Critical Reviews™ in Biomedical Engineering, 35(1-2), 37-121 (2007)

Thermal Therapy, Part III: Ablation Techniques

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ABSTRACT: Ablative treatments are gaining increasing attention as an alternative to standard surgical therapies, especially for patients with contraindication or those who refuse open surgery. Thermal ablation is used in clinical applications mainly for treating heart arrhythmias, benign prostate hyperplasia, and nonoperable liver tumors; there is also increasing application to other organ sites, including the kidney, lung, and brain. Potential benefits of thermal ablation include reduced morbidity and mortality in comparison with standard surgical resection and the ability to treat nonsurgical patients. The purpose of this review is to outline and discuss the engineering principles and biological responses by which thermal ablation techniques can provide elevation of temperature in organs within the human body. Because of the individual problems associated with each type of treatment, a wide range of ablation techniques have evolved including cryoablation as well as ultrasound, radiofrequency (RF), microwave, and laser ablation. Aspects of each ablation technique, including mechanisms of action, equipment required, selection of eligible patients, treatment techniques, and patient outcomes are presented, along with a discussion of limitations of the techniques and future research directions.

KEY WORDS: cryoablation, ultrasound ablation, RF ablation, microwave ablation, laser ablation

I. INTRODUCTION

The term ablation refers to the direct application of chemical or thermal therapies to a specific organ or tissue in an attempt to achieve eradication or substantial tissue destruction. The methods of tumor ablation most commonly used in current practice are divided into two main categories, namely, chemical ablation and thermal ablation. Chemical ablation includes therapies that are classified on the basis of universally accepted chemical nomenclature of agents such as ethanol and acetic acid that induce coagulation necrosis and cause tumor ablation.[1,2] Thermal

0278-940X/07 $35.00

ablation is performed by interventional radiologists and is much less invasive than open surgery. Recent developments in thermal ablation have expanded the treatment options for certain oncology patients. Minimally invasive, image-guided therapy may now provide effective local treatment of isolated or localized neoplastic disease, and may also be used as an adjunct to conventional surgery, systemic chemotherapy, or radiation. Thermal ablation can be an alternative to risky surgery, and may result in a patient with an inoperable tumor becoming a candidate for surgery.

This article reviews the engineering principles and biological responses by which thermal ablation techniques can provide the desired changes in temperature in organs within the human body. Ablation therapy includes vastly different techniques utilizing various sources to destroy tumors by applying thermal energy, with either heat produced by ultrasound, radiofrequency (RF), microwaves, and laser energy, or cold (cryoablation). Aspects of each ablation technique including mechanisms of action, equipment required, selection of eligible patients, treatment techniques, and patient outcomes are presented, along with a discussion of limitations of the techniques and future research directions.

II. THERMAL ABLATION THERAPY

Thermal ablation is the use of temperature change to destroy abnormal tissue or restore normal functioning. For both heating and cooling processes, thermal ablation or tissue destruction is a product of tissue temperature and treatment time. A low temperature requires longer treatment time, while a high-temperature treatment produces the same tissue effect in a short period of time. This relation is expressed as a thermal isoeffect dose.[3,4]

The main aim of thermal tumor ablation is to destroy an entire tumor by using heat to kill the malignant cells in a minimally invasive fashion without damaging adjacent vital structures. Heat from various sources can be used with equal effectiveness to destroy tumor cells. As long as adequate heat can be generated throughout the tumor volume, it is possible to eradicate the tumor.[5] Multiple energy sources can be used to provide the heat necessary to induce coagulation of malignant tissue by causing direct cell destruction. The bioheat equation describing induced heat transfer through tissue previously expressed by Pennes[6] and described in Part IV has been further simplified by Goldberg et al.[7] to the following.

$$\text{Coagulation necrosis} = \text{Energy deposited} \times \text{Local tissue interactions} - \text{Heat loss} \quad (1)$$

In general, “low-level” thermal therapy with temperatures ranging from 45°C to 55°C results in limited tissue ablation with insufficient success. On the other hand, thermal therapy with temperatures greater than 55°C (particularly temperatures ranging from 60°C to 100°C or even more) result in significant tissue ablation and a successful outcome.[8] Cell death results from coagulative necrosis, which occurs above 50°C after two minutes. The goal is to ablate the tumor plus a 1 cm margin of surrounding normal tissue. Current ablation devices can create coagulation zones 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.[9] Based on this, much attention has centered on increasing coagulation volume with the simultaneous use of multiple probes to increase overall energy deposition,[10–12] although this approach by itself may not produce the desired outcome of increased tumor destruction, given biologic limitations to energy deposition and tissue physiology (such as blood flow and poor thermal conductivity) that limit the effectiveness of increased energy deposition for in vivo coagulation.[13,14]

Stauffer and Goldberg[15] provided an introduction to thermal ablation therapy concerning all therapeutic treatments based on transfer of thermal energy into or out of the body. Their article introduces a special issue of the *International Journal of Hyperthermia* that contains nine articles covering a range of thermal ablation techniques from thermal conduction based cryotherapy and inductively coupled FerroRod implants, to EM techniques (such as RF electrodes, microwave antennas and laser sources), to large externally applied focused ultrasound sources.

II.A. Minimally Invasive Procedures

Some authors have referred to the procedures of thermal ablation as “minimally invasive” or “percutaneous” therapies; however, these terms should be used only where appropriate. Minimally invasive therapies refer to all therapeutic procedures that are less invasive than conventional open surgery. All percutaneous procedures are therefore minimally invasive, but not all minimally invasive therapies are performed or applied percutaneously. Indeed, the term “minimally invasive” is often used by surgeons to refer to procedures performed with minilaparotomy or laparoscopy.[16] Although less invasive than open surgery, these procedures are clearly more invasive than are percutaneous image-guided tumor ablation procedures. Inclusion of the term "percutaneous" as a prefix to "image-guided tumor ablation" is often too limiting because it does not reflect the fact that tumor ablation procedures can also be performed at laparoscopy, endoscopy, or surgery.[17,18] The choice of the approach for ablation is usually dictated by the training of the physician who is going to perform the ablation and suitability of the approach for patients.

Whenever possible, ablation is performed percutaneously. This approach is the least invasive, produces minimal morbidity, can be performed on an outpatient basis, requires only conscious sedation, is relatively inexpensive, and can be repeated as necessary to treat recurrent tumor. Advocates of laparoscopic thermal ablation claim that the laparoscopic approach provides some distinct advantages over the percutaneous approach.[19] General anesthesia is required for laparoscopy or open surgical treatment. However, conscious sedation is usually sufficient for a percutaneous approach. Recently, improvements in imaging technologies have enabled the development of minimally invasive tumor therapies, which rely on imaging guidance for the accurate percutaneous placement of needlelike applicators.[7,9] The potential benefits of minimally invasive, image-guided ablation of focal neoplasms, as compared with conventional surgical options, include (i) the ability to ablate and/or palliate tumors in nonsurgical candidates, (ii) reduced morbidity and costs and improved quality of life, and (iii) the ability to perform these procedures on an outpatient basis.[20]

II.B. Ablation Techniques

Ablation strategies, including cryoablation and the use of RF, microwaves, lasers, and high-intensity focused ultrasound (HIFU), are gaining increasing attention as an alternative to standard surgical therapies. Williams et al.[21] reviewed the above techniques to facilitate the creation of electrically isolated lesions within the atria. Although each of these techniques works slightly differently, the goal of all thermal sources (except those used in cryoablation—see Section III) is to heat tissue to a temperature (50°C) above which irreversible electrical isolation occurs.

Although ablation devices are often referred to as "needles" or other nonspecific terms, they do not always conform to these precise classifications. Hence, the term "applicator" should be used generally to describe all devices. For specificity, RF applicators are electrodes, microwave applicators are antennas, and laser applicators are fibers. On the basis of convention and consensus, cryoprobes are used to freeze tissue during cryoablation. For reporting completeness, a reference describing the appropriate applicator(s) should be cited unless the report describes a new prototype device, in which case an appropriate figure and/or schematic should be provided.[1]

A thermal ablation device generally consists of an applicator that is introduced into the tumor under imaging guidance. Energy deposited by this applicator results in heating of the surrounding tissue. The specific absorption rate (SAR) is only significant within a few millimeters of the applicator. Contrary to many hyperthermia devices, most of the tissue is heated mainly by thermal conduction from the hot region near the applicator.[22] Catheters are commonly used to insert devices, such as angioplasty balloons, through blood vessels into various sites within the body.[23] Catheter designs with multiple needle electrodes are of interest in some cases.[24]

Typically, thermal ablation is applied by surgeons, gastro oncologists, or radiologists using minimally invasive procedures (laparoscopy or percutaneously) using accurate monitoring systems such as magnetic resonance (MR), computed tomography (CT), or thermal mapping to guide the percutaneous placement of applicators into the selected target.[25,26] Because in most cases adequate lesion conspicuity and visualization of the applicator can be achieved with any of these methods, the choice of imaging technique is often dictated by personal preference or research interests.[7] Efforts to generate specific tissue interactions with tissue in a safe and reproducible manner have been restricted by the availability of controllable energy sources, accurate monitoring systems, and complications unique to treating each specific organ.[15]

II.C. Clinical Applications

Thermal ablation has been most commonly employed for the treatment of liver tumors; however, interest is growing for treatment of tumors in the kidney, lung, rectum, breast, prostate, and musculoskeletal system. Thermal ablation is also being investigated for several other malignancies, including carcinoma of the thyroid, primary breast tumors, and adrenal neoplasms.[22] A major advantage of thermal ablation is the ability to treat a tumor with a defined volume in sites where surgery itself is difficult (such as liver) or where organ function preservation is needed or desired (such as prostate and uterus). Nevertheless, this form of therapy may find little use for large bulky tumors such as bone[27,28] and neck nodules and superficial disease involving the skin.[29]

The clinical application of thermal ablation usually includes the following steps: preoperative evaluation, choice of approach (percutaneous, laparoscopy, or laparotomy), anesthesia and medications, applicator placement and treatment strategy, and follow-up. The preoperative evaluation begins with a review of the pertinent imaging studies. Good-quality imaging is the fundamental imaging examination on which the candidacy of a patient for thermal ablation is based. These preoperative imaging studies are used to determine the number and size of tumors and their relationship to surrounding structures such as blood vessels, bile ducts, gallbladder, diaphragm, and bowel. Patients are considered potential candidates if they have fewer than five tumors, each < 5 cm in diameter, and no evidence of extrahepatic tumor.[30]

Given the large number of potential energy sources available to achieve thermal therapy and the different strategies for applying them, important questions have emerged as to which modalities and modifications are most appropriate for given clinical scenarios. In this section, we provide a brief overview of the use of thermal ablation and other clinical modalities in the treatment of organ systems to date.

1. Liver

Cancerous (malignant) tumors in the liver may have either originated in the liver (primary liver cancer) or spread from cancer sites elsewhere in the body (metastatic liver cancer). Most cancerous tumors in the liver are metastatic. While there are other types of liver cancer, the most common form in adults is hepatocellular carcinoma (HCC). It begins in the hepatocytes, the main type of liver cell. About three out of four primary liver cancers are of this type. HCC is the fourth most common cause of cancer-related deaths worldwide, with approximately one million new cases are reported annually.[31] Mortality is virtually 100% when these tumors are not treated. Surgical resection is currently the standard treatment of choice, because it has been shown to provide survival benefits, while systemic chemotherapy and radiotherapy are largely ineffective. However, only 5–15% of patients with HCC or hepatic metastasis are candidates for curative surgery due to a variety of criteria, such as multifocal disease, tumor size, too many tumors, location of tumor in relation to a key vessel, and underlying medical problems that increase the surgical risk. Other treatment options include intra-arterial chemotherapy, transcatheter arterial chemoembolization, percutaneous ethanol injection, cryotherapy, thermotherapy, proton therapy, or combinations of these treatments.[32–36] There is also significant perioperative morbidity and mortality. The average five-year survival rate after successful resection for both HCC and metastasis is only 20–40%.[34] A considerable number of patients will develop recurrence of tumor, which is usually fatal.[37]

Today, there is a demand for minimally invasive techniques for treating hepatic malignancies, with an increasing number of relevant scientific articles that provide a good review on treatment of primary and secondary malignant hepatic tumors by thermal ablation.[5,9,38-48]

2. Lung

The lung is the most common site for primary cancer worldwide, as well as a common site of metastases for various malignancies.[49] The majority of patients with primary and secondary lung malignancies are not candidates for surgery owing to poor cardiorespiratory reserve. Conventional treatments for such patients typically include external-beam radiation therapy, with or without systemic chemotherapy.[50] One of the most promising alternatives to surgical removal of lung tumors is eliminating the tumor cells using heat, especially through electromagnetic (EM) energy. Thermal ablation is a useful alternative treatment for patients with small, early stage lung cancer who wish to avoid conventional surgery or are considered not fit to undergo surgery. The same applies to patients who have a small number of metastases in their lungs that have originated in other tissues such as kidney, intestine, or breast. Thermal ablation may be used to treat a lung tumor that is too large to remove surgically. Following thermal ablation, the lung tumor is reduced in size, so that the remaining tumor cells are more easily eliminated by chemotherapy or radiation therapy.

3. Prostate

The prostate is a walnut-sized gland that forms part of the male reproductive system. The gland is made of two regions, enclosed by an outer layer of tissue. It is located in front of the rectum and just below the bladder. It is common for the prostate gland to become enlarged as a man ages, a condition referred as benign prostatic hyperplasia (BPH). Pathological evidence of BPH is seen in more than 80% of the male population 75 years of age or older.[51] Since conventional treatment of prostate diseases can be associated with significant side effects and complications, less invasive treatment alternatives are available. Because of the anatomical location and easy accessibility of the prostate, many newer treatment modalities using thermal ablation have been applied to this organ. These include not only heating of the pathological tissue, but also freezing. Some of these treatment techniques have been shown to be effective and safe, and have been widely used clinically.[52] The current concept of thermal therapy for BPH is to destroy the hypertrophic tissue in the preurethral area (transition zone) by increasing tissue temperature to more than 45°C.

