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Review

Radiofrequency, microwave and laser ablation of pulmonary neoplasms: Clinical studies and technical considerations—Review article

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ABSTRACT

Image-guided thermal ablation therapy has received significant attention for the treatment of many focal primary and metastatic pulmonary neoplasms. This interest has been associated with progressive advances in energy development, approach, technical application and adjuvant therapeutic combinations to improve the outcome results concerning local tumor control, survival rate and symptoms relief. This review provides clinical outline of percutaneous thermal ablation of lung neoplasms using radiofrequency, microwave and laser techniques regarding their principles, theoretical background, devices and techniques, technical problems and recent protocols. Advantages, limitations and technical considerations of each method will be illustrated to provide a practical guideline.

1. Introduction

The evolving field of pulmonary interventional oncology can only be considered as a small integrative part in the complex area of oncology. The new field of interventional oncology needs adequate knowledge of the therapeutic tools, advantages and limitations of each method, when and how to apply as well as the new integrative protocols that improves the efficacy of each method. Recent years have evolved the refinement and significant development of several new, minimally invasive techniques for the non-surgical treatment of lung malignancies including percutaneous image-guided ablation therapy. Since the first reported use of thermal ablation for lung cancer in 2000 there has been an explosive use of the procedure, and by 2010 the number of procedures to treat thoracic malignancy is expected to exceed 150,000 per year.

For selected patients, these technologies offer an optimal treatment option given their availability in the outpatient setting and low associated morbidity and mortality. In the category "thermal ablation" all energy sources that destroy a tumor with thermal energy are included, either by heat (hyperthermal ablation) which include radiofrequency (RF), laser and microwave or by cold (cryoablation or hypothermal ablation).

In general, the various types of hyperthermal ablative techniques differ only by their physical method of generating heat (e.g. radiofrequency, laser, micro wave and focused ultrasound) while the tissue damage achieved is related directly to tissue temperature.

The main objectives of pulmonary tumor ablation therapy (and other malignancies) are: (1) to eradicate all viable malignant cells in the target volume, with a safety margin to ensure complete eradication, (2) minimizing the damage to certain targeted volume will provide a good functioning reserve of the rest of the lung. This is particularly important for patient with limited pulmonary functions due to extensive underlying emphysema and fibrosis (1, 2). The potential advantages of local tumor ablation therapy over surgical resection might include: (1) selective damage, (2) minimal treatment morbidity and mortality, (3) less breathing impairment in patients with borderline lung function through sparing healthy lung tissue, (4) repeatability, (5) fairly low costs, (6) excellent imaging during the procedure and for follow-up and last but not least (7) the gain in quality of life with less pain, much shorter hospitalization times with the interventions performed on an outpatient base or with overnight stays and thus a quicker re-access to social life [3].

2. Biological behavior and thermal physiology of the lung

2.1. Principle of hyperthermal ablation

Raising the tissue temperature of 45 °C for several hours results in irreversible cell damage. The latter cytotoxic effect can be

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drastically shortened down to a few minutes by increasing the temperature up to 50–60 °C. Almost instant coagulation of tissue is induced at temperatures between 60 °C and 100 °C and is manifest as irreversible damage to mitochondrial and cytosolic enzymes of the cells and to DNA. At more than 100–110 °C, tissue will vaporize and carbonize [4,5]. This thermo-biological effect is the main core of the hyperthermic ablation therapy. The lung has a complex structure of ventilated alveoli and bronchi in addition to blood vessels. The air-filled cavities work as heat insulators, while the enclosing capillary beds function as heat dissipaters. Air in the bronchial system is continually exchanged by ventilation, and, similarly, the high blood circulation carries away heat. The location dependent variability of these structures can lead to a variation in thermal parameters.

2.2. Principle of cryoablation (hypothermal ablation)

During cryoablation three basic phenomena occur resulting in cell death:

1. Rapid formation of intracellular and extracellular ice crystals, which leads to mechanical shear forces on cell membranes and organelles causing mechanical cell damage.
2. Cellular dehydration, which occurs due to shifting of water from intracellular to extracellular spaces by osmosis causing destruction of critical cellular components.
3. Ischemia as a result of vascular stasis and damage to the blood vessels, which prevents nutrients from reaching remnant viable cells.

The faster low temperatures are reached, the more severe is the damage to the treated tissue. Compared to nitrogen-based systems, operating temperature is reached faster with argon-based systems, and cells are damaged more effectively (6)

2.3. Indications of pulmonary ablation therapy

Still resection is the only proven curative approach for both primary (NSCLC) and secondary lung tumors and therefore the gold standard modality for the time being thermal ablation is the treatment of choice for the non-surgical patient. The indications for local ablation of primary and metastatic lung neoplasms are similar to those established for resection, although with some modifications. It is usually felt that the number of lesions per hemithorax should not be more than five and that the largest lesion diameter should be less than 5 cm. Ideally tumors should be smaller than 3.5 cm in diameter and completely surrounded by non-tumorous lung [5,7–19]. As a rising consensus the two major indications for ablation therapy are either (1) full therapy of pulmonary disease when there is no evidence of extrapulmonary spread or (2) supportive therapy as it can be applied for patients who are refractory to or not amenable to conventional therapies (surgery, chemotherapy, and radiation therapy) as a result of coexistent morbidity (pulmonary emphysema, liver cirrhosis, hemodialysis, and another coexistent tumor) or for pain relief [20,21]. Tumors abutting the pleura can be efficiently treated, but this is associated with increased pain during and after treatment.

The role of ablation therapy in metastatic lung disease has special considerations. According to literature the chances of curative success post-ablation therapy depend upon different variables, which are as follows: more favorable in solitary rather than multiple metastases, in metachronous rather than synchronous metastases, and in colorectal rather than other primary tumors [22].

Contraindication of ablation therapy includes bleeding coagulopathy including international normalized ratio greater than 1.8; and platelet count of less than $50 \times 10^3/\mu L$ [3–19].

3. Complications of pulmonary ablation therapy

From a procedural and technical point of view, pulmonary ablation therapy has been considered as a safe and minimally invasive method. Complications associated with pulmonary ablation therapy include.

3.1. Pneumothorax

In most large studies, the incidence of pneumothorax ranges between 15% and 45% which is similar to the incidence of pneumothorax after lung biopsy as reported in literature [1–5,7–18] (Fig. 1). Our technical experience accords with many of published researches in the literature which conclude that pneumothorax complicating ablation of lung neoplasms is rather unpredictable, but there are many risk factors that make its incidence higher in certain patients than others. Technically avoidable risk factors of pneumothorax include: (1) practicing the ablation by well trained interventionist with adequate technical experience to minimize technical defects, (2) planning of the needle access in the shortest distance between the pleural surface and the lesion to minimize the distance of traversed lung parenchyma, (3) avoiding crossing a major pulmonary fissure in the track of the needle, and (4) avoiding multiple pleural punctures by using expandable electrodes instead of multiple single electrodes. Inevitable risk factors include: age, COPD, and deep, basal, and small lesions; these inevitable risk factors comprise the patients high-risk group for pneumothorax [7–18].

