

UCSF

UC San Francisco Previously Published Works

Title

Addition of pulsed electric field ablation to SBRT for lung tumors: effect on health-related quality of life

Permalink

<https://escholarship.org/uc/item/8vx0p27z>

Journal

Lung Cancer Management, 15(1)

ISSN

1758-1966

Authors

Harris, Jeremy P

Boyd, Christina

Shi, Mengying

et al.

Publication Date

2026-12-31

DOI

10.1080/17581966.2026.2635332

Peer reviewed

RESEARCH ARTICLE



Addition of pulsed electric field ablation to SBRT for lung tumors: effect on health-related quality of life

Jeremy P. Harris^a , Christina Boyd^b, Mengying Shi^a, Michael Reilly^a, Aaron Simon^a, Steven N. Seyedin^c, Wen-Pin Chen^d, Misako Nagasaka^e, Nadine Abi-Jaoudeh^b and Michael A. Hoyt^f

^aDepartment of Radiation Oncology, University of California – Irvine, Orange, CA, USA; ^bDivision of Vascular & Interventional Radiology, University of California – Irvine, Orange, CA, USA; ^cDepartment of Radiation Oncology, University of California – San Francisco, San Francisco, CA, USA; ^dDepartment of Medicine, University of California – Irvine, Orange, CA, USA; ^eDivision of Hematology & Oncology, University of California – Irvine, Orange, CA, USA; ^fDepartment of Population Health & Disease Prevention, University of California Irvine – Irvine, Orange, CA, USA

ABSTRACT

Introduction: Treatment indications for oligometastatic/oligoprogressive lung tumors are growing. Safety and lack of detrimental effect on patients' quality of life are critical for novel local therapies.

Methods: We tested that the additive effect of pulsed electric field (PEF) ablation with lower-dose stereotactic body radiation therapy (SBRT) on health-related quality of life (HRQoL) as a secondary endpoint in a prospective clinical trial. FACT-Lung Cancer Subscale (FACT-LCS) and FACT-General domain surveys were collected at screening, 3 months, and 12 months. Functional clinical data included forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and diffusing capacity of the lung for carbon monoxide (DLCO).

Results: Six patients with eight tumors were enrolled. Baseline well-being domain scores were: Physical 25.9 (Std Dev 2.3), Social 21.0 (Std Dev 6.9), Emotional 17.3 (Std Dev 4.7), Functional 21.2 (Std Dev 5.8), and LCS 19.4 (Std Dev 5.3). There were no significant changes following combined modality treatment in HRQoL domain scores or pulmonary function metrics after treatment. Lower EWB and SWB were associated with worse FVC and FEV1.

Conclusion: In this small pilot study, no clinically meaningful declines in pulmonary function or patient-reported quality of life were observed at 3 months following combination therapy.

ARTICLE HIGHLIGHTS

- Oligometastatic and oligoprogressive cancer increasingly requires lung tumor therapy.
- Central and ultracentral tumors pose significant treatment challenges.
- Conventional stereotactic body radiation therapy (SBRT) can cause severe toxicity in these locations.
- Pulsed electric field (PEF) ablation is a novel tissue-sparing technique.
- However, PEF produces a small ablation zone.
- This prospective pilot trial tested a novel combination of PEF ablation followed by single-fraction 12Gy SBRT in six patients.
- No significant health-related quality of life changes occurred at 3 months across all five FACT-L domains.
- Pulmonary function testing showed no significant changes at 3 months post-treatment.
- Combination PEF ablation with lower-dose radiation represents a promising approach.
- These findings are hypothesis-generating, and larger controlled trials are needed for validation and comparative effectiveness.

PLAIN LANGUAGE SUMMARY

What is this article about? More patients who have a variety of solid-tumor cancers are presenting with a limited number of new or progressing metastases (oligometastatic/oligoprogressive). A common target for treatment is the lung, and certain regions of the lung space (central) present a particular challenge. We piloted a new therapy called pulsed electric field ablation with radiation therapy for six patients, and report patient-reported quality of life data here. What were the results? There were no demonstrated significant changes following the new combined modality treatment in any tested quality of life domain. Worse emotional and social well-being scores were associated with worse pulmonary function. What do the results of the study mean? What do the results of the study mean? In this small pilot study,

ARTICLE HISTORY

Received 17 June 2025
Accepted 18 February 2026

KEYWORDS

Radiation therapy; ablation; clinical trials; cancer; lung; metastasis; novel therapy

we did not observe concerning declines in breathing function or quality of life after the combination treatment. Because the study was small and did not include a comparison group, we cannot definitively conclude whether this treatment is better or worse than other approaches.

1. Introduction

Overall survival for patients with metastatic cancer has improved for most solid-tumor types over the past 20 years [1]. Combined with the fact that the overall population is aging, the prevalence of those living with metastatic cancer increased by 11% from 2018 to 2025 [1]. A subgroup of those patients have oligometastatic cancer, characterized by a small number of metastases. Some histologies, such as NSCLC, have an increasingly recognized oncologic benefit to local therapy to all sites of known disease [2–4]. The benefits include improved progression free survival, longer time on therapy, and symptom control. Beyond NSCLC, indications for oligometastatic treatment are growing [5]. Emerging data also implicate local therapy in the oligoprogressive setting, where a subset or small number of metastases are progressing [6].

A major subset of patients with oligometastatic/oligoprogressive disease require lung tumor treatment [5,6]. Lung targets present a challenge in light of respiratory motion and the sensitivity of the lung tissue to local therapies. A particular concern is paid to central or ultracentral tumors. A close distance to the proximal bronchial tree and/or mediastinum is associated with higher rates of severe toxicity for lung tumors treated with stereotactic body radiation therapy (SBRT) [7]. There have been reports of fatal pulmonary hemorrhage, symptomatic bronchial stricture, and bronchial fistula formation [8]. Electric ablation with pulsed electric fields (PEF) is a new ablation technique that may be able to help address central lung targets since it does not disrupt extracellular structures such as major airways or vessels [9]. However, the PEF ablation zone is relatively small, preventing its use as monotherapy. We performed a single-arm clinical trial testing the combination of PEF ablation with lower-dose SBRT evaluating the efficacy and safety of the combination treatment.

A critical issue for new therapies for those with metastatic disease is quality of life (QoL), since many patients would not be interested in therapies that negatively impact their QoL with some survival gains [10]. The National Cancer Institute has made recommendations for measuring core sets of symptoms in therapeutic clinical trials [11]. However, QoL data are frequently not reported – in a systematic review of trials that mandated patient-reported outcome collection, 38% never reported those data [12].

Thus, for new local therapies for patients with metastatic disease, it is critical to determine their impact on health-related quality of life (HRQoL). We hypothesized that the additive effect of PEF ablation with lower-dose SBRT would not negatively impact HRQoL.

