Thermal Ablation in Cancer Treatment

RCT summary for professionals

1. Abstract

2. What is it?
   2.1 Introduction
   2.2 Principles of thermal ablation
   2.3 Thermal ablation techniques
      2.3.1 Radiofrequency ablation
      2.3.2 Microwave ablation
      2.3.3 Ultrasound ablation
      2.3.4 Laser ablation
      2.3.5 Cryoablation
   2.4 Treatment monitoring
      2.4.1 Thermometry
      2.4.2 Image guidance
   2.5 Mechanisms of synergies
      2.5.1 Combination therapy for thermal ablation
      2.5.2 Nanoparticle-mediated thermal ablation therapy
      2.5.2.1 Near-infrared photothermal ablation
      2.5.2.2 Nanoparticle-based radiofrequency ablation
      2.5.2.3 Thermal ablation with chemotherapy

3. Does it work?
   3.1 Introduction
   3.2 Evidence-based results for using thermal ablation per anatomical location
      3.2.1 Bone cancer and soft tissue sarcoma
      3.2.2 Brain cancer
      3.2.3 Breast cancer
      3.2.4 Esophageal cancer
      3.2.5 Head and neck cancer
      3.2.6 Kidney cancer
      3.2.7 Liver cancer
      3.2.8 Lung cancer
      3.2.9 Pancreatic cancer
      3.2.10 Prostate cancer
      3.2.11 Rectal cancer
      3.2.12 Skin cancer
      3.2.13 Thyroid cancer
4. Is it safe? ..............................................................................................................................................43
   4.1 Does thermal ablation have any complications or side effects? .............................................43
   4.2 Contraindications for using thermal ablation .........................................................................45

5. Concluding remarks .........................................................................................................................45

6. References ........................................................................................................................................46
   6.1 Scientific publications ..................................................................................................................46
   6.2 Books .........................................................................................................................................68
   6.3 Professional Societies/Organizations .......................................................................................68
1. Abstract

The aim of thermal ablation is to destroy cancer tissue by generating cytotoxic temperatures for a short period of time in a minimally invasive fashion without damaging adjacent vital structures. Commonly used thermal ablation techniques that destroy tissue by locally elevating the tissue temperature above 55°C include radiofrequency, microwave, ultrasound, and laser ablation. Cryoablation uses subzero temperatures to selectively freeze and destroy undesirable tissue. These ablative procedures provide a minimal (e.g. percutaneously or laparoscopically) or non-invasive approach to cancer therapy.

Ablative treatments are gaining increasing attention as an alternative to standard surgical therapies, especially for patients with contraindications or those who refuse open surgery. Many of the research studies conducted evaluated the safety and feasibility of thermal ablation techniques. These studies have focused on the treatment of many types of cancer. Both clinical experience and studies have revealed a positive outcome in most of the thermal ablation applications depending on their endpoints and the investigated malignancy. The results of all of these trials suggest that thermal ablation can be performed with an acceptable safety profile and can result in reasonable local control of primary and metastatic tumors. However, limitations in thermal ablative efficacy exist, including determination of 100% tumor killing, persistent growth of residual tumor at the ablation margin, and the inability to effectively treat large tumors at a single treatment session. Today, thermal ablation is used in clinical applications mainly for treating kidney, prostate and non-operable liver tumors; there is also increasing application to other organ sites including the lung, breast, pancreas, thyroid, bone and brain. Potential benefits of thermal ablation include reduced morbidity and mortality in comparison with standard surgical resection and the ability to treat patients who are not surgical candidates.

In this review, aspects of each ablation technique, including mechanisms of action, limitations, synergies, and patient outcomes are presented. Our aim is to improve the general understanding of thermal ablation therapies in current clinical practice.

Keywords: BETA, bimodal electric tissue ablation, cryoablation, cryospray ablation, CSA, cryosurgery, cryotherapy, focal therapy, focused ultrasound surgery, high-intensity focused ultrasound, HIFU, interstitial laser coagulation, interstitial laser ablation, interstitial laser therapy, microwave ablation, laser ablation, laser-induced thermal therapy, LITT, magnetic fluid hyperthermia, MFH, nanophotothermolysis, phototherapy, photothermal ablation, photothermal therapy, preferential radiofrequency ablation, PRFA, probe ablative therapy, radiofrequency ablation, RFA, thermal ablation, ultrasound ablation

This text is written by Erik Cabuy (RCT) and reviewed by Dr. Gauthier Bouche (RCT) and Dr. Riadh Habash (Faculty of Engineering, University of Ottawa, Canada).
2. What is it?

2.1 Introduction

The last few years have seen a rapid expansion in the use and availability of thermal ablation techniques with hundreds of papers published. The primary purpose of these treatments is to completely eradicate all viable malignant cells within the tumor target. The methods of tumor ablation most commonly used in current practice are divided into two main categories, namely, hyperthermic ablation, in which heat may be generated by ultrasound or electromagnetic energy (i.e. radiofrequency, microwave, laser), and cryoablation to destroy tumor tissue by freezing it. These techniques achieve local irreversible cellular injury by modification of the tissue temperature. On the other hand, chemical ablation, photodynamic therapy, and electrotherapy are non-thermal ablation techniques that will be discussed elsewhere.

Of all of the ablative technologies available, cryoablation is the one that has been used and studied for the longest (Borofsky et al., 2011). It has its origins in the 1800s when advanced carcinomas of the breast and uterine cervix were treated with iced saline solutions. More recently, it was first described by Uchida et al. (1995). Radiofrequency ablation (McGahan et al., 1990; Rossi et al., 1999), ultrasound ablation (Ballantine et al., 1960; Fry and Fry, 1960; Madersbacher et al., 1995), and laser ablation (Hashimoto et al., 1985; Steger et al., 1989) have been developed since the 1960s. Microwave ablation is the most recent development in the field of local ablative therapies. What has emerged from the last decade of peer-reviewed research is the concept that thermal ablation, regardless of the thermal energy source, can create large areas of necrosis within tumors resulting in reductions in cancer tissue volume and associated symptoms. Thermal ablation also has many roles in the palliative treatment of benign and malignant tumors. An interesting observation in thermal ablation is that for a particular cancer type, different thermal ablation techniques are being investigated and used in clinical practice. The primary indication for thermal ablation is for treatment of focal cancer disease in those patients for whom surgery is not an option (Goldberg et al., 2009), who have refused or failed other treatments, or who require tissue-sparing procedures due to multiple tumor syndromes or previous organ resection. The advantages of replacing a conventional surgical intervention with a minimally invasive one are the potential reduction of the physical, emotional, and financial impacts of the procedure (Stafford et al., 2010). To implement this minimally invasive approach, several steps need to be taken. First, the exact tumor size should be reliably assessed. Second, the treatment should be safe and able to completely destroy all tumor tissue (including in situ cancer) locally. Finally, a reliable real-time way to monitor the treatment results should be available.

As a result of much experimental and clinical research, thermal ablation has rapidly evolved into a major player in the armamentarium of minimally invasive cancer therapies. These emerging ablation technologies are increasingly becoming a tool of surgery and interventional radiology. Typically, thermal ablation is applied by surgeons, gastro oncologists, or radiologists using minimally invasive procedures (laparoscopy or percutaneously) using monitoring systems such as magnetic resonance (MR), computed
tomography (CT), or thermal mapping to guide the percutaneous placement of applicators into the selected target. Success has been hindered, however, by problems of insufficient precision, inability to control the deposition of the heat-producing energy, lack of reliable real-time temperature measurements within the target, and the invasive nature of some of the technologies applied to produce thermal ablation. Thermal ablation treatments are usually carried out in a single session, often as a day case procedure, with the patient either fully conscious, lightly sedated or under light general anesthesia. Nowadays, most of these technologies have almost the same effectiveness in small tumors as would a surgical approach (Zhou, 2011) but as we will see, general statements like these are difficult to confirm.

The purpose of this review is to outline the principles by which thermal ablation techniques can provide elevation or decrease of temperature in tumors within the human body. Aspects of each ablation technique, including mechanisms of action, limitations, mechanisms of synergies, and patient outcomes are presented.

2.2 Principles of thermal ablation

Numerous studies over the last 2 decades have characterized many of the basic principles underlying ablative therapies. The term tumor ablation is defined as the direct application of thermal therapies to a specific tumor in an attempt to achieve eradication of substantial tumor destruction (Goldberg et al., 2009). Heat fixation or coagulation necrosis is used to describe this thermal damage, even though ultimate manifestations of cell death may not fulfill strict histopathological criteria of coagulative necrosis. Cell death is a result of irreversible coagulation of proteins, including enzymes, intranuclear proteins, DNA proteins, and DNA (Wong et al., 2010). Radiofrequency (RF), microwave (MW), laser, and ultrasound (US) ablate tissue by heating tissue to cytotoxic temperatures. Below 43°C, immediate thermal damage is not expected to be observed in most tissues, but above this temperature, thermal denaturation of critical enzymes and protein denaturation begin to accelerate, leading to a relationship between exposure time and temperature (Stafford et al. 2010). Temperatures in excess of 60°C are known to cause relatively instantaneous cell death, while temperatures from 50 to 60°C will induce coagulation and cell death in a matter of minutes (Brace, 2009b). Above 100°C, there is the potential for boiling and vaporization of tissue, followed by carbonization and charring which restricts total energy deposition and limits the size of the lesion produced. Thus optimal desired temperatures for ablation range from 50 to 100°C. The aims of these therapies are similar: coagulation of the tumor by sparing adjacent healthy tissue. On the other hand, cryoablation ablates tissue by freezing it to below -20-50°C. This causes intra-cellular ice-crystal formation and tissue osmosis leading to rupture of cell membranes.

Although differences exist in descriptions of the pathological changes following different thermal ablation procedures, the results are generally very similar and independent of the method employed. The ablated region is composed predominantly of two concentric zones with a central area of complete necrosis and a peripheral transitional rim of inflammation, congestion, hemorrhage and thrombosis (Gravante, 2010). While the coagulative zone is occupied entirely by dead cells and amorphous material, the transitional rim still contains

This document provided by Reliable Cancer Therapies (RCT) does not replace a medical consultation. Material in this document may not be reproduced in any form without explicit permission. For permission, please contact RCT at info@reliablecancertherapies.com
viable cells that may survive the adverse microconditions produced by the inflammatory environment and ultimately may give rise to tumor recurrences (Bhardwaj et al., 2009). In this area cells express heat shock proteins and die by apoptosis, the effect of which peaks a few hours following the ablation and expands the zone of definitive necrosis. The response of tumor tissue to the thermal effect depends also upon other factors including tissue material properties (e.g. thermal conductivity), tumor location and the electrode geometry. After thermal ablation, the killed tumor cells are gradually replaced by fibrosis and scar tissue. The treated tissue shrinks over the period of a few months. Complete and adequate destruction by thermal ablation requires that the entire tumor and an ablative margin be subjected to cytotoxic temperatures. The goal is thus to ablate the tumor plus a 0.5-1 cm margin of surrounding normal tissue based on the uncertainty concerning the exact tumor margin. If even a minimal amount of residual tumor remains after thermal ablation, the treatment is futile, with no impact on survival and no perspective of cure.

The effect of coagulation of tumor cells may induce other cellular processes. As part of the inflammatory process, antigen-presenting cells (APC) (e.g. dendritic cells, macrophages, and B lymphocytes) have been observed histologically at the periphery of ablated tumor lesions (Lu et al., 2009; Wu et al., 2009; Xu et al., 2009; Haraldsdóttir et al., 2011). Based on this observation, it has been postulated that thermal ablation of the tumor tissue may enhance tumor immunogenicity and subsequently augment the host immune response against the tumor (Wu et al., 2007b; Gravante et al., 2008; Dromi et al., 2009; Lu et al., 2009; Sabel, 2009; Haraldsdóttir et al., 2011). Also, it has been suggested that local thermal ablation treatments may have systemic effects and could potentially be combined with systemic chemotherapy for local therapy as well as control of local tumor recurrence and metastasis (Wu et al., 2007b; Dromi et al., 2009; Gravante et al., 2009; Lu et al., 2009; Sabel, 2009). Changes induced in the immune system, including those on the local and systematic inflammatory responses as well as modifications of immune cells and serum proteins, have been investigated for almost all the ablative techniques available, however, the mechanisms behind this enhanced immune response is still unknown. For instance, Biermann et al. (2010) found mild and chronic inflammation in US ablated prostate tumors up to 180 days post ablation, but were not able to distinguish between ablation-induced inflammation and tumor-associated or tumor-induced inflammation. It is unknown whether the remaining tumor debris after ablation may be a potential antigen source available for the induction of host antitumor immunity. In other words, it is not clear yet whether the in situ presence of debris from the tumor cells or the elevated temperatures elicit the immune response.

Numerous techniques have been developed for tissue ablation. Over the past 10 years, manufacturers have designed more powerful generators, developed special programs for heat deposition, and achieved improved needle designs that enable the creation of larger volumes of tissue necrosis. Most recently, a number of investigators have explored other methods of increasing the amount of RF-induced tissue necrosis (Mulier et al., in press). Others have used chemotherapy in combination with RF to increase the volume of tumor ablation. Local ablation of tumors is a procedure and, as such, is not subject to regulatory approval bodies such as the European Medicines Agency (EMA) or the USA Food and Drug Administration (FDA). However, the devices to ablate the tumors require regulatory clearance for marketing. The authorities cleared several ablation devices for commercial
A thermal ablation device generally consists of an applicator that is introduced into the tumor under imaging guidance. The procedure is usually performed by placing one or more electrodes through small (less than 1 cm) incisions in the skin and using either ultrasonography (US), computed tomography (CT), or magnetic resonance (MR) imaging to guide the tip into the tumor. Image guidance is critical to the success of these therapies. Precise thermal destruction is critical in the setting of treating tumors within highly functional organs, such as the brain. Also, imaging can be used to localize and target the thermal effects to the tumor for treatment, control the energy deposition, and assess treatment response. However, of all the minimally-invasive therapies, ultrasound ablation is the only non-invasive approach proposed to date. It employs extracorporeal ultrasound energy to ablate the targeted tumor at depth, without any needle insertion. Current ablation devices can create lesions of 3–6 cm in diameter. For large tumors (greater than 3 cm) multiple overlapping zones of ablation have to be created. Most devices only support a single applicator, making sequential ablation necessary. Based on this, much attention has centered on increasing ablated tissue volume with the simultaneous use of multiple probes to increase overall energy deposition. However, limitations in thermal ablative efficacy exist, including persistent growth of residual tumor at the ablation margin (e.g. Wu et al., 2007b), the inability to effectively treat larger tumors, and variability in complete treatment based on tumor location. Also, this form of therapy will find little use for large bulky tumors such as colorectal cancer primaries, soft tissue sarcomas, head and neck nodules, and superficial malignant disease involving the skin. A another major obstacle for all thermal ablation techniques is the heat sink effect, which describes how blood flow or airflow through or adjacent to the target tissue can offset the applied cooling or heating, thus limiting intended tissue damage (Sonntag et al., 2011).

The benefits of thermal therapeutics over conventional resection are numerous. One of the significant advantages of these minimally-invasive thermal therapies over conventional standard surgical resection are the potential minimal amount of normal tissue loss that occurs, less invasive with no incision, less pain and short recovery (Xu et al., 2010; Ahmed et al., 2011). These result in an associated reduction in mortality, morbidity, hospital stay, cost and improved quality of life for cancer patients (e.g. Liapi and Geschwind, 2007; Timmerman et al., 2009). In addition, the advantages of these methods include minimal trauma and less immunosuppression than standard surgical resection (Haraldsdóttir et al., 2011). One advantage of thermal ablation over surgical resection and radiation therapy is repeatability. The minimally invasive nature of percutaneous ablation allows for multiple treatment sessions on a given tumor or patient with relatively low complication risk (Sonntag et al., 2011).

### 2.3 Thermal ablation techniques

Aspects of each ablation technique will be presented including mechanisms of action, equipment, clinical applications, along with the limitations of thermal ablation techniques.
2.3.1 Radiofrequency ablation

Radiofrequency (RF) ablation is an electrosurgical technique that uses a high-frequency alternating current (AC) to heat tumor tissues to the point of desiccation (thermal coagulation). RF waves are comprised of electromagnetic (EM) energy composed of oscillating electric and magnetic fields. They apply to coagulation induction from all EM energy sources with frequencies less than 30 MHz, although most currently available devices function in the 375-500 kHz range (Goldberg et al., 2009). RF ablation is currently the most commonly used with an increasing number of scientific articles reviewing the physical background, technical realization, and clinical aspects of this technique.

