Editorial Commentary

Navigating restriction from interstitial lung disease (ILD) with stereotactic ablative radiotherapy (SABR) in early-stage non-small cell lung cancer: soaring beyond the current treatment paradigm

Ari A. Kassardjian[1]^, Jyoti Malhotra[2], Percy Lee[3]

[1]Department of Radiation Oncology, City of Hope, Duarte, CA, USA; [2]Department of Medical Oncology, City of Hope, Duarte, CA, USA; [3]Department of Radiation Oncology, City of Hope, Irvine, CA, USA

Correspondence to: Ari A. Kassardjian, MD. Department of Radiation Oncology, City of Hope, 1500 E. Duarte Rd., Duarte, CA 91010, USA.
Email: akassardjian@coh.org.

Comment on: Palma DA, Bahig H, Hope A, *et al.* Stereotactic radiation therapy in early non-small cell lung cancer and interstitial lung disease: a nonrandomized clinical trial. JAMA Oncol 2024;10:575-82.

Keywords: Non-small cell lung cancer (NSCLC); stereotactic body radiotherapy (SBRT); stereotactic ablative radiotherapy (SABR); interstitial lung disease (ILD)

Submitted Sep 25, 2024. Accepted for publication Dec 11, 2024. Published online Jan 07, 2025.
doi: 10.21037/tcr-24-1813
View this article at: https://dx.doi.org/10.21037/tcr-24-1813

For many decades, radiation pneumonitis (RP) has remained a major concern during radiation planning and treatment delivery for non-small cell lung cancer (NSCLC) patients. When considering stereotactic ablative radiotherapy (SABR), radiation oncologists often evaluate a patient's risk of RP by assessing their age, smoking status, gender, tumor location, and tumor burden. Techniques to limit the volume of lung receiving 10 and 20 Gy, as well as reduction of mean lung dose, have proven valuable in limiting rates of RP in NSCLC patients receiving definitive radiation therapy (RT) (1,2). Additionally, four-dimensional computed tomography (CT) scans monitor tumor motion due to respiration, and motion mitigating techniques, such as beam-gating, breath-hold, and tumor tracking allow for delivery of a personalized ablative dose of radiotherapy, irradiating a smaller volume of surrounding healthy lung tissue, and thereby limiting RP (3).

For patients with early-stage NSCLC and primary lung tumors less than 5 cm without nodal involvement, surgical resection remains the recommended approach for patients willing and able to undergo surgery (4). However, in medically or technically inoperable patients, SABR yields excellent local control (LC) rates, often greater than 90% at 3 years, and is the standard of care for these patients (5). These advances have led to a reduction in RP and overall toxicity for these patients.

The role of SABR continues to evolve given its overall favorable toxicity profile and comparable outcomes to surgery (6). Additionally, NSCLC with central or ultra-central locations may be amenable to SABR with similar 3-year LC rates while maintaining a reasonable toxicity profile (7). In the oligometastatic setting, SABR may also improve both long-term progression-free survival (PFS) and overall survival (OS) (8). Many different dose fractionation schemas exist for SABR in early-stage NSCLC with the central goal of achieving a biological effective dose (BED) of at least 100 Gy to optimize tumor control (9).

Thus, SABR is a safe and effective tool for the treatment of early-stage NSCLC with minimal risk of severe early or late thoracic toxicity. Although fluctuations in pulmonary function tests (PFTs) can arise during the treatment and natural history of NSCLC, SABR itself does not seem to negatively impact pulmonary function (10,11). In the

^ ORCID: 0000-0003-3588-1648.

setting of chronic obstructive pulmonary disease (COPD) or severe ventilatory dysfunction, a 2012 review comparing SABR to surgery by Palma *et al.* suggested that SABR is overall safe while maintaining an 89% LC benefit at 3-year (12). Although the long-term OS of patients with COPD was less than predicted for the general population of early-stage NSCLC patients, there was 0% measured mortality within 30 days of completing SABR, and overall, SABR is considered a preferred option in these patients.

