REVIEW ARTICLE

Thermal Ablation of Malignant Lung Tumors

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SUMMARY

Background: About 50 000 new cases of non-small-cell carcinoma of the lung are diagnosed in Germany each year. More than 20% of the affected patients cannot be offered radical resection because of comorbidity alone. The lung is also the second most common site of distant metastases of extrathoracic tumors; it is the only site of such metastases in 20% of cases. In recent years, image-guided thermoablation has been used with increasing frequency in patients who are unable to undergo surgery for medical reasons.

Methods: The PubMed database was selectively searched for publications on the indications, complications, and results of the thermoablative techniques currently in clinical use, with special attention to radiofrequency ablation (RFA).

Results: There is only a small evidence base to date concerning the treatment of malignant lung tumors with thermoablation. Retrospective and prospective case series have been published, but no randomized controlled trials have yet been conducted. RFA, the most common technique, involves the image-guided percutaneous placement of one or more probes in the tumor, to which thermal energy is then applied. For peripherally located tumors that measure less than 3 cm in diameter, local control of tumor growth can be achieved in about 90% of cases. The long-term results that are now available from smaller series provisionally indicate 5-year survival rates of 20% to 61%. The most common complication is pneumothorax requiring drainage, which occurs in about 10% of cases. In the intermediate term, thermoablation does not cause any clinically relevant loss of pulmonary function.

Conclusion: Image-guided thermoablation cannot now be considered an alternative to surgery for the treatment of malignant lung tumors with curative intent. It does, however, widen the spectrum of therapeutic options for patients who are medically unable to undergo a surgical procedure.

► **Cite this as:**

Schneider T, Heussel CP, Herth FJF, Dienemann H: Thermal ablation of malignant lung tumors. *Dtsch Arztebl Int* 2013; 110(22): 394–400. DOI: 10.3238/arztebl.2013.0394

Lung cancers are the tumors most likely to result in death. There are approximately 50 000 new cases in Germany each year. The lung is also the second-most common location for distant metastases of extrathoracic tumors and is their only location in 20% of cases (1). If certain requirements are met, surgical resection is first-line therapy in both cases. These requirements are for the focus to be technically resectable and the patient to be generally and functionally suitable for surgery, in addition to oncological criteria (2).

In lung cancer patients, comorbidity caused by cigarette consumption often limits eligibility for surgery. Reasons not to indicate surgery are major restrictions of functional pulmonary reserves, history of major pulmonary surgery, or a combination of multiple patient-specific factors (1). Surgery is impossible for functional reasons in approximately 20% of all patients with malignant lung tumors. The current German S3 Guideline on lung cancer treatment recommends radiotherapy for these patients (1). At early stages of non-small-cell lung cancer (NSCLC) percutaneous stereotactic radiotherapy achieves local tumor control in 92% of cases, with a three-year survival rate of 60% (3). Because pulmonary foci move during respiration, this procedure is technically demanding and to date is not available everywhere.

Over the last 10 years percutaneous thermal ablation has increasingly been performed on solid tumors of the liver, kidney, mammary and adrenal glands. It is also increasingly being used for lung tumors, with the aim of local tumor control (4). Radiofrequency ablation (RFA) is the procedure for which there is the most clinical experience to date; new thermal procedures that are particularly promising for the treatment of lung tumors are cryoablation, microwave ablation, and laser-induced thermal therapy.

The level of evidence for ablation procedures in the treatment of malignant lung tumors is low and is currently based on case series, descriptive comparative studies, and single-arm prospective studies (5–9). No randomized controlled trials comparing percutaneous ablation and percutaneous radiotherapy or limited surgical resection have yet been published. No uniform guidelines on the differentiated use of thermal ablation in lung tumors have yet been developed.

Indication

Image-guided tumor ablation is usually performed by radiologists, interventional oncologists, or surgeons. There are two groups of patients for whom percutaneous tumor ablation can currently be considered:

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- Patients with early-stage primary (non-small-cell) lung cancer with no lymph node metastasis who are not candidates for surgery as a result of comorbidity. Before ablation, malignancy has to be confirmed histologically. FDG-PET (2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography) evidence of a hypermetabolic focus alone is not reliable evidence of a malignant tumor. Approximately 10% of cases must be taken to be a benign tumor or a previously undetected secondary tumor (10). Diagnosis is confirmed using endoscopy and transbronchial biopsy or percutaneous biopsy.
- Patients with pulmonary metastases who are not candidates for curative resection of metastases or those with a limited number of pulmonary metastases, as part of palliative care. Histological confirmation is often unnecessary if X-ray morphology is typical (2).