4. Kidney

The kidneys are each filled with tiny tubules that clean and filter the blood to remove waste and make urine. Renal cell cancer is a malignancy involving these tubules. Renal tumor ablation is considered to be an effective, safe procedure for treating renal cell cancer. Indications include a prior partial or total nephrectomy, pre-existing renal insufficiency, and various comorbidities making the patient a high surgical risk. The retroperitoneal location minimizes the risk of major bleeding, while the exophytic (peripheral) location of many renal tumors decreases the chances of injury to the central collecting system.[22] Solid renal masses have been traditionally removed surgically with either total or, if possible, partial nephrectomy. Many patients who present with small incidental solid renal masses are in their later stages of life. These masses are often exophytic, slowly growing renal cell carcinomas that will not often affect patient longevity.[53] Although resection currently remains the standard of care for renal carcinoma, the search for less invasive treatments has led to alternative surgical approaches. Even less invasive, and appropriate for many groups of patients, is percutaneous thermal ablation, which induces tumor necrosis via lethal hyperthermia.[54] There are a number of relevant scientific articles that provide a good reviews of various ablation techniques as they apply to the management of renal tumors.[55,56]

5. Breast

At least 10% of the women in the western world face the prospect of developing breast cancer. The tendency in modern treatment of these tumors is toward less invasive local treatment. Today, breast conserving surgery (BCS) has become more common than mastectomy in many countries. BCS and mastectomy combined with radiation are associated with good long-term outcome. The survival rate after BCS of ductal carcinoma in situ is approximately 98%, whereas virtually 100% of these patents are cancer free after mastectomy.[57,58] However, multiple treatments and additional adjuvant care are needed in up to 50% of BCS cases, resulting in higher associated costs compared to mastectomy alone. Recently, approaches other than traditional surgery have been explored to satisfy these demands.[59–61] These techniques include cryosurgery, laser ablation, focused ultrasound, and RF ablation. Potential benefits with these techniques are reduced morbidity rates, reduced treatment duration, and the ability to perform therapy for patients in poor medical condition on an outpatient basis.[62]

6. Bone

Surgical treatment of bone tumors often requires a generous resection of bone, leaving defects that are difficult to span. 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.[63,64] With thermal ablation, painful bone tumors, such as osteoid osteoma and metastasesin vertebrae, can be treated effectively. The procedure is performed under local anesthesia/conscious sedation since there may be some bone drilling required.

7. Cardiac Arrhythmias

There are a variety of clinical conditions that can cause cardiac arrhythmia (abnormal heart rate or rhythm)[65]; however, all arrhythmias have at their root an abnormal focus of electrical activity or an abnormal conducting pathway within the heart. They all prevent the heart from pumping blood into the circulatory system at a rate sufficient to meet the body's needs.[66,67] Arrhythmias can arise from a focal region (resulting from triggered activity, abnormal automaticity, or microreentry), or can be due to a circus movement reentry, with the activation wave revolving around anatomical and/or functional obstacles.[67] The most common sources for abnormality lie above the atrioventricular (AV) node and are, therefore, referred to as supraventricular tachyarrhythmias (SVTs).[68] Atrial fibrillation (AF) is the most commonly encountered sustained arrhythmia in men over 60 years of age. It develops when a disturbance in the electrical signal causes the two upper atrial chambers of the heart to tremble rather than pump efficiently. It is associated with a twofold mortality risk and increased health-care costs. The relative inefficacy and the risks of pharmacologic approaches to AF therapy have contributed to increasing efforts to address AF with curative ablative strategies.

Until recently, the treatment of patients with cardiac arrhythmias was mostly palliative, involving lifelong dependence on medication. However, in a significant portion (10–15%) of these patients, available drug therapy has been found unsatisfactory because of a lack of meaningful response or unacceptable side effects. Surgical intervention has been the principal method of treatment in these cases.[66,69] In the last decade, minimally invasive thermal ablation has revolutionized the treatment of patients with cardiac diseases. Cardiac ablation is a procedure in which EM energy is delivered to the myocardium (heart muscle) via a catheter to create thermal lesions in order to disrupt or eliminate conduction pathways supporting the arrhythmia, instead of using a surgical blade.[69,70] The success of this therapy depends on two factors, namely, cardiac mapping and lesion formation.[71] Ablation approaches for AF focus on two alternate strategies, which are ablation of the substrate for initiation and ablation of the substrate for maintenance of AF.[72] There are an increasing number of articles being published that provide a good review on thermal ablation for cardiac treatments.[21,70,72–81]

III. CRYOABLATION

Cryoablation, also referred to as cryotherapy, cryosurgery, or cryosurgical ablation, is the oldest technique used for thermal ablation.[82] It is a treatment modality that uses subzero temperatures to selectively freeze and destroy undesirable tissue.[83] This technique, which falls within the larger category of thermal therapy, has its origins in the 1800s when advanced carcinomas of the breast and uterine cervix were treated with iced saline solutions. James Arnott applied iced saline solutions directly to large ulcerating cancers and observed a reduction in size, odor, discharge, pain, and hemorrhage.[84] Modern cryosurgery began through the collaborative work of a physician, Irving Cooper, and an engineer, Arnold Lee.[85] They built a cryosurgical probe capable of freezing brain tissues using liquid nitrogen. Since then, this technique has been used routinely to treat malignancies on the surface of the body (for example, dermatologic tumors), and has gained some acceptance as a clinical tool for the management of internal malignancies, including carcinoma of the prostate and kidney.[86] In the U.S., cryoablation is one of the most commonly used ablation methodologies.[87,88] Detailed reviews on cryoablation can be found in several publications.[38,83,89–97]

III.A. Technical Considerations

To apply cryablation precisely, it is necessary to understand the mechanisms of tissue destruction associated with this technique, and how to evaluate the extent of tissue freezing and thermal history in the frozen lesion. In the following sections, we discuss advances in mechanisms of tissue destruction and in cryoprobes and cryosurgical systems.

1. Mechanism of Tissue Destruction

The thermal history during cryoablation is complex, as is the mechanism of tissue destruction.[83,86,98] 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 cells at different locations in the frozen lesion will be at different temperatures for various periods of time, as a function of their distance from the probe surface, the cooling fluid employed, the shape of the probe, the number of probes used, and the type of tissue frozen. This complex thermal history, combined with the complex mechanism of damage during freezing, makes it difficult to predict the outcome of cryoablation protocol and the relation between the extent of freezing and the extent of tissue damage.[52,83]

Cell damage caused by cooling and freezing occurs at several levels, ranging from the nanoscale, molecular scale, mesoscale, cellular scale, and macroscale to whole tissue. The time scales relevant to cryoablation range from a few minutes to tens of minutes. Most types of mammalian cells can withstand low, nonfreezing temperatures for short periods of time. The phenomena related to cooling occur mainly at nanoscale and mesoscale length scales.[83] Cell damage may occur due to chemical damage or intracellular ice formation. The damage is of two types, namely, acute, which is immediate during cryosurgery, and long term. The lethal temperature is between – 20°C and – 40°C. In this temperature range, intracellular lethal ice crystals begin to form that will tear apart almost any cell. The cells are not the only structures damaged during cryoablation of the cancerous organ; the surrounding connective tissue and the smallest blood vessels (capillaries) are damaged and subsequently have an inadequate blood supply that is believed to slow the growth of cancer. The destructive process involves freezing the extracellular compartment and withdrawal of water from the cells occurring at – 15°C, creating dehydration. Intracellular ice crystal formation occurs at – 20°C to – 40°C, leading to mechanical cellular wall damage and denaturation of the proteins. Thawing results in fluid shift into the cells and cellular wall disruption.[99] Moreover, changes in intracellular ice growth speed indicate changes in the temperature gradient, and the distance between the ice front and the cell death boundary. Accordingly, different treatment end points should be chosen according to the speed of ice growth to increase accurate cell killing.[100] Various methods have been developed to increase the size of cryoablation (up to 10 cm diameter) in an attempt to treat large tumors.

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. After freezing, it is common to hold the tissue in a frozen state for a while, then either to completely thaw the tissue or to thaw only the outer edge of the frozen lesion and repeat the freeze-thaw cycle once or even twice more.[83] Repeated freeze-thaw cycles have been proven to be effective in animal studies,[101,102] and the technique has been practiced accordingly.[103] In addition, the application of a multineedle probe system can effectively increase the ablation volume and achieve complete tumor destruction.[104]

2. Probes

Cryoablation is performed by using a cryoprobe, a thin wandlike device with a handle or trigger or a series of small needles, attached via tubing to a source of nitrogen or argon, which supercools the probe tip to approximately – 100°C to 150°C. The 1966 advent[105] of probes cooled by liquid nitrogen in closed circulation marks the beginning of modern cryotherapy. A significant recent development is the introduction of cryotherapy probes based on argon gas rather than liquid nitrogen. Argon rapidly cools the probe tip to – 187°C and can be rapidly exchanged with helium at 67°C for an active thawing phase, producing a faster response to operator input and significantly accelerating the treatment.[106] Moreover, argon-based probes have a much smaller diameter, thus permitting direct, sharp transperineal insertion, avoiding the need for tract dilation and facilitating more conformal cryosurgery by allowing placement of more probes.[107]

Cryoablation probes (~ 10 mm diameter) are inserted into the organ under scanning guidance. 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. Under anesthesia, the organ is imaged and its dimensions measured. An aiming grid software program is then activated and images of the cancerous organ are projected on a screen. The ablative process is carried out by delivering the subfreezing temperature to the target lesion via penetrating vacuum cryoprobes. The process usually includes two or three freeze-thaw cycles, each freeze cycle lasting 7–30 min. Under continuous monitoring, cryotherapy probes are placed at predetermined sites within the object. The freezing starts at the front part of the target lesion by activating the front probes, followed by the middle, and finally the back probes. The simultaneous insertion of multiple probes into the target lesion can effectively increase the ablation area.

3. Mathematical Models and Computer Simulations

Theoretical models and computer simulations are powerful tools for improving currently used techniques and for investigating and improving new techniques, providing vital information on the electrical and thermal behavior of ablation rapidly and at low cost. In the future, they could even help to plan individual treatments for each patient.[108] Development of mathematical models to predict the extent of tissue freezing during cryoablation began soon after the development of the first modern cryosurgical probes in the late 1960s.[83] Cooper and Trezek[109,110] developed the first mathematical models to describe and predict the extent of the frozen region during cryosurgery. Comini and del Guidice[111] used the finite element technique to predict the extent of freezing in realistic geometries. Rubinsky and Shitzer[112,113] were the first to try to optimize cryosurgery mathematically. They suggested the use of inverse mathematical techniques for designing optimum cryosurgical protocols. Their model used experimental biophysical data on the thermal parameters required for tissue and combined this data with solutions to the inverse heat transfer equation. In the mid-1990s, Rabin and Shitzer[114] developed additional techniques for solving inverse problems in cryosurgery. They developed mathematical models for predicting the extent of freezing during cryosurgery.

Jankun et al.[115] developed an interactive tool to assist in cryoablation therapy through computer modeling, simulation, and visualization. CryoSim, a software package, accepts a set of acquired and processed three-dimensional (3D) ultrasound images, then models heat diffusion (formation of the ice ball) based on numerical approximation of the heat equation and knowledge of the thermal properties of the underlying tissues. Results of cryoexperiments were found to be significantly similar to those generated by CryoSim. The latest version of CryoSim is described in Wojtowicz et al.[116]

Hahn et al.[117] developed a computer-based cryotherapy simulation system that mimics the major surgical steps involved in the procedure. The simulated real-time ultrasound display is generated from 3D ultrasound data sets where the interaction of the ultrasound with the instruments as well as the frozen tissue are simulated by image processing. The thermal and mechanical simulations of the tissue are done using a modified finite element method (FEM) and finite difference time domain (FDTD) method optimized for real-time performance. The simulator developed is a part of a comprehensive training program, including a computer-based learning system and hands-on training program with a proctor, designed to familiarize the physician with the technique and equipment involved.

III.B. Clinical Advantages and Applications

The efficacy of cryotherapy is mainly reflected by the clinical outcome of patients in terms of the tumor recurrence rate and the survival benefit.

1. Cancer Treatment

Cryotherapy 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. It is a highly effective treatment for a broad range of cancers, including liver, prostate, and breast cancer as well as benign skin conditions. Cryoablation may be also 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).

a. Liver

The use of cryotherapy for treating liver tumors was first described by Cooper.[118] Korpan[119] conducted a randomized, controlled trial that evaluated survival and disease-free rates of patients with primary liver metastases treated with cryosurgery or conventional surgical techniques. A greater number of patients treated with cryogenic surgery survived at three, five, and ten years (60%, 44%, and 19%, respectively) compared with patients treated with conventional surgical techniques (51%, 36%, and 8%, respectively). Zhou et al.[120,121] reported a five-year survival rate of 34.8% for 145 patients with hepatic cryotherapy, which was almost comparable to the results with surgical resection. Five-year survival rates of 20%, 28%, and 39% were reported by Lam et al.,[122] Kerkar et al.,[123] and Goering et al.,[124] respectively. In a retrospective study of 308 patients, Bilchik et al.[125] compared cryoablation alone to cryoablation combined with RF ablation and/or resection in patients with unresectable primary and secondary liver tumors. The results suggest that RF ablation combined with cryosurgical ablation reduces the morbidity of multiple freezes; RF ablation alone is limited by tumor size (< 3 cm). Morbidity for patients who had cryosurgery with RF ablation was reported to be significantly lower than for those who had cryosurgery alone. An additional outcome measure included the local recurrence rate, which is another important outcome measure for cryotherapy. The recurrence rate is about 10–15% for hepatic cryotherapy and up to 40% for liver metastases.[126–128] Other encouraging clinical results were obtained by cryoablation alone,[129] by combining cryotherapy with surgical resection1,[27,130,131] and with chemotherapy.[132]

b. Prostate

One of the first applications of cryoablation technology was the transurethral cryoablation of BPH,[133] followed shortly thereafter by the treatment of prostate cancer via an open perineal approach.[134] The transperineal approach was introduced in 1974, initially using a single digitally guided cryoprobe repositioned as needed during the procedure.[135]

Tatsutani et al.[136] described the effect of cryoablation and rate of freezing in an in vivo prostate cancer cell experiment. The investigators showed that complete cell death is unlikely to occur at temperatures higher than – 20°C and that temperature lower than – 40°C are required to entirely destroy cells. Larson et al.[137] reported that cryoablation results in two human prostatic tissue zones, namely, a central zone of complete cellular necrosis surrounded by a more peripheral zone of cell damage, but not necrosis. They concluded that uniform coagulative necrosis of human prostatic tissue in vivo can be accomplished throughout a significantly larger zone with a double freeze than with a single freeze.