Based on these and other studies, patients should not be excluded from receiving SABR solely based on impaired pulmonary function or abnormal PFTs. In addition, SABR is a feasible option for elderly and frail patients, with one review of patients 75-year of age and older with significant co-morbidities again demonstrating 3-year LC of 89% and minimal toxicity (13). Despite these hallmarks of safety frequently associated with SABR, its safety profile is relatively unknown in patients with interstitial lung disease (ILD). This population may be at higher risk of severe RP following both conventional lung RT and SABR, making ILD a relative contraindication for SABR (14,15).

ILD patients compose a heterogeneous group characterized by chronic lung inflammation progressing into fibrosis and scarring of lung parenchyma, resulting in cough, dyspnea, and increasing levels of oxygen requirements (16). About one-third of patients with fibrotic ILD have idiopathic pulmonary fibrosis (IPF), roughly 25% have connective tissue disease-associated ILD (CTD-ILD), such as scleroderma, while 15% are classified as hypersensitivity pneumonitis (HP), and many are not otherwise specified, or are so-called "unclassifiable ILD".

As opposed to COPD, ILD patients typically demonstrate a restrictive pattern on PFTs with increased forced expiratory volume in 1 second (FEV_1) values typically over 80% predicted, but forced vital capacity (FVC) is significantly reduced, which ultimately results in an FEV_1/FVC ratio that is preserved or increased in ILD. Pathologically and radiographically distinguishing ILD and RP can prove exceedingly difficult, and a common pathophysiology of lung injury may exist between these two pathways (17).

Many clinicians fear the elevated risks and possible synergy of RP in ILD patients with baseline pulmonary fibrosis. One systematic review observed unacceptable rates of severe RP, with 25% risk of grade 3 or higher pneumonitis and 15% of grade 5 toxicity in ILD patients treated with SABR (18). These patients are thought to have a different risk-benefit profile than the average medically inoperable early-stage NSCLC patient treated with SABR.

The completed clinical trial featured in this editorial by Palma *et al.* utilizes a novel prospective phase 2 design that enrolled early-stage NSCLC patients with fibrotic ILD, delivered a standardized dose and fractionation of SABR, and assessed treatment outcomes and patient safety in this vulnerable patient population (19).

In the Assessment of Precision Irradiation in Early Non-Small Cell Lung Cancer and Interstitial Lung Disease (ASPIRE-ILD) study, 39 patients (median age of 78 years) with fibrotic ILD and T1–T2N0 NSCLC underwent SABR. Over half (59%) were male, almost all (92%) had an extensive smoking history with median 43 pack-years, and most (80%) had T1 disease. Biopsy was not required, with 20 patients (51%) having biopsy-confirmed NSCLC. SABR was given at a dose of 50 Gy in 5 fractions delivered every other day, achieving a BED_{10} of 100 Gy.

As outlined in their paper, Palma *et al.* prespecified that SABR would be considered worthwhile if OS at 1-year exceeds 50%: a historical control for OS of untreated stage I NSCLC patients generally not candidates for surgery. Furthermore, SABR would be worthwhile if grade 3 or 4 toxicity occurred in less than 35% of their cohort and rates of grade 5 toxicity were less than 15%.

After a median follow-up period of 19 months, there were 17 total deaths following SABR, and 1-year OS was 79% with 95% confidence interval (CI) of 62–89% versus their selected historical control of 50% ($P<0.001$). Median OS was 25 months, and there was no difference in OS between patients depending on whether they received a biopsy. PFS followed a similar trend as OS, with 1-year PFS of 74% (95% CI: 57–85%) and median PFS of 19 months. The 2-year LC rates following SABR was 92% (95% CI: 69–98%). At 2 years, regional and distant control rates were 86% and 91%, respectively.