2. Materials/methods

In this prospective clinical trial, adult patients with a metastatic lung tumor were eligible for inclusion. Any biopsy proven histology was allowed (non-small cell lung cancer [NSCLC] or other metastatic cancer), although biopsy of the lung tumor was not required. There were no exclusions based on prior systemic therapies, and prior treatment of the lung tumor by surgery or ablation was allowed. Prior radiation to the lung target was not allowed. For electric ablation, exclusions were also made for patients with cardiac arrhythmias, epilepsy/seizure disorders, and implanted pacemaker/defibrillator. This study was approved by the University of California, Irvine institutional review board (UCI IRB #1723) and registered with ClinicalTrials.gov. Written and informed consent was received from all participants.

Clinical trial methods and primary endpoint have been reported separately [13]. Briefly, patients were treated with PEF ablation on day 1 and single-fraction 12Gy SBRT between days 8 and 15. The dose was chosen as isotoxic to palliative doses of radiation (30Gy in 10 fractions) for an α/β of 3Gy, and the time was as short as reasonably allowable for hospital discharge and radiation planning so as to minimize cellular repopulation. Electric ablation was achieved the Aliya System (Galvanize Therapeutics, Inc, San Carlos, CA). The electric field was created by a single, 3,000V monopolar electrode at a frequency of 400kHz delivered as 100 packets. Radiation planning was done with multiple simulation CT scans for optimal motion management – a free breathing CT with abdominal compression and thrice repeated breath-hold gated CT. An internal target (iGTV) was created using a 4-dimensional CT or all breath-hold scans.

We allowed treatment of 1–3 lung tumors that were 1–6 cm in size. All lung subsites were included for treatment, with preference for central/ultracentral locations. Central tumors were those <2 cm of the proximal bronchial tree (PBT), or with the planning target volume (PTV) overlapping the mediastinal pleura. The PBT includes the carina, bronchus intermedius, right and left upper lobe bronchi, lingular bronchus, right middle lobe bronchus, and left and right lower lobe bronchi.

Here we report HRQoL endpoint data, which was collected as a secondary endpoint and included the Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS), FACT-Physical Well-Being (FACT-PWB), FACT-Social/Family Well-Being (FACT-SWB), FACT-Emotional Well-Being (FACT-EWB), and FACT-Functional Well-Being (FACT-FWB). Surveys were collected at initial screening and again at 3 and 12 months. Domain subscales were calculated with a range of 0–28 or 0–24 (FACT-EWB), with higher scores indicating more optimal HRQoL. The FACT-L subscale scoring system handles missing responses by prorating available responses [14].

Safety data included adverse event monitoring at 30-days post treatment and every 3 months (CTCAE v5.0). Functional clinical data included pulmonary function testing (PFT), including forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and diffusing capacity of the lung for carbon monoxide (DLCO).

Median and ranges of the HRQoL subscales were computed at the three timepoints: pretreatment, 3 months, and 12 months. The prespecified primary HRQoL endpoint was change FACT-LCS at 3 months, calculated using Wilcoxon signed-rank testing. Within-groups ANOVA testing was used to analyze differences across all timepoints. Changes in PFT metrics were computed with paired *t*-tests. Exploratory analyses were conducted to test associations between HRQoL domains and pulmonary function testing (PFT). R statistical software was used for analysis (version 4.3, the R foundation for Statistical Computing).

3. Results

Six patients with eight tumors were screened, registered, and enrolled (Table 1). The median age was 65 (range 44–67), and the cohort was demographically diverse. There were two women, two Hispanic, and three Asian individuals. One patient's primary language was Spanish, and another was Vietnamese. Likewise, representative diseases were diverse and included non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma, acinic cell carcinoma, and colorectal adenocarcinoma. Representative locations included peripheral location ($n=3$), central ($n=2$), and ultracentral ($n=3$). The ultracentral tumors were <1 cm from proximal bronchial tree.

All patients completed their course of treatment with electric ablation and radiation as well as the HRQoL surveys at screening and 3-months post-treatment (Figure 1) [15]. Off-target disease progression occurred in all patients within 18 months (median 4.6 months), and one patient died at 10.5 months. Four of six patients (67%) completed HRQoL surveys at 12-months. The two patients who did not complete 12-month assessments included one patient who died at 10.5 months from disease progression and one patient who was lost to follow-up due to disease progression requiring escalation of systemic therapy at an outside institution.

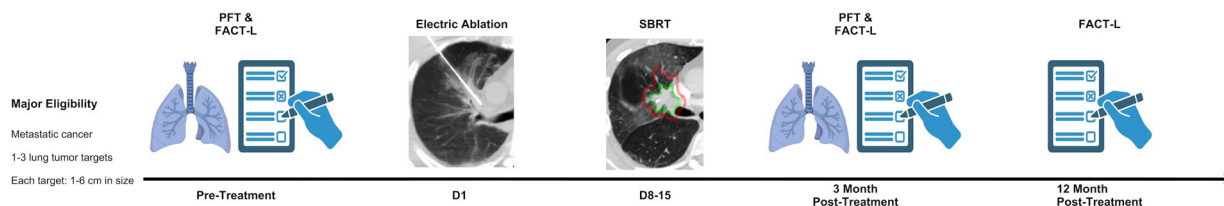
One patient (17%) experienced a Grade 3 adverse event (surgical procedure complication, inability to extubate until post-procedure day 1 due to laryngeal edema). No Grade 4–5 adverse events occurred. This patient appropriately reported lower quality of life scores and noted dissatisfaction with treatment side effects on HRQoL assessment (GP5: "I am bothered by side effects of treatment"). No other patients experienced Grade ≥ 3 toxicity. Grade 1–2 adverse events included asymptomatic pneumothorax, procedural pain, and fatigue [13].

Baseline domain scores were: PWB 25.9 (Std Dev 2.3), SWB 21.0 (Std Dev 6.9), EWB 17.3 (Std Dev 4.7), FWB 21.2 (Std Dev 5.8), and LCS 19.4 (Std Dev 5.3). Consistent with hypotheses, compared to pretreatment HRQoL domain scores, there were no significant changes following combined modality treatment (Figure 2), including the 3-month changes in PWB (change of -0.89 , 95% CI -3.82 to 2.04 , $p=0.47$), SWB (change of 4.78 , 95% CI -3.09 to 12.64 , $p=0.18$), EWB (change of -0.50 , 95% CI -3.52 to 2.52 , $p=0.69$), FWB (change of 2.83 , 95% CI -4.17 to 9.84 , $p=0.35$), or LCS (change of 3.62 , 95% CI -3.67 to 10.92 , $p=0.26$). Minimally important differences in the FACT-L subscore domains is often considered 2–3 points [16].

