

Diploma Thesis

**Thermal and Non-thermal Tumour Ablation Techniques in  
Interventional Radiology**

Submitted by  
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Graz, June the 13<sup>th</sup>, 2016

## Affidavit

Herewith I, Carmen Palfinger, declare that I have written the present diploma thesis fully on my own and without any assistance from third parties. I confirm that no sources have been used in the preparation of the thesis other than those indicated in the thesis itself.

Graz, June the 13<sup>th</sup>, 2016

Carmen Palfinger eh.

## Abstract

In the last decades percutaneous, image-guided tumor ablation techniques using both thermal and non-thermal energy sources have become well established for the treatment of focal malignancies. The purpose of this thesis is to describe and to compare different thermal and non-thermal ablation techniques, which are currently used for percutaneous image-guided tumor ablations in interventional radiology and oncology procedures, such as radiofrequency ablation, cryoablation, microwave ablation, high intensity focused ultrasound and irreversible electroporation.

Image-guided percutaneous treatment is gaining importance as minimally invasive therapeutic option in patients not suitable for surgical treatment, as salvage therapy and even as primary therapy for small tumors. Beside established ablation techniques, novel methods are emerging as new players in this field. Therefore, it is of particular importance to define the capabilities, advantages and disadvantages of each method in respect to various kinds of disease and patient outcome.

This thesis will deliver a side-by-side review of these techniques based on current literature including both basic translational science as well as clinical studies. Each technique will be covered from technical background, to current clinical applications and outcomes as well as future outlooks.

Apart from one part of this work, which will cover female breast tumor ablation and thus is specifically important for female patients, tumor ablation techniques are equally beneficial for both, male and female patients.

## Zusammenfassung

Sowohl thermische als auch nicht thermische, perkutane, bildgebungsgestützte Tumorablationsverfahren wurden in den letzten Jahrzehnten ein etablierter Bestandteil der Therapie von fokalen, bösartigen Neubildungen. Das Ziel dieser Arbeit ist es, die aktuell in der interventionellen Radiologie/Onkologie verwendeten thermischen und nicht thermischen Ablationsverfahren zu beschreiben und zu vergleichen. Diese sind Radiofrequenzablation, Kryoablation, Mikrowellenablation, hochintensiver, fokussierter Ultraschall und irreversible Elektroporation.

Die bildgebungsgestützte, perkutane Tumorablation hat vor allem als minimal invasive Therapieoption für eingeschränkt oder gar nicht operationstaugliche Patienten an Bedeutung gewonnen. Sie ist sowohl als Rezidivtherapie, als auch bei Versagen konventioneller Therapien und für Tumoren mit limitierter Ausdehnung auch als Primärtherapie einsetzbar. Neben bereits etablierten Techniken wie Radiofrequenzablation und Cryoablation, streben auch neuere Methoden, wie die irreversible Elektroporation, in diesem Bereich auf. Speziell aus diesem Grund und vor Allem hinsichtlich verschiedener Tumorentitäten und Patientenoutcome, ist es besonders wichtig die Einsatzmöglichkeiten und die Vor- und Nachteile der einzelnen Methoden zu kennen.

Diese Arbeit soll eine direkte Gegenüberstellung dieser Techniken, basierend auf aktueller Übersichtsliteratur, sowohl auf Grundlagenforschung als auch auf klinischen Studien, bieten. Jede Methode beinhaltet eine technische Übersicht, die aktuellen klinischen Anwendungsgebiete, Patientenoutcome und Zukunftsperspektiven.

Abgesehen von einem Teil der Arbeit, welcher sich mit Brusttumoren bei Frauen auseinandersetzt und aus diesem Grund speziell für Frauen einen wichtigen Teil darstellt, sollen beide Geschlechter, sowohl Mann als auch Frau, von den Erkenntnissen der interventionellen Radiologie/Onkologie profitieren.

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## Introduction

The purpose of this thesis is to give a side-by-side comparison of various thermal and non-thermal percutaneous image-guided ablation techniques used in interventional radiology. It is intended to present the currently available methods for specific indications and organ systems.

Various literature is available to cover specific methods, such as radiofrequency ablation, cryoablation, microwave ablation, high intensity focused ultrasound and irreversible electroporation. A broad comparison may be beneficial both for scientists and clinical practitioners in this field.

Image-guided percutaneous treatment is gaining importance as minimally invasive therapeutic option in patients not suitable for surgical treatment, as salvage therapy and even as primary therapy for small tumors. Besides established ablation techniques, novel methods are emerging as new players in this field. Therefore, it is of particular importance to define the capabilities, advantages and disadvantages of each method in respect to various kinds of cancer disease and patients' outcome.

Imaging in interventional oncology plays a key role, as it is required for every step of the treatment procedure. The main steps are (1) pre-procedure planning, (2) intraprocedural targeting and (3) monitoring, (4) intraprocedural control and modification and (5) postprocedure assessment of treatment response.

In addition to well established techniques including ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) with and without contrast agents, nuclear medicine techniques such as positron emission tomography combined with CT (PET/CT) and single photon emission computed tomography combined with CT (SPECT/CT) have been introduced to guide and monitor therapies.

In diagnostic imaging higher image quality is needed for diagnosis and in the pre and follow-up imaging of the interventional procedure. For intraprocedural image guidance lower image resolution is acceptable to allow repeated and real-time imaging and a lower radiation dose. For interventional procedures imaging should

be restricted to the region of interest while diagnostic imaging requires larger fields of view.

Therefore, the ideal imaging parameters during intervention provide sufficient image quality to visualise the tumour in size, shape and location within the organ and the position relative to blood vessels and other critical structures that might be at risk of being injured during the ablative intervention. Additional real time feedback of the therapy, such as thermometry, can help the interventionalist and health care personnel, such as nurses and anaesthetist, who should have access to the patient (Ahmed, Solbiati et al. 2014, Solomon, Silverman 2010).

## Methods

This thesis is expected to deliver an overview of various techniques in the field of interventional radiology with a special focus on image-guided percutaneous techniques and the current state of scientific knowledge, based on current literature including basic translational science as well as clinical studies. Each technique is covered from technical background, to current clinical applications and outcomes as well as future outlooks.

Apart from one part of this work, which will cover female breast tumor ablation and thus is specifically important for female patients, tumor ablation techniques are equally beneficial for both female and male patients.

For this purpose a comparative and systematic literature review constitutes the base of this work.

## Data Sources

- PubMed
- Google Scholar

## Literature research

The literature research was done between July 2014 and February 2015, including articles from 1993 to 2016. Source for the technology-based informations was a text book (Hong, Georgiades 2011). Additionally, 84 articles including reviews and clinical trials were researched.

## Key words

Technology-related: interventional ablation techniques, radiofrequency ablation, microwave ablation, irreversible electroporation, cryoablation, high intensity focused ultrasound

Organ-related: liver cancer, liver ablation, renal cell carcinoma, kidney ablation, breast cancer, breast ablation, prostate cancer, prostate ablation, lung and bronchial cancer, NSCLC, lung ablation, interventional oncology.

## Results

### Patient preparation and pre-procedure imaging

#### Procedural work up

In course of the pre-procedural workup every patient has to be seen in a standard outpatient consultation in order to review all relevant imaging studies and to perform a focused physical examination including laboratory testing and a detailed medical history. A coagulation profile including INR, prothrombin time and partial thromboplastin time are routinely evaluated. Patients with pacemakers or internal cardiac defibrillators are instructed to consult with the treating electrophysiologist pre- and postablation (Fiek, Dorwarth et al. 2004, Donohoo, Anderson et al. 2007, Tong, Ru et al. 2004).

#### Pre-procedure imaging

For pre-procedural diagnostic imaging high quality diagnostic imaging is desirable. Anatomic studies (CT, MRI) and functional studies (PET, SPECT) are both utilized as well as the comparison with previous examinations (if available) to assess disease activity and progression in order to determine the medical indication of the planned intervention. The basic questions to be answered before the procedure are:

- is the procedure medically indicated
- is the procedure technically feasible
- what is the best approach to the target
- are there any anatomic variants
- what are the potential hazardous effects on nearby structures

As patient position and position of organs (e.g. bowel) may shift and differ from pre-procedural imaging, additional intra-procedural imaging is required to complete the plan (Ahmed, Solbiati et al. 2014, Solomon, Silverman 2010).

#### Anaesthetic management

Usually interventional oncologic procedures are performed under conscious sedation and local anesthesia with 1% lidocaine injected intradermally and into

deeper tissues. For certain techniques and settings general anesthesia may be required or preferable. Intra-procedural monitoring consists of continuous pulse oximetry, ECG and blood pressure measurement every 5 minutes.

Before starting the session patient data and identification as well as the probe configuration and technical parameters (for instance number of probes, voltage, pulses length, number of pulses) are required (Hong, Georgiades 2011).

## Intra-procedural image guidance

### Targeting

Targeting is only one step of intra-procedural image guidance and means the correct placement of the applicator into the tumour. The ideal imaging device would offer real-time 3D depiction of the target with a clear delineation of the tumour and the surrounding anatomy, for a proper placement of the probes to cover the entire tumour in three dimensions, the interventional tools and even physiologic information (via contrast enhancement) and metabolic activity might be interesting for some applications. Currently imaging features provide some of these needs but none of them provides all the above-mentioned features (Ahmed, Solbiati et al. 2014, Solomon, Silverman 2010).

### Monitoring

For a safe and effective completion of tumour ablation, intra-procedural monitoring plays a key role to visualise changes during the oncologic treatment and keeps critical adjacent structures under surveillance so that they are not affected more than necessary. The most important parameters to be mentioned are blood flow, vascularity, echogenicity and tissue temperature. With Doppler US or contrast enhancement it is possible to determine if a tumour still has a viable blood supply after ablation and the vascularity of the treatment zone can be assessed. The ice ball formation during cryoablation may be noted as an echogenic mass like structure with distal acoustic shadowing. As a source of irritation increased echogenicity can be seen during RF ablation, which may obscure imaging and does not correlate well with tumour necrosis. Measuring tissue temperature is an important factor since different tissue types have different thresholds for inducing cell death. Primarily

developed for HIFU, MR thermometry by now has also been applied for RF ablation and microwave ablation. Temperature sensitive MR parameters are proton density, proton resonance frequency, T1 and T2 relaxation times, diffusion and magnetisation transfer. The most commonly used parameter is the proton resonance frequency change since temperature changes within to 1°C can be measured. Limitations are motion, magnetic field inhomogeneity, created by ablation tools, or fatty environment. Also CT attenuation and sound velocity have been shown to correlate with tissue temperature but are less developed and not yet used in clinical practice (Ahmed, Solbiati et al. 2014, Solomon, Silverman 2010).

### Control and Modification

For controlling a treatment and for intra-procedural treatment modification, such as repositioning of applicators, the imaging system must be capable of being monitored by the interventionist.

## Postablative imaging, follow up and patient recovery

### Post procedural therapy assessment

Imaging after interventional oncologic procedures should consist of a baseline imaging study directly after the intervention, to determine complications or adverse results, followed by several follow-up series. For a direct comparison the same imaging parameters should be used for the pre-treatment planning, the baseline imaging study and for all check-ups. The immediate assessment describes the technical effectiveness of the treatment and confirms if the target endpoint has been reached. When performing ablation with curative intent the baseline imaging should demonstrate that the ablation zone includes the target tumour and a circumferential tumour cell free ablative margin of 0,5 to 1 cm (Solomon, Silverman 2010, Ahmed, Solbiati et al. 2014).

Commonly, there are two important features, which are carefully analysed to identify remaining viable tumour tissue. The comparison of (a) tissue enhancement and (b) nodular growth on serial pre procedure and post procedure images. Because of considerable changes in the surrounding area of the tumour directly after oncologic interventions it is often difficult to make comparisons. For the detection of residual

or recurrent tumour it could be particularly useful to use subtraction imaging techniques in which unenhanced images are electronically subtracted from contrast enhanced images (Solomon, Silverman 2010).

Certain imaging characteristics are classically associated with an effective ablation therapy: The ablation zone contains non-enhancing tissue. Due to the ablation of a safety margin the ablation zone is usually larger than the original tumour. Frequently a peripheral thin rim of enhancement is found around the ablation zone, which might be inflammation or reactive hyperperfusion. In some imaging studies such as PET, contrast-enhanced CT or MR imaging this inflammatory rim makes the interpretation of the ablation result more difficult, as it is sometimes challenging to differentiate this phenomenon from residual tumour. However, a focus of residual tumour usually appears thicker and manifests as nodular enhancement. Postablative inflammation usually resolves and the ablation area normally decreases in size. Continued research for improving tools to identify tumour residuals or recurrence is still needed as some cases have been reported in which nodular enhancement represented inflammation and non-enhancing regions turned out to be viable tumour cells (Solomon, Silverman 2010).