The efficacy and safety of the long-term experience with targeted cryoablation of prostate cancer for 590 patients at a community hospital was retrospectively reviewed by Bahn et al.[138] The mean follow-up time for all patients was 5.43 years. The rates of morbidity were modest, and no serious complications were observed. Cryoablation was shown to equal or surpass the outcome data of external-beam radiation, 3D conformal radiation, and brachytherapy.[138]

Anastasiadis et al.[139] compared health-related quality of life (QOL) as well as prostate-associated symptoms in 131 patients after primary and salvage cryoablation for clinically localized prostate cancer using a self-administered questionnaire. The study demonstrated that in selected patients, cryotherapy is a treatment option that has a functional outcome comparable to traditionally used prostate cancer treatments. More information regarding QOL is necessary for appropriate patient counseling and individual decision making in the presence of various treatment alternatives.

In summary, the use of cryoablation for the treatment of prostate cancer is feasible and can easily be transferred from the pioneering centers to the community hospitals without sacrificing safety or efficacy.[140] Furthermore, chemocryotherapy offers a potential alternative treatment for the control and eradication of prostate cancer.[141]

c. Kidney

The first reported clinical study of cryoablation as a nephron-sparing procedure was published by Delworth et al.,[142] who performed open cryoablation in two patients with solitary kidneys. The first patient had a 3 cm renal cell cancer and the second had a 10 cm angiomyolipoma. Operative times were 3.5 and 4.5 hr, respectively. Follow-up consisted of a magnetic resonance imaging (MRI) at one month, revealing a significant decrease of the renal carcinoma dimensions and at three months, and a 10% enlargement in angiomyolipoma size. Although no pathologic data were included in the study, the authors concluded that renal cryotherapy could be performed safely with minimal loss of renal function. Uchida et al.[143] treated two patients with symptomatic, metastatic renal cell carcinoma using percutaneous renal cryoablation. A percutaneous puncture was performed under ultrasound control into the center of the tumor. Although follow-up was short in these patients and no pathologic data was available, since they died of metastatic disease at one and ten months postoperatively, follow-up CT scans showed shrinkage of the cryolesion by 20% at one month in one patient, and by 81% at eight months in the second patient. Carvalhal et al.[91] and Moinzadeh et al.[97] critically review the principles and cumulative evidence available regarding cryotherapy for the treatment of renal tumors.

d. Breast

Cryoablation was successfully performed for 29 patients with ultrasound-visible primary invasive breast cancer $\leq$ 2.0 cm in size in an office-based setting with only local anesthesia. There were no complications to the procedure or postprocedural pain requiring narcotic pain medications. Cryoablation successfully destroyed 100% of cancers < 1.0 cm. For tumors between 1.0 and 1.5 cm, this success rate was achieved only in patients with invasive ductal carcinoma without a significant ductal carcinoma in situ (DCIS) component. For unselected tumors > 1.5 cm, cryoablation was not reliable with this technique. Patients with noncalcified DCIS experienced most cryoablation failures.[144] Caleffi et al.[145] reported on improvements in cryoprobe design and techniques of cryoablation as a minimally invasive alternative to open surgery for the treatment of benign breast tumors. In this study, which was conducted in 12 centers, 124 lesions in 102 patients were monitored for a period of 12 months after cryoablation. Patient satisfaction was good to excellent in 92% of the patients. The safety profile of this technique was excellent; all complications were minor. Evolution of cryoablation freezing techniques, coupled with improvements in cryoprobe design, has resulted in significant improvements in both safety and effectiveness.

Whitworth and Rewcastle[96] reviewed the topic of cryoablation for breast diseases. The authors stated: "Recent studies have demonstrated that, as a primary therapy for breast fibroadenoma, cryoablation is safe and effective with durable results that can be reproduced in community practices. Certain barriers do exist before cryoablation, or any other in situ ablation, can become a standard therapy for the treatment of localized breast malignancy. Investigations are underway to refine patient selection criteria and develop valid confirmatory assays so that clinical trials can begin. Cryolocalization, which creates a well-delineated, palpable mass of frozen tissue encompassing a tumor, is a relatively new application of cold in medicine. This strategy promises to reduce positive margin rates during lumpectomy of non- or barely-palpable tumors."

2. Cardiac Diseases

The use of low temperature as a therapeutic agent in the treatment of cardiac diseases can be traced to a report by Harrison et al.,[146] in which they described a new method of producing AV block. Since then, the use of cryotherapy in the treatment of tachyarrhythmias has expanded as new techniques have evolved. With the accumulation of cardiac surgical experience, cryoablation has been found to be a safe, time-sparing, and effective means of mapping and treating the substrate of cardiac arrhythmias.[76,147–152] Cryoablation also seems to be less damaging than heat-producing energy sources when applied directly on structures such as coronary arteries and the esophagus.[153] One of the main advantages of this energy source for ablation is the extremely low risk of AV block. This technique is therefore especially beneficial if ablation is planned in the vicinity of the AV node.[154] Cryoablation may become the technology of choice for ablation in close proximity of the AV node for either low pathway or accessory pathway ablation.[92]

Cryoablation is best performed before the mitral valve procedure to avoid exposure of sutures and nonbiological materials to the very low temperatures. After dissection and institution of cardiopulmonary bypass, the tip of the cryoprobe is bent to a suitable shape and placed at each lesion position.[153]

Skanes et al.[92] reviewed some of the unique features of catheter-based cryoablation and highlighted some of its potential advantages. De Ponti et al.[155] reported the experience of successful cryoablation of fast AV nodal pathway in a patient with recurrent AV nodal reentrant tachycardia after previous unsuccessful attempts of slow pathway ablation. Slow formation of a permanent lesion by cryothermal energy application allowed precise modulation of AV nodal conduction until the end points of complete fast pathway ablation were met with long-term cure of the arrhythmia. The above paper describes this new procedure along with the experience with the first cases of cryoablation in Iceland.

Recently, Milla et al.[156] used a cryoclamp device to produce consistent transmural lesions. This device may be useful in treating patients with AF on the beating heart without cardiopulmonary bypass. This device proved more effective than linear epicardial cryoablation at producing consistent transmural lesions.

III.C. Limitations

Cryotherapy is an alternative cancer treatment when surgical removal of a tumor may be difficult or, for some patients, impossible. But its long-term effectiveness is still being examined. Cryoablation of unresectable tumors has been an option for several years, but complications associated with the freezing of tissue can be problematic. Cryotherapy still has limited applications due to the size of the treatment probe.

Cryoablation appears to be the most appropriate thermal approach for treating larger-volume tumors (> 3 cm), with long-term follow-up data showing some survival benefit. The technique offers precise real-time assessment of the ablation process with 85–90% successful local control, which is superior to other ablative techniques. The major limitation for cryoablation is that it requires a laparotomy or at least laparoscopy with general anesthesia and a few days of hospital stay. Consequently, it is substantially more expensive than percutaneous techniques.[9] Cryotherapy is considered a localized therapy. It can only treat disease at a single site. It cannot treat cancer that has spread to other parts of the body. Because physicians treat the tumors they see on radiologic images, microscopic cancer can be missed.

Even though its use in the bone, kidneys, liver, and lung is promising, cryotherapy may be considered experimental. Although the U.S. Food and Drug Administration (FDA) has given general approval for the use of cryotherapy, the experience with cryotherapy is still in its early stages, and most physicians reserve it for patients who are not good candidates for other cancer treatments.

III.D. Complications

Cryoablation is not as well tested as RF ablation. Despite the safety (< 5% mortality rate) and survival benefits of cryotherapy, its application for treatment is limited by the relatively high complication rate (up to 40%).[42] Cryoablation may carry an increased risk of bleeding, because blood vessels are not cauterized as they would be with RF ablation or other heat ablation methods. During the procedure of cryotherapy, 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.[82,157–159]

Other postoperative complications include bile leakage, renal failure, urinary infection, rectal pain, erectile dysfunction, scrotal edema, hemorrhage, abscess formation in the frozen area, coagulopathy as a result of thrombocytopenia, acute tubular necrosis as a result of myoplobinuria and less frequently the “cryoshock” phenomenon, which is a syndrome of multiorgan failure, severe coagulopathy without the evidence of sepsis, decrease in the peak velocity of blood flow within cavernosal arteries, and increase in the time to achieve peak arterial flow. Most of the complications can be managed conservatively, except the “cryoshock” phenomenon, which carries a high mortality rate (18.2%).[106,140,160–162]

In general, the majority of complications are minor and require observation only. Complications are considered to be less severe than those of radical surgery. The major impediment to acceptance of the modality, however, is the lack of ability to accurately monitor cryoprobe placement and ice-ball formation. Further studies and follow-up are necessary to determine long-term oncological efficacy.

IV. ULTRASOUND

Sound is vibration. Ultrasound waves can be created by a special type of crystal that vibrates at a specific frequency when an electric current passes through it. The reverse is also true. The crystal will create electricity when vibrated. Both effects are useful in medical applications of sound. Ultrasound involves the propagation of sound waves at a frequency of 2–20 MHz. In this frequency range, an ultrasound wave can be harmlessly propagated as a mechanical wave through soft tissues and brought into a tight focus. Absorption of the associated mechanical energy results in heating of the medium.

There are many relevant scientific articles that provide a good review on physical background, technical realization, and clinical trials of ultrasound ablation.[163–168]

IV.A. Technical Considerations

1. Mechanisms and Capabilities

The mechanisms of tissue destruction with HIFU ablation are related to hyperthermia and cavitations.[166] In HIFU, both strong focusing (100–1000 gain in cross-sectional area of the beam) and high power (100–1000 W) are used to induce a high-intensity acoustic field in the focal region. Thermal and mechanical mechanisms are principally responsible for the therapeutic effects. The thermal effect is due to the conversion of wave energy to heat by a variety of mechanisms, including viscous shearing effects and relaxation processes. As a result, the tissue temperature can rapidly increase to 70–100°C above the protein denaturization temperature (~ 43°C), i.e., in the range of 70–100°C. Such high temperatures lead to coagulative necrosis almost instantly.[163]

HIFU has many unique capabilities and qualities, including the following. (i) When used with appropriate peak focal in situ intensities, HIFU can elevate tissue temperature in the focal zone up to the 80–100°C range in a very short exposure duration (1–10 s) while maintaining the intervening tissue temperature at a physiologically safe level. (ii) HIFU has the ability to penetrate deep into the body and deliver to a specific site thermal or mechanical energy with submillimeter accuracy. (iii)

HIFU can be applied externally and contact free to the tissue or organs that are being treated. (iv) HIFU can produce sharply demarcated and predictable lesions; the size and shape of each lesion conforms to the ultrasound beam dimensions, site intensity, and exposure radiation. (v) When individual lesions are combined in a matrix format, one can create a large contiguous lesion of desired size and shape. (vi) Since the tissue temperature is raised rapidly, blood perfusion effects are minimized during the HIFU procedure. (vii) Ultrasound is nonionizing and can be applied repeatedly. (viii) HIFU does not require a sterile environment; therefore, it can be performed as an outpatient treatment.[163,169–172]

While other thermal ablation techniques are limited by dissipation of heat into adjacent tissues, the rapid, focused deposition of UIFU ablation (0.5–1.0 s) produces local cavitations and temperatures of 65–100°C with little heating of adjacent tissues. Temperatures above 56°C for a period of 1 sd result in irreversible cell death, with a sharply defined region of tissue necrosis.[173] A major advantage of ultrasound is that the lesion formation is not dependent on surface heating, as in RF ablation.[73]

Ultrasound therapy has the potential to be combined with ultrasound imaging devices.[76] The ability to focus and accurately target a lesion with HIFU by using real-time ultrasound or MRI guidance allows precise ablation of lesions of any shape without damage to surrounding structures.[173]

2. Equipment and Approaches

A focused ultrasound ablation device includes an ultrasound source that might be an array of ultrasound emitting elements. The ultrasound emitting elements can be used selectively, and independently actuatable to emit ultrasound energy and focus the emitted ultrasound energy at a predetermined distance from the source such that the ultrasound energy is focused within anatomical tissue adjacent to the source. The anatomical tissue is heated by the focused ultrasound energy to form a lesion in the tissue of desired size and/or surface configuration. 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. To provide a focus with a given depth and shape, single element therapy transducers are designed using a flat piezoelectric element with a lens, a spherically curved element with concavity in the propagation direction, or a combination of transducer curvature and a lens. Such applicators may provide a fixed focus; however, they are limited in high-power applications because of mechanical self-heating of the element.

The most useful frequencies for depositing power in human sized anatomy (0.5–10 MHz) have wavelengths ranging from 0.1 to 3 mm, which are much shorter than the dimensions of both tumors and applicators. Thus, dispersion of the beam is minimal and well-collimated beams are directed into tumor size volumes. Due to the combination of short wavelength and low attenuation, ultrasound sources can be used to penetrate deep in the body while still focusing into small tumors. Ultrasound intensity decreases exponentially with depth in tissue, with a trade-off between effective localization of power superficially at the higher frequencies and deeper penetration due to decreased attenuation at the lower frequencies. Technological changes are under way to make the HIFU devices more user friendly and effective.

There are currently two methods for the application of ultrasound energy, namely, extracorporeal (or transcutaneous)[174] and direct for percutaneous application with a needlelike applicator[175] and for intracavitary (and intracardiac) devices. HIFU ablation focuses an extracorporeal source of ultrasound to a specific target tissue. The ultrasound energy passes harmlessly through overlying tissues en route to a tightly focused target area. The rapid rate of energy deposition at the target tissue far exceeds the rate of heat dissipation, resulting in a rapid rate of temperature rise.[173]

The implementation of concurrent ultrasound imaging and therapy is an important requirement for successful acoustic therapy. One technique is to mount the imaging transducer confocally (usually through an aperture in the center) with the therapy transducer. Another technique is to use an ultrasound phased-array system for both imaging and therapy. A phased-array system would deliver HIFU to any location within a volume of tissue while providing simultaneous imaging of the treatment volume. One of the greatest challenges is to provide the wide bandwidth needed for high-resolution imaging while providing the narrow bandwidth required for optimal focusing. This promising technology would provide a highly versatile tool for image-guided acoustic therapy.[163]

Gentry and Smith[176] introduced a catheter device with integrated ultrasound imaging array and ultrasound ablation transducer. This device has been designed for use in interventional cardiac procedures in which the cardiac anatomy is first imaged using real-time 3D ultrasound, then ablated to treat arrhythmias. They used a concentric piezoelectric transducer ring operating at 10 MHz that surrounds the imaging array. It can produce a spatial-peak, temporal-average intensity up to 16 W/

cm^2. The ablation device has been used to heat tissue-mimicking rubber 14°C, as well as create lesions in fresh bovine tissue.

