

Special topics in immunotherapy and radiation therapy: reirradiation and palliation

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Abstract: Immunotherapy has revolutionized the treatment of non-small cell lung cancer (NSCLC). However, thus far, its use has only been established in patients with advanced disease either as first-line therapy in selected patients or following chemotherapy. What is not yet known is how best to incorporate radiation with immunotherapy agents. Many patients with advanced disease can benefit from palliative radiation, but the combination of radiation with immunotherapy has the potential to increase the toxicity of both modalities. Intriguingly, the combination also has the potential to enhance the efficacy of both modalities. For this reason, combining immunotherapy and radiation may help salvage patients with recurrent localized disease who are candidates for re-irradiation. We review the current data evaluating immunotherapy with both palliative radiation as well as definitive re-irradiation in NSCLC.

Keywords: Immunotherapy; palliative; reirradiation; non-small cell lung cancer (NSCLC)

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Immunotherapy has revolutionized the treatment of non-small cell lung cancer (NSCLC). In advanced disease, inhibitors of the PD-1/PD-L1 pathway have proven superior to cytotoxic chemotherapy in all-comers in the second-line setting (1-3), and in patients with high expression of PD-L1 in the first-line setting (4). Also showing promise in lung cancer are CTLA-4 blocking antibodies (5). Not yet established is the proper way to incorporate these agents in earlier stages of NSCLC, nor do we completely understand how these agents can be used safely in conjunction with radiation. There is, nevertheless, evidence that radiation can enhance the efficacy of immune agents even outside of the radiation portal. This review focuses on what is known about the use of immunotherapy in concert with palliative radiation as well as what opportunities exist of the potential benefit of immunotherapy to assist in salvaging patients eligible for

definitive re-irradiation.

Palliative radiation and immunotherapy

Palliative radiation is a cornerstone of the treatment for patients with advanced, metastatic NSCLC. While this is clearly a systemic disease requiring a systemic approach, individual tumors causing local complications can negatively impact a patient's quality of life, and radiation may ameliorate many such local complications. Patients often require relief more quickly and reliably than our systemic treatments can provide. In addition, for central nervous system (CNS) disease, systemic approaches are less likely to be effective due to the blood brain barrier. Therefore, often in the treatment of metastatic NSCLC, there exists simultaneously a need to initiate radiation treatment along with a desire to embark on a proven-effective systemic

therapy without additional delay. Can radiation and immunotherapy be delivered together safely?

The toxicities of immunotherapy are, logically, immune-mediated (immune-related adverse events or irAE's). Generally, irAE's have been more severe with the anti-CTLA-4 monoclonal antibodies such as ipilimumab which is approved for the treatment of melanoma. The PD1/PD-L1 inhibitors such as the three currently approved for use in NSCLC (nivolumab, pembrolizumab, and atezolizumab) are generally less toxic. However, combinations of CTLA-4 and PD-1/PD-L1 agents are being actively explored in clinical trials in NSCLC. While adverse events related to immunotherapies are generally less common than what we are used to seeing with traditional cytotoxic chemotherapy, the most commonly observed toxicities include rash, thyroid and pituitary dysfunction, colitis, nephritis, hepatitis, and pneumonitis. Fatal cases of pneumonitis have occurred, and given this is an overlapping toxicity of radiation therapy to the chest, it represents a particular concern.

The pivotal randomized studies leading to the approval of the checkpoint inhibitors in NSCLC included strict instructions about the use of radiation. They also excluded patients with active brain metastases. In the study of first-line pembrolizumab *vs.* chemotherapy (Keynote 24), patients were ineligible if they had received thoracic radiation >30 Gy within 6 months of the first dose of study drug (6). In the second-line nivolumab studies, prior radiation or surgery must have been completed at least two weeks prior to randomization (1,2), and patients with interstitial lung disease were also excluded. Therefore, in the large prospective studies, radiotherapy was limited due to the concern for pneumonitis.

Pneumonitis risk of immunotherapy with thoracic radiation

Pneumonitis is one of the most feared complications of immunotherapy and early on was known to be a potential cause of death in treated patients (7). In a detailed retrospective review of 915 patients treated with anti-PD-1/PD-L1 monoclonal antibodies, 43 patients (5%) developed pneumonitis and 1% developed grade 3 or higher (8). Two hundred nine of the patients had NSCLC of which nine had pneumonitis. Sixty-one percent of the patients with pneumonitis had a RECIST response. The incidence of pneumonitis was higher in patients receiving combination immunotherapy (PD-1/PD-L1 inhibitor given in conjunction with anti-CTLA-4 mAb) versus those receiving