Methods for volumetric measurements in order to determine tumour volumes and to distinguish tumour from peri-tumoural ablation changes may be useful. Some newer imaging modalities such as diffusion-weighted MR imaging, MR spectroscopy, CT and MR perfusion imaging, contrast-enhanced US and PET imaging may provide improved capabilities for the assessment of the ablation zone.

In diffusion-weighted MR imaging diffusion of water molecules in tissue is assessed. Necrotic cells with disrupted cell membranes show increased water molecule movement whereas viable tumour cells show restricted diffusion due to the stable lipid bilayers of the cell membranes. This modality is limited in respiratory or hollow organs due to air as well as in areas of increased magnetic susceptibility.

As choline is an essential component of the biosynthesis of the cell membrane the assessment of choline levels with hydrogen MR spectroscopy is another opportunity to assess the viability of post ablative tissue. Therefore elevated choline levels are indicative of viable tumour tissue as they are associated with increased cell proliferation, whereas necrotic areas are believed to contain low amounts of choline.

CT and MR perfusion imaging using dynamic contrast enhancement additionally to structural information, may provide additional information about tumour physiology, such as perfusion parameters, and thus depict tumour neovascularisation as well as viable tumor tissue. Arterial spin labelling MR imaging also measures perfusion of a particular area but with endogenous tracers especially in patients with contrast agent intolerance or for multiple measurements. For patients not eligible for CT or MR imaging US contrast agents like microbubbles with target specific ligands have been used.

Another functional imaging modality, which provides physiologic information to identify residual or recurrent disease is FDG PET imaging. Similar to techniques mentioned above PET imaging has its limitations since post therapy inflammation and residual cancer both lead to increased FDG uptake. Therefore, novel tracers, such as choline or other metabolites as well as target specific antibodies, which can be labelled, might be more specific to distinguish between inflammatory process or post therapy residual tumour and to assess treatment response (Solomon, Silverman 2010).

#### Postablative patient recovery

After completion of the treatment the patient remains in a recovery room for 1-3 hours until the effects of sedation resolve. Vital signs keep monitored until the patient is awake. Before being discharged the patient has to be prescribed and instructed on painkillers like nonsteroidal anti-inflammatory drugs for several days in case of discomfort and he has to be informed to immediately come back or call in case of swelling, redness, increasing pain, bleeding at the ablation site or fever more than 38,6°C.

While in the United States such procedures are typically handled as outpatient procedures, and patients are discharged on the day of the procedure given the absence of complications, in Europe and Austria patients are usually admitted one day before the procedure, monitored in an inpatient setting and discharged one day after the procedure.

Follow up outpatient visits are routinely scheduled within one week and 3, 6 and 12 month after ablation, or as clinically indicated (Hong, Georgiades 2011).

### Technical success

The term 'technical success' describes whether the tumor was treated according to the protocol and covered completely by the ablation zone. To evaluate tumor coverage ideally either contrast-enhanced CT or contrast-enhanced US images are acquired during or immediately after the procedure. A completely covered tumor encompasses the target tumor plus an ablative margin. Hence a tumor that is treated according to protocol and covered completely, as determined at the time of procedure, is technically successful. This helps clinicians to identify those patients to whom the protocol could not be executed completely, either for reasons related to comorbidity or for technical reasons, among those who were treated according to protocol. The primary technical success should be determined at the first follow-up imaging study after completion of the predetermined course of treatment, which may also include several ablation procedures spaced out over time (Ahmed, Solbiati et al. 2014).

## Radiofrequency Ablation (RFA)

### History and principles

The application of radiofrequency energy and its thermal effects on tissue was first described in 1891 by d'Arsonval, whose area of research was electrophysiology and diathermia. He recognized the local increase of tissue temperature when RF waves passed through it (Hong, Georgiades 2011).

The invention of the Bovie knife was the first incorporation of RF energy in practical medicine. It was used for cauterization, by applying a pulsed current, and for cutting tissue, by using a more continuous current (Hong, Georgiades 2011).

In 1992 RF ablation was first used in the field of interventional oncology for liver tumour ablation. From these days to 2011 around 100.000 RF ablation procedures in the liver were performed worldwide (Brown, Gould et al. 2007). Even though several other minimal invasive ablation techniques were introduced, RFA still remains the prototypical ablation technique and the cornerstone of any ablation practice with the greatest amount of empirical data available (Livraghi, Goldberg et al. 2000, Goldberg, Gazelle et al. 2000) .

Thermal RF ablation is reached by transforming electrical current in the RF range into heat. This is limited to a range of the electromagnetic spectrum between 3Hz und 300GHz. Radiofrequency waves used in interventional radiology cause thermal ablation of a defined volume of tissue (Venkatesan, Wood et al. 2011, Hong, Georgiades 2011, Goldberg, Gazelle et al. 2000) .

RF ablation is accomplished by creating a closed electrical circuit consisting of a RFA probe, acting as cathode and dispersing pads usually positioned on the patients thighs (figure 1). Due to the small cross sectional area of the probe tip there is a very high energy flux around it but due to the large cross-sectional area of the grounding pads energy is dispersed which minimizes the energy flux so that tissue damage is limited to the surrounding area of the probe tip (Venkatesan, Wood et al. 2011, Hong, Georgiades 2011, Goldberg, Gazelle et al. 2000) .

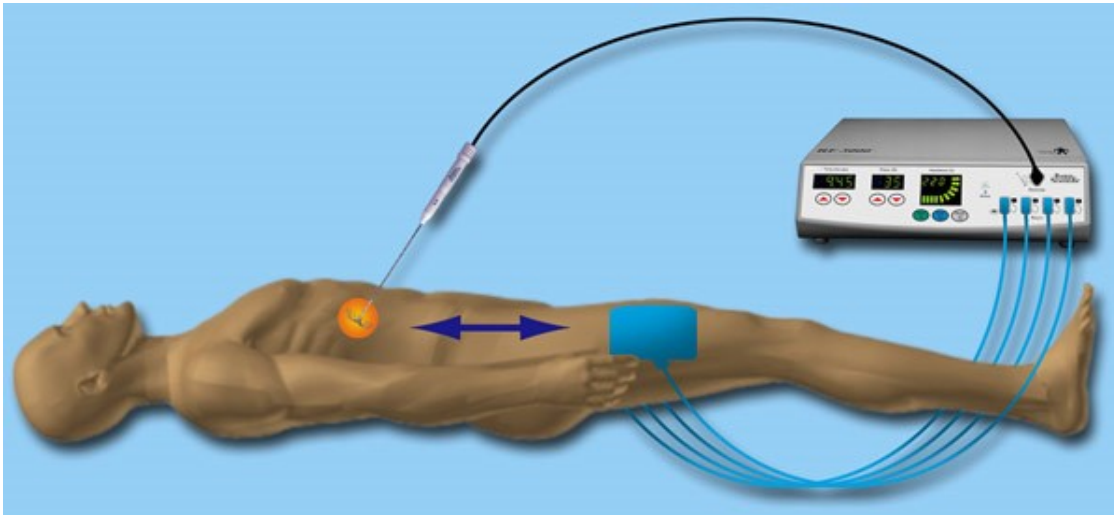


Figure 1 RFA generator and positioning of probes and dispersing pads (image courtesy of Dr. Portugaller Rupert, University Hospital Graz, Austria)

Energy is applied through a needle electrode, which is usually positioned in the centre of the targeted tissue. As a rapidly alternating current is applied, dipole molecules, mostly water, immediately adjacent to the RF electrode are forced to vibrate and molecules farther away from the tip are set into agitation by adjacent vibrating molecules. Due to the resulting frictional heat, coagulation necrosis of the tissue around the probe tip is induced. The sources of heat in case of RF ablation are the molecules in the surrounding area of the probe, which are set into motion and intense agitation by an alternating electromagnetic field (Hong, Georgiades 2011).

One of the most important factors for effective tissue ablation is the thermal and electrical tissue conductivity. Desiccated tissue, which acts as an isolation around the probe tip as a result of excessive generator power in a short time period, limits further transmission of electrical and thermal energy and subsequently limits any further extension of tissue destruction. The crucial factors for achieving a large ablation zone are the ablation time and maximum temperature reached (Nahum Goldberg, Dupuy 2001).

In table 1 temperature-time relations to achieve cell death are listed.

Table 1 RFA parameters, temperature-time relations

Time to cell death depending on temperature	
15mins	45°C
20sec	50°C
2sec	55°C
<1sec	100°C

The aim of RF ablation is to heat tissue without causing excessive desiccation, charring or vaporisation, which would decrease energy transmission and subsequently limit ablation size. Thus, a slow, methodical energy deposition, which is possible by heating tissue to 50°C to 100°C for 4 to 6 minutes is more effective than a rapid temperature rise (Hong, Georgiades 2011).

The tumour cell free margin of the ablated tissue should be around 0,5 to 1 cm analogous to the surgical margin.

A considerable limitation of the effectiveness of all thermal ablation methods is a phenomenon called 'heat-sink'. The most significant structures with regard to heat-sink effects are blood vessels larger than 3 mm. The size of coagulation necrosis depends on the energy deposited, which is the result of local tissue interaction minus the heat loss from cooling effects caused by nearby blood vessels. This phenomenon potentially leaves behind residual unablated tumour near the vessel wall, which increases the chance of local tumour progression. Further important factors that influence post RFA tumour progression are tumour size, tumour site, orientation, organ, tumour histology and tumour biology. Technical influence factors are electrodes, generator power, heat sink and time (Dupuy, Goldberg 2001).

#### RF generators and probes

Today's RF generators (figure 2) are manufactured by three major companies in the US. All of them are capable of outputs of 150 to 200W, delivering alternating current at frequencies around 460 to 500kHz via 14 to 17 gauge electrodes, in contrast to earlier generators with outputs of only 50W (Hong, Georgiades 2011).



Figure 2 RFA generator (image courtesy of Dr. Portugaller Rupert, University Hospital of Graz, Austria)

In order to increase the ablation zone and reduce heat-sink effects, charring and impedance, a clear need concerning the elongation of the active areas of any existing system was identified. This was achieved by several strategies:

Multitined expandable arrays: in contrast to the single monopolar needle (figure 4) this electrode has multiple curved uninsulated prongs in the shape of an umbrella when deployed from the needle tip central cannula (figure 3). Every of these prongs creates its own area of ablation which increases in size by applying increasing amounts of RF energy. Finally single lesions merge with the lesions of the neighbouring prong resulting in one larger area of necrosis (Hong, Georgiades 2011).



Figure 3 Multitined expandable array (image courtesy of Dr. Portugaller Rupert, University Hospital of Graz, Austria)

Internally cooled electrodes: to reduce charring and impedance chilled saline is pumped through the chamber shaft inside the electrodes active tip of a single needle to increase the ablated tumour volume (Nahum Goldberg, Dupuy 2001).

Perfusion electrodes: due to the fact that high sodium chloride ion concentration can expand the volume of ablation by modifying tissue conductivity a system were developed whereby saline or hypertonic saline is injected into the target lesion (Hong, Georgiades 2011).

Bipolar RF ablation electrodes: in this recently developed bipolar system two or more electrodes are placed into the tumour. The administered RF current runs from

one electrode to another (figure 5). This allows a greater ablation volume in a shorter time-period and negates the risk of skin pad burns because no grounding pads are required. This system is also helpful with regard to tumours whose integrity may not be penetrated (mobile or hard lesions) because the two probes are placed on each side of the tumour (Hong, Georgiades 2011).