The mean baseline PFT metrics were: FVC 3.60 L (Std Dev 0.84 L), FEV1 2.67 L (Std Dev 0.80 L), and DLCO 20.58 mL/mmHg/min (Std Dev 6.18 mL/mmHg/min). The patient cohort was heterogeneous with respect to baseline pulmonary function; one patient had a baseline DLCO of 59% predicted, consistent with mild-to-moderate diffusion impairment. There were no significant changes in PFT metrics following clinical trial treatment

Table 1. Patient demographic, medical, cancer, and radiation characteristics. NSCLC, non-small cell lung cancer; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe.

	<i>n</i> (%)
Age (median, range)	65 years (44-67 years)
Sex	
Female	2 (33%)
Male	4 (67%)
Race	
Asian	3 (50%)
White	2 (33%)
Unknown	1 (17%)
Ethnicity	
Non-Hispanic	4 (67%)
Hispanic	2 (33%)
Primary Language	
English	4 (67%)
Spanish	1 (17%)
Vietnamese	1 (17%)
Performance status	
0	1 (17%)
1	5 (83%)
Comorbidities	
Diabetes	1 (17%)
Hyperlipidemia	2 (33%)
Hypertension	2 (33%)
Histology	
NSCLC	2 (33%)
Head and neck squamous cell carcinoma	2 (33%)
Acinic cell carcinoma	1 (17%)
Colorectal adenocarcinoma	1 (17%)
Prior lines of systemic therapy	
0	2 (33%)
1	3 (50%)
>2	1 (17%)
Tumor Targets	
1	4 (67%)
2	2 (33%)
Target Size (median, range)	1.60 cm (1.3-2.8 cm)
Radiation Gross Tumor Volume (median, range)	4.3 mL (2.9-16.7 mL)
Tumor Location	
LUL	3 (38%)
LLL	2 (25%)
RUL	3 (38%)
Tumor Description	
Peripheral	3 (38%)
Central	2 (25%)
Ultracentral	3 (38%)
Dosimetry (median, range)	
Mean Lung	0.73 Gy (0.48-1.45 Gy)
V5Gy	3.6% (1.4-7.0%)
V10Gy	0.8% (0-1.7%)

**Figure 1.** Trial Schema. Tumor assessment was with CT chest imaging every 3 months for 1 year, and adverse event monitoring was at Day 45 and every 3 months for 1 year [15]. PFT, pulmonary function tests; FACT-L, Functional Assessment of Cancer Therapy-Lung; SBRT, stereotactic body radiation therapy.

with FVC (-0.032 L, 95% CI -0.219 to 0.156 L, $p=0.68$), FEV1 (0.058 L, 95% CI -0.033 to 0.149 L, $p=0.16$), or DLCO (-1.54 mL/mmHg/min, 95% CI -4.96 to 1.87 mL/mmHg/min, $p=0.30$).

Exploratory analyses were conducted to examine potential associations between HRQoL and PFT testing (Figure 3). At 3 months post-treatment, there were suggestive associations between lower FVC and lower EWB ($\rho = 0.55$, $\beta = 5.3$, $p=0.04$) and SWB ($\rho = 0.58$, $\beta = 2.9$, $p=0.01$). Similarly, lower FEV1 showed

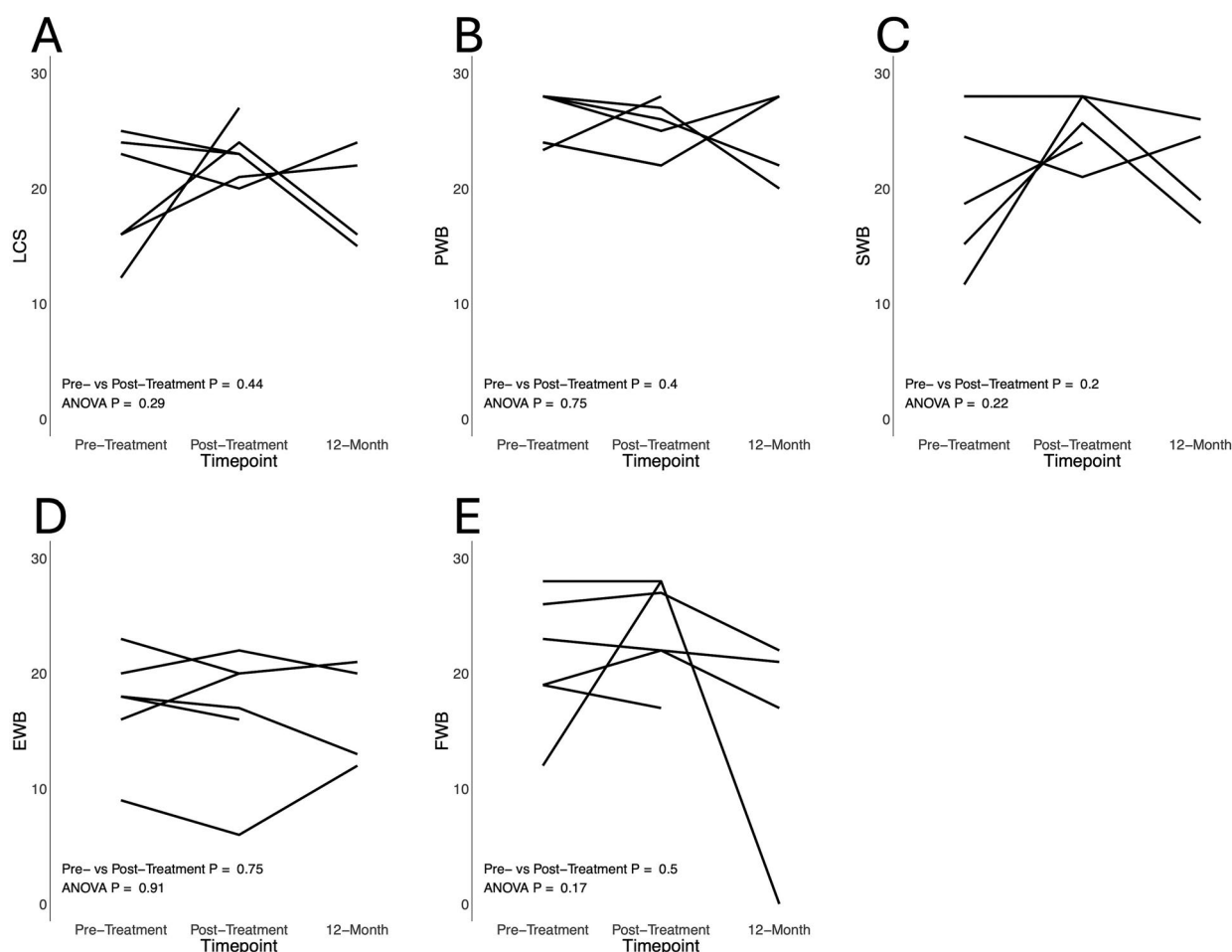


Figure 2. FACT-L subsdomains from Pretreatment, 3 month Post-Treatment, and 12 month Post-Treatment timepoints. Domains included Functional Assessment of Cancer Therapy-Lung Cancer Subscale (LCS), FACT-Physical Well-Being (PWB), FACT-Social/Family Well-Being (SWB), FACT-Emotional Well-Being (EWB), and FACT-Functional Well-Being (FWB). Domain subscales were calculated with a range of 0-28 or 0-24 (FACT-EWB), with higher scores indicating more optimal health-related quality of life (HRQoL). The prespecified primary HRQoL endpoints were the differences between Pretreatment and 3 month Post-Treatment.

