Chapter

Image-Guided Ablative Therapies for Lung Tumors

Joyce W.Y. Chan, Rainbow W.H. Lau and Calvin S.H. Ng

Abstract

While the gold standard for early stage lung cancers is still surgical resection, many patients have comorbidities or suboptimal lung function making surgery unfavorable. At the same time, more and more small lung nodules are being incidentally discovered on computer tomography (CT), leading to the discovery of pre-malignant or very early stage lung cancers without regional spread, which could probably be eradicated without anatomical surgical resection. Various ablative energies and technologies are available on the market, including radiofrequency ablation, microwave ablation, cryoablation, and less commonly laser ablation and irreversible electroporation. For each technology, the mechanism of action, advantages, limitations, potential complications and evidence-based outcomes will be reviewed. Traditionally, these ablative therapies were done under CT guidance with percutaneous insertion of ablative probes. Recently, bronchoscopic ablation under ultrasound, CT, or electromagnetic navigation bronchoscopy guidance is gaining popularity due to improved navigation precision, reduced pleural-based complications, and providing a true "wound-less" option.

Keywords: radiofrequency ablation, microwave ablation, cryoablation, percutaneous ablation, bronchoscopic ablation, electromagnetic navigation bronchoscopy

1. Introduction

With the increasing availability of computer tomography (CT) scans and enlarging body of evidence for low-dose CT screening in high risk populations, a rising number of lung nodules are discovered incidentally. Many of them are small, sub-solid, and harbor pre-malignant or early stage cancers. Local therapies for these lesions are gaining evidence support, especially in patients with high surgical risks or decline surgery. Sublobar resection has been shown to confer similar 5-year survival rates, especially in older patients, tumor smaller than 2 cm, and pure bronchoalveolar carcinoma [1–3]. Stereotactic body radiation therapy (SBRT) is targeted toward patients with stage I or II non-small cell lung carcinoma (NSCLC) without lymph node involvement and who are medically inoperable. SBRT has a local control rate of more than 80% in multiple retrospective series [4], and disease-free survival of 26% and overall survival of 40% at 4 years in a multicentre phase II study [5]. However, sublobar resection still carries surgical risks while SBRT has up to 22.3% risk of radiation pneumonitis and pneumonia. Since the early 2000s, percutaneous ablation of lung tumors has been attempted [6] following reports of efficacy of local ablation in liver cancers. The subsequent decade saw the blossom

of image-guided local ablative therapies of lung tumors, first with radiofrequency ablation (RFA), later with microwave ablation (MWA) and cryoablation. In this chapter, we discuss the preparation and procedure of lung ablative therapies, the various energy used, their pros and cons, evidence for safety and efficacy, and a glimpse into the future with a special section on bronchoscopic ablation.

2. Patient and nodule selection

Image-guided lung ablation is best suited for patients who have high surgical risks, either due to underlying medical comorbidities, or due to inadequate respiratory reserve, for instance significant chronic obstructive pulmonary disease (COPD) or previous contralateral lobectomy or pneumonectomy making intra-operative one-lung ventilation difficult. In general, there are no lower limits of lung function requirement for ablation candidates [7], but patients should be expected to tolerate sedation or general anesthesia at supine, lateral decubitus or semi-prone position for at least an hour. Contraindications for ablation include severe interstitial lung disease (ILD), where exacerbation of ILD may lead to severe pulmonary failure and death [8].

When ablation is intended for local control of early stage lung cancer, the tumor should ideally be small enough to be covered by the expected ablation zone with adequate margin, and there should be no nodal or extrathoracic metastasis based on pre-operative imaging. Ablation with palliative intent is best suited for lung cancers with tumor-related symptoms, for example pain and airway obstruction. Tumor size must be considered, and numerous lung ablation studies have demonstrated increased risk of local recurrence for increasing size of tumors, with cut-off of 2 cm [9] and 3 cm [10, 11] reported. In case of larger tumors, double ablation may be required, which either involves re-ablating in the same position, after pull-back of electrode, or after repositioning of electrode. Alternatively, ablation catheters with multiple electrodes can be used to generate a larger ablation zone.

Tumor location is also important to consider before submitting patient to thermal ablation. Nodules which are not suitable candidates for CT-guided biopsy are generally not recommended for percutaneous ablation, for example those shielded by the bony scapula, very close to diaphragm or hilar structures. Tumors located close to medium to large blood vessels are susceptible to heat-sink effects and ablation efficacy may be reduced. Ablation of tumors close to the apex or mediastinal structures may risk thermal injury to brachial plexus, phrenic nerve and adjacent organs such as the heart and esophagus, although hydro-dissection or artificial pneumothorax to protect surrounding structures have been reported with success [12].

3. Procedure and planning

Pre-procedure workup includes CT imaging ideally within 4 weeks of the planned ablation date. Patients were fasted overnight before ablation to reduce risk of sedation-induced nausea and aspiration. Anti-coagulation or anti-platelet medications were stopped as per regional guidelines for invasive procedures. Implantable cardiac devices like pacemakers or defibrillators are susceptible to interference from certain ablation modalities, and should be interrogated and programed by cardiac electrophysiologist to automatic pacing modes, or by placing a magnet over the device, while defibrillation should be turned off during ablation. Grounding pads should be placed to guide the flow of current away from the cardiac device and

electrodes should be inserted at least 5 cm away from pacemaker or defibrillator leads. External pacing and defibrillator system should be readily available in case of emergency.

Most ablation strategies are performed percutaneously, and nearly all are done under CT guidance. The great majority of ablation are performed with conscious sedation, while general anesthesia is reserved for pediatric patients or patients who cannot tolerate sedation alone, although some authors have reported higher feasibility rates and lower peri-procedural pain with general anesthesia [13]. For certain ablation energies, a reference electrode or grounding pad is necessary, which is attached to patient's skin usually on the opposite chest wall or thigh. Initial scout CT images are acquired; the skin entry site is determined and cross-marked on the skin by laser lights from the CT gantry. Following sterile preparation and draping, local anesthesia is injected along the tract from skin to the level of pleura. A spinal needle is advanced according to the planned trajectory with CT and/or fluoroscopy guidance, which is then exchanged to the ablation electrode after confirmation of correct placement.

The aim of all ablation modalities is to create a zone of tissue necrosis that encompasses both the tumor and a margin of normal parenchyma surrounding it. The choice of electrode length, active tip length and the number of electrodes is determined by the size and location of tumor. The actual ablation zone size may differ from the predicted size. Factors include the heat-sink effect [14], which refers to the fact that medium to large blood vessels or airways carry heat away leading to asymmetrical or truncated ablation zones. Depending on the energy used, the lung's conductivity, impedance and density also play a role in affecting the eventual ablation zone volume. In general, microwave is able to produce a larger ablation zone than radiofrequency due to its mechanism of energy deposition [15], with explanation detailed later in the chapter. After the initial ablation, a CT evaluation of ablation effect should be performed. In case of inadequate ablation volume, re-ablation with several overlapping ablation zones, or exchange to larger and more powerful electrodes can be performed.

After ablation and removal of electrode, CT images are acquired to evaluate technical success and rule out any complications, for example pneumothorax and bleeding. Patients are observed for 2–4 hours and a repeat chest x-ray confirms the absence of pneumothorax. Most patients are discharged the same day if no complications arise. Median length of stay was 1 day in a nation-wide review [16].