Most patients in the study (82%) reported baseline ILD symptoms, such as cough, dyspnea, reduced exercise tolerance, and/or generalized weakness. For risk stratification, the authors employed the ILD-GAP model from the 2014 *Chest* article by Ryerson *et al.*, which encompasses ILD subtype, patient sex, age, and physiology (PFT data) (20). Applying their ILD-GAP model stratification, 14 patients (36%) had ILD-GAP scores of 0–2, 23 patients (59%) with ILD-GAP of 3–5, and 2 (5%) had severe ILD-GAP scores of 6 or higher. Overall, this patient population was likely representative of patients with mild to moderate ILD, yet it may have fallen short of capturing patients with severe ILD (i.e., ILD-GAP 6 or higher).

Most patients (54%) had unclassifiable/other ILD while 21% had IPF, 21% had CTD-ILD, 5% had chronic HP, and 0 had nonspecific interstitial pneumonia (NSIP). Interestingly, their rates of IPF and CTD-ILD were less than expected for the general ILD population (33% and 25%, respectively), and chronic HP was well below the 15% commonly observed (16). Furthermore, the rate of unclassifiable/other ILD was higher than expected, possibly suggesting other etiologies of ILD in the study population, such as drug-induced or post-infectious ILD, such as from coronavirus disease 2019 (COVID-19).

Interestingly, there was no significant difference in OS based on ILD-GAP index. For reference, patients in the *Chest* article with ILD-GAP scores of 6 or higher had 1-year OS of 66.5%, which improves to 82% with ILD-GAP scores of 4 to 5, subsequently to 91.8% for ILD-GAP 2 to 3, and finally 96.9% for ILD-GAP 0 to 1 (20). However, study patients with other/unclassifiable ILD had significantly higher OS (P=0.020) and PFS (P=0.026) rates compared to the other enrolled ILD subtypes. At 1-year, OS was approximately 90% for the other/unclassifiable subgroup compared to 62.5% for both IPF and CTD-ILD subgroups, raising some questions regarding the severity of ILD in those that were in the other/unclassified subgroup. Similarly, 1-year PFS was 90% for the other/unclassifiable subgroup and 50% for IPF and CTD-ILD. Both 1-year OS and PFS for chronic HP were 100%, albeit there were only two patients within that ILD subgroup.

Ultimately, most patients on ASPIRE-ILD were older with overall mild to moderate baseline ILD, and the authors acknowledge that their findings may not be representative of patients with higher ILD-GAP scores. In addition, they state the smaller sample size precludes drawing robust conclusions within individual subgroups.

Regarding toxicity, 12 patients (30.8%) experienced grade 1 to 2 adverse events, and there were six total toxicities across 4 patients (10.3%). No patients developed any grade 4 adverse events. However, three patients experienced grade 5 toxicity related to SABR, which were all due to respiratory deterioration. The authors meticulously aimed to minimize underestimating pulmonary, cardiac, and gastrointestinal toxicity from SABR, and they automatically pre-specified grade 3–5 adverse events from these categories as attributable to treatment.

Furthermore, patient-reported outcomes and quality of life slightly decreased over time, and patient-reported cough increased over the 24 months following SABR. The ASPIRE-ILD team also observed changes to PFT results. Expectantly, there was a significant 4% decrease in diffusion capacity of the lung for carbon monoxide (DLCO) (P=0.046) compared to baseline at a median 13 months from enrollment. This coincides with previous data suggesting that DLCO may decrease 11% at 1-year following lung SABR (10). Conversely, there were no statistically significant differences observed for FVC or FEV_1.

To summarize, in this prospective phase 2 nonrandomized study by Palma *et al.*, 39 patients with early-stage NSCLC and ILD underwent SABR with a prescribed dose of 50 Gy in 5 fractions delivered every other day. The authors met their primary endpoint with a median 1-year OS of 79% compared to a median OS of 12 months, or 1-year OS of 50% as a historical control. Moreover, delivery of SABR in this population resulted in favorable rates of grade 3 or higher toxicity (17.9%), which were lower than the 25% rate previously described (18). There were 3 total deaths attributed to SABR (7.7%), about half of previous series' grade 5 toxicity rate of 15%. Furthermore, their SABR regimen with BED_{10} of 100 Gy provided excellent 2-year LC of 92%. Like other studies in this area of investigation, regional control was 86% and distant control was 91% at 1-year, attributing to 1-year PFS of 74%.

