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Scientific letter

Bronchoscopic Pulsed Electric Field for Ablation and Inmunomodulation in Early-stage Non-small Lung Cancer: A Case Report

Campos eléctricos pulsados mediante broncoscopia para el tratamiento ablativo y modulación inmunitaria del cáncer de pulmón no-microcítico en estadio temprano: caso clínico

Dear Editor,

Lung cancer is the second most prevalent type of cancer and the leading cause of cancer-related deaths worldwide.[1,2] Early diagnosis is imperative for improving survival rates, hence the increasing implementation of lung cancer screening programmes. Surgery remains the standard of care for non-small cell lung cancer (NSCLC), particularly in early-stage disease. However, for patients who are considered unsuitable for surgical intervention, minimally invasive ablative therapies have emerged as a viable therapeutic alternative.[3]

Thermal ablation techniques, including radiofrequency ablation (RFA) and microwave ablation (MWA), have exhibited efficacy in the treatment of peripheral NSCLC. RFA has been demonstrated to yield local control rates ranging from 80% to 90% for tumors measuring less than 3 cm in diameter.[4] Conversely, MWA generates larger and more consistent ablation zones due to its elevated intratumoral temperatures and diminished sensitivity to heat-sink effects.[5]

The development of minimally invasive procedures has been a milestone, offering high diagnostic accuracy with reduced complication rates. Electromagnetic navigation bronchoscopy (ENB) combined with cone beam computed tomography (CBCT) facilitates precise access to peripheral pulmonary lesions and enables the application of ablative techniques for NSCLC.

Pulsed electric field (PEF) ablation is a non-thermal technique that has emerged as a promising method of inducing cell death through irreversible electroporation. A significant benefit is its capacity to preserve the extracellular matrix and critical structures, which has the potential to induce antitumor immune responses.

A 67-year-old male, a former smoker with mild chronic obstructive pulmonary disease (COPD), presented with a 2 cm peripheral pulmonary nodule in the right upper lobe (RUL), identified during routine low-dose CT screening (Fig. 1). He exhibited no symptoms of clinical significance and demonstrated preserved pulmonary function (FEV1 75% predicted) and was subsequently enrolled in a first-in-human trial investigating the safety and immunomodulatory effects of bronchoscopic PEF ablation using the Aliya™ system (Galvanize Therapeutics, USA). ENB combined with CBCT facilitated precise targeting and tissue sampling of the lesion (Fig. 1). Histopathological analysis confirmed the presence of lung adenocarcinoma (TTF-1 positive, PD-L1 <1%). Following the confirmation of the biopsy result, PEF ablation was performed during the same surgical procedure. The energy delivery was well tolerated, with no immediate complications such as bleeding, pneumothorax, or bronchospasm. The patient was monitored and discharged the following day, found to be in a stable condition.

Peripheral blood samples were obtained at multiple time points in order to evaluate systemic immune responses. These time points included baseline, day of ablation, days 5 and 15 post-treatment, and the day of planned surgical resection. Surgical lobectomy was performed approximately 30 days after the initial ablation. The resected specimen exhibited three distinctly delineated zones: a depletion cell zone corresponding to the ablation area, a surrounding region with immune cell infiltration and preserved bronchovascular structures representing a transition zone, and a residual tumor zone.

PEF ablation represents a novel, non-thermal modality for tumor ablation, distinguished by its ability to induce irreversible electroporation, leading to targeted cell death while preserving the extracellular matrix and adjacent critical structures. This characteristic is particularly advantageous in pulmonary applications, where preserving lung architecture is paramount. Unlike thermal ablation techniques such as RFA and MWA, which rely on heat to induce coagulative necrosis, PEF utilizes high-voltage, short-duration electrical pulses to permeabilize cell membranes, resulting in apoptosis without significant thermal injury to surrounding tissues.[6]

The immunomodulatory potential of PEF is a distinguishing feature that sets it apart from conventional ablation methods. Preclinical studies have demonstrated that PEF can stimulate both innate and adaptive immune responses by promoting immunogenic cell death and the release of damage-associated molecular patterns (DAMPs). This process facilitates the recruitment and activation of antigen-presenting cells, leading to the priming of tumor-specific T cells. Moreover, PEF has been associated with the formation of tertiary lymphoid structures (TLS) within the tumor microenvironment, which are predictive biomarkers for responsiveness to immune checkpoint inhibitors.[7]

