Dahele M, de Haan PF, et al. High-dose, conventionally fractionated thoracic reirradiation for lung tumors. *Lung Cancer*. 2014;83(3):356-62.
4. Binkley MS, Hiniker SM, Chaudhuri A, et al. Dosimetric Factors and Toxicity in Highly Conformal Thoracic Reirradiation. *Int J Radiat Oncol Biol Phys*. 2016;94(4):808-815.
5. Yoshitake T, Shioyama Y, Nakamura K, et al. Definitive fractionated re-irradiation for local recurrence following stereotactic body radiotherapy for primary lung cancer. *Anticancer Res*. 2013;33(12):5649-53.
6. Hong JH, Kim YS, Lee SW, et al. High-Dose Thoracic Re-irradiation of Lung Cancer Using Highly Conformal Radiotherapy Is Effective with Acceptable Toxicity. *Cancer Res Treat*. 2019;51(3):1156-1166.
7. Ren C, Ji T, Liu T, et al. The risk and predictors for severe radiation pneumonitis in lung cancer patients treated with thoracic reirradiation. *Radiat Oncol*. 2018;13(1):69.
8. Verma V, Simone CB 2nd, Werner-Wasik M. Acute and Late Toxicities of Concurrent Chemoradiotherapy for Locally-Advanced Non-Small Cell Lung Cancer. *Cancers (Basel)*. 2017;9(9).
9. De Ruysscher D, Faivre-Finn C, Le Pechoux C, et al. High-dose re-irradiation following radical radiotherapy for non-small-cell lung cancer. *Lancet Oncol*. 2014;15(13):e620-624.
10. Evans JD, Gomez DR, Amini A, et al. Aortic dose constraints when reirradiating thoracic tumors. *Radiother Oncol*. 2013;106(3):327-332.
11. Meijneke TR, Petit SF, Wentzler D, et al. Reirradiation and stereotactic radiotherapy for tumors in the lung: dose summation and toxicity. *Radiother Oncol*. 2013;107(3):423-427.
12. Simone CB 2nd. New Era in Radiation Oncology for Lung Cancer: Recognizing the Importance of Cardiac Irradiation. *J Clin Oncol*. 2017;35(13):1381-1383.
13. Simone CB 2nd. Thoracic Radiation Normal Tissue Injury. *Semin Radiat Oncol*. 2017;27(4):370-377.
14. Vyfhuis MAL, Rice S, Remick J, et al. Reirradiation for locoregionally recurrent non-small cell lung cancer. *J Thorac Dis*. 2018;10(Suppl 21):S2522-S2536.
15. Tada T, Fukuda H, Matsui K, et al. Non-small-cell lung cancer: reirradiation for loco-regional relapse previously treated with radiation therapy. *Int J Clin Oncol*. 2005;10(4):247-50.
16. Okamoto Y, Murakami M, Yoden E, et al. Reirradiaton for locally recurrent lung cancer previously treated with radiation therapy. *Int J Radiat Oncol Biol Phys*. 2002;52(1):390-6.
17. Green N, Melbye RW. Lung cancer: retreatment of local recurrence after definitive irradiation. *Cancer*. 1982;49(5):865-8.
18. Montebello JF, Aron BS, Manatunga AK, et al. The reirradiation of recurrent bronchogenic carcinoma with external beam irradiation. *Am J Clin Oncol*. 1993;16(3):482-8.
19. Molitoris JK, Diwanji T, Snider JW 3rd, et al. Optimizing immobilization, margins, and imaging for lung stereotactic body radiation therapy. *Transl Lung Cancer Res*. 2019;8(1):24-31.
20. Cai G, Zhu J, Hu W, Zhang Z. Accelerated hyperfractionated intensity-modulated radiotherapy for recurrent/unresectable rectal cancer in patients with previous pelvic irradiation: results of a phase II study. *Radiat Oncol*. 2014;9:278.
21. Tao R, Tsai CJ, Jensen G, et al. Hyperfractionated accelerated reirradiation for rectal cancer: An analysis of outcomes and toxicity. *Radiother Oncol*. 2017;122(1):146-151
22. Youssef FF, Parikh PJ, DeWees TA, et al. Efficacy and toxicity of rectal cancer reirradiation using IMRT for patients who have received prior pelvic radiation therapy. *Adv Radiat Oncol*. 2016;1(2):94-100
23. Tao Y, Faivre L, Laprie A,et al.Randomized trial comparing two methods of re-irradiation after salvage surgery in head and neck squamous cell carcinoma:Once daily split-course radiotherapy with concomitant chemotherapy or twice daily radiotherapy with cetuximab. *Radiother Oncol*. 2018;128(3):467-471
24. Chang JY, Jabbour SK, De Ruysscher D, et al; International Particle Therapy Co-operative Group (PTCOG) Thoracic Subcommittee. Consensus statement on proton therapy in early-stage and locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2016;95(1):505-16.