single agent (10% *vs.* 3%, $P < 0.01$), but there was no difference in pneumonitis rates between patients receiving PD-1 *vs.* PD-L1 inhibitors. The incidence was similar in patients with melanoma *vs.* NSCLC. The majority of patients developing pneumonitis [27/43 (63%)] had not received prior thoracic radiation, and pneumonitis was seen in both never smokers [19 of 43 (44%)] and current/former smokers [24 of 43 (56%)]. The median time to pneumonitis onset was 2.8 months (range, 9 days to 19.2 months) and occurred earlier in patients getting combination therapy (median 2.7 months, range, 9 days to 6.9 months) than monotherapy (4.6 months, range, 21 days to 19.2 months). The grade of pneumonitis was grade 1 in 40%, grade 2 in 33%, 23% grade 3, and one patient each (2%) experienced grade 4 and 5 toxicities. Dyspnea (53%), cough (35%), fever (12%) and chest pain (7%) were the most common presenting symptoms. The majority of grade 1/2 patients were managed as outpatients while 19% of the grade 2 and all of the higher grade patients were hospitalized. Treatment consisted of holding drug (which was the only approach in 88% of the grade 1 patients) and initiating corticosteroids (all patients with grade 2 or higher toxicity and 12% of the grade 1 patients). Five of 12 grade 3 patients received additional immunosuppression (infliximab in three and two with both infliximab and cyclophosphamide). The median starting dose of prednisone was 50 mg (range, 20 to 80 mg) and the median duration of corticosteroid treatment was 68 days (range, 20 to 154 days). Pneumonitis improved and resolved in 88% of patients. Five patients clinically worsened while on treatment and ultimately died, one of the pneumonitis itself, three due to infections related to immunosuppression, and one of progressive malignancy. These were the same five patients who received immunosuppression in addition to steroids. Twelve patients were rechallenged with immunotherapy following a complete resolution of their pneumonitis. Nine patients did not get recurrent pneumonitis, and of the three (25%) who did, one resolved with holding drug only and two others with corticosteroids.

In the above mentioned review of pneumonitis from immunotherapy, chest X-rays were not always diagnostic, showing possible pneumonitis in only six of nine cases. One X-ray was interpreted as showing progressive cancer and two had no reported new radiographic abnormality. Radiographic features of pneumonitis consisted of cryptogenic organizing pneumonia-like in 19%, ground glass opacities in 37%, interstitial (7%), hypersensitivity (22%) and not otherwise specified (15%). Eleven patients

underwent biopsy at time of pneumonitis diagnosis. Histopathologic findings included cellular interstitial pneumonitis (4/11), organizing pneumonia (3/11), diffuse alveolar damage (1/11), and no observed abnormalities (3/11). Of the five patients who did not improve, all were current smokers ($P=0.053$ vs. not current smokers) and four of them had underlying lung conditions ($P=0.047$).

In another series presented at ASCO 2016, 24 patients with NSCLC and pneumonitis from PD-1 or PD-L1 inhibitors were identified (9). Five had been treated in combination with an anti-CTLA4-Ab and one in combination with chemotherapy. The response rate across all patients was 50%. The median onset to pneumonitis was 75 days (range, 8–549 days). Nineteen patients were treated with steroids. All resolved to grade 0 or 1. Three types of radiographic patterns were noted: organizing pneumonia (consolidation with or without ground glass opacity in peripheral/peribronchovascular distribution) (52%), ground glass opacity (diffuse or focal GGO's) (28%), and nodular (perilymphatic or centrilobular nodules) (8%), while 12% had a mixed pattern. Transbronchial biopsies were done on 20 patients. All biopsied patients were found to have varying degrees of lymphocytic infiltrate, mainly T cells. Seven also had granulomas, and eight had eosinophils. CD8 cells predominated with a CD4/CD8 ratio of 0.46.

Of course, pulmonary toxicity in the form of radiation pneumonitis and radiation fibrosis are well-recognized dose limiting toxicities (DLTs) and common adverse events associated with radiation to the lung. Therefore, the combination of immunotherapy with radiation is a potential concern. The likelihood of radiation pulmonary toxicity is dependent on dose. Therefore, this is a greater concern for patients undergoing definitive radiation. Radiation pneumonitis generally occurs approximately 12 weeks following pulmonary irradiation and involves the accumulation of inflammatory cells within the interstitium (10). Concurrent traditional cytotoxic chemotherapy clearly increases the risk of pneumonitis. Risk factors for pneumonitis from radiation include treatment factors such as use of concurrent chemotherapy, radiation dose, volume of lung irradiated, and fractionation schedule. Also important are patient factors like poor pulmonary function, smoking status, and pre-existing lung disease.