Altogether, these findings are reassuring for clinicians treating patients with ILD and early-stage NSCLC, a combination historically thought to be too high risk for SABR and associated with significant morbidity and mortality. However, there exist differences between the ASPIRE-ILD and general population of ILD patients that cannot be overlooked. Most patients captured on the study had mild to moderate ILD, and only two patients had an ILD-GAP score of 6 or higher signifying severe disease, stressing the importance of patient selection based on the severity of ILD.

Since most patients in ASPIRE-ILD had other/unclassifiable type of ILD, additional questions remain regarding the pathophysiology of these "other" types of ILD and how SABR can further impact lung function in these subgroups compared to IPF or CTD-ILD. Furthermore, immune checkpoint inhibitors (ICIs) can stimulate the host immune system leading to a downstream pro-inflammatory cytokine cascade resulting in pulmonary inflammation, resulting in ICI-related ILD (21). For instance, one meta-analysis reported 4.2% of patients treated with nivolumab for NSCLC-developed ILD, yet other retrospective studies indicate that the risk of ICI-related ILD may be above 14% (22,23). Currently, ICIs following SABR for early-stage NSCLC is not considered standard of care, however there

are ongoing studies evaluating the benefit of consolidative ICI in this patient population.

ILD is a rare, but serious side effect associated with tyrosine kinase inhibitors (TKIs), whereby TKIs directly disrupt the alveolar endothelium, resulting in pulmonary edema and inflammation with an increase in proinflammatory cytokines like IL-6 (24). Other systemic agents, such as the bispecific antibody amivantamab have also been associated with a risk of ILD and pneumonitis, which is synergistically increased in combination with TKIs, such as lazertinib for *EGFR*-mutated NSCLC (25). Caution must be undertaken to treat future patients who have had these novel TKIs associated with ILD with SABR in the setting of oligometastatic or oligoprogressive disease.

Although rates of ILD patients among the general population are low, they represent a heterogenous and frequently underserved population for whom treatment options for NSCLC are very limited. As discussed previously, RT and SABR were often deemed relative contraindications for ILD patients. However, the ASPIRE-ILD study has provided valuable prospective data for SABR in ILD patients, which has shed light on the safety and efficacy profile of SABR in these patients.

Additional research is warranted to identify ILD patients at highest risk of pulmonary deterioration following SABR and to design intervention-based clinical trials. Novel technology, such as advanced imaging and online adaptive radiotherapy may continue to decrease the volume of irradiated healthy lung tissue, while increased time between fractions and radioprotectors could provide insight into minimizing potential impact of SABR on pulmonary function.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1813/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1813/coif). P.L. has received consulting fees from Varian, ViewRay, AstraZeneca, Genentech, Johnson & Johnson, Roche, and RTOG foundation, honoraria for presentations from Varian, ViewRay, and AstraZeneca, support for attending meetings from Radiosurgery Society, participated in data safety monitoring boards for Genentech, ViewRay, AstraZeneca, and Roche, and served a leadership or fiduciary role as Radiosurgery Society Board of Director, Radiosurgery Society Treasurer, and with ASTRO. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45:323-9.
2. Palma DA, Senan S, Tsujino K, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys 2013;85:444-50.
3. Kraus KM, Simonetto C, Kundrát P, et al. Potential Morbidity Reduction for Lung Stereotactic Body Radiation Therapy Using Respiratory Gating. Cancers (Basel) 2021;13:5092.
4. National Comprehensive Cancer Network. NCCN Clinical practice guidelines in oncology: non-small cell lung cancer. version 7.2024. Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
5. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer.