Absolute contraindications for ablation procedures are severe coagulation disorders and life expectancy of less than three months. A relative contraindication is central tumor location and proximity to large blood vessels. Thermal dissipation due to the vascular blood flow results in a high risk of recurrence and increased risk of hemorrhage (11, 12) (*Box 1, Box 2*).

Techniques

Percutaneous ablation

Percutaneous ablation is performed using real-time imaging (by computed tomography [CT] or magnetic resonance imaging [MRI]). One or several RF probes are inserted percutaneously into the tumor via the shortest possible route without piercing any bronchi, pulmonary fissures, or major vessels. Thermal energy is then applied (*Figures 1a, 1b*). Imaging at the end of the procedure should show a characteristic halo sign surrounding the treated tumor (13). Ablation is performed under sedation analgesia, local anesthesia of the needle track, or general anesthesia with double-lumen intubation, depending on the number, size, and location of tumors. Double-lumen intubation anesthesia allows for a calculated pause in respiration during probe insertion and protects the untreated opposite side from hemorrhage (14).

Radiofrequency ablation

Radiofrequency ablation (RFA) is currently the most widely used procedure for interventional treatment of malignant lung tumors. High-frequency sine wave alternating current (375 to 460 kHz) is applied to the tumor. For monopolar RFA, the current must be diverted through large grounding pads on the thighs; for bipolar RFA it flows between the poles at the tip of the RF probe; and for multipolar RFA it flows between the poles of several bipolar electrodes inserted into the tumor. The resulting friction (at temperatures of 60 to 100 °C) gives rise to protein denaturation and coagulative necrosis. If the site is close to the bronchovascular bundle, pulmonary veins, mediastinal organs,

BOX 1

Influencing factors and comorbidities contraindicating surgery for lung cancer or pulmonary metastasis

- Refusal by patient to undergo surgery
- Limited pulmonary function (<40% predicted FEV1, diffusing capacity <40%)
- Cardiac morbidity (NYHA III, limited cardiac function)
- History of lung resection
- History of thoracic radiotherapy
- Non-compliance (ECOG >2)
- Multiple comorbidities

FEV1: forced expiratory volume in 1 second; NYHA: New York Heart Association; ECOG: Eastern Cooperative Oncology Group

or chest wall, this must be taken into account when planning the procedure: In these cases the cooling effect of perfusing pulmonary vessels close to the zone of ablation reduces the local effect of tissue heating (this is the heat sink effect) (15, 16). Inclusion of the bronchovascular bundle in ablation can lead to infarction and favor postinterventional cavity or fistula formation (13).

Central tumors (approximately 64% of all lung cancers) are therefore problematic, whereas peripheral foci and foci surrounded on all sides by the pulmonary parenchyma are suitable for percutaneous ablation. A small amount of contact with the pleura has no substantial effect on current flow but in approximately 20% of cases can lead to postinterventional pleurisy with pleural effusion (17). If a larger surface area is in contact with the pleura or infiltration of the chest wall has begun, the extent of the zone of ablation cannot be confidently predicted (16). In order to increase local effectiveness, particularly for larger tumors (diameter more than 3 cm), multiple probes can be inserted or the impedance of the treated tumor tissue can be reduced by introducing concentrated saline solution through the RF probe (18).

Microwave ablation

In microwave ablation, water molecules in the tissue are agitated by electromagnetic waves (900 to 2500 MHz). As a result, they oscillate, and the tissue is heated. Protein denaturation occurs at temperatures of approximately 60° C or above. This procedure can generate higher temperatures in larger zones than RFA. Zones of ablation up to 50% larger than with RFA have been achieved in animal testing (19).

BOX 2

Indications and contraindications

Indications

- Functional or technical inoperability
- Diameter <5 cm
- Peripheral location

Contraindications

- Proximity to hilum
- Proximity to large blood vessels and bronchi
- Coagulation disorders
- Life expectancy <3 months

Cryoablation

In cryoablation tissue is cooled to approximately -40°C using a probe inserted percutaneously into the tumor (by means of argon or helium). Cell death occurs during multiple coolings and thaws as a result of catabolism, dehydration, and intracellular cell membrane destruction caused by ice crystal formation. The frozen region shows up well on CT and correlates with the destroyed area of tissue (20).