3. Modeling and Simulation

The feasibility of using ultrasound to induce cardiac tissue necrosis for the treatment of arrhythmias was investigated by Zimmer et al.[177] A theoretical model was used to optimize the operating frequency for necrosis of highly perfused muscle tissue. From these simulations it appeared that frequencies from 10 to 15 MHz produce the deepest lesions at ultrasound intensities between 15 and 30 W/cm^2.

Malinen et al.[178] simulated the thermal dose in ultrasound surgery of the breast. The optimization algorithm is extended by setting the inequality constraint approximations to temperature in healthy tissue as well as in the tumor region. In addition, the simulations are accomplished in realistic 3D geometry with varying thermal parameters. The authors also showed the potential of the hemispherical phased-array applicator for ultrasound surgery of the breast. With such an applicator, larger tissue volumes can be treated with shorter time as compared to single element transducers. In the simulation, the geometrical focus of the applicator was placed mechanically in the middle of the treatable region. The whole tumor region was then scanned electrically by changing the phase of the emitted wave from individual elements. The simulation indicated that a feasible treatment plan can be achieved. The desired thermal dose was achieved for tumors with diameter from 1.5 to 2.4 cm, depending on the position of the tumor. The maximum temperature limitations of 45°C in a healthy region and 80°C in a tumor region could be maintained.

IV.B. Clinical Advantages and Applications

The concept of using HIFU as a noninvasive therapy has attracted attention in medicine for 60 years.[179] Its therapeutic applications were first envisioned in the 1940s by Lynn et al.,[180] and later pursued by Fry et al.[169] The main advantage of ultrasound is that it can be collimated or focused and has a long depth of penetration.[181] During treatment, temperatures at the point of focus rapidly rise to greater than 80°C. In recent years, HIFU has been used successfully for several deep tissue thermal ablation applications.[182–184]

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. Advantages of HIFU include the ability to focus the area of therapy with remarkably sharp margins. In contrast to radiation therapy, there is no limitation on the cumulative HIFU dose; thus, the procedure can be repeated as many times as required. Also, performance of HIFU does not preclude other therapeutic options, including subsequent surgery. Clinical side effects in early trials involved damage to tissue outside the target area.[173]

1. Cancer Treatment

HIFU therapy may be used alone or in combination with other therapies for cancer treatment. A study by Wu et al.,[185] in which consecutive patients were alternately assigned to one of two treatment protocols, provides convincing evidence that subjects treated with chemoembolization (embolization is the process of injecting a foreign substance into the tumor to stop the blood flow) and HIFU ablation have greater tumor regression and a significant survival advantage compared with the group treated with chemoembolization alone.

HIFU therapy is currently in clinical and trial use to treat cancer of the breast,[183,186–188] brain,[189] prostate,[165,168,190–195] liver,[185,196] kidney,[197] uterus,[184,198,199] and pancreas.[200] Enhancement of drug delivery to tumors with focused ultrasound has been demonstrated.[201,202] Proliferation and tumorigenesis after HIFU treatment has been significantly reduced with little or no toxicity and no adverse effects. In a number of studies, HIFU treatment has been administered extracorporeally, without sedation or anesthesia, with complete patient tolerance.[163] The concern of tumor metastasis due to HIFU has been addressed and evidence against it has been presented.[203]

2. Cardiac Diseases

Ultrasound has been investigated for use in performing the actual ablations necessary to treat AF. The amount of energy transferred from the acoustic wave to the tissue is directly proportional to both the intensity of the wave and the absorption coefficient of the tissue.[204] Thus, if the ultrasound ablation transducer transmits into a medium with a low absorption coefficient (for example, water and blood), unlike RF ablation, the catheter tip need not be in direct contact with the myocardium.[176]

A commercial ablation transducer was reported to have created circumferential lesions in human pulmonary vein ostia after a 2 min ablation procedure. The ablation catheter operated with an 8 MHz transducer mounted in the center of a saline filled balloon. In one single center series, an ultrasound balloon was deployed in 15 patients in the superior and left interior pulmonary veins. The ablation time for each application was two minutes and the balloon was left inflated for a further minute postablation to reduce the possibility of acute contraction of the vein. The mean number of ultrasound applications required to isolate each vein was four with a range of 1–29 applications. Over a 35 week clinical follow-up period, nine of the fifteen patients remained in sinus rhythm off antiarrhythmic drug therapy.[205]

Ninet et al.[206] carried out a multicenter trial study for 103 patients from September 2002 through February 2004. AF duration ranged from 6 to 240 months (mean, 44 months) and was permanent in 76 (74%) patients, paroxysmal in 22 (21%) patients, and persistent in 5 (5%) patients. All patients had concomitant operations, and ablation was performed epicardially on the beating heart before the concomitant procedure. The device automatically created a circumferential left atrial ablation around the pulmonary veins in an average of 10 min, and an additional mitral line was created epicardially in 35 (34%) patients with a handheld device by using the same technology. No complications or deaths were device or procedure related. There were 4 (3.8%) early deaths and 2 late extracardiac deaths. The 6-month follow-up was complete in all survivors. At the 6-month visit, freedom from AF was 85% in the entire study group.

IV.C. Limitations

HIFU ablation offers a truly noninvasive treatment method with no skin incision, yet with precise targeting of tissues for therapy.[173] The main drawback of ultrasound has been the difficulty in producing stable and durable transducers of small enough dimensions for use in catheters.

There are potential limitations to the clinical application of HIFU, and to the planning and the actual delivery of treatment. HIFU cannot be directed through air-filled viscera such as the lung or bowel, and other obstructions such as bone can absorb or reflect an ultrasound beam. For this reason, tumors in the dome of the liver are not likely to be suitable targets for HIFU, unless further invasive procedures are performed, such as injection of saline into the pleural cavity to produce an acoustic window. HIFU is usually performed under general anesthesia to ensure patient comfort and immobility. This is generally regarded as a limitation, but general anesthesia does provide a means to control respiratory excursion in organs such as liver and kidney.[207] Realizing the full potential of HIFU ablation, however, requires precise targeting and monitoring. A major limitation in this regard is the lack of real-time high-quality imaging and treatment monitoring.

IV.D. Complications

As a noninvasive therapy, ultrasound appears to be effective, safe, and feasible in the treatment of tumors. It may play an important role in the ablation of large tumors. HIFU is a potential treatment that can induce complete coagulation necrosis of a targeted tumor, at depth, through the intact skin.[179] A Chinese study[200] evaluated sonographically guided HIFU ablation in the treatment of patients with advanced-stage pancreatic cancer. The team followed eight patients who underwent HIFU ablation and noted changes in symptoms and survival time. No complications were observed, and preexisting severe back pain disappeared after intervention. Follow-up images revealed an absence of tumor blood supply and shrinkage of the ablated tumor. Four patients died, and four patients were alive at the time of this writing, with a median survival time of 11.25 months. The authors concluded that HIFU ablation is safe and feasible in the treatment of advanced pancreatic cancer.

V. RF ABLATION

RF waves (ranging from hundreds of kilohertz to a several megahertz) are comprised of EM energy composed of oscillating electric and magnetic fields that travel through space at the speed of light (3×10^8 m/s) that do not require a medium for transmission. RF waves radiate outward from their transmission source in energy packets that combine the characteristics of waves and particles. They are reflected from, refracted around, or absorbed by their receivers or by any object in their path. The use of RF energy to produce thermal tissue destruction has been the focus of increasing research and applications in recent years.[19,208] RF ablation is the most commonly used in the United States,[209] with an increasing number of scientific articles reviewing the physical background, technical realization, and clinical aspects of this technique appearing worldwide.[37,45,59,158,210–221]

V.A. Technical Considerations

RF ablation is an electrosurgical technique that uses a high-frequency alternating current to heat tissues to the point of desiccation (thermal coagulation).[14] RF ablation applies to coagulation induction from RF energy sources with frequencies less than 30 MHz, although most currently available devices function in the 375–500 kHz range.[222]

1. Mechanisms

RF generators approved for clinical catheter ablation are limited to around 200 W output. The ability of RF applicator to induce ablation depends on the conduction of localized RF energy and heat convection by blood.[223] RF energy is capable of creating therapeutic tissue ablation by achieving higher temperatures (> 60°C) over a shorter duration (3–5 min) when compared with other thermal modalities. This offers an advantage over other systems, especially when compared with the conventional 30–60 min needed for the treatment of tissue via hyperthermia (40–44°C) and for low-range microwave thermal therapy (in the range of 45–55°C).[8]

With RF ablation, relatively small probes are placed into the tumor and RF energy deposited into the tumor tissue. The RF energy causes the tissue around the tip of the probe to heat up to a high temperature above which cells break apart and die. Since RF energy kills both tumor and nontumor cells, the goal is to place the probes so that they destroy the entire tumor as well as an adequate rim of nontumorous tissue around the tumor. This procedure is usually performed by placing one or more probes through small (less than 1 cm) incisions in the skin and using either ultrasound or a CT scanner to guide the tip into the tumor. For those tumors difficult to visualize, this procedure can also be performed in the operating room using a standard and much larger upper abdominal incision.

An effective approach to increase the efficacy of RF ablation is to modulate the biologic environment of treated tissues.[7] Along these lines, several investigators have demonstrated the possibility of increasing RF tissue heating and coagulation during RF ablation by altering electrical and/or thermal conduction by injecting a concentrated NaCl solution into the tissues during RF application.[224,225]

In two animal studies alone,[226,227] vascular occlusion combined with RF ablation increased the volume of necrosis in a short period of time, created a more spherical lesion, and increased the time tissue is exposed to lethal temperatures when compared with RF ablation alone. This technique could therefore be applied to humans to destroy large tumor nodules.

2. Electrodes and Approaches

The first generation of monopolar electrodes was introduced in 1990 by McGahan et al.[228] They showed that RF electrocautery could ablate hepatic lesions up to 10 mm in diameter. However, larger lesions could not be coagulated with a single probe because of charring, which limits the effectiveness of the probe by preventing thermal destruction of liver parenchyma beyond the region of ablation. Technical developments of probes aim to maintain high probe-tip temperatures (around 90°C) without loss of contact caused by tissue desiccation or increased impedance resulting from passage of current through charred tissue.

Today, RF ablation can be performed through percutaneous, laparoscopic, thoracoscopic, and open approaches. The percutaneous approach is the least invasive route for RF ablation.[45] The probe placement can be guided by use of CT, MRI, or ultrasonography. Commercially available RF probes have an insulated shaft with the high-temperature component confined to the tip. The insulated shaft of the RF probe broadens the applicability of the technique for use in percutaneous and laparoscopic procedures. Early expandable electrodes had few prongs, no saline infusion, and low-power (around 50 W) generators.[215] The increase in RF power is in response to the small irregular lesions, created with less powerful devices that led to a high local recurrence rate and the need for multiple, overlapping ablations, even when treating small tumors. This problem is exacerbated when attempting to ablate lesions near major blood vessels.

Several innovations, such as pulsed energy deposition,[229] umbrella-shaped or multiprong electrodes,[7] saline infusion,[230] bipolar electrodes,[231–235] multipolar systems,[236–238] internally cooled electrode and an expandable electrode,[239] and multiple probes[240] have been introduced. The aim of the above innovations is to improve the effectiveness of RF ablation devices and enable the creation of larger lesions and therefore expand the potential clinical applications of RF ablation.

3. Multiple Applicators

Both RF ablation and microwave ablation necessitate multiple applications or multiple applicators to treat tumors greater than 2 cm, including a 1 cm ablation margin. For example, adequate treatment of a 3 cm tumor would require creation of a 5 cm zone of ablation assuming perfect placement of the probes. Since current clinically used RF devices can drive only a single applicator (electrode) at a time, large tumors have to be treated by multiple sequential applications.[241] Larger tumors can thus be treated either by sequential application or simultaneous application. Three distinct methods have been investigated by different groups that allow the simultaneous employment of multiple electrodes during RF ablation, namely, bipolar RF, simultaneous RF, and rapidly switched RF.[242] Laeseke et al.[243] developed a multiple-electrode RF system based on rapid switching between electrodes that allows for the simultaneous use of as many as three electrically independent electrodes. This system would allow physicians to simultaneously treat multiple tumors, substantially reducing procedure time and anesthesia risk.

Effective local ablation of different sizes of tumors with RF energy has been made possible by recent advancements in biomedical engineering. A RF interstitial tumor ablation (RITA) system has been applied to various tumors, such as hepatoma or renal cell carcinoma.[17,244,245] This system consists of a small needle with multiple antennas extending from the tip of the needle once the needle is inserted in the tissue. The energy heats the tissues surrounding the multihook antenna to 100°C, resulting in thermal damage and subsequent necrosis of spherical shape tissue 2 cm in diameter. Multiple needles can be inserted in the tissue to achieve a larger area of necrosis.[52] If multiple needle units become clinically available, large or irregularly shaped lesions could be treated more effectively than with conventional single probe units, and multiple tumors could be ablated simultaneously, thus potentially decreasing procedure time and anesthetic complications.[240]

4. Localization

The most difficult aspect of RF catheter ablation is localization of the correct ablation site. A method known as “entrainment mapping” can be employed for localization of reentrant pathways for hemodynamically stable reentrant arrhythmias. In this technique, the target tachyarrhythmia is first induced using stimulation approaches. Next, the ablation catheter is repeatedly repositioned within the suspected region of the heart. Trains of low-energy stimuli are then delivered at various sites while the arrhythmia continues, at a rate slightly faster (10–50 ms) than the intrinsic rate of the tachyarrhythmia. Certain criteria must be met before the catheter location is achieved. Pace mapping is another localization method that may be used for either focal or reentrant arrhythmias. In this technique, trains of low-energy stimuli are also delivered from multiple catheter positions within the suspected target region. The location in which the observed surface electrocardiogram is morphologically identical to that of the targeted tachyarrhythmia is considered to be at, or in very close proximity to, the site of initiation of the arrhythmia. Electroanatomical mapping, analogous to the use of a global positioning system (GPS), represents another localization method. This technique combines electrophysiological and spatial information and allows visualization of atrial activation in a 3D anatomical reconstruction of the atria. A catheter with a localization sensor on its top is repeatedly repositioned within the heart. Electrophysiological recordings from each site are recorded and associated with a specific spatial location relative to a system of localization sensors located under the patient.[67,246]

5. Thermal-Electrical Modeling

Temperature is a frequently used parameter to describe the predicted size of lesions computed by computational models. In many cases, temperature correlates poorly with lesion size.[247] Many computational studies have been reported in the literature to predict the growth of lesion size during ablation.[248–251] Still, the majority of these studies do not directly calculate lesion size. Surrogate end points, such as temperature,[225,229] are calculated and interpreted as being equivalent to lesion size. In many cases, these surrogate end points do not correlate well with clinical outcome and vary considerably. Many computational studies justify these surrogate end points by showing a high correlation between temperature isotherms and lesion size. However, temperature isotherms and lesion size have never actually been shown to be equivalent. On the other hand, there have been many FEM studies of cardiac RF ablation.[252,253] Fewer FEM modeling studies were conducted on cancer ablation, [254] hepatic ablation,[255] blood, myocardium, and torso tissues.[256]

Gopalakrishnan[257] proposed a theoretical model for epicardial RF ablation. However, such a model does not consider a dry ablation, but rather an irrigated electrode similar to the “pen electrode” introduced by Medtronics Inc. (Minneapolis, MN) for endocardial ablation.[258] Results from a computer implementation of the model using FEM suggest that transmural ablation lesions can be made in 4 mm-thick tissue. Effects of parameters such as tissue and saline layer thickness, irrigation rate, blood flow rate, and applied power are investigated. Saline is found to irrigate as well as ablate. Rise in saline temperature and consequent ablation by saline is more pronounced as saline layer becomes thicker.