3.2. Intraparenchymal hemorrhage

Hemorrhage is a known complication in lung ablation, and results from the positioning of the device rather than from the ablation process. The reported incidence of hemorrhage is <1% and it seems to be underestimated [21,22]. Nevertheless, based on the principle of cauterization, the coagulative potential of the thermal ablation procedure itself makes the bleeding of a treated lesion quite unusual. To avoid needle track bleeding it is recommended to perform “hot” probe repositioning and removal (i.e. needle track ablation).

3.3. Pleural effusion

A small amount of pleural effusion is usually seen during the hyperthermal pulmonary ablation, increasing in size with ablation duration and number of lesions treated. On the control erect chest radiograph post-intervention the lateral costophrenic angle

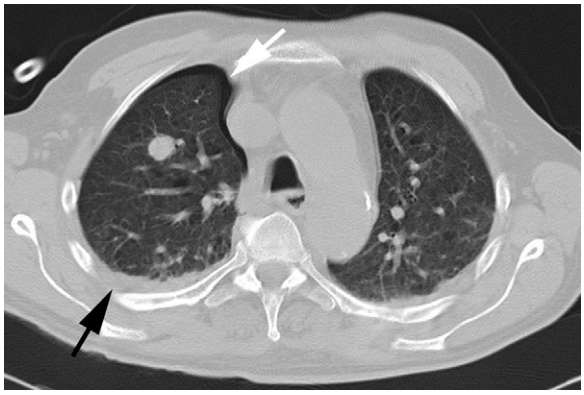

Fig. 1. A 56-year-old male patient with pulmonary metastases from colorectal carcinoma. RF ablation was performed which is complicated by mild pneumothorax (white arrow) and mild pleural effusion (black arrow).

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is obliterated. These effusions, sympathetic in character, do not require tapping. They usually resolve within a couple of days and are asymptomatic [3] (Fig. 1).

3.4. Tumor seeding

Tumor seeding by the carrying of tumor cells along the probe's pathway(s) is basically an issue of inappropriate technique and is typically detected 3–12 months after the procedure [23,24]. This risk can be almost eliminated if the probe is properly positioned on the first pass and does not cross the tumor primarily, otherwise tumor cells can be pushed out of the tumor in its periphery. A sufficient safety margin around the tumor and removing the probe by additional ablation of the needle tract will further lower the risk of tumor cell spread. Llovet reported a tumor seeding frequency of 12.5% (4 cases out of 32) while in a large Italian multicentre trial including more than 2000 patients the frequency was only 0.6% [25,26]. In general, multiple or large tumors necessitating several needle passes, subpleural (pulmonary) locations, and poor tumor differentiation may favour tumor seeding.

3.5. Unintentional thermal damage

Complications related to the thermal ablation itself include unintentional thermal harm to non-targeted areas including burns at the grounding pads (particularly in monopolar RF electrodes system) and interference with metallic implants such as pacemaker wires and cardioverter defibrillators. More critical are unintentional burns to anatomical structures within the vicinity (distance less than 1 cm) of the treated lesion. A thorough planning of the access route and final electrode placement may help to avoid damage of such structures, for example the trachea or major vasculature [3].

3.6. Common minor side effects

These include pain in the area of the puncture site, pleuritic pain, nausea, vomiting, moderate fever, tiredness and headache. Fever, nausea, tiredness and vomiting are the main elements of post-ablation syndrome, which is seen in about two-thirds of patients and might last for several weeks. In general supportive therapy including mild analgesics and non-steroidals is sufficient in such cases [28].

3.7. Other rare complications

Other rare complications of ablation therapy include cavitations, infection, mechanical injuries by the ablation probe traversing a vessel, bronchopleural fistula and pulmonary edema due to extensive ablation [29]. As for CT-guided biopsy the risk for air embolism applies similarly for RFA, especially if a coaxial technique is used. These complications can generally be avoided by applying real-time imaging guidance such as CT-fluoroscopy for placing the probe. It is speculated that the air embolism complicating ablation therapy of the lung develops when the electrode establishes a communication between the pulmonary vein and airways. If the electrode tip is placed into the pulmonary vein, communication with the atmosphere may also occur. Some reports noted that elevation of airway pressure due to cough, positive pressure ventilation, or the Valsalva maneuver may be contributing factors to the development of air embolism [30]. CT-fluoroscopy from the technical point of view can minimize this complication by: (1) minimizing the manipulation required to hit the target lesion thus minimizing excessive parenchymal injury, (2) providing a real-time monitoring of the needle track, in order to avoid traversing pulmonary vessels and (3) reducing the time required during the application of the electrode within the lesion. However, proper planning of the needle access in the shortest access away from pulmonary vessels and practicing the ablation by experienced interventionist are also important factors to minimize the risk of air embolism.

4. Radiofrequency ablation of pulmonary neoplasms

4.1. Basic principles of radiofrequency ablation and physical background

The fundamental principle of RFA is based upon the biophysical interaction of high-frequency alternating current (typically 450–500 kHz) and biological tissue in terms of resistive (frictional) energy loss. Therefore, the term radiofrequency alludes to the alternating electric current oscillating in a high-frequency range of the alternating current. Between the active and the reference electrode (or two active electrodes in bipolar systems) an electric field is established which oscillates with RF frequency. Ionic oscillatory agitation induced by this oscillating field results in frictional heat followed by "coagulative" necrosis if enough energy is deployed, whereas the field intensity determines directly the frequency of the oscillation. In consequence, the heat emerges into tissue in the immediate vicinity of the electrode. Further heat dispersion is a result of heat conductivity and convection effects [31].

The generated frictional heat is directly and proportionally dependent on the RF energy delivered, while the total thermal damage caused to the tissue is dependent on both the tissue temperature finally achieved and the duration of heating. Due to the specific tissue resistance and the energy dispersion between the needle-like electrode and the dispersive ground pad there is a rapid decay of energy and consequently of heat around the electrode, where the temperature is inversely proportional to the distance from the electrode ($T \times 1/r4$; T = temperature, r = radius around the electrode). This means that destructive thermal energy can be deployed sufficiently only within a volume of a maximum diameter of 2.2–2.4 cm around a single electrode.