A comparative study conducted in murine models has indicated that PEF is superior to RFA in terms of its capacity to elicit systemic immune responses. PEF-treated tumors exhibited increased infiltration of dendritic cells, M1 macrophages, and natural killer cells, along with a reduction in immunosuppressive cell populations such as M2 macrophages and myeloid-derived suppressor cells. The aforementioned changes were accompanied by enhanced antigen-specific T cell responses and a decrease in regulatory T cells. This culminated in improved tumor control and survival outcomes.[8,9]

The immunostimulatory properties of PEF open avenues for its integration into multimodal treatment strategies. Preclinical studies have demonstrated that combining PEF with immune checkpoint inhibitors, such as anti-PD-1 therapy, can potentiate systemic antitumor immunity and enhance the abscopal effect, leading to regression of distant, untreated tumors. Fur-

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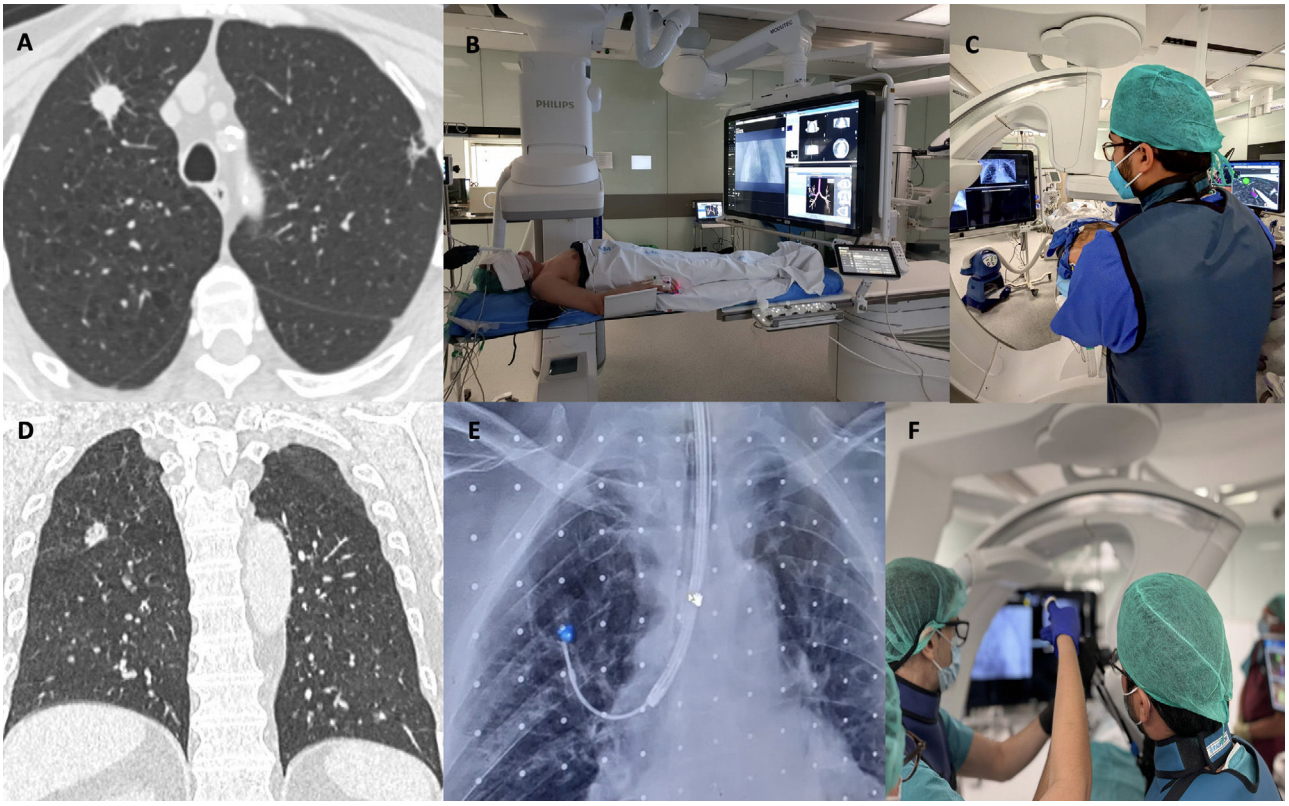

Fig. 1. (A) Pulmonary nodule in the RUL on axial chest CT imaging. (B) Hybrid operating room setting. (C) ENB combined with CBCT. (D) Pulmonary nodule in the RUL visualized on coronal chest CT imaging. (E) Augmented fluoroscopy image showing the RUL nodule. (F) ENB combined with CBCT during the diagnostic phase, with transbronchial biopsy sampling.