potential associations with lower EWB ($\rho = 0.81$, $\beta = 5.6$, $p = 0.04$) and SWB ($\rho = 0.70$, $\beta = 3.0$, $p = 0.01$). Other HRQoL domains were not significantly associated with PFT measurements ($p > 0.05$, for all).

4. Discussion

In this single-institutional clinical trial, the treatment of predominantly centrally located lung tumors with combination PEF ablation and SBRT was well-tolerated. Patient-reported responses from standardized instruments showed no significant treatment-related declines in HRQoL. Functional outcomes as measured by pulmonary function testing similarly demonstrated no significant changes. Exploratory analyses identified associations between worse pulmonary function with poorer well-being scores.

This study represents the first reported combination of PEF ablation with SBRT for lung tumors, demonstrating a novel approach that leverages the unique tissue-sparing properties of PEF. The clinical significance of this finding is particularly important for patients with central and ultracentral tumors, who face the highest risk of severe complications with conventional ablative approaches and may have limited local therapy options. This preservation of pulmonary function and quality of life is especially clinically relevant given that many patients with oligometastatic disease require multiple lung treatments over time.

As the indications for local therapy in the metastatic setting increase, it seems likely that there will continue to be more patients with metastatic cancer treated with ablative therapy [2–6,17]. Independent of histology, lung tumors account for 26–47% of targets of metastatic disease ablative treatment [5,6]. Of course, treatment

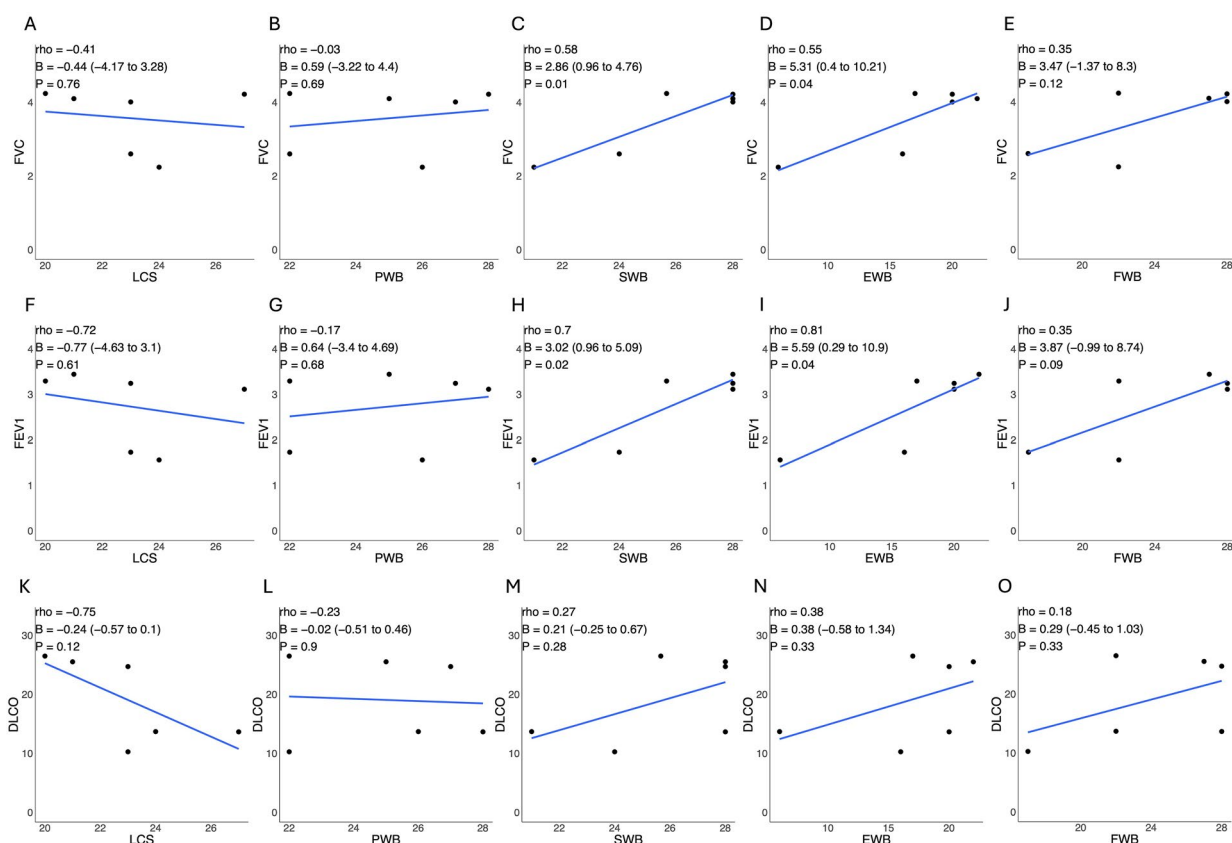


Figure 3. Association between PFT and FACT-L subdomains. PFT included forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and diffusing capacity of the lung for carbon monoxide (DLCO). Computed statistics included Spearman correlation coefficients and linear regression models. PFT, pulmonary function tests; FACT-L, Functional Assessment of Cancer Therapy-Lung; FACT-LCS, Functional Assessment of Cancer Therapy-Lung Cancer Subscale; PWB, Physical Well-Being; SWB, Social/Family Well-Being; EWB, Emotional Well-Being; FWB, Functional Well-Being.

of metastatic disease changes the equation between the balance of local control and quality of life. In the incurable setting, typical oncologic surgeries such as resection with wide margins, lymph node dissection, amputation, and lobectomy would generally not be considered. Attention must be made to HRQoL and patient functional status, in particular when some prioritize over incremental survival benefit [10].