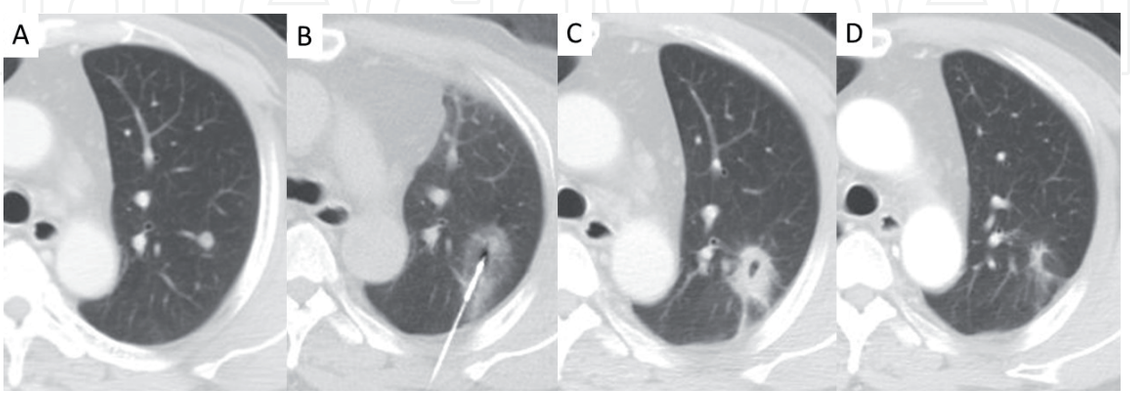

Figure 1.
(A) CT scan shows a biopsy proven left upper lobe lung metastasis in a patient with stage III colonic cancer who was treated with colectomy and chemoradiation previously. (B) CT-guided radiofrequency ablation of the lung metastasis was performed with ablation catheter in-situ and an area of surrounding ground glass opacities (GGO). (C)The ablated area evolved into a denser GGO with central cavitation at 1 month after ablation. (D) CT scan at 6 months after ablation showed evolution of the ablated area into a smaller contracted scar with no signs of recurrence.

Subsequent follow up required interval CT scans for evaluation of treatment response, usually every 3 months although no international guideline exists [17]. Typical early CT appearances following heat-based thermal ablation (eg. RFA, MWA) include ground glass opacities (GGO) or cavities, with or without soft tissue components. The GGO is typically concentric with three layers, the central consolidation represents ablated tumor tissue, the middle layer of faint GGO represents necrotic surrounding parenchyma, and an outer rim of denser GGO contains congested lung tissue and hemorrhage than may retain viability [17]. Cavitation, which is considered a positive response, is most likely to appear in the intermediate phase (1 week to 2 months after ablation). At 3 to 6 months post-ablation, the ablated area continues to involute and shrink down to a linear or nodular scar, or even a thin-walled cavity. Enlarging ablation zone beyond 6 months is highly suggestive for tumor recurrence. Central enhancement >10 mm or > 15HU suggests progression of incompletely ablated disease on contrast CT scans [18], while increased metabolic

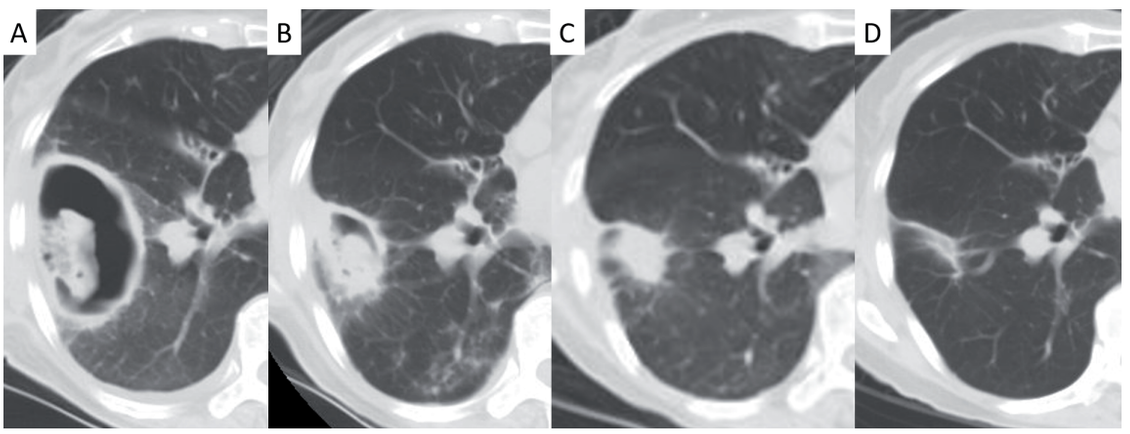

Figure 2.
(A): At 2 weeks after microwave ablation of a small right lower lobe lung tumor, there was a larger-than-expected cavity noted in chest x-ray upon follow up. CT showed a large thick-walled cavity with central soft tissue likely representing necrotic lung and tumor tissue. There was no pneumothorax. (B) CT scan at 3 months post-ablation showed reduction in size of the cavity and soft tissue component. (C) CT scan at 6 months post-ablation showed disappearance of cavity and further reduction in overall size of the ablated area, now consisting of soft tissue density. (D) CT scan at 9 months post-ablation showed a contracted scar representing good treatment response.

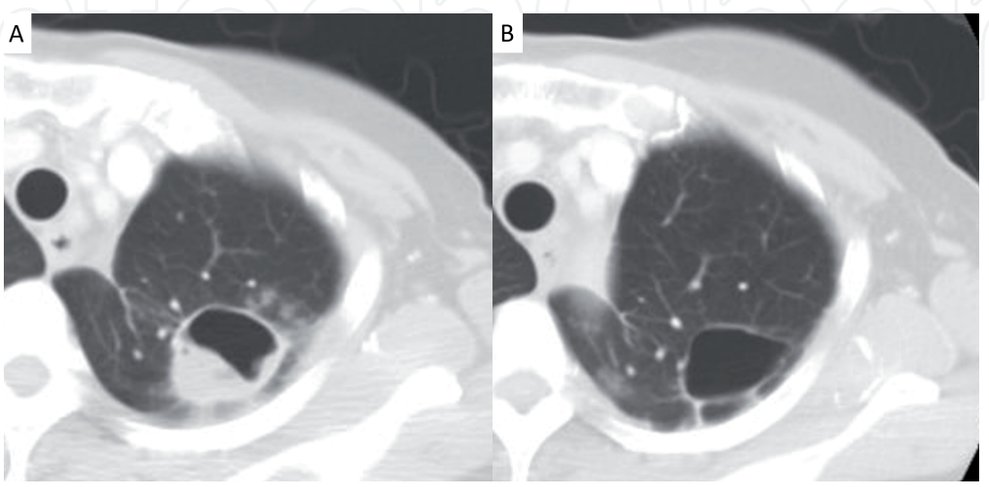

Figure 3.
(A) A cavity with soft tissue component surrounded by patchy ground-glass consolidations at 1 month after microwave ablation of a left upper lobe lung cancer. (B) Complete response as the ablation zone turned into a thin-walled cavity without soft tissue component at 6 months after ablation, which persisted with static appearance thereafter.