V.B. Clinical Advantages and Applications

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. It is currently receiving the greatest clinical attention in Italy and the Far East, where HCC is more prevalent.[5,53,259] RF ablation is especially useful for patients who are not ideal surgical candidates, cannot undergo surgery, have recurrent tumors, or do not respond to conventional therapies. RF ablation may be reserved for patients at high risk for anesthesia, those with recurrent or progressive lesions, and those with smaller lesions sufficiently isolated from adjacent organs.[260]

Potential advantages of RF ablation include low complication rates (0–12%), reduced morbidity and mortality rates compared with standard surgical resection, and the ability to treat nonsurgical patients.[42,214] RF ablation may be performed as an open,[261] laparoscopic,[262] or percutaneous[263] procedure.

1. Cancer Treatment

RF ablation is an effective technique for treating tumors localized to certain organs such as the liver, lung, kidney, prostate, and others.

a. Liver

RF ablation has been increasingly used in modern management of unresectable malignant liver tumors.[45] It was first proposed in 1990 for the treatment of liver tumors.[46] Although surgery and liver transplant are considered the only curative treatment for HCC, few patients are eligible for RF ablation.[264] Eligibility criteria tend to vary by institution and physician. Contraindications include multiple tumors, decreased liver function, or multiple medical problems.

Percutaneous RF ablation of liver tumors is used in patients who have fewer than five hepatic tumors, each measuring < 5 cm, all of which are visible by sonography (or CT scan) with a safe and acceptable route of access. RF ablation by laparoscopy or laparotomy is reserved for patients with tumors that are not accessible by percutaneous RF ablation, tumors > 5 cm, and tumors in direct contact with the bowel. The laparoscopy approach offers the advantages of a quick recovery, combined with the advantages of a surgical approach. The procedure requires experience in laparoscopic ultrasound as well as laparoscopic, ultrasound-guided needle placement.[18,265]

There are several groups of patients who may derive benefit from RF ablation of liver tumors, such as cirrhotic patients with early stage HCC. Patients with bilobar, otherwise unresectable colorectal carcinoma liver metastases, unresectable colorectal carcinoma liver metastases who are treated on protocol with adjuvant hepatic artery infusion chemotherapy, and patients with symptomatic neuroendocrine tumor liver metastases may also benefit from this technique, along with selected patients with otherwise unresectable, nonneuroendocrine liver metastases with disease confined to the liver.[265]

Although many clinical investigations and trials have suggested that RF ablation could represent a viable and safe treatment option for nonsurgical patients with HCC or colorectal hepatic metastases,[18,208,209,266–289] the technique did not enjoy support until recently, in part because of the paucity of studies reporting long-term outcomes of treated patients. Shiina et al.,[275] who reported the largest single series study in Japan, recommended RF ablation to be used as the first-line nonsurgical treatment of choice because it requires fewer treatment sessions and shorter hospital stay to achieve complete necrosis of the tumor.

Allgaier et al.,[290] Mulier et al.,[291,292] and Lencioni[47] reviewed the status of RF thermal ablation as a new, minimally invasive technique and discussed its use for the nonsurgical treatment of HCCs. They indicated that preliminary short-term results are promising, although long-term studies (currently under way) are needed to fully evaluate the efficacy of RF ablation for liver tumors. Ng and Poon[45] reviewed this subject and focused on the role of RF ablation for liver malignancies, with special attention to the indication, approaches, complications, survival benefits, combination therapies, and comparison with other treatment modalities.

In the Netherlands, single-center reports suggest that RF ablation may be used successfully to control HCC in those patients awaiting liver transplantation. RF ablation is being increasingly used for colorectal liver metastases as an adjunct to surgical resection in cases of unresectable lesions. To date, there are still no data showing that such an approach is beneficial. For this reason, RF ablation for unresectable colorectal liver metastases is mainly used in clinical trials in the Netherlands. Within the multimodality of treatments for neuroendocrine metastases, RF ablation may be considered for either intention to cure (a somewhat rare outcome) or with the aim of reducing symptoms or prolonging life.[284]

In addition to the low complication rate, most, if not all, percutaneous RF ablation procedures can be performed in an outpatient setting under conscious sedation. However, optimal sedation regimens are required to minimize patient discomfort. The early clinical studies are very promising and it is clear that RF ablation is and will be a major therapeutic intervention in the local treatment of liver neoplasms for local cure.[53]

Rhim et al.[44] reviewed the Asian experience in the field of tumor ablation. Based on the survey data from Asian physicians who are currently performing image-guided tumor ablation, thermal ablation appears to have been mainly performed for patients with unresectable liver tumors. RF ablation has replaced many other local ablation techniques such as microwave or ethanol ablation in treating small focal hepatic tumors in recent years.

b. Lung

Success in treating liver malignancies with a percutaneous approach has created interest in active ongoing research on the ablation of tumors other than those of the liver. Lung tumors are well suited to RF ablation because the surrounding air in adjacent normal lung parenchyma provides an insulating effect and concentrates the RF energy within the tumor tissue.[224] Hence, less RF energy deposition is required to achieve adequate tumor heating than with intrahepatic pathology.

In patients with non-small-cell lung malignancy that are not candidates for surgery owing to poor cardiorespiratory reserve, RF ablation alone or followed by conventional radiation therapy with or without chemotherapy may prove to be a viable treatment option. In patients with metastatic disease, RF ablation may be suitable for treatment of a small tumor burden or for palliation of larger tumors that cause symptoms such as cough, hemoptysis, or pain. Patients with chest wall or osseous metastatic tumors in whom other therapies have failed may benefit from RF ablation as an alternative to radiation therapy.[212] Several hundred treatments of lung tumors have been performed worldwide, a sufficient number to develop a reasonable safety profile with negligible mortality, limited morbidity, short hospital stays, and enhanced quality of life.[49,220,293–304]

c. Kidney

RF ablation is also being studied as a minimally invasive treatment for patients with kidney cancer. An effective, minimally invasive therapy could postpone kidney failure and prolong kidney function in patients with multiple or hereditary kidney cancer, such as von Hippel-Lindau disease, which causes multiple, recurrent, and diffuse tumors. RF ablation may also provide a useful option for patients who are not operative candidates or have solitary kidneys, multiple medical problems, or unresectable tumors. Since the kidney is surrounded by fat, which has limited blood supply for cooling, the effectiveness of RF ablation for exophytic tumors is high. Since its first application in 1977,[305] many investigators have suggested that RF ablation could represent a promising, safe, and well-tolerated treatment for renal tumors.[54,245,306–314] Hines-Peralta and Goldberg[214] discussed how minimally invasive, image-guided RF tumor ablation is being incorporated as a clinical tool for the treatment of renal cell carcinoma. More recently, this technique has been introduced to treat focal renal tumors, particularly incidental lesions smaller than 3 cm in elderly patients and those with comorbid conditions.

d. Breast

RF ablation is considered to be the most promising treatment for breast cancer because of its effective destruction of cancer cells and its having a low complication rate.[315,316] A small case series involving the use of RF ablation in breast cancer in five patients suggests that it might play a role in select patient populations. However, it is too early to say that RF ablation is the therapy of choice for breast cancer. It is most likely that different techniques are necessary for different patients. Each of these techniques holds tremendous potential, and continued research is crucial. Currently, most of the ongoing trials consist of in situ ablation followed by standard surgical resection. The barrier to the widespread use of RF ablation in the breast at present is the lack of surgical excision data whereby the tumors are graded histologically and the margins are analyzed.[211] Finally, Bansal[317] described a successful clinical trial of RF ablation for breast cancer treatment.

e. Other Cancers

RF ablation may provide a safer option for removing abnormal prostate tissue,[318] as well as predictably destroying the entire gland with a low complication rate to the adjacent rectum, sphincter, bladder base, and urethra.[210,319] RF ablation can be the treatment of choice for the majority of patients suffering with a benign but painful bone tumor known as osteoid osteoma.[28,64,320] Osteoid osteomas predominantly occur in the pediatric age group and arise within the cortex of long bones.[53] Ablation of nerve tissue and nerve ganglia continues to be done safely and effectively in the treatment of multiple pain syndromes, including trigeminal neuralgia, cluster headaches, chronic segmental thoracic pain, cervicobrachialgia, and plantar fasciitis.[321–325]

Patients with functional or tumor disorders of the brain, such as Parkinson's disease, and benign or malignant lesions may also be candidates for RF ablation.[326] Recently, therapeutic efficacy of RF thermal ablation on primary pleural synovial sarcoma has been reported.[327]

A venue in which RF ablation may hold promise is the treatment of recurrent head and neck tumors. Many patients may not be surgical candidates for tumor resection because of the location and extent of tumors, concomitant debilitating medical conditions, or a history of multiple surgeries. These patients may be safely treated with RF ablation because the procedure is performed almost exclusively in the outpatient setting with local anesthesia and intravenous conscious sedation.[53]

2. Cardiac Diseases

RF ablation is increasingly being used for intraoperative treatment for arrhythmias such an AF, AV nodal reentrant tachycardia, and Wolf-Parkinson-White syndrome. A major drawback of these procedures, especially those that necessitate ablation close to the atriocentriclar node, is the risk of inadvertent AV block. In the cardiac ablation literature, 47°C is generally accepted as the point of onset of tissue damage.[293]

McRury and Haines discussed the role of electrical ablation, especially RF ablation, as a treatment for SVTs and reviewed the engineering principles and biological responses to ablation. The authors stated that RF catheter ablation is a successful technique in clinical arrhythmia management, with reported success rates of greater than 95% in many series. The indications for clinical RF catheter ablation continue to broaden.

Different electrode designs for cardiac RF ablation, such as handheld probes,[328–332] catheters,[333–336] and irrigated-tip probes,[337,338] have been used both experimentally and clinically. Several models of percutaneous RF cardiac ablation have been proposed, with several experimentally validated.[339,340]

Intensive research is currently under way in this area in both animal models and in clinical trials. The literature shows that RF ablation as an adjunctive procedure is a feasible, safe, time-saving, and effective means to cure cardiac diseases with negligible technical and time requirements.[329,341–357] Early reports of RF ablation for AF suggested that a limited right atrial linear ablation procedure might be able to terminate and prevent its recurrence.[335,358,359] However, right atrial ablation is not uniformly effective in preventing recurrence of atrial fibrillation. Accordingly, additional studies have been done combining right and left atrial linear ablation.[333]

Most electrophysiology laboratories have been working on catheter ablation for paroxysmal AF target pulmonary veins using a transseptal approach. The aim of the procedure is to achieve complete disconnection of the pulmonary veins, demonstrated by the disappearance or dissociation of their potentials. This is facilitated by the use of a circular catheter dedicated to the mapping of the pulmonary vein ostia, which allows the identification of the connections from the atrium to the vein. Using this approach to target all four pulmonary veins, 70% of patients are cured without the need for antiarrhythmic drugs. Some complications have been described, including tamponade, embolic events, and pulmonary vein stenosis.[360]

3. Snoring and Obstructive Sleep Apnea (OSA)

Snoring is a common affliction affecting persons of all ages, but particularly middle-aged and elderly men and women who are overweight. OSA is a disorder in which the sufferer's upper airway becomes intermittently blocked during sleep, creating an interruption in normal breathing. Although not all snorers have sleep apnea, snoring is a cardinal symptom of OSA and may, by this mechanism, be associated with increased morbidity.[361] Treatment of snoring and OSA is directed at the upper airway, with the therapeutic approach depending on the frequency and severity of the symptoms. Dental appliances and ventilators have both been effective at maintaining airway patency. However, these therapies are uncomfortable and suffer from low patient compliance rates (40–70%). Cure rates using surgical interventions have been between 30% and 75%.[362]

RF ablation of the soft palate aims to reduce the volume of the palate tissue and to improve the texture of the remaining palate for snoring so that it becomes more dynamically stable. It is usually an outpatient procedure that involves the use of a topical local anesthetic.[363] RF systems, which use needle electrodes to create precise regions of submucosal tissue coagulation, have been developed. Therefore, both the tissue volume and its resulting airway obstruction are reduced. Applicator probes have been developed to target specific tissues, including the base of the tongue.[68]

The National Institute for Clinical Excellence (NICE)[363] presented an overview of the subject based on medical literature and specialist opinion that included six studies, one randomized controlled study, two comparative studies, and three case studies. This overview was prepared to assist members of the Interventional Procedures Advisory Committee in making recommendations about the safety and efficacy of this interventional procedure. No existing systematic reviews or guidelines on this topic were identified during the literature search. The overview concluded that most studies use a carefully selected patient population, whose snoring has been determined to be attributable to the soft palate. Also, RF ablation was found to be less painful than other invasive alternatives.

V.C. Limitations

The limitation of the RF method can be traced to the physics of its operation. In particular, current flow away from the electrode is virtually omnidirectional, creating a time-averaged power deposition decay rate $P \sim 1/r^4$, where r is the radial distance from the electrode.[364] A fundamental understanding of RF principles is necessary to ensure maximum performance safety when performing this procedure in clinical practice.

