CHAPTER 1

ELECTROMAGNETIC FIELDS IN MEDICAL APPLICATIONS

1.1 Introduction

During the past few decades, the advances in electromagnetic and modern electronics have led the stage for an unprecedented drive towards the development of medical devices with various medical diagnostic and therapeutic applications. Electromagnetic fields can treat a wide range of ailments including ulcers, chronic pain, nerve disorders, spinal, gum infections, asthma, bronchitis, arthritis, cancer and heart disease. Cancer has become one of the most devastating diseases in the world. The major question arises that: why haven't we found a cure for cancer yet? The main problem is that there are many kinds of cancers, so it is very difficult to find a general cure, since the treatments vary with the type of cancer and location.

In the ancient time, liver was considered to be a source for myths, legends, spirituality and was thought to bear the soul during Babylonian era (3000 – 1500 BC) [1]. The liver is among the most complex and important organs in the human body as it creates, regulates, stores a variety of substances used by the gastrointestinal system and serves a number of important digestive functions, formation of certain blood proteins, metabolism of carbohydrates, fats, and proteins. Hepatocellular carcinoma (HCC), or primary liver cancer, is the 6th most common cancer worldwide and third most common cause of death from cancer and survival rates for liver cancer are only 3–5% globally if left untreated [2]. Maximum cases of HCC are due to chronic liver diseases, and risk
factors associated with it include cirrhosis, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcohol consumption, tobacco consumption, iron overload, hereditary hemochromatosis, obesity, and ingestion of aflatoxin - contaminated food [1]. Chemotherapy is ineffective for the patients with metastatic disease. Radiation therapy is also not effective because HCC is radiation resistant [3]. Liver transplantation is best option for liver cancer but critical shortage of size matched liver donor limits its applicability [4].

Surgical resection is the gold standard to treat the patient suffering from HCC. Only patients diagnosed at early stage are optimal candidates to receive potentially curative therapy such as surgical resection [2]. Unfortunately only 15-25 % of patients are candidate for curative surgery due to number of factors like multifocal diseases, tumor size, too many tumors, location of tumor in relation to the key vessels and other medical problems that may increase the surgical risk. Because most patients with HCC are not the candidates for resection or transplantation, the ablative treatments have started to become viable alternative methods to treat patients who cannot be treated by surgery. The ablative technologies may be classified as non thermal and thermal ablation. The non thermal ablation technique use chemicals, while the thermal ablation techniques use heating energy or cooling energy to eradicate the tumors.

Chemical ablation i.e. non thermal ablation refers to percutaneous ethanol injection (PEI), emerged as minimally invasive treatment modality for the ablation of small hepatocellular carcinomas (HCCs) in 1980s. In the last decade it has become very popular because of low cost and a high antitumoral efficacy in small solitary tumors. The mechanism of action of ethanol depends on its ability to penetrate the tumoral cells, producing coagulative necrosis as a consequence of cellular death after some time and its by-products are absorbed in the body. PEI has proven to be highly effective in single
HCC up to 2 cm, obtaining a complete response in 80% of cases, but the success rates are less than 30% for the tumors larger than 2 cm. The decreased efficacy in the treatment of large tumors in case of HCC is due to its hardness that limits ethanol diffusion, prevents homogeneous distribution throughout the tumor which causes leakage of injected ethanol into healthy tissue results in incomplete necrosis as well as destruction of healthy tissue [5, 6]. Also, prolonged treatment period due to multiple treatment sessions, may increase the chance of tumor cell seeding.

Thermal ablation is direct application of heat to a specific tumor in order to achieve complete eradication of tumor. There are five methods used to produce thermal ablation: cryoablation, radiofrequency (RF), laser, ultrasound and microwave (MW). These five technologies were introduced by James Arnott in 1850s [7], Beer in 1910 [8] McGuff et al in 1963 [9], Lynn et al. in the early 1940s [10] and Denier in 1936 [11] respectively. Initially there was great enthusiasm, but the technologies at that time were not so advanced for development of clinically used therapies. However thermal ablation received more attention from research community when they realized its potential to become the superior treatment modality with the advancement in technology. The thermal ablation device consists of an antenna applicator inserted into the liver tissue through imaging guidance, which results in heating/cooling of surrounding tissue to ablate the tumor.

The principle of cryoablation involves rapid cooling, slow thawing, and a repetition of the freeze–thaw cycle. The thermal history during cryoablation is complex, as is the mechanism of tissue destruction. Two major parameters are correlated with the likelihood of cell destruction, namely, the cooling rate during freezing and the lowest temperature achieved. Radio frequency ablation (RFA) is an interstitial technique that uses a high-frequency alternating current to heat tissues to the point of desiccation.
(thermal coagulation). The potential advantages of RFA include low complication rates (0–12%), reduced morbidity and mortality rates compared with standard surgical resection.

In laser (light amplification by stimulated emission of radiation) ablation, a monochromatic, intense, phase-coherent, directional beam of light, delivers a highly focused dose of energy of specified duration of irradiation and power intensity is used to destroy the liver metastasis. The wavelengths covered by optical radiation ranges from 1 nm to 1 mm are used for laser ablation. The concept of using ultrasound ablation as a non-invasive therapy has attracted attention in medicine for 60 years. Ultrasound involves the propagation of sound waves at a frequency of 2–20 MHz. 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 increase rapidly, which leads to coagulative necrosis almost instantly. Microwave tumor ablation (MWA) deposits thermal energy produced by the vibration and rotation of water molecules in tissue induced by microwaves emitted from an antenna. The rise in temperature in the targeted tissue produces predictable patterns of thermal coagulation. Microwave ablation (MWA) is similar to RFA which uses microwaves to heat tissues and allows for flexible approaches to treatment, including percutaneous, laparoscopic, and open surgical access.