The safety of radiation and ablation thoracic techniques have been established and extrapolated from NSCLC treatments [18–22]. In metastatic NSCLC, improvements in outcomes with novel immunotherapy and targeted therapy regimens have changed the landscape of available systemic options [23]. However, the use of local therapy has been tested only for a limited number of systemic therapies [3,17,24]. More studies lean on the histology agnostic mechanisms of local therapies and tend to stratify by histology and/or systemic agents [5,6,25]. And while histology is important for predicting radiation control rates, studies of the molecular mechanisms of treatment response indicate there may be shared immune microenvironment characteristics such as certain interferon-associated signaling pathways that can predict favorable outcomes [26]. In general, the molecular responses to local radiation therapy can be both immune stimulating and suppressive. Following radiation, a number of immune modulatory factors are released, including TGF β , TNF α , reactive oxygen species, nucleic acids, interleukins, heat shock proteins (HSP), and high mobility group box 1 molecules (HMGB1) [27]. As a result, there can be upregulation of tumor antigen presentation [28]. However, radiation can also promote immunosuppressive phenotypes in myeloid cells through increased amphiregulin expression [29]. Lastly, biomarker testing with multigene panel testing and immunohistochemistry is now standard as part of the workup in advanced NSCLC, including for PD-L1 and other mutations that have therapeutic relevance (e.g., EGFR, ALK, KRAS) [30]. One class of biomarkers that has shown promise both in optimizing patient selection for local therapy as well as predicting subsequent relapse is ctDNA [31,32].

The rate of local failures with SBRT for peripheral tumors on clinical trials has ranged from 2.7% to 10.6% [33,34]. With central tumors, SBRT has resulted in failure rates in the range of 7–17% [18,35–37]. With lung

SBRT, symptomatic pneumonitis rates are 10–15% with contemporary planning, and the rate of severe toxicity (Grade 3–5) is <5% [38]. However, higher risk of severe toxicity or death has been associated with treatment of central tumors [7]. Dose to the major airways seems to be the main contributing factor for severe toxicity, putting ultracentral tumors at highest risk [35]. As for HRQoL, data in the early stage setting suggest there is no early or late detriment with lung SBRT for peripheral or central lung tumors [39]. Functional outcomes as measured by decreases in FEV1, FVC, and DLCO following SBRT have not been clinically meaningful and difficult to measure with statistical confidence [40,41]. After longer periods (>12 mo) from the time from SBRT, modest decreases in lung function can be seen, but have not been correlated with radiation dose to the lungs [42].

Most experience with percutaneous ablation is with temperature-based approaches (radiofrequency, microwave, cryoablation). In clinical trials, temperature-based techniques resulted in a 12% 1-year local failure in the RAPTURE trial and 23% 2-year local failure rate in the SOLSTICE trial [20,21,43]. Temperature-based percutaneous ablation techniques also suffer concern of injury to central thoracic structures (major airways, esophagus) and the heat sink effect (great vessels, heart) [44]. Unlike temperature-based techniques, PEF ablation does not disrupt extracellular structures such as blood vessels or cartilaginous airways, and so is thought to be safer for the treatment of central tumors [45,46]. In addition, the preservation of pulmonary function with PEF ablation can be attributed to several distinct mechanisms. Unlike radiofrequency or microwave ablation, which cause nonselective tissue destruction, PEF ablation utilizes high-voltage pulsed electric fields to create nanoscale pores in cellular membranes, leading to apoptosis while preserving the structural integrity of the extracellular matrix [45,47]. The spared lung architecture includes collagen scaffolding, elastin fibers, and the basement membranes of airways and blood vessels. The preservation of these structural elements is particularly important for maintaining pulmonary mechanics, which is important for the integrity of airways and ventilatory function.

With PEF ablation, the largest experience comes from a retrospective study of 77 patients treated with lung tumors [48]. In that study, 21.5% of the 177 lung procedures resulted in pneumothorax and 11.3% required chest tube. There are retrospective data of PEF ablation for lung tumors, although local control is not described in the largest such experience [49]. In one series of PEF ablation that included 4 lung tumors, all 4 had local progression in under 6 months [50]. A related study was done with PEF ablation followed by lobectomy, which allowed histologic examination and response characterization *in vivo* [9]. In that prospective study, patients with early stage NSCLC were treated with percutaneous ($n=10$) or endobronchial ($n=28$) PEF ablation, resulting in 2 cases of pneumothorax. There are no data reported of HRQoL or pulmonary function changes following PEF ablation. However, data from temperature-based ablation suggests there is likely little impact on either HRQoL or pulmonary function [21].

While there are no prior combination PEF-SBRT approaches, there is one study that tested the combination of lung SBRT with radiofrequency or microwave ablation for patients with central lung tumors [51]. That study reported a severe toxicity rate of 19%. Additionally, at 3 months post-treatment, there were significant decreases in FVC (8.5%, $p=0.0001$) and FEV1 (8.0%, $p=0.0007$), and a non-significant decrease in DLCO (10.2%, $p=0.10$). Thus, it is notable that there were no similar detriments to pulmonary function in the current study. It may be that these pulmonary function metrics are more related to radiation dose and the volume of lung exposed, which would support a combination approach that allowed decreased radiation dose.

An additional challenge to treating metastatic disease is that there are often multiple lung tumors to treat simultaneously. For example, in an analysis of the German Radiation Oncology Society working group, 14% of patients with oligometastatic disease had multiple lung tumors treated simultaneously, and 9% required multiple lung SBRT courses [52]. In the current study two out of six patients required multiple metastases treated on trial, and two had subsequent lung SBRT (one for local failure and another for a new lung tumor). The proportion of patients who require multiple lung treatments gives credence to greater consideration of the safety, functional outcome, and HRQoL associated with the local therapies.

The most critical limitation of this study is the very small sample size, which is insufficient to support statistical inference about HRQoL or pulmonary function changes. These results serve as preliminary descriptive data demonstrating absence of obvious safety signals in a small cohort but cannot be interpreted as evidence that the combination therapy definitively preserves HRQoL or pulmonary function. In addition, the study was designed to test feasibility and lacked statistical power to detect small-to-moderate differences in HRQoL or pulmonary function metrics. The patient cohort was heterogeneous with respect to multiple factors including

primary cancer histology (NSCLC, head and neck squamous cell carcinoma, acinic cell carcinoma, and colorectal adenocarcinoma), tumor locations (peripheral, central, and ultracentral), and baseline comorbidities. This heterogeneity substantially increases variability in both HRQoL and PFT outcomes. While the within-subject design partially mitigates concerns about baseline differences, there remains limited statistical power and wide confidence intervals. Different patient subgroups may respond differently to the combination therapy: for example, a patient with NSCLC and smoking-related chronic obstructive pulmonary disease likely has different baseline pulmonary reserve and treatment response compared to a patient with colorectal cancer metastases and normal baseline lung function. The small sample size precludes meaningful subgroup analyses to address these questions. Additionally, attrition at the 12-month timepoint (4 of 6 patients, 33%) substantially limits interpretation of longer-term HRQoL outcomes. The two patients who did not complete 12-month assessments included one patient who died at 10.5 months from disease progression and one patient who was lost to follow-up due to disease progression requiring escalation of systemic therapy at an outside institution. These missing data represent a missing not at random (MNAR) pattern, as patients with progressive disease may have worse HRQoL than those who remain evaluable. Therefore, the 12-month data likely overestimate HRQoL stability in the overall population and should not be interpreted as representative of treatment effects beyond the 3-month primary endpoint. The rapid disease progression observed in all patients (median 4.6 months to off-target progression) suggests that any observed HRQoL stability at 12 months in evaluable patients is likely attributable to lack of treatment-related toxicity rather than favorable disease control, but this cannot be definitively established.

