



Combining stereotactic body radiation therapy with immunotherapy: current data and future directions

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Abstract: Stereotactic body radiation therapy (SBRT) offers excellent local control of early-stage non-small cell lung cancer (NSCLC), but there currently is a need for tolerable systemic therapy to address regional and distant disease progression. One potential option is immunotherapy, which in metastatic NSCLC has shown promise for sustained disease control in a subset of patients. There is also growing evidence for a clinical synergy between radiation and immunotherapy, with several ongoing trials studying the abscopal effect. This review summarizes the current data in the fast-changing field of immuno-radiation therapy, highlighting updates from recent clinical trials.

Keywords: Stereotactic body radiation therapy (SBRT); stereotactic ablative radiotherapy; immunotherapy; checkpoint inhibitor; lung cancer

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Introduction

Stereotactic body radiation therapy (SBRT) combines conformal radiation dose-shaping, tumor motion management, and on-board daily imaging to deliver high doses of radiation in five or fewer treatments (1,2). These technological advances in radiation delivery over the last decade have allowed safer and more effective dose escalation to patients with non-small cell lung cancer (NSCLC). For early-stage, medically non-operable NSCLC, SBRT has become the standard of care (3). RTOG 0236 established SBRT could achieve an impressive 5-year tumor control rate of 93% (4,5), with minimal pulmonary toxicity (6).

However, systemic progression remains problematic. Regional and distant failure rates occur in at least 30% of patients, with even higher rates with increasing tumor size (5,7-11). Medically inoperable patients often cannot safely receive adjuvant chemotherapy to help with distant control. Immunotherapy, which is better tolerated than

chemotherapy (12), has recently been heralded as the “fourth pillar” of oncologic treatment (13). Food and Drug Administration (FDA)-approved antibody drugs currently target cytotoxic T-lymphocyte protein 4 (CTLA-4), programmed cell-death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). Activation of CTLA-4 and PD-1 receptors on T cells downregulates the adaptive immune response. This prevents auto-immunity, but checkpoint inhibition can also be hijacked by tumors seeking to avoid immune surveillance (14). By targeting these checkpoint inhibitors, immunotherapy has the potential to take the brakes off one’s own immune system to seek out and destroy cancer cells.

Immunotherapy has had mixed success in the locally advanced and metastatic NSCLC setting. Nivolumab, a PD-1 inhibitor, was compared in a phase 3 trial to platinum-based chemotherapy for metastatic or recurrent NSCLC with PD-L1 expression $\geq 5\%$ (15). There was no difference in progression-free survival (PFS) or overall survival

(OS), but patients tolerated nivolumab better (grades 3–4 adverse event 18% vs. 51%). Similarly, ipilimumab, a CTLA-4 inhibitor, did not improve PFS or OS when added to carboplatin/paclitaxel in metastatic NSCLC (16). In contrast, KEYNOTE 24 tested pembrolizumab, a PD-1 inhibitor, compared to platinum-based chemotherapy in metastatic NSCLC patients with tumor PD-L1 expression $\geq 50\%$, and both PFS and OS were significantly improved with a 45% response rate (17). The PACIFIC trial tested adjuvant durvalumab, a PD-L1 inhibitor, against placebo after definitive chemoradiation for stage III NSCLC (18). Durvalumab significantly improved median PFS from 5.6 to 16.8 months. The PFS benefit was seen even when the tumor had PD-L1 expression $< 25\%$. Atezolizumab, also a PD-L1 inhibitor, improved OS compared to docetaxel in metastatic NSCLC regardless of PD-L1 expression (19). The overall success of checkpoint inhibitors is tempered by the variable response rate, which may be improved upon when combined with radiation therapy. Several excellent reviews on this subject have been recently published and we refer you to them for additional references (20–24). In this fast-changing field of immuno-radiation therapy, we will highlight updates from ongoing clinical trials and offer our perspective for future trials.