*Figure 4 Monopolar RFA probe (image courtesy of Dr. Portugaller Rupert, University Hospital Graz, Austria)*

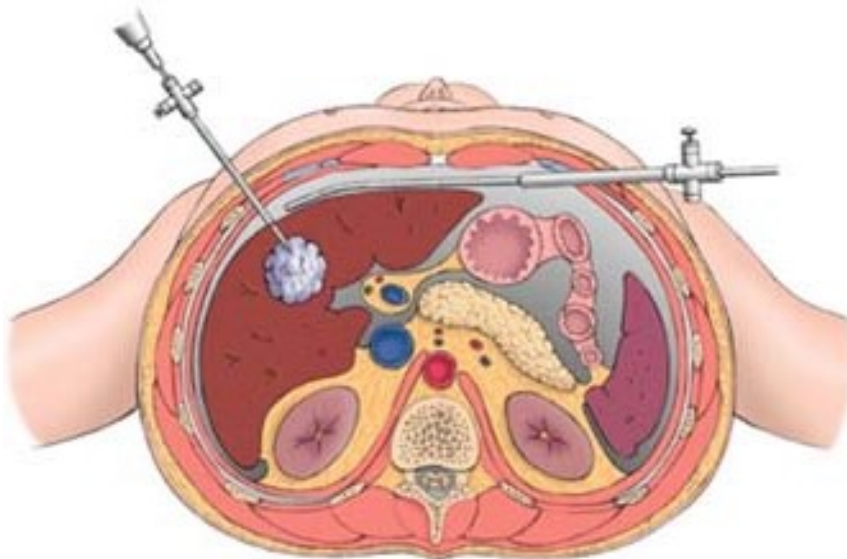
### Clinical practice

RFA is the most well-studied and clinically relevant percutaneous ablation source. In clinical practice it has been widely used in many solid organ malignancies and therefore it is now part of standard therapy in several tumors including primary and secondary neoplasms of the liver, kidney, lung and bone. Moreover, RFA is the predominantly used technique for combination with adjuvant tumor therapies, such as chemotherapy and radiation therapy. The goal of this combined approach is to achieve complete and uniform eradication of all malignant cells and to reduce the duration or course of therapy especially for larger tumors (Ahmed, Brace et al. 2011).

## Cryoablation

### History and principles

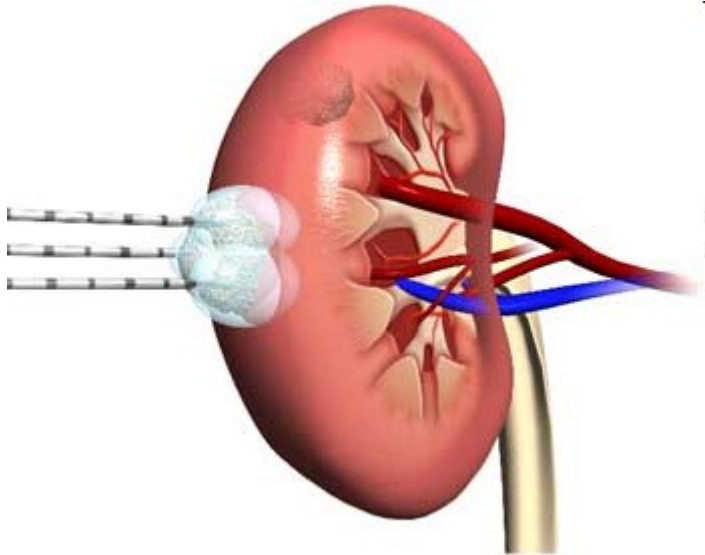
Cryoablation is a technique which uses the effects of temperature reduction below the lethal level of at least  $-20^{\circ}$  to  $-25^{\circ}\text{C}$  to ablate tissue. Although it was initially introduced as early as in the 19<sup>th</sup> century, it is used in clinical practice since the mid-1960s (Theodorescu 2004). For many years its use was restricted to open surgical access because of various technical limitations such as large-bore probes to place the large required gas flow and to facilitate adequate heat exchange. Since technology allowed thinner cryoprobes, down to 13-gauge, in the last years, cryoablation was also used in the field of percutaneous interventional oncology (figure 6).



*Figure 5 Percutaneous cryoablation (image courtesy of Dr. Portugaller Rupert, University Hospital Graz, Austria)*

The technical aim of cryoablation is to reduce temperature by removing energy to cause cell damage of the targeted tissue including a surrounding margin, equivalent to the surgical margin, but without affecting nearby vital organs. These effects are obtained by a variable number of freezing and rapid thawing cycles. To achieve cytotoxic effects, such as ischemia, denaturation of protein structures and the breakdown of cellular and intracellular membranes, a temperature below  $-20^{\circ}$  to  $-25^{\circ}\text{C}$  is needed. Cell death is caused by the formation of ice crystals (figure 7). In case of a non-target ablation, cryoablation is more forgiving compared to other

ablation techniques. This might be due to the fact that the scaffolding structure of intracellular membranes is relatively preserved, which also allows cellular repopulation of the tissue .



*Figure 6 Ice ball formation in kidney tissue (image courtesy of Dr. Portugaller Rupert, University Hospital Graz, Austria)*

Cooling down tissue to a lethal level requires the continuous removal of thermal energy of the entire volume. Due to the fact that total energy must be conserved the transfer of thermal energy in case of cryoablation results from convection or conduction of heat.

Conduction, as it depends on temperature difference between tissue ( $37^{\circ}\text{C}$ ) and cryoprobe ( $-140^{\circ}\text{C}$ ) is a steady state transfer while convection depends on the flow rate of blood through the target tissue and the adjacent structures. Hence, very vascular tissues and large-diameter arteries will limit the dimension of cryoablation but to a minor degree than the reverse phenomenon, termed heat-sink, observed in heat based ablation techniques such as RFA.

To cause cooling or heating of tissue through gas expansion two mechanisms take effect following the Joule-Thomson law. As energy always must be conserved lower molecular kinetic energy results in lower tissue temperature and greater molecular kinetic energy results in higher temperature. Which one of these two mechanisms dominates depends on the inversion temperature of the gas. In cryoablation argon, nitrogen or oxygen is used because the inversion temperature factor is greater than room temperature. Thus, the expansion of compressed argon, nitrogen or oxygen

causes cooling whereas helium or hydrogen causes warming as their inversion temperature is less than ambient temperature.

Gas is administered by a dual chambered cryoprobe. When high-pressure argon gas flows through the lumen of the cryoprobe temperature drops and once it expands in the target tissue it cools, absorbs thermal energy from the adjacent tissue and is siphoned back through the tubing. The so-formed ice ball is thawed by circulating helium gas through the probe lumen, which leads to the formation of large ice crystals by recrystallization or mutual confluence of diminutive ice crystals. At this point extracellular water re-enters the cell and makes it swelling, which induces more damage to the cell. The dimension of the ablation depends on the flow rate of the cooling gas and on the length of the uninsulated length of the probe (Niu, Li et al. 2014, Rewcastle, Sandison et al. 2001) .



Figure 7 Cryoablation generator, [www.galilmedical.com](http://www.galilmedical.com)

### Cryoablation generators and probes

Whereas early cryoablation systems were bulky and limited to open surgical access, modern systems (figure 8) use more advanced cooling techniques that allow laparoscopic and percutaneous approaches in combination with imaging guidance. Recent progress in design and construction have enabled the use of

smaller cryoprobes (figure 9), with a diameter less than 13-gauge, which are more suitable for percutaneous procedures (Ahmed, Brace et al. 2011).

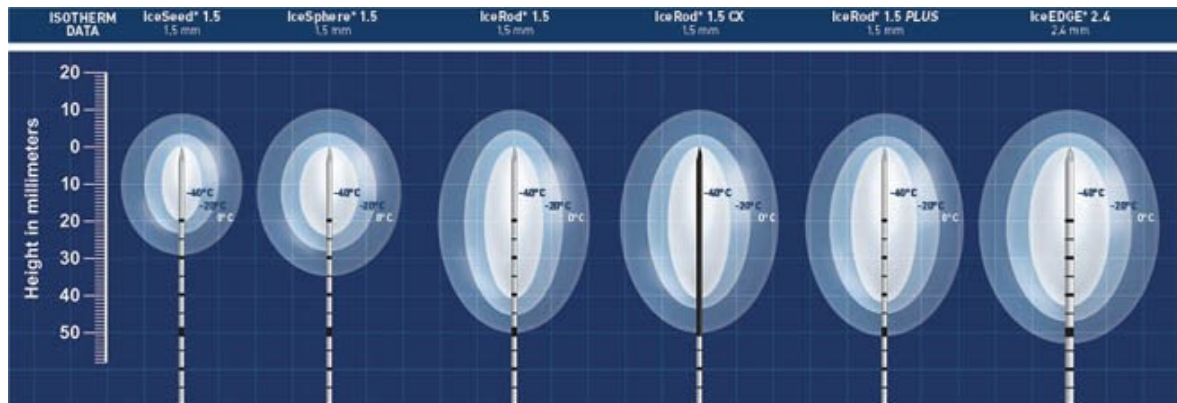


Figure 8 Different types of cryoprobes, [www.galilmedical.com](http://www.galilmedical.com)

To date there are three major cryoablation systems available, Endocare (Irvine, CA), Galil (Yokneam, Israel) and Medtronic (Minnesota, US), which all make use of the above-described technical details (Hong, Georgiades 2011).

### Clinical practice

The tumor entities with the most published efficacy and safety data, as they are the most commonly treated tumours with cryoablation, are the renal cell carcinoma as well as prostate cancer. The technique is more extensively used during open or laparoscopic surgery. Small renal cancers and painful bone lesions are mainly treated with image guided percutaneous cryoablation and to a lesser extent also primary and secondary chest and liver neoplasms. Although cryoablation could theoretically be used in any organ, its specific risks and benefits have to be weighed against those of other ablation techniques. Regarding liver tumors cryoablation might come up with similar efficacy and safety as RFA does, however there is considerably more published data on the latter. In case of liver tumours the effectiveness of cryoablation might be affected by nearby blood vessels larger than 3 mm in diameter. To counteract this phenomenon additional probes or even balloon occlusion of the hepatic vein may be required. In lung, cryoablation of peripheral pleura-based lesions may be safer than central lesions with a higher risk of pulmonary hemorrhage compared to RFA. This can be clinically significant in patients with severe COPD. In contrast to RFA, cryoablation is essentially painless for pleura-based lesions. For metastatic disease the use of cryoablation should only be considered for 3 indications: (1) metastasis whose further growth is supposed to

result in substantial impairment, (2) when tumor cell reduction is expected to improve survival and (3) for the palliation of painful metastasis (Hong, Georgiades 2011).

## Microwave Ablation (MWA)

### History and principles

Microwave ablation, a rather novel treatment technique, which belongs to the field of heat-based thermal ablation modalities, incorporates the application of electromagnetic radiation at frequencies from 900 to 2450 MHz on the electromagnetic spectrum between radio waves and infrared radiation. It is performed under image guidance during open or laparoscopic surgery or percutaneous, as an outpatient treatment for non-surgical candidates (Jain, Dupuy et al. 2003, Simon, Dupuy et al. 2005, Xia, Sun et al. 2001) .

The electromagnetic wave oscillates between negative and positive charge. Water molecules within biological tissue carry electric charge as well, so that these molecules are caused to flip by exposing them to an oscillating electric charge from radiation (figure 10). To optimize this interaction, MW radiation is specially tuned to the natural frequency of water molecules. Depending on the frequency of MW energy as a result water molecules spin and change orientation around 2-5 billion times a second. Thus, electromagnetic microwaves produce friction and heat by agitating water molecules in the surrounding area of the targeted tissue, which induces cell death via coagulation necrosis. Thus, tissues with high water content, such as liver and kidney, are heated more rapidly during MWA. Since MW energy deposition is not dependent on an electrical current but rather on a propagating electrical field it is especially useful in tissues with poor electrical conductance (Simon, Dupuy et al. 2005, Knavel, Brace 2013).

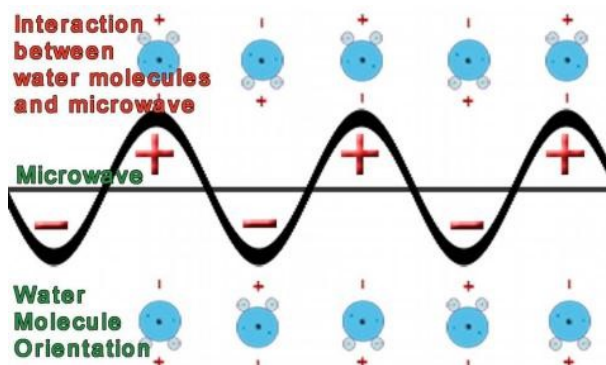


Figure 9 Principle of MWA (image courtesy of Dr. Portugaller Rupert, University Hospital Graz, Austria)

Between 40°C and 45°C cells become increasingly vulnerable to damaging agents but still remain resistant to cell death. The cytotoxic temperature which induces protein and enzymatic denaturation and destruction of the tertiary structure of DNA is between 50°C and 100°C. Between these temperatures an exposure of only 4-5 minutes leads to cellular death by means of coagulation necrosis. In contrast to RFA, microwave ablation creates larger ablation zones in a shorter time period, due to the fact that MWA is not restricted by the raise of impedance caused by charring and vaporization, which considerably limits the size of the ablation area with RFA (Nahum Goldberg, Dupuy 2001, Goldberg, Gazelle et al. 1996, Goldberg, Gazelle et al. 2000) .