Although surgery and liver transplant are considered the only curative treatment for HCC, few patients are eligible for RFA and MWA. On one hand RFA devices are more technically developed than MW ablation (MWA), but RFA is fundamentally restricted by the need to conduct electric energy into the body [13]. RFA relies on more of a linear or curvilinear heat source, which conducts from the center outwardly. MWA is more broadly heated simultaneously, similar to a microwave oven. This proves to
have the advantage of improved uniformity of the thermal lesion, although this too is speculative at this time. MWA is faster and less dependent on thermal conduction than RFA, as a larger volume of tissue is heated to higher temperatures in a shorter time frame. Moreover, the main advantages of microwave technology in treating the HCC, when compared with existing thermoablative technologies are higher intramural temperature, larger tumor ablation volume, faster ablation time and improved convection profile [14].

1.2 Liver

The liver is the largest organ in the body, located in the right upper quadrant of the abdomen. Its primary function is to control the flow and safety of substances absorbed from the digestive system before distribution of these substances to the systemic circulatory system. A total loss of liver functioning leads to death within minutes, demonstrating the liver’s importance [15]. It is closely associated with the small intestine, processing the nutrient-enriched venous blood that leaves the digestive tract. The liver performs over 500 metabolic functions, primarily including:

- Acts as a gatekeeper between the digestive system and the circulatory system
- Processes toxic substances before they enter general circulation, toxins are detoxified by the liver’s ability to metabolize lipophillic compounds.
- Stores and convert nutrients for future usage. For example, the liver stores glucose as glycogen, and converts it back to glucose as needed. If the supply of glycogen is depleted, the liver can also synthesize glucose from amino acids, lactate, and glycerol, although this is less efficient than breaking down glycogen into glucose.
Performs synthesis of many proteins that circulate in the blood. These include albumin, coagulation factors, alpha1-antitrypsin, very low density lipoprotein, and many others.

Bile duct acts as a detergent, and breaks fats down into smaller components so that the liver interacts with many other organs.

It plays an important role in blood circulation; the liver receives oxygen-rich blood from the aorta through the hepatic artery, which accounts for 25% of the blood flow into the liver [16]. The remaining 75% of the blood comes to the liver through the portal vein which carries nutrient-rich blood from the small intestine. Processed blood leaving the liver through the hepatic veins, drains into the inferior vena cava, completes the connection to the heart. The liver affects digestion through its formation of bile, which is secreted into the small intestine. The gall bladder is essentially an overflow area for the liver's bile duct. The liver also has a supply of nerves, showing its relationship with the nervous system. Finally, liver disease often causes problems in the renal system, demonstrating a relationship with the kidneys [16].

1.2.1 Liver Cancer

Liver tumors are not always malignant. One type of benign tumor is Hemangioma, which is a non-malignant tumor filled with blood. Treatment is not necessary for these tumors. Malignant tumors fall into two major categories:

- Primary liver tumors or HCC
- Metastatic or secondary liver tumors

Liver tumors can be detected and identified using a combination of blood tests, imaging studies, and liver biopsies.

1.2.2 Primary Liver Cancer
Primary liver cancer or HCC is one of the most common cancers in the world, accounts for 80% - 90% of all liver cancer. It occurs more often in men than women, and occurs mostly in people of the age of 50 to 60 years. This disease is more prevalent in Africa and Asia due to the higher incidence of viral hepatitis, but becoming more common in the west recently due to an increase in hepatitis cases there [17]. Hepatitis C often leads to cirrhosis, and cirrhosis often leads to primary liver cancer. The worldwide incidence is 4 out of 10,000 people [18].

Figure 1.1 shows the blood supply to the liver and hepatic tumor [19]. The tumor receives 95% of its blood supply from the hepatic artery, while the normal liver tissue receives 75% of its blood from the portal vein and the rest from the hepatic artery.

![Figure 1.1 Blood supply to the liver and hepatic tumor](image)

HCC tumors usually grow in one or more focal nodules with typical doubling time of 30 - 200 days. The neovasculature that stems from the hepatic artery and surrounds the tumor is abnormal, and the endothelial lining of the newly formed vessels is fine and easily damaged [19]. The large vessel is the portal vein, and the thin red vessel is the hepatic artery which feeds the tumor.

### 1.2.3 Secondary Liver Cancer
Metastasis is the movement of cancer cells from one organ or tissue to another. The liver is a frequent target of metastatic cancers as it is the primary filter of venous blood from several organs, such as the lung, breast, colon and rectum. The prognosis for patients with metastatic liver cancer is typically poor; most patients die within 1 year of diagnosis. Because the liver is close to or actually connected to several significant organ, and because the liver plays an important role in blood circulation by acting as a filter, metastatic liver cancer occurs in over 75% of all terminal cancer patients [20].