Rationale for combining SBRT with immunotherapy

SBRT tumor debulking may improve immunotherapy response. A recent publication in 29 patients with stage IV melanoma treated with pembrolizumab found 74% of patients had an immunologic response seen in peripheral blood draws, but only 38% achieved a radiographic clinical response (25). Using Ki-67 as a marker of proliferation of PD-1+ T cells, the authors measured the Ki-67 percentage cell staining to tumor burden (sum of the long-axis of all measurable lesions) ratio after patients received pembrolizumab. A ratio > 1.9 was associated with improved response and OS. One rationale for tumor debulking lies in T cell exhaustion, a phenomenon whereby inhibitory signals from the tumor overwhelm T cell activation (26). In patients with limited or oligometastatic disease, SBRT could reduce the tumor burden and allow re-invigorated T cells to find and destroy micrometastatic disease.

Radiation has also been shown to upregulate immunogenic cell surface markers. MHC class I is a molecule that presents intracellular antigens to the cell surface for T cells to recognize foreign peptides.

Their expression is down-regulated in tumors to evade immune recognition (20). Reits *et al.* were able to show that radiation increases MHC class I expression in a dose dependent manner, and mice exposed to both radiation and immunotherapy had a prolonged tumor response compared to mice receiving either therapy alone (27). Calreticulin and HMGB1 are other antigen-presenting proteins that have been found to be upregulated by radiation (28). Thus, radiation may synergize with immunotherapy by helping unmask tumor antigens.

Radiation can also engage the innate immune system. FAS is a death receptor that catalyzes the apoptotic cascade when it encounters FAS ligand, found on activated T cells. Chakraborty *et al.* found that one 8 Gy dose of radiation upregulated FAS on tumor cells *in situ* for up to 11 days and increased T cell infiltration and killing (29). Natural killer cells can also be alerted to kill tumor cells by radiation-induced NKG2D expression (30). There is thus a halo effect, where tumor cells primed to be recognized by undergoing apoptosis after radiation are engulfed in an overwhelming immune response from neighboring activated immune cells.

Radiation, unfortunately, is a double-edged sword. Prolonged fractionated radiation courses to large vascular volumes have been shown to deplete circulating lymphocytes in all body sites, sometimes up to a year after radiation (31–34). Lymphocytes are among the most radiosensitive cells in the body, with *in vitro* data showing 50% cell killing after 2 Gy and 10% cell killing after 0.5 Gy (35). In locally advanced lung cancer, both cumulative lung and heart dose were associated with worsening lymphopenia and poor survival (34,36). Hypofractionation or SBRT could potentially reduce this iatrogenic immunosuppression by limiting the blood pool volume exposed to daily low-intermediate dose radiation (37,38). Furthermore, radiation up-regulates cell surface PD-L1 expression (39), which by itself can limit the immunogenic cell death desired for optimal local control. However, Deng *et al.* has shown blockade of PD-L1 after irradiation diminishes the infiltration of tumor suppressor cells (39), further rationalizing the combination of hypofractionated radiation with checkpoint inhibitors.

The abscopal effect is a much-discussed hope of many radiation oncologists. Simply put, can we radiate a tumor and create anti-tumor effects outside of the irradiated field? The mechanism of the abscopal effect is hypothesized to be immune-mediated. Tumor-specific antigens revealed by irradiation need to be recognized and picked up by

dendritic cells, which then activate T cells at neighboring lymph nodes (40). Efforts to understand and exploit the abscopal effect have ramped up since checkpoint inhibitors were found to have increased immunomodulatory activity compared to activating cytokines (e.g., IL-2) and infusions of activated immune cells. However, it is still unclear what the optimal radiation dose, fractionation schedule, and timing with immunotherapy is to induce an abscopal effect. Most pre-clinical studies have used single dose or hypofractionated courses with large (≥ 6 Gy) doses per fraction (40). In order to better study this, clinically relevant models of cancer development beyond orthotopic tumor models need to be developed.