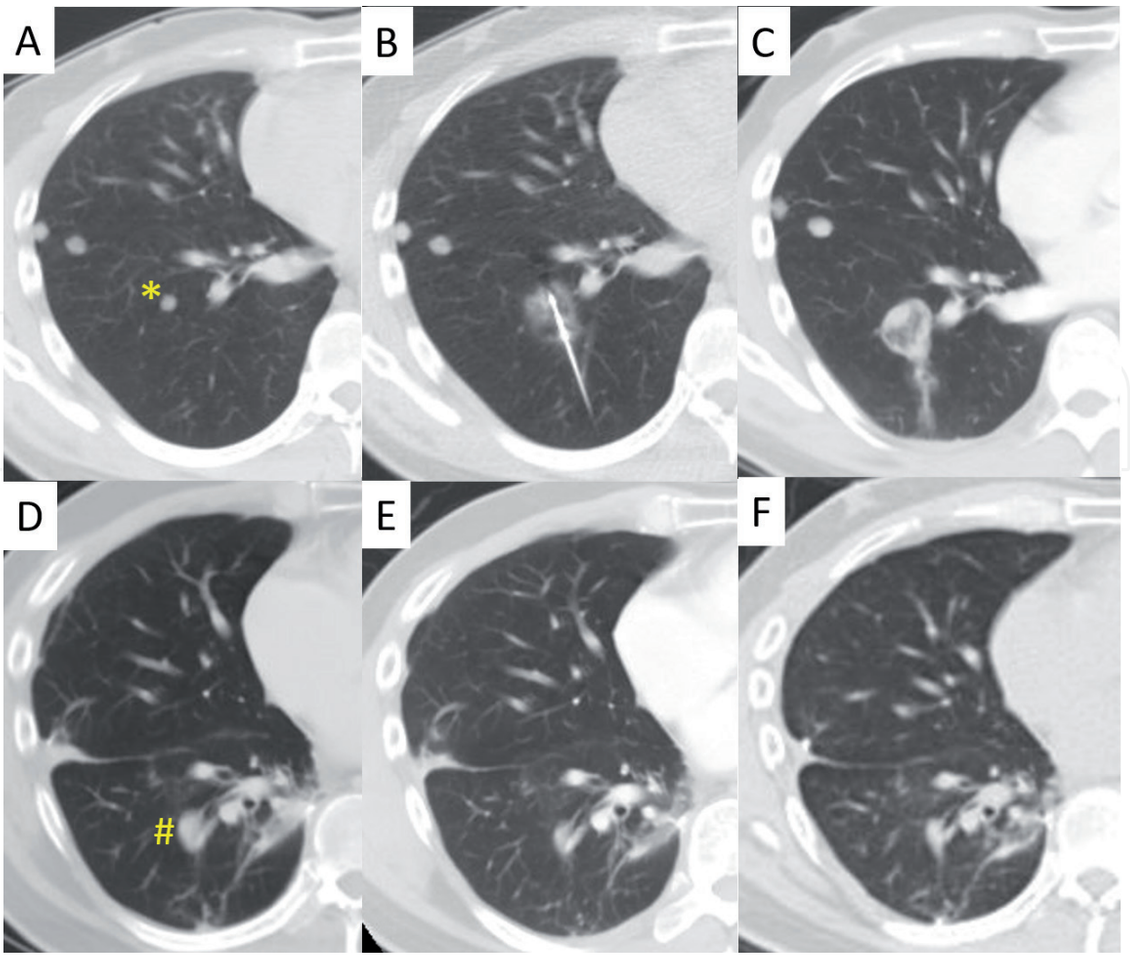

Figure 4.
(A) A 43 year old patient had curative resection of a hepatocellular carcinoma, but was found to have 5 lung metastases on surveillance CT, 3 of which in the right lower lobe (RLL) (as shown), and 2 more in the right middle lobe (not shown). The deepest lung metastasis in the RLL (*) would be difficult to palpate intra-operatively, making wedge resection difficult. Patient was keen for lung-preserving treatment, thus a combined strategy of CT-guided ablation and surgical wedge resection was planned. (B) CT guided radiofrequency ablation of the deepest RLL lung metastasis was performed. (C) The ablation zone evolved into a well-demarcated ground glass opacity with soft tissue component 2 weeks after ablation. (D) Wedge resection of the remaining 4 lung metastases located in peripheral right lower and middle lobe was performed with video-assisted thoracoscopic surgery. CT scan at 3 months after ablation showed contraction of the ablation zone (#) and disappearance of the other 2 RLL lung metastases after surgery. (E) CT scan at 7 months after ablation showed further contraction of the ablated area. (F) CT scan at 1 year after ablation showed a small contracted lobulated scar remaining at the ablated area, and no recurrence of lung metastasis.

activity or new uptake inside the ablation zone beyond 2 months post-ablation are worrisome of recurrence on PET/CT scans [19]. Patients with local recurrence can undergo repeated ablation to improve local control. **Figures 1–3** show the typical appearance of successfully ablated lung tumors over serial CT imagings. CT-guided ablation of centrally located metastasis can be combined with surgical resection of other more peripheral lung metastases as part of lung-preserving strategy, as illustrated in **Figure 4**.

4. Ablation energies

Ablation techniques can be divided into thermal or non-thermal ablations (e.g. irreversible electroporation). Among thermal ablations, heat-based techniques include radiofrequency ablation, microwave ablation and laser ablation, while cold-based technique includes cryoablation. **Table 1** shows the comparison of thermal ablation modalities in the lung.

	Radiofrequency ablation	Microwave Ablation	Cryoablation
Mechanism of action	Frictional heating from electron collisions under oscillating electric field	Frictional heating from rapidly realigning polar water molecules under oscillating electric field	Ultracold temperature when pressurized argon gas expands (Joule Thomson effect)
History of application in lung cancer	Since early 2000s	Since mid 2000s	Since mid 2000s
Temperature (°C)	60 to 100	Around 150	−20 to −40
Grounding pad	Required	Not required	Not required
Ablation zone size	Smaller	Larger	Larger
Dependence on impedance	Yes	No	No
Affected by tissue charring	Yes	No	No
Ablation time per ablation	Medium (10–15 minutes)	Shortest (2–10 minutes)	Longest (25 minutes)
Visibility on CT/MRI	Fair (concentric GGO)	Fair (concentric GGO)	Best (iceballs)
Heat sink effect	Larger	Smaller	—
Preservation of bronchovascular structures	Fair	Fair	Best
Procedural pain	Fair	Less	Least

GGO, ground glass opacity.

Table 1.
Comparison between different modalities of lung cancer thermal ablation.

4.1 Radiofrequency ablation (RFA)

Radiofrequency ablation is the most widely used ablative modality in the lung, and utilizes heat as a form of thermal ablation. Radiofrequency refers to a section in the electromagnetic spectrum with frequency ranging between 20 kHz to 30 MHz, but most clinically available devices function in the 375-500KHz range. A grounding pad or reference electrode is required in RFA, while the active electrode placed inside the tumor is coupled to an RF generator. The RF generator establishes a voltage between the active electrode and reference electrode, producing electric field lines that oscillate with alternating current. At the area closest to the applicator, electrons collide with adjacent molecules under the influence of oscillating electric field, inducing frictional heating [20]. Immediate cell death occurs at temperatures greater than 60°C. RF electrodes have an internal thermocouple that measures the temperature at the tip. Charring and desiccation at the electrode increases impedance and reduces heat conduction, thus most commercially available electrodes are coupled with infusion pumps that pump cold saline to internally cool the electrode tip. Treatments usually range between 4 and 12 minutes, and RFA electrodes may be single-tip applicators or cluster electrodes.