1.3 Treatment Methods for HCC

Historically, cancer treatments have been very invasive and body detrimental. Nicola Spirtos, a gynecologic oncologist and surgeon said that, "The most exciting development in terms of merging technology and cancer treatments is the integration of minimally invasive surgical techniques in oncology". Radiation, chemotherapy, and surgery were the only type of treatments available for those afflicted with cancer [21]. The liver is necessary for survival, there is currently no way to compensate for the absence of liver function long term. The treatment options for the cure of liver cancer can be estimated by the stage of HCC and the overall condition of the patient. In view of one physician the best treatment for primary liver cancer may be to remove it surgically, for small (< 3 cm) tumor. Many physicians may dispute this statement by claiming liver transplantation as the best method so that reoccurrence of tumor does not happen. But critical shortage of the size matched with donor limits its applicability. Moreover, the appearance of hair loss, dry mouth and sores make chemotherapy unfit for liver tumor treatment. Similarly, the application of X-rays involves heavy loss of blood accounting for the ineffectiveness of the treatment for the liver tumor. On the other hand ablation is new emerging treatment option for liver cancer which particularly
focuses on the tumor and lesion size. The various treatment options are discussed below:

### 1.3.1 Surgical Removal or Resection

The primary liver cancer can be removed surgically, unfortunately, that is seldom possible in fact, and fewer than 30% of patients are suitable for surgery. This may be because either the liver function is too poor due to the causes of the liver cancer for the patients to go under surgery safely or there are several tumors that are too widespread to remove them all. For example, cirrhosis makes it difficult for patients to get safely through almost any type of operation, and when cutting the liver is involved, half might die due to bleeding, infection, or liver failure. The liver failure can occur if the remaining portion of the liver is inadequate to provide the necessary support for life. Even in carefully selected patients, about 10% of them are expected to die shortly after surgery, usually as a result of liver failure. When a portion of a normal liver is removed, the remaining liver can grow back (regenerate) to the original size within one to two weeks but a cirrhotic liver, however cannot grow back. Therefore, before resection is performed for liver cancer, the non-tumor portion of the liver should be biopsied to determine whether there is associated cirrhosis [2]. Frequently, there are other tiny cancers that are not visible but can eventually grow back after successful surgery. Moreover surgical options are limited to individuals whose tumors are less than 5 cm and confined to the liver only with no invasion of the blood vessels.

### 1.3.2 Liver Transplantation

Liver transplantation involves removing the entire liver surgically and replacing it with a healthy liver from a living donor. In order for the new liver to be accepted by
the body, the immune system of the body has to be severely strong and held back from attacking the new liver. Recent advances in transplant techniques and immune medications have made transplantation to be the first choice for patients with cirrhosis and small tumors that are less than 5 cm in size. These are people who would not have been able to undergo surgery due to their liver disease but now have a more than 70% chances of living more than five years [22]. Unfortunately, there are not enough liver donors for everyone, and the waiting time on the transplant list can be over years. The serious drawback of this treatment is the continuous risk of organ rejection by the body.

### 1.3.3 Chemotherapy

Chemotherapy is a process in which drugs are given directly into the blood vessel that feeds the liver and the tumors. These drugs came into existence during World War II, when the U.S. Army was studying compound called nitrogen mustard in an attempt to develop protective measures against mustard gas [23]. Since then, researchers have discovered a variety of drugs that block cell functions involving growth and replication, controlling cancer for long periods of time, if not curing them [2]. Chemoembolization is procedure in which the blood flow to the tumor can be cut off by injecting tiny particles that block the feeding arteries, which attempts to kill the tumor in two ways: by bathing the tumor directly in a very high concentration of chemotherapy drugs and by starving it of its blood supply. Chemotherapy is not really an effective treatment for primary liver cancer. This therapy can be used in combination with liver surgery to offer cure for large liver tumors and the treatment is known as hepatoblastoma [24]. In this method doctors may give chemotherapy before surgery to shrink a cancer which makes it easier to remove. The patients mainly suffer from some common type of side effects like sickness, hair loss or thinning, feeling tired and run down, sore mouth or mouth ulcers, diarrhea.
1.3.4 Radiation Therapy

This therapy came into existence in 1896 by a German physics professor, Wilhelm Conrad Roentgen and very soon it became a popular way to treat the cancer. It uses high-dose energy like X-rays aimed at a small part of the body and can frequently destroy cancer cells. Today, advances in technology enable doctors to aim radiation precisely to destroy malignant tumors while leaving adjacent normal tissue somewhat unscathed [25]. The liver, though, may be more sensitive to the radiation than the tumor is, so standard radiation is seldom used.

External-beam radiation therapy is radiation given from a machine outside the body. External-beam radiation therapy is not often used for HCC. Internal radiation therapy may be used for HCC which involves placing radioactive beads into the artery that supplies the blood to tumor with a manner similar to chemoembolization. The general side effects from radiation therapy may include fatigue, mild skin reactions, upset stomach, and loose bowel movements. But for internal radiation therapy, the side effects may include damage to the stomach as well as the lungs [25].

1.3.5 Ablation

In recent years, many efforts have been made to investigate alternative percutaneous treatment modalities of HCC. Ablation can be an alternative to risky surgery, and may be an alternative choice for patients with an inoperable tumor. Ablation refers to the direct application of chemical or thermal therapy to a specific organ or tissue in order to achieve complete eradication of tumor. This technique helps in tissue destruction by the formation of a scar tissue (by shrinking) and gradually removing it, sparing the normal tissue. Ablation technologies for hepatic malignancy have developed rapidly in the past decade, with advances in several percutaneous or externally delivered treatment methods including cryoablation, laser ablation, and high-
intensity focused ultrasound radiofrequency ablation, microwave ablation. Researchers have focused on increasing the size of the ablation zone and minimizing heat-sink effects.