As a consequence, the energy is delivered quite precisely and focused to the volume around the electrode, making heat induced damage remote to the source of heat (RFA) rather unlikely. Using advanced needle designs volumes of up to 5 cm diameter can be ablated. Accepting an increased time for treatment needle repositioning and creating overlapping volumes may result in even larger volumes [32,33]. Nevertheless, the finally resulting volume of ablation is also considerably dependent on the intrinsic tissue properties such as heat conductivity and convection. In this regard a crucial effect must be mentioned: the so-called heat sink effect. The heat sink effect is caused by large vessels – the pulmonary arteries and aorta in case of lung ablation – near to the heat source resulting in heat loss.

For practical reasons the complex theoretical considerations can be simplified by correlating tissue destruction (coagulation) to: the energy delivered corrected by a factor (tissue-specific correction factor) in clinical reality this means that more energy is needed than expected. Energy loss results from tissue-specific cooling effects including vascular perfusion, insulation effects, etc. [34].

4.2. The monopolar and bipolar systems

The mechanism of action and physical background of both unipolar and bipolar systems are summarized in Table 1.

4.3. RF generator, electrode design and energy delivery

The data regarding the principles of the RF generators, properties of different electrode designs and mechanism of energy delivery are summarized in Table 2.

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Table 1
Demonstrates the principles and differences between monopolar and bipolar systems.

Item	Monopolar system	Bipolar system
Role of patient in electrical connection	The patient is turned into a resistor within a closed-loop circuit consisting of: (a) RF generator, (b) dispersive electrode (grounding pads placed on patient thigh), (c) needle electrode.	The patient is not connected in the loop circuit. The Circuit consists of: (a) RF generator, (b) needle consisting of two non-insulated electrodes are placed in situ in the same probe.
Role of the needle in the ablation process	The needle acts as a focusing electrode while the grounding pad acts as a dispersive electrode.	The current will flow between the two poles located in the same probe.
The path of electrical current	An alternating electric field is created within the tissue of the patient concentrating the electrical energy around the non-insulated tip of the needle-like electrode.	The bipolar system avoids the energy dispersion between the dispersive and focusing electrodes. Thus avoids the unintentional skin burns from the dispersive electrode.
Principle of ablation	Due to high electrical resistance of tissue in comparison with the metal electrodes, there is marked agitation of the ions present in the tissue surrounding the needle-like electrode, concentrating the energy	The same.
Reference	[1,24–28]	[39–45]

4.4. Practical considerations and technical limitations of RF ablation of pulmonary neoplasms

The efficacy of the RF energy deposition is determined by: (a) the amount and duration of the energy exposure (watts, time) and, (b) probe design (Fig. 2).

Intrinsic tissue factors (heat connectivity and conversion) which is limited in the normal pulmonary parenchyma in comparison to the hepatic parenchyma due to the presence of air inside the alveoli which act as an insulator to both heat and electrical connectivity. This means that to ensure adequate current flow and heat dispersion, central positioning of the electrode within the lesion is mandatory. This limiting effect appears more significantly in small lesions (<1 cm), particularly when we add the technical difficulty due to respiratory movement and subcostal or subscapular location of the lesion.

To destroy any given tumor completely the ablation volume should envelope the tumor entirely together with a safety margin (5–10 mm) according to surgical rules (Fig. 3). The pathophysiological rationale for the safety margin is the high likelihood of scattered tumor cells (invisible to imaging) immediately around the tumor nodule visible by imaging. If only the visible tumor is treated; then local recurrence can easily emerge from the tumor cells remaining around the visible tumor. In these cases, multiple overlapping ablations or simultaneous use of multiple applicators may be required to successfully treat the entire tumor and ablative margin, though accurate targeting and probe placement can often be technically challenging [34–47]. This may be also applicable to other ablation techniques.

Another independent predictor of a successful ablation is the tumor's vicinity to major vessels causing heat sink effects. Lu et al. [47] showed that, in 105 tumors with a mean diameter of 2.4 cm

Table 2
Illustrates the different electrode designs, RF generators and mechanism of energy delivery.

Electrode design	RF generators	Energy delivery
RF electrode consists of an insulated metallic shaft and a non-insulated, active tip of variable length and/or design.	In the internally cooled single and cluster electrode system (Cool-tip, Valleylab, Tyco Healthcare) are mainly algorithms that are applied, with pulsed delivery of high-energy levels over a relatively short period of time (10–15 min) without feedback control.	The control of the process of ablation itself is device dependent.
To close the electric circuit between RF generator, electrodes and patient, the active tip must be located in contact with the target tissue.	In the multi-tined system with impedance control (Boston Scientific) and the bipolar, single or multi-electrode system (Olympus Celon) a step-wise increased or fixed amount of energy is controlled by the tissue resistance rising with increasing desiccation.	The heat-related dehydration results in a progressive coagulative necrosis and a loss of conductibility followed by rising tissue impedance.
To increase the volume of ablation modifications have been made to the probe design, e.g. extending the length of the antenna (cluster needle, umbrella/inverted umbrella-like design) or internal cooling of the needle to avoid premature carbonization around the probe followed by insulation and energy decay.	In the second multi-tined system (AngioDynamics RITA) the power delivery is controlled by temperature feedback derived from thermostats at the tips of the tines.	Most RFA systems use the relative increase of impedance as a parameter for controlling the ablative process, while ascending impedance down regulates the delivered power.
Larger coagulation volumes could be obtained with the internally cooled cluster devices.		At present, only one system is equipped with multiple thermostats at the tips of the antennas, thus offering on-line monitoring of the temperature. In general, the ablation process takes 10–30 min per needle placement to provide complete tissue necrosis.
The available electrodes provide ablation volumes with more or less spherical diameters of between 2 and 5 cm.		
Reference: [37,42,43]	Reference: [31]	Reference: [31]