Clinical data combining radiation with immunotherapy

The introduction of immunotherapy for metastatic cancer treatment has corresponded with increasing clinical case reports of the abscopal effect. Reynders *et al.* compiled data from 23 case reports, in an effort to generate momentum in studying this phenomenon (41). Radiation dose and fractionation varied, ranging from 14.4 Gy in 12 fractions to 18–26 Gy in a single fraction. Time to documented abscopal response ranged between less than 1 and 24 months, with a median reported time of 5 months. Once an abscopal response was achieved, a median time of 13 months went by before disease progression occurred or the reported follow-up ended (range, 3–39 months). Of four reported cases of abscopal effect in a patient with a primary lung tumor, two were in combination with immunotherapy.

The combination of immunotherapy and radiation therapy has been studied more systematically in the metastatic setting as well. A secondary analysis of 98 metastatic NSCLC patients treated on the phase 1 KEYNOTE-001 pembrolizumab trial from the University of California, Los Angeles found that PFS [hazard ratio (HR) =0.56, 95% confidence interval (CI), 0.34–0.91] and OS (HR =0.58, 95% CI, 0.36–0.94) were improved in patients that had received any prior radiation (43%) (42). There was no difference in positive PD-L1 status in patients receiving prior radiation *vs.* not (71% *vs.* 80%, respectively, $P=0.75$). Of the patients receiving prior radiation, 91% was to extracranial sites; 74% was delivered with palliative intent; SBRT was used in 29% of cases. However, the group with prior radiation had been exposed to more lines of systemic therapy ($P=0.02$) and time from diagnosis to starting pembrolizumab was longer (26 *vs.* 17

months, $P=0.04$).

Similarly, a retrospective analysis of 164 metastatic NSCLC patients treated with PD-1/PD-L1 inhibitors from Massachusetts General Hospital compared outcomes in patients receiving thoracic radiation ($n=73$) or not ($n=91$) (43). Most patients were treated with a definitive radiation dose (median 60 Gy, range, 44–79.1 Gy), and the median time to checkpoint inhibitor initiation after radiation was 8.6 months. In multivariable analysis, the thoracic radiation group trended to improved OS (HR =0.66, 95% CI, 0.42–1.01) despite including fewer favorable adenocarcinoma patients (49% *vs.* 75%, $P=0.001$) with targetable mutation (4% *vs.* 16%, $P=0.01$). Thus, the two prior studies suggest there may be clinical synergy between checkpoint inhibitors and radiation therapy.

In an interesting retrospective study from China, outcomes of patients with a variety of advanced malignancies receiving SBRT combined with adoptive immunotherapy were better than outcomes of patients receiving SBRT alone (44). In the study, re-injection of the patient's own interferon-activated monocytes combined with SBRT improved the total response rate (RECIST partial or complete response) compared to SBRT alone (66.8% *vs.* 60.2%, $P<0.05$). A median total dose of 43 Gy (range, 18–65 Gy) given in 4–18 Gy per fraction was prescribed. However, this was a heterogeneous group of patients and tumor response outside of the irradiated field was not specified, which limits interpretation and generalization for this review.

The first phase I–II prospective trial combining SBRT with immunotherapy was updated last year. Tang *et al.* from MD Anderson Cancer Center designed a trial testing concurrent *vs.* sequential ipilimumab (4 cycles every 3 weeks, 3 mg/kg) and SBRT (50 Gy in 4 fractions or 60 Gy in 10 fractions) targeted to liver or lung metastases. In the phase I portion, 7/31 (23%) had clinical benefit, either a partial response (3 patients) or stable disease lasting more than 6 months (4 patients) outside the irradiated field, but 34% of patients experienced grade 3 toxicity (most commonly colitis, liver toxicity, and a maculopapular rash). Liver SBRT produced greater T cell activation, which was associated with clinical benefit (45). In the phase 2 update at the 2017 American Society for Radiation Oncology (ASTRO) annual conference, 100 patients had been enrolled. Clinical benefit, defined as stable disease or response, was seen in 67% of patients with NSCLC. Stable disease was seen in 60% of the sequential 60 Gy group, 50% of the sequential 50 Gy lung group, 45% of the