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>Technique</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
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<tbody>
<tr>
<td>Surgically Removal</td>
<td>Surgical removal of complete tumor</td>
<td>Most successful treatment</td>
<td>Not suitable for small cancers. Risk of patient death</td>
</tr>
<tr>
<td>Liver Transplantation</td>
<td>The entire liver is replaced with a healthy liver</td>
<td>For patients who have signs of liver failure</td>
<td>Requirement of living donor. Risk of rejection of the donor organ</td>
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<tr>
<td>Chemotherapy</td>
<td>It uses drugs to stop the growth of cancer cells</td>
<td>It offers cure when surgery is not possible</td>
<td>Loss of patients’ hair and appetite. Create nausea and vomiting</td>
</tr>
<tr>
<td>Radiation</td>
<td>It uses high-energy X-rays to kill cancer cells</td>
<td>This allows matching dose of radiation to fit the exact shape of the tumor</td>
<td>The dose is low so large sittings are required</td>
</tr>
<tr>
<td>Ablation</td>
<td>Application of heat, cold, Chemicals directly to cause tumor death</td>
<td>This technique is focal in nature, spares the normal tissues</td>
<td>Central liver lesions are somewhat difficult to focus</td>
</tr>
</tbody>
</table>

Concluding all the methods, the ablation technique offers no side effects and is best suited method when other treatment options offer no cure. It leads to low patient morbidity and a very attractive alternative method for tumor treatment [26]. The relative comparison of various treatment options for HCC based upon its advantages and disadvantages has been shown in Table 1.1.

1.4 Thermal Ablation Techniques

Human cells can survive up to the 42°C temperatures [25], at 43°C, cells die after 30 min, as temperature is increased, the time to death of cells decreases; at 50°C
death occurs in 30s; at 55°C it occurs at 1s, and above 60°C death of cells is instantaneous. If the cells are cooled to a sufficiently low temperature i.e. < -40°C cell necrosis occur. The cell response to the temperature changes in the body can be analyzed in Figure 1.2.

Figure 1.2 Cell responses to temperature change

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. Ablation has become an important strategy in the treatment of hepatocellular carcinoma and is increasingly applied to liver metastases from colorectal carcinoma, as well as tumors from other origins. The mechanism of all thermal ablative technologies has been summarized below.

1.4.1 Cryoablation

Cryoablation uses extreme cooling to destroy cancer cells. It was the first widely available ablative therapy which came into use in 1955 as slow cooling by liquid Nitrogen [27]. It is performed via open surgical, laproscopic or percutaneous approach. Cell death is due to rapid freezing of intercellular water and subsequent cell lysis [28].
Cryoablation uses repetitive freezing and thawing of tissue to produce necrosis and irreversible tissue destruction will occur between -40°C and -60°C. Liquid Nitrogen and Argon gas can both be used as coolants and are capable of producing temperatures of at least -60°C [29].

For implementing cryoablation physician will perform a percutaneous procedure, which involves image-guidance assurance to insert cryoprobes or a series of small hollow needles through the skin to the site of the diseased tissue. Once the needles or cryoprobe(s) are in place, the liquid nitrogen or argon gas is delivered, due to which an ice ball is created in the target tissue [30, 31]. The completeness of cell destruction is directly proportional to the rapidity and duration of freezing and the rate of thawing. The temperature drops faster and to lower temperatures with decreasing distance from the cryoprobe. Visualization in real time with ultrasound for monitoring liver necrosis by the ice ball is one of the major advantages.

Another advantage of cryo energy is that it allows the doctor to freeze tissue to test whether it is responsible for cryomapping, however heat-based therapies don’t allow the doctor to do that – once the tissue is burned, it stays burned. In contrast, cryoablation allows re-warming of the frozen tissue to restore its function. The main disadvantage is that, cryoablation can be applied only for small tumors up to 4 cm [32]. Moreover, this technique has fallen out of favor for the treatment of HCC, primarily because the complication rate described are high as 40.7% [33-34] and the risk of “cryoshock,” a life-threatening condition resulting in multi-organ failure, severe coagulopathy and disseminated intravascular coagulation following cryoablation. Although cryoablation has been challenged in many cases and replaced by RFA because it is a viable technique for treatment of patients with primary liver tumors.
1.4.2 Laser Thermal Ablation

Laser is a monochromatic, collimated and coherent radiation with a wavelength of 1024 nm, which concentrates extremely high energy in small focalized areas. It may be transmitted inside the tumor by single or multiple quartz optical fibers inserted through fine needles, thus converting the intense light energy to tissue heating. As the amount of energy increases interstitial and intracellular water is vaporized and the tissue contracts. At higher energy levels, all cellular material is vaporized and a crater is created in the treated tissue [35]. One of the major disadvantages of laser is its small penetration depth less than 1 mm in the tissue, which restricts its use only for eye and cosmetic surgery. Further it generates relatively small ablation zone when used for deep seated organs, which generally make its use restricted. Moreover high vascularity or the presence of large vessels near the tumor can result in small or irregular lesions, leading to treatment failure or early recurrence. Laser ablation has been used in the treatment of liver metastases, while very few data is available on the treatment of HCC.