The goal of RF ablation is to achieve temperatures between 60°C and 100°C, where there is near instantaneous induction of protein coagulation with damage to cytosolic and mitochondrial enzymes and DNA-histone complexes leading to coagulative necrosis. Coagulative necrosis begins at around 50°C, and as a result of heat conduction, a necrotic ablation zone is created. Biophysically, RF energy deposition in the tissue is governed by various factors including RF current density, current intensity, surface area of the electrodes, tissue conductivity, and ablation time. The alternating current oscillates at the frequency of radio waves between the tips of the electrodes within a tumor. Under a certain voltage as the potential energy, electrons travel smoothly, without significant thermal effect, from one atom to the orbit of the next along that part of the circuit made up of metal conductors; the only poor conductors in this circuit are biological tissues with higher impedance. As the ions of the tissue attempt to follow the change in direction of the AC, ionic agitation occurs, resulting in frictional heat of the tissue, i.e., resistive or ohmic heating. Direct RF heating occurs within a few millimeters of the electrode, but a large portion of the final ablation zone is created when thermal conduction pushes heat into more peripheral areas around the electrode (Brace, 2009b).

Ablative heating leads to tissue dehydration and water vaporization. At the metal electrode-tissue interface tissue charring may occur during RF ablation which results in elevated circuit impedance and markedly reduced RF output, limiting the heat diffusion. In addition, RF ablation requires a closed circuit between the ablation probe and the grounding pad for the flow of electrical current; therefore, RF ablation is subject to the distortion of the ablation zone when this current follows the path of least resistance, as well as increased tissue impedance if the tissue is heated too rapidly or to >100°C because the tissue chars and/or the tissue water boils (Brace, 2009b). When these effects begin to inhibit current flow from a generator, alternative methods to decrease circuit impedance, such as expanding the electrode surface area and pulsing the input power can be used to augment RF current flow. Another strategy to overcome low tissue conductivity is by infusion of sodium chloride solutions into the targeted ablation zone. Sodium chloride is ionic and thus improves the electrical conductivity of the surrounding tissue. However, saline infusion can produce irregular and unpredictable ablations with potentially serious complications and thus is not routinely performed. RF ablation also appears susceptible to ‘heat sink’ whereby thermal energy is diverted from the target tissue by the flow of blood through adjacent vessels (Kim et al., 2005).
Numerous electrodes have been developed and tested. Some of the designed electrodes are commercially available, others are under preclinical investigation. Four different concepts have led to the development of five basic types of electrodes: monopolar (monopolar electrodes), bipolar (bipolar electrodes), enlargement of the electric field (multiple and expandable electrodes), internal cooling (cooled electrodes), and saline perfusion through the electrode into the tissue (wet electrodes). In monopolar systems, a single interstitial electrode (or group of electrodes) is used to deliver current at the tumor site, while surface electrodes (ground pads) complete the electrical circuit through the body. RF current flows back and forth between the electrode and the ground pad. In bipolar systems, current oscillates between two interstitial electrodes, which are usually placed in proximity, without the need for a ground pad. One recent discovery is bimodal electric tissue ablation (BETA) which combines the cathode of a DC circuit to the radiofrequency electrode to increase the size of tissue ablation (Tiong et al., 2011). The cathode will increase the hydration of the tissues around it which will delay tissue desiccation and roll off during an ablation. Therefore it allows the ablation process to continue for a longer period of time resulting in larger ablations. Cluster or array electrodes are devices in which three or more closely spaced (<2cm) electrodes are used simultaneously to approximate an electrode with a larger diameter (Mulier et al., in press). In contrast, electrodes with multiple tines emanating from a single electrode sheath or handle assembly aim to distribute energy spatially. Currently, these are referred to as umbrella electrodes, multitined electrodes, multiple hooked electrodes or arrays. The use of multiple tines improves heating efficiency in the target volume and also increases total electrode surface area, thereby reducing circuit impedance and promoting greater energy deposition. As a result, larger zones of ablation and potentially faster heating can be achieved (Ahmed et al., 2011). Internally cooled electrodes make use of a perfusate (such as saline or water) that flows in internal lumina that does not come into direct contact with patient tissues and temperatures at the electrode-tissue interface are reduced. Internally cooled electrodes reduce tissue charring near the electrode and permit greater energy delivery. Perfusion or wet electrodes have small apertures at the active tip that allow fluids (i.e. normal or hypertonic saline) to be infused or injected into the tissue before, during, or after the ablation procedure. A detailed description of these RF techniques can be found elsewhere (Ni et al., 2005; Habash et al., 2007; Goldberg et al., 2009). In several clinical studies, RF tissue ablation has been performed by using percutaneous and laparoscopic techniques. The percutaneous approach is the least invasive route for RF ablation. The probe placement can be guided by use of CT, MRI, or ultrasonography.

RF ablation remains the most widely accepted thermoablative technique worldwide, presumably because of its ability to create a well-controlled focal thermal injury and its superior relation between probe diameter and size of ablated tissue (Habash et al., 2007). Potential advantages of RF ablation include low complication rates, reduced morbidity and mortality rates compared to standard surgical resection, and the ability to treat nonsurgical patients. Clinical applications of RF ablation include treatment of breast tumors, liver tumors, lung tumors, renal tumors, and bone metastases.
2.3.2 Microwave ablation

Microwaves are a second thermal energy source that has been used for thermal ablation. It is a more recent development in the field of tumor ablation and therefore is less studied. Microwave (MW) ablation also uses radiofrequency (RF) energy, but it operates at a much higher frequency between 915 MHz and 9.2 GHz (Lloyd et al., 2011). In contrast to RF, in which the inserted electrode functions as the active source, in MW ablation the inserted probes function as antennae or waveguides which emit microwaves. The energy deposition for MW ablation is also completely different from that for RF ablation. MW ablation does not rely on a flow of electrical current as in RF ablation; rather, microwave energy is broadcast from the ablation antenna to create an electromagnetic (EM) field within the surrounding tissue. Water molecules within this field oscillate rapidly in accordance with the MW frequency, causing molecular friction and a rapid rise in thermal energy throughout the field (Brace, 2009a). Unlike RF ablation, the volume heating due to MW energy is dielectric, not resistive. It has a broader zone of active heating and as it does not rely on the conduction of electricity into the tissue, the transmission of energy is not limited by tissue charring (Livraghi et al., 2011b). MW ablation produces higher temperatures more quickly than is possible with RF ablation (Sonntag et al., 2011). All tissues in this zone are heated homogenously without being influenced by local tissue factors such as close proximity to blood vessels (i.e. heat sink effect) (Simon et al., 2005). Since MW power deposition inside tissues decays with distance more slowly as compared to the distance dependence of RF ablation, deeper lesions can be accessed (Habash et al., 2007). Consequently, MW power can be continually applied to produce extremely high (>150°C) temperatures, which improves ablation efficacy by increasing thermal conduction into the surrounding tissue (Yang et al., 2007). MW technology also allows for the simultaneous treatment of multiple tumors, in which RF ablation is technically limited (Lloyd et al., 2011). Microwaves readily penetrate through biologic materials, including those with low electrical conductivity, such as lung, bone, and dehydrated or charred and desiccated tissue while RF, laser and ultrasound energies can be substantially affected by different tissue types, especially as a result of thermal ablation (Yang et al., 2007; Brace, 2010). Microwaves do not require ground pads, and multiple antennas can be operated simultaneously (Brace, 2010). These properties distinguish MW from RF ablation and render MW ablation a more attractive option for hepatic ablation (Brace, 2009b, 2010). In addition, recent comparisons of RF and MW ablation have demonstrated improved performance with microwaves in lung and kidney, even when the total energy applied was equivalent (Wright et al., 2005; Brace et al., 2009; Laeseke et al., 2009).

The basic MW ablation systems contain many of the same components as an RF ablation system: a generator, a power distribution system, and an applicator antenna. Numerous antenna designs for MW ablation have been presented in the literature (Habash et al., 2007). These antennas are grouped into three categories, namely, monopolar antennas, dipole antennas, and helical coil antennas. The most general system design consists of an interstitial antenna (or array of antennas) receiving power from a MW generator through a distribution system. Antenna properties, such as efficiency and heating pattern, are primarily controlled by the surrounding tissue properties and antenna geometry. Due to a theoretical limit in the amount of power able to be distributed by a single antenna, antenna arrays are
also being investigated. The power is more efficiently distributed by using an array of antennas. Three antennas can be activated synergically to produce fast ablation of large tumors. Air and water-cooled antenna designs have existed for several years, with water-cooled MW ablation antennas recently described in widespread clinical use. Newer microwave ablation systems utilize both 915 MHz and 2.45 GHz, with most systems now employing dipole antennas. In several clinical studies, microwave tissue coagulation has been performed by using both percutaneous and laparoscopic techniques. Perhaps the most commonly cited drawback is the difficulty in treating large tumors, which are routinely defined as those exceeding 3 cm in diameter. Although the use of multiple sessions or multiple electrodes to achieve greater coagulation has been attempted, limitations with this practice center on the impracticality of multiple puncture wounds within a small area in the tumor (Habash et al., 2007). The technology is still in its infancy, and future developments and clinical implementation will help improve the care of patients with cancer (Simon et al., 2005). The most common anatomic sites for MW ablation are the liver, lung, kidney, and bone.

2.3.3 Ultrasound ablation

High-intensity focused ultrasound (HIFU) ablation or focused ultrasound surgery (FUS) is a third option that has been studied as a potential method for minimally invasive treatment of localized and malignant tumors. HIFU has many unique capabilities and qualities. While other minimally invasive therapies such as radiofrequency (RF) or microwave (MW) ablation use an electrode or antenna to deliver electromagnetic waves, HIFU therapy makes use of ultrasound (US) waves as carriers of energy, which is propagated through human tissues. Frequencies in the range of 600 kHz to 7 MHz are used depending on the application type and the penetration depth (Al-Bataineh et al., 2011). The intention of a HIFU treatment is to raise the temperature of a selected, isolated tissue volume above 55°C and to maintain this temperature for 1 s or longer. It is known that 55°C held for this time will lead to coagulative necrosis and immediate cell death (Haar and Coussios, 2007; Kim et al., 2010). In theory, this is possible with a focused ultrasound beam since the short (mm) wavelengths of ultrasound at megahertz frequencies in soft tissue allows it to be focused into small, clinically relevant, volumes. Focusing of the ultrasound energy minimizes the potential for thermal damage to intervening tissue between the transducer and the focal point because the intensities are substantially lower outside the focal region.

Two mechanisms of tissue damage are involved: thermal effect and cavitation. Thermal effects from HIFU result from heat generation at the focus due to absorption of acoustic energy in tissue. Ultrasound propagates as mechanical vibrations that cause molecules within the medium to oscillate around their rest positions in the direction of wave propagation. The molecules forming compressions and rarefactions propagate the wave. As the ultrasound energy passes through tissue it is attenuated exponentially (Tempany et al., 2011). Due to the high local concentration of acoustic energy in the focal spot, the tissue in a small volume is heated rapidly and a sharp circumscribed lesion caused by thermal coagulation will be induced. The temperature reached within the focal point during a single sonication should be between 60 and 95°C to induce tissue coagulation and necrosis (Al-Bataineh et al., 2011). If the temperature is elevated to 100°C then boiling occurs at the
focus and coagulative necrosis occurs immediately. However, if the temperature is not elevated to over 100°C then a phenomenon termed thermal fixation can occur where the cells do not undergo lysis and the tissue architecture remains relatively intact but the cells are no longer viable (Jang et al., 2010). Another mechanism of tissue damage is called acoustic cavitation. At high pressure amplitudes, small gas pockets in fluids can grow into microbubbles. The formation and interaction of these microbubbles with the ultrasound field in the sonicated tissue is referred to as acoustic cavitation. This interaction may lead to oscillation of these micro-bubbles, violent collapses and dispersion of energy enhancing tissue ablation (Crouzet et al., 2010a; Krasovitski et al., 2011). The end result of the two forces (thermal energy, acoustic cavitation or mechanical stress) is a precisely controlled zone of coagulative necrosis. However, microbubbles can cause more undefined and less predictable lesion growth. In addition to coagulative necrosis and acoustic cavitation of tumors, preliminary clinical studies have suggested that the immune response can be altered after HIFU treatment (Wu et al., 2007c; Jang et al., 2010). In addition to an enhanced systemic immune response, HIFU may lead to enhance local antitumor immunity as well. Some clinical studies have shown greater concentrations of dendritic cells (DC), macrophages, and B lymphocytes in the HIFU treatment group than control groups (Wu et al., 2007c; Deng et al., 2010). In addition, an acute inflammatory response has been observed at the margins of the treated tissue after HIFU. This leads to the rapid infiltration of a large numbers of leukocytes and antigen presenting cells including DCs (Xu et al., 2009) around the treated tumor.

Devices designed for HIFU use higher power ultrasound waves at lower frequencies, between 0.8 and 3.5 MHz (Brenin, 2011). The energy is typically delivered to a small cigar-shaped target volume measuring up to 3 x 15 mm. The treatment zone is precisely controlled, leaving the surrounding tissue unaffected. The clinical advantage of such a precise application is that the effect of undesired thermal spread can be limited, which is often the undesired effect of other thermoablative technologies. However, since an ablation zone caused by a single ultrasonic exposure is very small, mostly multiple row ablation zones are arrayed side by side, to cover the entire tumor and a small zone of surrounding tissue. This technique uses a parabolic transducer to focus the ultrasound energy at a distance that creates a focused beam of energy with very high peak intensity. The focused energy is transmitted transcutaneously into the target tissue without requiring percutaneous insertion of an electrode or transducer, making it the only truly non-invasive ablative technique. Preliminary reports suggest that there is reduced toxicity with HIFU ablation compared with other ablation techniques, such as cryoablation and either percutaneous or laparoscopic RF because of the non-invasive nature of the procedure (Dubinsky et al., 2008). A transducer with a piezoelectric crystal can be used as a source of ultrasound that vibrates at a fixed frequency when electrical energy is applied. The ultrasound source is brought as close as possible to the target in order to minimize the effects of attenuation and phase aberration along the ultrasound pathway (Lafon et al., 2007). HIFU devices for clinical use fall into three main categories: extracorporeal, transrectal, and interstitial. Extracorporeal transducers are used for targeting organs that are readily accessible through an acoustic window on the skin, whereas transrectal devices are used for the treatment of the prostate and interstitial probes are being developed for the treatment of biliary duct and esophageal tumors (Zhou, 2011). Interstitial US applicators have been proposed for treating deep-seated tumors that
cannot be reached with extra-corporeal HIFU. In addition, interstitial ultrasound offers several advantages compared to conventional ablation technology (radiofrequency, microwaves, cryotherapy) in terms of penetration, speed of coagulation, ability to direct and control the thermal lesion and compatibility with image monitoring. Several commercial HIFU devices are in clinical use. Most devices use US or MR for imaging guidance and are approved for clinical use in many parts of the world.

One disadvantage of HIFU when considering large tumors embedded in critical normal tissues, is the requirement of precisely placing and applying a large number of heating pulses can result in very long treatment times (Zhou, 2011). Therefore, an upper size limit for tumors that can be treated is approximately 3-4 cm in diameter (Dubinsky et al., 2008). Another potential limitation to the clinical application of HIFU is that it cannot be directed through air-filled viscera such as the lung or bowel, and other obstructions such as bone can absorb or reflect a US beam. Because of the large impedance mismatch between soft tissue and air and between soft tissue and bone, these interfaces cause almost complete reflection of the US energy. The efficacy and accuracy of such systems is decreased when trying to treat a tumor located behind a bone barrier such as skull bone in the treatment of brain tumors or ribs in the treatment of liver (Tanter et al., 2007). The anatomic locations where US can be applied are thus limited. However, recent technological advances are expected to resolve these problems (Kim et al., 2008).