concurrent 50 Gy lung group, 35% of the concurrent 50 Gy liver group, and 30% of the sequential 50 Gy liver group. In contrast to the phase I results, patients who received sequential radiation to lung metastases rather than to liver metastases had better PFS ($P=0.055$, 95% CI, 3.7–6.4) and OS ($P=0.059$, CI, 7.9–20.0). No differences were found between the concurrent lung or liver groups for PFS ($P=0.2$) or OS ($P=0.3$) (46).

Most recently, the University of Chicago published a phase I study of multisite SBRT followed by pembrolizumab in metastatic solid tumor patients (47). Two to four metastases (94.5% were two metastases) were targeted with SBRT to 30–50 Gy in 3–5 fractions, and pembrolizumab 200 mg every 3 weeks was initiated 7 days after completion of SBRT. The cohort of 73 patients was heavily pre-treated, with a median of five prior therapies. Out of 151 metastases irradiated, 68 were in the lung, 24 in the liver, 28 in other abdomen/pelvis sites, 16 in the bone, and 15 near the spine. The abscopal response rate (RECIST, 30% reduction) using the aggregate diameter of all nonirradiated target metastases was 13.5%; however, the response rate in any single nonirradiated target metastasis was an impressive 26.9%. Median PFS was 3.1 months, but it was not reported if patients with an initial response had a sustained response. Grade 3 toxicity was seen in 6 patients (pneumonitis $n=3$; colitis $n=2$; hepatic toxicity $n=1$). These promising results in a heterogenous group of tumors with agnostic PD-L1 status support further studies combining checkpoint inhibitors with SBRT.

Finally, short-term safety of combining thoracic SBRT and immunotherapy was recently explored in a combined analysis of two prospective trials ongoing at MD Anderson (48). The first was the phase 1–2 trial testing SBRT with ipilimumab detailed above. The second was another ongoing phase 1–2 trial testing SBRT with concurrent pembrolizumab in metastatic NSCLC. SBRT dose was 50 Gy in 4 fractions or 60 Gy in 10 fractions. Out of 60 patients with a median follow up of 6.9 months (range, 0.5–30.9 months), there were no grade ≥ 4 toxicities. There were 34 grade 3 toxicities experienced by 15 patients (9 grade 3 pulmonary toxicities experienced by 4 patients) with no difference between the ipilimumab and pembrolizumab groups. These short-term pulmonary toxicity rates were on par with RTOG 0236, in which 8 of 55 patients developed grade 3 respiratory events (4). Notably, no iatrogenic leukopenia was seen with SBRT, suggesting SBRT and immunotherapy have non-intersecting and complementary toxicity profiles.

Future directions

As more interest is generated in combining radiation with immunotherapy, it is important to recognize that tumors with a higher mutational burden like NSCLC and melanoma appear to be more likely to respond to protocols involving immunotherapy (49). Prior trials combining ipilimumab with a palliative 8 Gy single dose of radiation in metastatic prostate cancer (50,51) were possibly doomed by choosing a non-ablative dose in a mutationally quiet cancer (52). The optimal dose and fractionation may also differ for each cancer type. A recent case series of 47 metastatic melanoma patients found an abscopal effect was most likely to occur when fraction sizes ≤ 3 Gy were utilized (53). Preliminary evidence from the MD Anderson phase II trial indicate that treating the largest lesion in metastatic NSCLC with 60 Gy in 10 fractions may have the most activity when combined with ipilimumab (46). Pre-clinical data supports using a hypofractionated regimen of 3–5 fractions with dose per fraction <10 –12 Gy, but dose and fractionation will need to be further evaluated in clinical trials (54). Response rates and clinical benefit of other immune checkpoint inhibitors are also actively being investigated (Table 1), and the optimal combination of therapy and sequencing with SBRT is still to be determined.