1.4.3 Ultrasound Ablation

High intensity focused ultrasound (HIFU) functions as a thermal therapy for tumors at a frequency range of 0.8 to 3.5 MHz. In HIFU, the intensity of the US beams is substantially increased by converging the beams within a tight focal zone. It is a truly non-invasive approach as the ultrasound transducer transmits the beams from outside the body. The intensity of the ultrasonic waves is below the threshold to cause damage as they pass through the tissue toward the focal zone [36]. Early clinical results of HIFU promised the local ablation of liver tumors, although there are time constraints that limit the practicality of current technologies for thermal ablation in many oncology settings. The length of treatment time needed is one of the major limitations for ultrasound ablation.
Although HIFU can reach various locations in the body with insertion depths dependent on the focal length of the transducer, the ability of HIFU to generate a lesion can be limited by air-filled organs such as the lung and the bowel. Focusing the HIFU beam through bone is also a major problem; however, attenuation correction and prediction based upon reference computed tomography (CT) or magnetic resonance (MR) has been performed [37].

1.4.4 Radiofrequency Ablation (RFA)

The use of RF alternating current to heat living tissue is credited to d’Arsonval in 1891, which showed that RF waves of high frequencies (> 10 kHz) can pass through living tissue causing an elevation in tissue temperature without causing neuromuscular excitation. These observations eventually led to the development of electrocautery and medical diathermy in the early- to mid-1900s. In the year 1990, both Rossi et al and McGahan et al published papers on ultrasound-guided RFA of hepatic tissue [38-39]. Both groups suggested that RF could be used to create focal coagulative necrosis of hepatic tumors while sparing normal liver tissue.

RFA uses radio-frequency current, usually around 500 kHz to deposit energy over a sizeable region to heat up tissue. The voltage applied is approximately ~100 V, with applied power up to 200 W. RFA works by converting radiofrequency waves into heat through ionic vibration. The ionic friction generates the heat within the tissue only, leading to coagulation necrosis and cell death. The higher the current, the more vigorous is the motion of ions and higher temperature is reached over a certain time. The RFA probe is introduced transcutaneously, in a minimally invasive fashion, into the tumor. The ability to efficiently and predictably create an ablation is based on the energy balance between the heat conduction of localized radiofrequency energy and the heat convection from the circulation of blood, lymph, or extra and intracellular fluid [40].
The performance of RF ablation is hindered by tissue charring which occurs if the temperature reaches nearly 100°C. At this temperature water begins to boil out of the tissue and tissue becomes dehydrated. The current path in dehydrated tissue is depleted. To work out this problem, the driving voltage may be impedance/temperature controlled to be switched off when impedance/temperature rises too high. Due to this reason, a cooling system was introduced in RF ablation to control the temperature at the electrode interface and increasing the ablation zone and keeping zone being too hydrated [41-42].

The RF ablation is handicapped in the areas of elevated blood perfusion, especially in liver and kidney and where tissue is desiccated. The major drawbacks encountered are that organs and tissues near the liver, such as the gallbladder, bile ducts, diaphragm and bowel loops, are at risk of being injured as the procedure may involve exposure to x-rays. In RFA complete ablation of lesions smaller than 2 cm is possible in more than 90% of patients with local recurrence in less than 1% [43]. In larger tumors five-year survival rates are somewhat lower, at 70-80% for nodules less than 3 cm in diameter, and 50% for tumors between 3 and 5 cm [44], hence it is unacceptable.

### 1.4.5 Microwave Ablation (MWA)

In 1936, Denier reported the use of low – frequency MW therapy to treat a tumor [11]. The basic principle of microwave ablation (MWA) is to apply microwave power to the liver tissue through the microwave antenna. Microwaves produce effective ablation without islands of viable cells in a rapid and reproducible fashion. The microwave region of the electromagnetic spectrum is well suited to such a role due to the efficient conversion of electromagnetic energy to heat. This translation of energy is a result of the strong interaction between polar molecules and microwaves that causes oscillation of molecules, which is dissipated as heat. Water is a highly polar molecule,
abundant in both normal liver tissue and hepatic neoplasms: it is the interaction between the microwaves and water that is principally responsible for the rise in temperature. The interaction between water and the entire range of frequencies in the microwave bandwidth is particularly strong. Another advantage of microwave ablation is the manner in which the heating occurs. Unlike the alternative ablative devices such as radiofrequency or cryotherapy, the passage of heat is not solely reliant on conduction.

The fundamental reason why microwave energy is unique and efficient is that it is transmitted from a suitable application or probe as a “field” around its tip. Direct heating of water molecules occurs within the whole microwave field, not simply by conduction of heat from the surface of a hot probe. A whole spherical area, perhaps the size of a tennis ball, is heated simultaneously and uniformly within minutes [45].

Microwave-generated heat is used to shrink and/or destroy cancerous tumors. Microwave ablation has generally utilized microwave antennas working at 915 MHz, and 2450 MHz [46]. A hyperthermia system includes the antenna and a non-contacting temperature sensor that scan a predetermined path over the surface of tissue to be treated. The temperature sensor senses the temperature of the tissue, and a controller closes a feedback loop that adjusts the microwave power applied to the antenna in a manner that raises the temperature of the tissue uniformly.

The early systems had the disadvantage of having heating patterns with lateral SAR contours that are significantly smaller than the applicator dimensions, thus causing under-heating problems in early trials when investigators used applicators that covered the tumors visually, but heated only their central region. Also, at the frequency of operation, these systems have relatively long wavelengths, limiting their ability to focus on tumors. To overcome these limitations, improved antenna-based systems and multiple-applicator systems have been used clinically for large tumors. Szwanowski et
al [47] developed implantable coaxial systems that were used to treat deep-seated tumors without affecting the overlying tissue. In the early 1980s, MW ablation (MWA) was developed as a technique to obtain hemostasis along the hepatic resection plane [48]. In 1983, Coughlin et al were the first to report the use of interstitial MW therapy for the treatment of a brain tumor. However, the electrode was prohibitively large, measuring 1 cm in diameter. This limitation was overcome in 1986 when Tabuse et al designed a small (2.8-mm diameter) coaxial interstitial MW system [48]. Currently MWA is in clinical use in a number of Asian centers [49-50]. Recently, advances in antenna design have led to a new MWA system in which power feedback is markedly reduced, allowing for longer times of application, greater power deposition, and larger ablation lesion sizes [51].