Multiple RFA systems are commercially available (Boston Scientific, Watertown, MA, USA; StarBurst (RITA) Medical Systems, Mountain View, CA, USA; Cool-Tip, Covidien, Boulder, CO, USA). The first two use a deployable radiofrequency array electrode with 4–16 small wires tines through a 14- to 17-gauge needle. The

third system consists of a single or triple cluster (3 electrodes spaced 5 mm apart) electrode perfused with saline, and a switching controller allow for simultaneous placement of up to three separate single electrodes to create a greater volume of thermocoagulation in a single application.

4.1.1 Efficacy of radiofrequency ablation

The local control and survival rates of RFA have been examined in a handful of non-randomized single-institutional series and a few multicenter trials. The RAPTURE study published in 2008 is a prospective, intention-to-treat, multicenter trial involving seven centres in Europe, USA and Australia [21]. It included 106 patients with 183 biopsy-proven lung tumors, although there was a mixture of NSCLC and lung metastases. Technical success rate was 99%, and a confirmed complete response lasting at least 1 year was achieved in 88% of patients. For patients with NSCLC, overall survival was 70% at 1 year and 48% at 2 years, cancer-specific survival was 92% at 1 year and 73% at 2 years. Selecting those with stage 1 NSCLC, the 2-year overall survival was 75% and cancer-specific survival was 92%. More recently, another multicenter trial, the ALLIANCE Trial, was published in 2015 [9]. The overall survival was 86.3% at one year and 69.8% at two years, while local recurrence-free rate was 68.9% at one year and 59.8% at two years.

Regarding long term efficacy, a retrospective study revealed that for stage I NSCLC, the overall survival rate was 36% and 27% at 3 and 5 years respectively [10]. In another prospective intention-to-treat study, the complete response rate was 59.3% at a mean follow-up of 47 months, with a mean local recurrence interval of 25.9 months [22]. Median overall survival and cancer-specific survival were 33.4 and 41.4 months respectively, while cancer-specific actuarial survival was 59% at 3 years and 40% at 5 years [22].

Tumor diameter was found to be a negative prognostic factor. The difference between survival curves associated with large (>3 cm) and small (<=3 cm) lung tumors was significant ($p = 0.002$, 10], and there was a trend toward better efficacy for tumors smaller than 2 cm in diameter ($p = 0.066$, 23]. Tumor size less than 2 cm was associated with a statistically significant improved survival of 83% at two years in the ALLIANCE Trial [9]. In another study, complete necrosis was attained in all tumors less than 3 cm but only in 23% of larger tumors, and the mean survival of patients with complete necrosis was significantly better than that with partial necrosis [11]. An ablation area of at least 4 times larger than initial tumor was reported to be predictive of complete ablation treatment [23].

To date, there are no properly powered prospective trials comparing one RFA system with another or comparing RFA with other treatment modalities. There has been a propensity-matched analysis comparing RFA and surgery for stage 1 NSCLC, and the mean survival duration of RFA group and surgery group was 33.2 +/− 7.9 and 45.4 +/− 7.2 months respectively, although the difference is not statistically significant [24]. A large propensity-matched retrospective study comparing thermal ablation (mostly RFA) with SBRT using the National Cancer Database reported no significant difference in overall survival at a mean follow up of 52.4 months, however unplanned hospital readmission rates were high in the thermal ablation group [25]. In a systemic analysis and pooled review, the local control rate was significantly lower in the RFA group compared to SBRT, although the overall survival remained similar [26].

4.2 Microwave ablation (MWA)

Microwave ablation for lung tumors has been gaining increasing momentum since the mid-2000s. Microwave occupies a much higher frequency range in the

electromagnetic spectrum between 300 MHz to 300 GHz. Compared to radiofrequency, microwave energy is able to create a much larger zone of active heating due to broader deposition of energy. Clinically available microwave applicators generally operate in the 900-245 MHz range [27]. MWA directly heats tissue to lethal temperatures greater than 150°C through dielectric hysteresis, which is a process in which the polar water molecules realign with the oscillating electric field generating kinetic energy, which is then transferred to neighboring tissues [28]. Being completely independent from electrical conductance, microwave energy deposition is less susceptible to tissue impedance, and is able to produce faster, larger and more predictable ablation zones than RFA [15]. The aerated lung has a relatively high impedance among all solid organs, thus making MWA a better modality than RFA in lungs [15, 29]. Heat-sink effect is also smaller with microwave [28].

There are 7 microwave systems commercially available in the United States and Europe, using either 915 MHz or 2450 MHz generators [30]. The antennae are generally straight, ranging from 14 to 17 gauge, with varying active tips of 0.6–4.0 cm in length. Five out of seven systems require perfusion of antenna shaft with room-temperature fluid or carbon dioxide to reduce conductive heating of the non-active portion of the antennae, which protects the skin and other tissues from thermal damage.

4.2.1 Efficacy of microwave ablation

The majority of evidence supporting the efficacy of MWA comes from retrospective data. The earlier studies reported an actuarial survival of 65% at 1 year, 55% at 2 years and 45% at 3 years, while cancer-specific survival was 83%, 73% and 61% at 1, 2 and 3 years respectively [31]. A more recent retrospective study reported cancer-specific survival of 69%, 54% and 49% at 1, 2 and 3 years respectively, and the mean survival was 27.8 months [32]. Local control rate was 84.4% at a mean follow-up of 446 days in another retrospective series [33]. A larger retrospective review of 108 patients reported that the median time to tumor recurrence was 62 months, and recurrence rates were 22%, 36% and 44% at 1, 2 and 3 years respectively [34]. It should be noted that the majority of the studies include both primary and secondary lung tumors, and results for NSCLC may not be separately reported. Longer term results were reported in a study involving large NSCLC (mean tumor size of 5.0+/− 1.8 cm). Owing to the larger tumor size, only 44.6% of cases achieved complete tumor ablation after first ablation, and 18.5% required a re-do MWA session. The 3- and 5-year cancer-specific survival rates were 42.1% and 30.0% respectively, and the median cancer-specific survival was 25 months [35].

Similar to RFA, tumor size is associated with poorer prognosis. For every millimeter increase in tumor maximal diameter, the odds of not attaining technical success increased by 7% [34]. Tumor size >4 cm is a significant predictor for local tumor progression and poorer survival [35]. Recurrence rate was 17% for tumors smaller than 3 cm, and increased to 31% for those greater than 3 cm [34]. A risk-factor analysis demonstrated that local tumor progression was significantly correlated with tumor diameter of more than 15.5 mm, irregular shape of index tumor, pleural contact and low energy deployed per unit volume of index tumor [36]. On the other hand, cavitation was associated with reduced cancer-specific mortality [31].

Again, there are no prospective studies comparing one MWA system with another, or with other modalities. There was a propensity-score matched analysis comparing MWA with lobectomy for stage I NSCLC, which reported no significant difference in overall survival and disease free survival (1,3 and 5-year disease free survival of 98.1%, 79.6% and 37.0% for MWA group and 98.1%, 81.5% and 29.6%

for lobectomy group) [37]. The complication rate in MWA group was significantly lower than lobectomy group ($p = 0.008$). However, the power of this study is undermined by the relatively poor results in lobectomy group when compared to international standard, probably due to poor patient premorbid. In a best evidence topic review, the best available evidence for MWA (7 studies) was compared to that for SBRT (5 studies) [38]. The 3-year survival was 29.2–84.7% for MWA and 42.7–63.5% for SBRT, while the median survival was 35–60 months for MWA and 32.6–48 months for SBRT. The authors concluded that MWA appears comparable to SBRT in terms of local control and survival rates. In the randomized controlled LUMIRA trial, 52 patients with stage IV lung tumors were recruited, and there was no significant difference in survival between the MWA group and RFA group, but MWA was found to produce less intraprocedural pain and a more significant reduction in tumor mass [39].