Is it safe to administer palliative radiation to the lung simultaneous with currently approved immunotherapy? Unfortunately, data are limited. However, in a phase I study of ipilimumab in conjunction with stereotactic ablative radiation (SABR) therapy in patients with metastatic solid

tumors, fourteen patients had lung lesions radiated (11). None of the patients developed > grade 1 pneumonitis. However, one patient with a significant metastatic disease burden and a recent myocardial infarction died following the second ipilimumab dose and after two out of four planned fractions of lung SABR; cause of death was unknown, and the patient was not experiencing any treatment-related toxicity at the time of death. In another phase I study of patients with metastatic melanoma (12), patients received ipilimumab 3–5 days following SABR to an index lesion. In the 22 patients treated of whom 10 had lung lesions radiated (either 8 Gy \times 2 or 8 Gy \times 3), there were no DLTs observed. DLTs were defined as any treatment-related grade 4 or higher immune related toxicity during the study or within 30 days of the last dose of ipilimumab. These studies as well as other ongoing studies addressed below will hopefully provide better answers in the near future.

Radiation of brain metastases in patients on immunotherapy

Registration trials of immune therapies excluded patients with active brain metastases and thus far there have been no published data evaluating the pharmacokinetic or pharmacodynamic data within brain tissue to evaluate penetration into brain tissue or brain tumors (13). The treatment of brain metastases with systemic agents has been challenging due to the blood-brain barrier.

Theories as to how immune-oncology agents may treat brain tumors include disruption of the blood brain barrier (made up of endothelial cells, astrocytes, and pericytes) by the brain metastases themselves allowing for migration of agents into the perivascular space. This phenomenon is also seen with many chemotherapy agents that do not have much CNS penetration under normal circumstances, but nevertheless can lead to tumor response within the CNS (14). Another possibility is not that the drug itself enters the CNS, but that the T cells are activated peripherally and then are able to enter the CNS. Preclinical data in animals with brain tumors has shown improved survival for those treated with CTLA-4 and PD-1 blockade as well as with the combination (15–17).

Immunotherapy was initially approved in melanoma based upon a three-arm randomized trial in which the two ipilimumab arms (ipilimumab alone and ipilimumab with an experimental vaccine) demonstrated improved survival compared to the vaccine alone (18). Because of this and

the propensity of melanoma to spread to the brain, much of the data for use of radiation to the brain in combination with immunotherapy has been in melanoma. Multiple studies have demonstrated the efficacy of ipilimumab in the treatment of brain metastases from melanoma with response and disease control rates similar (range, 19–55%) to those seen systemically, suggesting the blood-brain barrier is actually not much of a “barrier” (19–21). In a study of pembrolizumab in patients with untreated brain metastases from either NSCLC or melanoma, 6 of 18 (33%) of the patients with lung cancer and four out of 18 (22%) of the patients with melanoma experienced responses in the brain (22).

Nevertheless, these results are not as good as what are typically seen with stereotactic radiosurgery (SRS) for the treatment of brain metastases (23), and progressive disease within the brain can cause significant morbidity and mortality (19). Therefore, the combination of radiation therapy and immunotherapy may be required for more reliable durable control. In a series of 77 patients with metastatic melanoma with brain metastases all of whom were treated with SRS to the brain and 27 additionally received ipilimumab, the ipilimumab group had a 21.3 months median survival *vs.* 4.9 months (24). In another study of 25 patients with melanoma brain metastases treated with SRS and ipilimumab *vs.* 33 treated with SRS alone, no benefit in overall survival (OS) was observed (25). A third study also showed a survival advantage for those patients undergoing ipilimumab in addition to SRS for brain metastases, though there were prognostic imbalances in the study favoring the immunotherapy arm (26). Symptomatic radiation necrosis has been noted in patients treated with a combination of immunotherapy and SRS. Case series have suggested a connection (27,28), though in randomized comparisons it is not clear that the rates are any higher than with SRS alone.

The abscopal effect for palliation

One attractive potential advantage of delivering palliative radiation to patients with metastatic disease is the hope of eliciting an abscopal effect. This means causing a response in tumors distant from the radiated lesion (Ab-scopus is Latin for “away from the target”). Radiation therapy may serve to act as an *in situ* vaccine. Release of tumor antigens during radiation therapy may prime the immune system to act on disease outside the radiation portal, leading to the abscopal

effect (29). This rare phenomenon has been observed prior to the advent of immunotherapy. Patients who have previously progressed on immunotherapy have been shown to have a systemic response following administration of local radiation (30). In mouse models, the abscopal effect is only observed in the presence of a functioning immune system (31,32). There are many theories as to why radiation would lead to such a phenomenon. Radiation induces upregulation of immunogenic cell surface markers (33–35). Radiation-induced inflammation can cause secretion of cytokines as well as infiltration of tumor-specific T cells through vascular normalization (36,37). Radiation can also lead to the destruction of potentially immunosuppressive stromal cells. It may also lead to improved T cell extravasation and homing to tumors (37) and radiation therapy can directly upregulate the PD-1/PD-L1 pathway (38). Case reports exist where it appears that immunotherapy can enhance an abscopal effect when radiation is delivered along with it (30).