Laser-induced thermal ablation

Laser-induced thermal ablation involves a 1064 nm Nd:YAG laser or 820 nm diode laser. Cell death occurs as a result of protein denaturation caused by an increase in tissue temperature induced by photons (21). The size of the zone of ablation is limited by the carbonization zone arising close to the applicator. Multiple lasers can be used for larger tumors.

Costs

An ablation probe can cost up to €1500, depending on the manufacturer; for large tumors (diameter 5 cm), up to three probes may be required. In the 2012 DRG system, percutaneous thermal ablation of lung tumors is given a relative weight of 2.918 (DRG, Diagnosis Related Group).

Image guidance during follow-up

Imaging immediately after ablation can be used to detect or rule out typical complications (pneumothorax, hemorrhage) and to document the effects of treatment. In order to detect complications early for proper treatment, CT should be performed postinterventionally, immediately after the ablation probe has been removed. As with lung biopsies, chest X-rays should be performed at 4 hours and 24 hours to rule out delayed-onset pneumothorax.

No guidelines on further oncological follow-up after ablation of lung tumors have yet been developed; follow-up examinations consisting of chest CT and/or PET/CT are usually performed at three-month intervals

(22, 23). At early stages (24 to 48 hours after ablation) following successful RFA, an expansion of the zone of ablation of up to 50% is observed, in addition to the characteristic halo sign (*Figure 1c*). The halo disappears within a month of ablation, but the zone of ablation shrinks slowly. Pulmonary cavities are observed in up to 30% of cases, particularly following ablation of larger tumors (*Figure 1d*), but usually disappear subsequently (24) (*Figure 1e*). After three months the diameter of the zone of ablation should be less than the initial size of the untreated tumor (24). PET/CT appears to be useful in detecting renewed tumor growth. Increased FDG uptake is seen up to six months after RFA in mediastinal lymph nodes that have become enlarged in reaction to ablation. Uptake then declines. A new hypermetabolic focus on a PET scan, in contrast, may indicate a local recurrence (25).

Results

Several case series following up RFA of malignant lung tumors have already been published. They vary widely in terms of number of cases, follow-up, and target variables (survival, local tumor control). The *Table* provides an overview of representative publications and their results. The best survival figures reported to date ($n = 44$ patients; follow-up: 28.6 months) are 97% at one year, 73% at three years, and 56% at five years (26).

No effect on local effectiveness has yet been shown for tissue type (primary lung cancer versus pulmonary metastasis) (27). However, the size of the tumor to be treated has been shown to be relevant: Local recurrences were significantly more common for diameters of more than 3 cm (28). In stage I NSCLC following RFA (as a result of functional ineligibility for surgery), small case series report one-year survival of 67% to 97%, two-year survival of 35% to 74%, and five-year survival of 20% to 61%. No significant long-term deterioration in pulmonary function parameters (vital capacity, FEV1) following RFA has been reported to date (23).

Clinical experience following microwave ablation is very limited; only a few case series have been published to date (29–32). As for RFA, no randomized trials are yet available. A mean survival time of 27.8 months has been reported in a series of 56 patients with a follow-up period of 36 months (32).

Following cryoablation ($n = 46$ patients) complete response is reported in 83.7% of cases (24-month follow-up) (33). For laser-induced thermal ablation too, only individual case series are available to date; five-year survival following treatment of pulmonary metastases (64 patients) is 27% (21).

Complications

Peri-interventional or postinterventional pneumothorax is described as being the most common complication following percutaneous tumor ablation, but chest drainage is required in only approximately one-third of patients (34). Smaller alveolar hemorrhages are relatively

TABLE

Selection of relevant publications that comment on complications, local tumor control, and survival