thermore, PEF has shown promise as a neoadjuvant therapy. In murine models, the addition of PEF to standard neoadjuvant chemo-immunotherapy regimens resulted in improved local tumor control, reduced metastatic spread, and prolonged survival compared to systemic therapy alone. These findings suggest that PEF could be employed to convert immunologically "cold" tumors into "hot" ones, thereby enhancing the efficacy of subsequent systemic therapies.[10]

Pulsed electric field ablation has emerged as a promising, minimally invasive approach for the treatment of peripheral lung cancer particularly in patients who are unsuitable for surgery. Its mechanism of inducing non-thermal cell death while preserving surrounding structures, coupled with its capacity to stimulate robust antitumor immune responses, positions PEF as a valuable addition to the therapeutic arsenal against lung cancer. It is recommended that future clinical studies be conducted in order to validate these findings and to explore the integration of PEF with systemic therapies, including immunotherapy and chemotherapy, in both neoadjuvant and adjuvant settings.

Declaration of generative AI and AI-assisted technologies in the writing process

The material has been produced by the authors, without partial or total help of artificial intelligence software or tools.

Informed consent

The authors declare that they have obtained the patient's informed consent in accordance with the ethical guidelines of the institution. This document is held by the corresponding author.

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Conflicts of interest

The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73:17–48, http://dx.doi.org/10.3322/caac.21763.
2. Zhang Y, Vaccarella S, Morgan E, Li M, Etxeberria J, Chokunonga E, et al. Global variations in lung cancer incidence by histological subtype in 2020: a population-based study. Lancet Oncol. 2023;24:1206–18, http://dx.doi.org/10.1016/S1470-2045(23) 00444-8.
3. Palussière J, Catena V, Buy X. Percutaneous thermal ablation of lung tumors – radiofrequency, microwave and cryotherapy: where are we going? Diagn Interv Imaging. 2017;98:619–25, http://dx.doi.org/10.1016/j.diii.2017.07.003 [Epub 24 August 2017; PMID: 28844613].
4. Xie F, Zheng X, Xiao B, Han B, Herth FJF, Sun J. Navigation bronchoscopy-guided radiofrequency ablation for nonsurgical peripheral pulmonary tumors. Respiration. 2017;94:293–8, http://dx.doi.org/10.1159/000477764 [Epub 6 July 2017; PMID: 28683443].
5. Chan JWY, Lau RWH, Ngai JCL, Tsoi C, Chu CM, Mok TSK, et al. Transbronchial microwave ablation of lung nodules with electromagnetic navigation bronchoscopy guidance – a novel technique and initial experience with 30 cases. Transl Lung Cancer Res. 2021;10:1608–22,

http://dx.doi.org/10.21037/tlcr-20-1231 [PMID: 34012778; PMCID: PMC8107744].
6. Arciga BM, Walters DM, Kimchi ET, Staveley-O'Carroll KF, Li G, Teixeiro E, et al. Pulsed electric field ablation as a candidate to enhance the anti-tumor immune response to immune checkpoint inhibitors. Cancer Lett. 2025;609:217361, http://dx.doi.org/10.1016/j.canlet.2024.217361 [Epub 26 November 2024; PMID: 39608443; PMCID: PMC11625606].
7. Jimenez M, Flandes J, van der Heijden EHFM, Ng CSH, Iding JS, Garcia-Hierro JF, 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, http://dx.doi.org/10.1002/jso.28110 [Epub ahead of print; PMID: 40152831].
8. Wang Y, Jiang T, Xie L, Wang H, Zhao J, Xu L, et al. Effect of pulsed field ablation on solid tumor cells and microenvironment. Front Oncol. 2022;12:899722, http://dx.doi.org/10.3389/fonc.2022.899722 [PMID: 36081554; PMCID: PMC9447365].
9. Pastori C, Nafie EHO, Wagh MS, Mammarappallil JG, Neal RE 2nd. Pulsed electric field ablation versus radiofrequency thermal ablation in murine breast cancer models: anticancer immune stimulation tumor response, and abscopal effects. J Vasc Interv Radiol. 2024;35, http://dx.doi.org/10.1016/j.jvir.2023.11.021, 442–451.e7 [Epub 30 November 2023; PMID: 38042523].
10. Pastori C, Nafie EHO, Wagh MS, Hunt SJ, Neal RE 2nd. Neoadjuvant chemo-immunotherapy is improved with a novel pulsed electric field technology in an immune-cold murine model. PLoS One. 2024;19:e0299499, http://dx.doi.org/10.1371/journal.pone.0299499 [PMID: 38527041; PMCID: PMC10962799].

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