SBRT and immunotherapy protocols are now in development for non-metastatic NSCLC patients (Table 2). Since decreased tumor burden has been associated with increased response to immunotherapy (25), this strategy is promising. Results from the PACIFIC trial already showed adjuvant immunotherapy after definitive chemoradiation in stage III NSCLC improved PFS (18), regardless of tumor PD-L1 expression. This suggests that radiation may work synergistically with immunotherapy, as prior trials in the metastatic setting using immunotherapy alone were mostly only positive in tumors with positive PD-L1 expression. However, the local failure rate of conventionally fractionated radiation with concurrent chemotherapy approaches 40%, and efforts to dose-escalate conventional radiation have been limited by cardiac and pulmonary toxicity (55–58). The future may combine the conformal ablative power of an SBRT boost to residual PET-avid disease (59) to further maximize the efficacy of adjuvant immunotherapy.

In early stage NSCLC, the rationale for adding adjuvant immunotherapy to SBRT is even greater. Regional and distant failure rates of at least 30% (11) demand a tolerable systemic solution in this medically frail population.

Table 1 Active clinical trials involving SBRT and immunotherapy in metastatic lung cancer

NCT number	Title (study drug if not in title)	Recruitment	Study endpoint	Phase	Enrollment
NCT02239900	Ipilimumab and Stereotactic Body Radiation Therapy (SBRT) in Advanced Solid Tumors	MD Anderson, Houston, TX; recruiting 120	Safety, irRC response rate	1–2	Active, closed to enrollment
NCT02444741	Pembrolizumab and Stereotactic Body Radiation Therapy (SBRT) in Patients With Non-Small Cell Lung Cancer (NSCLC)	MD Anderson, Houston, TX; recruiting 104	Safety, irRC response rate, PFS	1–2	Open
NCT02839265	FLT3 Ligand Immunotherapy and Stereotactic Radiotherapy for Advanced Non-small Cell Lung Cancer (FLT3)	Albert Einstein, NYC, NY; recruiting 29	4-month PFS	2	Open
NCT03168464	Radiation and Immune Checkpoints Blockade in Metastatic NSCLC (nivolumab/ipilimumab)	Cornell, NYC, NY; recruiting 45	Response rate, PFS, OS	1–2	
NCT03275597	Phase Ib Study of Stereotactic Body Radiotherapy (SBRT) in Oligometastatic Non-small Lung Cancer (NSCLC) With Dual Immune Checkpoint Inhibition (durvalumab/tremelimumab)	University of Wisconsin, Madison; recruiting 21	Safety, PFS, OS	1	Open
NCT03223155	Evaluate Concurrent Or Sequential Ipilimumab, Nivolumab, and Stereotactic Body Radiotherapy in Patients With Stage IV Non-Small Cell Lung Cancer	University of Chicago, IL; recruiting 80	Safety, response rate	1	Open
NCT03313804	Priming Immunotherapy in Advanced Disease With Radiation (any checkpoint inhibitor)	University of Kentucky, Lexington; recruiting 57	6-month PFS	2	Open
NCT03035890	Hypofractionated Radiation Therapy to Improve Immunotherapy Response in Non-Small Cell Lung Cancer (nivolumab, pembrolizumab, or atezolizumab)	West Virginia University; recruiting 33	Response rate, OS, PFS, QoL	1	
NCT02831933	Trial of Stereotactic Body Radiation and Gene Therapy Before Nivolumab for Metastatic Non-Small Cell Lung Carcinoma (ENSIGN)	Methodist Hospital, Houston, TX; recruiting 29	Response rate, PFS, OS	2	Open
NCT03224871	A Pilot Study of Interlesional IL-2 and RT in Patients With NSCLC (nivolumab/pembrolizumab)	University of California, Davis; recruiting 30	Safety, DFS	1	Open
NCT03158883	Avelumab and Stereotactic Ablative Radiotherapy in Non-responding and Progressing NSCLC Patients	University of California, Davis; recruiting 26	Response rate, PFS, OS, irRC	1	Open
NCT03176173	Radical-Dose Image Guided Radiation Therapy in Treating Patients With Metastatic Non-small Cell Lung Cancer Undergoing Immunotherapy (nivolumab, pembrolizumab, or atezolizumab)	Stanford University, CA; recruiting 85	PFS, OS, ctDNA changes	2	Open
NCT03050060	Image Guided Hypofractionated Radiation Therapy, Nelfinavir Mesylate, Pembrolizumab, Nivolumab and Atezolizumab in Treating Patients With Advanced Melanoma, Lung, or Kidney Cancer	University of Washington, Seattle; recruiting 120	Response rate, PFS, OS	2	Open
NCT02623595	A Study of SBRT in Combination With rhGM-CSF for Stage IV NSCLC Patients Who Failed in Second-line Chemotherapy	Wuhan University, China; recruiting 60	Abscopal effect rate, OS, PFS	2	Open
NCT03509584	Phase I Multicenter Trial Combining Nivolumab, Ipilimumab and Hypo-fractionated Radiotherapy for Pretreated Advanced Stage Non-small Cell Lung Cancer Patients	France; recruiting 24	Safety	1	Not yet open