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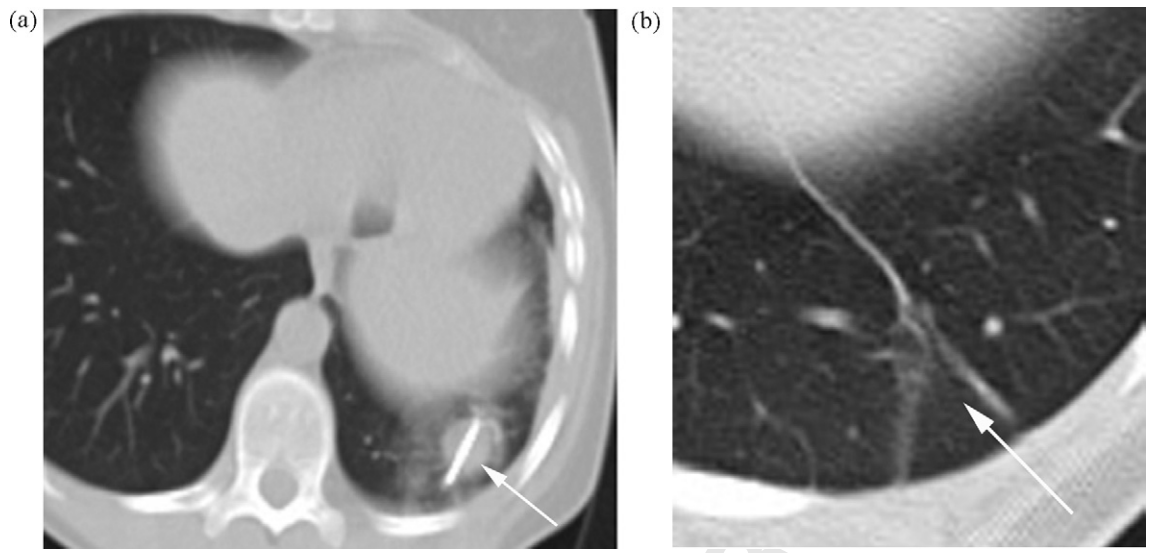

Fig. 2. A metastatic deposit from breast carcinoma treated by RF ablation. (a) RF electrode within the vicinity of the lesion during ablation using Celon–Prosurg bipolar system (arrow). (b) Follow-up post-9 months showing local scarring of the lesion with no evidence of tumor remnants (arrow).

treated with two different multi-tined and one cluster RFA system, lesions at least 3 mm from a major vessel presented a primarily incomplete ablation or recurrence only in 7%, while this was true in 48% of tumors that were in the direct vicinity of major vessels [47]. In consequence, both these independent predictors of success – lesion size and vascular proximity – have to be incorporated into a RFA treatment concept. Overall, the primary success rates of RFA in liver, kidney, lung and bone tumors range from 70% to more than 95%, depending on the tumor localization and type.

Growth patterns of the tumor itself can affect the end response of the ablation. Slowly growing tumors are more amenable to multiple treatment sessions over longer periods of time. This renders metastases from sarcomas or other hypervascular metastases from the technical point of view more liable for rapid recurrence if not properly ablated.

An individual learning curve is necessary to collect enough personal experience to understand and to control the process of ablation sufficiently and to warrant an efficient result in terms of tumor control [48–50].

Technical problems occur in <5% and consist of hard tumors bouncing off the electrode tip, desiccated tissue that adheres to the electrode tines and possibly preventing the easy withdrawal of the electrodes into the trocar, and failure to reach target temperature. Lesions abutting the heart or major bronchi and vessels also constitute a technical challenge, both for spiking the tumor without harming these structures, but mainly for a successful and complete ablation due to cooling effects of the circulating blood [3].

Charred tissue sticking to the electrodes is very often observed. In case of use of cluster electrodes, it can be usually overcome by redeploying and retracting the hooks a few times. To prevent or minimize tissue charring in the setting of rising impedance, it may be useful to pause the delivery of RF energy, fully retract the electrode arrays, rotate and re-deploy the arrays and then resume delivery of RF energy.

Compared to the liver, which is a homogeneous solid organ, the lung seems to be predisposed more to charring due to its tissue composition with alternating air-filled spaces and bronchovascular bundles. As the aim of the RFA is not only to ablate the solid tumor, but also a 1-cm safety margin surrounding the tumor, this safety margin consists of normal healthy air-filled lung tissue that may lead to charring. A possible solution to this problem might be injection of saline, either through a central access provided on the probe or through holes within the retractable needle tips, not only decreasing the impedance, but also allowing for shorter ablation times and significantly larger ablation lesions [46].

In order to avoid bleeding from the needle track and tumor seeding along the track cauterization of the track is recommended. This is also recommended for other ablation techniques.

First-, second- and third-degree skin burns at the grounding pad site during and after RFA do occasionally occur. The use of higher

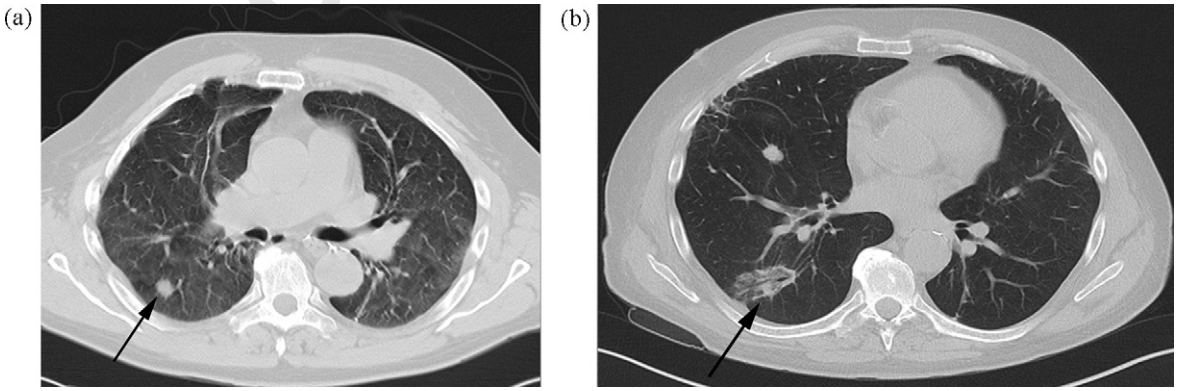

Fig. 3. A metastatic deposit from hepatocellular carcinoma treated by MW ablation using Covidien, Valley Lab system. (a) The lesion before ablation (black arrow). (b) Follow-up post-3 months showing local scarring of the lesion with marked diminution of the size of the lesion.

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Table 3
Q5 Demonstrates the results of variable clinical studies published in the literature regarding RF ablation of lung tumors.