1.5 Comparison between MWA and other Therapies

There is no consensus on the “perfect” local ablation technique. The survival data must be fully elucidated for the different techniques and the growing implementation ablation treatments adds more complexity to the choice of techniques. Survival data should be expected to be similar for similar ablation techniques of local tissue destruction. If differences exist, it may be due to differing technical aspects such as operator variability, reliability and precision of the device, and specific needle/probe/antenna geometries used. Techniques producing smaller treatment volumes per needle or catheter insertion for laser and cryoablation, or treatment time in ultrasound ablation, may be more susceptible to treatment gaps and treatment failure. Because of this, radiofrequency and microwave may have advantages over laser, cryoablation, and ultrasound ablation, especially in liver tumor ablation where larger volumes of tumor burden are present. The Image-guided deposition of electromagnetic energy for killing tumor, drug delivery, gene transfection, or enhancement of radiation
or immunotherapy will play an emerging role in targeted local and regional oncology, guided by multimodality navigation, automation, and visualization [52]. The comparison between microwave ablation and other therapies as per their advantages and disadvantages is shown in Table 1.2.
<table>
<thead>
<tr>
<th>S. No.</th>
<th>Heating Techniques</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Microwaves</td>
<td>1. Large technology aspects. 2. Heating of large volumes theoretically possible. 3. Multiple applicators, coherent or incoherent, can be used. 4. Specialized antennas for heating from body cavities have been developed. 5. Skin cooling feasible. 6. Interstitial use has been demonstrated.</td>
<td>1. Heating not localized at depth. 2. Limited penetration at high frequencies. 3. Possible adverse effects on personnel. 4. Shielding of treatment rooms required, except at medically reserved frequencies (e.g. 915MHz). 5. Thermometry requires non interacting probes. 6. Temperature distributions subject to variations in local blood flow. 7. Commercial antennas available are of fixed length. 8. Depth of tissue implant alters specific absorption rate pattern.</td>
<td>Surface or near surface lesions, liver cancer treatment, Lesions on breast, chest wall, extremities (external applicators), bladder prostate, esophagus cervix, brain, head and neck with specialized or interstitial applicators.</td>
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<tr>
<td>2.</td>
<td>Radiofrequency (direct current or capacitive coupling)</td>
<td>1. Equipment relatively simple. 2. No special shielding required. Large volumes may be heated. Heating of deep-seated lesions sometimes possible. 3. Interstitial use has been demonstrated. 4. Electrodes not limited in size.</td>
<td>1. Fat tissue may heat preferentially. 2. Current flow subject to local electrical tissue characteristics. 3. Temperature distribution additionally subject to blood flow variations. 4. Heating regional with external applicators.</td>
<td>Large surface tumors, lesions in extremities, lung, pancreas, liver, bladder. Interstitial applications, chest wall head and neck, prostate, uterine cervical cancer.</td>
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<tr>
<td>1.</td>
<td>No penetration of tissue-air interfaces.</td>
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<td>2.</td>
<td>“Shadowing” by bone.</td>
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<td>“Shadowing” by bone.</td>
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<tr>
<td>3.</td>
<td>Bone tends to heat preferentially.</td>
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<td>4.</td>
<td>Patients may experience pain during treatment.</td>
<td>4.</td>
<td>Patients may experience pain during treatment.</td>
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</tbody>
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3. **Ultrasound single transducers**

1. Readily focuses on tissue.
2. Heating possible to 5-10 cm depth with focused transducers.
3. Dynamic systems have been demonstrated.
4. Shielding not required and no health hazard to.
5. In dynamic systems, effects of the blood flow can be reduced by minimizing focal volume.

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1.</td>
<td>Easy to focus</td>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
<td>Shielding not required</td>
<td>2.</td>
</tr>
<tr>
<td>3.</td>
<td>Easy to automate</td>
<td>3.</td>
</tr>
<tr>
<td>4.</td>
<td>Less costly</td>
<td>4.</td>
</tr>
</tbody>
</table>

4. **Laser Ablation**

1. Irregular lesions near blood vessels
2. Small heat generation rate
3. Limited used for abdominal tumors
4. Low penetration depth
5. Time consuming
6. Very costly

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1.</td>
<td>Complication rates are higher</td>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
<td>Risk of cryoshock</td>
<td>2.</td>
</tr>
<tr>
<td>3.</td>
<td>Risk of liver hemorrhage</td>
<td>3.</td>
</tr>
<tr>
<td>4.</td>
<td>Use repetitive freezing and thawing</td>
<td>4.</td>
</tr>
<tr>
<td>5.</td>
<td>Applied for small tumors only</td>
<td>5.</td>
</tr>
<tr>
<td>6.</td>
<td>Large time required to produce a lesion</td>
<td>6.</td>
</tr>
</tbody>
</table>

5. **Cryo-ablation**

1. Cryoablation is much safer
2. Does not weaken the tissue
3. Re-warming of the frozen tissue, restore its normal function.