Ongoing studies in palliative radiation therapy and immunotherapy

Table 1 depicts studies that are anticipated or currently open which combine radiation therapy and immunotherapy in lung cancer. An exploration of these studies demonstrates that a variety of radiation regimens and immunotherapy agents are recommended, and that the endpoints range from safety to response rate to survival outcomes such as PFS. It is also clear given the large number of trials that within the next 5–10 years, much more will be known about the combination of these two modalities, including in the context of palliative radiation. As one example, a recent study examined the safety, efficacy, and immunologic correlates from peripheral T cells with the combination of ipilimumab and SABR to the liver or lung. Of the 35 patients in this trial, the authors found that the rate of grade 3 or higher toxicity was 40%. Approximately 25% of patients experienced what was defined as a “clinical benefit”, a partial response or stable disease at least 6 months in duration. Several T cell markers were found to be associated with a clinical benefit, including increases in CD8+ cells, CD8+/CD4+ T-cell ratio, and the proportion of CD8+ T cells that expressed 4-1BB and PD1 (11). The study suggests that toxicity with this combination regimen needs to be closely monitored, and therefore that much data is needed regarding the frequency and relevance of the abscopal effect with this paradigm.

Table 1 Ongoing studies of radiation plus immunotherapy

Regimen	Study	Status	Phase	Primary objective	Sponsor
Pembrolizumab, nivolumab or atezolizumab and hypofractionated radiation therapy	Use of Response-Adapted Hypofractionated Radiation Therapy to Potentiate the Systemic Immune Response to Checkpoint Inhibitors in Non-Small Cell Lung Cancer	R	NR	ORR	West Virginia University
Nivolumab ± ipilimumab and radiation	Phase I/II Trial of Nivolumab With Radiation or Nivolumab and Ipilimumab With Radiation for the Treatment of Intracranial Metastases From Non-Small Cell Lung Cancer	R	1/2	RP2D	M.D. Anderson Cancer Center
Atezolizumab and stereotactic body radiation therapy	A Phase I Trial of an Immune Checkpoint Inhibitor Plus Stereotactic Ablative Radiotherapy in Patients With Inoperable Stage I Non-Small Cell Lung Cancer	R	1	Incidence of adverse events, RR, PFS	University of California, Davis
MPDL3280A and stereotactic ablative radiotherapy	Pilot Study of MPDL3280A Plus Stereotactic Ablative Radiotherapy (SAR) in Stage IV Non-small Cell Lung Cancer	R	1	Incidence of adverse events, RR, PFS	University of California, Davis
Atezolizumab and stereotactic ablative radiotherapy	A Phase II Study to Assess the Efficacy of the Anti-PD-L1 Antibody Atezolizumab (MPDL3280A) Administered With Stereotactic Ablative Radiotherapy (SABR) in Patients With Metastatic Tumours	R	2	PFS	Gustave Roussy, Cancer Campus, Grand Paris
MPDL3280A and HIGRT	A Pilot Study of MPDL3280A (PD-L1) Antibody Therapy and Hypofractionated Image-guided Radiotherapy (HIGRT) in Patients With Metastatic Non-Small Cell Lung Cancer	R	1	ORR	University of Michigan Cancer Center
Nivolumab and hypofractionated radiation therapy	ImmunoRad: Stratified Phase II Trial of Image Guided Hypofractionated Radiotherapy With Concurrent Nelfinavir and Nivolumab in Advanced Melanoma, Lung Cancer, and Renal Cell Carcinoma	NYR	2	Safety, tolerability, ORR	University of Washington
Ipilimumab + nivolumab and thoracic radiotherapy	Consolidative Ipilimumab and Nivolumab With Thoracic Radiotherapy After Platinum Based Chemotherapy for Patients With Extensive-Stage Small Cell Lung Cancer	R	1/2	RP2D, PFS	H. Lee Moffitt Cancer Center and Research Institute
Nivolumab and stereotactic body radiation plus gene therapy	ENSIGN: Phase II Window of Opportunity Trial of Stereotactic Body Radiation Therapy and In Situ Gene Therapy Followed by Nivolumab in Metastatic Squamous or Non-Squamous Non-Small Cell Lung Carcinoma	R	2	ORR	The Methodist Hospital System
Nivolumab and radiotherapy	Fostering Efficacy of Anti - PD-1 - Treatment: Nivolumab Plus Radiotherapy in Advanced NSCLC	NYR	2	ORR	AIO-Studien-gGmbH
Nivolumab and radiosurgery	A Phase II, Multi-centre Study, of Combining Radiosurgery and Nivolumab in the Treatment of Brain Metastases From Non-small Cell Lung Cancer and Renal Cell Cancer	NYR	2	Intracranial PFS	Centre hospitalier de l'Université de Montréal (CHUM)
MK-3475 and hypofractionated stereotactic radiation therapy	Phase I/II Trial of MK-3475 and Hypofractionated Stereotactic Radiation Therapy in Patients With Non-Small Cell Lung Cancer (NSCLC)	R	1/2	MTD	M.D. Anderson Cancer Center

