



Time to get started with endobronchial microwave ablation—chances, pitfalls and limits for interventional pulmonologists

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In the article, “Flexible bronchoscopy-guided microwave ablation in peripheral porcine lung: a new minimally-invasive ablation” (1) of Yuan and colleagues a comparison of the similar ablation work levels in endobronchial and transcutaneous microwave ablation (MWA) in healthy porcine lung models is well described in regards to *ex-vivo* with uninflated (but still perfused at 37 °C) and *ex-vivo* respectively *in-vivo* inflated perfused lung conditions. Unfortunately, in this reported systematic approach the authors should have realized another study group comprising endobronchial MWA in uninflated but perfused condition. Of utmost interest is the result that the accomplished treatment zone of the endobronchial MWA in the *in-vivo* model group by far not reached the same ablation effect as in the *ex-vivo* inflated and perfused MWA model group although ablation work parameters induced by the same generator in all groups were set equally. As reference served the same MWA generator setting in a transcutaneous uninflated but perfused *ex-vivo* approach with a safety margin of 2 cm (e.g., the parallel distance between antenna and temperature couple) in which the intended temperature of >60 °C was reached much over 4 minutes believed to be sufficient for a successful ablative tissue effect. In the light of the fact that Interventional Pulmonology paired with different energy delivery systems and sophisticated (partly near real-time) navigation systems is on its way to be transformed in a minimal invasive

treatment modality for peripheral lung malignancies this—on first sight—disappointing difference of an *ex-vivo* (inflated and perfused) model versus the desired endobronchial approach in an *in-vivo* model raises the question for specific reasons. First of all, some of the key issues are mentioned in the article: although radiofrequency ablation (RFA) is believed to be less effective than MWA in lung ablation due to the different energy output especially in *aerated lung tissue*. Vogl and colleagues (2) showed that this seems to be not true when comparing thermal ablation of lung malignancies (except for small cell lung cancer) by RFA versus MWA in regards to complication rate and parameters of progression after successful ablation. The LUMIRA trial (3) confirmed no difference in overall survival (OS) in lung cancer patients comparing head-to-head experienced MWA and RFA although MWA seems to deliver more energy with a bigger clinical reductive effect in tumor mass. At this point we have to remember the prominent Medtronic sponsored EMPRESS (4) trial (NCT02323854) in which highly experienced interventional radiologists ablated lung malignancies ≤3 cm of diameter with a planned resection one day later. Primary outcome measures were dose response defined by comparing actual ablation zone size and volume to predicted ablation zone size and volume prescribed by the physician using the Emprint™ Procedure Planning Application and furthermore measurement of ablation zone shape in regards

to sphericity defined as width to height ratio. The secondary outcome measures were the number of participants with complete or incomplete tumor ablation using histologic analysis with a definition of complete ablation with 100% nonviable cells. The results of this trial were first posted on 5th April 2018 after enrolling 15 participants in 4 centres (US and Germany) starting on 24th December 2014. There was a loss of follow-up of 4 participants with respect to not obtained imaging sets or inability to evaluate. Primary outcome parameters for ablated volume in 11 of 15 participants showed a mean (standard deviation) percent in difference between actual volume (defined after resection) versus predicted volume (defined by CT images post ablation) of -63.5 (26.3) percent. In regards to width (X), height (Y) and depth (Z) parameters the mean (standard deviation) percent difference was -43.6 (18.8), -15.1 (31.7) and -32.8 (26.0) percent. Radiologists use as one key imaging control the ground glass opacity (GGO) induced by thermal ablation. The key message is therefore that we need more data on the induced GGO diameters in reference to the biological effect. Taking the EMPRESS trial as reference the key message could be the need (as one axis parameter) as a safety margin of at least up to 50% induced GGO of the same axis diameter of our target—which is mostly not possible to achieve until now with the existing MWA alone—but possibly in combination with other means. The secondary outcome showed in 11 participants 6 (54.5) percent complete ablations, 4 incomplete ablations and 1 delayed necrosis. Of note is the fact that histologically viable tumor cells in a nearly completely ablated necrotic tumor bed do not mean in all cases a progression scenario as tumor growth is depending on environmental factors. Despite these histological data transthoracically applied MWA in lung malignancies seems to deliver very promising outcomes in a dataset of early lung cancer in elderly patients (5) which has been already shown retrospectively in even bigger datasets comparing RFA with stereotactic body radiation therapy (SBRT) with no statistical differences in OS (6) especially in tumors below 2 cm (7). Coming back to the study of Hai-Bin Yuan the volumetric difference in ablated aereated tissue (around a subsegmental bronchus)—which is believed to be less feasible than MWA of small solid tumors—in the endobronchial inflated and perfused study groups 2 (*ex-vivo*) and 3 (*in-vivo*) was only -34.2% which is roughly the half of what has been reported as volumetric difference between expectation and actual outcome by highly experienced interventional radiologists in the EMPRESS trial with a classical transthoracical