4.3 Percutaneous Cryoablation

Cryoablation makes use of the Joule-Thomson effect by distributing pressured argon gas to an area of lower pressure and reaching ultracold temperatures when the gas expands [40]. As low as −140°C can be achieved, although living tissue destruction already happens at −40°C. Cryogenic destruction occurs via a number of mechanisms, including protein denaturation, cell rupture due to osmotic shifts, and tissue ischemia from microvascular thrombosis [41]. Meanwhile, the term "cryosurgery" includes cryoablation performed through endobronchial, direct intrathoracic or percutaneous routes.

Traditionally, each cryoablation consists of a dual freeze cycle, involving a 10-minute freeze, followed by 8-minute helium thaw and another 10-minute freeze. Early animal models suggest that air leaks and bleeding could be reduced with this protocol [42]. Current commercially available cryoablation devices (for example Cryocare CS® system, Endocare, Irvine, CA, USA) use a faster cycle of 3-minute freeze, 3-minute thaw, 7-minute freeze, 7-minute thaw and a final 5-minute freeze. These systems allow placement of 1–10 individual 1.5–2.4 mm diameter cryoprobes, and one freeze–thaw–freeze cycle at a single probe position usually suffice. The faster cycle produces interstitial fluid in adjacent lung tissue and improves margin control. Radiologically, a visible "ice ball" and surrounding edematous changes can be seen on CT and serve as an estimation of ablation zone. The true volume of tissue necrosis has been shown to be 3-7 mm from the ice-ball edge [43], and should be taken into consideration when determining cytotoxic ice margin clearance.

Compared with heat-based thermoablation like RFA and MWA, cryoablation has the advantage of larger ablation volumes, availability of multiple applicators, a highly visible ablation zone (a clearly defined ice ball as opposed to concentric ground glass opacities in RFA or microwave), and less pain due to analgesic effect of freezing [44]. Another benefit is its safety near vasculature or bronchi due to the ability to preserve collagenous tissue and cellular architecture in frozen tissue [45]. Disadvantages of cryoablation include a longer procedural time (25 minutes per freeze–thaw–freeze cycle compared to roughly 5 to 10 minutes per ablation in MWA) and a higher incidence of pneumothorax up to 62% [46]. The latter can be tackled with fibrin glue tract coagulation or radiofrequency thermocoagulation of needle tract provided by one of the cryoablation systems.

4.3.1 Efficacy of Cryoablation

A retrospective review of 25 stage I NSCLC treated with cryoablation reported 3-year overall survival of 88% and mean overall survival of 62+/−4 months [47].

Another study involving 27 cryoablated stage I NSCLC demonstrated 3-year survival of 77%, 3-year cancer-specific survival of 90.2% and cancer-free survival of 45.6% [48]. In a study comprising of cryoablation of both primary and secondary lung tumors, the 1-, 2- and 3-year local progression free rates were reported to be 80.4%, 69.0% and 67.7% respectively [49]. In a long-term analysis of 47 stage I NSCLC treated with cryoablation, the 5-year cancer-specific survival rate was 56.6+/−16.5% and 5-year progression free survival rate was 87.9+/−9% [50]. There were two randomized controlled trials, the ECLIPSE trial [51] and SOLSTICE trial [52], evaluating cryoablation of metastatic lung tumors, which report favorable safety and efficacy, but are out of the scope of this chapter.

Cryoablation has been performed for stage IV lung cancer for palliation of symptoms. In a comparative study between cryoablation and palliative treatment alone, the overall survival of the cryoablation group was significantly longer, with median survival of 14 months compared to 7 months [53]. The same group has performed cryosurgery in various stages of NSCLC yielding an overall survival of 64%, 45% and 32% at 1, 2 and 3 years respectively [54].

Few studies have compared cryoablation with other treatment modalities. In 64 patients with stage I NSCLC deemed medically unfit for lobectomy, 25 were treated with sublobar resection, 12 with RFA and 27 with cryoablation. The 3-year survival rate was similar for the three groups (87.1% for sublobar resection, 87.5% for RFA and 77% for cryoablation) [48]. In a comparative study for stage IIIB or IV NSCLC treated with cryoablation or MWA, the overall survival and progression-free survival were similar for tumors ≤3 cm in diameter, but were poorer in tumors greater than 3 cm which are treated with cryoablation [44].

4.4 Percutaneous laser ablation

Laser ablation is a thermal technique where light energy is converted into heat by interaction with sources such as an Nd: YAG laser. Typically, energy is transmitted through a flexible fiberoptic cable which is percutaneously inserted into the lung through an outer sheath. Cooling of the fiberoptic cable enables greater energy deposition and a 50 percent increase in size of thermocoagulation [55], as the size of ablation zone is limited by tissue carbonization near the applicator. To date, there have been limited reports on the efficacy of laser ablation in humans [56]. A long term analysis of laser ablation for lung metastases reported 1-, 3- and 5-year survival of 81%, 44% and 27% respectively [57], with a relatively high rate of pneumothorax (38%). No data is available for primary lung cancers.

4.5 Irreversible electroporation (IRE)

Electroporation is a phenomenon in which cell membrane permeability to ions and macromolecules is increased by exposure to high voltage electric pulses. It can be reversible or irreversible, with the latter leading to cell death from loss of homeostasis and osmotic effects. Since IRE is a non-thermal ablation modality, its theoretical advantage includes overcoming the heat-sink effect [58] and preservation of structural integrity of nearby bronchovascular structures [59]. Although there have been reports on its efficacy in animal models [60] and in other organs such as the liver [61], there were few reports on its use in human lungs [62]. In fact, in the multicenter phase II ALICE trial for treatment of primary and secondary lung malignancies, IRE failed to meet the expected efficacy and the trial was terminated prematurely after inclusion of 23 patients, in which 61% showed progressive disease [63]. The disappointing results may be explained by high differences in electric

conductivity between normal lung parenchyma and tumor tissue. Of note, needle tract seeding happened in 13% of cases.

5. Safety and complications of percutaneous ablation

Percutaneous ablation of lung tumors is generally considered safe. A list of potential complications is presented in **Table 2**. In a nationwide analysis of 3344 patients who underwent percutaneous lung ablation in the United States [16], in-hospital mortality was 1.3%, and patients with more comorbidities (Charlson comorbidity index score ≥ 4) was associated with significantly higher mortality. The most common complication was pneumothorax (38.4%), followed by pneumonia (5.7%) and effusion (4.0%). In a Japanese review of 1000 RFA sessions [64], there was a 0.4% procedure-related mortality, of which three died of interstitial pneumonia and another died of hemothorax. Major complication rate was 9.8%, consisting of 2.3% aseptic pleuritis, 1.9% pneumonia, 1.6% lung abscess (**Figure 5**), 1.6% pneumothorax requiring pleural sclerosis, 0.4% bronchopleural fistula and 0.3% brachial nerve injury. Previous radiotherapy and age were significant risk factors for pneumonia, as were emphysema for lung abscess, and platelet count and tumor size for bleeding [64].