Author	Histology	Confir- mation	No.		Complications						Mortali- ty rate (%)	Survi- val (m) (m)	Local re- currence (%)	Follow- up (m)	Survival rate			
			(n)		(%)										(%)			
			Pa- tients	Abla- tions	Pneu- motho- rax	Effu- sion	Hemo- thorax	Chest drain	Pneu- monia	Fistula					1y	2y	3y	5y
Simon, 2007 (28)	LC: 116 Met: 73	Biop	153	189	28			10	2		4	29		21	78	57	36	27
Hiraki 2007 (e1)	Met.: 27	nm	27	41	49	15		15			0	33	31	20	88	54	48	
Yamakado 2007 (e2)	Met.: 71	Rad./ Biop.	71	155	37			20			0		17	19	84	62	46	
Lencioni 2008 (23)	LC: 33 Met.: 73	Biop.	106	137	40	11		23			0		12	24	70	48		
Choe, 2009 (e3)	LC: 67	Biop., Rad.	65	67	8		2	2		2	0	21	57	21	67	46	27	
Pennathur 2009 (e4)	LC: 71 Met.: 29	Biop.	100	100				59			1	23	35	17		49		
Chua 2010 (e5)	Met.: 148	nm	148	188	45	11		30			0.7			29			60	45
Hiraki 2011 (e6)	LC: 50	Biop.	50	52	42			6			0	67	30	37	94	74		61
Kashima 2011 (e7)	LC: 137 Met.: 283	Rad./ Biop.	420	1000	45		0.1		0.3	0.4	0.4	36			89	62		40
Huang 2011 (e8)	LC: 237 Met.: 92	nm	329	436	19		3		5		0.6		24		68	35		20
Ambrogi 2011 (7)	LC: 57	Biop.	57	80	11	4		5			0		41	47	83		40	25
Kodama 2011 (26)	LC: 44	Rad./ Biop.	44	55	35	6		20			0		11	29	97		73	56

LC: primary lung cancer; Met.: metastasis, usually of extrathoracic malignancies; Biop.: histology confirmed by biopsy; Rad.: ablation due to suspected tumor on radiological examination; y: years; m: months

common primarily in cases of percutaneous needle biopsy or along the ablation needle track, as a result of damage to extremely small blood vessels. However, these do not usually require treatment. In individual cases, hemorrhagic pleural effusion or hemothorax has occurred after ablation (22).

In most cases hemothorax will require thoracic surgery; hemorrhaging pulmonary vessels can be selectively embolized. The literature describes one case of massive fatal hemothorax after RFA of a central recurrent tumor following radiotherapy (35). A productive cough may be slightly tinged with blood two to four weeks after ablation; hemoptysis has been reported in 36% of cases as a result of cryoablation (36). Pain, which can begin up to two weeks after ablation, is usually caused by pleural irritation if a peripheral tumor has been ablated. Postinterventional reactive effusions may require drainage (22, 23). Cavity formation as

result of tumor colliquation or of postinterventional pneumonia following RFA are reported in up to 30% of cases. Only rarely do they induce further complications but in individual cases infection or hemorrhage may occur (24). For monopolar RFA burns have been described around the grounding pads; the temperature at the grounding pads must therefore be monitored during the intervention. Cutaneous metastases (tumor seeding) at the electrode insertion site have been described in individual cases (37). Several authors recommend withdrawing the RF probe slowly and performing track ablation in order to prevent hemorrhages from the needle track and seeding of tumor cells (26, 38, 39).

Discussion

Surgical removal is first-line therapy for early-stage NSCLC and pulmonary metastases (provided the criteria for surgical metastasis resection are met).

Figure 1: CT-guided bipolar radiofrequency ablation of NSCLC

- a) Preintervention CT: suspected malignant lesion in the right upper lobe in a patient with stage III COPD; FEV1 = 0.8l. Histology (NSCLC: adenocarcinoma) was confirmed by bronchoscopy before treatment
- b) Patient in prone position. The RFA (radiofrequency ablation) probe is inserted centrally into the tumor under CT guidance for ablation
- c) Follow-up one day postintervention: an infiltration/halo sign surrounding the ablated tumor makes the tumor appear larger
- d) Follow-up one month after RFA: the infiltration is no longer visible; colliquation has occurred and an air-filled cavity has formed in the location of the ablated tumor tissue
- e) Follow-up six months after RFA: a clinically asymptomatic cavity with thickened walls remains after further shrinkage

Image-guided thermal ablation is not yet an alternative as curative treatment. Image-guided thermal ablation can be considered for patients who are ineligible for surgery as a result of high comorbidity or reasons relating to pulmonary function, or those with local disease progression despite chemotherapy or radiotherapy. RFA is the procedure for which there is the most clinical experience in the lungs; peripheral tumors (diameter less than 3 cm) are best suited to the procedure.