Authors	Number of patients	Tumor pathology	Complications	Method of follow-up	Follow-up period	Response to treatment	Survival rate
Pennathur et al. (Ref. [52])	19 patients	Stage I non-small-cell lung cancer	Pneumothorax (63%) drainage with pig tail	CECT and PET scan	29 months (range, 9–52 months)	CR: 10.5%, PR: 53%, SD: 26%, EP: 10.5%, LP: 42%. Median TP: 27 months.	1 year survival 95% (confidence interval, 0.85–1.0)
Lencioni et al. (Ref. [1])	106 patients (multicentre study)	Non-small-cell lung cancer (NSCLC) in 33 patients, metastasis 160 patients (183 lung tumours. 3.5 cm in diameter or smaller)	Pneumothorax ($n = 27$) or pleural effusion ($n = 4$), which needed drainage	CT, CECT		CR: 88%. No differences in response were noted between patients with NSCLC or lung metastases.	For NSCLC: 1 year survival 70%, 2 years survival: 48%, For Colorectal Met: 1 year survival 89%, 2 years survival 66%, for other Met: 1 year survival 92%, 2 years survival 64%.
Simon et al. (Ref. [8])	153 patients	189 lesions primary and metastases	Pneumothorax 28.4%. 9.8% chest tube insertion rate. 30-day mortality rate 3.9%. 2.6% procedure-specific 30-day mortality rate.	CT and PET scanning	Up to 5 years		1-, 2-, 3-, 4-, and 5-year survival rates, respectively, for NSCLC were 78%, 57%, 36%, 27%, and 27%; rates for colorectal pulmonary metastasis were 87%, 78%, 57%, 57%, and 57%.
Grieco et al. (Ref. [53])	37 by RF 4 by MW followed by brachytherapy and fractional radiotherapy	Inoperable stage I/II NSCLC tumors	Nine of 15 pneumothoraces required chest tube drainage (22.0%)		The median follow-up was 19.5 months	Local recurrence in 11.8% of tumors <3 cm after an average of 45.6 ± 4.1 months and in 33.3% of the larger tumors after an average of 34.0 ± 7.8 months.	97.6% at 6 months, 86.8% at 1 year, 70.4% at 2 years, and 57.1% at 3 years.
Steinke et al. (Ref. [54])	23 patients	52 colorectal pulmonary metastases tumor diameter ranged from 3 to 4.2 cm.	Pneumothorax: 43%. Chest tube in 6 patients. Malignant effusion: 1 patient. Cavitation in 17%.	CT, CECT	The median follow-up was 428 days (range, 173–829 days)	CR: at 1 year in 40 lesions, PR: in 17, decreased in 5, SD: 4, PD: 14	Five patients died at 5, 6, 8, 8, and 12 months after RFA.
Yasui et al. (Ref. [10])	35 patients in 54 sessions	Primary: 3 Met: 96 lesions 3–80 mm in largest diameter; mean, 19.5 mm	Mild Pneumothorax 35.2% pneumothorax requiring Chest tube (7.2%) haemoptysis (11.1%) pleural effusion 3.2% abscess 1.9% hemothorax 1.9%	CT, CECT an histopathology	Follow-up was 1–17 months (mean, 7.1 months)	Complete coagulation necrosis was achieved in 91%	
Yamagami et al. (Ref. [55])	34 patients	82 tumors in 103 RF ablation sessions	Pneumothorax occurred in 27 procedures	CT, CECT	Mean follow-up period of 10 months (range, 6–28 months)	LP: 22.0% at 3 months, in 10 lesions at 6 months in 5 lesions at 9 months and in 1esion, and in 2 lesions after 12 months. Mean local progression-free duration was 8.7 ± 4.5 months.	

Hiraki et al. (Ref. [56])	105patients	252 tumors mean size mean size, 13.5 mm primary and metastatic			6–24 months	Local control rates were 97%, 86%, 81%, and 76% at 6, 12, 18, and 24 months
Yamakado (Ref. [57])	71 patients (multicentre study)	155 unresectable colorectal metastases, mean tumor size ≤3 cm	Pneumothorax 37%, chest tube was placed in (20%). Empyema developed in 1%.	CT and PET-CT	4–42 months post-ablation (mean 19 months).	47% patients developed intrapulmonary recurrence and 58% of them received repeat lung RF ablation.
Yan et al. (Ref. [58])	55 patients	Unresectable colorectal metastases				The largest size of lung metastasis, location of lung metastases, and repeat percutaneous RFA for pulmonary recurrence were statistically significant for overall survival.

Hiraki et al. (Ref. [56])	3-year survival rate: 46%. Extrapulmonary metastasis, tumor size, and the carcinoembryonic antigen level were significant prognostic factors in the univariate analysis.
Yamakado (Ref. [57])	Median survival was 33 months (range, 4–40 months), 1-, 2-, and 3-year survival of 85%, 64%, and 46%, respectively.
Yan et al. (Ref. [58])	

currents for a longer period of time in RFA of tumors and when the contact of the grounding pads to the skin surface is not sufficient (e.g. by sweat or hairs under the pad) the RF power is not dispersed efficiently and "spots" of high current flow may be generated, resulting in burns. Defects of the electrode's insulation or metallic coaxial introducers, which may act as secondary antenna by induction, can also create burns at the skin entry site [3].

4.5. Clinical studies using RF ablation technique

Results of variable clinical studies are summarized in Table 3.

5. Microwave ablation

5.1. Physics of microwave heating

Microwaves belong to the electromagnetic waves with wavelengths in the range of 30 cm (frequency = 1 GHz) to 1 mm (300 GHz). For medical uses specific frequencies between 915 mHz and 2.4 GHz are employed. As the water molecule exhibits an electric dipole moment, the electric field of the MW excites harmonic oscillations in the water as they try to align themselves with the alternating electric field, resulting in warming. Other molecules are heated by convection due to the fact that macromolecules are not directly affected by microwaves. The lowest resonance frequency of the water molecule is at 22.2 GHz. However, even at MW frequencies in the range of 1–2 GHz, the electromagnetic energy is effectively absorbed with a typical efficiency factor of 50–60% [58].

5.2. Microwave ablation compared to radiofrequency ablation

Compared to RF ablation, which deposits thermal energy in the tissue by resistive heating using alternating current at 365–480 kHz, MW ablation uses a different principle providing theoretically several advantages (Table 4). The MW antenna emits electromagnetic radiation into the tissue without the necessity of an electrical current. The resulting coagulation necrosis, however, is similar in histopathological examination in both modalities [59,60]. As no electrical current is applied, carbonization, tissue boiling and steam bubbles surrounding the applicator do not hamper the energy deposition. Much higher tumor temperatures may, therefore, be reached as compared to RF ablation of up to temperatures of 150 °C. As there is an exponential dependence between tissue temperature and induced cell death, complete coagulation of malignant tissue may be achieved in much shorter treatment time. As no electric current is passing through the patient's body in MW ablation, there is no necessity for the placement of grounding pads. The danger of tissue heating in unwanted areas is strongly reduced, which may occur in RF ablation especially at transitions of anatomical structures with relatively high electrical resistance, such as vessel walls and the skin-to grounding pad transition. Both modalities are reported to show comparable ablation diameters. RF ablation typically creates ablation diameters of 2–4 cm depending on the ablation system applied (multi-tined, internally cooled single or cluster) [61]. The clinically used MW devices show varying sizes of coagulation volume depending on their geometry: applicators of straight geometry are reported to achieve coagulation diameters of up to 2.5 cm [62], whereas single loop-antenna applicators were reported to result in coagulation diameters of up to 3.5 cm [63]. To increase the coagulation volume, multi-applicator approaches may be used (multi-polar RF devices, multi-applicator MW). With increasing ablation power, however, the danger of tissue heating in unwanted areas significantly increases in RF ablation, whereas this is not an issue in MW ablation. The pathway of the electrical current through the body in RF ablation is dependent on anatomical structures, and notable distortions of the spherical geometry of

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Table 4
Illustrates the advantages and disadvantages of radiofrequency (RF), microwave (MW) and laser interstitial thermotherapy (LITT).

