Editorial

Therapy option for early-stage lung cancer in nonsurgical patients

Seyer Safi[1]^, Gregor S. Zimmermann[2]

[1]Division of Thoracic Surgery, School of Medicine, University Hospital Rechts der Isar, Technical University of Munich, Munich, Germany; [2]Department of Internal Medicine I, School of Medicine, University Hospital Rechts der Isar, Technical University of Munich, Munich, Germany

Correspondence to: Seyer Safi. Division of Thoracic Surgery, School of Medicine, University Hospital rechts der Isar, Technical University of Munich, 81675 Munich, Germany. Email: seyer.safi@mri.tum.de.

Comment on: Bao F, Yu F, Wang R, *et al.* Electromagnetic bronchoscopy guided microwave ablation for early stage lung cancer presenting as ground glass nodule. Transl Lung Cancer Res 2021;10:3759-70.

Submitted Dec 07, 2021. Accepted for publication Dec 31, 2021.
doi: 10.21037/tlcr-21-972
View this article at: https://dx.doi.org/10.21037/tlcr-21-972

The treatment of choice for early-stage lung cancer, both small cell and non-small cell lung cancer, is complete surgical resection with lymph node evaluation (1,2).

However, the best local therapy for medically inoperable patients, those with multiple lung tumors, or those who refuse surgery is not clearly established.

Bao and colleagues (3) reported their experience with electromagnetic navigation bronchoscopy (ENB)-guided microwave ablation (MWA) in 15 patients with ground glass nodules, in which a large proportion of patients underwent additional surgery. This was a pilot study demonstrating the feasibility of ENB-guided MWA and the potential advantages of ENB-guided MWA over computed tomography (CT)-guided transcutaneous radiofrequency ablation (RFA), which is otherwise commonly performed in this nonsurgical patient population.

ENB, a technology to guide tissue sampling by virtual bronchoscopy based on reconstructions of previously performed CT thorax images, was introduced for peripheral lung nodules in humans in 2005 (4) and demonstrated to be safe in a large prospective trial (5). Data are available on ENB-guided RFA of lung tumors (6) and on transcutaneous MWA of lung tumors (7), but there are only a few reports on ENB-guided MWA of lung tumors, including the study by Bao and colleagues. The advantages of MWA in general compared to RFA are a shorter ablation time, more homogeneous ablation zones and the application of MWA in air-enriched ground glass nodules without injection of saline.

ENB-guided MWA, similar to transcutaneous RFA but different from stereotactic body radiotherapy (SBRT), has the advantage of allowing pathologic confirmation of the malignancy followed by tumor ablation during the same anesthesia.

The idea behind ENB-guided MWA of avoiding subsequent procedures and thus increasing patient comfort is also being considered in thoracic surgery through the introduction of hybrid operations. Diagnostics and therapy merge into one intervention when a small lung lesion is first biopsied and, in the case of intraoperative evidence of malignancy, is subsequently resected completely in a minimally invasive operative procedure during the same anesthesia (8).

Bao and colleagues cytologically evaluated small samples of lung lesions with rapid onsite evaluation (ROSE). A limitation of this approach is the decreased reliability of the pathologic assessment compared to frozen section examination or final pathology. In a study comparing frozen section examination with final pathology in CT-guided biopsies of lung nodules, 18 out of 163 lung cancers were undefined with frozen section examination but were diagnosed as adenocarcinoma with final pathology (9). The relatively high rate of false-negative biopsy results was also evident in the study by Bao and colleagues as two patients were ablated despite a negative intraoperative biopsy result because the radiomorphology appeared typical of malignancy. This example underscores the advantage of surgical resection compared to biopsy or liquid biopsy, which represents the high quality of pathology that is a

^ ORCID: 0000-0002-2335-4309.

prerequisite for mutational analyses for targeted therapies.

Persistence of an ablated tumor *in situ* indicates limited pathologic accessibility for the pathologist and a lack of reliable, postinterventional accessibility regarding response to ablation for the clinician, which is true for all forms of tumor ablation, including ENB-guided MWA, RFA or SBRT. However, the persistence of an ablated tumor can also be reinterpreted as an advantage in view of the abscopal effect, according to which after local tumor therapy, a systemic immune response not only shrinks the targeted tumor but also leads to the shrinkage of untreated tumors elsewhere in the body, which has been reported for MWA of lung cancer (10). The abscopal effect was first described in 1953 (11) and is explained by the release of tumor antigens during ablation, which leads to a form of *in situ* vaccination. In recent years, it has become apparent that lung carcinoma is also an immunogenic tumor, contrary to what has been assumed for a long time. The study of Bao and colleagues supports the idea of therapeutic induction of an abscopal effect by ablation, which is of great interest in oncology in general and is currently being investigated in clinical trials.

The scope of the work performed by Bao and colleagues is clinically relevant because the ability to access and assess small lung lesions will become more important in the future as it is anticipated that the introduction of CT lung cancer screening will increasingly detect lung cancer at earlier stages. However, not only interventional ablation methods but also surgical options to target small lung lesions in a navigation-guided approach and to resect them completely in a parenchyma-sparing procedure to preserve lung function are evolving. For many years, lobectomy has been the recommended therapy, even for small lung cancer (12). However, the first randomized phase 3 trial of segmentectomy versus lobectomy in small peripheral non-small cell lung cancer (JCOG0802/WJOG4607L) suggests an advantage of segmentectomy with significant benefits in survival and lung function, such that in the future, parenchyma-sparing segmentectomy may replace lobectomy as surgical therapy for certain small peripheral non-small cell lung cancers (NSCLCs) (13).

