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Up and-coming Bronchoscopic Ablation Therapies for Treatment of Lung Cancer

Muhammad Sajawal Ali MD
Assistant Professor of Medicine,
Weill Cornell Medicine,
New York, NY

Ali Musani MD
Professor of Medicine and Surgery,
University of Colorado School of Medicine, Denver

Stereotactic beam radiation therapy (SBRT) has traditionally been the standard of care for patients with early-stage lung cancer and thoracic oligometastatic disease who are not surgical candidates. SBRT has been defined as large doses of radiation (> 6 Gy/ fraction) administered over a few (<=5) fractions [1]. This administration of large doses of radiation can be associated with significant toxicities both to the treatment sites and the adjacent normal structures that can become collateral damage. Complications include pneumonia, pneumonitis, chest wall pain, rib fractures, brachial plexus injury, etc. [2 3] The risk of complications seems to be higher for more central and 'ultra' central tumors as they are situated closer to the critical thoracic structures[4]. Similarly, patients with pre-existing interstitial lung diseases are at a higher risk of pneumonitis as well, with some studies reporting a risk of fatal radiation pneumonitis at 6% [5].

Given the above limitations, there has been a significant interest in developing minimally invasive ablative technologies that can be administered via transbronchial or image-guided transthoracic routes. These modalities include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, and more recently pulsed electric field (PEF) systems. RFA involves placing a probe into the lesion, through which alternating current is passed. This produces heat and can generate a temperature of > 100◦C in the vicinity of the target with resultant necrosis of the lesion [6 7]. However, as the lesion is charred, it impedes the conductance of current and heat, which may limit the ablation zone. Similarly, blood flowing through any adjacent vessels acts as a 'heat sink', thereby making it harder to reach the intended target temperature and therefore limiting the ablation efficacy and zone. MWA which uses alternating electromagnetic waves to oscillate water molecules and generate frictional heat, is more resistant to these limitations and therefore can potentially achieve higher temperature and a larger ablation zone [6]. Pneumothoraces and bleeding are the most significant complications for MWA[8 9]. Tumor cryoablation involves introducing a cryoprobe into the lesion; multiple freeze-thaw cycles are then used to induce cell death. Like most image-guided transthoracic ablative modalities, the most frequent complication is pneumothorax; however, more serious complications such as hemopneumothorax and hemoptysis have also been reported [10].

The newest ablation modality is the pulsed electric field (PEF) therapy. Unlike the aforementioned therapies, it doesn't rely on heat or cold to degenerate tumors; rather, it uses brief high voltage current to alter the cell membrane potentials, thereby interfering with normal cell homeostasis and eventually leading the cell death f[11 12]. As a result, the extracellular matrix is preserved. Furthermore, antigens are released from the tumor, which may induce an anti-tumor immune response as well. The fact that extracellular matrix and lymphatic drainage are preserved, together with the

fact that a capsule of scar tissue doesn't form, can potentially further enhance the immune response. The anti-tumor effect is achieved via both direct ablation and indirect immune response. The anti-tumor immune response can be observed at distal tumor sites as well. INCITE-ES is an international treat and resect study for early-stage non-small cell lung cancers to assess the safety and immune activation[13]. Early results suggest PEF therapy induces a strong immune response in the tumors[14]. AFFINITY is another major multicenter prospective study assessing the safety and effectiveness of PEF therapy in patients with metastatic pulmonary lesions [15].

In summary, while the data is still limited on the safety, efficacy, and technical parameters for lung cancer ablative therapies, multiple modalities appear promising. There is significant excitement around PEF therapy, since in addition to local ablation it may increase the efficacy of immunotherapy both locally and at distant sites. These therapies can be administered both via transthoracic and bronchoscopic routes. Therefore, it would be feasible to potentially offer a tumor biopsy and therapy in the same setting. Further studies are needed before these ablative therapies can be routinely adopted. However, they are well and truly on the way to becoming alternatives and, in some cases, even replacing SBRT and surgery.

References:

1. Potters L et al. *Int J Radiat Oncol Biol Phys.* 2010;76(2):326–332.
2. Andolino DL et al. *Int J Radiat Oncol Biol Phys.* 2011;80(3):692–697.
3. Forquer JA et al. *Radiother Oncol.* 2009;93(3):408–413.
4. Lindberg K et al. *J Thorac Oncol.* 2021;16(7):1200–1210.
5. Onishi H et al. *Cancers (Basel).* 2018;10(8):257.
6. Bartlett EC et al. *Lung Cancer* 2023;176:14–23.
7. Zhong C-H et al. *European Respiratory Journal* [Internet] 2023 [cited 2024 Jan 3];62(suppl 67). Available from: https://erj.ersjournals.com/content/62/suppl_67/OA2598
8. Tran S et al. *European Respiratory Journal* [Internet] 2017 [cited 2024 Jan 3];50(suppl 61). Available from: https://erj.ersjournals.com/content/50/suppl_61/PA4282
9. Lau KKW et al. J *Bronchology Interv Pulmonol.* 2023 Sep 25. doi: 10.1097/LBR.0000000000000950.
10. Zhang Y-S et al. *J Thorac Dis.* 2016;8(Suppl 9):S705–S709.
11. Wagstaff PG et al.. *Onco Targets Ther.* 2016;9:2437–2446.
12. Irreversible electroporation of lung neoplasm: A case series - PMC [Internet]. [cited 2024 Jan 3];Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3560719/
13. Galvanize Therapeutics, Inc. The Galvanize Therapeutics Early Stage, Non-Small Cell Lung Cancer, Treat and Resect Study [Internet]. clinicaltrials.gov; 2023 [cited 2023 Dec 31]. Available from: https://clinicaltrials.gov/study/NCT04732520
14. Inc GT. Galvanize Therapeutics Announces Promising Data on the Aliya™ Pulsed Electric Field (PEF) System in Early-Stage Non-Small Cell Lung Cancer [Internet]. [cited 2024 Jan 3];Available from: https://www.prnewswire.com/news-releases/galvanize-therapeutics-announces-promising-data-on-the-aliya-pulsed-electric-field-pef-system-in-early-stage-non-small-cell-lung-cancer-301977976.html
15. Inc GT. Galvanize Therapeutics Begins U.S. Clinical Study Using Aliya™ Pulsed Electric Field (PEF) for Stage IV Non-Small Cell Lung Cancer or Metastasis to the Lung [Internet]. [cited 2024 Jan 3];Available from: https://www.prnewswire.com/news-releases/galvanize-therapeutics-begins-us-clinical-study-using-aliya-pulsed-electric-field-pef-for-stage-iv-non-small-cell-lung-cancer-or-metastasis-to-the-lung-301932837.html