25. Simone CB 2nd, Rengan R. The use of proton therapy in the treatment of lung cancers. *Cancer J*. 2014;20(6):427-32
26. Troost EGC, Wink KCJ, Roelofs E, et al. Photons or protons for reirradiation in (non-)small cell lung cancer: Results of the multicentric ROCOCO in silico study. *Br J Radiol*. 2020;93(1107):20190879.
27. Fischer-Valuck BW, Robinson CG, Simone CB 2nd, Gomez DR, Bradley JD. Challenges in Re-Irradiation in the Thorax: Managing Patients with Locally Recurrent Non-Small Cell Lung Cancer. *Semin Radiat Oncol*. 2020;30(3):223-231.
28. Simone CB 2nd, Plastaras JP, Jabbour SK, et al. Proton Reirradiation: Expert Recommendations for Reducing Toxicities and Offering New Chances of Cure in Patients With Challenging Recurrence Malignancies. *Semin Radiat Oncol*. 2020;30(3):253-261.
29. Chang JY, Zhang X, Knopf A, et al. Consensus Guidelines for Implementing Pencil-Beam Scanning Proton Therapy for Thoracic Malignancies on Behalf of the PTCOG Thoracic and Lymphoma Subcommittee. *Int J Radiat Oncol Biol Phys*. 2017;99(1):41-50.
30. Lin L, Kang M, Huang S, et al. Beam-specific planning target volumes incorporating 4D CT for pencil beam scanning proton therapy of thoracic tumors. *J Appl Clin Med Phys*. 2015;16(6):5678
31. Kang M, Huang S, Solberg TD, et al. A study of the beam-specific interplay effect in proton pencil beam scanning delivery in lung cancer. *Acta Oncol*. 2017;56(4):531-540.
32. Chang JW, Li H, Zhu XR, et al. Clinical implementation of intensity modulated proton therapy for thoracic malignancies. *Int J Radiat Oncol Biol Phys*. 2014;90(4):809-18.
33. Kesarwala AH, Ko CJ, Ning H, et al. Intensity-modulated proton therapy for elective nodal irradiation and involved-field radiation in the definitive treatment of locally advanced non-small-cell lung cancer: a dosimetric study. *Clin Lung Cancer*. 2015;16(3):237-44.
34. Zhang X, Li Y, Pan X, et al. Intensity-modulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: a virtual clinical study. *Int J Radiat Oncol Biol Phys*. 2010;77(2):357-66.
35. Register SP, Zhang X, Mohan R, et al. Proton stereotactic body radiation therapy for clinically challenging cases of centrally and superiorly located stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;80(4):1015-22.
36. Chun SG, Solberg TD, Grosshans DR, et al. The Potential of Heavy-Ion Therapy to Improve Outcomes for Locally Advanced Non-Small Cell Lung Cancer. *Front Oncol*. 2017;7:201
37. Hayashi K, Yamamoto N, Karube M, et al. Feasibility of carbon-ion radiotherapy for re-irradiation of locoregionally recurrent, metastatic, or secondary lung tumors. *Cancer Sci*. 2018;109(5):1562-1569
38. Verma V, Rwigema JM, Malyapa RS, et al. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. *Radiother Oncol*. 2017;125(1):21-30.
39. Veiga C, Janssens G, Teng CL, et al. First Clinical Investigation of Cone Beam Computed Tomography and Deformable Registration for Adaptive Proton Therapy for Lung Cancer. *Int J Radiat Oncol Biol Phys*. 2016;95(1):549-59.
40. Brooks ED, Zhang XD, De B, Chang JY. Dose-Toxicity Relationship Algorithm for Reirradiation: A Novel Tool for "How to Treat in a ‘No-Treatment’ Zone." American Society for Radiation Oncology Annual Meeting. 2020.
41. Kang S, Lang J, Wang P, et al. Optimization strategies for pulsed low-dose-rate IMRT of recurrent lung and head and neck cancers. *J Appl Clin Med Phys*. 2014;15:4661
42. Lin MH, Price RA Jr, Li J, et al. Investigation of pulsed IMRT and VMAT for re-irradiation treatments: dosimetric and delivery feasibilities. *Phys Med Biol*. 2013;58(22):8179-96.
43. Lin M, Price R, Koren S, et al. SU-E-T-383: Pulsed Low Dose Rate Radiotherapy Using Advanced Treatment Methods: A Novel Technique for Patient Re-Irradiation. *Med Phys*. 2012;39(6Part16):3792.
44. Favaudon V, Caplier L, Monceau V, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Sci Transl Med*. 2014;6(245):245ra93.
45. Griffin RJ, Limoli CL, Simone CB. Radiation Research Special Issue: New Beam Delivery Modalities are Shaping the Future of Radiotherapy. Radiat Res. 2020; ePub in press.