In conclusion, this small pilot feasibility study observed no clinically meaningful declines in pulmonary function or patient-reported quality of life at 3 months following combination PEF ablation with lower-dose SBRT for predominantly central/ultracentral lung tumors. However, the small sample size and single-arm design preclude definitive conclusions about treatment effects. Whether this combination approach truly preserves functional and quality of life outcomes compared to conventional therapies requires validation in larger, adequately powered prospective trials with appropriate control groups. The number of patients with metastatic disease in need of local lung tumor treatment is expected to increase, and particular attention should be paid to functional and quality of life outcomes with new approaches.

Acknowledgements

Generative AI tools were not used for the writing of this report.

Author contribution statement

Jeremy Harris: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, Writing – original draft, Writing – review & editing.

Christina Boyd: Investigation, methodology, Writing – original draft, Writing – review & editing.

Mengying Shi: Investigation, Writing – original draft, Writing – review & editing.

Michael Reilly: Investigation, Writing – original draft, Writing – review & editing.

Aaron Simon: Methodology, Investigation, Writing – original draft, Writing – review & editing.

Steven Seyedin: Methodology, Investigation, Writing – original draft, Writing – review & editing.

Wen-Pin Chen: data curation, formal analysis, Writing – original draft, Writing – review & editing.

Misako Nagasaka: Investigation, Writing – original draft, Writing – review & editing.

Nadine Abi-Jaoudeh: Methodology, Investigation, Writing – original draft, Writing – review & editing.

Michael Hoyt: Conceptualization, data curation, formal analysis, Writing – original draft, Writing – review & editing.

Clinical trial registration

This trial was registered with ClinicalTrials.gov (NCT05555342).

Funding

This work was supported in part by the ACS Seed Grant 129801-IRG-16-187-13-IRG from the American Cancer Society and a gift from the Stern Center for Cancer Clinical Trials and Research. We also wish to acknowledge the support of the Chao Family Comprehensive Cancer Center Biostatistics Shared Resource, supported by the National Cancer Institute of the

National Institutes of Health under award number P30CA062203. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ORCID

Jeremy P. Harris  <http://orcid.org/0000-0001-7603-0263>

References

Papers of special note have been highlighted as either of interest () or of considerable interest (**) to readers.*

- [1] Gallicchio L, Devasia TP, Tonorezos E, et al. Estimation of the number of individuals living with metastatic cancer in the United States. *J Natl Cancer Inst.* 2022;114(11):1476–1483. doi: [10.1093/jnci/djac158](https://doi.org/10.1093/jnci/djac158)
- [2] Gomez DR, Blumenschein GR, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol.* 2016;17(12):1672–1682. doi: [10.1016/S1470-2045\(16\)30532-0](https://doi.org/10.1016/S1470-2045(16)30532-0)
- [3] Wang X-S, Bai Y-F, Verma V, et al. Randomized trial of first-line tyrosine kinase inhibitor with or without radiotherapy for synchronous oligometastatic EGFR-mutated non-small cell lung cancer. *J Natl Cancer Inst.* 2023;115(6):742–748. doi: [10.1093/jnci/djac015](https://doi.org/10.1093/jnci/djac015)
- [4] Chalkidou A, Macmillan T, Grzeda MT, et al. Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study. *Lancet Oncol.* 2021;22(1):98–106. doi: [10.1016/S1470-2045\(20\)30537-4](https://doi.org/10.1016/S1470-2045(20)30537-4)
- [5] Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. *JCO.* 2020;38(25):2830–2838. doi: [10.1200/JCO.20.00818](https://doi.org/10.1200/JCO.20.00818)
- [6] Tsai CJ, Yang JT, Shaverdian N, et al. Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study. *Lancet.* 2024;403(10422):171–182. doi: [10.1016/S0140-6736\(23\)01857-3](https://doi.org/10.1016/S0140-6736(23)01857-3)
- [7] Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *JCO.* 2006;24(30):4833–4839. doi: [10.1200/JCO.2006.07.5937](https://doi.org/10.1200/JCO.2006.07.5937)
- [8] Chen H, Laba JM, Zayed S, et al. Safety and effectiveness of stereotactic ablative radiotherapy for ultra-central lung lesions: a systematic review. *J Thorac Oncol.* 2019;14(8):1332–1342. doi: [10.1016/j.jtho.2019.04.018](https://doi.org/10.1016/j.jtho.2019.04.018)
- [9] Jimenez M, Flandes J, van der Heijden EHFM, et al. Safety and feasibility of pulsed electric field ablation for early-stage non-small cell lung cancer prior to surgical resection. *J Surg Oncol.* 2025;131(8):1529–1542. doi: [10.1002/jso.28110](https://doi.org/10.1002/jso.28110)
*This prospective clinical trial treated 38 patients with early-stage NSCLC with PEF ablation followed by surgical resection, providing unique in vivo histologic characterization of the ablation zone and demonstrating feasibility.
- [10] Shrestha A, Martin C, Burton M, et al. Quality of life versus length of life considerations in cancer patients: A systematic literature review. *Psychooncology.* [Internet]. 2019;28(7):1367–1380. doi: [10.1002/pon.5054](https://doi.org/10.1002/pon.5054)
- [11] Reeve BB, Mitchell SA, Dueck AC, et al. Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *J Natl Cancer Inst.* 2014;106(7):dju129–dju129. doi: [10.1093/jnci/dju129](https://doi.org/10.1093/jnci/dju129)
- [12] Kyte D, Retzer A, Ahmed K, et al. Systematic evaluation of patient-reported outcome protocol content and reporting in cancer trials. *J Natl Cancer Inst.* 2019;111(11):1170–1178. doi: [10.1093/jnci/djz038](https://doi.org/10.1093/jnci/djz038)
- [13] Harris JP, Boyd C, Shi M, et al. Pilot Study of combining stereotactic body radiation therapy with pulsed field ablation for oligometastatic/oligoprogressive lung tumors. *J Vasc Interv Radiol.* 2025;36(11):1687–1695. doi: [10.1016/j.jvir.2025.08.005](https://doi.org/10.1016/j.jvir.2025.08.005)
**This article reports the primary safety and oncologic efficacy endpoint of the clinical trial combining PEF ablation with lower-dose SBRT, demonstrating acceptable toxicity and preliminary local control in predominantly central/ultra-central oligometasta
- [14] Cella DF, Bonomi AE, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer.* 1995;12(3):199–220. doi: [10.1016/0169-5002\(95\)00450-f](https://doi.org/10.1016/0169-5002(95)00450-f)
- [15] Created in <https://BioRender.com>.
- [16] Cella D, Eton DT, Fairclough DL, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. *J Clin Epidemiol.* 2002;55(3):285–295. doi: [10.1016/s0895-4356\(01\)00477-2](https://doi.org/10.1016/s0895-4356(01)00477-2)
- [17] Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol.* 2019;37(18):1558–1565. doi: [10.1200/JCO.19.00201](https://doi.org/10.1200/JCO.19.00201)