approach. What an encouraging result for Interventional Pulmonology yet not comparing predictive GGO dependent volume directly post ablation with resected ablated volume as in the EMPRESS trial! Although not directly comparable it is of undoubted advantage that by now the complication rate of endobronchial MWA as here reported in animals was zero and especially critical structures like bronchial cartilage remained vital. The EMPRESS trial showed the following complication rates (incomplete list): pneumothorax 6/15, pulmonary haemorrhage 4/15, haemothorax 2/15 and 1/15 acute respiratory failure with pulmonary air leakage and respiratory arrest. These figures may not represent the average complication rate of a today's transthoracic approach—however this has been reported from a highly experienced interventional radiology group recently. We as Interventional Pulmonologists should ask ourselves: how can we increase our clinical performance? We can merely influence basic physics of MWA (8,9): tissue dielectric parameters are the cornerstone of local energy deployment which is in the end the all decisive mean to treat and cure locally by a minimally invasive thermal method. Physical tissue parameters like effective conductivity, relative permittivity and their threshold temperature in transitioning to lower values by desiccation were identified as the most important parameters for the shape of the ablation zone. Of thermal parameters, nominal blood perfusion rate was identified among others as the most influential. What can we take out of this information clinically? The heat sink effect exists for either RFA and MWA, the latter shows with higher frequency a better energy deployment due to ameliorated tissue dielectric parameters (8). High-frequency-MWA (as used in the study of Hai-Bin Yuan) seems to translate into better clinical performance (10) in humans with ablation zones closer to an ideal sphere and achieve significantly larger ablative margins than low-frequency-MWA (11). Another opportunity to increase ablative effects simply due to protocol could be the repetition of an ablation after a certain time of delay as rehydration of tumor beds lead to ameliorated dielectric effects as mentioned above (8,12). Increased local rehydration could be reached with intermittent (between 2 MWA cycles) local intratumoral chemotherapy (13) by a needle approach over the same bronchoscopically guided working channel with a simple water-based cisplatin solution which itself has shown in several trials a major reduction (at least on average 75% of the untreated volume) of central obstructive cancer volume

measured after one month after treatment initiation applying simultaneously with Endobronchial Ultrasound Guided Transbronchial Needle Injection (EBUS-TBNI) into affected mediastinal lymph nodes (13). One can reduce perfusion by transvascular localised embolization methods (14) which induces on the other side a higher complexity of a minimal invasive procedure and prolongs the time of intervention. This parameter should be always in our mind as the main competitor to thermal ablation—SBRT—is very easy to perform for the patient in an around 10–15 minutes lying on a table and breathing spontaneously without any other intervention. As all these minimal-invasive procedures are mainly applied in elderly and fragile patients prolonged time of intervention is a risk factor for unintended interruptions or increased adverse event rates. But there are other opportunities to induce perfusion reduction by simple physiology—partly mentioned by Hai-Bin Yuan: Blockade of the segmental path towards a tumor beside the endobronchial MWA application seems feasible with balloons or slowly degradable gel which could be used as a carrier for local chemotherapy. Such a blockade induces local atelectasis which induces a reduced local perfusion simply due to physiology. Positioning of the tumor towards the highest point clinically feasible for the intervention by positioning of the patient's body could influence perfusion for 16–33% shown in healthy humans when compared supine to dependent lateral lung position during magnetic resonance pulmonary artery flow measurements (15). Optimal near real-time navigation control with the ability to repeat instantly three dimensional confirmation of the ablation device in the best centred intratumoral position—beside undiscovered complications—without the use of an intrabronchoscopic device such as electromagnetic navigation has been shown for lung interventions with computer tomography (CT) and cone beam computer tomography (CBCT) (16). Lung and tumor tissue movement by ventilation can be reduced nearly to zero by application of Nasal Superimposed High Frequency Jet Ventilation during the MWA (17) without loss of control over blood gases. To increase the local cellular damage induced by thermal ablations the combination with Enhanced Penetration and Retention Drugs (EPR) drugs like liposomal paclitaxel (LipPTXL) with confirmed apoptotic effects as well as inhibition of heat shock protein 70—a well-known factor for cancer progression—has been described in a rat liver animal model (12): LipPTXL intravenous (iv.) application alone