Pneumothorax occurs as a result of pleural puncture by the ablation catheter leading to air leak. Hence, unlike standard lung biopsy technique, in which the shortest path to tumor is preferred, some operators advocated a longer distance between pleura puncture site and tumor is more desirable for ablation. An indirect approach that leaves an unablated tract of at least 2 cm of normal lung is preferable [29], because

Complications		**Treatment/remarks**
Pneumothorax	3.5–54% (Up to 10% delayed pneumothorax)	Only 6–29% require chest tube insertion
Pleural effusion/aseptic pleuritis	2.3–19%	Only a minority require drainage
Bleeding	1.6–18%	Rarely require emergency arterial embolization or surgery
Pneumonia	1.8%	Antibiotics
Lung abscess	1.6%	Antibiotics, drainage
Bronchopleural fistula	0.4–0.6%	Prolonged chest tube drainage, chemical pleurodesis, endobronchial valves/ embolization
Needle tract seeding	0.3–0.7%	Associated with biopsy prior to RFA
Thermal injury to nearby structures	0.3–0.5% (brachial plexus) 1.3% (phrenic nerve) 0.1% (diaphragm)	Phrenic nerve injury can lead to significant reduction in vital capacity and referred pain to shoulder
Pneumonitis	0.4%	Pulse steroid
Pulmonary artery pseudoaneurysm	0.2%	Transcatheter coil embolization
Systemic air embolism	Very rare	Hyperbaric oxygen

Table 2.
Complications following thermal ablation in the lung.

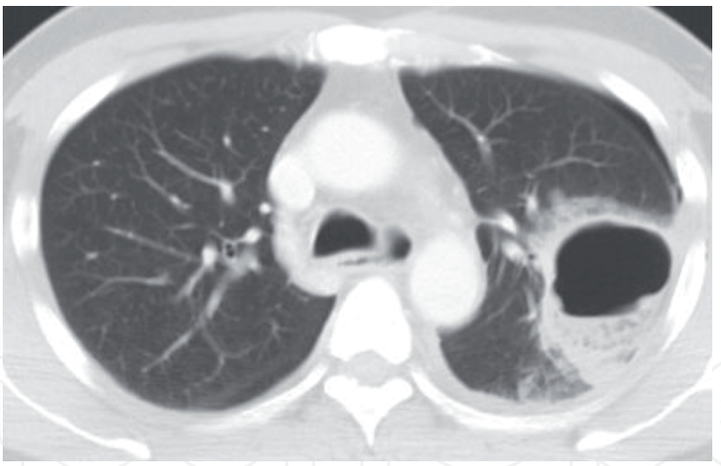

Figure 5.
A small pneumothorax and a large cavity with soft tissue content at 2 weeks after microwave ablation of a left upper lobe lung tumor. If the patient had fever and air-fluid level was seen in the cavity, a suspicion for lung abscess should be raised, and the abscess should be drained with contents sent for culture and intravenous antibiotics should be commenced.

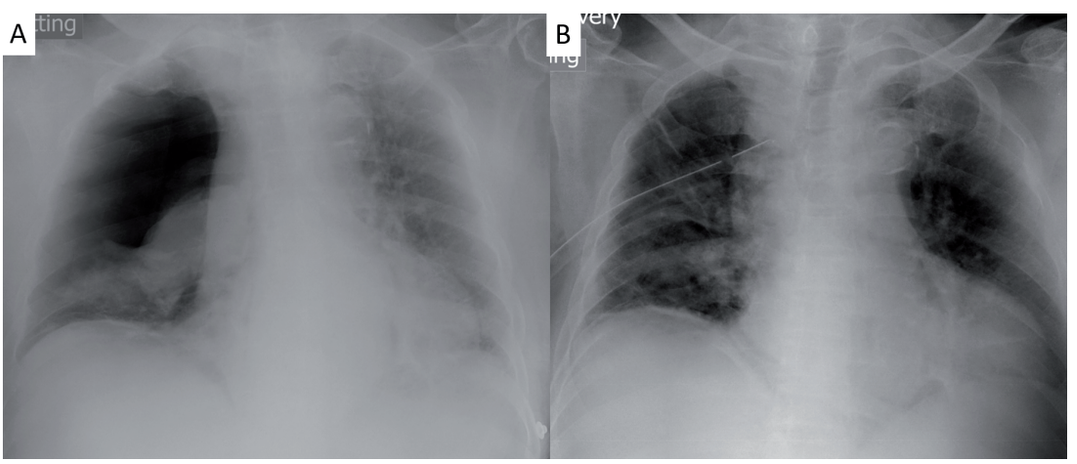

Figure 6.
(A) A large right pneumothorax immediately after CT-guided radiofrequency ablation of a right lower lobe lung cancer. (B) Shows the lung re-expands after right chest drain insertion in the same patient.

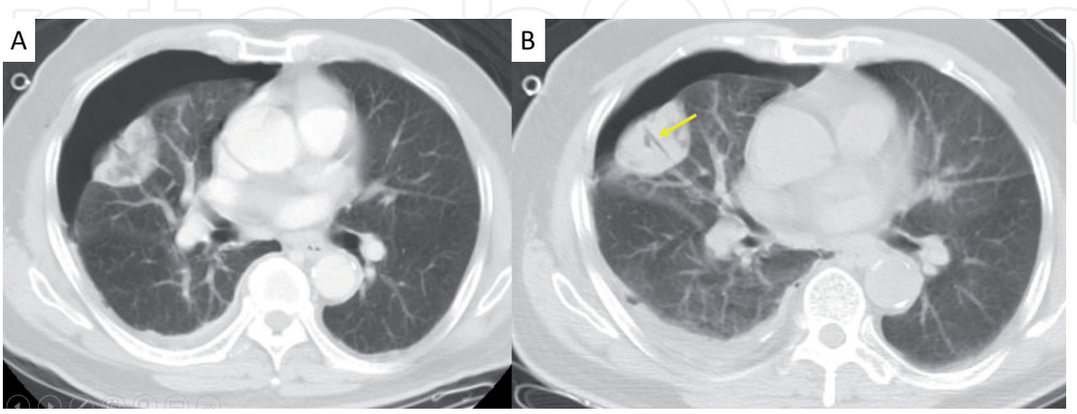

Figure 7.
(A) A patient with right lower lobe lung cancer was treated with CT-guided microwave ablation, but complicated by persistent air leak for 2 weeks despite chest drain insertion. CT scan showed a moderate right pneumothorax and an area of ground glass opacity in the anterior right lower lobe representing the ablation zone. (B) CT scan performed at 3 weeks after ablation demonstrated a bronchopleural fistula (yellow arrow) joining a lobar bronchus to the pleural space through the ablated needle tract.

unablated pleura contracts less and heals quicker. Emphysema is the most significant risk factor for pneumothorax in multiple studies [65, 66]. Other risk factors include male gender, no previous lung surgery, high number of tumors ablated, advanced age, and traversal of major fissure by electrode [67]. The rate of pneumothorax ranges from 3.5–54%, but only 6–29% required chest tube placement [68] (**Figure 6**). Delayed pneumothorax could occur in up to 10% of cases [69, 70]. Around 0.4–0.6% of all patients develop bronchopleural fistula [64, 71] leading to intractable pneumothorax not resolving with chest drainage (**Figure 7**). Treatment strategies include repeated chemical pleurodesis, placement of endobronchial valves (**Figure 8**), and bronchoscopic embolization of relevant fistulae [68].