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<tbody>
<tr>
<td>2.</td>
<td>Brain, primary and metastatic on the spine, eye and cosmetic surgery.</td>
<td>2.</td>
</tr>
</tbody>
</table>
MWA offers many benefits over RFA and Ultrasound ablation and has many theoretical advantages that may result in improved performance near blood vessels. Although RF ablation is most widely used thermo-ablative technique worldwide but main limitations of RF ablation are high local recurrence rates, particularly in the treatment of masses larger than 3.0 cm in diameter, the potential for incomplete tumor ablation near blood vessels because of the heat sink effect of local blood flow [53], difficulty in Ultrasound imaging of RF lesions, and evidence of surviving tumor cells even within RF lesions [54]. Ultrasound technique also offer major disadvantages like difficulty in penetration to tissue-air interfaces, shadowing by bone which tends to heat preferentially and patients may experience pain during treatment [55].

Table 1.3. Comparison of microwave ablation versus. radiofrequency ablation

<table>
<thead>
<tr>
<th>Features</th>
<th>Microwave ablation</th>
<th>Radiofrequency ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Frequency</td>
<td>915 MHz, 2.45GHz</td>
<td>365-480 KHz</td>
</tr>
<tr>
<td>Physics of energy deposition</td>
<td>Induction of oscillation in water molecules by propagating electromagnetic waves</td>
<td>Resistive heating by electrical alternating current</td>
</tr>
<tr>
<td>Generator power control</td>
<td>No feedback used</td>
<td>Temperature/impedance</td>
</tr>
<tr>
<td>Temperature</td>
<td>Higher</td>
<td>Comparatively lower</td>
</tr>
<tr>
<td>Thermal conduction</td>
<td>Less dependent</td>
<td>Dependent</td>
</tr>
<tr>
<td>Grounding pad</td>
<td>Not needed</td>
<td>Needed</td>
</tr>
<tr>
<td>Duration</td>
<td>Shorter</td>
<td>Long</td>
</tr>
<tr>
<td>Lesion Size</td>
<td>Larger lesions with single probe</td>
<td>Less larger lesion</td>
</tr>
<tr>
<td>Multiple MWA probes Interference</td>
<td>No interference with each Other</td>
<td>Interference with each other</td>
</tr>
<tr>
<td>Lesions near blood vessels</td>
<td>Better</td>
<td>Moderate</td>
</tr>
<tr>
<td>Multi applicator approach</td>
<td>Possible</td>
<td>Limited</td>
</tr>
<tr>
<td>Available Device</td>
<td>No FDA-approved devices (Vivant Medical)</td>
<td>FDA-approved devices (Valley Lab, Boston Scientific, RITA)</td>
</tr>
</tbody>
</table>
Microwave ablation results in consistently higher intra-tumoral temperatures, larger
tumor ablation volumes, faster ablation times, ability to use multiple applicators,
improved convection profile, optimal heating of cystic masses, and less procedural pain
[56-59]. In addition, microwave ablation does not require the placement of grounding
pads. Because of the drawbacks of RF ablation, several groups have successfully proved
the efficacious nature of microwave ablation in the treatment of hepatocellular
carcinoma [60]. The comparison of microwave ablation compared to radiofrequency
ablation based upon its important features is shown in Table 1.3.

1.6 State of Art on Microwave Thermal Ablation

Figure 1.3 shows the basic set up for performing MWA, the main components
used in system are; microwave generator, microwave applicator—the antenna, and a
section of flexible coaxial cable to connect the antenna to the microwave generator.
Computed tomography (CT) and ultrasound (US) are widely used for positioning of
applicators into the tumor, and for treatment monitoring. Thermocouples, RTD or Fiber-
optic thermometers can be used to measure tissue temperature. MRI scanners can be
used to examine lesion size after the procedures.

The microwave antenna, as the applicator for MWA, is the integral and most
important part of the MWA system. In this field of microwave ablation therapy, the use
of minimally invasive antenna is recognized as a very promising technique for the
treatment of small tumors because a very thin antenna can be easily inserted inside the
body and precisely localized using the advanced 3D imaging techniques and surgical
robots.

The antenna is connected to the microwave generator, the power level and
heating duration are selected in advance according to the shape and size of the tumor.
When the microwave power is applied to the targeted tumor, thermal lesion of predicted volume is created by the antenna. The microwave antenna is then safely retrieved. Despite of many promising advantages over other thermal ablative technologies, MWA still is in its infancy and has many significant technical challenges, which include, lesion size limitation, undesired backward heating along the antenna, and a non-spherical shape of heat lesion.

![Figure 1.3 Schematic diagram of MWA](image)

The primary goal of MWA is to treat liver tumor by creating a heat lesion covering the entire tumor. To treat a tumor of size $3 \text{ cm} \times 3 \text{ cm} \times 3 \text{ cm}$, a thermal lesion size of $6 \text{ cm} \times 6 \text{ cm} \times 6 \text{ cm}$ is required to destroy the entire tumor. Current MWA probes are apparently not powerful enough for such a requirement. Tumors generated in human liver are of spherical shape and could be of sizes up to 10 cm in diameter. Although large antennas are able to deliver high power and create large thermal lesions, but the antenna size is the conflict with the percutaneous operations. Hence it is desirable for MWA to generate a thermal lesion as large as possible with one antenna probe of miniature size, in one pass of treatment.
Detrimental backward heating is the major challenge for MWA, especially for percutaneous treatments. The backward heating problem basically refers to the undesired heating along the feed-line of the antenna. It causes damage to the healthy liver tissues and can also lead to burning of the skin during percutaneous treatment. There are three potential causes of detrimental heating along the coaxial feed-line.