- [18] Bezjak A, Paulus R, Gaspar LE, et al. Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non-small-cell lung cancer: NRG oncology/RTOG 0813 trial. *J Clin Oncol*. 2019;37(15):1316–1325. doi: [10.1200/JCO.18.00622](https://doi.org/10.1200/JCO.18.00622)
- [19] Videtic GMM, Hu C, Singh AK, et al. A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer: NRG Oncology RTOG 0915 (NCCTG N0927). *Int J Radiat Oncol Biol Phys*. 2015;93(4):757–764. doi: [10.1016/j.ijrobp.2015.07.2260](https://doi.org/10.1016/j.ijrobp.2015.07.2260)
- [20] Callstrom MR, Woodrum DA, Nichols FC, et al. Multicenter study of metastatic lung tumors targeted by interventional cryoablation evaluation (SOLSTICE). *J Thorac Oncol*. 2020;15(7):1200–1209. doi: [10.1016/j.jtho.2020.02.022](https://doi.org/10.1016/j.jtho.2020.02.022)
- [21] Lencioni R, Crocetti L, Cioni R, et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). *Lancet Oncol*. 2008;9(7):621–628. doi: [10.1016/S1470-2045\(08\)70155-4](https://doi.org/10.1016/S1470-2045(08)70155-4)
- [22] de Baère T, Woodrum D, Tselikas L, et al. The ECLIPSE study: efficacy of cryoablation on metastatic lung tumors with a 5-year follow-up. *J Thorac Oncol*. 2021;16(11):1840–1849. doi: [10.1016/j.jtho.2021.07.021](https://doi.org/10.1016/j.jtho.2021.07.021)
- [23] Reuss JE, Bazhenova L, Ismaila N, et al. Therapy for stage IV non-small cell lung cancer without driver. *Alterations ASCO Living Guideline 3.0*. *J Clin Oncol* [Internet]. 2026;0(0):JCO-25-02825.
- [24] Elamin YY, Gandhi S, Antonoff M, et al. LBA72 NorthStar: A phase II randomized study of osimertinib (OSI) with or without local consolidative therapy (LCT) for metastatic EGFR-mutant non-small cell lung cancer (NSCLC). *Annals of Oncology* [Internet]. 2025;36:S1614. doi: [10.1016/j.annonc.2025.09.086](https://doi.org/10.1016/j.annonc.2025.09.086)
- [25] Iyengar P, Hu C, Gomez DR, et al. NRG-LU002: Randomized phase II/III trial of maintenance systemic therapy versus local consolidative therapy (LCT) plus maintenance systemic therapy for limited metastatic non-small cell lung cancer (NSCLC). *JCO*. 2024;42(16_suppl):8506–8506. doi: [10.1200/JCO.2024.42.16_suppl.8506](https://doi.org/10.1200/JCO.2024.42.16_suppl.8506)
- [26] Grass GD, Alfonso JCL, Welsh E, et al. The radiosensitivity index gene signature identifies distinct tumor immune microenvironment characteristics associated with susceptibility to radiation therapy. *Int J Radiat Oncol Biol Phys*. 2022;113(3):635–647. doi: [10.1016/j.ijrobp.2022.03.006](https://doi.org/10.1016/j.ijrobp.2022.03.006)
- [27] Derer A, Deloch L, Rubner Y, et al. Radio-immunotherapy-induced immunogenic cancer cells as basis for induction of systemic anti-tumor immune responses – pre-clinical evidence and ongoing clinical applications. *Front Immunol*. 2015;6:505. doi: [10.3389/fimmu.2015.00505](https://doi.org/10.3389/fimmu.2015.00505)
- [28] Gallo PM, Gallucci S. The dendritic cell response to classic, emerging, and homeostatic danger signals. Implications for autoimmunity. *Front Immunol*. 2013;4:138. doi: [10.3389/fimmu.2013.00138](https://doi.org/10.3389/fimmu.2013.00138)
- [29] Piffkó A, Yang K, Panda A, et al. Radiation-induced amphiregulin drives tumour metastasis. *Nature* [Internet]. 2025;643(8072):810–819. doi: [10.1038/s41586-025-08994-0](https://doi.org/10.1038/s41586-025-08994-0)
- [30] Puri S, Leighl NB, Ismaila N, et al. Therapy for stage IV non-small cell lung cancer with driver. *Alterations ASCO Living Guideline; 2026.3.0*. *J Clin Oncol* [Internet]. 2026;0(0):JCO-25-02822.
- [31] Semenkovich NP, Badiyan SN, Samson PP, et al. Pre-radiotherapy ctDNA liquid biopsy for risk stratification of oligo-metastatic non-small cell lung cancer. *NPJ Precis Oncol*. 2023;7(1):100. doi: [10.1038/s41698-023-00440-6](https://doi.org/10.1038/s41698-023-00440-6)
- [32] Walls GM, Pellini B, Chaudhuri AA. Circulating tumor DNA kinetics: A future tool for radiation therapy personalization in lung cancer? *J Liq Biopsy*. 2024;6:100160. doi: [10.1016/j.jlb.2024.100160](https://doi.org/10.1016/j.jlb.2024.100160)
- [33] Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA*. 2010;303(11):1070–1076. doi: [10.1001/jama.2010.261](https://doi.org/10.1001/jama.2010.261)
- [34] Videtic GM, Paulus R, Singh AK, et al. Long-term follow-up on NRG oncology RTOG 0915 (NCCTG N0927): a randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2019;103(5):1077–1084. doi: [10.1016/j.ijrobp.2018.11.051](https://doi.org/10.1016/j.ijrobp.2018.11.051)
- [35] Lindberg K, Grozman V, Karlsson K, et al. The HILUS-trial – a prospective Nordic multi-center phase II study of ultra-central lung tumors treated with stereotactic body radiotherapy. *J Thorac Oncol*. 2021;16(7):1200–1210. doi: [10.1016/j.jtho.2021.03.019](https://doi.org/10.1016/j.jtho.2021.03.019)
 *The HILUS trial is a prospective Nordic multi-center phase II study of 65 patients with ultra-central NSCLC treated with SBRT, reporting 2-year local control of 83% but highlighting the critical safety concern of 34% severe toxicity rate (including 10 treatment-related deaths), underscoring the need for tissue-sparing approaches for these high-risk tumors.
- [36] Meredith EG, 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(3):669–677.
- [37] Levy A, Adebahr S, Hurkmans C, et al. Stereotactic body radiotherapy for centrally located inoperable early-stage NSCLC: EORTC 22113–08113 LungTech Phase II trial results. *Journal of Thoracic Oncology*. [Internet]. 2024;19(10):e57–e59. doi: [10.1016/j.jtho.2024.08.001](https://doi.org/10.1016/j.jtho.2024.08.001)
- [38] Kong F-MS, Moiseenko V, Zhao J, et al. Organs at risk considerations for thoracic stereotactic body radiation therapy: what is safe for lung parenchyma? *Int J Radiat Oncol Biol Phys*. 2021;110(1):172–187. doi: [10.1016/j.ijrobp.2018.11.028](https://doi.org/10.1016/j.ijrobp.2018.11.028)
- [39] Iovoli AJ, Yu B, Ma SJ, et al. Quality of life after stereotactic body radiation therapy or surgery for early-stage NSCLC: a systematic review. *JTO Clin Res Rep*. 2022;3(11):100417. doi: [10.1016/j.jtocrr.2022.100417](https://doi.org/10.1016/j.jtocrr.2022.100417)