During the past decade, HIFU has been used in a wide range of therapeutic applications such as breast cancer, prostatic cancer, uterine fibroids, lung tumors, renal tumors, and pancreatic cancers. Results of early trials have demonstrated the feasibility of HIFU ablation to provide therapy in situations not amenable to conventional surgery or as salvage therapy for recurrent disease. Presently, HIFU is being investigated in clinical trials for the treatment of other malignancies such as kidney tumors, liver tumors and gliomas. More recent horizons have broadened the application of HIFU in tumor treatment, such as HIFU-mediated drug delivery, vessel occlusion, and soft tissue erosion (histotripsy) (Zhou, 2011).

2.3.4. Laser ablation

Laser ablation is another method to induce thermally mediated coagulation necrosis that has been employed for tumor destruction. Laser ablation is a surgical procedure in which destruction of soft tissues in the body is effected through high temperatures generated by the local absorption of laser energy. Thus like radiofrequency (RF) and microwave (MW) energy, lasers induce electromagnetic heating to elevate tissue temperatures to cytotoxic levels. A laser which is a monochromatic, intense, phase-coherent, directional beam of light can deliver a highly focused dose of energy of specified duration of irradiation and power intensity. The term laser ablation is associated with several alternative acronyms in the literature, including laser-induced thermal therapy (LITT), interstitial laser coagulation, interstitial laser therapy, interstitial laser phototherapy, laser photocoagulation, and photothermal therapy (Stafford et al., 2010). The term interstitial laser ablation refers to the fact that the laser fiber is inserted into the tissue as opposed to ablating tissue with a laser while maintaining a buffer medium between the fiber emitting the energy and the tissue being ablated (e.g. air for cutaneous application, saline when applying laser energy in the
bladder/ureter) (Lindner et al., 2009). Photodynamic therapy that also makes use of laser energy is a non-thermal ablation technology that will be described elsewhere.

The basic principles behind laser ablation are the conversion of laser light into heat by tissue. The optical and thermal properties of the tissue as well as the parameters of the laser beam influence the extent of the thermal ablation. The optical and thermal properties of the tissue are determined by the structure, water content, and blood circulation. The key concepts are absorption, scattering, reflection, thermal conductivity, and heat capacity (Lindner et al., 2009). Laser ablation is generally performed at power and energy settings designed to achieve temperatures of 50°C to 100°C. Tissue temperature can easily reach 100°C or higher, depending on the delivery system and duration of the process. It uses the absorbed energy of infrared light to produce heat and ablate the tumor. Laser therapy for tumor ablation induces photothermal interactions in which light is absorbed, putting the molecules into a higher energy state. That energy is subsequently exchanged with the environment, increasing the overall kinetic energy within the tumor. The delivered photons induce an increase in temperature. Local tissue temperatures above 60°C cause rapid coagulative necrosis and instant cell death, but irreversible cell death can also be achieved at lower hyperthermic temperatures (>42°C), although longer durations are necessary (see review of Hyperthermia). Temperatures above 100°C will cause vaporization of cellular protoplasm, followed by desiccation and shrinkage of the tissue; afterward, any additional laser energy causes a quick temperature rise, and temperatures above 300°C cause the tissue to burn and carbonization occurs (Lindner et al., 2009).

For this procedure, flexible tin optic fibers are inserted into the target through percutaneously placed needles using imaging guidance. The laser provides sufficient energy to allow for significant heat deposition surrounding the fiber tip, inducing protein denaturation and cellular death. Multiple laser fibers can be placed into the treatment volume and, unlike other interstitial heating techniques, can be fired simultaneously to rapidly treat large volumes of tissue. Light does not penetrate blood or tissue easily so, like RF and MW, laser ablation requires catheter-tissue contact with the target. Laser light delivered into tissue is absorbed by tissue-specific chromospheres, and photon energy is transferred into heat to produce thermal injury. Laser units consist of a power source, a lasing medium, and reflecting mirrors. The laser most commonly used for laser ablation is the neodymium-doped yttrium aluminum garnet (Nd-YAG, $\lambda = 1064$ nm) laser operating in the range of 2 to 40 W but it is being replaced by more compact and less expensive infrared diode lasers. Modern systems utilize small, compact, high-power laser diode systems ($\lambda =$ 800-980 nm) with actively cooled applicators to help keep tissue from charring during procedures (Stafford et al. 2010). The laser light is transmitted into the patient at the tip of the fiber optic. The interstitial quartz fibers have flat or cylindrical diffusing tips of 10 to 40 mm long providing an ablative area of up to 50mm. Most systems utilize a double-lumen design to circulate cooling fluid (often room-temperature water) around the fiber during therapy to keep from carbonizing the fiber and nearby tissue. During laser application time (~3 min), ellipsoid volumes of tissue coagulation are created, which surround the axis of the fiber. The affected tissue corresponds to the length of the energy-diffusing fiber tip. Single applicators operating at 980 nm are capable of generating lesions of up to 2cm depending on the combination of power, exposure time, and tissue irradiated. To generate larger diameter lesions, or to conformally deliver the energy to an irregular volume, multiple
applicators can be placed and fired in tandem or simultaneously. Image guidance in the form of real-time ultrasound, computed tomography (CT), fluoroscopy, or MRI is used to guide either an applicator or, more likely, a coaxial guide needle through tissue and into a lesion.

Laser light is an efficient and precise energy source for tissue heating. However, because light is scattered and absorbed rapidly by most body tissues, lasers have limited energy penetration and create smaller ablation zones (1-2 cm diameter) than other devices currently in use. The major limitation of laser therapy is the small volume of tumor ablation and the inability to achieve large volumes of necrosis with a single fiber application, although the current new devices may help ease this limitation.

Lasers can be found in most clinical centers, but they are rarely used for thermal tumor ablation. Lasers are most commonly used to treat superficial cancers (cancers on the surface of the body or the lining of internal organs) such as basal cell skin cancer and the very early stages of some cancers, such as cervical, penile, vaginal, vulvar, and non-small cell lung cancer. Lasers may also be used to relieve certain symptoms of cancer, such as bleeding or obstruction or in the prevention and treatment of oral mucositis (Bjordal et al., 2011). In addition, lasers can be used to shrink or destroy a tumor that is blocking a patient’s trachea or esophagus or can be used to remove colon polyps or tumors that are blocking the colon or stomach. Lasers can seal nerve endings to reduce pain after surgery and seal lymph vessels to reduce swelling and limit the spread of tumor cells. In clinical trials, laser ablation is used to treat cancers of the brain, liver, prostate, and breast among others.

2.3.5 Cryoablation

Cryoablation, also called cryotherapy, cryosurgery, or cryosurgical ablation, is a minimally invasive treatment that uses extreme cold to freeze and destroy tumors. During cryoablation, liquid nitrogen or argon gas flows through a needle-like applicator (a cryoprobe) creating intense cold that is placed in contact to diseased tissue. The lethal temperature is between -20°C and -40°C. To avoid uncertain cell death with temperatures between 0 to -20°C, repeated freeze-thaw-freeze cycles are needed. The cell damage is of two types, namely, acute, which is immediate during cryosurgery, and long term (Habash et al., 2007). As the temperature decreases, tissues are damaged by failed metabolism, extracellular crystallization causing cell dehydration, and finally and most severely by intracellular ice crystal formation disrupting organelles and cell membranes (Sonntag et al., 2011). The cooling media are alternatively delivered to achieve extra- and intra-cellular ice-crystal formation and tissue osmosis. Ice crystals are formed mainly extracellular during the first freezing phase. Extracellular ice formation increases the osmolarity in the extracellular space, leading to a shift of fluid from the intracellular to extracellular compartment. In this hypertonic environment, cells are damaged due to changes in pH, intracellular solute composition, and protein denaturation. During thawing phase, water diffuses into the intracellular compartment due to osmotic gradients, and the second freezing phase achieves intracellular ice crystals, leading to membrane rupture and cell death. Additionally, post-freezing damage occurs during thawing as ice crystals coalesce into larger crystals that disrupt cell membranes. Finally, these changes result in vascular thrombosis and stasis in the
post-freezing period. Cell death may continue as a result of delayed tissue necrosis from thermal injury to local microvasculature.

Two major parameters are correlated with the likelihood of cell destruction, namely, the cooling rate during freezing and the lowest temperature achieved. The cells near the cryoprobe surface are cooled with a higher cooling rate and to lower temperatures than those farther away from the probe. The edge of the ice-ball represents the 0°C isotherm. Cell death occurs around -40°C and this isotherm lies approximately 5 mm inside the ice-ball. In treating cancer, it is recommended that freezing extend beyond the margin of the tumor in such a way that the highest temperature that the frozen tumor will experience is the limit set for treatment. The time scales relevant to cryoablation range from a few minutes to tens of minutes. Various methods have been developed to increase the size of cryoablation (up to 10 cm diameter) in an attempt to treat large tumors.

While early cryoablation systems were bulky and limited to open surgical use, modern systems use more advanced cooling techniques that allow laparoscopic and percutaneous approaches. The general setup of cryosurgical devices use a segmental insulated probe through which the cryogen is delivered, causing rapid expansion of the cryogenic gas, with rapid cooling to temperatures approaching -100°C in a few seconds. The common cryogens used for ablation are liquid nitrogen and argon. Different types of cryoprobes are available, resulting in different volumes and shapes of the ice ball. Cryoablation probes (~10 mm diameter) are inserted into the organ under scanning guidance of ultrasound, computed tomography (CT) or magnetic resonance (MR). Important factors influencing freezing injury are the rate of temperature reduction after the initiation of freezing, the time cells remain frozen, and the subsequent heating rate during thawing (Habash et al., 2007). The process usually includes two or three freeze-thaw cycles, each freeze cycle lasting 7-30 min. The simultaneous insertion of multiple probes into the target lesion can effectively increase the ablation area.

Cryospray ablation (CSA) is another developed noncontact method of eradicating precancerous and cancerous tissue by using low-pressure liquid nitrogen spray (Johnston, 2003). The advantages of using a liquid nitrogen spray cryocatheter system through an upper endoscope include the ability to control the cryogen without direct contact with tissue, which is ideal for the natural curvature of the esophageal lumen and uneven surfaces of nodular neoplastic epithelium (Dumot et al. (2009).

Cryoablation possesses several properties that make it an attractive option as a thermal ablation technique. The first advantage is visualization of the ablation zone. Radiologic–pathologic studies have shown that the ice ball visualized on CT scans correlates well with the pathologic zone of ablation. Second, cryoablation preserves the collagenous architecture of the tissue being ablated. Third, for curative cryoablation, the margins of the ice ball should extend 3 to 5 mm beyond the tumor margins. In addition, cryoablation has intrinsic anesthetic properties that allow performing the procedure under mild sedation, or even local anesthetic. Cryoablation appears to be the most appropriate thermal approach for treating larger-volume liver tumors (> 3 cm), with long-term follow-up data showing some survival benefit (Habash et al., 2007). Cryoablation efficacy, however, may be compromised by tissue thawing form nearby high-flow vascular structures resulting in the cool sink effect.
Cryoablation is used to treat some kinds of cancer and some precancerous or noncancerous conditions, and can be used both inside the body and on the skin. Cryoablation is being used to treat tumors such as in the kidneys, lung, prostate and palliative treatment of osseous metastases. Topical cryoablation is used typically in the case of skin cancer. Cryoablation may also be an effective treatment for retinoblastoma (a childhood cancer that affects the retina of the eye) and precancerous conditions of the cervix known as cervical intraepithelial neoplasia (abnormal cell changes in the cervix that can develop into cervical cancer).

2.4 Treatment monitoring

Treatment monitoring is defined as the process with which therapy effects are viewed during a procedure. Treatment monitoring includes the assessment of both efficacy and safety (i.e. whether any adjacent normal structures are adversely affected) (Rivens et al., 2007). There are two aspects to treatment efficacy. The first is to know, preferably in real-time, the extent of damage after each thermal energy exposure in order to proceed or plan the next. The second is to know the extent of damage at the end of all the exposures to ensure complete treatment.

2.4.1 Thermometry

Generally, there are two basic methods for checking the technical success of ablative therapies. One option is contrast-enhanced imaging (Computed tomography (CT) or magnetic resonance imaging (MRI)), during or after completion of thermal ablation (see 2.4.2). The other is synchronous temperature monitoring in the target area. The ability to measure temperature rise within the patient is important for all thermal ablation therapies. Thermometry can be used to localize the ablation source relative to the treatment volume, avoid damage to surrounding tissues and predict the extent of damage. Temperature monitoring consists of different techniques that can be applied to measure directly (use of thermocouples or fiberoptic thermosensors) or indirectly (MRI thermometry) the temperature range near the structure at risk. The thermocouple (when using CT or US guidance) or the fiberoptic thermosensor (when using MRI guidance) is advanced with the tip positioned in contact with the structure at risk. The most common invasive technique is the use of small wire thermocouples. These temperature-monitoring techniques can be used alone or in combination with the different thermal insulation techniques if necessary to reduce unintended thermal injury to the non-target structures. However, due to the variations in the heat transfer properties of the tissues, temperature elevation cannot be accurately predicted in vivo. Most notably, blood flow and perfusion are highly variable from location to location and from tissue to tissue. In addition, tissue close to large blood vessels will be cooled by the flow if the energy delivery is long or slow (Tempany et al., 2011). The ability to use MR techniques to perform real-time thermometry makes MR the most reliable and comprehensive modality available for real-time (noninvasive) temperature monitoring (Tempany et al., 2011). This technique makes use of the phenomenon of temperature sensitivity of the water proton resonance frequency (PRF) shift. MR thermometry can provide temperature information that indicates the thermal dose delivered to a tumor (Rivens et al., 2007). MR can quantify changes in temperature and thermal dose (calculated value of equivalent time at a reference temperature of 43°C) of the treated tissue directly.
MR thermometry, however, is vulnerable to the accumulation of errors associated with thermal damage modeling, tissue displacement, temperature accuracy, tissue property variations and other transient changes during the thermal ablation process (Xu et al., 2010). Non-invasive temperature monitoring has been established in the thermal treatment of specific soft tissue organs such as the brain (Hynynen and Clement, 2007), liver (Holbrook et al., 2010; Grissom et al., 2011), and prostate (Rieke et al., 2007).

### 2.4.2 Image guidance

The ability to visualize the tumor, navigate and position the ablation tool, and monitor the ablation process is crucial to perform a thermal ablation therapy and minimize morbidity. Monitoring not only provides the operating clinician with information relating to the effectiveness of treatment, but can also provide an early alert to the onset of adverse effects in normal tissue. Ideally, all three-dimensional measurements of the ablation zone and tumor should be provided (Goldberg et al., 2009). Clinical imaging systems that have been explored for tumor ablation applications include ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and more recently positron emission tomography (PET). These imaging techniques are also used to help determine whether patients are suitable candidates for thermal ablation. Imaging aspects that are particularly important include tumor size and shape, number, and location within the organ relative to blood vessels, as well as critical structures that might be at risk for injury during an ablative procedure. Modalities such as combined PET and CT and three-dimensional reconstructions of cross-sectional imaging data may be used more often in the planning of image-guided tumor ablations in the future. Many centers perform an examination by imaging on the day of the initial procedure and thereafter every 3-4 months to determine technique effectiveness. Imaging intervals may vary depending on the type of underlying tumor and the goals of treatment. Post-procedural imaging findings, however, are only a rough guide to the success of ablation therapy, since microscopic foci of residual disease, by definition, cannot be expected to be identified (Goldberg et al., 2009).

The imaging systems are not fully optimized for real-time imaging owing to various related factors, such as low sensitivity to tissue thermal damage, motion artifacts, high susceptibility to ablation-induced tissue gas bubbles, potential for concomitant radiation exposure and cost and complexity of such imaging systems (Jang et al., 2010; Xu et al., 2010). One major challenge is the lack of imaging tools for quantitative assessment of the tumor boundaries and of the margins of the ablation zone. Recent advances in MRI would allow real-time thermal dose monitoring as well as anatomical imaging during treatment (Haar and Coussios, 2007; Lindner et al., 2010b; Ahrar and Stafford, 2011). It also provides contrast-enhanced images for evaluating treatment effectiveness after the treatment. Although MRI has shown to be more accurate than mammography or US in size assessment, it currently cannot exclude small amounts of residual invasive cancer (Zhou, 2011). MRI, however, is extremely sensitive to ferrous materials and electromagnetic disturbances. Although HIFU, radiofrequency ablation, and cryoablation have been used with MRI, laser ablation is uniquely suited for MR because the fibers used are made of quartz and do not cause any disturbance in the bore of the magnet (Stafford et al., 2010; Ahmed et al., 2011). Furthermore, the energy being used is non-electromagnetic whereas the other modalities
have to undergo specific modifications to be MR compatible (Lindner et al., 2010b). MRI-guided focused ultrasound surgery (MRgFUS) is a relatively recent approach to thermal ablation therapy, which integrates imaging feedback control. The advantage of cryoablation is its ability to be visualized with US, CT or MRI because of ice ball formation.