### MWA generators and probes

The microwave delivery system consists of a MW generator (figure 11), a flexible coaxial cable and an internally water-cooled-shaft antenna (figure 12). Grounding pads or other ancillary devices are not required (Yu, Burke 2014).



Figure 10 MWA generator (image courtesy of Dr. Rupert Portugaller, University Hospital Graz, Austria)

For selecting the appropriate antenna (active tip, overall length, gauge and multiplicity) two factors of influence regarding the outcome have to be considered: (1) complete eradication of all viable tumor cells and a 1 cm margin of normal tissue are required and (2) minimal destruction of the surrounding tissue. Some additional relevant factors for performing a sufficient ablation are tumor size, distance of the lesion from the percutaneous access site and adjacency of nearby vital structures such as vessels. By inserting the microwave antenna through the trajectory, on approximately half way a CT-fluoroscopy is made for adjusting the antenna in any of the three dimensions. The so-called “sweet spot”, which is the hottest spot of the shaft and is seen as a grey stripe, has to be centered within the target lesion. Due to the fact that the “sweet spot” is the point where energy is generated placing it into the center of the tumor ensures optimum ablation geometry. Lesions greater than 2 cm in diameter require the use of multiple antennae or sequential single antenna treatments. Every additional antenna has to be placed in the same way as described above. The effectiveness of the treatment has to be evaluated immediately after the ablation by viewing the CT-fluoroscopic slides and tracking postablative imaging changes within the ablation zone (Hong, Georgiades 2011, Simon, Dupuy et al. 2005).



*Figure 11 MWA antenna (image courtesy of Dr. Rupert Portugaller, University Hospital Graz, Austria)*

### Clinical practice

Microwave ablation is the modality of choice for lesions larger than 4 cm in size, for lesions in close proximity to vessels larger than 3 mm in diameter due to the minimal heat-sink effects and for lesions that recurred after prior thermal ablation (Hong, Georgiades 2011).

Compared with other thermal ablation techniques, such as RF ablation or cryoablation, larger tissue volumes can be ablated due to the use of multiple antenna applicators simultaneously, the possibility of operating with higher intratumoural temperatures is given, patients are suffering from less postprocedural pain and treatment time and costs can be reduced.

## Irreversible Electroporation (IRE)

### History and principles

The observation of biological effects supposedly caused by electroporation dates back to the mid-1700s, when Jean-Antoine Nollet studied the discharge of a static electrical generator on the skin. However, its application for tissue ablation was developed in the 1980s. At the same time the term electroporation was coined (Rubinsky 2007).

In the last three decades priority was given to reversible electroporation (RE), a technique, which produces a temporary disruption of the cells' lipid bilayers to vary the membrane permeability by using relatively low electric energy. Under the electric field the membranes rearrange themselves to form temporary pores. Through these pores intracellular contents can freely communicate with the extracellular environment. Additionally, the electrical field supplies a local driving force, which propels larger or polar molecules and ions, which the membrane would usually be impermeable to, into the cell. This technique has been used to introduce a variety of vectors, ranging from DNA and enzymes to macromolecules and viruses, into the cell. These alterations in membrane permeability are transient so that RE does not induce cell death (Weaver 1995).

In interventional oncology, irreversible electroporation (IRE) is used as ablation technique. This is a predominantly non-thermal method, which has recently gained attention as a novel minimally invasive tumor ablation method. It uses a high voltage external electric field to permanently increase the permeability of the cell membrane by exposing it to repeated short-duration high-voltage electric pulses (figure 13). It was hypothesized that the created increased transmembrane potential causes the formation of innumerable nanoscale pores in the cells lipid bilayers of the targeted tissue (Narayanan, Froud et al. 2013, Hong, Georgiades 2011).

Depending on tissue and cell type the critical potential difference threshold value between extracellular and intracellular space is usually around 200 – 300 mV/cm (Gabriel, Teissie 1997, Teissie, Rols 1993). IRE surpasses this critical threshold value, which results in a voltage potential difference across the plasma membrane rendering the cell membrane unstable. The transmembrane potential difference is

caused by the fact that the current passes around the cell and not through it (Weaver 1993). As a consequence the ATP-dependent protein ionic pumps are no longer able to compensate the transmembrane ionic concentration difference and the cell's homeostatic mechanisms are irreversibly disrupted. Both, apoptosis and coagulation necrosis, are ultimately induced by the transformed intracellular environment (Keane, Bramis et al. 2014, Rols 2006, Pavselj, Preat et al. 2007) .

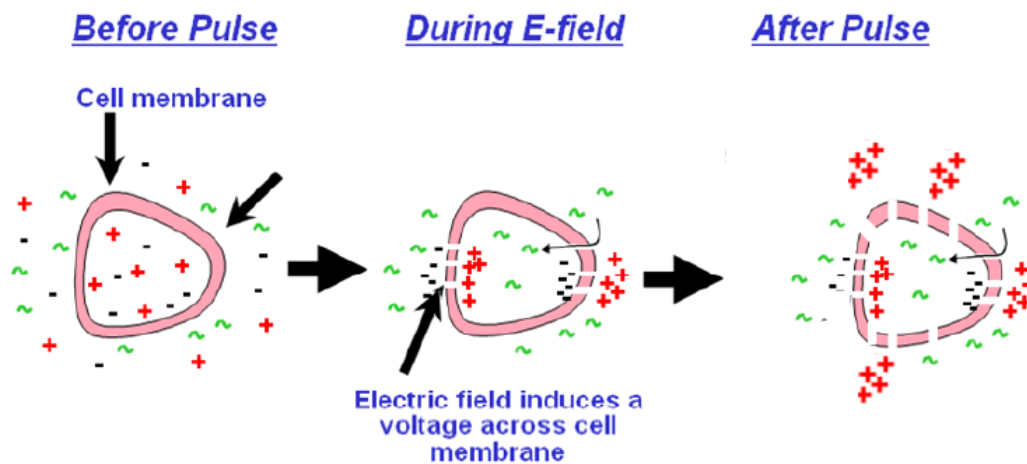


Figure 12 Concept of IRE (image courtesy of Dr. Wimmer Thomas, University Hospital Graz, Austria)

Referring to recent data increased apoptotic markers may be found in post IRE ablated tissue. As apoptosis is a controlled shutdown, damaged cells may be removed by the immune system and no significant inflammatory reaction or permanent fibrosis and scarring may occur, therefore preventing unnecessary damage of the ablated organ (Narayanan, Froud et al. 2013, Hong, Georgiades 2011, Lee, Loh et al. 2007) .

#### IRE equipment and generator setup

The below mentioned technical details are all based on the NanoKnife® Generators and Probes (AngioDynamics Inc., Queensbury, New York, figure 16). For the operation of IRE there are two main types of applicators: monopolar and bipolar probes. All technical details are shown in Table 2.

Using monopolar probes, at least two probes are positioned into or around the targeted tissue so that the electric current can travel between the tips to create an electric field, which causes ablation. For creating larger treatment zones a maximum number of 6 probes can be used simultaneously.

Using the bipolar system the placement of a lower gauge single probe with 2 electric poles in its distal portion is required (Hong, Georgiades 2011).

Table 2 technical details of monopolar and bipolar probes

	Monopolar Probe	Bipolar Probe
Diameter	19 gauge	16 gauge
Uninsulated tip length	2cm	2cm
Max. penetration depth	15cm	18cm
Maximum probe distance	1,5cm	Single probe
Max. voltage	2500V	2500V
Ablation zone diameter	2x3x3cm	2x2x3cm

A software simulation is used for suggesting the optimal ablation parameters such as voltage and probe distance depending on the required ablation zone size. Based on the studies of Georgiades et al. and the manufacturer's recommendation the optimal ablation zone regarding the monopolar probe system requires a minimum electric field strength of 1500V/cm, a maximal probe distance of 1.7cm and 90 pulses for a single session. Apart from the electrode geometry, depending on the number of pulses the size of ablation may also be varied to a certain extent (Hong, Georgiades 2011). The duration of the conventional 90-pulse protocol is approximately 11 minutes for tumors with a diameter of approximately 3 cm.

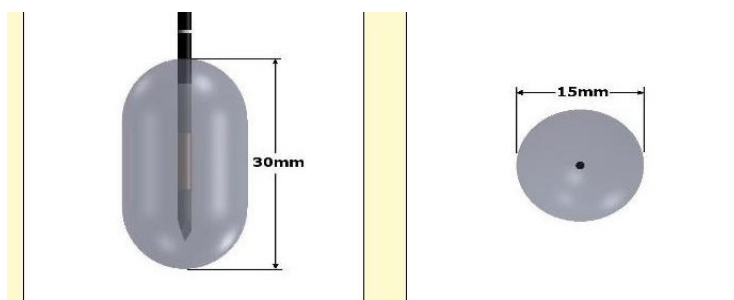


Figure 13 Demonstration of single probe positioning and the resulting ablation zone (image courtesy of Dr. Rupert Portugaller, University Hospital Graz, Austria)

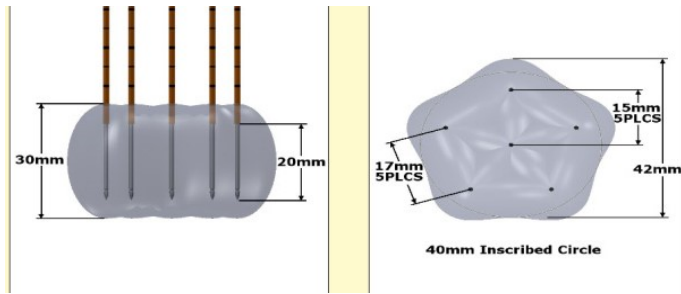


Figure 14 Overlapping of probes for tumors larger than 1cm in diameter (image courtesy of Dr. Rupert Portugaller, University Hospital Graz, Austria)

For the use of the bipolar probe is the optimal position is in the center of the tumor (figure 14). For any tumor larger than 1 cm in diameter more than a single ablation session or overlapping of probes (figure 15) will be necessary (Hong, Georgiades 2011).



Figure 15 IRE generator, probes and heart rate synchronisation device, [www.fudahospital.com](http://www.fudahospital.com)

### Clinical practice

When using IRE as an ablation modality general anesthesia and complete muscle paralysis are required. The percutaneous electrode placement and the whole

procedure are performed either under CT or ultrasound guidance (Narayanan, Froud et al. 2013, Silk, Tahour et al. 2014)

The application of high voltage electrical pulses may potentially trigger cardiac arrhythmias caused by the increased transmembrane permeability, which opens a path for ion transport and stimulation of muscular and nervous tissue can cause severe muscle contractions and epileptic seizures. Hence, specific precautions in intraprocedural management are required including the standard monitoring such as electrocardiogram (ECG), oximetry, end-tidal carbon dioxide concentration ( $E_TCO_2$ ), blood pressure and temperature. Additionally the level of neuromuscular blockade should be constantly monitored as well as regular blood gases as due to the cellular destruction of IRE some patients have shown mild transient metabolic acidosis and hyperkalemia. (Hong, Georgiades 2011, Nielsen, Scheffer et al. 2014).

In interventions with close proximity to the diaphragm and heart transient ventricular arrhythmias may occur and an ECG gating synchronization mode, which administers pulses synchronously to the heart rhythm is recommended. The gating device senses the rising slope of the R wave and delivers the electrical pulse seconds after the R-wave and during or just before the ventricular refractory period. These external electrical stimuli administered during the absolute refractory period are unable to induce an action potential and therefore prevent arrhythmias (Hong, Georgiades 2011, Narayanan, Froud et al. 2013, Nielsen, Scheffer et al. 2014).