Although less lung volume is resected in segmentectomy than in lobectomy, segmentectomy is a technically sophisticated operation because it requires a thorough understanding of the complex segmental anatomy, which is often associated with abnormalities. Currently, thoracic surgery centers are increasingly able to perform segmentectomy for small, difficult-to-locate and nonpalpable lung nodules using minimally invasive techniques, such as videothoracoscopy or robotic surgery. Thus, it may become possible to extend the use of new ablation methods to certain operable patients. At the same time, new less invasive surgical and anesthetic techniques, such as nonintubated videothoracoscopy (14) or an "all-in-one" hybrid operation room technology (8), could be offered in the future to patients who are currently considered nonsurgical candidates.

Bao and colleagues are to be congratulated for enhancing treatment options for nonsurgical patients, including not only those with ground glass nodules but also, for example, patients with interstitial lung diseases, in whom standard therapy is only possible with increased perioperative morbidity. The presented work is a clinical pilot study that, due to the small number of cases, cannot answer the question of whether the new method is safe or how to evaluate the long-term outcome of the ablation method. The study shows that ENB-guided MWA is feasible in ground glass nodules, but it clearly requires larger, prospective, randomized studies to clarify the value of ENB-guided MWA in NSCLC.

Finally, there is the question of the perspective for this new ablation method. Bao and colleagues presented the ENB-guided MWA in NSCLC for patients who were nonsurgical candidates following precise staging without signs of lymph node metastasis or other metastases. In the future, the indication may be extended to other patients, and ENB-guided MWA will have to compete with other therapeutic options, perhaps even in surgical candidates. In this context, it is important that future studies of therapy outcomes consider not only short-term but also long-term outcomes. For example, the LungArt study indicated that postoperative mediastinal irradiation has high toxicity in the long term (15), a toxicity that is generally not observed during short time periods.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-972/coif). SS reports

grants or contracts from Else Kröner Fresenius Stiftung, and payment or honoraria from Coliquio. GSZ reports grants or contracts from AstraZeneca, and payment or honoraria Roche, AstraZeneca, GSK, Pfizer, Boehringer Ingelheim, and Novartis. All payments were approved by the Klinikum rechts der Isar, Technical University of Munich. The authors have no other 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. Ganti AKP, Loo BW Jr, Michael Bassetti M, et al. Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network 2021;19:1441-64.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. Available online: https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (Accessed on Jan 15, 2022).
3. Bao F, Yu F, Wang R, et al. Electromagnetic bronchoscopy guided microwave ablation for early stage lung cancer presenting as ground glass nodule. Transl Lung Cancer Res 2021;10:3759-70.
4. Becker HD, Herth F, Ernst A, et al. Bronchoscopic biopsy of peripheral lung lesions under electromagnetic guidance: a pilot study. Journal of Bronchology & Interventional Pulmonology 2005;12:9-13.
5. Khandhar SJ, Bowling MR, Flandes J, et al. Electromagnetic navigation bronchoscopy to access lung lesions in 1,000 subjects: first results of the prospective, multicenter NAVIGATE study. BMC Pulm Med 2017;17:59.
6. Xie F, Zheng X, Xiao B, et al. Navigation bronchoscopy-guided radiofrequency ablation for nonsurgical peripheral pulmonary tumors. Respiration 2017;94:293-8.
7. Zheng A, Ye X, Yang X, et al. Local efficacy and survival after microwave ablation of lung tumors: a retrospective study in 183 patients. J Vasc Interv Radiol 2016;27:1806-14.
8. Schroeder C, Chung JM, Mitchell AB, et al. Using the hybrid operating room in thoracic surgery: a paradigm shift. Innovations (Phila) 2018;13:372-7.
9. Wei Z, Yang X, Feng Y, et al. Could concurrent biopsy and microwave ablation be reliable? Concordance between frozen section examination and final pathology in CT-guided biopsy of lung cancer. Int J Hyperthermia 2021;38:1031-6.
10. Shao C, Yang M, Pan Y, et al. Case report: abscopal effect of microwave ablation in a patient with advanced squamous NSCLC and resistance to immunotherapy. Front Immunol 2021;12:696749.
11. MOLE RH. Whole body irradiation; radiobiology or medicine? Br J Radiol 1953;26:234-41.
12. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
13. Asamura H, Okada M, Saji H, et al. Randomized trial of segmentectomy compared to lobectomy in small-sized peripheral non- small cell lung cancer. 101st Annual Meeting of American Association for Thoracic Surgery 2021:311-2.
14. Starke H, Zinne N, Leffler A, et al. Developing a minimally-invasive anaesthesiological approach to non-intubated uniportal video-assisted thoracoscopic surgery in minor and major thoracic surgery. J Thorac Dis 2020;12:7202-17.
15. Pechoux CL, Pourel N, Barlesi F, et al. Presentation at ESMO Virtual Congress 2020, An international randomized trial, comparing post-operative conformal radiotherapy (PORT) to no PORT, in patients with completely resected non-small cell lung cancer (NSCLC) and mediastinal N2 involvement: primary end-point analysis of LungART (IFCT-0503, UK NCRI, SAKK) NCT00410683. Ann Oncol 2020;31:S1142-215.

Cite this article as: Safi S, Zimmermann GS. Therapy option for early-stage lung cancer in nonsurgical patients. Transl Lung Cancer Res 2022;11(1):1-3. doi: 10.21037/tlcr-21-972