compared with RFA and the same amount of LipPTXL iv. 15 minutes after the RFA resulted in an increased local intratumoral paclitaxel uptake around 15 times higher in the combination with RFA than without. Tumor growth was significantly reduced and OS was significantly prolonged by the combination of RFA and PTXL in comparison to either factor alone. To the best of our knowledge this has not been shown in lung cancer models yet. However early clinical studies seem to show a benefit of a combination of iv. chemotherapy with thermal ablation even in late stage lung cancer (18) and EPR-drugs like liposomal cisplatin passed successfully phase-III trials (19) showing non-inferiority to the non-liposomal combination treatment arms in regards to OS and progression free survival (PFS) with a significant reduction of toxicity especially linked to the cornerstone drug cisplatin. Having in mind that fragile patients will be a typical patient volume for thermal ablative treatment approaches the field is now open for the interventional combination of MWA and in human lung cancer approved iv. liposomal drugs. Already ongoing trials (20) are combining immune checkpoint inhibitors with thermal ablation with the fundamental fact in mind that after thermal ablation especially in the rim of a lung cancer one can find a “oup” of different antigens including tumor DNA, different proteins and tumor cell membrane properties (21). All these by intervention induced new targets offer the opportunity to induce anticancer immunity by adding immune stimulating drugs (22) with induced autovaccination against the specific cancer properties. In this context the time setting of the different treatment components are until today not well understood. Based on the fundamentals of perfusion and ventilation. Al-Hakim (23) and colleagues introduced the Ablation Resistance Score which showed in a retrospective manner to a certain degree that ablative effects of MWA depends on the localization of a tumor in the lung. Therefore a “one fits all” rule in respect to the ablation work protocol for a specific generator and antenna is not justified—preprocedural-planning is essential and may lead to significant changing of the interventional setting. Of note is the fact that tumor density with increased caloric capacity raises the amount of ablative work to reach a complete tumor necrosis (24). Therefore, the relative new technology of Elastography (25) could play in future a role in pre-MWA adjustment as its cornerstone is strain rate which is highly depending on tumor density. All this raises the opportunity that interdisciplinary groups with

Interventional Radiologists by far having a vast and the most experience in thermal ablation over 2 decades together with early protagonists of Interventional Pulmonologists form an institutional Lung Ablation Working Group (as already realised in my institution) with a lot of chances to help technically each other in regards to optimize patients benefit. Even if endobronchial MWA is not yet available in all highly sophisticated Interventional Pulmonology Departments Interventional Radiologists could benefit from nasal jet ventilation, endobronchial blockade and complication management like endobronchial bleeding—all covered by an Interventional Pulmonologist. The same is true for the availability of CBCT—only a few Interventional Pulmonologists have access to their, “own” CBCT. Furthermore, combined approaches with easy to reach endobronchially nodule areas could increase the safety margins of a complex transthoracic applied MWA—and this could be accomplished in the same setting and imaging. Such a therapeutic combination of Interventional Radiology and Interventional Pulmonology approaches is called in our institution, “The KISS” approach. As MWA induced GGO as imaging control of intended complete ablation does not render in all aspects a biological equivalent the idea of real-time measuring local temperature peritumoral by small (below 1 mm diameter) endobronchially applied thermocouples (e.g., Physitemp Instruments LLC, Clifton, New Jersey, USA) in neighbored subsegmental areas are theoretically possible and could increase the quality of complete ablation especially in the margin of nodules. Relapse after SBRT does not allow Re-SBRT and offers the chance for thermal ablation. This is especially true for post-SBRT squamous lung cancer nodule relapse (26). Taking all this together the here presented study by Hai-Bin Yuan with the first-time comparison of *ex-vivo* and *in-vivo* endobronchial MWA of areated tissue in an animal lung model is one exciting step towards a rising 4th arrow in our quiver of interventional minimal-invasive anti-cancer treatment in the lung with MWA. There is still a lot of room for improvement but even in the early stage of the approved devices there is a definite ablative effect by endobronchial MWA—with respect to the above-mentioned limitations we could even now find our niches and start working safely on behalf of patients outcome. Stay excited and keep going.

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Footnote

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