## High Intensity Focused Ultrasound (HIFU)

### History and principles

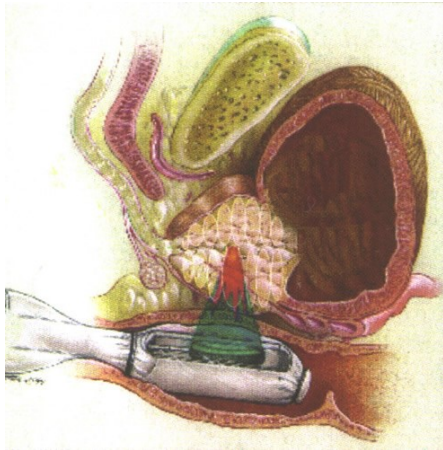
Currently there are two methods to deliver ultrasound energy: (1) direct percutaneous, interstitial or trans rectal (figure 17) application with a needle like device placed within the targeted lesion or intracavitary, which is termed interstitial ultrasound ablation and (2) extracorporeal or transcutaneous ablation (Ahmed, Solbiati et al. 2014).

Lynn et al. introduced HIFU first in 1942. Although four types of HIFU devices have been developed (extracorporeal, trans rectal, interstitial and percutaneous) it is the only technique, which can be used as a completely non-invasive and extracorporeal option for the treatment of primary solid tumors and metastatic disease (Knavel, Brace 2013, Yu, Burke 2014).

HIFU is a thermal ablation technique, which creates cell damage primarily by generating high temperatures but also induces mechanical effects in the tissue. The technique of HIFU relies on the same principles as conventional diagnostic ultrasound, but with increased energy deposition. Ultrasound waves are acoustic pressure waves with a frequency range from 16kHz extending into the megahertz range. Transmission of Ultrasound waves into human tissue follows two physical behaviors, reflection and absorption. The basis of conventional diagnostic ultrasound is reflection of low-energy ultrasound waves, whereas absorption predominates in HIFU, when high-power ultrasound waves are focused on a single point. Compared to the typical diagnostic ultrasound with time-averaged intensities up to 720 mW/cm<sup>2</sup> the intensity of HIFU is several orders higher, 100 – 10 000 W/cm<sup>2</sup> in the focal zone (Knavel, Brace 2013, Zhou 2011, Geiger, Napoli et al. 2014).

Through an ultrasound transducer a high frequency ultrasound beam (0.5 – 10 MHz) is generated, which is arranged into a spherical form, usually 1 mm in diameter and 10 mm in depth, in order to localize thermal effects. At the focus the high-intensity-focused energy is converted into heat due to absorption of acoustic energy with a rapid increase of temperature in the target up to the cytotoxic level of more than 60°C for several seconds. Temperatures can rise to 65°C to 85°C. Higher

temperatures have to be avoided to prevent boiling of liquids within the tissue. This phenomenon subsequently leads to instantaneous and irreversible cell death via coagulation necrosis without damaging adjacent structures, like blood vessels etc., due to the fact that in the surrounding area of the focus energy density is significantly lower (Yu, Burke 2014, Zhou 2011, Phenix, Togtema et al. 2014).



*Figure 16 Principle of focused US beam, [www.hifunews.com](http://www.hifunews.com)*

Mechanical effects induced by HIFU are cavitation, microstreaming and radiation force. The phenomenon of cavitation appears when gas filled cavities, so called microbubbles, spontaneously oscillate in an acoustic field as a result of alternating compression and expansion of tissue as an ultrasound burst propagates through it. There are two forms of cavitation: (1) stable or non-inertial cavitation and (2) inertial cavitation. Stable or non-inertial cavitation is caused by the constant oscillation of a gas filled-body in an ultrasonic field. Inertial cavitation is caused by violent oscillations, which result when a gas-filled cavity rapidly expands during part of the acoustic cycle and then collapses in consequence of erratic oscillations and rapid growth of the cavity. The violent collapse produces shock waves of very high temperature and pressure in the microenvironment inducing light emission and the formation of reactive chemical species. In contrast, stable cavitation causes the so-called microstreaming effect. As a result of rapid movement of a fluid near the bubble due to its oscillating motion high shear forces are produced in the microenvironment. Due to the effect of shear forces transient damage to the cell membrane can be caused. Radiation force is developed by a viscous surrounding fluid, which either absorbs or reflects an acoustic wave (Phenix, Togtema et al. 2014, Zhou 2011).

The prediction of thermal tissue damage can be done by using the Arrhenius analysis or the Sapareto Dewey iso-effect thermal dose relationship. Both describe the time-temperature relationship, which is required to irreversibly damage the cells' integrity. Sapareto and Dewey demonstrated that thermal damage of tissue is linearly dependent on exposure time and exponentially dependent on temperature elevation. Nevertheless, the threshold varies with tissue type and the ideal choice of ultrasound parameters is application-specific.

#### HIFU generators and probes

Initially tumor ablation was performed by a single point ablation system, which was inefficient and time consuming as a large part of the applied energy got lost through heat diffusion. Another major handicap was the inhomogeneous heat distribution. In order to improve ablation efficiency a system that uses volumetric ablation technique and real-time temperature measuring was designed (figure 18). Due to the advantages of this system it was possible to ablate larger and more homogeneously tissue volumes and additionally the system is able to automatically stop the sonication if the temperature reaches a user-predefined threshold in order to prevent under- or overtreatment (Huisman, van den Bosch 2011).



Figure 17 HIFU ablation generator, [www.medicalexpo.de](http://www.medicalexpo.de)

## Clinical practice

Due to the lack of image guidance for soft tissue visualization in the 1990s MR imaging in combination with HIFU was introduced, which made real-time imaging for tumor targeting and focused ultrasound beams for thermal ablation possible. In addition MR imaging supports thermal mapping within the targeted tissue in a quantitative way. The first commercially available MR-HIFU system was authorized in 2004 for the ablation of benign uterine fibroids (Huisman, van den Bosch 2011).

For oncologic applications several important factors should be considered regarding MR-HIFU to achieve 100% tumor necrosis so to be able to compete with oncologic surgery. For an ideal patient selection and to identify patients estimated to benefit from MR-HIFU in a curative setting the optimal imaging technology, treatment protocols for various tumor types and organs and the use of treatment margins are required (Huisman, van den Bosch 2011).

## Interventional techniques in respect to different organ systems

### Liver ablation

Hepatocellular carcinoma (figure 19 and 20) is a major health problem worldwide, as it is the sixth most common malignancy and the third most common reason for cancer related deaths (Morimoto, Numata et al. 2010) . Risk factors for HCC and several other malignant liver diseases are cirrhosis of varied cause, hepatitis B and C virus infection, hemochromatosis, longtime alcohol abuse, nonalcoholic fatty liver disease (NAFLD) and steatohepatitis. In developed countries especially diabetes mellitus and obesity are major risk factors for the severest form of NAFLD supposedly leading to HCC via liver cirrhosis (Narayanan, Froud et al. 2013).

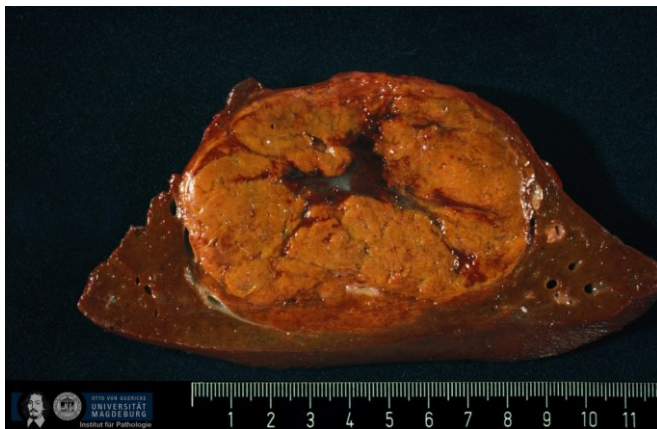


Figure 18 Specimen of HCC, 67-year old male patient, [www.medicaltribune.de](http://www.medicaltribune.de)

To date the standard curative approach for liver cancer treatment is surgical resection, or liver transplantation. But only a limited number of approximately 5-40% are surgical candidates (Morimoto, Numata et al. 2010). Currently the staging of HCC is based on the Barcelona Clinic Liver Cancer Staging classification (BCLC). The BCLC was evolved in 1999 and classifies patients according to the size and number of tumors, degree of liver function impairment and performance status. In accordance to the BCLC stage, which includes stage 0 (very early), stage A (early), stage B (intermediate), stage C (advanced) and stage D (end-stage) the best treatment option is chosen. In addition the Child-Turcotte-Pugh system is used to quantify the severity of liver cirrhosis by evaluating variables like ascites, albumin, bilirubin, international normalized ratio (INR) and hepatic encephalopathy. The sum of these items categorizes patients into Child-Pugh grades A (5-6 points), B (7-9

points) or C (10-15 points) as to be seen in table 3. Liver transplantation is limited to patients with a single tumor <5 cm in diameter or three or fewer tumors each <3 cm, no extrahepatic manifestations and no vascular invasion, based upon the Milan criteria (Narayanan, Froud et al. 2013).

Table 3 Child-Turcotte-Pugh score

Factor	1 point	2 points	3 points
Albumin (g/L)	>35	28-35	<28
Bilirubin (µmol/L)	<34	34-50	>50
INR	<1.7	1.7-2.3	>2.3
Ascites	none	mild	moderate to severe
Hepatic encephalopathy	none	Grade I-II	Grade III-IV

Locoregional treatment choices including transarterial embolization or chemoembolisation and ablative methods have gained acceptance for maintaining patients on the transplant list on the one hand but also to downstage patients who do not fit the Milan criteria. Moreover, interventional oncologic ablation techniques are a primary treatment option for non-surgical candidates. The aim of these ablation techniques is to ablate the entire lesion via coagulation necrosis and cell death within a single treatment session. Advantages over traditional liver resection for focal HCC are reduced morbidity and mortality, increased preservation of hepatic function and the possibility to repeat the treatment in case of local tumor progression or newly appeared lesions in the setting of underlying cirrhosis (Narayanan, Froud et al. 2013, Hong, Georgiades 2011).

Different kinds of hepatic cancer have been treated with cryosurgery for a longer period of time than with other techniques. For cryotherapy the best results have been achieved with small single tumors not larger than 2-3 cm. Currently RFA is the best studied and most widely used ablation modality for primary liver cancer (figure 21 and 22), which provides increased local tumor progression control for a broad spectrum of tumor sizes. Regarding RFA, limiting factors are thermosensitive

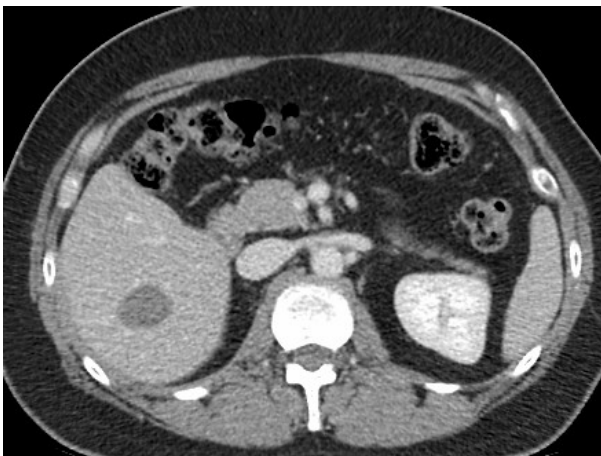
adjacent structures such as bile ducts, gallbladder or the hepatic, capsule which can be damaged and complications induced. Large blood vessels within or close to the treatment area may restrain complete treatment of the target area by causing thermal sinks (heat-sink effect). Due to these limitations several other ablation methods were taken under consideration, which are less damaging to non-target tissue and not affected by heat-sink effects. IRE, for example, can ablate volumes of tissue comparable to those of thermal ablation modalities but without causing detrimental thermal effects such as inflammatory reaction or vascular occlusion. Also microwave ablation has achieved mature development and is routinely used in the field of liver cancer therapy. The most important advantage is that lesions from <3 cm up to >5 cm can be ablated. In addition MWA shows higher thermal efficacy than other heat based ablation methods (Baust, Gage et al. 2014, Yu, Liang et al. 2014, Narayanan, Froud et al. 2013).



*Figure 19 CT-scan of HCC, 41-year old female patient (image courtesy of Dr. Rupert Portugaller, University Hospital Graz, Austria)*



*Figure 20 RFA ablation of HCC, 41-year old female patient (image courtesy of Dr. Portugaller Rupert, University Hospital Graz, Austria)*



*Figure 21 Tumor necrosis 5 years after RF ablation, 41-year old female patient (image courtesy of Dr. Portugaller Rupert, University Hospital Graz, Austria)*

The liver is a very common site of metastatic involvement from distant primary tumors, especially from gastrointestinal tract and breast cancer.