RF	1. Direct puncture of the lesion with simple manipulation	1. Impedance problem 2. Smaller ablation volumes 3. Thermometry is not possible
MW	1. Direct puncture of the lesion with simple manipulation 2. Absence of impedance problem 3. Induction of larger ablation volumes	1. Tissue carbonization 2. Thermometry is not possible
LITT	1. Lower cooling effect 2. Absence of impedance problem 3. Induction of larger ablation volumes 4. Possible thermometry	1. Insertion of the applicator by coaxial sheath system 2. Applicator diameter is relatively larger than that of RF and MW 3. Tissue carbonization

the ablation volume have been reported for RF ablation, decreasing the predictability of the ablation outcome. Another drawback of RF ablation is the limited possibility of multi-applicator use in conventional monopolar techniques due to a shielding effect of the electric current among the multiple RF applicators [64], leading to unpredictable coagulation geometries for arbitrary placement of electrodes. No interference between different electrodes is found in MW ablation [62]. Three different modalities of energy disposition in a MW multi-applicator approach have been described [65]: the coherent application of energy with one generator for each electrode, which is the conventionally applied technique. In the incoherent approach, one generator switches rapidly between the multiple applicators. To further improve uniformity of power deposition, phase modulation between applicators has been proposed. The last two modalities, however, have not as yet been sufficiently investigated. Vascular flow may cause a significant reduction in the effectiveness of RF ablation due to cooling of the perivascular area, which is called the heat sink effect [66]. In several recent publications [66,67], the opposite effect was described for MW ablation, where a selective tracking of the ablation zone along blood vessels was discovered. Up to now, no complete explanation has been found for this effect. It was suggested that the presence of a vessel causes a distortion or extension of the energy distribution pattern of the electromagnetic irradiation [67,68]. The effect was also suggested to possibly be caused by thermally produced vapor traveling though the vessel [62]. The increased performance of MW ablation close to vessels may reduce the local relapse rate close to liver veins as compared to RF ablation. However, it may carry an increased risk of complications associated with thrombosis of major vessels.

5.3. Clinical studies

Microwave ablation represents the most recent addition to the growing armamentarium of available ablative technologies. Administered in a manner similar to radiofrequency ablation, the lung tumor is localized under imaging guidance, and a microwave antenna is placed directly into the tumor bed. In contrast to existing thermoablative technologies, however, microwave treatment offers several key theoretical advantages. These include consistently higher intratumoral temperatures, larger ablation volumes,

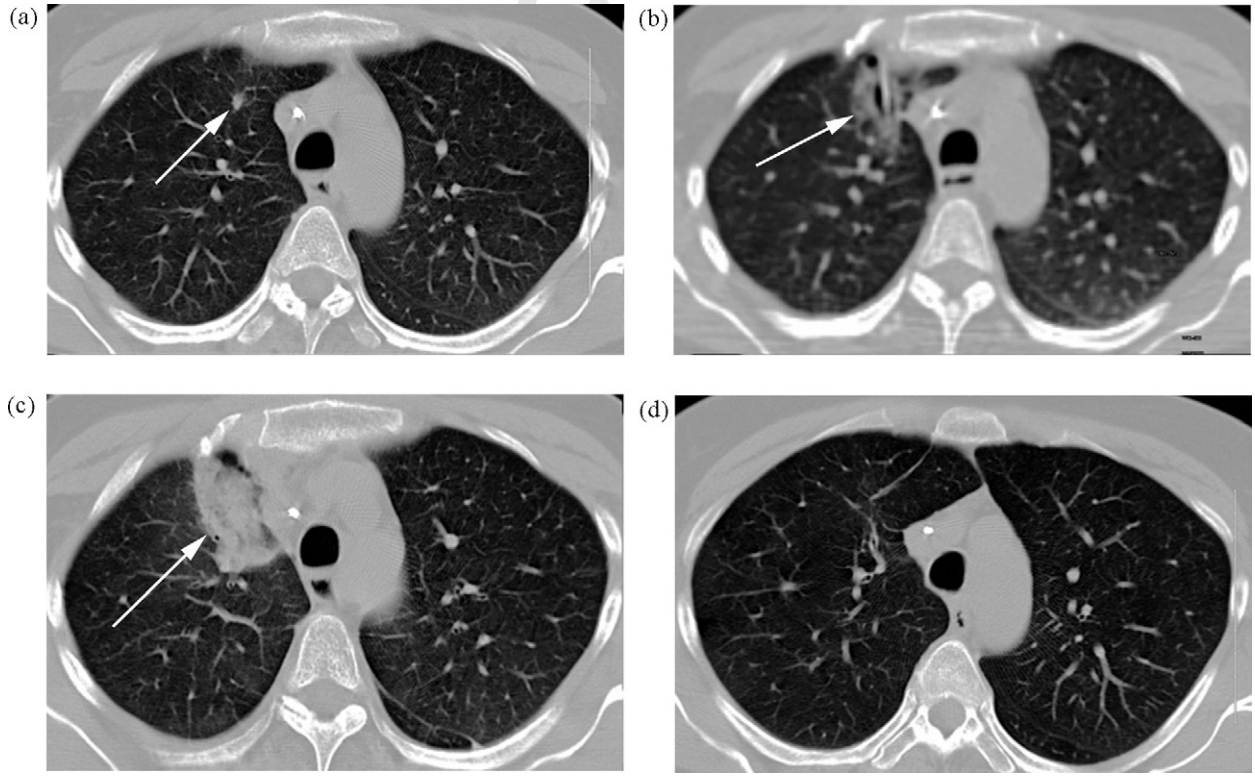

Fig. 4. A metastatic deposit from breast carcinoma treated by LITT. (a) A 6-mm left upper lobe metastatic lesion (arrow). (b) During LITT ablation therapy. Notice the gaseous evaporation and ground glass opacity surrounding the fiber optic sheath (arrow). (c) CT follow-up 24 h post-ablation showing a localized hematoma at the ablation bed. (d) CT scan 6 months follow-up post-ablation showing complete resolution of the hematoma and residual scarring in the ablation bed with no evidence residual or recurrent lesions in the ablated zone.