Table 1 (continued)

Table 1 (continued)

Regimen	Study	Status	Phase	Primary objective	Sponsor
MK-3475 and concurrent chemo/radiation	Phase I Trial of MK-3475 and Concurrent Chemo/Radiation for the Elimination of Small Cell Lung Cancer	R	1	MTD	M.D. Anderson Cancer Center
Pembrolizumab and chemotherapy with or without radiation	A Phase II Study of Pembrolizumab and Dynamic PD-L1 Expression in Extensive Stage Small Cell Lung Cancer (SCLC)	NYR	2	Change in PD-L1 expression status	New York University School of Medicine
MK-3475 and radiation therapy	An Exploratory Study to Investigate the Immunomodulatory Activity of Radiation Therapy (RT) in Combination With MK-3475 in Patients With Recurrent/Metastatic Head and Neck, Renal Cell Cancer, Melanoma and Lung Cancer	R	1	Change in PD-L1 levels	Sidney Kimmel Cancer Center at Thomas Jefferson University
Pembrolizumab and single fraction non-ablative radiation	A Phase II Trial of Pembrolizumab Sequentially Following Single Fraction Non-ablative Radiation to One of the Target Lesions, in Previously Treated Patients With Stage IV NSCLC	NYR	2	ORR	Case Comprehensive Cancer Center
Pembrolizumab and SBRT	Randomized Phase II, 2-arm Study of Pembrolizumab After High Dose Radiation (SBRT) Versus Pembrolizumab Alone in Patients With Advanced Non-small Cell Lung Cancer	R	2	ORR	The Netherlands Cancer Institute
Pembrolizumab and stereotactic	Pilot Study of Pembrolizumab and Stereotactic Radio-Surgery (SRS) for Patients With Melanoma or Non-Small Cell Lung Cancer (NSCLC) Brain Metastases (BM)	R	1	Proportion of dose limiting toxicities	Emory University
Pembrolizumab SBRT and oncolytic virus therapy	Phase II Window of Opportunity Trial of Stereotactic Body Radiation Therapy and In Situ Oncolytic Virus Therapy in Metastatic Triple Negative Breast Cancer and Metastatic Non-Small Cell Lung Cancer Followed by Pembrolizumab	NYR	2	ORR	The Methodist Hospital System
MK-3475 and stereotactic body radiotherapy	A Phase I/II Trial of Evaluating the Combination of MK-3475 and Stereotactic Body Radiotherapy in Patients With Metastatic Melanoma or NSCLC	R	1/2	ORR	Yale University
Pembrolizumab and stereotactic body radiotherapy	Phase I Study of PD1 Blockade by Pembrolizumab With Stereotactic Body Radiotherapy in Advanced Solid Tumors	R	1	SBRT dose	University of Chicago
Pembrolizumab and palliative radiotherapy	Phase I Dose Escalation of Palliative Radiotherapy With Anti-PD1 Antibody Pembrolizumab in Thoracic Tumours	R	1	Toxicity rate of DLTs, MTD	Royal Marsden NHS Foundation Trust
Consolidation pembrolizumab after concurrent chemotherapy and proton reirradiation	Phase II Trial of Consolidation Pembrolizumab after Concurrent Chemotherapy and Proton Reirradiation for Thoracic Recurrence of Non-Small Cell Lung Cancer	NYR	2	PFS	University of Pennsylvania
Ipilimumab and ionizing radiation	Phase II Study of Combined Ionizing Radiation and Ipilimumab in Metastatic Non-small Cell Lung Cancer (NSCLC)	C	2	irRC best response	New York University School of Medicine
Ipilimumab and stereotactic body radiation therapy (SBRT) in advanced solid tumors	Phase I/II Trial of Ipilimumab (Immunotherapy) and Hypofractionated Stereotactic Radiation Therapy in Patients With Advanced Solid Malignancies	R	1/2	MTD	M.D. Anderson Cancer Center

R, recruiting; RP2D, recommended phase 2 dose; RR, response rate; PFS, progression free survival; ORR, overall response rate; NYR, not yet recruiting; MTD, maximum tolerated dose; DLTs, dose limiting toxicities, C, completed; irRC, immune-related response criteria.