Conventional chemotherapy has shown limited response in patients with liver metastasis in contrast to newer agents, such as Oxaliplatin and Irinotecan and antiangiogenic agents have shown improved patient survival in palliative regimens and in downstaging initially unresectable into resectable tumors. For patients with a liver-only disease (metastasis confined to the liver) surgical resection remains the gold standard of treatment as the five-year survival in well-selected patients is as high as 40 to 50%. More than three hepatic metastases, extrahepatic manifestation, tumor diameter >5 cm and a positive resection margin are associated with a very

poor prognosis and overall survival rates are similar to that of unresected tumor (Hong, Georgiades 2011).

The largest experience using thermal ablation techniques is available in patients with colorectal liver-only metastatic disease who either do not meet surgical resection criteria but would still benefit from liver directed therapy (Liang, Wang et al. 2009). Although initial studies using RFA had a relatively poor 5-year survival rate compared to surgical resection. Due to improvements in patient selection, more accurate follow up, advances in chemotherapy regimens and immediate retreatment of persistent or untreated tumor, subsequently more improved outcomes, closely to those of surgical resection, could be achieved.

For percutaneous ablation of other types of liver metastases fewer data is available in the literature.

#### Kidney ablation

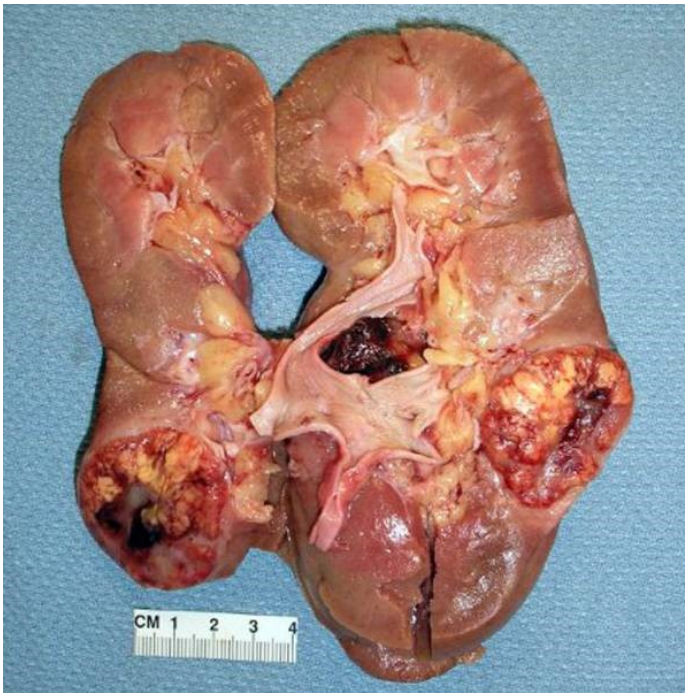
Renal cell carcinoma (RCC, figure 23) is the 9<sup>th</sup> most common cancer worldwide, whereupon incidence rates are highest in Europe, North America and Australia (Jonasch, Gao et al. 2014). Due to the widespread use of cross-sectional imaging, the incidental detection of RCC (figure 24) has become a frequent occurrence in the last decades and the incidence of RCC has constantly increased. The most common treatment option for RCC is open surgical or laparoscopic nephrectomy, which is the most radical operation and should therefore be the choice of last resort. Following the TNM staging for renal cell carcinoma (table 4), in the last decade treatment has shifted to nephron-sparing procedures, including open or laparoscopic partial nephrectomy, wedge resection and most recently percutaneous thermal ablation modalities, for the management of small renal cancers have gained acceptance (Ridge, Pua et al. 2014, Kawamoto, Solomon et al. 2009).

Table 4 TNM classification of RCC

TNM classification	
T	T <sub>1</sub> : limited to kidney <ul style="list-style-type: none"> <li>• T<sub>1a</sub>: &lt;4cm</li> <li>• T<sub>1b</sub>: &gt;4cm but &lt;7cm</li> </ul>
	T <sub>2</sub> : limited to kidney <ul style="list-style-type: none"> <li>• T<sub>2a</sub>: &gt;7cm but &lt;10cm</li> <li>• T<sub>2b</sub>: &gt;10cm</li> </ul>
	T <sub>3</sub> : tumor/tumor thrombus extension into major veins or perinephric tissue, but not into ipsilateral adrenal gland or beyond Gerota's fascia <ul style="list-style-type: none"> <li>• T<sub>3a</sub>: spread to renal vein</li> <li>• T<sub>3b</sub>: spread to infra diaphragmatic IVC</li> <li>• T<sub>3c</sub>: spread to supra diaphragmatic IVC or invades the wall of the IVC</li> </ul>
	T <sub>4</sub> : involves ipsilateral adrenal gland or invades beyond Gerota's fascia
N	N <sub>0</sub> : no nodal involvement
	N <sub>1</sub> : metastatic involvement for regional lymph node/s
M	M <sub>0</sub> : no distant metastases
	M <sub>1</sub> : distant metastases

Regarding percutaneous ablation techniques, the most valuable data are available for RFA and cryoablation, which mainly come into consideration for high risk anesthesia/surgery patients with comorbid conditions, renal dysfunction, multiple RCCs and hereditary metachronous renal cancer syndromes, in order to obtain as much renal function as possible. Apart from patients who are not surgical candidates, these techniques can also be an option for patients who wish to avoid surgery. The success rate for RFA and cryoablation is mainly dependent on tumor size and tumor location. The highest chance of complete ablation is given for lesions with less than 4 cm in diameter. According to tumor location RCCs can be classified as exophytic (protruding into the perirenal fat), parenchymal, central (protruding into the renal sinus or the main renal vessel) or mixed with central and exophytic components. Exophytic lesions may be easier to treat than central or hilar tumors as perirenal fat may function as an insulating agent. In contrast, major renal vessel

proximity can cause a heat-sink phenomenon, which may result in incomplete ablation and recurrence. As many incidental tumors are usually small at the time of diagnosis minimally invasive therapeutic alternatives to open surgery are increasingly used. Since non-surgical patients are often driven towards percutaneous ablation techniques it should be considered that ablation of large tumors should be done in two or even three sessions. Especially in patients with preexistent cardiopulmonary disease, minor complications seem to have more pronounced effects (Venkatesan, Wood et al. 2011, Hong, Georgiades 2011).



*Figure 22 Specimen of RCC, 57-year old female patient, [www.radiopaedia.org](http://www.radiopaedia.org)*

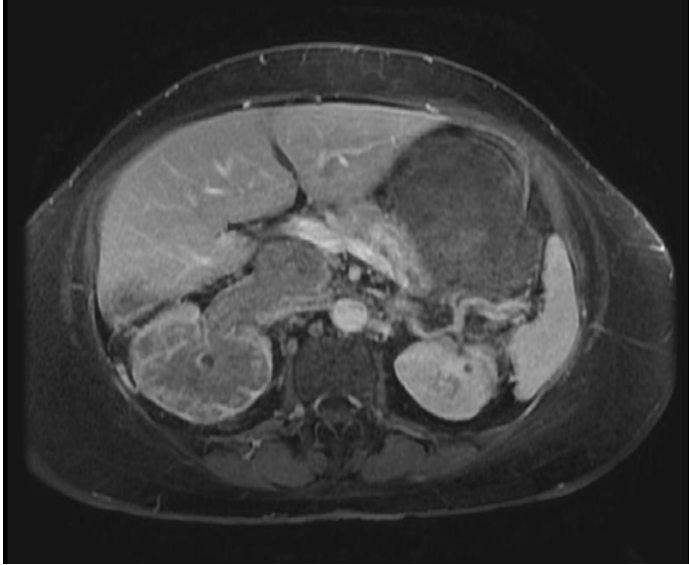


Figure 23 MR image of RCC, 61-year old female patient, [www.radiopaedia.org](http://www.radiopaedia.org)

### Breast ablation

Breast cancer (figure 25) is the most common cancer disease in women worldwide and the most common cause of death in the western population in women between the age of 35 and 55 years (Baldassarre, Belletti 2016). The major risk factors are inherited mutations of the breast cancer susceptibility genes BRCA1 und BRCA2 and personal or family history of the disease. Furthermore obesity, hormone therapy, smoking, alcohol and increased breast tissue density may forward cancerogenesis. A detailed staging system is to be seen in table 5.

Due to the implementation of screening mammography and improved patient education more patients present with smaller breast cancer ( $\leq 3\text{cm}$ ). For women with small, non-metastasized carcinoma and carcinoma in situ the diagnosis and therapy has shifted rapidly in the past decades, which means a higher number of patients are amenable for breast conserving surgical approaches. Radical mastectomy or complete axillary lymph node dissection, have been replaced by less extensive procedures like core needle biopsy, lumpectomy with radiation therapy and minimally invasive techniques, such as RFA, HIFU, microwave ablation IRE and cryoablation (Zhou, Zha et al. 2012, Roubidoux, Sabel et al. 2004).

Table 5 TNM classification of breast cancer

Primary tumor (T-stages)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ DCIS and/or LCIS in the underlying breast parenchyma. Breast parenchyma cancer associated with Paget disease are categorized on basis of the size and characteristics of the parenchymal disease, although the presence of the Paget disease should still be noted.
T1	Tumor ≤20mm in greatest diameter <ul style="list-style-type: none"> <li>• T1mi: ≤1mm in greatest dimension</li> <li>• T1a: &gt;1mm but ≤5mm in greatest dimension</li> <li>• T1b: &gt;5mm but ≤10mm in greatest dimension</li> <li>• T1c: &gt;10mm but ≤20mm in greatest dimension</li> </ul>
T2	Tumor >20mm but ≤50mm in greatest dimension
T3	Tumor >50mm in greatest dimension
T4	Tumor of any size with direct extension on the chest wall and/or ulceration of the skin or skin nodules <ul style="list-style-type: none"> <li>• T4a: Extension to chest wall not including only pectoralis muscle adherence/invasion</li> <li>• T4b: Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma</li> <li>• T4c: both T4a and T4b</li> <li>• T4d: inflammatory carcinoma</li> </ul>
Regional lymph nodes (pN)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastases identified histologically

	<ul style="list-style-type: none"> <li>• pN0(i-): no regional lymph node metastases histologically, negative IHC (immunohistochemical method)</li> <li>• pN0(i+): malignant cells in regional lymph node(s) <math>\leq 2</math>mm (detected by hematoxylin-eosin stain or IHC, including isolated tumor cell clusters)</li> <li>• pN0(mol-): no regional lymph node metastases histologically, negative molecular findings (reverse transcriptase polymerase chain reaction (RT-PCR))</li> <li>• pN0(mol+): positive molecular findings (RT-PCR) but no regional lymph node metastases found by histology or IHC</li> </ul>
<b>PN1</b>	<p>Micrometastases; or metastases in 1-3 axillary lymph nodes and/or in internal mammary lymph nodes, with metastases detected by sentinel lymph node biopsy but not clinically detected</p> <ul style="list-style-type: none"> <li>• pN1mi: micrometastases (<math>&gt;0,2</math>mm and /or <math>&gt;200</math> cells but none <math>&gt;2</math>mm)</li> <li>• pN1a: metastases in 1-3 axillary lymph nodes (at least one <math>&gt;2</math>mm)</li> <li>• pN1b: metastases in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected</li> <li>• pN1c: metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected</li> </ul>
<b>pN2</b>	<p>Metastases in 4-9 axillary lymph nodes or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases</p> <ul style="list-style-type: none"> <li>• pN2a: metastases in 4-9 axillary lymph nodes (at least one tumor deposit <math>&gt;2</math>mm)</li> <li>• pN2b: clinically detected internal mammary lymph node metastases in the absence of axillary lymph node metastases</li> </ul>
<b>pN3</b>	<p>Metastases in <math>\geq 10</math> axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal</p>

	<p>mammary lymph node metastases in the presence of <math>\geq 1</math> positive level I, II axillary lymph nodes; or in <math>&gt;3</math> axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes</p> <ul style="list-style-type: none"> <li>• pN3a: metastases in <math>\geq 10</math> axillary lymph nodes (at least one tumor deposit <math>&gt;2\text{mm}</math>); or in infraclavicular (level III axillary) lymph nodes</li> <li>• pN3b: clinically detected ipsilateral internal mammary lymph node metastases in the presence of <math>\geq 1</math> axillary lymph nodes; or in <math>&gt;3</math> axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected</li> <li>• pN3c: metastases in ipsilateral supraclavicular lymph nodes</li> </ul>
<b>Distant metastases (M)</b>	
<b>M0</b>	No clinical or radiographic evidence of distant metastases
<b>cM0(i+)</b>	No clinical or radiographic evidence of distant metastases but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow or other non regional nodule tissue that are no larger than 0,2mm in a patient without symptoms or signs of metastases
<b>M1</b>	Distant detectable metastases as determined by classic clinical and radiographical means and/or histologically proven $>0,2\text{mm}$

The change to minimal invasive methods and breast conservation therapy has brought more favorable cosmetic and functional outcomes, which have helped to improve the patient's body image, quality of life and satisfaction with treatment. Nevertheless, tumors should be carefully selected because of the complex anatomic structure of the breast and the variability of normal breast tissue (dense or fatty). The challenge is to provide adequate local tumor control by preserving the greatest amount of normal breast tissue (Manenti, Bolacchi et al. 2009, Roubidoux, Sabel et al. 2004, Grotenhuis, Vrijland et al. 2013).