Aseptic pleuritis and pleural effusion is postulated to be due to ablation zone reaching pleura leading of pleural inflammation, and is associated with higher

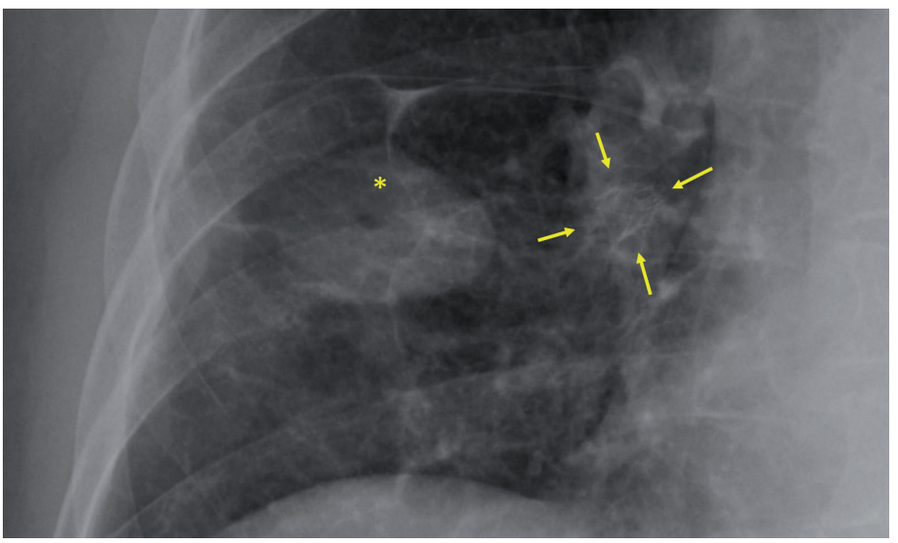

Figure 8.
Resolution of pneumothorax after implantation of an endobronchial valve (faint metallic shadow surrounded by yellow arrows) for bronchopleural fistula. This is the same patient as ***Figure 7*** *And the ablation zone is marked by (*) on this chest x-ray.*

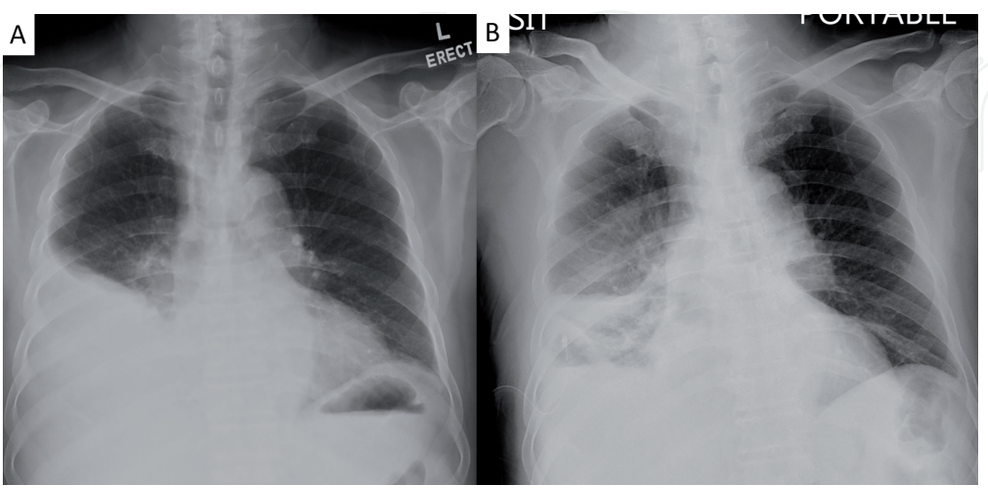

Figure 9.
(A) Moderate right pleural effusion that has accumulated for 3 days following CT-guided microwave ablation of a right lower lobe lung tumor. The patient had low grade fever and complained of shortness of breath. (B) partial drainage of the effusion by a medium bore chest drain. The pleural fluid was exudative but sterile, and the patient was discharged home after a course of antibiotics and complete drainage of the effusion.

pleural temperatures [72]. Repeated punctures and previous systemic chemotherapy were significant risk factors [64]. Aseptic pleuritis gives rise to pleuritic pain, but most resolve spontaneously. Only a minority of pleural effusion required drainage (**Figure 9**).

The incidence of hemoptysis after percutaneous RFA is 3–9% [68], while the incidence of all forms of hemorrhage is approximately double that rate. Risk factors for intraparenchymal hemorrhage include basal and middle lung zone lesions, needle track traversing lung parenchyma by more than 2.5 cm, electrode traversing pulmonary vessels and the use of multi-tined electrodes [73]. Although most hemorrhages are self-limiting, rarely ablation injury to intercostal artery may occur leading to massive bleeding [68].

6. Bronchoscopic ablation techniques

Most of the thermal ablative techniques in literature involved percutaneous placement of electrodes. Since 2010, a Japanese group pioneered a bronchoscopy-guided cooled RFA technique for lung tumors in humans [74, 75], followed by a Chinese group using electromagnetic navigation bronchoscopy (ENB) guidance [76]. Compared to percutaneous approach, a major advantage of bronchoscopic ablation is lack of pleural puncture, and hence fewer pleural-based complications. The Japanese group reported no pneumothorax, bronchopleural fistula nor pleural effusion in 28 cases of bronchoscopic RFA [75], while the rate of pneumothorax for percutaneous ablation ranges from 3.5–54% as mentioned above. Bronchoscopic ablation also eliminates the risk of needle tract seeding. Another edge of bronchoscopic ablation is its ability to reach certain regions of lung which are otherwise difficult or dangerous for percutaneous access, for instance areas near mediastinal pleura, diaphragm, lung apex, or areas shielded by scapula.

Figure 10.
The set-up for microwave ablation of lung nodules under electromagnetic navigation bronchoscopy (ENB) is shown. Within the hybrid theater, the patient lies supine and is intubated with single lumen endotracheal tube. With the help of navigation software like SuperDimension™ (@), and fine adjustment of position with cone-beam CT (#), the target lung lesion is localized with a ENB bronchoscope. The microwave ablation catheter is inserted through the bronchoscope into the lung tumor, which is then connected to the microwave generator (*). The yellow arrow is pointing to the external part of microwave ablation catheter.

With evidence of safety and technical success of bronchoscopic ablation in animal models [77], and the above-mentioned advantages in mind, the author's institute is one of the first to perform ENB-guided microwave ablation on patients in the hybrid operating room (**Figure 10**). Navigation precision has been much improved following the advent of ENB with the help of navigation systems like SuperDimension™ (Covidien, Plymouth, MN, USA) (**Figures 11** and **12**), supplemented by position confirmation by fluoroscopy and cone beam CT. The microwave catheter (Emprint™ Ablation Catheter with Thermosphere™ technology, Covidien, Plymouth, MN, USA) is inserted within the lung tumor via bronchoscopy and ablated for up to 10 minutes per burn (**Figure 13**). Since early