i. Any impedance mismatch between the antenna and the surrounding medium will create reflections that set up standing waves within the coaxial feed-line. Under such conditions, the local currents on the inside of the outer conductor can become large enough to cause local heating. If the wall of the outer conductor is thin, the heat may transfer to the surrounding tissue.

ii. An impedance mismatch between the antenna and surrounding medium may also result in unbalanced currents on the inner and outer conductors of the coaxial feed. In this case, a remainder current flows along the outside of the outer conductor of the coaxial feed-line. The ‘tail’ seen in many of the specific absorption rate (SAR) patterns computed from simulations of MWA antennas is attributed to this current flow.

iii. Finally, most antenna designs are based upon copper coaxial cables. Since copper is a good thermal conductor, heat generated near the distal tip of antenna may be conducted along the feed-line.

Thermal lesions usually have tear-drop shapes. The backward heating problem will become more serious when power levels and application durations are increased in order to achieve larger lesions. The backward heating problem posts a huge challenge for MWA antenna designs. Despite many promising advantages over other thermal ablative technologies, MWA have many challenges like lesion size limitation, detrimental backwards heating, control of lesion generation and transient behavior of
tissue physical properties. Although large antennas are able to deliver high power and create larger thermal lesions, but it will also increase the backward heating, moreover large antenna size could also conflict with the desirable size required by percutaneous operations. To address these issues various coaxial and dipole antennas have been developed. Although clinical trials are the ultimate test for evaluating the performance of antennas, but simulated models play a crucial role while the designing the antennas for MWA – serving as a quick, convenient and inexpensive evaluation to isolate and optimize promising devices for prototyping. They also serve as a means of understanding the interaction between the various physical phenomena that occur during ablation treatments.

With the development of modern computers, the computational methods are becoming increasingly popular because of their simplicity, versatility, and the availability of software based on them. Several numerical techniques for computational electromagnetics were proposed, such as Method of Moments (MoM), Finite Difference Time Domain method (FDTD) in 1966 and Finite Element Method (FEM), which are described in detail in Chapter 3. MoM is efficient for analyzing open region geometries, FDTD method is economical in providing broad band behavior and animation, which is useful in diagnostics of the device. The most popular of these methods is FEM because it can be efficiently adapted to arbitrary device geometry and dielectric configuration. Often computational methods are chosen on the basis of trade-offs between accuracy, speed, storage requirements, versatility, and so on, and are structure dependent.

1.7 Objectives of the Proposed Work
The significant technical challenges of the research mentioned in previous section are analyzed in details and the information is utilized to identify the objectives of thesis. The Present research work is carried out keeping in view the following objectives.

1. To optimize the antenna design and predict heating pattern by numerical, electromagnetic and thermal simulation

2. Identifying and quantifying the trade-offs between various design parameters, including uniformity of heating pattern, the depth of penetration, and the impedance-matching.

3. Feasibility of using multi-section antennas to achieve the desired optimum designs.

4. To develop rational and reasonable sized lesion that does not require inordinate amount of time to create.

5. Improvement in thermometry techniques

In the proposed work, Finite Element Method (FEM) has been used to simulate microwave interstitial antenna with an aim to determine the optimal antenna design, optimal placement of inner temperature sensors for the purpose of efficient temperature-controlled ablation and optimal power application.

1.8 Chapter Outline

The contents of this thesis have been organized as per the following chapters:

**Chapter 1:** This chapter identifies the advantages of microwave ablation with respect to other treatment options in the light of present state of art. It covers basic anatomy of Liver, types of liver cancer, its causes and all treatment options of primary liver cancer i.e. Hepatocellular carcinoma (HCC) including the thermal ablations. Moreover it
includes main objectives and scope of research work.

Chapter 2: This chapter includes an exhaustive literature review on microwave antennas design based upon significant development and their performance parameters, clinical trial and numerical techniques used for computer simulation. Based upon review, research areas are identified for further investigations.

Chapter 3: In this chapter the analysis of interaction of microwaves with tissue and heat transfer in the tissue has been presented. Dielectric properties of liver tissues used for evaluating and thermal responses of biological tissues during microwave ablation have been discussed in elaborated way. It also introduces the thermometry techniques for monitoring the temperatures at critical locations and numerical methods framework in microwave ablation. COMSOL Multiphysics 3.4, modeling and simulation package used in the present research work has also been explained briefly.

Chapter 4: This chapter presents the fundamental concepts for the design and analysis of various numerically simulated antennas for MWA available till date. The basic computer models of antennas for microwave ablation, development and initial results have been discussed.

Chapter 5: The challenges discussed in Chapter 1 and various antenna designs in Chapter 4 reveals that the problems with the lesion size limitation and detrimental backward heating are both directly related to inefficient design of microwave antennas. Hence it is essential requirement to design a novel antenna in order to have improved performance over the current antenna designs. This chapter therefore deals with design, analysis and mathematical modeling for coaxial slot antenna and simulation analysis. The various performance parameters for MWA antenna such as temperature distribution and thermal
Lesion, antenna efficiency i.e. S11 parameter, SAR and power deposition have been introduced.

Chapter 6: This chapter presents the design and theoretical performance analysis of the new antennas: tapered cap floating sleeve antenna, needle tip choke antenna and multi-section floating sleeve antenna.

Chapter 7: This chapter includes the main conclusions and future scope of the proposed investigations.