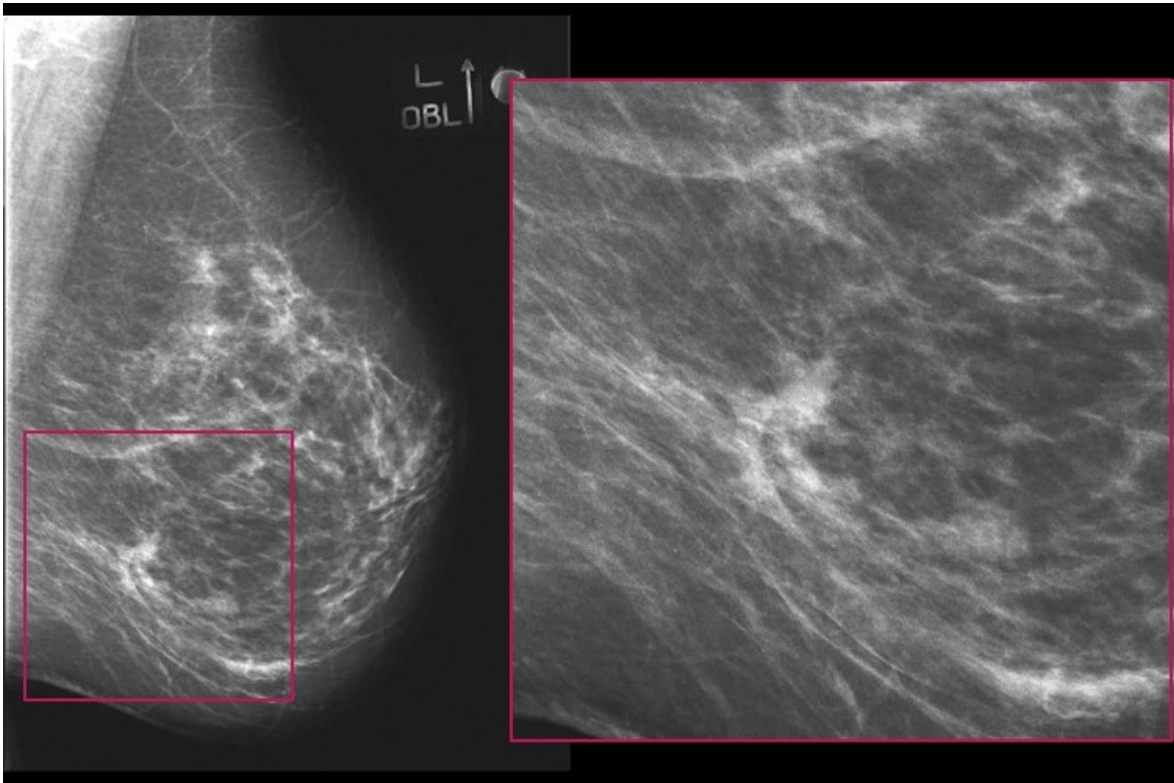


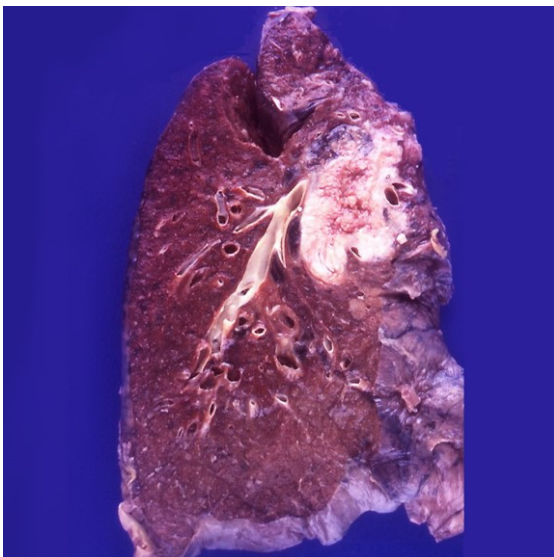
Figure 24 X-ray mammography of breast cancer, 47-year old female patient, [www.uni-marburg.de](http://www.uni-marburg.de)

### Lung and bronchial cancer

Lung cancer (figure 26 and 27) remains the leading cause of cancer death among males in developed countries as well as in developing countries. Among females lung cancer has overtaken breast cancer deaths in more developed countries (Marcus, Raji et al. 2015). In both, more or less developed countries, lung cancer comes with a very poor prognosis as by the time of diagnosis two-thirds are in a late stage, where surgery is difficult or even no longer possible (Palussiere, Lagarde et al. 2015). A detailed summary of the NSCLC staging system is to be seen in table 6. Hence, conservative therapies play an important role, but in spite of constant improvement of therapies, lung cancer does still not respond well to treatments (Lee, Choi et al. 2011, Marcus, Raji et al. 2015).



*Figure 25 X-ray of NSCLC, 51-year old male patient, [www.medscape.com](http://www.medscape.com)*



*Figure 26 Specimen of squamous cell carcinoma (one of the NSCLC) of the lung, 66-year old female patient, [www.radiopaedia.org](http://www.radiopaedia.org)*

The vast majority of lung cancer is induced by cigarette smoking, which occurs in 80-90% of patients. Further risk factors are occupational exposure especially to asbestos, arsenic and radon gas as well as previous lung diseases such as COPD, pneumonia or tuberculosis, ionizing radiation and family history (Marcus, Raji et al. 2015).

Table 6 lung cancer staging including tumor, node and distant metastasis

	TNM staging
Stage 1	T1, N0, M0 and T2, N0, M0
Stage 2	T1, N1, M0 and T2, N1, M0 and T3, N0, M0
Stage 3a	T1, N2, M0 and T2, N2, M0 and T3, N1, M0 and T3, N2, M0
Stage 3b	any T, N3, M0 and T4, any N, M0
Stage 4	any T, any N, M1

The current gold standard of treatment for early stage non-small-cell lung cancer (NSCLC) is pneumonectomy or lobectomy with hilar and mediastinal lymph node sampling. Unfortunately, only a small number of about 15% are diagnosed with stage 1 or 2 NSCLC and many of these patients are not eligible for surgical intervention due to cardiorespiratory comorbidity or insufficient vital lung function. The treatment options of choice in stage 3a are radio- or chemotherapy, surgery or a combination of these modalities. In stage 3b disease a combination of radio- and chemotherapy is used but with a very poor 5-year survival rate. In stage 4 disease a palliative chemotherapy is the only option but with a median survival of only 7.9 month (Jemal, Murray et al. 2005, Schiller, Harrington et al. 2002) .

Due to these facts especially non-surgical patients may benefit from minimal invasive percutaneous tumor ablation methods including RFA, MWA and cryoablation and IRE, which may bring a benefit particularly for tumors in risky locations in proximity to vessels or the hilum (Sonntag, Hinshaw et al. 2011).

The successful use of RFA in non-operable NSCLC was first described in 2000 (Ridge, Solomon et al. 2014). Conversely to normal lung tissue, which has low thermal and electrical conductivity, fortunately lung tumors with densely packed cells have higher conductivity than surrounding tissue. In case of MWA the low permittivity and effective conductivity brings a benefit as it allows a deeper tissue penetration than in other solid organs. With regard to cryoablation the low thermal conductivity is the main limiting factor, which can be overcome by the formation of a progressive iceball that raises the thermal conductivity of the target tissue. Another limiting factor that occurs in all the above-mentioned ablation methods is the heat

sink phenomenon but can be handled by adjusting temperature. As IRE is a non-thermal ablation technique there is no heat sink effect. For these reasons IRE is an option for the treatment of unresectable, anatomically sensitive locations as it is preserving airways, nerve sheaths and mediastinal vessels (Ridge, Solomon et al. 2014).

The indications for thermal ablation are stage I NSCLC in patients who are not candidates for curative surgical resection due to comorbidity and tumors, which do not exceed a maximum diameter of 3 to 3,5 cm. As RFA is the most frequently applied method with the highest grade of evidence it is the ablation modality of first choice and has besides inoperable stage I lung cancer further indications such as advanced-stage lung cancer treated with radiation or chemotherapy with a persistent solitary, peripheral nodule; recurrent isolated tumor after previous lung resection and salvage therapy of residual or recurrent disease after resection, chemotherapy and/or radiation. Due to its theoretical gain over RFA including faster and greater heating and a less severe heat sink effect, MWA is likely to be increasingly applied. Cryoablation and IRE are both not approved outside of a research setting (Ridge, Solomon et al. 2014).

The main postprocedure imaging modalities for lung cancer are CT and/or PET/CT. The baseline images for surveillance are usually acquired within two months following thermal ablation. After this the patient undergoes imaging every 3 months over a year and thereafter annual monitoring. Initially, due to inflammation, a perilesional ground glass halo with or without an increased lesion size is likely but is expected to decrease in size over time. In the follow up complete disappearance of the initial nodule is rarely observed. The expected CT appearances include a residual node, which is stable or decreasing in size, atelectasis, an elongated linear nodule due to fibrosis or cavitation. Regarding PET-CT tracer activity can occur up to one month following treatment despite technical success due to inflammation. The initial inflammation signs are expected to resolve 3 months post ablation. After that a relatively uniform ring of low level FDG activity and central photopenia is typical and may resolve between 6 and 12 month after treatment (Ridge, Solomon et al. 2014).

If there is increased metabolic activity noted centrally or in a nodular structure at the ablation site on PET-CT more than 3 month after ablation therapy or any contrast

enhancement on CT in the ablation zone, peripheral nodular growth, regional or distant lymph node enlargement, a transformation from ground glass to solid opacity, new sites of intrathoracic disease or new extrathoracic disease residual of disease or disease recurrence may be present (Ridge, Solomon et al. 2014).

Also when it comes to oligometastatic pulmonary disease percutaneous ablation techniques, especially RFA, may be an alternative to surgical resection with less morbidity and less negative side effects, whereas surgical treatment requires sufficient cardiopulmonary reserve and is associated with a risk of morbidity and relapse. In particular non-surgical candidates have shown treatment efficacy comparable to open resection in several reports. The main adverse event is pneumothorax requiring chest tube drainage and procedure related mortality has been reported to be low.

### Prostate ablation

Prostate cancer (figure 28) is the most frequently diagnosed cancer in the United States, counting 28% of all newly diagnosed cancers and the second most cause of cancer death in men (Bomers, Sedelaar et al. 2012). Since the widespread use of the prostate specific antigen (PSA) as a diagnostic marker, the number of newly detected prostate cancer has increased strongly. Base for the treatment decision is the Gleason histological grading score (table 7), TNM classification and tumor size (Bomers, Sedelaar et al. 2012). The most common grading system for prostate cancer is the Gleason score, which describes how aggressive a tumor is and how likely it is to spread. To assign a Gleason score the sum of the two most common glandular growth patterns of the biopsies from the tumor is taken. A grade from a scale between one (high differentiated) and five (low differentiated) is given to each of these two patterns (Ahmed, Zacharakis et al. 2009, Bomers, Sedelaar et al. 2012).