2.5 Mechanisms of synergies

2.5.1 Combination therapy for thermal ablation

At present, thermal ablation only takes advantage of temperatures (i.e. >55°C) that are sufficient by themselves to induce coagulation necrosis. However, when incomplete treatment or recurrence by heat-based techniques is expected, thermal ablation may be combined with other therapies. The rationale for this approach is to increase tumor destruction occurring within the sizable peripheral zone of sub-lethal, temperatures surrounding the heat-induced coagulation (Ahmed and Goldberg, 2004). Improved tumor cytotoxicity is also likely to reduce the local recurrence rate at the treatment site (Ahmed and Goldberg, 2011). The ability to achieve complete and uniform eradication of all malignant cells remains a key barrier to clinical success, and therefore, strategies that can increase the completeness of tumor destruction with thermal ablation, even for small lesions, are needed. Adjuvant therapies that have been proposed are those such as radiotherapy, chemotherapy, or chemoembolization. However, large-scale randomized clinical trials are needed to determine the future role of these treatments.

2.5.1.1 Thermal ablation with radiotherapy

Several studies have reported early investigation into combination thermal ablation and radiation therapy. According to Dupuy et al. (2006), RF ablation is most effective in the center of relatively avascular tumors, while external beam radiation and stereotactic radiosurgery are most effective at the periphery of the tumor where there is high oxygen content and a hyperthermic rim around the ablation zone. Combining the two therapies has been shown to increase survival, at no additional toxicity, as compared with radiation therapy alone (Dupuy et al., 2006). Dupuy et al. reported their experience with combined CT-guided RF ablation and conventional radiotherapy in 24 inoperable patients (stage I NSCLC) with a minimum of 2-year study follow-up in surviving patients. Combinations of radiotherapy and RF ablation have also been used to good effect in primary lung cancer in operable patients (Simon et al. 2007). Oura et al. (2007) performed RF ablation, followed by breast radiation therapy in 52 patients, and reported no breast recurrence with a mean follow-up of 15 months. RF ablation and cryoablation have been advocated in the symptomatic palliation of bone metastases following radiotherapy (Gillams, 2009). More recently, Ahmed et al. (2011a) reported on the use of HIFU after external beam radiation therapy for localized prostate cancer recurrence. The potential synergistic effects of combining thermal ablation with ionizing radiation have yet to be further explored.
2.5.1.2 Thermal ablation with chemotherapy

There has been some interest in combining thermal ablation with chemotherapy. Combining thermal ablation with chemotherapy (free or contained within liposomes; administered through direct injection, intravenously, or intra-vascularly or intra-arterially) would increase the overall volume of tumor necrosis and intratumoral drug accumulation (Ahmed and Goldberg, 2004). Several investigators have combined thermal ablation with adjuvant chemotherapy, mostly using RF and doxorubicin or paclitaxel agents (Ahmed and Goldberg, 2004; Kang et al., 2009; Head et al., 2010). However, as initial image-guided direct intratumoral injection strategies have encountered many difficulties in clinical practice such as non-uniform drug diffusion and limited operator control on drug distribution, subsequent studies have combined RF ablation with drug agents encapsulated within a liposome (e.g. Ahmed et al., 2005; Yang et al., 2010; Poon and Borys, 2011). Liposomes have a long history of delivering both therapeutic and diagnostic agents resulting in a number of liposomal agents being used in the clinic. Water-soluble drugs can be trapped in the inner aqueous compartment, whereas lipophilic compounds may be incorporated into the liposomal lipid membrane. Incorporation into liposomes protects the drug from the destructive environment in vivo.

Molecular adjuvant administration may improve local control and spare healthy adjacent tissue by increasing the susceptibility of the tumor to thermal injury. In a recent study, Yang et al. (2010) characterized the effects of combining RF ablation with proapoptotic intravenous liposome-encapsulated paclitaxel and doxorubicin on tumor destruction, apoptosis and heat-shock protein (HSP) production, intratumoral drug accumulation, and end-point survival. Combination RF-paclitaxel increased tumor coagulation and animal survival compared with RF alone, with greater gains observed for RF-paclitaxel-doxorubicin. Chen et al. (2010) evaluated the long-term follow-up results of US-guided HIFU ablation in 80 patients with primary bone malignancy. Among the patients with stage IIb disease, long-term survival rates were substantially improved in the 30 patients who received HIFU and chemotherapy compared with the survival rates for the 24 patients who did not finish the chemotherapy and the remaining patients who underwent partial ablation only. Poon and Borys (2011) performed a phase I trial with lyso-thermosensitive liposomal doxorubicin (LTLD), which was infused intravenously prior to RF ablation in patients with hepatocellular carcinoma. The RF ablation plus LTLD combination showed a dose-response effect for time to treatment failure in which most subjects had tumors >3 cm. RF ablation plus LTLD is currently being evaluated in a 600-patient randomized, double-blind, dummy-controlled trial. Other molecular adjuvants to enhance cellular killing and local control have been proposed. Recently, sorafenib (an antiangiogenic drug) was used to reduce tumor size in a single functioning kidney facilitating RF ablation (Grenier et al., 2009). Several studies combining RF ablation with anti-heat shock protein agents such as quercetin have increased tumor coagulation and animal endpoint survival in small animal tumor models (Yang et al., 2010, 2011a). A recent clinical safety and efficacy study was undertaken to examine concurrent gemcitabine and HIFU therapy in patients with locally advanced pancreatic cancer (Zhao et al., 2010). These are examples of studies that have analyzed the synergistic effects of thermal ablation with chemotherapeutic agents such as liposomal doxorubicin, yet the precise mechanisms for increased efficacy have thus far lacked adequate
characterization (Solazzo et al., 2010). Most experimental work has been *in vitro*, and more *in vivo* evidence is needed to address the issues of exact mechanism of injury, dose, timing, and drug selection.

### 2.5.1.3 Thermal ablation with chemoembolization

In pilot studies of liver tumors, thermal ablation has been combined with transcatheter arterial chemoembolization (TACE) which is based on the therapeutic principle of regional chemotherapy and partial obstruction of the blood supply. This is of benefit because the cooling effect of blood flow is one of the main limiting factors for thermal ablation. Hence, transarterial occlusion of the blood supply before heat ablation by percutaneous or laparoscopic approach may significantly increase the size of the ablation area (Wang et al., 2009). TACE as an adjuvant therapy after radiofrequency ablation (Wang et al., 2009) or after microwave ablation (Liu et al., 2011) has been studied. Also US-guided HIFU has shown the advantage of combining it with TACE. For example, Wu et al. (2005) showed that in a prospective study of 50 patients, an increase in median survival time occurred for patients with stage IVA hepatocellular carcinoma who underwent US-guided HIFU. The patients in the HIFU/TACE group survived a median time of 11.3 months versus 4.0 months for those in the TACE only group. Zangos et al. (2007) and Vogl et al. (2011b) have reported treatment of large-sized HCC with repeated TACE before MR-guided laser-induced thermotherapy.

### 2.5.2 Nanoparticle-mediated thermal ablation therapy

Currently available thermal ablation techniques cannot always precisely distinguish normal from diseased tissue. Also achieving complete ablation in many cases can be challenging particularly at margins of tumors >3 cm in diameter and adjacent to blood vessels. To overcome these limitations researchers are evaluating strategies that incorporate nanoparticles as exogenous energy absorbers to provide specific delivery of heat selectively to tumors, sparing normal surrounding tissue (Day et al., 2009). The combination of thermal ablation with adjuvant nanoparticle-based chemotherapy agents may improve efficiency (Ahmed et al., 2011).

Nanotechnology-based cancer therapy is a special form of interstitial thermotherapy with the advantage of selective heat deposition to the tumor cells. This new therapy is one of the first applications of nanotechnology in medicine. Depending on the duration of treatment and the achieved intratumoral temperatures, the tumor cells are either directly destroyed (thermal ablation) or sensitized for concomitant chemo or radiotherapy. The nanoparticles would remain in place at the treatment area, allowing for repeated treatments and the integration of multimodal therapy concepts. Recent advances in nanotechnology have resulted in the manufacture of a plethora of nanoparticles of different sizes, shapes, core physicochemical properties and surface modifications that are being investigated for the treatment of cancer. Examples are the therapeutic use of customized gold nanoparticles, magnetic nanoparticles, silica-gold nanoshells, nanorods and carbon nanotubes that efficiently generate heat upon electromagnetic (radiofrequency or magnetic fields, near infrared light) stimulation after direct injection into tumors or accumulation in tumors following systemic administration. By labeling these nanoparticles with antibodies against
cancer cells, higher concentrations of nanoparticles in cancer cells can be achieved. Generally, the use of targeting molecules such as antibodies, cytostatic drugs, and folates have been specifically proposed for carrying nanomaterials to the cancer cells and tumors. However, 100% selective internalization of nanobioconjugates in the cancer cells remains problematic as there is a significant lack of knowledge on how to obtain selectivity of these compounds for a single type of cancer cell. Also the exact physical basis of heat generation by nanoparticles is not entirely clear and is an area of active investigation (Raoof and Curley, 2011). Once these particles are internalized, EM fields applied to cells results in localized heat and killing of cancer cells.

Nanoparticle-mediated thermal therapies have indicated promise in animal studies and early clinical testing is currently underway. Encouraging results have been achieved in in vivo with a variety of nanoparticles, including iron oxide nanoparticles (Jordan et al., 2006; Maier-Hauff et al., 2011), gold nanorods (Dickerson et al., 2008), carbon nanotubes (Moon et al., 2009), and silica-gold nanoshells (Gobin et al., 2007). However, the incorporation of ablation techniques as adjuvants to improve effects of primary nanoparticle-based chemotherapies remains to be experimental. Nanoparticle-mediated thermal therapies are being studied worldwide by using near-infrared light, a radiofrequency field, or an alternating magnetic field as a source of delivering energy which will be described hereafter.

2.5.2.1 Near-infrared photothermal ablation

The basic principle behind photothermal ablation is to use heat generated from near-infrared (NIR) laser light. The photothermal interaction result from light energy conversion to heat within the tumor in a selective and targeted manner, potentially providing the sustained elevated temperatures required for thermal ablation. In general, photothermal ablation can operate in three basic modes; light without sensitizers, light with molecular sensitizers for photothermal conversion, and light with nanostructures for photothermal conversion. The latter approach is the most effective in terms of heat generation (Rozanova and Zhang, 2009). Photodynamic therapy (PDT) (i.e. photoactivation of specific chemical agents to produce single state oxygen or radicals that are cytotoxic for surrounding cells) will be discussed elsewhere as this has a photochemical not a photothermal effect on cancer cells.

Due to the diverse surface chemistry and thermal properties, nanomaterials can act as strong optical absorbers. For instance, nanoshells consist of a spherical dielectric core nanoparticle encapsulated by an ultrathin metal shell. The ratio of core radius to shell thickness dictates the scattering and absorbing properties of the particle. Nanoshells have been shown to passively accumulate in tumors after intravenous injection (James et al., 2007) as a result of the leaky vasculature characteristic of neoplastic tumors (Hashizume et al., 2000). Using strategies such as antibody-antigen or ligand-receptor interaction, one could actively target and deliver the metal nanostructures to specific cancer tissues. Several different nanostructures have been utilized for photothermal ablation, including nanoparticles, nanorods, nanoshells, nanocages, and hollow nanospheres. After systemic injection and accumulation at the tumor site, NIR light is applied over the tumor region. The absorbed energy causes the nanoparticle to heat, allowing local destruction of the tumor.
tissue. The tumors receiving the therapy, experience rapid temperature rises sufficient to cause irreversible tissue damage (temperatures of 50°C have been achieved within 30 s from the start of laser irradiation). Unlike RF fields, however, NIR is not transmitted more than a few centimeters through the body tissues, and as such, NIR therapy is limited to the treatment of subcutaneous or superficial tumors. NIR absorbing gold nanoshells have been extensively investigated for NIR photothermal therapy (Stern et al., 2008; Melancon et al., 2011), with phase I human clinical trials ongoing. Some of the other materials that have been recently investigated include gold nanoclusters (Zharov et al., 2005), gold nanorods (Robinson et al., 2010), and gold nanocages (Au et al., 2010). The research mechanisms of selective tumor targeting with biofunctionalized carbon nanotubes are currently being explored due to their ability to convert NIR laser radiation into heat as well (Iancu and Mocan, 2011).

2.5.2.2 Nanoparticle-based radiofrequency ablation

Another type of nanoparticle-based thermal therapy relies on the administration of radiofrequency (RF) irradiation. It has been shown that the presence of gold nanoparticles within a tumor significantly increases the temperature experienced by the tumor upon exposure to RF energy (Day et al., 2009). The extent of increase in temperature is dependent on the power of the RF field. RF ablation has shown promise in creating thermal lesions within liver tumors, and the addition of absorptive mediators, such as gold nanoparticles (Cardinal et al., 2008) or carbon nanotubes (Gannon et al., 2007), has been found to enhance this effect. Glazer et al. (2010) have previously reported on the use of non-invasive RF fields to induce thermal cytotoxicity in cancer cells exposed to targeted solid gold nanoparticles. The surfaces of these nanoparticles are conjugated with specific antibodies that would be recognized by the cell-surface receptors of cancer cells. Cancer cells would endocytose these nanoparticles with subsequent intracellular heat release during shortwave RF field treatment sufficient to produce cellular cytotoxicity. Initial studies have validated the efficacy, consistency and safety in in vitro research.

2.5.2.3 Magnetic fluid hyperthermia

A similar technique based on nanoparticles for local treatment of solid tumors has been developed. The principle of the therapy is the use of magnetic nanoparticles, which are delivered to a tumor either intravenously or through direct injection. The patient is then placed in a magnetic field applicator, a machine that produces an alternating magnetic field. Through this high frequency magnetic field, the nanoparticles begin to oscillate and warmth is produced from directly within the tumor tissue. As the particle moment returns to its equilibrium position, the magnetic energy dissipates as thermal energy. The method is also known as magnetic fluid hyperthermia (MFH) or nanohyperthermia. Although MFH generally refers to temperatures between 41-45°C to sensitize the tumor cells for the accompanying chemotherapy or radiation (see text on Hyperthermia), in some applications higher temperatures are reached leading to tumor ablation. Maximum temperatures of up to 55°C were achieved in prostate cancer (Johannsen et al., 2010). Iron oxide nanoparticles are most commonly used owing to their established biocompatibility and the availability of methods for chemical modification. To encourage tumor targeting and even tissue distribution of iron
oxide nanoparticles, various schemes have been employed, such as coating the surface with antibodies. The nanoparticles remain in place at the treatment area, allowing for repeated treatments and the integration of multimodal therapy concepts. Another mechanism that has been developed to increase tumor uptake of iron oxide particles is to encapsulate them inside liposomes, which may also be conjugated to antibodies for further targeting enhancement. Some of the limitations of MFH are the difficulty of temperature monitoring and quantification of the magnetic fluid distribution inside the tissue. Recently, the first phase I clinical studies regarding MFH have been terminated for glioblastoma (Maier-Hauff et al., 2007; 2011) and prostate carcinoma (Krishnan et al., 2010; Johannsen et al., 2010) in which longer survivals than expected have been observed.

