



A glimpse of the future? – bronchoscopic ablation of peripheral early stage lung cancer

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The rapid expansion of the field of Interventional Pulmonology was initially driven by diagnostic techniques, but more recently has extended into therapeutic interventions. These initially were for airway disease including emphysema (1) and chronic bronchitis (2), but with development of flexible ablation probes, the potential for bronchoscopic therapy of peripheral lung cancer is now closer than ever. Bronchoscopic tumour ablation offers the promise of minimally invasive lung-sparing curative-intent therapy of pulmonary tumours, with a safety likely to be significantly superior to percutaneous ablation modalities. In this issue of *Translational Lung Cancer Research*, Bao and colleagues present exciting new data regarding a novel microwave ablation (MWA) catheter, combined with electromagnetic navigation (EMN) guidance for treatment of ground-glass lesions in patients with multi-focal lung adenocarcinoma (3). Their study is a further step towards bronchoscopic treatment for lung cancer, and illustrates how such technology may alter treatment paradigms in future for patients with localized lung tumours.

Surgical resection has historically been the standard of care for early stage non-small cell lung cancer. Lobectomy is recommended, and consequently patients may lose a significant amount of lung parenchyma even for small lesions. Despite extensive resection, recurrence of disease in Stage I patients occurs in 20–30% of patients, and frequently occurs early—median time to recurrence is approximately 12–17 months (4–6). Peri-operative mortality following lobectomy exceeds 1.5% and does not appear

to be smaller following sub-lobar resection (7). Even for a gold standard, surgical resection leaves much room for improvement.

Additionally, surgery is precluded in many patients, either due to co-existent medical co-morbidities (8), advanced age/frailty (9), or multiple synchronous primaries, or multi-focal adenocarcinoma. Up to 25% of patients with radiologically resectable disease are medically inoperable and thus, effective and safe minimally invasive therapies for pulmonary malignancy are keenly needed.

Multiple percutaneous ablation modalities are available established, with MWA, radiofrequency ablation (RFA), and cryoablation all reported to achieve reasonable local control of Stage I NSCLC. Their use is significantly limited by high rates of complications observed due to the percutaneous introduction of the ablation probes. Pneumothorax rates may exceed 60% (10) with intercostal drains required in 8–38% (11), which is clearly problematic for a modality likely to be applied in multiply co-morbid patients. Safety concerns may also preclude use in central tumours, or those in close proximity to chest wall or mediastinal structures. Isolated reports of needle tract seeding following percutaneous ablation are rare but have been reported following RFA and MWA (12).

Bronchoscopic ablation of peripheral tumours was first reported in 2010 (13), but until recently the only modality used in clinical studies was RFA, and even then, only by two groups (12). The publication by Bao and colleagues is just the second report on EMN-guided MWA for treatment

of peripheral NSCLC, following the study by Chan and colleagues, also published in *Translational Lung Cancer Research* earlier this year (14). Bao and colleagues have used EMN guidance to accurately target fifteen sub-solid lesions ranging from 5–17 mm (only three were larger than 11 mm). Their findings clearly establish technical efficacy and safety of bronchoscopic MWA for ablation of parenchymal lesions. The primary outcome of ablation efficacy, established by radiologic evidence of target lesion ablation on CT 1-week following RFA, was achieved in 11 of 15 patients (73%).

The study also hints at some paradigm changes that may accompany development of bronchoscopic therapy for localized lung cancers—use of rapid on-site cytology to establish intra-procedural diagnosis (and obviate a stand-alone diagnostic procedure) (15), and treatment in the absence of tissue confirmation, as was performed in two patients in this study. Positive predictive value of ROSE examination of bronchial brushings is extremely high (15), and “empiric” stereotactic radiotherapy (SABR) is frequently utilized for stage I NSCLC given the risks of biopsy frequently exceed the risks of SABR (16).

There are some procedural aspects that may need to be incorporated into future studies to improve technical success. Importantly both studies appear to be clinical case series, which may help explain why clinical features of four patients where effective ablation was not demonstrated on CT are not presented. We therefore do not know if this due to insufficient ablation volume, in which case increased energy dose (not reported in this study) may be required. Or was it due to inaccurate targeting, in which case localization tools may be required. Importantly, EMN is a “guidance” tool, and does not provide target localization. Studies reporting accuracy of EMN-guided pleural tattoo are instructive in illustrating that EMN guidance is not 100% accurate (17).

In contrast, endobronchial ultrasound (EBUS) is able to confirm the localization of peripheral lesions prior to treatment. EMN improves the EBUS localization rate of peripheral tumours by approximately 30% (18), suggesting it is likely in future that multiple modalities may be required to ensure accurate targeting of ablation. The retrospective series by Chen & colleagues (14) utilized EMN guidance together with cone-beam CT intra-procedural imaging to confirm accurate probe positioning within the target lesion to achieve EMN ablation in biopsy-confirmed NSCLC ranging 7–29 mm diameter. Perhaps as a result they achieved technical success (defined *a priori* as inclusion of lesion into ablation zone with minimum of 5 mm margin

around lesion) in 100% of cases. This study also reported radiologic outcomes at six months for 15 of 30 patients, with complete response achieved in 1 patient, partial response in 12 patients, and stable disease in the remaining 2 patients.

While feasibility and technical success is established in both studies, what clearly remains to be established is clinical efficacy. Future prospective registered studies of bronchoscopic MWA establishing disease-specific local control, and overall survival will be needed before this modality is ready for clinical use. As the authors note, microscopic foci of residual tumor is impossible to identify on imaging. Indeed, a treat-and-resect study completed at our institution examining efficacy of bronchoscopic thermal vapor ablation for minimally invasive treatment of localized lung cancer demonstrated viable tumour within the radiologic ablation zone in 1 of 4 patients (19). Equally, despite percutaneous MWA ablation with apparent complete ablation, 1-year progression-free survival is only 65% (20).

In addition to the suggested paradigm changes including ROSE, or empiric treatment of suspicious lesions, future studies may also incorporate other novel paradigm elements. Given systematic lymph node staging, routine at the time of lobectomy, will not be performed, systematic EBUS-guided lymph node staging (21,22) may be performed at the time of therapeutic bronchoscopic to ensure absence of lymph node metastases (which would preclude use of localized ablative therapies), or use of validated models for prediction of lymph node metastases (23) may be incorporated into routine pre-procedure work-up to identify those at high risk of PET-occult lymph node involvement. Equally, given the apparent safety & accuracy of bronchoscopic thermal ablation of lung tumours, MWA or other modalities may be use to elicit an anticancer immune response (24), augmenting immune checkpoint inhibitors and other immunotherapies (25).

We warmly congratulate Bao & colleagues on their study which marks a significant advance in the expanding field of interventional pulmonology. In addition to demonstrating the feasibility and technical success of bronchoscopic MWA for ablation of ground-glass lung lesions, they have taken an even more significant step in demonstrating a new paradigm for therapeutic combinations and patient selection for minimally invasive treatment of lung cancer. Future success in establishing bronchoscopic therapies for treatment of pulmonary malignancies will be built upon studies such as this one, and we should all be grateful for their work.

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