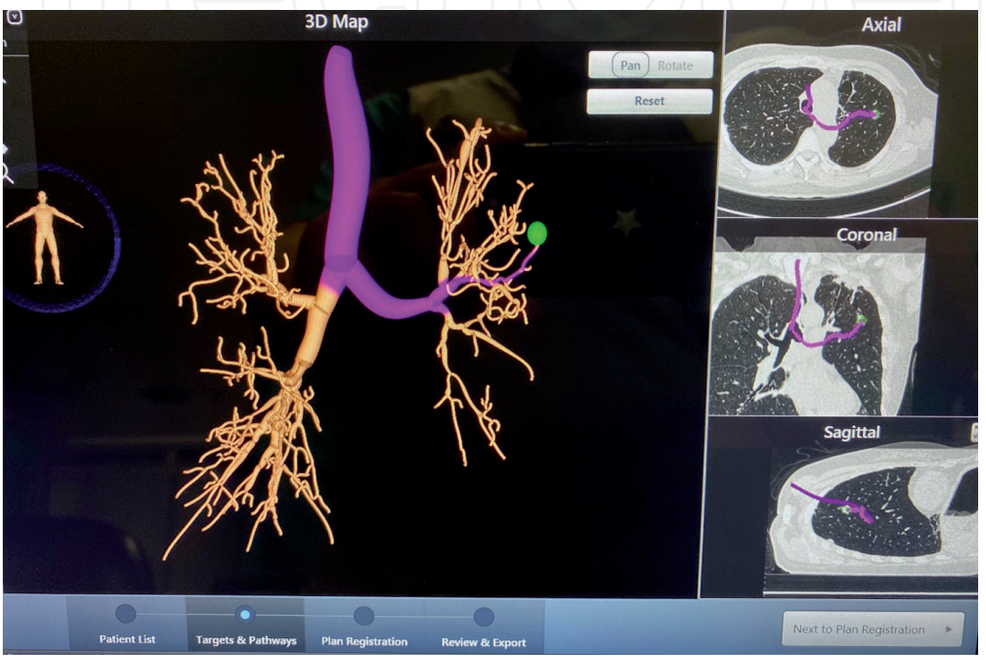

Figure 11.
The planned navigation pathway (pink) from trachea to the target lung lesion in left upper lobe with the help of navigation software like SuperDimension™.

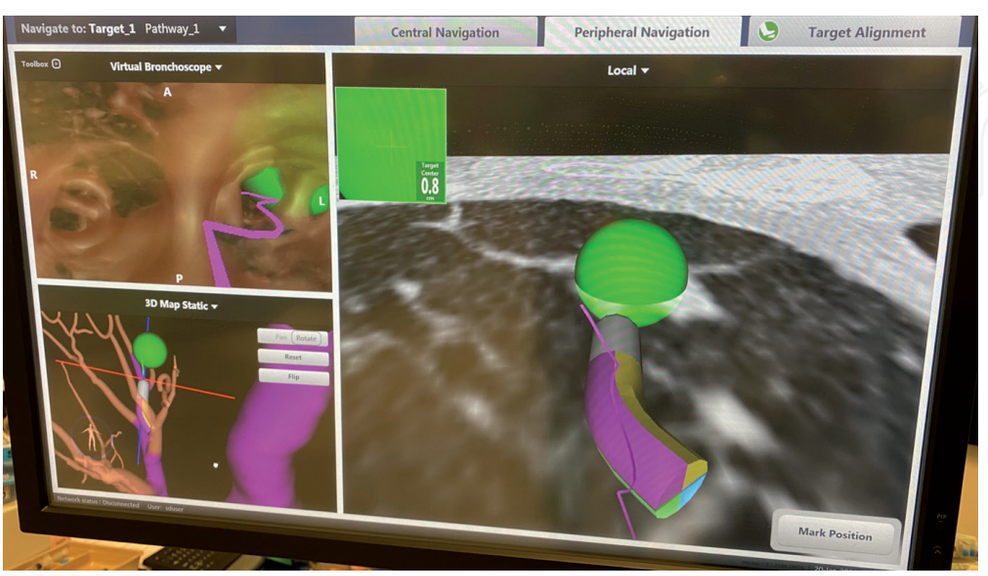

Figure 12.
The SuperDimension™ software allows multiple views to guide navigation to a target lung lesion (green ball). The upper left panel shows the navigation pathway (pink) in virtual bronchoscopy view, while the lower left panel shows it in 3D map view. On the right side panel, the Centre of the target lung lesion is shown to be 0.8 cm from the tip of the locatable guide.

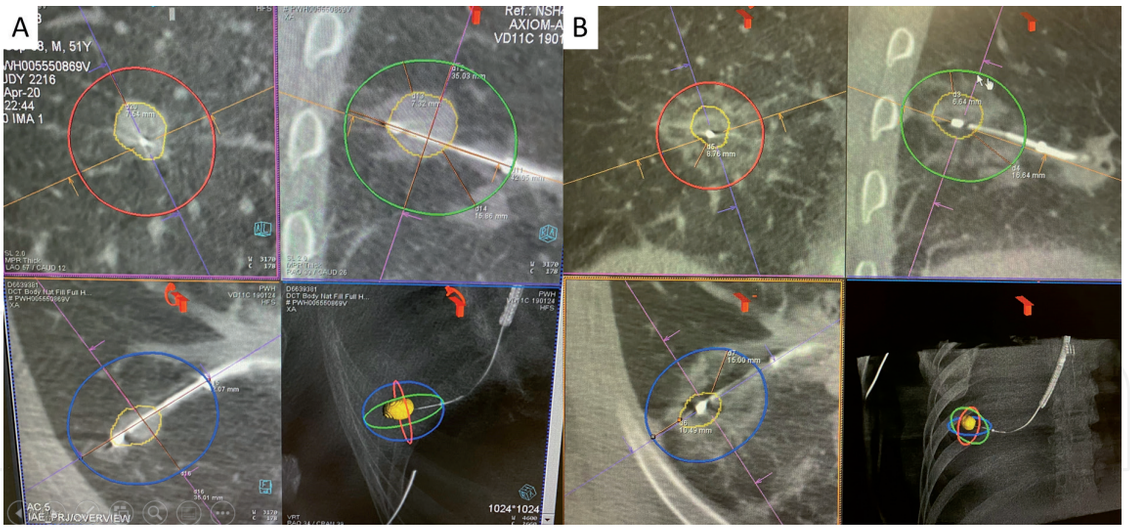

Figure 13.
(A) The target lung lesion (yellow tracing) in 3 axes on CT before bronchoscopic microwave ablation. The green, red and blue ovals mark the expected ablation zone margins. (B) The post-ablation appearance of the same lung nodule. The lung tumor has been encompassed in the ablation zone, represented by ground-glass opacities.

2019, we have performed 45 cases with 100% technical success rate. Similar to percutaneous approach, the median length of stay was 1 day only. Only 2 patients (4.4%) developed pneumothorax requiring chest drainage. Post-ablation reaction and fever occurred in 8.9%, minor hemoptysis or hemorrhage in 4.4%, and pleural effusion in 2.2%. As of the time of writing, there was no progressive disease at a mean follow up of 290 days. We believe that bronchoscopic ablation represents the future for lung cancer ablation as it offers a truly wound-less option with likely fewer complications.

7. Conclusions

Image-guided ablative therapy is an important armamentarium in the treatment of lung cancers, either for early stage lung cancers in patients who are medically inoperable or refuse surgery, or for palliation of late stage lung cancers. Radiofrequency ablation is the most studied modality with a large body of evidence supporting its safety and efficacy, with comparable outcomes to sublobar resections and stereotactic radiation therapy in select patients. Nonetheless, microwave ablation is quickly catching up in popularity due to its superior properties over RFA. Traditionally, lung ablation was performed percutaneously, but the latest development of bronchoscopic ablation techniques are promising and may drive the future of lung cancer ablation research.

Conflict of interest

Dr. Joyce WY Chan and Dr. Rainbow WH Lau declare no conflict of interest.

Professor Calvin SH Ng is a consultant for Johnson and Johnson; Medtronic, USA.

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Author details

Joyce W.Y. Chan, Rainbow W.H. Lau and Calvin S.H. Ng*
Division of Cardiothoracic Surgery, Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR

*Address all correspondence to: calvinng@surgery.cuhk.edu.hk

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