3. Does it work?

3.1 Introduction

This section reviews examples of recent outcomes of thermal ablation for different types of cancer. Benign tumors, such as uterine fibroids or thyroid nodules, are also treated with thermal ablation techniques, however, are not the focus of this review. The purpose is to summarize and evaluate the clinical safety, feasibility and efficacy of thermal ablation for each anatomical tumor location. Evidence for its efficacy comes from published research studies and clinical trials. The main focus is on phase II and III randomized controlled clinical trials, if available. Over two hundred clinical trials are registered in the ClinicalTrials.gov (access December 2011, conditions: the different cancer types; interventions: the different modalities of thermal ablation). An electronic search of the Medline, Embase, Cochrane Library, CancerLit, and ClinicalTrials.gov databases was undertaken between November 2011 and January 2012. Articles selected were published in English between January 2005 and January 2012. Two sets of keywords were used for the search strategy. One was for the ablative interventions, including radiofrequency, microwave, high-intensity focused ultrasound, laser, and cryoablation. The other set was for each cancer type per anatomical location. In vitro and animal studies, as well as case reports and abstracts have been omitted, including studies published before 2005, however, review studies generally go further back in time. Case reports have been omitted mainly because they are based on an individual patients profile, hence results cannot be generalized. Nevertheless RCT acknowledges their scientific value however limited. Thus these selection criteria would benefit the rationale for rating the efficacy of thermal ablation based on what is available in clinical practice today.

3.2 Evidence-based results for using thermal ablation per anatomical location

3.2.1 Bone cancer and soft tissue sarcoma

Thermoablation techniques are now preferred for the management of musculoskeletal tumors as they produce more controllable ablation (Gangi and Buy, 2010). Within the musculoskeletal system, tumor ablation has become a common treatment for osteomas (small benign tumors that are often painful and usually occur in the extremities of children and young adults) and to relieve symptoms from painful bone metastases. Gangi et al.
(2007) proposed that all osteoid osteomas be treated with radiofrequency (RF) or laser ablation, rather than with surgical or percutaneous resection. They believed surgical resection should be performed only in rare cases of percutaneously inaccessible osteoid osteoma. Treatment by RF ablation may be curative, but is more likely to form part of a palliative treatment regimen (Gillams, 2009; Gangi and Buy, 2010). However, the low conductivity and poor thermal conduction in bone are limiting factors for RF ablation (Brace, 2009b; 2010). Nevertheless, many clinics perform RF ablation to treat osteoid osteomas and palliation of painful bone metastases. Larger studies with a longer follow-up are needed to further delineate the safety and efficacy of these ablation techniques.

**Radiofrequency ablation**

Thermal ablation of musculoskeletal tumors by using percutaneously placed RF electrodes has been described in several early studies. Jones et al. (2010) evaluated the efficacy and safety of RF ablation in a series of sarcoma patients (13 gastrointestinal stromal tumor (GIST) and 12 with other histological subtypes). They found that RF ablation was effective and well tolerated in this series of patients. Thacker et al. (2011) retrospectively reviewed patients who underwent either percutaneous RF ablation or cryoablation (see further) for painful metastatic tumors involving bone. Fifty-eight patients underwent either RF ablation (n=22) or cryoablation (n=36) for painful metastatic tumors involving bone. Analgesic use in the 24 hours immediately after the procedure decreased significantly for both ablation modalities. Spinal tumors may be treated by using RF ablation as well even when they are abutting the spinal canal (Dasenbrock et al., 2011). The percutaneous procedure consists of using a plasma-mediated RF-based device to etch a cavity within the affected vertebral body and filling the cavity and adjacent interstices with bone cement. The technique is called plasma mediated RF ablation and may cause a decreased risk of thermal injury to neural structures compared with traditional (RF or interstitial laser) ablation. The three patients studied experienced a decrease in back pain and no tumor recurrence during the mean follow-up of 20.7 months. RF ablation is recommended by the ESMO and NCCN guidelines as an option for managing metastasis of soft-tissue sarcomas.

**Microwave ablation**

Only a few reports of microwave ablation for osteoid osteomas exist (Simon et al., 2005). Larger series in the treatment of bone tumors and metastatic disease have been reported, with encouraging results (e.g. Carrafiello et al., 2009). However, no recent data about its use in musculoskeletal tumors is available.

**Ultrasound ablation**

Initially high intensity focused ultrasound (HIFU) was not considered as a suitable modality for bone cancer because of the great difference of acoustic impedance of bone from that of the surrounding soft tissue (ultrasound beams are strongly reflected and attenuated by bone). However, because of the high acoustic absorption and low thermal conductivity of bone cortex, it is possible to use a relatively low level of ultrasound (US) energy and still achieve a localized heating effect without damaging adjacent tissue (Chen et al., 2010). HIFU
has been used in clinical practice for treatment of primary bone tumors and palliation of pain from bone metastases.

Different HIFU studies have been conducted for treatment of primary bone malignancies such as those from Chen et al. (2010) and Li et al. (2009; 2010). Radiological evaluations of treated primary lesions revealed complete tumor ablation in 86% (Chen et al., 2010) and 46.2% (Li et al., 2010) for treated patients while metastatic bone tumors showed 41.7% complete tumor ablation among treated patients (Li et al., 2010). With different patient numbers, the reported 5-year overall survival rates for primary bone tumors were 50.5% (Chen et al., 2010) and 38.5% (Li et al., 2010). The survival rates for patients with primary bone tumors were significantly better than for those with metastatic tumors. The reported 5-year survival rate for metastatic bone tumors was 0%. Chen et al. on the other hand, studied the effect of HIFU treatment on the primary tumor staging and found that the 5-year disease free survival rates increased by 47.9% for treated IIb staged bone cancers compared to stage III cancers among all treated patients. HIFU safely and non-invasively ablated malignant bone tumors and relieved pain. However, in both studies, most patients received chemotherapy before and after HIFU therapy. After HIFU treatment, all patients experienced a significant relief of pain (Li et al., 2010). Results of these studies indicate that therapeutic US-guided HIFU ablation of malignant bone tumors is effective and thus may contribute to the existing chemotherapy and limb-salvaging surgical regimens.

Different HIFU studies have also been conducted for palliation of pain from bone metastases. The pain palliation is thought to be due to focused US denervation of the nerves in the periosteal layer of bone (Tempany et al., 2011). The reported pain associated with the bone lesion decreased by 92% (Gianfelice et al., 2008) and 69.5% (Liberman et al., 2009) after three months of HIFU treatment compared to original pain scores before treatment. Consequently, all patients diminished their intake of analgesics; 64% of treated patients no longer needed any pain medication for their treated bone metastasis, and the remaining patients decreased their dosage of pain medication by 50% or greater (Gianfelici et al., 2008). Also Lieberman et al. (2009) reported a 67% reduction in the use of opioid pain medication. These results suggest that MR imaging-guided focused ultrasound has the ability to provide an effective and safe non-invasive palliative treatment for patients with bone metastases with little or no morbidity.

- **Laser ablation**

Gangi and Buy (2010) suggested that osteoid osteomas are one of the best indications for laser ablation in bone. Nevertheless, the number of laser ablation-treated osteoid osteoma cases reported in the literature, suggests this treatment method is currently less commonly used than RF ablation. In a recent retrospective study Gangi et al. (2007) evaluated the effectiveness of interstitial laser ablation as a curative treatment of osteoid osteoma in 114 patients. One week after ablation therapy, 112 patients experienced complete pain relief without medication. At mean follow-up of 58.5 months, six patients had recurrence of pain after the initial therapy which was treated successfully with a second ablation.
• **Cryoablation**

Recent studies also report the interest of cryoablation for the palliative treatment of musculoskeletal metastases (Ullrick et al., 2008). There is evidence now that cryoablation may be a more effective option for reducing pain caused by bone tumors than heat-based therapies. The retrospective review conducted by Tacker et al. (2011) mentioned earlier of patients who underwent either cryoablation or RF ablation for painful metastatic tumors involving bone, indicated that the analgesic use in the 24 hours immediately after the procedure decreased significantly for both ablation modalities. Moreover, the use of cryoablation compared with RF ablation was associated with a greater reduction in analgesic dose and shorter hospital stays after the procedure. Cryoablation is recommended by the ESMO and NCCN guidelines as an option for the primary treatment of low-grade chondrosarcomas (based on Veth et al., 2005; Ahlmann et al., 2006; Mohler et al., 2010) as well as to manage metastasis of soft-tissue sarcomas.

### 3.2.2 Brain cancer

Local destruction of both primary and metastatic intracranial tumors through minimally invasive stereotactic techniques has been recently investigated clinically using a variety of techniques, including high-intensity focused ultrasound (Ram et al., 2006) and laser ablation (Schwarzmaier et al., 2005; 2006; Carpentier et al., 2008; Hawasli et al., 2011). However, the current body of literature regarding thermal ablation therapies of brain tumors is very limited.

• **Ultrasound ablation**

A phase I clinical trial was initiated in 2006 by Ram et al. to treat patients with recurrent gliomas with transcranial MRI-guided focused ultrasound (MRigFUS) surgery. The data demonstrate the feasibility of using MRigFUS for the targeting and destruction of malignant brain tumors by thermocoagulation, although with an associated morbidity and the inherent invasive nature of the procedure requiring creation of a bone window. The technology was associated with some toxicity resulting from localized brain response to the coagulative process in one patient and to a presumed formation of a secondary, reflected lesion in another. Only three patients were treated and no efficacy data are available. McDannold et al. (2010) also evaluated the clinical feasibility of MRigFUS in glioblastoma patients. For this study a clinical prototype of a phased array transcranial MRigFUS surgery device for thermal ablation was developed in which the scalp is actively cooled. Initial technical results of this device from patient treatments are presented in this study, demonstrating the feasibility of focusing through the skull and measuring the temperature rise at the focus and on the brain surface using MRI.

• **Laser ablation**

Schwarzmaier et al. (2005; 2006) investigated MR-guided laser ablation of recurrent glioblastomas in a study of 16 patients. MRI imaging follow-up examinations revealed a volume reduction of the laser-irradiated areas. The median overall survival after laser...
coagulation was 6.9 months which is not longer than those reported for the natural history (<5 months) or after temozolomide as stand-alone chemotherapy. Carpentier et al. (2011) reported the final results of a pilot clinical trial exploring the safety and feasibility of real-time MR-guided laser ablation for treatment of resistant focal metastatic intracranial tumors in 7 patients. The minimally invasive stereotaxic placement of a saline-cooled interstitial fiberoptic laser applicator under local anesthesia was followed by laser irradiation during continuous MRI scanning. Follow-up imaging at up to 30 months showed an acute increase in apparent lesion volume followed by a gradual and steady decrease. No tumor recurrence within thermal ablation zones was noted and median survival was 19.8 months. According to these researchers, MR-guided laser ablation appears to provide a safe and potentially effective treatment for recurrent focal brain cancer.

3.2.3 Breast cancer

Breast cancer tumor ablation as part of a multimodality approach in the treatment of breast cancer is a subject of recent interest. Various attempts have been made to replace the surgery by inducing local tumor necrosis with minimally invasive or non-invasive techniques, including radiofrequency (RF), microwave (MW), focused ultrasound (US), laser ablation, and cryoablation. Zhao and Wu (2010) conducted a broad search of minimally-invasive thermal ablation techniques for local destruction of early-stage breast carcinoma in Pubmed, Embase and the Cochrane databases between January 1990 and December 2009. The authors found that complete tumor ablation could be achieved in 76-100% of breast cancer patients treated with RF ablation, 0-8% in MW ablation, 20-100% in US ablation, 13-76% in laser ablation, and 36-83% in cryoablation. Many different methodological approaches were included to summarize these results, nevertheless, minimally-invasive thermal ablation shows to be a promising new tool for local destruction of small carcinomas of the breast.

- Radiofrequency ablation

Several phase I trials have been performed to investigate the effectiveness of RF ablation for treatment of small breast tumors. Currently, most of the ongoing trials consist of in situ ablation followed by standard surgical resection. Manenti et al. (2009) evaluated the efficacy of RF ablation in 34 women with small invasive breast carcinomas in terms of induction of complete tumor necrosis and cosmetic outcome. For 97% of the procedures staining showed no evidence of viable cells and cosmesis was generally excellent. Wiksell et al. (2010) used a technique called preferential radiofrequency ablation (PRFA) to treat unifocal invasive breast carcinoma under US guidance. PRFA is a heat induced enzymatic destruction of breast cancer tumors with the surrounding fibrous and fatty tissue left unharmed. Thirty-three patients were enrolled in this study to be treated prior to scheduled partial mastectomy. In 26 (84%) patients a complete ablation of the tumor was achieved. The success rate depended on accurate preoperative diagnostic imaging as well as an exact position of the needle electrode. Klimberg et al. (2011) conducted a pilot study (randomized phase I/II design) to demonstrate the feasibility of a novel approach to minimally invasive therapy: percutaneous excision and cytoreduction, followed by RF of margins for the treatment of breast cancer. The authors hypothesized that percutaneous removal of breast cancer followed by percutaneous ablation to sterilize and widen the margins would better achieve
negative margins after ablation. Fifteen patients received RF ablation and all showed 100% ablation and negative margins.

- **Microwave ablation**

Clinical experiences of using MW ablation for breast cancer are limited and to our knowledge no data has been published in recent years.

- **Ultrasound ablation**

Several phase I studies have shown that ultrasound ablation is a safe and feasible modality for the treatment of breast cancer (Gombos et al., 2006; Wu et al., 2007a; Schmitz et al., 2008). The reported efficacy of HIFU ablation as measured by percentages of complete tumor necrosis ranged from 20% to 100% (Zippel et al., 2005; Wu et al., 2005a; 2007; Khiat et al., 2006; Furusawa et al., 2006; 2007). The difference in outcome between HIFU ablation studies can be explained by differences in patient selection, imaging techniques, and tumor ablation protocols used (Schmitz et al., 2008). Wu et al. (2005; 2007) reported two studies on the accuracy of US-guided FUS ablation for breast cancer treatment. Studies such as these are exploratory and the data remains incomplete (Brenin, 2011). MRI plays a critical role in assessing the effectiveness of HIFU treatment (Kim et al., 2010). However, there are currently three significant obstacles to the clinical implementation of MRgFUS ablation: long duration of treatment, uncertainty of margin status, and the persistence of a breast mass after ablation in some patients (Brenin, 2011). To confirm that HIFU ablation can be used as an alternative treatment option for breast cancer, further long-term follow-up studies on safety, technical effectiveness and survival rate are required (Kim et al., 2010).

- **Laser ablation**

So far all studies on laser ablation are designed to investigate the safety and feasibility of laser ablation for the treatment of breast cancer and more recently only a few studies have been published. Haraldsdóttir et al. (2008) evaluated whether US-guided interstitial laser therapy (ILT) can be used to treat breast cancer. Complete necrosis of a tumor could be achieved in only 3 (12.5%) of the 24 patients. Efficacy of treatment varied negatively with tumor size. The inefficacy of ILT was mainly due to the underestimation of tumor size by mammography and ultrasound and the shortcomings of these methods to demonstrate tumor borders, tumor irregularity and carcinoma in situ. In a similar study by van Esser et al. (2009), the tumor in 7 (50%) out of 14 patients was completely ablated. Also in this study, a clear association was found between the success rate of laser ablation and tumor size. This method needs further refinement if it is going to be employed for radical treatment.

- **Cryoablation**

Almost all clinical trials using cryoablation for breast cancer are both pilot and feasibility studies (Pfleiderer et al., 2005; Pusztaszeri et al., 2007; Manenti et al., 2009). More recently, Manenti et al. (2011) assessed the ablative effectiveness, the oncological and cosmetic efficacy of US-guided percutaneous cryoablation in the treatment of small single breast
nodules. In 14 of the 15 patients studied a complete necrosis was observed of the cryoablated lesion. The authors concluded that percutaneous cryoablation as a minimally invasive technique can provide excellent oncological and cosmetic results on selected cases if handled by experienced operators.

3.2.4 Esophageal cancer

Radiofrequency (RF), cryoablation and photodynamic therapy (see review of Photodynamic therapy) are mentioned in the NCCN guidelines as possible alternatives to endomucosal resection in patients with superficial esophageal cancer as well as for high-grade dysplasia and Barrett’s esophagus, a condition predisposing one to esophageal cancer. These techniques are also recommended to relieve symptoms of dysphagia in palliative care.