The heat sink effect of large blood vessels limits the use of thermal ablation in central lung structures. There is also evidence of perivascular live tumor tissue following ablation in approximately 10% of cases for peripheral pulmonary foci (27). No prospective

randomized trials comparing ablation to other local procedures (stereotactic radiotherapy, limited surgical resection) are available, and according to information available to us no such trials have yet been performed. Because the level of evidence is very low, as yet patients should only receive such treatment as part of clinical studies or when other treatment methods have been exhausted or are contraindicated.

The current evidence is insufficient to develop a procedure for differential indication of thermal ablation versus stereotactic radiotherapy. A retrospective comparative study found no significant difference in survival between patients who underwent limited resection as a result of functional limitations and those

who received RFA (40). No clinically significant loss of pulmonary function has been reported following ablation; however, transient inflammation and infiltrations occurring immediately after ablation certainly may become functionally significant for patients with very severely limited pulmonary function. Because the patient population is high-risk, and because populations are often heterogeneous in terms of tumors and tumor stages, it is difficult to compare the reported survival figures. While the one-year survival figures reported, 67% to 90%, are favorable, five-year survival figures, 20% to 60%, cover a very wide range, due to heterogeneous patient groups and comorbidity (Table). According to the convention for classification of complications of Germany's Federal Institute for Drugs and Medical Devices (BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte), the rate of complications (pneumothorax requiring drainage: approximately 10%) is "very common." In addition, when thermal ablation is indicated for high-risk patients it should be remembered that even "minor complications" (e.g. focal hemorrhage, postinterventional infiltration) can lead to severe deterioration in patients whose functional pulmonary reserves are already very low.

Both clinical practice and the literature show an increasing tendency to perform RFA under local anesthesia or under sedation. Although this makes it easier to perform the procedure on an outpatient basis, delayed onset of complications (particularly pneumothorax) must be considered on the basis of a patient's risk profile. Deprogrammed implanted defibrillators or pacemakers have been described in RFA, but not in microwave ablation, cryoablation, or laser-induced thermal therapy. Devices should therefore be tested after ablation in these cases. No information on quality of life after ablation of malignant lung tumors has yet been published.

KEY MESSAGES

- Image-guided thermal ablation of lung tumors is a new treatment option for patients in whom surgical resection is impossible.
- It should always be indicated on the basis of interdisciplinary consensus (a tumor board) and after weighing all treatment options.
- Radiofrequency ablation is currently the most widely used technique. Microwave ablation, cryoablation, and laser ablation are new procedures.
- No prospective randomized trials comparing different local procedures (limited resection, stereotactic radiotherapy, thermal ablation) have yet been published.
- Because the level of evidence is still low, thermal ablation should only be used as part of clinical studies as yet.

Conclusion

Percutaneous thermal ablation broadens the range of treatment options for patients who are not candidates for surgery. However, the local control that can currently be achieved must be measured against that achieved by stereotactic radiotherapy. Tumor ablation should always be indicated on the basis of interdisciplinary consensus through a tumor board (including pulmonologists, oncologists, thoracic surgeons, radiotherapists, and radiologists in line with the certification guidelines of the German Cancer Society [Deutsche Krebsgesellschaft] for lung cancer facilities) and after all treatment options have been weighed.

Conflict of interest statement

Prof. Heussel holds shares in Stada and GSK and patents for Methods and Device for representing the microstructure of the lungs; IPC Class: AA61B5055FI, PAN: 20080208038. He has received consultancy fees from Schering-Plough, Pfizer, Basilea, Boehringer Ingelheim, Novartis, Roche, Astellas, Gilead, MSD, and Lilly. He has received lecture fees from Gilead, Essex, Schering-Plough, AstraZeneca, Lilly, Roche, MSD, Pfizer, Bracco, MEDA Pharma, Intermune, Chiesi, Siemens, Covidien, Pierre Fabre, Boehringer Ingelheim, Grifols, and Novartis. He has received funding for studies (third-party funding) from Siemens, Novartis, Pfizer, Intermune, and MeVis.

Dr. Schneider, Prof. Dienemann, and Prof. Herth declare that no conflict of interest exists.

Manuscript received on 30 July 2012, revised version accepted on 18 February 2013.

Translated from the original German by Caroline Devitt, M.A.

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