DFS, disease free survival; irRC, immune related response criteria; PFS, progression free survival; OS, overall survival; QoL, quality of life; ctDNA, circulating tumor DNA.

Table 2 Active clinical trials involving SBRT and immunotherapy in non-metastatic lung cancer

NCT number	Title (study drug if not in title)	Recruitment	Study endpoint	Phase	Enrollment
NCT03574220	Pembrolizumab After Lung SBRT for Medically Inoperable Early Stage Non-small Cell Lung Cancer	Cleveland Clinic, Ohio; recruiting 15	Safety, DMFS, DFS, OS, LC	1	Not yet open
NCT03383302	SBRT With Immunotherapy in Early Stage Non-small Cell Lung Cancer: Tolerability and Lung Effects (STILE) (nivolumab)	United Kingdom; recruiting 31	Lung toxicity, DFS, OS, QoL	1–2	Not yet open
NCT03446547	Ablative STEReotactic RadiOtherapy wth Durvalumab (durvalumab) (ASTEROID)	Sweden; recruiting 216	PFS, OS, LC, QoL	2	Open
NCT03050554	Stereotactic Body Radiation Therapy (SBRT) Combined With Avelumab (Anti-PD-L1) for Management of Early Stage Non-Small Cell Lung Cancer (NSCLC)	University of California, San Diego; recruiting 56	Safety, PFS, LRC, OS	1–2	Open
NCT03110978	Clinical Trials Comparing Immunotherapy Plus Stereotactic Ablative Radiotherapy (I-SABR) Versus SABR Alone for Stage I, Selected Stage IIa or Isolated Lung Parenchymal Recurrent Non-Small Cell Lung Cancer: I-SABR (nivolumab)	MD Anderson, Houston, TX; recruiting 140	EFS, OS, toxicity	2	Open

DMFS, distant metastasis free survival; DFS, disease free survival; EFS, event free survival; PFS, progression free survival; OS, overall survival; LC, local control; LRC, locoregional control; QoL, quality of life.

We hypothesize that use of adjuvant immunotherapy will reduce locoregional and distant recurrence with a resultant improvement in OS following SBRT for early stage NSCLC. Compared with cytotoxic chemotherapy, we expect that this will be readily tolerable in this patient population, and lead to minimal impact in quality of life. NRG Oncology is developing a phase 3 trial of adjuvant durvalumab after SBRT in early stage NSCLC, which will test this hypothesis. In the marriage of SBRT with immunotherapy, we are still in the honeymoon period. Time will tell if these early promises will last.

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Footnote

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