Reirradiation and immunotherapy

Locoregional recurrence (LRR) remains a leading cause of death in lung cancer (39,40). Therefore, the primary option in this clinical context has historically been systemic therapy, but response rates for salvage chemotherapy are typically low (41,42). Consequently, due in part to technologic advancements in radiation therapy, in the past several years, there has been increasing interest in reirradiation. There are two primary scenarios that pertain to reirradiation in the setting of locoregionally recurrent diseases (LRRs). The first is in the context of lung parenchymal recurrences, in which SABR is an option. The second pertains to LRRs involving critical structures such as the mediastinum, in which conventionally fractionated radiation (\pm chemotherapy) are the only feasible option if the intent is definitive.

SABR as reirradiation for parenchymal recurrence

There have been several reports of SABR alone for this indication. Overall, these trials have shown that treatment is tolerated well and with promising short-term control rates. For example, in one study of 278 patients, 26 (29 tumors) were treated with SABR for recurrent disease. One- and 2-year progression-free survival rates were 56% and 37%, respectively, with no grade 3 or higher toxicities (43). In a publication from Memorial Sloan-Kettering Cancer Center, 39 patients previously treated with conventionally fractionated radiation were then retreated with SABR for either recurrent primary or metastatic disease. Median recurrence-free survival and OS rates were 13.8 and 22.0 months, respectively, and patients without overlap in the high dose regions had both higher biologically effective doses as well as better control rates. In this study, grade 3 toxicity was approximately 20% (44). Finally, a report from MD Anderson Cancer Center assessing the role of SABR and measuring the rate of toxicity and control in centrally/superiorly located or isolated recurrent NSCLC showed that, while in-field control rate was 100%, 20% of patients developed mediastinal nodal recurrence and an additional 35% eventually had distant metastases. Of note, one patient with an apical tumor did develop brachial plexopathy, and 11% of other patients had grade 2–3 chest wall pain (45).

Standard fractionated reirradiation for LRR

There are also several reports of reirradiation outside of the context of SABR (46–52), but most are limited by

their retrospective nature, small patient numbers, and heterogeneity in diagnosis, treatment intent, and radiation dose/fractionation regimens. In particular, reports of definitive locoregional radiation for curative intent using advanced techniques in the reirradiation setting are sparse, and a brief examination of the literature demonstrates these limitations. A recent study from Japan examined 21 patients treated with both NSCLC and SCLC who had LRR and an overlap of prior dose distributions at the 80% dose level. The median time from initial course to reirradiation was 26.8 months, and the median dose of reirradiation was 60 Gy in 2 Gy equivalents. The authors reported median local PFS to be 12.9 months, with a median OS time of 31.9 months. There was only one grade 3 or higher complication, radiation pneumonitis, leading the authors to conclude that the regimen appeared safe. Interestingly, patients treated to a dose of ≥ 60 Gy had improved local PFS (53). In another study, 24 patients were identified who received standard fractionated therapy both for the initial disease and at the time of LRR. The median dose at initial treatment was 59.8 Gy, and at reirradiation was 60 Gy in 2 Gy fractions. The median interval between courses of radiation was 51 months, and median OS after reirradiation was 13.5 months. The median survival at 1 year was 51%. Toxicity was non-negligible, with 3/24 patients possibly experiencing a grade 5 adverse event (bleeding) (54).

Investigators from MD Anderson Cancer Center recently published the largest series of retrospective and prospectively analyzed patients. In this study, 102 patients underwent reirradiation with intensity modulated radiation therapy (IMRT) or proton beam therapy (PBT) for intrathoracic recurrent NSCLC and were not candidates for SABR. The authors found that median local failure-free survival (LFFS), distant metastasis-free survival (DMFS), and OS times were 11.4 months (range, 8.6–22.6 months), 11.4 months (range, 6.3–23.8 months), and 14.7 months (range, 10.3–20.6 months), respectively. Notably, of the patients who developed local failure after reirradiation, 88% occurred within the original or reirradiation field. Squamous cell cancer (SCC) histology and T4 disease at the time of reirradiation were associated with reduced local control. Toxicity was acceptable, with a <10% rate of grade ≥ 3 toxicity. The authors concluded that IMRT and PBT appeared to be feasible options for treating recurrent NSCLC, though local failure and distant metastasis were still common, and that the overall benefit compared to systemic therapy was questionable. Furthermore, patients