JAMA 2010;303:1070-6.
6. 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;16:630-7. Erratum in: Lancet Oncol 2015;16:e427.
7. Giuliani ME, Filion E, Faria S, et al. Stereotactic Radiation for Ultra-Central Non-Small Cell Lung Cancer: A Safety and Efficacy Trial (SUNSET). Int J Radiat Oncol Biol Phys 2024;120:669-77.
8. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 2019;393:2051-8.
9. Onishi H, Nagata Y, Shirato H, et al. Stereotactic body radiotherapy (SBRT, BED≥ 100 Gy) for operable stage I non-small cell lung cancer: Is SBRT comparable to surgery? Int J Radiat Oncol Biol Phys 2007;69:S86-7.
10. Stanic S, Paulus R, Timmerman RD, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early- stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. Int J Radiat Oncol Biol Phys 2014;88:1092-9.
11. Stephans KL, Djemil T, Reddy CA, et al. Comprehensive analysis of pulmonary function Test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. J Thorac Oncol 2009;4:838-44.
12. Palma D, Lagerwaard F, Rodrigues G, et al. Curative treatment of Stage I non-small-cell lung cancer in patients with severe COPD: stereotactic radiotherapy outcomes and systematic review. Int J Radiat Oncol Biol Phys 2012;82:1149-56.
13. Haasbeek CJ, Lagerwaard FJ, Antonisse ME, et al. Stage I nonsmall cell lung cancer in patients aged > or =75 years: outcomes after stereotactic radiotherapy. Cancer 2010;116:406-14.
14. Glick D, Lyen S, Kandel S, et al. Impact of Pretreatment Interstitial Lung Disease on Radiation Pneumonitis and Survival in Patients Treated With Lung Stereotactic Body Radiation Therapy (SBRT). Clin Lung Cancer 2018;19:e219-26.
15. Bahig H, Filion E, Vu T, et al. Severe radiation pneumonitis after lung stereotactic ablative radiation therapy in patients with interstitial lung disease. Pract Radiat Oncol 2016;6:367-74.
16. Maher TM. Interstitial Lung Disease: A Review. JAMA 2024;331:1655-65.
17. Türkkan G, Willems Y, Hendriks LEL, et al. Idiopathic pulmonary fibrosis: Current knowledge, future perspectives and its importance in radiation oncology. Radiother Oncol 2021;155:269-77.
18. Chen H, Senan S, Nossent EJ, et al. Treatment-Related Toxicity in Patients With Early-Stage Non-Small Cell Lung Cancer and Coexisting Interstitial Lung Disease: A Systematic Review. Int J Radiat Oncol Biol Phys 2017;98:622-31.
19. Palma DA, Bahig H, Hope A, et al. Stereotactic radiation therapy in early non-small cell lung cancer and interstitial lung disease: a nonrandomized clinical trial. JAMA Oncol 2024;10:575-82.
20. Ryerson CJ, Vittinghoff E, Ley B, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. Chest 2014;145:723-8.
21. Kim S, Lim JU. Immune checkpoint inhibitor-related interstitial lung disease in patients with advanced non-small cell lung cancer: systematic review of characteristics, incidence, risk factors, and management. J Thorac Dis 2022;14:1684-95.
22. Wu J, Hong D, Zhang X, et al. PD-1 inhibitors increase the incidence and risk of pneumonitis in cancer patients in a dose-independent manner: a meta-analysis. Sci Rep 2017;7:44173.
23. Suzuki Y, Karayama M, Uto T, et al. Assessment of Immune-Related Interstitial Lung Disease in Patients With NSCLC Treated with Immune Checkpoint Inhibitors: A Multicenter Prospective Study. J Thorac Oncol 2020;15:1317-27.
24. Vahid B, Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. Chest 2008;133:528-38.
25. Cho BC, Wang Y, Felip E, et al. Amivantamab plus lazertinib in atypical EGFR-mutated advanced non-small cell lung cancer (NSCLC): Results from CHRYSALIS-2. J Clin Oncol 2024;42:8516.

Cite this article as: Kassardjian AA, Malhotra J, Lee P. Navigating restriction from interstitial lung disease (ILD) with stereotactic ablative radiotherapy (SABR) in early-stage non-small cell lung cancer: soaring beyond the current treatment paradigm. Transl Cancer Res 2025;14(1):11-15. doi: 10.21037/tcr-24-1813