RF ablation is a highly complex procedure that mandates appropriate and adequate training, operator skill, and dedicated clinical resources. Accordingly, the safety and efficacy of the RF ablation procedure will be highly dependent on the degree of operator experience and familiarity with RF ablation procedures.[53]

One of the major limitations of RF ablation is the extent of induced necrosis. The size of potentially treatable tumors is limited because the volume of active heating caused by this technique is limited to a few millimeters from the active element, with the remainder of tissue being heated by thermal conduction.[365] In addition, the diameter of the ablation zone usually does not exceed 4 cm unless the ablation probe is repositioned for a second ablation to obtain complete tumor necrosis.[366] Often, tumor cells survive, which leads to high recurrence rates.[209,266,367] Several techniques have been investigated for increasing lesion size and improving efficacy including cooled probes,[10] pulsed RF,[229] and saline-enhanced RF.[232,252]

Unpredictable electrical current paths between the ablation electrode and the grounding pad may lead to heterogeneous energy deposition and thus to eccentric ablation zones or even collateral damage. Skin burns at the grounding pad have been reported in a few instances.[368] Criticism of RF ablation has focused on the potential for incomplete ablation near blood vessels because of the heat sink effect of local blood flow.[369] If a tumor is near large vessels (for example, > 1–2 mm, or the vessels are visible by CT), it is unlikely that all the malignant cells adjacent to the vessel will be completely eradicated as a result of the previously described perfusion-mediated tissue cooling.[14] That does not mean such areas cannot undergo repeat treatment; a single RF ablation session is unlikely to adequately treat these lesions.[53]

Strategies are being pursued to improve RF ablation efficacy by altering the physiologic characteristics of the tumor, including tissue ionic conductivity and blood flow. Several investigators have been able to increase RF-induced necrosis by occluding blood flow to the liver during ablation procedures.[271,307,370,371]

V.D. Complications

RF ablation has a low complication rate (0–12%).[42,218,372] However, like all other ablation procedures, RF ablation involves some element of risk. The main criticisms of RF ablation have focused on (i) high local recurrence rates, particularly in the treatment of masses larger than 3 cm in diameter, (ii) the potential for incomplete tumor ablation near blood vessels because of the heat sink effect of local blood flow, (iii) difficulty in imaging of RF lesions, and (iv) evidence of surveying tumor cells even within RF lesions.[50] Varying degrees of complications can be expected, depending on factors such as the organ site and the aggressiveness of the procedure.[44] These complications range from reversible problems such as bleeding, damage to the arteries or veins, and blood clots, to potentially life-threatening complications such as cardiac perforation, valve trauma, and stroke. In addition to the well-known complications,[373] two broad categories of complications specific to methods of thermal ablation therapy, namely, grounding pad burns[374] and thermal damage to adjacent organs,[375] need to be fully addressed. The use of the high-current RF technique has increased the risk of one significant potential complication, which is burns at the grounding pad site. Deleterious heating has been encountered at grounding pad sites in several cases in which high-current RF has been used.[375] Goldberg et al.[374] determined which factors promote inappropriate thermal deposition at the grounding pad site during RF ablation. Temperatures were found not to be uniform underneath the entire grounding pad surface, with the greatest heating at the edges of the pad. Third-degree burns were observed when inappropriate grounding was used. Grounding pad construction was also found to influence the formation of skin burns, with lower temperatures achieved with use of foil pads than with mesh pads.

Initial reported success with RF ablation in liver tumors is coupled with its very low complication rate.[268,269,375] The most common reported complications in liver tumor ablation are focal pain, pleural effusion, and regional hemorrhage, with most requiring no surgical intervention. Mulier et al.[291] reported ten treatment-related deaths in their review of 1931 patients treated with RF ablation. Major complications occurred in 137 patients (7%) and the most common complications were impairment of hepatic function, hemorrhage, and infection.[215]

According to the multicenter (1139 patients in 11 institutions) survey data of the Korean study group of RF ablation, a spectrum of complications occurred after RF ablation of hepatic tumors. The prevalence of major complications was 2.43%. The most common complications were hepatic abscess (0.66%), peritoneal hemorrhage (0.46%), biloma (0.20%), ground pad burn (0.20%), pneumothorax (0.20%), and vasovagal reflex (0.13%). Other complications were biliary stricture, diaphragmatic injury, gastric ulcer, hemothorax, hepatic failure, hepatic infarction, renal infarction, sepsis, and transient ischemic attack. One procedure-related death (0.09%) occurred (due to peritoneal hemorrhage).[376]

Buscarini and Buscarini[377] conducted a study to describe the type and rate of complications in a series of patients with liver tumors treated by RF ablation. A total of 166 patients, 114 with HCC and 52 with liver metastasis, were treated by the percutaneous RF expandable system. Among 151 patients followed, there were 7 (4.6%) early major complications, severe pain with session interruption in 3 cases, capsular necrosis in 1 case, 1 abdominal wall necrosis, 1 dorsal burning, 1 peritoneal hemorrhage, and 3 (1.9%) delayed major complications, including sterile fluid collection at the site of the treated tumor in 2 cases and coetaneous seeding in 1 case. There were 49 (32.5%) minor complications. The complication rate is similar to that observed after percutaneous alcohol injection.

A team from the Netherlands evaluated the complication rates encountered in 122 patients after treatment of 143 liver tumors with RF ablation between June 1999 and November 2003. Death occurred in two cases. In both, RF ablation was combined with partial hepatectomy. The team found 19 major complications, including biliary tract damage, liver failure, hepatic abscess, peritoneal infection, intrahepatic hematoma, hepatic artery aneurysm, and pulmonary embolism, and 24 minor complications related to concomitant partial hepatectomy or laparotomy. The overall complication rate was 20.3%, and the rate of complications related directly to RF ablation was 9.8%. The team recommended that RF ablation be performed only by an experienced team comprising a hepatobiliary surgeon, gastroenterologist, hepatologist, and interventional radiologist.[378]

A Japanese research team detailed the types of complications found over five years of experience performing RF ablation for the treatment of unresectable HCC. Complications are classified in three groups, namely, vascular (portal vein thrombosis, hepatic vein thrombosis with partial hepatic congestion, hepatic infarction, and subcapsular hematoma), biliary (bile duct stenosis and biloma, abscess, and hemobilia), and extrahepatic (injury to the gastrointestinal tract, injury to the gallbladder, pneumothorax and hemothorax, and tumor seeding). The team concluded that most complications can be managed with conservative treatment, percutaneous or endoscopic drainage, or surgical repair.[379]

While controlled, long-term studies of RF ablation have not been done, survival rates are likely to be similar to that of patients undergoing surgery.[268,269,375] Sutherland et al.[48] conducted a systematic review of RF ablation for treating liver tumors. They compared RF ablation with other therapies for 13 cases of HCC and 13 cases for colorectal liver metastases (CLMs). There did not seem to be any distinct differences in the complication rates between RF ablation and any of the other procedures for treatment of HCC.

Finally, three important strategies for decreasing the rate of complications are prevention, early detection, and proper management. A physician who performs RF ablation of hepatic malignancies should be aware of the broad spectrum of major complications so that these strategies can be used.[375]

VI. MICROWAVE ABLATION

Microwaves occupy that portion of the EM spectrum between frequencies of 300 MHz to 300 GHz with wavelengths of approximately 1 m to 1 mm. Microwave ablation is the most recent development in the field of tumor ablation. The technique is similar to RF ablation in that it uses microwaves to heat tissues and it allows for flexible approaches to treatment, including percutaneous, laparoscopic, and open surgical access.[50] RF heating techniques use frequencies in the RF band where a near-field (quasi-static) condition applies. In the microwave frequency range, energy is coupled into tissues through waveguides or antennas (applicators) that emit microwaves (typically 915 MHz or 2.45 GHz). The shorter wavelengths of microwaves, as compared to RF, provide the capability to direct and focus the energy into tissues by direct radiation from a small applicator. There exists a number of scientific reviews that provide information on physical background, technical realization, and clinical trials of microwave ablation.[50,162,219,220,380–382]

VI.A. Technical Considerations

1. Mechanisms

Microwave energy is known for its potential for creating larger and more effective lesions (up to 2.6 cm in diameter) at greater depth, resulting in shorter application times (typically 1–5 min) than RF devices.[261] Compared with RF, microwaves have a much broader field of power density (up to 2 cm surrounding the antenna), with a correspondingly larger zone of active heating.[383] This may allow for more uniform killing of tumor cells both within a targeted zone and next to vessels. Since microwave power deposition inside tissues decays with distance more slowly as compared to the distance dependence of RF ablation, deeper lesions can be accessed.[384] Unlike RF ablation, the volume heating due to microwave energy is dielectric, not resistive. Heating by microwave energy is determined by the complex permittivity of tissue. Microwave radiation stimulates oscillation of dipoles such as water molecules in material, resulting in kinetic energy (heat). Also in contrast to RF ablation, increasing the applied microwave power results in a significant increase in the volume of lesions, without causing charring.[385] The lesion dimensions are proportional to the power and duration of energy delivery. Poor dielectric properties and improper impedance matching result in power reflection and energy dissipation within the catheter transmission line and antenna, and inadequate lesion formation. Hines-Peralta et al.[386] characterized the relationship between applied power and treatment duration in their effect on extent of coagulation produced with a 2.45 GHz microwave applicator in both an ex vivo and a perfused in vivo liver model. Large zones of ablation were achieved. For higher-power ablations, larger zones of coagulation were achieved for in vivo liver than for ex vivo liver with short energy applications, a finding previously not seen with other ablation devices, to the authors' knowledge.

Currently, RF ablation devices are more technically advanced than microwave ablation devices, likely because of their effectiveness, safety in both percutaneous and surgical settings, and relative ease of use. However, RF ablation is fundamentally restricted by the need to conduct electric energy into the body.[387] Microwave ablation devices, while not yet commercially available in the United States, have the potential to become the superior treatment modality if they receive more attention from the research community. These devices still use comparably simple control algorithms (i.e., constant power) without any sort of feedback to adjust power according to requirements, compared to temperature or impedance feedback used in RF devices.[242]

According to Simon et al.,[50] the main advantages of microwave technology, when compared with existing thermoablative technologies, include consistently higher intratumoral temperatures, larger tumor ablation volumes, faster ablation times, and an improved convection profile.

2. Antenna Designs

Microwave antennas are the critical elements in the microwave ablation procedure, since the generation of continuous linear transmural lesions depends on the control of radiation characteristics of the antenna.[388] Most ablation antennas are fed by coaxial lines, which have an unbalanced design that allows return current flow on the outer conductor. These currents restrict impedance matching. If the antenna's input impedance is not matched to the feed line, too much of the applied power is reflected from the antenna and, hence not deposited in the tissue.[365] Poor dielectric and impedance matching results in power reflection and energy dissipation within the transmission line and antenna, and accordingly leads to improper lesion formation. Recent engineering advances have allowed the design of microwave antennas that are tuned to the dielectric properties of tissues, reducing feedback and increasing the amount of energy deposited into the surrounding tissue. This new microwave ablation system (Vivant Medical Inc., Mountain View, CA) has the potential to create larger, hotter lesions than previously possible. Additionally, the prototype microwave generator has the capacity to drive up to eight antennas at one time.[389]

Numerous antenna designs have been presented in the literature for microwave ablation.[23,286,364,365,390–402] Several of the designs are targeted for cancer treatment and others for cardiac ablation. Antennas are grouped into three categories, namely, the monopolar antennas, dipole antennas, and helical coil antennas. With the exception of the split-tip dipole, each type radiates in the normal mode, with waves propagating perpendicular to the axis of the helix.[385] In general, microwave catheter antennas can broadly be categorized into two types—those antennas that are designed to produce radiation mainly around the antenna tip[393–

[395] and those that produce radiation normal to the antenna axis.[364,394]

Nevels et al.[364] observed that coating the catheter with a Teflon® sheath prevents a radiation "hot spot" at the feed line-antenna junction and antenna tip. It was shown that a disk placed at the end of the antenna probe forces the radiated power forward, toward the probe tip, which is the part of the antenna in closest contact with the tissue. The terminating disk provides an additional benefit by halving the length of the antenna at the 2.45 GHz frequency, which is an advantage in the confined space of the heart cavity. Gu et al.[395] reported on a wide-aperture microwave spiral antenna for cardiac ablation that created lesions that are too wide for ablation in the atrium where the available cardiac tissue is limited. The antenna reported by Pisa et al.[396] has shown increased radiation along the antenna length as well as around the tip. The enhanced radiation around the tip of the antenna can be problematic when the antenna is placed near the valves because it may cause unintentional valvular damage due to EM radiation. Chiu et al.[388] proposed a novel expanded-tip wire (ETW) catheter antenna for the treatment of aterial fibrillation. The antenna is designed as an integral part of the coaxial cable so that it can be inserted via a catheter. Both numerical modeling and in vitro experimentation show that the proposed ETW antenna produces a well-defined electric field distribution that provides continuous long and linear lesions for the treatment of AF. Rappaport[23] described a novel catheter-based unfurling wide-aperture antenna. This antenna consists of the center conductor of a coaxial line, shaped into a spiral and insulated from blood and tissue by a nonconductive fluid-filled balloon. Initially stretched straight inside a catheter for transluminal guiding, once in place at the cardiac target, the coiled spiral antenna is advanced into the inflated balloon. Power is applied in the range of 50–150 W at the reserved industrial, scientific, and medical (ISM) frequency of 915 MHz for 30–90 s to create an irreversible lesion. Yang et al.[402] reported a novel coaxial antenna operating at 2.45 GHz for hepatic microwave ablation. This device uses a floating sleeve, that is, a metal conductor electrically isolated from the outer connector of the antenna coaxial body, to achieve a highly localized SAR that is independent of insertion length.

3. Multiple Insertions and Multiple Antennas

Similar to current clinical practice in RF ablation, multiple sequential insertions are typically used to treat large tumors by microwave ablation.[403,404] Because of the limited size of the ablation zone, this practice may require a large number of insertions. For example, Sato et al.[261] used 46 antenna insertions for treatment of HCC. Three different methods have been described in the literature that allow simultaneous use of multiple microwave antennas, namely, coherent, incoherent, and phase modulated.[242] Wright et al.[389] found that simultaneous three-probe microwave ablation lesions were three times larger than sequential lesions and nearly six times greater in volume than single-probe lesions. Additionally, simultaneous multiple-probe ablation resulted in qualitatively better lesions, with more uniform coagulation and better performance near blood vessels. The investigators found also that simultaneous multiple-probe ablation may decrease inadequate treatment of large tumors and decrease recurrence rates after tumor ablation. Yu et al.[401] evaluated the clinical implementation of triangular and spherical designs for simultaneous multiple-antenna ablation of human HCC with a recently engineered microwave coagulation system. The triple-loop configuration yielded the most uniformly round ablation shape. Simultaneous activation of multiple straight or loop antennas is a potentially promising technique for rapid and effective treatment of large HCCs.