- Radiofrequency ablation

Studies of the efficacy of RF ablation are evolving rapidly as the frequency of its use in patients with early esophageal neoplasia is increasing (Galey et al., 2011). Bergman et al. (2011) evaluated in a prospective trial, RF ablation for eradicating early esophageal squamous cell neoplasia in 29 patients. 97% of patients (28/29) achieved a complete response at 12 months in the treated area and no neoplastic progression. However, the limitations of this study include its small size and the lack of a control group.

- Cryoablation

Also cryoablation has been studied as a primary modality to achieve neoplasia eradication of the esophagus. Dumot et al. (2009) assessed the safety and efficacy in a nonrandomized trial of liquid nitrogen cryoablation/endoscopic spray cryoablation as measured by histologic response rate and cancer-free survival. The 30 patients included were deemed inoperable or refused esophagectomy. In this single-center cohort study it was found that 80% of patients with early esophageal cancer responded with downgrading of pathology stage at 1-year follow-up.

3.2.5 Head and neck cancer

- Radiofrequency ablation

The first report on using radiofrequency (RF) ablation on unresectable head and neck cancer (HCN) came from Brook et al. (2008). They evaluated the safety and effectiveness of CT-guided RF ablation in the palliative treatment of recurrent advanced HNC in 14 patients. University of Washington quality of life surveys completed by six of 14 patients showed an index increase by a median of 3.1 percentage points, with four of six patients demonstrating improvement. In a follow-up series, Owen et al. (2011) examined in a non-randomized controlled trial if the application of RF ablation to advanced HNC would result in local control of the tumor. Eight of 13 participants had stable disease after intervention. Median survival was 127 days, and an improvement in University of Washington quality-of-life scores was
noted. The authors concluded that RF ablation is a palliative treatment alternative for addressing the challenges of local control and quality of life in patients with incurable HNC.

3.2.6 Kidney cancer

Patients at high surgical risk may be offered other minimally invasive nephron-sparing therapies such as focal ablation of kidney tumor than partial nephrectomy (Autorino et al., 2010). An effective, minimally invasive therapy could postpone kidney failure and prolong kidney function in patients with kidney cancer. Thermal ablative treatment of small renal masses have been applied for selected cases, with the potential benefits of decreased morbidity, shorter hospitalization, preservation of renal function, and the ability to treat patients who are at poor surgical risks (Vricella et al., 2009). Clinically, radiofrequency (RF) ablation and cryoablation are the two modalities currently used in the treatment of small renal masses and are considered as an option in selected cases in current clinical guidelines (Campbell et al., 2009; Duffey and Anderson, 2010). For instance, the American Urological Association recommends probe ablation as a treatment option in select patients, such as those with comorbidities and at increased surgical risk (Campbell et al., 2009). Renal tumors of up to 3.5 cm in diameter can be destroyed in situ by RF or cryoablation with virtually no damage to the surrounding normal renal tissue (Gillams, 2009). NCCN guidelines indicate that RF ablation and cryoablation are alternatives to surgical nephron-sparing procedures in poor surgical candidates and elderly (conclusion mainly based on Kunkle and Uzzo, 2008). Both ablation techniques for early stage kidney cancer are also under investigation by ESMO.

- Radiofrequency ablation

RF ablation is being studied as a minimally invasive treatment for patients with small renal-cell carcinomas. Studies have shown RF energy to be relatively ineffective for large or centrally located tumors, citing an increase in tumor recurrence and reduced efficacy for tumors greater than 3 cm in diameter or in proximity to the collecting systems (Gervais et al., 2005). Several series have been published including a retrospective comparison with partial nephrectomy (Stern et al., 2007) which showed comparable oncologic efficacy albeit with a shorter mean follow-up in the RF group (30 months versus 47 months). The overall actuarial disease-free probability for the partial nephrectomy and RF ablation groups, respectively, was 95.8% and 93.4%. In a follow-up study, Stern et al. (2009) confirmed that RF ablation might be a reasonable treatment choice and that their intermediate results suggest excellent oncological outcomes and preservation of renal function. In this study, however, two patients (3.1%) experienced a recurrence. More recently, Choueri et al. (2011) evaluated RF ablation and cryoablation in the management of stage I renal cell carcinoma (RCC) versus partial (PN) or radical nephrectomy (RN). In total, 15,145 patients underwent a procedure for an RCC that was organ-confined and ≤7 cm. Of these, 578 underwent thermal ablation, 4402 underwent PN, and 10,165 underwent RN. This study revealed no statistical difference in cancer-specific or overall survival between RF thermal ablation versus PN or RN.
• **Microwave ablation**

Some clinical data support the use of microwave (MW) ablation for treating renal-cell carcinoma (RCC), but additional study is needed to verify these results (Clark et al., 2007). Liang et al. (2008) evaluated the feasibility, safety and efficacy of US-guided percutaneous MW ablation for small renal cell cancers. In all 12 patients the tumors were completely ablated in a single session and no complications occurred. No residual tumor or recurrence was observed at a median follow-up of 11 months. The ablation zone was well defined on contrast enhanced imaging and it gradually shrank with time. The authors concluded that US-guided percutaneous MW ablation appears to be a safe and effective technique for small renal cell cancer in select patients.

• **Ultrasound ablation**

Ultrasound ablation of renal tumors remains in the early stages of clinical trials. Few clinical studies were performed to treat small locally confined renal tumors (Illing et al., 2005; Marberger et al., 2005; Klingler et al., 2008) using HIFU with small numbers of patients. To date, these studies evaluating transcutaneous renal HIFU have been disappointing and must be considered experimental (Duffey and Anderson, 2010). Laparoscopic HIFU has the potential to overcome the limitations associated with transcutaneous treatment, but further studies evaluating oncologic efficacy are necessary.

• **Cryoablation**

Cryoablation has recently gained interest as an alternative option for the treatment of localized RCC (Levy et al., 2010). Based upon tumor location, renal cryoablation can be delivered laparoscopically or percutaneously, which affords the patient more rapid convalescence (Finley et al., 2008). Intermediate oncologic outcomes indicate that cryoablation is a curative option for the treatment of small renal masses in patients unfit or unwilling to undergo partial nephrectomy (Duffey and Anderson, 2010). Long-term follow-up data reflect cancer-specific survival rates at 5- and 10-year intervals of 93% and 81%, respectively (Berger et al., 2009). Davol et al. (2006) reported on 48 patients with up to a 5-year follow-up. Twenty-four patients had open cryoablation and the other 24 were treated laparoscopically. Overall survival rate was 89.5% and cancer-specific survival rate was 100%. In a cryoablation/RF ablation comparison study, Hegarty et al. (2006) retrospectively reviewed the Cleveland Clinic experience with laparoscopic cryoablation versus RF ablation and noted evidence of disease persistence in 1.8% of lesions after cryoablation versus 11.1% of lesions after RF ablation. A similar outcome was found in a meta-analysis of the available literature comparing cryoablation with RF ablation (Kutikov et al., 2009). Forty-six studies from 44 institutions including 1,234 localized renal lesions, treated with either open, laparoscopic, or percutaneous cryoablation or RF ablation, were analyzed. Repeat ablation was performed less often after cryoablation (1.3%) than RF ablation (8.5%). The current data suggest that cryoablation results in fewer retreatments and improved local tumor control, and it may be associated with a lower risk of metastatic progression compared with RF ablation (Kunkle and Uzzo, 2008).
More recently, Aron et al. (2010) presented in a follow-up study 5 to 11-year oncological outcomes after laparoscopic renal cryoablation in 340 patients, of whom 80 were treated laparoscopically by a single surgeon. In the 80 patients with minimum 5-year follow-up mean tumor size was 2.3 cm. Five patients had local recurrence, 2 had loco-regional recurrence with metastasis and 4 had distant metastasis without loco-regional recurrence. In the 55 patients with renal cell cancer at a median follow-up of 93 months, disease specific survival rate was 92% at 5 years and 83% at 10 years. Preceding radical nephrectomy for renal cell carcinoma was the only independent factor predicting disease-free and disease-specific survival. Atwell et al. (2010) retrospectively determined the efficacy of percutaneous renal cryoablation based on a mean follow-up of more than 2 years. 91 patients underwent percutaneous cryoablation procedures. Technically successful ablation was performed in the treatment of 87 of the 91 patients (96%). Only a single case of local tumor progression occurred. Overall local control was achieved in 86 of 91 (95%) patients. Altunrende et al. (2011) evaluated the oncological and functional outcomes of CT-guided percutaneous cryoablation or RF ablation of kidney tumors in patients with a solitary kidney. Overall 65 patients were included in this retrospective analysis, of whom 29 (44.6%) underwent cryotherapy and 36 (55.4%) underwent RF ablation. There were 14 recurrences after RF ablation and 3 after cryoablation. Two-year cancer specific survival rates for cryoablation versus RF ablation were 100% versus 96%, respectively. CT-guided cryoablation provides low morbidity, acceptable short-term cancer control and minimal clinical impact on postoperative renal function.

3.2.7 Liver cancer

In liver cancer patients for which surgery is not possible, ablative techniques are an attractive option and offer an opportunity to increase survival (Gravante, 2010; Sindram et al., 2010; Lau et al., 2011). Contraindications include multiple tumors, decreased liver function, or multiple medical problems. There are several groups of patients who may derive benefit from thermal ablation of liver tumors, such as cirrhotic patients with early stage hepatocellular carcinomas (HCC). Radiofrequency (RF), microwave (MW), ultrasound (US), laser, and cryoablation have all been used for the local ablation of liver lesions. These minimally invasive technologies are principally performed in patients with small volume HCC no larger than 3-4 cm in diameter. The specific choice of the treatment modality for HCC depends on the size and the number of tumors, the stage and the cause of cirrhosis and finally on the availability of various modalities in each center (Livraghi et al., 2011a). Image-guided thermal ablation for the treatment of focal liver cancer is gaining acceptance in evidenced-based clinical practice guidelines (Bruix and Sherman, 2010; Kudo et al, 2011). RF ablation, cryoablation and MW ablation are mentioned in the ESMO and NCCN guidelines as possibilities either for palliative care of HCC or for patients awaiting a liver transplantation. NCCN also recommends these techniques as an option for local control of small tumors (<3 cm). In addition, both guidelines regard RF ablation as an alternative to surgery for solitary or confined colorectal liver metastases.
• Radiofrequency ablation

RF ablation is increasingly being used to treat unresectable liver tumors (Brace, 2009b) and several reports with different conclusions have been published recently. Karabulut et al. (2011) have been utilizing both resection and laparoscopic RF ablation to treat HCC. Medical records of HCC patients who underwent resection (n=92) or laparoscopic (RF ablation) (n=92) between 1997 and 2010 were reviewed. Patients with normal liver function and larger tumors were resected, and those with liver dysfunction, portal hypertension, and multiple tumors were ablated. Hospital stay was longer, and morbidity and mortality higher in the Resection versus the RF ablation group. There was no difference in disease-free survival, but the 5-year actual survival was significantly higher (40% versus 21%) in the Resection group. The authors suggest that RF ablation and resection should be used complementarily, not competitively, to each other. Cho et al. (2011) performed a systematic review to compare the results of hepatic resection and percutaneous RF ablation as a primary treatment option of HCC. In all six identified observational studies, there were no statistically significant differences in overall survival rates between the two treatment modalities but the authors acknowledge that the power of two randomized trials is too limited to reach a general reliable conclusion.

In a preliminary report by Hasegawa et al. (2008) it is suggested that surgical resection may provide less time-to-recurrence rate than either RF ablation or percutaneous ethanol injection (PEI) in patients with HCC. The 2-year time-to-recurrence rate for RF ablation was high (55.4%) but data was based on somewhat older ablation technologies. Also, Tiong et al. (2011) concluded in a study revealing an improved RF ablation technique (see 2.3.1) that the long term outcomes of RF ablation for liver tumors are still inferior to surgical resection due to the high local tumor recurrence rates. Muller et al. (2008), however, critically reviewed the oncological evidence in favor of and against the use of RF ablation for small resectable colorectal liver metastases (CRLM) in a selected subgroup of patients published before 2008. They also found a difference between local recurrence rate, i.e. after resection of CRLM it is 1.2-10.4% while local recurrence rate after RF ablation of CRLM is between 1.7 and 66.7%. However, local recurrence rate after open RF ablation for CRLM <3 cm seems to be equivalent to resection. Similarly, a study conducted by the American Society of Clinical Oncology (ASCO), reviewing the evidence published till 2007, report for RF ablation a 5-year variable survival rate of 14% to 55% and local tumor recurrence rate of 3.6% to 60% (Wong et al., 2010).

Akyildiz et al. (2010) published long-term oncologic results of 89 patients with neuroendocrine liver metastases (LM) treated with laparoscopic RF ablation. Twenty-two percent of patients developed local liver recurrence, 63% developed new liver lesions, and 59% developed extra-hepatic disease in follow-up. Median disease-free survival was 1.3 years and the overall survival was 6 years after RF ablation. Pathak et al. (2011) reviewed the long-term outcome and complication rates of various ablative therapies used in the management of CRLM. 226 potentially relevant studies were identified, of which 75 met the inclusion criteria. RF ablation (36 studies) had a local recurrence rate of 10-31%, with a mean 1-, 3- and 5-year survival of 85%, 36% and 24%, respectively. The technical efficacy and survival following RF ablation of LM from nasopharyngeal carcinoma (NPC) has also been
evaluated in a retrospective study of 376 patients (Pan et al., 2011). Of these 17 patients with 31 LM from NPC underwent CT-guided percutaneous RF ablation. Technical success was achieved in 30/31 metastases (96.7%). The median overall survival was 16.5 months from the time of diagnosis of LM for all the 376 NPC patients with LM, and 48.1 months for the 17 NPC patients with LM who received RF ablation treatment. For selected NPC patients with LM, RF ablation is safe and effective and appears to prolong survival compared to patients treated with chemotherapy alone without local therapeutic measures.

• Microwave ablation

Also MW ablation is increasingly utilized in the treatment of hepatic tumors (Lloyd et al., 2011) particularly in China to treat small HCC (Zhou, 2011). Some studies reporting three-year survival near 90% in small HCC (Lu et al., 2005; Shiomi et al., 2008) and in accordance with Nicholl et al. (2010) MW technology will replace RF ablation in the treatment of liver tumors. Current clinical trials consist of single-institution case series with promising results (Iannitti et al., 2007; Jagad et al., 2008; Liang et al., 2009; Martin et al., 2010). In addition, Lloyd et al. (2011) conducted a prospective, multicenter study. Eighteen international centers recorded operative and perioperative data for patients undergoing MW ablation for tumors of any origin in a voluntary Internet-based database. Of the 140 patients, 114 (81.4%) were treated with MW ablation alone and 26 (18.6%) were treated with MW ablation combined with resection. These multi-institution data demonstrate low morbidity and mortality rates in patients undergoing operative MW ablation with a high rate of multiple ablations and concomitant hepatic resection. The review study by Pathak et al. (2011) mentioned earlier found that MW ablation (13 studies) for CRLM had a local recurrence rate of 5-13%, with a mean 1-, 3- and 5-year survival of 73%, 30% and 16%. Long-term follow-up will be required to determine the efficacy of MW ablation relative to other forms of ablative therapy. Interestingly, Liu et al. (2011) evaluated retrospectively (without a control group) the efficiency and feasibility of contrast-enhanced ultrasound (CEUS)-guided MW ablation for HCC. 107 patients with HCC nodules inconspicuous on conventional US underwent MW ablation under CEUS guidance. CEUS was performed first, and then MW ablation was carried out by means of CEUS guidance. The technical success rate was 98.13% (105/107) and the local tumor progression rate was 1.9% (2/105) all indicating that CEUS-guided MW ablation is a feasible treatment method for patients with HCC inconspicuous on conventional US.

• Ultrasound ablation

Ultrasound ablation has been applied non-invasively for either focal ablation or palliative reduction of liver tumors. Both primary liver cancer (HCC) (Zhu et al., 2009; Zhang et al., 2009) and liver metastasis from colon and stomach cancers (Park et al., 2009) were treated using HIFU ablation. A randomized trial has compared transcatheter arterial chemoembolization (TACE) alone with TACE and HIFU for the treatment of HCC (Wu et al., 2005b). The HIFU-TACE group demonstrated a survival benefit of 6 months over the TACE alone group. Results of other research showed that complete tumor necrosis was achieved in 69.6% (Zhu et al., 2009) and 50% (Zhang et al., 2009) of lesions after the first session of HIFU treatment. After the second session of HIFU treatment, all the tumors achieved
complete tumor necrosis with absence of tumor blood supply and shrinkage of all treated lesions with survival rates of 55.6% (Zhu et al., 2009) and 31.8% (Zhang et al., 2009) at 5 years. For treating liver metastasis from colon and stomach cancer HIFU seems safe but its efficacy is questionable (Park et al., 2009).