Table 7 Gleason score

Gleason sum	description
10, 9, 8, 7(4+3)	High grade PC poorly differentiated cells, completely dedifferentiated from original tissue, aggressive tumor with poor prognosis
7(3+4), 6, 5	Intermediate grade PC
4, 3, 2	Low grade PC, cells are well differentiated, forming well-defined glands, tumor has grown into or invaded the surrounding prostate tissue, less aggressive with favourable prognosis

At present the common treatment possibilities are either active surveillance or radical treatment that is radical prostatectomy or radiotherapy. For the treatment of aggressive prostate cancer (Gleason score >6) radical therapy is in contrast to low-grade prostate cancer (Gleason score ≤6) where active surveillance strategies are adequate. Choosing between these two extremes could still be challenging as whole-gland treatment comes with a significant morbidity, such as incontinence, impotence and can have a notable impact on quality of life. Surveillance strategies come up with minimal treatment related harms but can possibly carry psychological burden and delayed radical treatment can result in tumor progression (Bomers, Sedelaar et al. 2012, Ahmed, Zacharakis et al. 2009).

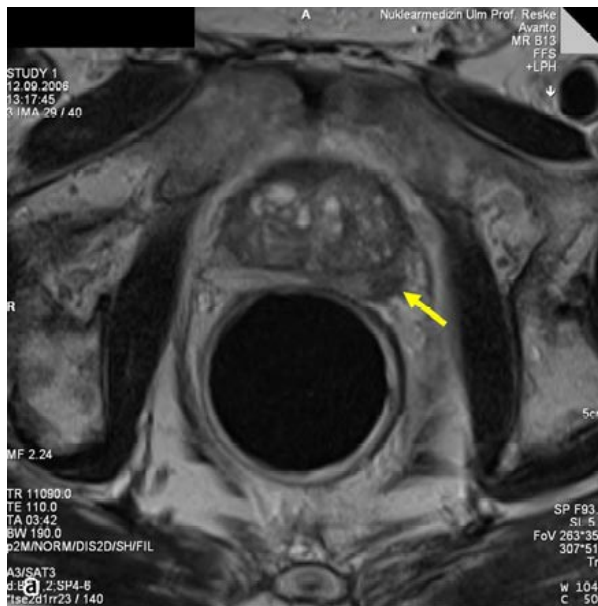


Figure 27 MR image of prostate cancer, 75-year old male patient, [www.springermedizin.de](http://www.springermedizin.de)

Promising minimally invasive focal treatment techniques, such as cryoablation (figure 29), MWA, RFA and HIFU offer a treatment approach between these extremes (Ahmed, Zacharakis et al. 2009). Although some of these modalities are still in experimental use they have gained attention in the last decades in the focal treatment of prostate cancer. Imaging guidance is provided by MRI and transrectal US. Multiparametric MRI is the most specific and sensitive imaging modality for prostate cancer. Focal therapy has on the one hand the potential to reduce treatment related complications such as impotence and incontinence without reducing the cancer specific outcome and may on the other hand offer greater progression freedom than active surveillance does. The definition of focal therapy of prostate cancer, fixed by a consensus panel of urologic surgeons, radiation oncologists, radiologists and histopathologists from Europe and North America reads: *“A type of treatment that aims to eradicate known cancer within the prostate and at the same time preserves uninvolved prostatic tissue with the aim of preserving genitourinary function”* (Bomers, Sedelaar et al. 2012). Different types of focal therapy are hemiablation (treatment of the tumor affected hemisphere), hockey stick ablation (hemiablation and half of the contralateral hemisphere) and targeted focal therapy (only the tumor itself is ablated).

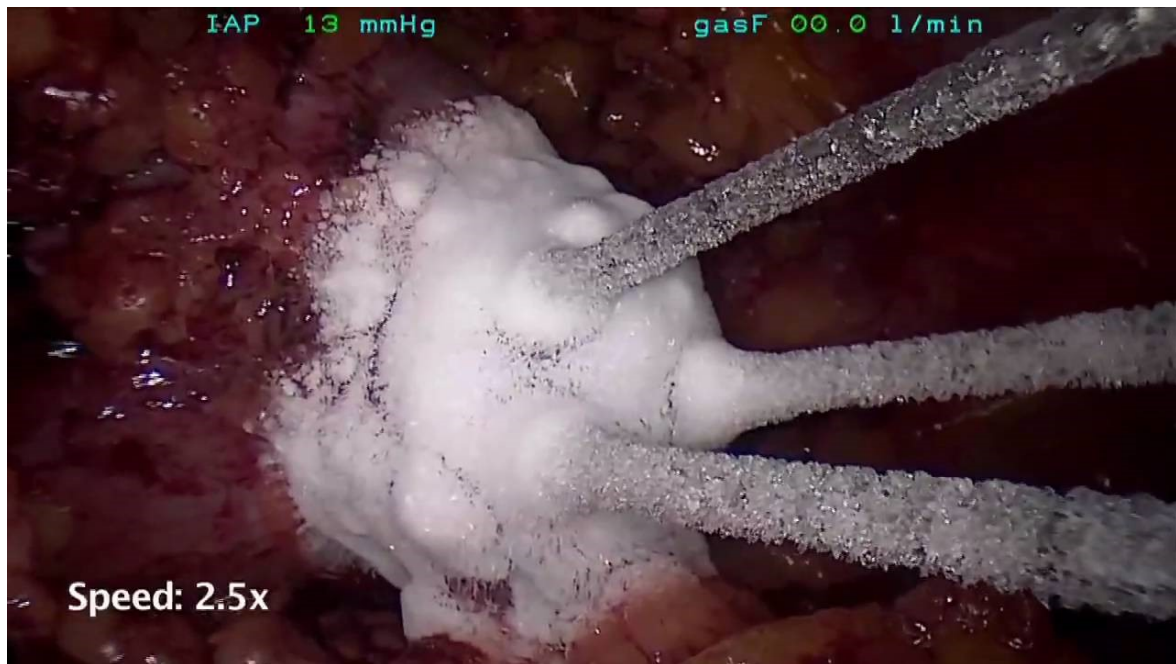


Figure 28 Cryoablation - ice ball formation within prostate cancer, 72-year old male patient, [www.prostatecancernewstoday.com](http://www.prostatecancernewstoday.com)

### Bone ablation

Osteoid osteoma (OO, figure 30 and 31) is a benign bone tumor of childhood and adolescence. The nidus of OO consists of immature bone, is rich in nerve cells and blood vessels and it usually appears in patients between the age of 10 and 30 years. The most representative symptom is localized, severe bone pain that flares up during nighttime due to excessive prostaglandin (especially prostaglandin E2) production of the intratumoral nerve cells. The typical radiological appearance of OO is the central, radiotransparent, partly ossifying nidus measuring not more than 15-20 mm surrounded by a zone of reactive ossification. Any tumor larger than 20 mm is called Osteoblastoma, which is four times less frequent but presents a noticeable histological similarity. Osteoblastoma mostly forms a more expansive and less sclerotic lesion and may exhibit a more aggressive imaging and histological pattern. Left untreated, OO shows both radiological and clinical natural regression during an average of six years. NSAIDs do not only palliate the symptoms of OO, but also accelerate the clinical regression of OO to an average of 33 month (Gebauer, Colletini et al. 2013, Rehnitz, Sprengel et al. 2013).

The common pre-procedural diagnostic work-up for surgery and percutaneous ablation consists of CT and MRI imaging studies with CT being superior in the

visualization of the nidus and MRI being superior in the detection of the mostly extensive bone marrow edema (Gebauer, Colletini et al. 2013).



Figure 29 OO of the right tibia, 20-year old male patient, [www.charite.de](http://www.charite.de)

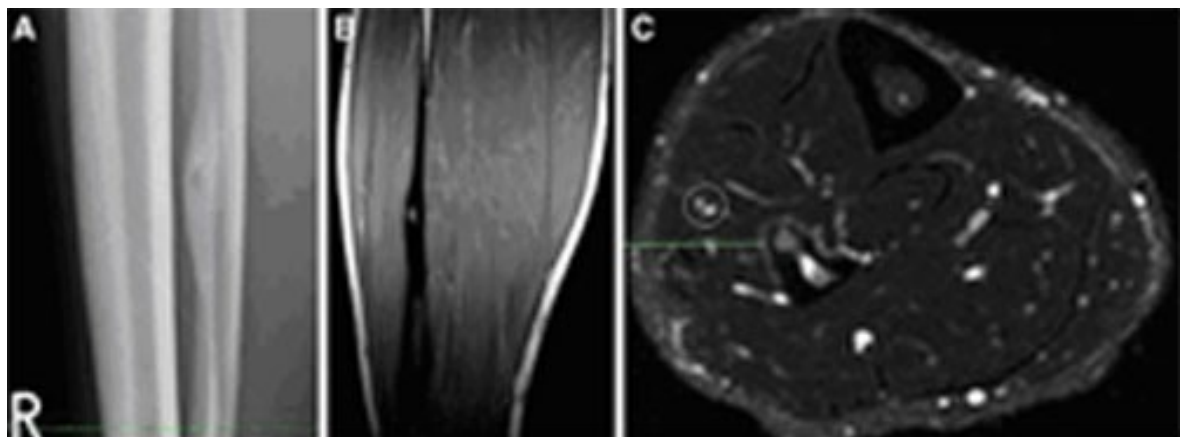


Figure 30 MR-guided thermal ablation of OO of the right tibia, 20-year old male patient, [www.charite.de](http://www.charite.de)

To date the common treatment options include conservative long-term treatment with non-steroid anti-inflammatory drugs (NSAID), surgical resection and several minimal invasive treatment options, such as percutaneous ablation modalities. Since NSAIDs are problematic due to the side effects and surgery could be very challenging and often requires a long way of recovery, minimally invasive treatment

options are gaining interest. At present the most common modality is CT-guided RFA, which is reported to be safe, more cost effective than open surgery and shows success rates between 85-98% at one year (Napoli, Mastantuono et al. 2013). With the same technique and the same coaxial introduction systems microwave antennas can be placed instead of RFA needles, which can overcome major limitations of RFA related to incomplete nidus ablation. Another common method for the treatment of localized bone tumors is HIFU. HIFU is a completely non-invasive and conformal method, which enables ablation of large-volume tumors (Napoli, Mastantuono et al. 2013, Rehnitz, Sprengel et al. 2013).

The skeleton is one of the most common metastatic site for prostate, breast, lung, kidney and thyroid malignancies. The vast majority of patients who are affected from metastatic bone disease (figure 32) develop poorly controllable pain, movement limitations in the affected limb, hypercalcemia and a tendency for pathological fractures. To date the standard-of-care treatment for symptomatic bone metastases are primarily palliative, including mainly beam radiation and surgery for focal lesions and chemotherapy, hormonal therapy, radiopharmaceuticals and bisphosphonates for diffuse metastases. Despite adequate conventional therapies, many patients fail to derive sufficient pain relief. Hence, percutaneous ablation methods have been explored for the palliation of painful metastatic disease, to increase the quality of life, prevent complications, improve prognosis and to extend survival time (Callstrom, Dupuy et al. 2013, Li, Zhang et al. 2010).



Figure 31 Specimen of metastatic bone disease, 51-year old female patient, [www.bronchialkarzinom-aktuell.de](http://www.bronchialkarzinom-aktuell.de)

## Discussion

As tumor ablation has been in clinical practice for more than 20 years it has gained interest as an important treatment option for a variety of focal organ malignancies. Numerous studies in the last decades have increased its clinical relevance and have made it an accepted oncologic treatment modality.

Nevertheless, for most of the ablation techniques long-term survival data and large prospective randomized studies are still missing. Hence, additional studies will be required to verify treatment efficacy and safety and to provide appropriate treatment guidelines.

Patient selection is based on patient and lesion characteristics and influences clinical outcome in terms of local recurrence, survival and complication rates. To date thermal as well as non-thermal ablation modalities constitute a therapeutic alternative for patients ineligible for surgical intervention as they can be performed with high rates of technical success, decreased complication rates and mortality and cost lower than in surgery. Many studies show that percutaneous ablation is feasible and reproducible and previous technical and safety limitations have been addressed with device development and modification of technique.

Conventional RF technology is significantly limited for large tumors (>5cm) mainly by incomplete tumor necrosis. MW systems can adequately treat tumors that RF currently covers plus tumors in tissue of high impedance, high perfusion or larger tumors. IRE is a non-thermal ablation method lacking a heat-sink-effect, thus enabling tumor ablation close to large vessels and with less risk of damage to adjacent vessels, ducts or critical organs. HIFU presents a completely non-invasive ablation option, but similarly to IRE with limited clinical data available.

Future directions include a combined approach using percutaneous ablation techniques in combination with other therapy modalities, which may synergistically result in an improved clinical outcome.

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