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reduced treatment times, and improved convection profile. As a nascent technology, efficacy and outcomes data for microwave ablation of pulmonary malignancies remain relatively lacking compared with other thermoablative techniques; however, early trials have demonstrated promising results. It is hoped that further refinements in the clinical application of this technology will continue to improve the care of patients with lung cancer (Fig. 4).

Wolf et al. carried out the largest available clinical study of microwave ablation of lung malignancies including 50 patients who underwent 66 ablation sessions. They used a single microwave antenna in 53% ($n = 35$), two antennae in 5% ($n = 3$), three antennae in 27% ($n = 18$), four antennae in 9% ($n = 6$), and multi-tine deployable ring was used in 6% ($n = 4$). 74% of patients had no recurrence of disease at the ablation site (residual disease) that was evidenced at imaging longer than 6 months after initial ablation. Presence of residual enhancing tumor was more commonly found at follow-up of treated tumors that were larger than 3 cm. Thus, index tumor size larger than 3 cm was predictive of residual disease in these patients. As a result, the 1-year local control rate was 67% ± 10, with a mean of 16.2 months ± 1.3 to first recurrence distant from the ablation site. The 1-, 2-, and 3-year actuarial survival rates were 65% ± 7, 55% ± 9, and 45% ± 11, respectively. No intraprocedural deaths occurred. Overall 30-day post-ablation mortality rate was 0%. Pneumothorax occurred after 39% (26 of 66) of ablation sessions, and 69% (18 of 26) of these occurrences of pneumothorax were classified as mild and did not require chest tube placement. Of the cases of pneumothorax that occurred in 26 ablation sessions, eight were classified as moderate to severe pneumothorax and required chest tube placement [69].

6. Laser ablation

6.1. Basic principles of laser ablation and physical background

Interstitial laser-induced thermotherapy (LITT) is a minimally invasive technique using optical fibers to deliver high-energy laser radiation to the target lesion. The physical mechanism of tumor destruction using laser ablation is temperature elevation within the tumor core by the laser fiber high enough to induce coagulation necrosis. Laser coagulation is performed by using neodymium–yttrium aluminium garnet (Nd:YAG) laser light with a wavelength of 1064 nm. The light is delivered through 400-mm-long fibers terminated by a specially developed diffuser which emits laser light to an effective distance of up to 12–15 mm [70]. The water content was estimated to be 83.7% of human lung parenchyma. This relatively high water content leads to good thermal conduction and high thermal capacity. Thus, induced warmth is stored, and the heat effect spreads slowly into the periphery. Hence, high temperature yet long exposure times are required ranging between 10 and 30 min for clinically relevant lesion sizes. An effective rise in temperature leads to thermal change and tissue damage. Since a part of the energy as a function of the temperature gradient diffuses into the colder environment, thermally induced necroses can reach sizes that exceed the optical penetration depth [69].

6.2. Laser ablation compared to RF ablation

Energy propagation from radiofrequency ablation is focused on the solid tumor portions due to the insulating effects of the surrounding lung tissue. However, the same effect limits further energy deposition, and the impedance rise at the zone of transition between tumor and lung parenchyma leads to a break of current flow (roll off). In contrast to RFA, the laser functions with the irradiation of coherent monochromatic light, which is appropriately absorbed by the tissue and works independently of the impedance rise [70] (Table 4).

The thermosensitivity of certain MR sequences is the key to real-time monitoring, allowing accurate estimation of the actual extent of thermal damage. Thus, laser can destroy tumor by direct heating, while greatly limiting damage to surrounding structures. Experimental work has shown that a well-defined area of coagulative necrosis is obtained around the fiber tip, with minimal damage to surrounding structures. The success of LITT is dependent on delivering the optical fibers to the target area, real-time monitoring of the effects of the treatment and subsequent evaluation of the extent of thermal damage. The key to achieving these objectives is the imaging method used. MR-guided laser-induced thermotherapy offers a number of potential treatment benefits. First, MR imaging provides unparalleled topographic accuracy due to its excellent soft-tissue contrast, high spatial resolution and multi-planar reconstruction. Secondly, the temperature sensitivity of specially designed MR sequences can be used to monitor the temperature elevation in the tumor and surrounding normal tissues. This enables the exact visualization of the growing coagulative necrosis. A big advantage of laser ablation over radiofrequency (RF) ablation is that it can be combined with MR because (laser) light is used instead of RF. To generate an MR image an RF pulse is used. If there is any RF source in the MR room there is always interference between the radiofrequencies from the RF generator and the radiofrequencies from the MR scanner. The result is that the MR image is completely destroyed. Even with an MR-compatible RF probe it is necessary to disconnect the probes for every MR scan and this is quite uncomfortable.

6.3. Technique of LITT

Laser coagulation is performed using a Neodymium-YAG laser (Dornier MediLas 5060 or Dornier MediLas 5100) with a specially developed flexible laser applicator. Furthermore an application kit for percutaneous treatment was developed and optimized for our purposes. Laser light with a wavelength of 1046 nm is transmitted to tissue with a diffusing applicator. Laser light of this wavelength penetrates deeply into biological tissue, where photon absorption and heat conduction lead to hyperthermic and coagulative effects. The tissue destruction may be immediate or delayed. The cooled power laser system (SOMATEX, Germany) for MR-guided minimally invasive percutaneous laser-induced thermotherapy of soft-tissue tumors consists of an MR-compatible cannulation needle (length 20 cm, diameter 1.3 mm) with a tetragonal beveled tip and stylet; guide-wire (length 100 cm); 9-French sheath with stylet; and a 7-French double-tube thermo-stable (up to 400 °C) protective catheter (length 40 cm) also with a stylet, which enables internal cooling with saline solution. Cooling of the surface of the laser applicator modifies the radial temperature distribution so that the maximum temperature shifts into deeper tissue layers. The protective catheter prevents direct contact of the laser applicator with the patient and enables complete removal of the applicator even in the unlikely event of damage during treatment. This increases patient safety and simplifies the procedure. The catheter is transparent for laser radiation and resistant to heat (up to 400 °C). Marks on the sheath and the protective catheter allow exact positioning of both in the lesion. The system is fully compatible with MR imaging systems. Magnetite markers on the laser applicator allow an easier visualizing and positioning procedure. The laser itself is installed outside of the examination unit. The laser light is transmitted via a 10-m long optical fiber. Prior to LITT treatment all patients undergo CT and a contrast-enhanced MRI study at least 2 days prior to the intervention. After localization of the tumor with CT, local anesthesia is achieved with 20–30 ml of 1% mepivacaine. Distance to the lesion and the puncture angle are calculated electronically.