• Laser ablation

In the past there have been numerous studies regarding the effectiveness of laser ablation for inoperable HCC and unresectable liver metastasis. In a large non-randomized study, Vogl et al. (2004) treated 1801 colorectal cancer liver metastasis in 603 patients with MRI-guided laser ablation. Local tumor control rates of 97.3% at 6 months based on MR imaging were achieved, with an overall complication rate of 1.5% and a 30-day mortality of 0.1%. No tumor seeding was noted, and a median survival of 4.4 years after diagnosis of metastases was achieved, being superior to the 17.4 months median survival after receiving chemotherapy alone during that time. Several contemporary studies of outcomes of laser ablation for inoperable HCC have achieved acceptable complete ablation rates of 82% to 97.5% with tumors smaller than 3 cm, and from 60% to 82% in tumors 3 to 4 cm (Gough-Palmer and Gedroyc, 2008; Pacella et al., 2009). Mortality is very low considering the patient population at 0.1% to 0.2% and major complications around 1.5%. When compared with RF ablation and HIFU, laser ablation was shown to be equivalent and less morbid (Ferrari et al., 2006).

• Cryoablation

Cryoablation in the liver is less well studied in the percutaneous setting (Hinshaw and Lee, 2007). Recently, Yang et al. (2011b) evaluated the efficacy and safety of US-guided percutaneous cryoablation in 300 patients with HCC. The local tumor recurrence rate was 31%, and was related to tumor size and tumor location. The mean survival duration of patients with early, intermediate and advanced HCC was 45.7, 28.4 and 17.7 months, respectively. Cryoablation is often contraindicated for primary liver cancer due to underlying coagulopathy and associated bleeding risks frequently seen in cirrhotic patients. In addition, sudden release of tumor cellular contents when the frozen tissue thaws, can lead to a potentially serious condition known as cryoshock (Brace et al., 2011). The review study by Pathak et al. (2011) mentioned earlier found that cryoablation (26 studies) for CRLM had local recurrence rates of 12-39%, with mean 1-, 3- and 5-year survival rates of 84%, 37% and 17%.

3.2.8 Lung cancer

Radiofrequency (RF), microwave (MW), laser ablation, and cryoablation have all been used for inoperable primary and secondary lung malignancies. Currently, the most widely used technique is RF ablation; however, the other thermal ablation techniques have also been successfully applied in this group of patients (Dupuy, 2011). Most preclinical and clinical trials have focused on demonstrating the feasibility of the following modalities.
• **Radiofrequency ablation**

Single-institution case series and large, multicenter intention-to-treat clinical trials have suggested that RF ablation can be a valuable treatment option for patients with unresectable or medically inoperable lung malignancies (Lencioni et al., 2008; Lanuti et al., 2009; Yamakado et al., 2009). A systematic review by Lencioni et al. published in 2008 summarized the literature regarding RF ablation of malignant lung tumors. A series of 106 patients were enrolled in a prospective, intention-to-treat, single-arm, multicenter clinical trial. A confirmed complete response of target tumors lasting at least 1 year was shown in 75 (88%) of 85 assessable patients. Patients with stage I non-small cell lung cancer (NSCLC) (n=13) had a 2-year overall survival of 75% and a 2-year cancer-specific survival of 92%. Thus percutaneous RF ablation yields high proportions of sustained complete responses in selected patients with pulmonary malignancies. More recently, Ambrogi et al. (2011) reported the results of an intention-to-treat study of 59 patients with NSCLC by RF ablation. At a mean follow-up of 47 months, the complete response rate was 59.3%, with a mean local recurrence interval of 25.9 months. Median overall survival and cancer-specific survival were 33.4 and 41.4 months, respectively. Cancer-specific actuarial survival was 89% at 1 year, 59% at 3 years, and 40% at 5 years. Previously, Lanuti et al. (2009) found somewhat similar results. Both studies conclude that RF ablation of medically inoperable early-stage lung cancer in carefully selected patients yields encouraging midterm results without significant loss of pulmonary function. However, ESMO do not mention RF ablation but indicates Stereotactic Radio Surgery (SRS) as the preferred option for early stage cancer in inoperable patients while NCCN regards RF ablation inferior to SRS based on a recent study by Sher et al. (2011).

The clinical utility of lung RF ablation in recurrent NSCLC after surgical intervention has also been examined. In a retrospective evaluation conducted by Kodama et al. (2011) 44 consecutive patients received curative lung RF ablation for 51 recurrent NSCLC after surgical intervention. The 1-, 3-, and 5-year overall survival rates were 97.7, 72.9, and 55.7%, respectively. The 1- and 3-year recurrence-free survival rates were 76.7 and 41.1%, respectively. These results suggest that lung RF ablation is a safe and useful therapeutic option for obtaining long-term survival in treated patients. Finally, pulmonary metastases resulting from hepatocellular carcinoma (HCC) treated with CT-guided percutaneous RF ablation was examined by Hiraki et al. (2011). Thirty-two patients from six institutions were included, with a total of 83 pulmonary metastases. Overall survival rates were 87% at 1 year and 57% each at 2 and 3 years. This study finding suggests that RF ablation appears effective, with an acceptable safety profile, in selected patients with pulmonary metastases resulting from HCC.

• **Microwave ablation**

The current body of literature regarding clinical MW ablation in the lungs is limited. There have been a few early clinical studies of MW ablation for lung tumors in people which have shown promising rates of local control even with tumors larger than 3 cm (Wolf et al., 2008; Vogl et al., 2011). Wolf et al. (2008) retrospectively evaluated effectiveness and safety of CT-guided MW ablation in 50 patients with intraparenchymal pulmonary malignancies. At a
mean follow-up of 10 months, 13 patients (26%) had residual disease at the ablation site. Another 11 patients (22%) had recurrent disease resulting in a 1-year local control rate of 67%, with a mean time to first recurrence of 16.2 months. Actuarial survival was 65% at 1 year, 55% at 2 years, and 45% at 3 years from ablation. Cancer-specific mortality yielded a 1-year survival of 83%, a 2-year survival of 73%, and a 3-year survival of 61%. A similar study was performed by Vogl et al. (2011a). Eighty patients underwent CT-guided percutaneous MW ablation of pulmonary metastatic lesions. Complete, successful ablation was achieved in 95 (73.1%) of 130 lesions. Successful tumor ablation was significantly more frequent for lesions with a maximal axial diameter of 3 cm or smaller. The 12- and 24-month survival rates were 91.3% and 75%, respectively. Higher survival rates were observed in patients with tumor-free states after successful ablation than in patients with failed ablation. Both studies indicate that MW ablation therapy may be safely and effectively used as a therapeutic tool for treatment of lung tumors.

• Laser ablation

Percutaneous laser ablation has only recently been applied to pulmonary tumors. Rosenberg et al. (2009) evaluated the long-term safety and efficacy of laser ablation for the treatment of pulmonary metastatic disease. They treated 64 patients with a total of 108 tumors and reported a primary technical success rate of 79%. In that series, patients were treated for both definitive local control and tumor debulking. Local tumor progression was seen in 28% of tumors after an initial technical success rate. Median survival was 23.1 months, with overall 1-, 3-, and 5-year survival rates of 69%, 30%, and 18%, respectively. The survival increased to a median of 32.4 months and overall 1-, 3-, and 5-year survival rates of 81%, 44%, and 27%, respectively, in the group being treated for definitive local control (31 of 64 patients). The pneumothorax rate was 38%, with 5% of procedures requiring insertion of a chest tube. Three grade 3 or higher adverse events were noted. These included one patient with hemorrhage, one with dyspnea, and one with delayed pneumonia and empyema.

• Cryoablation

In the largest clinical series to date, pulmonary cryoablation was performed on 187 patients (165 primary lung, 22 metastatic), many with advanced stage disease who had failed traditional therapies (Wang et al., 2005). At 6 months after treatment, the tumors were seen to be stable or smaller on 86% of the available 6-month CT scans than on the original scans. Higher technical success rates were achieved in patients with tumors less than 4 cm in diameter and peripheral tumors. Follow-up was too short to determine post-procedure survival but palliative benefits of cryoablation were noted. Kawamura et al. (2006) treated 35 metastatic tumors in 20 patients and achieved an overall local control rate of 80% and a 1-year rate of 89%. Tumors progressed in 35% of patients, with a median time to progression of 9 months. They reported a pneumothorax rate of 50%, a hemoptysis rate of 36%, and one case of phrenic nerve injury. Zemlyak et al. (2010) compared sublobar resection, RF ablation, and cryoablation in a prospective randomized fashion in 64 patients with NSCLC. The probability of 3-year survival for the surgical, RF ablation, and cryoablation groups was 87.1%, 87.5%, and 77%, respectively. The 3-year cancer-specific and cancer-free survival rates, respectively, for the surgical, RF ablation, and cryoablation groups were 90.6% and
60.8% versus 87.5% and 50% versus 90.2% and 45.6%. This experience suggests comparable survival after sublobar resections and ablative therapies at 3 years. Yamauchi et al. (2011) evaluated the safety and efficacy of cryoablation for metastatic lung tumors from colorectal cancer. The procedures were performed on 24 patients for 55 metastatic tumors in the lung. The 1- and 3-year local progression free intervals were 90.8% and 59%, respectively. The 3-years local progression free intervals of tumors ≤15 mm in diameter was 79.8% and that of tumors >15 mm was 28.6%. The 1- and 3-year overall survival rates were 91% and 59.6%, respectively. The results of all of these trials suggest that cryoablation can be performed with an acceptable safety profile and can result in reasonable local control rates for both primary and metastatic lung tumors.

3.2.9 Pancreatic cancer

- **Radiofrequency ablation**

Radiofrequency (RF) ablation may seem risky due to the friable pancreatic parenchyma and fear of pancreatitis. Nevertheless, Hadjicostas et al. (2006) concluded from their initial results, intraoperative RF ablation to be feasible, potentially safe and a promising option in patients with locally advanced and unresectable pancreatic cancer. No clinical trials have been published recently except for some case reports (e.g. Sugito et al., 2010; Ikuta et al., 2012).

- **Ultrasound ablation**

Preliminary studies suggest that HIFU may be useful for the palliative treatment of cancer-related pain in patients with unresectable pancreatic cancer (Wu et al., 2005c; Xiong et al., 2009; Zhao et al., 2010; Wang et al., 2011). Wu et al. (2005c) treated eight patients with advanced pancreatic cancer by using US-guided HIFU for palliation. In this small series, the treatment proved to be safe. Following HIFU, pre-existing severe back pain of presumed malignant origin disappeared in every patient. Follow-up imaging with MRI, showed reduced or absent tumor blood supply in the treated regions and there was significant shrinkage of the ablated tumors. More studies followed in which HIFU has been used to treat localized advanced pancreatic cancer either with HIFU alone (Xiong et al., 2009; Wang et al., 2011), HIFU concurrently with chemotherapy using gemcitabine drug (Xiong et al., 2009; Zhao et al., 2010), or HIFU therapy after failure of treatment with chemotherapy and/or radiotherapy (Xiong et al., 2009). Results of this research showed that the average tumor reduction rate was 50% after treatment with HIFU alone (Wu et al., 2005c), an overall response rate of 43.6% after concurrent gemcitabine and HIFU treatment (Zhao et al., 2010), a partial response rate of 14.6% in the latter group (Xiong et al., 2009). Pain relief was achieved in about 80% of patients (Xiong et al., 2009; Wang et al., 2011). In addition, Lee et al. (2011) performed a study to evaluate the potential clinical value of concurrent chemotherapy and pulsed HIFU therapy for the treatment of unresectable pancreatic cancer but this combined therapy remains experimental. There have been no comparative studies performed to demonstrate that treatment with HIFU confers a survival benefit (Jang et al., 2010). Currently, HIFU treatment of pancreatic cancer is widely available in China, with limited availability in South Korea and Europe (Xiong et al., 2010).
3.2.10 Prostate cancer

A number of different ablative techniques have been under evaluation for treatment of prostate cancer, a multi-focal disease. Evidence is accumulating that radically treating prostate cancer holds survival benefit for patients (Lindner et al., 2010a). There is, however, no consensus on the ideal energy source that should be used to ablate the prostate cancer, imaging to monitor the tissue destruction in real time, numbers of treatments, and the ideal follow-up regimen (Lindner et al., 2009a).

• Microwave ablation

Some success was noted a decade ago in reducing tumor bulk and delaying growth of the primary tumor. However, enthusiasm for MW ablation in the prostate has waned in recent years, possibly in part due to challenges in avoiding thermal damage to nearby nerves and collagenous tissues such as the urethra, difficulty in visualizing the ablation zone at imaging, and improvements in other thermal ablation therapies.

• Ultrasound ablation

Ultrasound ablation of prostate tumors has been widely investigated. Both benign prostate hyperplasia and prostate cancer have been targeted. To date, more than 15,000 patients with prostate cancer have been treated worldwide with more than 100 sites in Europe, USA and Asia that offer this treatment modality (Al-Bataineh et al., 2011). The majority of published results using HIFU have investigated its efficacy as a whole-gland treatment. These studies show a significant decrease in prostate-specific antigen (PSA) nadir levels after HIFU treatment (e.g. Uchida et al., 2006; Koch et al., 2007; Crouzet et al., 2010a; 2010b). The biochemical progression-free survival ranges from 45% to 84% at 5 years and 69% at 7 years using either ASTRO or Phoenix criteria (Warmuth et al., 2010). Overall, reported results show high percentages of no evidence of disease among treated patients (e.g. Uchida et al., 2006; Muto et al., 2008; Crouzet et al., 2010a; Ahmed et al., 2009; 2011b). Crouzet et al. (2010a) reviewed in a single institute the outcomes of 880 patients with median follow-up of 41 months. The overall and cancer-specific survival rates at 7 years were 90% and 98%, respectively. Crouzet et al. (2010b) reported the outcome of HIFU as a primary care option for localized prostate cancer from a multicenter database. They found that local control and disease-free survival (DFSR) achieved with HIFU were similar to those expected with conformal external-beam radiation therapy (EBRT). Most recently, Lukka et al. (2011) undertook a systematic review to evaluate the evidence comparing it with standard treatment in patients with localized prostate cancer. Twenty-nine clinical studies evaluated HIFU as the primary treatment and five examined HIFU as salvage treatment for recurrence after radiotherapy. Among the studies of HIFU as the primary treatment, negative biopsy rates ranged from 35 to 95% in 21 studies, a PSA nadir of <0.5 ng/ml ranged from 55 to 91% in 10 studies and mean PSA nadirs ranged from 0 to 1.9 ng/ml in 17 studies. Five studies reported 5-year DFSR rates ranging from 55 to 95%. Among five studies of HIFU as salvage treatment, negative biopsy rates ranged from 73 to 84% in four studies, a PSA nadir of <0.5 ng/ml ranged from 57 to 66% in three studies and mean PSA nadirs were 1.97 and 2.38
ng/ml in two studies, respectively. Most studies conclude that HIFU for localized prostate cancer offered high control of local disease with low morbidity. Nevertheless, the available evidence on HIFU is comprised of case series data; prospective randomized controlled trials have not been performed to date (Lukka et al., 2011).

• **Laser ablation**

Laser ablation experience for prostate cancer is limited. Lindner et al., (2009) ascertained the feasibility and safety of MRI-guided laser ablation therapy for localized prostate cancer. Twelve patients with low risk prostate cancer underwent interstitial laser ablation of the cancer. Based on multicore total prostate biopsy at 6 months, 67% of patients were free of tumor in the targeted area and 50% were free of disease. Early clinical, histological and MRI responses suggest that the targeted region can be ablated with minimal adverse effects. It may represent an alternate treatment approach to observation or delayed standard therapy in carefully selected patients.