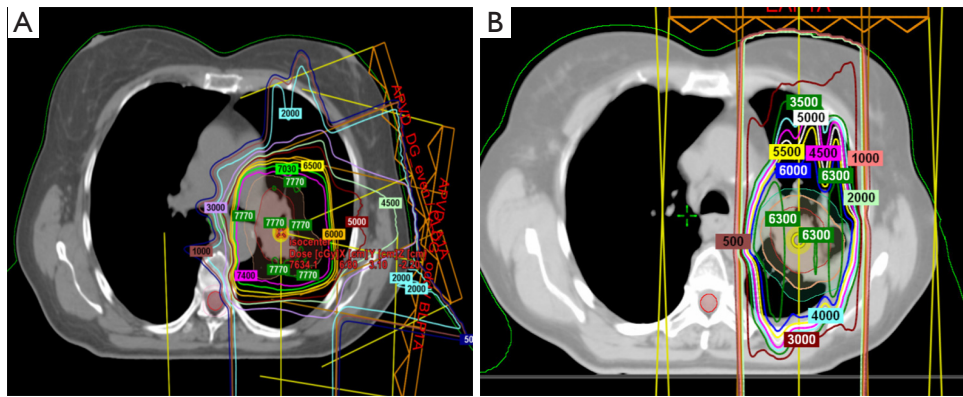


Figure 1 Standard fractionated reirradiation course in a patient with locoregionally recurrent non-small cell lung cancer (NSCLC). (A) demonstrates the initial course and (B) the reirradiation course. It is evident that there is overlap on multiple critical structures, including the bronchus, vessels, lung, and chest wall. Note that the second course was delivered with proton beam therapy (PBT), to achieve optimal dose falloff in this context.

in which at least 6 months had elapsed since the initial course of radiation had superior survival outcomes. Finally, the authors concluded that randomized trials are needed to more definitively address the role of reirradiation in this scenario (47). *Figure 1* depicts the isodose curves from a patient that is reported in this study, with both the initial course and reirradiation course. Note that in the reirradiation setting proton therapy was utilized to achieve maximum dose falloff given the proximity of several critical structures, and that with this approach the esophagus was entirely spared in the reirradiation plan.

Proton reirradiation for LRR

The University of Pennsylvania recently published data from a prospective trial studying the potential toxicities of proton reirradiation for local recurrences of NSCLC (55). Proton therapy has been utilized as a potential strategy to minimize harm to surrounding tissues while treating thoracic tumors aggressively. Therefore proton therapy is ideally suited to minimize toxicities in the reirradiation setting. This multi-institutional trial included 57 patients with recurrent NSCLC in or near their prior radiation field. Ninety-three percent of patients completed the reirradiation course. Sixty-seven percent received concurrent chemotherapy. Patients with high tumor volume (clinical target volume-to-internal target volume ratio $\geq 250 \text{ cm}^3$) were closed to enrollment owing to infeasibility. The 1-year rates of overall and progression-free survival were 59% and 58%, respectively. In total, grade 3 or

higher acute and/or late toxicity developed in 24 patients (42%), acute toxicity developed in 22 (39%), and late toxicity developed in seven (12%). Six grade 5 toxicities were observed. Increased overlap with the central airway region, mean esophagus and heart doses, and concurrent chemotherapy were associated with significantly higher rates of grade 3 or higher toxicity. Decreased OS was seen with increased mean esophagus dose ($P=0.007$). While proton reirradiation was deemed feasible in the low tumor volume setting, given the observed toxicities, the authors cautioned providers to consider tumor volume, location, and relevant dosimetric parameters when selecting patients for treatment with this modality.

Conclusions of reirradiation and proposed algorithm for evaluation

The primary conclusions that can be drawn by the current reirradiation literature in thoracic malignancies are as follows. First, while in principal there may be a benefit to targeting recurrent localized disease with radiation therapy, the evidence supporting reirradiation in this setting is evolving, without strong comparative effectiveness data demonstrating superiority of reirradiation compared to second-line systemic therapy. Second, reirradiation in the context of parenchymal recurrences is stronger than that of standard fractionated radiation with mediastinal relapse, with retrospective trials demonstrating higher control rates and lower toxicity with stereotactic treatment when feasible (e.g., without exceeding critical structure constraints at