Using a different microwave system, Sato et al.[405] described their experience with multiple-probe microwave ablation in a small clinical study. Using a disk-shaped introducer to guide the placement of seven antennas, they were able to create lesions from 5 to 6 cm in diameter, successfully treating three of six tumors. However, the multiple-antenna system was activated sequentially rather than simultaneously. Similarly, Lu et al.[404] used sequential multiple-probe ablation to treat tumors > 2 cm in 61 patients with a 92% technical success rate and 8% recurrence after a mean 18-month follow-up.

With continuing technical advances in microwave medical technology, minimally invasive treatments have emerged to treat common medical conditions. One such advance is transurethral microwave thermotherapy (TUMT) to treat BPH or the enlarged prostate. TUMT uses a catheter with a microwave antenna built in just below the balloon. The balloon at the tip localizes the antenna at the correct position in the object area. Thermosensors on the catheter and in the surrounding area autoregulate power outage to optimally heat the object. Different types of microwave antennas are used for TUMT, including helical, dipole, and whip designs.[76]

VI.B. Clinical Advantages and Applications

1. Treating Cancer

Clinical applications of microwave ablation include treatment of liver tumors, lung tumors, renal and adrenal disease, and bone metastases. In several clinical studies, microwave tissue coagulation has been performed by using both percutaneous and laparoscopic techniques. The technology is still in its infancy, and future developments and clinical implementation will help improve the care of patients with cancer.[50]

Clinical use of microwave ablation has been most prevalent in Asia to date, where a number of case series have shown it to be effective in local control of both HCC and metastatic colorectal carcinoma.[44,406–409] Currently, there are no FDA-approved commercial microwave ablation devices available in the United States.[242]

a. Liver

The first clinical report of microwave therapy in Asia was made by Seki et al.[410] in 1994. They evaluated the efficacy of this technique in 18 patients with single unresectable HCCs, all of which were 2 cm in diameter or smaller. Microwaves at 60 W for 120 s were used to irradiate the tumor and surrounding area. They used a 1450 MHz generator and a 15 gauge coaxial electrode. No recurrences were noted at the treated sites during 11–33 months of follow-up. Three patients developed new tumors in sites remote from the treated sites. No serious complications were encountered. The investigators treated a total of 650 patients from 1992. Five-year survival rates were 70% in tumors < 2 cm and 52% in tumors measuring 2–3 cm. More promising clinical results for the treatment of liver tumors by microwave ablation were reported in the following years, with low complication rates.[239,262,401,406,411–418]

b. Prostate

One of the most prolific areas of development of microwave ablation technology is for treating disease of the prostate. To date, few examples of clinical trials that have demonstrated durability and efficacy.[419–421]

c. Lung

Furukawa et al.[422] evaluated the use of microwave coagulation therapy, which has been used successfully for coagulation of hepatic tumors in normal canine lung tissue to evaluate its efficacy and safety. Measurements of thermal response and coagulation area and histological examinations after microwave coagulation were performed in normal canine lung tissue. The temperature in normal canine lung tissue increased to 90–100°C at 5 mm from the electrode after 60 s, and 70–80°C at 10 mm after 90 s at 40 or 60 W. The coagulation area was ~ 20 mm in diameter at 40 and 60 W. Histological analysis demonstrated thickening of collagen fiber shortly after coagulation, stromal edema and granulation tissue after three months, and, finally, scar tissue was seen after six months.

2. Cardiac Diseases

New approaches are steadily emerging in the fast-paced progress of treating cardiac diseases using microwave energy.

a. Microwave Balloon Angioplasty (MBA)

MBA is a surgical repair of a blood vessel by inserting a balloon-tipped catheter to unblock it. MBA combines conventional balloon angioplasty techniques with microwave heating to help enlarge the lumen of narrowed arteries and to reduce the occurrence of restenosis.[423] Balloons can be produced with diameters from 0.5 to 50 mm or more, in any working length, with very thin walls. They can be custom designed with varying diameters. The process employs a narrow balloon catheter that is advanced to the site of arterial stenosis through an incision in the neck or leg, and fed through blood vessels. Fluid is then pumped into the balloon, inflating it to several times its normal diameter. The enlarged tip quickly compresses the layer of plaque that is clogging the artery, leaving a much wider opening for blood flow. The balloon is then deflated and it is withdrawn with the catheter. The procedure avoids cardiac bypass surgery. An alternative process to deposit power is microwave irradiation. MBA takes advantage of the volume heating property of microwave irradiation. MBA devices were first reported by Rosen and Walinsky[423] and clinically tested by Smith et al.[424] and Nardone et al.[425] These devices used a variety of narrow antennas incorporated within and surrounding a catheter balloon. The design of the antenna is a key to the success of the MBA. A cable-antenna assembly is threaded through the catheter, with the antenna centered in the balloon portion of the catheter. The first MBA devices employed dipoles and small helical antennas. Although the healthy tissue may still be heated less than the inner plaque surface, it is important to avoid overheating the artery wall, if possible.[426] Figure 1 shows a schematic view of an MBA.

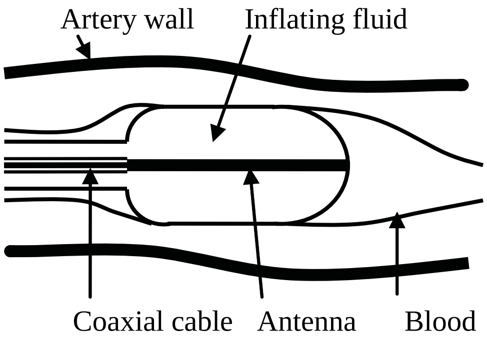

FIGURE 1. A schematic view of a MBA.

b. Microwave Ablation Catheter

Another application of microwaves is the treatment of abnormal heart rhythm or some cardiac arrhythmias, such as AV node reentrant tachycardias, accessory pathways, ventricular tachycardias, SVTs, atrial fibrillation, and atrial flutter. Cardiac ablation reached a successful rate of about 75–95%, depending on the heart rhythm disorders.[70,75,427] The procedure involves having catheters threaded through veins or arteries to the site of the abnormal electrical pathway responsible for the arrhythmia. Catheter ablation is usually performed in conjunction with an invasive diagnostic electrophysiology study, which will identify the origin of abnormal impulse formation. RF ablation operating at frequencies between 100 kHz and 10 MHz has a high success rate in treating a wide range of cardiac arrhythmias. An electric current is applied between the catheter electrode (~ 2.6 mm in diameter) in contact with the endocardium and a rectangular (~ 15 × 9 cm) dispersive electrode attached at the back of the patient. Microwave power is also used to treat abnormal heart rhythm, especially ventricular tachycardia. Microwave power can ablate tissues at a greater depth and across a larger volume heating than RF ablation by using monopole and helical antennas.[426]

In the literature, several investigators confirm that microwave ablation is a satisfactory and safe method of cardiac ablation, and that it can be added to surgical procedures without undue risk to the patient.[428–433] The use of microwave energy for cardiac ablation was also successfully examined in open-chest dogs[434] and domestic pigs.[435] Rappaport[23] reviewed the recent state of the art in microwave cardiac ablation and described a novel catheter-based unfurling wide-aperture antenna.

3. Microwave Endometrial Ablation (MEA)

MEA is an effective treatment for dysfunctional uterine bleeding. Patients with leiomyomata, including submucosal leiomyomata up to 3 cm, may also be treated with microwave endometrial ablation. Goldberg et al.[1] conducted a microwave endometrial ablation on a 46-year-old woman with multiple leiomyomata and menometrorrhagia. Two months after microwave endometrial ablation, she developed signs of peritoneal irritation. A negative laparoscopy excluded a thermal bowel injury. Imaging and clinical examination ultimately determined that her symptoms were due to leiomyoma degeneration. A 38-year-old woman with menometrorrhagia and leiomyomata underwent microwave endometrial ablation. Fifteen days after microwave endometrial ablation, she developed signs of peritoneal irritation. With a presumptive clinical diagnosis of microwave endometrial ablation degeneration, the patient was effectively managed with pain medications and observation.

Jack and Cooper[436] reviewed the scientific basis, clinical research, safety, and clinical applications of the endometrial ablative technique. The investigators concluded that this technology is suitable for the majority of women who present with the complaint of excessive menstrual bleeding. The treatment is effective and acceptable to patients, giving high levels of reported satisfaction. Randomized evidence supports its use in a variety of clinical situations using general or local anesthesia, with or without drug preparation, in theater or outpatient environment, and without loss of clinical or economic effectiveness.

In 2002, the NICE requested that the effectiveness of microwave and thermal balloon endometrial ablation be systematically reviewed. MEA and thermal balloon endometrial ablation were identified as the most commonly used second-generation techniques in the UK. Garside et al.[382] reviewed two randomized controlled trials of MEA and eight trials (six randomized controlled trials) of thermal balloon endometrial ablation. Both techniques had significantly shorter operating and theater times than first-generation techniques (transcervical resection, roller-ball ablation, and laser ablation). Adverse effects were few with all techniques, but there were fewer preoperative adverse effects with the second-generation techniques. The investigators concluded that MEA and thermal balloon endometrial ablation are effective alternatives in the surgical treatment of women with heavy menstrual bleeding.

Downes and O'Donovan[437] described the status of MEA, its clinical efficacy, its safety profile, and future development. According to Jameel et al.,[438] MEA is regarded as an effective nonsurgical option for managing dysfunctional uterine bleeding. It is believed to be safe, quick, and easy to perform. There has been only one reported case of a serious complication of a bowel injury during MEA.

VI.C. Limitations

RF ablation and microwave ablation share several common advantages and disadvantages. They both allow flexible treatment approaches, including percutaneous, laparoscopic, or open surgical access, with convenient ultrasonographic or CT guidance. Perhaps the most commonly cited drawback is the difficulty in treating large tumors, which are routinely defined as those exceeding 3 cm in diameter.[401] However, microwave ablation has several theoretical advantages that may result in improved performance, especially near blood vessels. During RF ablation, the zone of active tissue heating is limited to a few millimeters surrounding the active electrode, with the remainder of the ablation zone being heated via thermal conduction.[383] Due to the much broader field of power density (up to 2 cm surrounding the antenna), microwave ablation results in a much larger zone of active heating.[402] This larger heating zone has the potential to allow for a more uniform tumor kill in the ablation zone, but within the targeted zone and next to blood vessels.

In spite of significant success in the clinical application of microwave ablation, as with other thermal-based therapies, tumor size continues to limit overall complete response rates. Perfusion-mediated vascular cooling appears to produce a heat sink effect that prevents greater volumes of coagulation. In addition, the application of microwave energy by means of single electrode insertions results in necrosis measuring 2.5 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. There is also reduced penetration with microwave energy compared to several other thermoablative strategies, which makes this particular thermal ablative strategy less suitable for deeply placed tumors.

Practical problems remain to be solved before microwaves can become a useful energy source. These problems include (i) power loss in the coaxial cable, (ii) resultant heating of the coaxial cable during power delivery that may lead to breakdown in the dielectric and catheter material, and (iii) lack of a unidirectional antenna that can radiate energy into tissue and not the circulating blood pool, a condition that prevents proper catheter operation over the range of dielectric properties of human blood and heart tissue.[68,364] An important limitation of microwave ablation is the complexity of microwave antenna design, which limits the antenna to specific lengths corresponding to the microwave generator waveform. This differs from RF and laser ablation, where a more variable length of tissue can be subjected to treatment. Even greater limitations in lesion geometry are imposed when microwave arrays are used.[439,440] Thus far, microwave antenna designs have not achieved efficient energy transfer into an object. Poor dielectric and impedance matching have resulted in power reflection and energy dissipation within the catheter transmission line and antenna, and inadequate lesion formation.[73]

VI.D. Complications

Although complication rates for microwave ablation are lower than those for surgical resection, clinical studies in which microwave ablation has been used to treat HCC have reported relatively higher complication rates compared with other thermal ablation strategies. Murakami et al.[411] reported clinical results of microwave ablation in nine patients with HCCs greater than 3 cm in diameter. Three to twelve ablations were performed per tumor. Four of nine patients developed recurrent tumors within six months of treatment. No major complications were noted. Matsukawa et al.[403] examined postprocedural complications in 20 patients with HCC. Their patients experienced slight pain (24%), fever (20%), and subcutaneous hematomas (8%) after microwave ablation sessions. Beppu et al.[412] reported a 12% complication rate when using microwave ablation to treat 84 patients with HCC. Shimada et al.[406] reported a 14.2% complication rate in 42 patients with HCC. Complications included abscesses, a biloma, bleeding, hepatic failure, and tumor seeding in the microwave needle track. Significantly higher complication rates were seen in patients with higher clinical stages of disease and larger tumor size (diameter > 4 cm). Although abscesses and bleeding were treated without incident, other serious complications were unsuccessfully treated after they developed. The authors recommended several prophylactic measures to reduce the incidence of complications, including transcatheter cooling of the intrahepatic bile duct and administration of an anticancer agent in the abdominal cavity to prevent bilomas and tumor dissemination. Shibata et al.[418] evaluated the effectiveness of percutaneous RF ablation and microwave ablation for treatment of HCC in 72 patients with 94 HCC nodules. Complete therapeutic effect was achieved in 46 (96%) of 48 nodules treated with

RF ablation and 41 (89%) of 46 nodules treated with microwave ablation. Major complications occurred in one patient treated with RF ablation and in four patients treated with microwave ablation.