**This systematic review comprehensively evaluates quality of life changes following SBRT monotherapy for early-stage NSCLC, providing important context that SBRT alone does not significantly impair quality of life in peripheral or central lung tumors.

- [40] Stanic S, Paulus R, Timmerman RD, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy (SBRT) for early stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. *Int J Radiat Oncol Biol Phys*. 2014;88(5):1092–1099. doi: [10.1016/j.ijrobp.2013.12.050](https://doi.org/10.1016/j.ijrobp.2013.12.050)
- [41] 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(7):838–844. doi: [10.1097/JTO.0b013e3181a99ff6](https://doi.org/10.1097/JTO.0b013e3181a99ff6)
- [42] Guckenberger M, Klement RJ, Kestin LL, et al. Lack of a dose-effect relationship for pulmonary function changes after stereotactic body radiation therapy for early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2013;85(4):1074–1081. doi: [10.1016/j.ijrobp.2012.09.016](https://doi.org/10.1016/j.ijrobp.2012.09.016)
- [43] de Baere T, Tselikas L, Woodrum D, et al. Evaluating cryoablation of metastatic lung tumors in patients—safety and efficacy the ECLIPSE trial—interim analysis at 1 year. *J Thorac Oncol*. 2015;10(10):1468–1474. doi: [10.1097/JTO.0000000000000632](https://doi.org/10.1097/JTO.0000000000000632)
- [44] Colak E, Tatli S, Shyn PB, et al. CT-guided percutaneous cryoablation of central lung tumors. *Diagn Interv Radiol*. 2014;20(4):316–322. doi: [10.5152/dir.2014.13440](https://doi.org/10.5152/dir.2014.13440)
- [45] Maor E, Ivorra A, Leor J, et al. The effect of irreversible electroporation on blood vessels. *Technol Cancer Res Treat*. 2007;6(4):307–312. doi: [10.1177/153303460700600407](https://doi.org/10.1177/153303460700600407)
- [46] Thomson KR, Cheung W, Ellis SJ, et al. Investigation of the safety of irreversible electroporation in humans. *J Vasc Interv Radiol*. 2011;22(5):611–621. doi: [10.1016/j.jvir.2010.12.014](https://doi.org/10.1016/j.jvir.2010.12.014)
- [47] Gissel H, Lee RC, Gehl J. Electroporation and cellular physiology. In: Kee ST, Gehl J, Lee EW, editors. *Clinical Aspects of Electroporation* [Internet]. New York, NY: Springer New York; 2011, p. 9–17. doi: [10.1007/978-1-4419-8363-3_2](https://doi.org/10.1007/978-1-4419-8363-3_2)
- [48] Moore WH, Silk M, Bhattacharji P, et al. Safety and feasibility of percutaneous pulsed electrical field ablation in multiple organs: A multi-center retrospective study*. *Eur J Radiol*. 2025;187:112078. doi: [10.1016/j.ejrad.2025.112078](https://doi.org/10.1016/j.ejrad.2025.112078)
 *This multi-center retrospective study of 155 patients treated with PEF ablation across multiple organs (predominantly lung tumors) demonstrates the feasibility and safety profile of PEF ablation, reporting pneumothorax rates of 21.5% with 11.3% requiring chest tube placement.
- [49] Moore WH, Silk M, Bhattacharji P, et al. Early experience with PEF in the setting of recalcitrant stage IV lung cancer. *Lung Cancer*. 2025;204:108575. doi: [10.1016/j.lungcan.2025.108575](https://doi.org/10.1016/j.lungcan.2025.108575)
- [50] Rouhezamin MR, Fintelmann FJ, Huang AJ, et al. Limited effectiveness in early human clinical experience with pulsed electrical field ablation. *J Vasc Interv Radiol*. 2025;36(2):274–281. doi: [10.1016/j.jvir.2024.10.033](https://doi.org/10.1016/j.jvir.2024.10.033)
- [51] Sandler KA, Abtin F, Suh R, et al. A prospective phase 2 study evaluating safety and efficacy of combining stereotactic body radiation therapy with heat-based ablation for centrally located lung tumors. *Int J Radiat Oncol Biol Phys*. 2018;101(3):564–573. doi: [10.1016/j.ijrobp.2018.03.011](https://doi.org/10.1016/j.ijrobp.2018.03.011)
 **This prospective phase II trial of 16 patients tested combination SBRT (36–42 Gy in 3 fractions) followed by heat-based ablation for central lung tumors, reporting 2-year local control of 81% but notable toxicity including 19% severe adverse events and statistically significant pulmonary function declines, providing critical comparative context for tissue-sparing approaches.
- [52] Klement RJ, Hoerner-Rieber J, Adebahr S, et al. Stereotactic body radiotherapy (SBRT) for multiple pulmonary oligometastases: Analysis of number and timing of repeat SBRT as impact factors on treatment safety and efficacy. *Radiother Oncol*. 2018;127(2):246–252. doi: [10.1016/j.radonc.2018.02.016](https://doi.org/10.1016/j.radonc.2018.02.016)