After CT-guided puncture of the lesion and positioning of the laser application system, the patient is transferred to a conventional

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MR system. First of all a magnetite marker is placed for verification of the positioning of the laser application systems. After verifying the correct positioning of the laser application systems in relation to the lesion, the magnetite markers are removed and the laser applicator inserted in the laser application system. In most cases a 3-cm active length of the laser applicator is used (2 and 4 cm active lengths are also available). For larger lesions the multi-applicator technique and the pull-back technique are used. All laser applicators per lesions are used simultaneously in order to get synergistic effects.

Therefore, in all patients the ablation procedure is performed by using T1-weighted thermal imaging to monitor the LITT procedures, and in all patients the procedure is modified concerning the duration of ablation. Moreover, the pull-back procedure is calculated on the basis of the thermal imaging. The pull-back procedure is used to enlarge the coagulation necrosis in the longitudinal axis by pulling back the laser fiber between 1 and 3 cm (depending on the size of the lesion, the relationship to surrounding structures, and the thermal imaging) within the protective catheter. In no case is the ablation procedure performed on a time or energy basis.

The LITT treatment is performed under MR guidance using T1-weighted GE sequences (TR/TE = 140/12, flip angle = 80°, matrix 128–256, 5 slices, slice thickness 8 mm, interslice gap 30%, acquisition time 15 s) in axial slice orientation and parallel to the laser applicators. These two sequences are repeated every minute. Increasing tissue temperature results in an increase in the T1 relaxation time. Finally this results in a decrease of signal intensity. The entire LITT treatment is performed using local anesthesia and intravenously injected analgesics (Pethidin 10–80 mg) and/or Piritramid 5–15 mg and sedation (2–10 mg midazolam). After the procedure the needle track is closed with fibrin glue as a local haemostatic agent.

6.4. Practical considerations and technical limitations of LITT therapy for treatment of lung neoplasms

1. The efficacy of the LITT energy deposition is determined by the:

a. Amount and duration of the energy exposure (watts, time).
b. Technical experience of the interventionist teamwork being a multistage procedure that requires in the first stage proper application of the sheath within or in the periphery of the lesion under CT guidance then the ablation stage of the targeted lesion under MRI guidance. Technical failure in any stage means inadequate ablation.

2. The most important advantage of LITT over other ablative procedure is the real-time monitoring of ablation under MRI guidance. This allows optimal adjustment of energy required for ablation. Each of excess or less energy than optimal carries its drawbacks; the former means excess destruction of normal pulmonary parenchyma and the latter causes inadequate ablation.
3. Although LITT has been proved high efficacy of ablation of liver tumors with a success comparable to surgical resection in large series in literature [71–73] it is not widely used for ablation of lung tumors. This could be due to:

a. The need of a specialized center with well-trained personnel, being a team work procedure rather than mono-therapist.
b. The need for sheath system (applied coaxially using guide-wire system) makes the bore used for application relatively larger than that used by the RF or MW electrodes. In addition the relatively longer time required to accomplish the ablation procedure. These factors render the procedure liable for higher incidence of pneumothorax and bleeding.

6.5. Clinical studies

Percutaneous laser ablation or laser-induced thermal therapy is a local treatment of primary and secondary malignant lung tumors, primarily in patients whose condition is not amenable to surgical resection. Rosenberg et al. [74] recently showed their experience in studying the efficacy of LITT therapy in pulmonary metastases of different primary of origins including colorectal carcinoma, renal cell carcinoma, malignant melanoma, breast carcinoma, sarcoma, and others. They used another laser applicator system which is modified to decrease required manipulation for application and with smaller diameter to be optimized for pulmonary ablation (miniaturized internally cooled applicator system, Monocath, Trumpf Medizinsysteme). This system consisted of a 5.5-French polytetrafluoroethylene tube carrying a titanium mandrin for catheter placement. The mandrin was later replaced by an optical laser fiber with a flexible diffuser tip. Diffuser tips of different lengths (1, 2, 2.5, and 3 cm) were available, as were catheter lengths of 12, 14, 16 and 18 cm. The use of three Nd:YAG laser generators at 1064 nm fitted with optional two- and four-time beam splitters provided a variety of setting designs for simultaneous use of multiple fibers.

Their clinical outcome data strongly support the potential of laser ablation for improving long-term survival. Their prospective study included 64 patients with pulmonary metastases underwent laser-induced thermal ablation. A total of 129 percutaneous procedures were performed to manage a total of 108 lung lesions. The median tumor size was 2.0 cm (range, 0.4–8.5 cm). Definitive management of initial pulmonary disease was achieved in 31 of 64 patients. The 1-, 2-, 3-, 4-, and 5-year survival rates after ablative therapy were 81%, 59%, 44%, 44%, and 27%. The median progression-free interval was 7.4 months. There were no therapy related deaths. Pneumothorax occurred in 38% of the patients, necessitating periprocedural drainage in 5% of all cases. Parenchymal bleeding (13% of cases) was self-limited [74].

7. Conclusion

The ablation therapy of pulmonary neoplasms whether primary or metastatic can be classified into curative, neoadjuvant, and palliative and/or symptomatic. The curative potential of ablation can be defined as the achievement of long-term survival associated with effective local control. In a patient whose condition is so serious this can be a goal worth achieving. The nature of disseminated malignancies limits the chances of a complete cure because the development of new metastases in the same or another organ is always possible. Besides, there is always the risk of recurrence at the treated location due to incomplete ablation. Thus, cure should not always be the primary intention of ablation application in patients with metastases although complete remission can be achieved in some cases. Neoadjuvant ablation treatment associated with surgery aims mainly at converting inoperable conditions, due to the tumor extent, into operable ones. An example of this is a patient with bilateral involvement of both lung lobes. The ablation of a solitary lesion in one of these lobes would spare this lobe from resection and hence preserve lung tissue which otherwise could not be totally resected surgically. This approach can also spare a whole lung from being surgically resected. In other words, neoadjuvant ablation can minimize the extent of surgical resection by changing the option of pneumonectomy into a lobectomy and lobectomy to segmentectomy or localized resection. Ablation can be used as a neoadjuvant measure to systemic chemotherapy especially in the presence of extrapulmonary spread. On the other hand, it can be used as a palliative measure in cases of inoperability, post-surgical recurrence, or failed systemic chemotherapy leading to symptomatic relief, and

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hence a better life quality in this group of patients. According to our knowledge there is no prospective randomized comparative study that determines the superiority of certain ablative modality over the other.

Generally we consider evolving field of ablation therapy can only be considered as an integrative part in the complex area of pulmonary oncology and the outcome is determined by: (1) adequate estimation of the advantages and limitations of the therapeutic ablative tools, (2) proper patient selection, (3) tumor size and stage and (4) adequate integration of the ablation therapy among surgery and chemotherapy protocols.

Q3 Uncited references

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