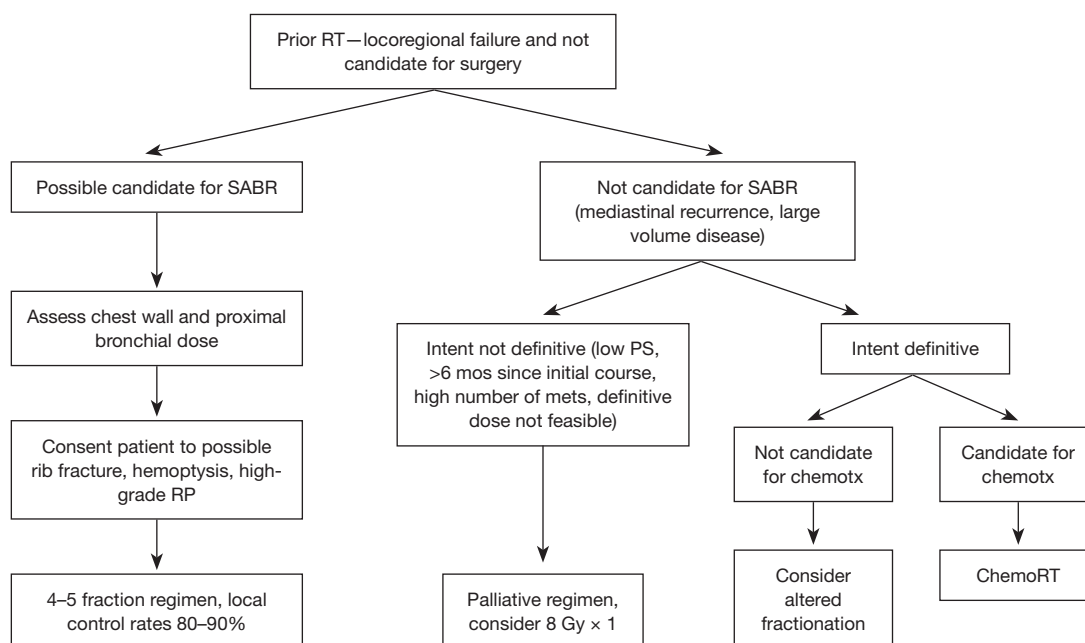


Figure 2 Proposed algorithm for the evaluation of patients with locoregional recurrence (LRR) after previous in-field high dose radiation therapy.

hypofractionated doses).

Figure 2 presents one algorithm that can be used in approaching a patient with LRR who has previously received high dose radiation. Pertinent decision points are the feasibility of SABR, the role of chemotherapy in conjunction with radiation, and patient/disease characteristics that would preclude definitive treatment given the high potential toxicity, including performance status, time since initial course of radiation (with 6 months being a reasonable cutoff as noted above), and the absence or presence of distant metastases. Of note, many patients may be candidates for a palliative course of reirradiation rather than a definitive course, and the regimen of 8 Gy \times 1 has been shown to provide “safe, effective, and durable pain palliation” for patients who had previously received concurrent chemoradiation to a total dose of 52–66 Gy (56). Three additional guiding principles can also be used in this context. First, if a surgical option is present, it should strongly be considered. Second, when there is overlap with prior radiation fields, patients should be consented to high-grade and even fatal toxicity such as radiation pneumonitis, esophageal fistula, bronchial stricture/fistula, and grade 5 bleeding. Finally, the best context for reirradiation is in a clinical trial when available.

The role of immunotherapy and reirradiation clinical trials

There is a clear role for immunotherapy to enhance the efficacy of reirradiation. As systemic therapies improve, the observed incidence of isolated LRR is likely to continue to increase. Furthermore, patients treated with reirradiation appear to have a higher potential for both local recurrence (due to established radioresistance) as well as systemic failure (due to aggressive disease), and the addition of immunotherapy could potentially improve both of these endpoints. In an ideal scenario, high dose reirradiation would reduce the rate of local progression, while the abscopal effect of combined modality treatment would improve the rate distant metastases. The University of Pennsylvania opened a phase II study of consolidation pembrolizumab after concurrent chemotherapy and proton reirradiation for thoracic recurrences of NSCLC. There are several unanswered questions. First, will the risk of toxicities such as pneumonitis and cardiac toxicity (5,57) with both checkpoint inhibitors and radiation preclude combination of these agents? Second, what is the optimal timing of immunotherapy in relation to reirradiation (neoadjuvant, concurrent, adjuvant)? Third, what is the role of standard systemic therapy and other targeted treatments in this

paradigm? Fourth, will the addition of immunotherapy allow for a dose reduction in radiation, thereby reducing the risk of exceeding dose thresholds to the lung and mediastinal structures? And finally, how much, if any, will the combination treatment improve survival outcomes, and will this differ with SABR *vs.* conventionally fractionated radiation? Prospective, and ideally randomized, trials addressing these questions would be of great utility.

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Footnote

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