VII. LASER ABLATION

A laser (light amplification by stimulated emission of radiation), 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 wavelengths covered by optical radiation ranges from 1 nm to 1 mm. This wavelength region includes not only the visible part of the EM spectrum, but also the ultraviolet (UV) down to the soft ionizing X-ray region, and the infrared (IR) up to the microwave region. Various solids, liquids, gases, and light-emitting diodes (LEDs) can achieve stimulated emission at distinct wavelengths throughout the visible, UV, and IR spectrums. Increasing numbers of relevant scientific articles have been published in high-ranked journals that provide a good review on laser ablation.[441-443]

VII.A. Technical Considerations

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.[394] Some of the common lasers used for such a purpose are the neodymium yttrium-aluminum-garnet (Nd:YAG, wavelength of 1064 nm) and CO_2 lasers. The Nd:YAG laser is one of the most versatile and safest laser sources, and the safest used in therapy. The relative robustness and compactness of the laser and the possibility for the coherent light it produces to be transmitted to the object via optical fibers are two features that contribute to its success.

Light does not penetrate blood or tissue easily so, like RF and microwaves, 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. With higher-frequency lasers, the tissue in contact with the laser is vaporized and the deeper myocardial tissue is heated through passive thermal energy exchange. With Nd:YAG lasers, significant volume heating without surface vaporization occurs.[73,444]

Laser units consist of a power source, a lasing medium, and reflecting mirrors.[443] An infrared light wavelength of between 800 and 1100 nm achieves maximal tissue penetration and homogeneous spread when delivered into tumors by an optical fiber.[445,446] Laser ablation uses a narrow, flexible optical fiber for the delivery of laser energy. As the laser energy passes through a medium it is absorbed, resulting in heating, or scattered, resulting in lesion enlargement.[76] Early fibers were fragile and had a tendency to break during insertion. Recognizing the potential usefulness of this procedure, new fibers were specially designed for ablation. The new fibers are larger in diameter and have pointed distal-diffusing tips that radiate 360°. 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. Still, the laser modality remains less popular because of tissue evaporation and perforation issues, as well as the high cost for both the laser power supply and the special catheter.[73]

VII.B. Clinical Advantages and Applications

Although RF ablation techniques can deliver more energy into tissue than laser ablation techniques, there is little practical difference between RF ablation and laser ablation technology. The laser technique has the advantage of being fully compatible with MR imaging, whereas RF ablation is not. Both techniques are now so powerful that control of energy deposition is a major issue; only MRI offers the potential for accurate real-time monitoring of the extent of the ablation. Numerous groups are active with laser ablation, including among others the clinical efforts of Bremer et al.,[447] Shankar et al.,[448] Pacella et al.,[449] and Ricke et al.[450]

1. Treating Cancer

The first interstitial thermal ablation of a tumor performed with laser therapy was reported by Bown.[451] Since then, experimental studies have shown that a reproducible thermal injury can be produced with Nd:YAG lasers.[452]

a. Liver

Laser therapy has been used to treat liver tumors since the 1980s, mostly in Western countries. The first use of lasers to treat patients with hepatomas and hepatic metastases was reported by Hashimoto et al.[453] and Steger et al.,[454] respectively. Subsequently, more successful and safe studies on laser therapy involved patients with liver tumors.[447,448,450,454–458]

The only reported preliminary study using a newly designed interstitial probe for treating small HCCs is that of Wang et al.[441]

Gilliams et al.[459] reported an 86% one-year survival of 55 patients with colorectal liver metastases, with a mean survival time from the detection of metastases of 18 months. Vogl et al.[457] achieved mean survival times of up to 32 months for patients with HCC treated with laser ablation. Muralidharan and Christophi[444] used laser to treat eight patients with HCC (tumor diameter, 3.0–7.0 cm). Complete necrosis and avascularity was seen at CT in tumors smaller than 4 cm, but incomplete responses were seen for tumors larger than 5 cm, even with multiple treatments.

Vogl et al.[460] present a review of large clinical experience with laser ablation in both liver and other soft-tissue tumors. No statistically significant difference in survival rates was observed in patients with liver metastases from colorectal cancer versus metastases from other primary tumors. The rate of clinically relevant side effects and complications requiring secondary treatment was 2.2%.

b. Prostate

Initial clinical usage of laser-induced tissue ablation of prostate started with transurethral incision of the prostate.[461] This device is composed of a probe equipped with a side-firing Nd:YAG laser fiber. The probe is placed in the prostatic urethra under ultrasound guidance. The laser fiber emits a tightly focused beam laterally to create coagulation necrosis of prostate adenoma. This procedure was soon replaced by a lower-cost and more urologist-friendly procedure, cytoscopic-induced visual laser ablation (VLAP). VLAP was once a popular treatment for prostate in the U.S.[462–464] The procedure requires the application of the ND:YAG laser to the hyperplastic portion of the prostate intraurethrally under cytoscopic observation. Each application lasts 60–90 s and 4–12 applications of free-beam laser are applied, depending on the gland size. A lesson learned from VLAP was that the necrotic tissue exposed to the urethral lumen is not a desirable form BPH treatment. Following this experience, various tissue ablation techniques not damaging the urethra have been created.[52] Kursh et al.[465] reported a multi-institutional randomized study between two procedures called interstitial laser coagulation (ILC) and transurethral resection of prostate (TURP). At two-year follow-up, the TURP group showed better urinary flow rates, but both groups similarly improved the symptoms and quality-of-life measure.

2. Cardiac Diseases

The laser ablation technique is investigated as an option for efficiently delivering a large magnitude of energy through a small diameter flexible catheter.[73] It has been tested experimentally for the alteration of AV nodal conduction[466] and intraoperatively for the treatment of ventricular arrhythmias.[467–469]

Earlier studies of laser cardiac ablation used a high-energy pulsed laser that was difficult to titrate and carried a risk of cancer formation.[470] More recently, the diode laser has been pursued as a means of providing continuous low-energy ablation with an anticipated lower risk of endocardial disruption or perforation.[76] Lee et al.[470] evaluated the Nd: YAG laser in vitro and in vivo in canine hearts. Lesions created by laser in vitro were characterized by a central vaporized crater surrounded by a rim of necrotic tissue; however, crater formation was not seen at lower energy settings in vivo. Lesion depth was found to be more closely dependent on duration rather than power. Laser application of 40–80 Joules/0.5–2.0 s produced ventricular lesions of 7 mm^3.

VII.C. Limitations

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.[82] Additional efforts to overcome this limitation include simultaneous multiple fiber application, use of diffuser-tipped fibers,[455] use of splitters with multiple fibers,[471] modulation of blood flow,[472,473] and pharmacologic thermosensitization of tissue before laser application.[444]

VII.D. Complications

Mack et al.[474] reported a complication rate of 7.5% in 705 patients with focal hepatic malignancies of varying origins treated with laser ablation. Complications included reactive pleural effusion, intrahepatic abscess, incidents secondary to percutaneous needle insertion (for example, pneumothorax, transient bile leaks, and subclinical hemorrhage), and side effects resulting from hyperthermia (for example, transient bradycardia, right upper quadrant pain, and transient fever). Although early use of gas coolants within laser systems resulted in one reported fatal gas embolization, current water coolant-based laser systems have eliminated this danger.[475] High-power laser generation systems can produce extensive rapid tissue carbonization, which has potential patient fatality risks. Tranberg et al.[456] reported one fatality due to rapid tissue carbonization in 13 patients with primary and secondary liver tumors. Most current systems used in patients, however, are low-power systems (on the order of 3 W) with little risk of rapid carbonization and subsequent patient death.[476] Other drawbacks of laser ablation include tissue charring around the tip of the fiber, much more pain experienced by the patient, and survival rates less than with RF ablation.[213]

VIII. CHALLENGES AND FUTURE RESEARCH

The most important issues regarding thermal ablation are the safety, true efficacy, and survival benefits of the techniques. None of the five ablative techniques discussed in this article are directly comparable, since the patient populations, extent of disease, and other conditions are somewhat different. In addition, no prospective comparative studies in this regard have been reported to date.

VIII.A. Improved Techniques

Although thermal ablation is a relatively new modality, thermal ablation techniques have evolved rapidly. The extensive laboratory and animal experiences in combination with the results from preliminary clinical studies suggest that these techniques may have an important role to play in the treatment of patients. Continued developments may permit more rapid ablation, treatment of large volumes of tumor tissues, and more precise monitoring when sufficient cell kill with adequate margins has been achieved. Presently, many ablation techniques are being studied, with multiple commercial devices now becoming available. Given the rapid pace of evolution in the state of the art for ablation technologies, we cannot confidently predict which method, if any, will prove dominant for any given clinical application. Competitive technologies must be able to maximize tissue heating and prevent charring and cavitation to ablate the desired volume of tissue in a reproducible and predictable fashion. However, other factors, including ease of clinical use and cost, will play a role in determining which of these technologies will receive the greatest attention. Table I compares the five ablation techniques considered in this article.

Among EM ablation techniques, RF ablation devices are more technically advanced than microwave devices, in part because they received more attention to date. Microwave ablation devices, while not

TABLE I. Comparison of Various Ablation Techniques

Type of Ablation	Mechanism	Advantages	Disadvantages
Cryoablation	Freeze-thaw cycle.	Virtual absence of pain. Can create large lesions and is effective in treating tumors in multiple lobes. Ability to reversibly test the effectiveness of an ablation site.	Lesions are significantly affected by blood flow. High complication rate.
Ultrasound	Transducer driven by sinusoidal signals in a continuous wave or quasi-continuous wave mode to generate ultrasound.	Ability to focus the area under treatment. Lesion formation is not dependent on surface heating. Good depth of penetration with the ability to pass harmlessly through tissues. Large scope for treatment of different tumor types. Potentially curative and repeatable.	Requires general anesthetic. Difficult to produce stable and durable transducers of small enough dimensions for use in catheters. Long time taken to ablate given object. Cannot be directed through air-filled viscera such as the lung.
Radiofrequency	Resistive heating by RF current.	Simple system design, proven effectiveness and worldwide availability. The complication profile is acceptable. Ability to treat different tumor types.	Limited extent of induced necrosis. Ablation zones do not exceed 4 cm unless the ablation probe is repositioned for another ablation. Necrosis incomplete in ablation near blood vessels.
Microwaves	Heating by propagating EM waves.	High temperature available. Capable of forming large lesions in the presence of blood perfusion.	Complications include pleural effusion, hemorrhage, and abscess.
Laser	Convert light to heat.	Fully compatible with MRI. Can deliver controlled low energy through a variety of fiber configurations to achieve thin, continuous lesions in and around defined structures.	Expensive and bulky system. Successful ablation of only 2 cm. Tissue charring around the tip of the fiber. Pain expected by the patient. Not very good survival rate.

yet commercially available in the U.S., have the potential to become the superior treatment modality if they receive more attention from the research community. Microwaves provide deeper tissue heating compared to RF, and multiple antenna arrays provide the advantage of constructive interference between antennas. This may eventually enable more rapid creation of large ablation zones and more effective treatment of tumors located close to vessels.[242]

Even with the considerable progress that has been made to date, a number of challenges remain for the future. These include (i) the development of techniques that can increase the volume of tissue destroyed at a single treatment session, (ii) the development of more suitable and accurate imaging tests, and (iii) a better understanding of how to integrate ablation techniques into the overall care of patients.[59] Additional device developments will likely help the field of tumor ablation to continue to grow in the years to come.

VIII.B. Ablation in Clinical Practice

Among the five thermal ablative techniques discussed in this article, cryoablation is limited in application by the relatively high complication rate (up to 40%). In addition to bleeding from cracking, the cryoshock phenomenon is potentially fatal. Currently, there is more enthusiasm for RF ablation. Its main advantages are the low complication (0–12%) and mortality (0–1%) rates, and the ability of RF ablation to ablate large tumors.[42] Microwave ablation, however, also has a low complication rate (11–14%), as reported in many studies.[262,406,415]

The relative risks and benefits of ablation must be rigorously measured to better define its role in clinical practice. Future improvements in patient survival will require multidisciplinary treatment approaches that include cytoxic and novel agents to prevent tumor recurrence. Well-designed and controlled multicenter clinical trials are required to determine the extent of benefit provided by ablation techniques for any given indication. Success in the use of ablation techniques can be achieved only with better understanding of the biological features and natural history of tumors. It is very important for physicians performing ablation to work closely with oncologists and surgeons to ensure precise selection of the treatment options that best serve patients.

Clinical results from single-center or retrospective studies vary significantly. Therefore, good communication between centers will be required to assist the rapid diffusion of the many new ways in which thermal ablation is being used to help individual patients, especially the approach in which the role of thermal ablation will likely be developed to include additional organ sites.

Given the high likelihood of incomplete treatment by heat-based techniques alone, the case for combining thermal ablation with other therapies such as radiotherapy, chemotherapy, or chemoembolization cannot be overstated. A similar multidisciplinary approach including surgery, radiation, and chemotherapy is used for the treatment of most solid tumors.

VIII.C. Future Research

The ultimate goal of current research on ablation techniques is to develop technologies to increase the induced coagulation volume while reducing the treatment time associated with the ablation technique. However, clinical research focuses on the implementation of ablation in clinical practice and patient outcomes. The desired advances include improvements in image guidance for targeting tumors to be ablated, better detection of residual disease, and making the therapy more straightforward by reducing device complexity and the overall time required to ablate a given tumor.

Current research is based on developing rational and reasonably sized lesions that do not require inordinate amounts of time to create. Bigger is not always better, because injury to surrounding tissues and organs may be more likely.[265] The use of multiple applicators is one way to reach this target, which may help decrease the number of local tumor progressions that result when treating a large tumor with overlapping sequential ablations. In addition, multiple tumors could be treated simultaneously with multiple applicator devices and treatment times, and anesthetic complications and costs could potentially be decreased.[242]

Over the next several years, we expect more substantial research efforts combining various ablation techniques with adjunctive therapies, such as chemotherapy, to improve overall tumor destruction.[265] In order to study, investigate, and develop new techniques and to improve those currently employed, research can make use of clinical and experimental studies, phantoms, and theoretical models. The latter are powerful tools in this kind of investigation, since they rapidly and economically provide an understanding of the electrical and thermal behavior involved in ablation.[108]

Much of the future success in this field will be based on (i) accurate modeling of the electrical and thermal characteristics of biological systems, (ii) realistic modeling of the cooling effect of large and medium blood vessels, (iii) determining the parameters (for example, frequency and energy) of the thermal damage function for different types of tissues (such as hepatic, breast, and cardiac), (iv) technological advances in electrode and generator design, (v) better understanding of methods to ensure adequacy of tumor necrosis, and (vi) conducting research on new histological markers of thermal injury. Furthermore, successful ablation of all tumors may be improved in the future using fast computer simulation and accurate imaging and mapping techniques that are used not only to help detect treatable tumors and guide probe placement, but also to examine the effect of therapy and determine the adequacy of complete thermal coagulation.

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