• **Cryoablation**

More recently, whole gland cryoablation, focal cryoablation, and salvage have been investigated as a tool for treating primary prostate cancer. In addition, numerous studies detail outcomes of using cryoablation as a salvage therapy for recurrent prostate cancer after local failure of radiotherapy surgery (Pisters et al., 2009; Wiegel et al., 2009). Cohen et al. (2008) reported 10-year outcomes data on 204 patients who underwent primary cryoablation of the prostate. In this report, the 10-year biochemical disease-free survival (bDFS) rates were 80%, 74% and 45% for, low-, intermediate- and high-risk patients, respectively. Several similar reports have been published on outcomes after cryosurgical ablation of the prostate. Truesdale et al. (2010) reported a biochemical failure rate of 27.3% according to the Phoenix definition and a 46% positive rebiopsy rate amongst cases with suspicion for recurrence.

Ward and Jones (2011) presented the largest retrospective registry report of men treated with subtotal prostate cryoablation. They conducted an analysis of the COLD Registry to identify patients treated with partial gland prostate cryoablation between 1997 and 2007. The COLD Registry contained information for 5,853 patients and focal cryoablation was the codified procedure in 1,160 patients (19.8%). A dramatic increase in focal treatments was observed from 46 in 1999 to 567 in 2005. The biochemical recurrence-free rate (ASTRO definition) at 36 months was 75.7%. Prostate biopsy, performed in 164/1160 of patients (14.1%), was positive in 43 (26.3%) of those suspected of cancer recurrence, but in only 3.7% (43/1160) of treated patients. Focal cryoablation is increasingly used for selected patients with prostate cancer. The impact of focal cryoablation on urinary, sexual and bowel function appears to be less than that of radical therapies. Oncological efficacy in the present series appears similar to that of whole-gland cryoablation (Ward and Jones, 2011). Overall, the available data indicate similar efficacy to alternative curative approaches to the disease. Hence, cryoablation is now used more often as a primary treatment (Dhar et al., 2011) despite the fact that to date, there are no data that support an evidence-based definition of treatment success for any type of cryoablative technique directed at prostate cancer (Levy et al., 2010).
ESMO indicates cryosurgery as salvage therapy after failure of primary treatment while NCCN mentions cryoablation as one of several options for treating recurrence after radiotherapy.

### 3.2.11 Rectal cancer

- **Radiofrequency ablation**

  Mylona et al. (2011) evaluated the safety and efficacy of CT-guided radiofrequency ablation for the palliative treatment of recurrent unresectable rectal tumors in 27 patients. The complete tumor necrosis rate was 77.8% (21 of a total of 27 procedures) despite lesion location. The mean pre-procedure Brief Pain Inventory (BPI) score was 6.59, which decreased to 3.15, 1.15, and 0.11 at postprocedure day 1, week 1, and month 1, respectively, after the procedure. This decrease was significant for all periods during follow-up.

- **Laser ablation**

  Laser ablation is a well-established treatment modality for palliation of rectal cancer, in which endoscopy is utilized to deliver focused energy to the rectal lesion (Kimmey, 2004; Nesbakken et al., 2011). For instance, Courtney et al. (2005) found lifelong symptom relief in 51/57 of patients with unresectable rectal cancer utilizing endoscopic laser therapy. Obstruction was relieved in 22/24 patients and bleeding controlled in 29/30.

### 3.2.12 Skin cancer

The recent literature regarding thermal ablation of superficial benign and low-risk skin cancer is limited but sufficient clinical evidence supports its use (Bath-Hextall et al., 2007; Patel et al., 2011).

- **Laser ablation**

  Laser ablation has been used in the treatment of low-risk basal cell carcinoma (BCC) in combination with curettage, but supportive data is generally lacking (Smith and Walton, 2011). The group of benign skin tumors that might be treated by laser therapy can be roughly classified as epidermal tumors/nevi, adnexal, fibrous and neural tumors, as well as xanthelasmas and cysts. Many different laser systems have shown to be effective in the treatment of these tumors (Klein et al., 2011).

- **Cryoablation**

  Cryoablation tends to be most useful in the treatment of low-risk BCCs (Smith and Walton, 2011). Recurrence rates are very variable, but when the lesion is carefully selected and in expert hands recurrence rates may be as low as 1% (Kuflik, 2004). A similar recurrence rate was recently confirmed by Peikert (2011) in a study in which he determined the long-term cure rate to be associated with curettage and cryoablation in the treatment of small, non-
facial, superficial BCCs and squamous cell carcinomas (SCC). Sixty-nine patients with 100 non-facial tumors, ≤ 2 cm in diameter were prospectively treated with curettage and cryoablation, and subsequently evaluated at 1- and 5-year intervals. No tumor except for one recurred after 5 year of follow-up, for a 99% recurrence-free endpoint. Lindemalm-Lundstam and Dalenbäck (2009) applied the same combined technique in the treatment of 926 patients with non-melanoma skin cancers (NMSCs) on the face and the scalp. An expected recurrence-free rate/cure rate of > 97% after 14 years was calculated. Curettage and cryoablation is thus a viable alternative in the treatment of NMSCs in the face and on the scalp. Cryoablation for skin cancers is mentioned in the NCCN clinical guidelines as an alternative to surgery when surgery is not feasible, or for very low-risk BCC and SCC. However, according to these guidelines, cryoablation is indicated to be inferior to photodynamic therapy (see review of Photodynamic therapy).

3.2.13 Thyroid cancer

Although radiofrequency (RF), ultrasound and laser ablation have been used to treat benign thyroid nodules (Jeong et al., 2008; Baek et al., 2010; Esnault et al., 2011; Piana et al., 2012), treatment of thyroid carcinoma is being examined by RF ablation only.

• Radiofrequency ablation

Monchik et al. (2006) assessed the long-term efficacy of RF ablation of local recurrence or focal distant metastases of well-differentiated thyroid cancer (WTC) in 16 patients. Four patients underwent RF ablation treatment of focal distant metastases from WTC. No recurrent disease was detected at the treatment site in 14 of the 16 patients treated at a mean follow-up of 40.7 months. More recently, Baek et al. (2011) evaluated the efficacy and safety of US-guided RF ablation in the control of metastatic WTC in 10 patients. The inclusion criteria for RF ablation were fewer than three metastatic tumors confirmed with US-guided fine-needle aspiration biopsy, and no metastatic tumor beyond the neck. After treatment, the mean volume of tumor decreased significantly. The authors concluded that RF ablation is effective for locoregional control of metastatic WTC in patients for whom surgery is not possible. Treatment of thyroid cancer with RF ablation is not mentioned in the ESMO and NCCN guidelines.

4. Is it safe?

4.1 Does thermal ablation have any complications or side effects?

The complications of using thermal ablation therapies are very diverse depending on tumor location and method of ablation but also the operator’s skills and familiarity with thermal ablation procedures may have as much influence on performance as device technology. In general, complications are considered to be less severe than those of radical surgery. One of the most common ones is the unintended thermal damage to nearby healthy structures. For instance, a number of reports in the literature have described bowel perforation during thermal ablation of liver, kidney, or prostate tumors (Tsoumakido et al., 2011), biliary stenosis, hepatic infraction, and grounding pad burn (Livraghi et al., 2011b). A potentially
devastating complication of thermal bone ablation is damage to the adjacent neural elements, particularly when treating vertebral, paraspinal, and pelvic tumors, in which the spinal cord and nerve roots are at risk of thermal injury (Ahrar and Stafford, 2011). Thermal ablation of musculoskeletal tumors near articulations can cause severe cartilage damage while thermal ablation of superficial tumors can result in painful skin burns. Tsoumakidou et al. (2011) describes in an article several insulation techniques (such as gas dissection, fluid injection, balloon interposition) that can be adopted to prevent some of these damages. Tumor recurrence after therapy may be regarded as another general complication of thermal ablation techniques. While the coagulative zone is occupied entirely by dead cells and amorphous material, the transitional rim still contain viable cells that may survive the adverse microconditions produced by the inflammatory environment and ultimately may give rise to tumor recurrences (Bhardwaj et al., 2009). Tumors of 3 cm or larger are most likely to recur and this is related to difficulties with achieving a complete ablation at the initial treatment. Large blood vessels are relatively protected from thermal injuries as the inflowing warm blood conducts the excessive temperature from the vessel wall, but the blood flow also prevents an adequate heating/freezing of perivascular tissues with consequent reduced destruction of tumor cells. The phenomenon is called “heat (or cold)-sink effect” and is the basis for incomplete ablations. No specific methods have presently been developed to overcome this problem (Gravante, 2010).

Radiofrequency (RF) ablation is a relatively safe procedure with a low mortality rate (0% to 2%) and a low major complication rate (6 to 9 %) in the treatment of liver metastasis (Wong et al., 2010). However, complications rates (major and minor) varied widely in the published literature (Livraghi et al., 2011b). The most common reported complications in liver tumor ablation are focal pain, pleural effusion, and regional hemorrhage, with most requiring no surgical intervention.

Complications of microwave (MW) ablation do not generally differ from those of RF ablation (Livraghi et al., 2011b). Liang et al. (2009) reported the complications for percutaneous MW ablation for the treatment of malignant liver tumors and the possible risk factors for complications in a large series of 1136 patients. Major complications occurred in 30 (2.6%) patients and included liver abscess and empyema, bile duct injury, perforation of the colon, tumor seeding, pleural effusion requiring thoracentesis, hemorrhage requiring arterial embolization, and skin burn requiring resection. Minor complications included fever, pain, asymptomatic pleural effusion, gallbladder wall thickening, and arterio-portal shunt, small stricture of the bile duct, and skin burn requiring no treatment. Livraghi et al. (2011b) reported complications by using precautions MW ablation in 736 patients with focal liver cancer. Major complications occurred in 22 cases (2.9%), and minor complications in 54 patients (7.3%). Results of this multicenter study confirmed those of single-center experiences, indicating that MW ablation is a safe procedure, with no mortality and a low rate of major complications.

Several complications have been known to occur after ultrasound ablation as well. These are mostly due to high-energy US waves reflected on gas or bony structures (Li et al., 2007). Gas in the bowel cannot be penetrated by HIFU, and sound waves are reflected back toward the transducer, which have high energy and may produce burns in the intervening tissue. Skin-burn can be caused by poor acoustic coupling between the skin and the therapeutic window or a previous operation scar. In cases of liver treatment, reflected US waves on ribs can
induce overlying soft tissue damage including the skin. Gas-containing bowel loops act in the same manner and can cause thermal injury of the bowel wall (Kim Y-S et al., 2008). Refraction artifacts can result in energy deposition in the soft tissues adjacent to the target area, and energy deposition can occur superficially to the target (Zhou, 2011).

Percutaneous laser ablation may be considered a safe treatment for small hepatocellular carcinoma (Arienti et al., 2008).

In general, the majority of complications for cryoablation are minor. Nevertheless, it may carry an increased risk of bleeding, because blood vessels are not cauterized as they would be with other heat ablation methods. During the procedure of cryoablation, patients may develop hypothermia (body temperature <35°C) and minor complications such as pain, low-grade fever, and bleeding complications as a result of cracking of the tumor on thawing. Most of the complications can be managed conservatively (Habash et al., 2007).

In contrast to surgery, chemotherapy and radiation therapy, thermal ablation may have almost no side effects. Depending on the organ site, patients may experience grade 1-2 pain for several days, occasionally lasting 1-2 weeks following an ablation procedure. Post ablation syndrome is characterized by a low-grade fever, malaise, chills, myalgia, delayed pain, and nausea and vomiting and appears, on average, 3 days after ablation and lasts 5 days (Wong et al., 2010). The duration depends on the volume of necrosis produced and the overall condition of the patient. The potential etiology is an inflammatory response as a result of the formation of necrotic tissue. Regardless of the resulting benefits, the performance of image-guided ablation procedures will always entail some degree of risk. Characterization of these risks and determination of precautions to avoid these complications are of extreme importance.

4.2 Contraindications for using thermal ablation

The exclusion criteria for using thermal ablation therapies are specific per tumor location and applied technology. Some of the general exclusion criteria for using thermal ablation are: women who are pregnant or nursing, clinical evidence of brain metastases, subjects with tumors lying <5 mm from vital structures or either adjacent to the skin or the chest wall, concurrent antiarrhythmic, disease with good prognostic factors, anticoagulant or immunosuppressive medication, cancers with an extensive intra-ductal component or lymphovascular invasion, tumors with very irregular margins, too large a size, scattered multiple foci, significant background illness or underlying medical condition (e.g. congestive heart failure, chronic obstructive pulmonary disease), metallic implants or other incompatibility with MRI (e.g. permanent implanted pacemakers).

5. Concluding remarks

Ablative technologies are relatively new and are still undergoing development. As a result, trials may not be comparable because of the different techniques, instruments and manufacturers, patients, tumor characteristics, ablation settings and operator skills. In addition, the current literature is dominated by small case series that are difficult to interpret and compare with each other. From a clinical point of view, except for kidney, liver and prostate cancer, the numbers of patients treated in clinical studies are rather small. The
lack of randomized controlled trial (RCT)-level evidence comparing thermal ablation with currently accepted curative treatments for cancer and small numbers of long-term follow-up studies makes drawing general conclusions concerning this treatment difficult. Moreover, meta-analyses are sometimes heavily skewed by excluding studies describing recent technologies and procedures.

Many of the research studies conducted evaluated the safety and feasibility of thermal ablation techniques. These studies have focused on the treatment of many types of cancer. Thermal ablation therapies provide a minimal or non-invasive approach to cancer therapy that is gaining clinical acceptance. Both clinical experience and studies have revealed a positive outcome in most of the thermal ablation applications depending on their endpoints and the investigated malignancy. The results of all of these trials suggest that thermal ablation can be performed with an acceptable safety profile and can result in reasonable local control of primary and metastatic tumors. Thermal ablative techniques may offer a palliative option and the ability to treat patients who are not surgical candidates. In some cases it may offer complete ablation of cancer, with less morbidity, better cosmetic results, shorter hospital stay and, for instance in liver, it may offer rates of cure approaching that of surgical resection (Bhardwaj et al., 2010). However, limitations in thermal ablative efficacy exist, including determination of 100% tumor killing, persistent growth of residual tumor at the ablation margin, the inability to effectively treat larger tumors at a single treatment session, and variability in complete treatment based on tumor location.

The role of thermal ablation in almost all clinical situations needs more study in large prospective trials with rigorous entry criteria, uniform treatment protocols, and precise outcome measurements over adequate follow-up time. There is much scientific work ahead to further evaluate thermal ablation therapy, including evaluating what is the preferred imaging modality to be deployed and what source of ablation energy to use. The question as of which thermal ablation technique is better has yet to be answered and would be better addressed with mature technologies and in a specific tumor cohort. While some energy sources may be better suited to certain applications, none has proved itself a clear favorite for all applications. In any case, the trend in all surgical disciplines is for less invasive treatments. Open surgery has given way to laparoscopic procedures in many areas, and minimally invasive thermal ablation therapies are gaining ground.

6. References

6.1 Scientific publications


Ballantine HT, Bell E, Manlapaz J. Progress and problems in the neurological applications of focused ultrasound. J Neurosurg 1960;17:858-76.


Dhar N, Ward JF, Cher ML, Jones JS. Primary full-gland prostate cryoablation in older men (> age of 75 years): results from 860 patients tracked with the COLD Registry. BJU Int. 2011;108(4):508-12.


Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. BJU Int. 2011. [Epub ahead of print]


6.2 Books

Tumor Ablation: Principles and Practice. Tito Livraghi (Adapter), Peter R. Mueller (Adapter), Stuart G. Silverman (Adapter), Eric van Sonnenberg (Editor), William McMullen (Editor), Luigi Solbiati (Editor) Springer 1st ed. 2005.

Percutaneous Tumor Ablation: Strategies and Techniques. Kelvin Hong (Editor), Christos Georgiades (Editor) Thieme ed. 2010.


6.3 Professional Societies/Organizations

European Society for Hyperthermic Oncology (www.esho.info)
Society for Thermal Medicine (www.thermaltherapy.org)
Japanese Society for Thermal Medicine (www.jsho.jp)
The Bioelectromagnetics Society (www.bems.org)
Focused Ultrasound Surgery Foundation (www.fusfoundation.org)
International Society for Therapeutic Ultrasound (www.istu.org)