博士論文

Combination of Hyperthermia and Radiation Brachytherapy on Breast Tumor

（マイクロ波温熱と放射線近接照射の組み合わせによる、乳がん向け治療法の検討）

ボウミク　デブナート　オイエンズリラ

Bhowmik Debnath Oiendrila

Abstract

Combination of hyperthermia and radiation brachytherapy has been shown to be effective for treatment of a tumor. After increasing the temperature, the tumor becomes sensitive to radiation dose, and as a result the radiation dose can be reduced.

The purpose of this study was to identify the appropriate antenna array which can be effectively used on a deep-seated breast tumor to increase the temperature to more than 42.5˚C, and to examine the effect of a smaller cumulative radiation dose of 30 Gy.

In this research different antenna and its parameters are tried and it was found coaxial-slot antenna array to be the most appropriate for applying hyperthermia on a deep-seated breast tumor. The temperature distributions were measured with a breast phantom, and specific absorption rate (SAR) distributions were calculated using a simulation software. Coaxial-slot antenna array, consisting of two coaxial-slot antennas, separated by a distance, and using a microwave power of 15 W increased the temperature of a tumor phantom, in an area of 30 mm in diameter, to over 42.5˚C in 30 min. The temperature as well as SAR were observed to have increased more in the tumor tissue than in the other types of tissues which were tested. Thereafter, we have examined the radiation dose distribution of brachytherapy using a treatment planning software. Simulations were conducted on the Computed Tomography image of an anonymous breast tumor patient; the tumor's dimensions were 40 mm (length) × 30 mm (width). A radiation dose of 30 Gy given in 5 fractions of 6 Gy each, which is lesser than the conventional radiation doses used in external beam radiation therapy, was applied to the tumor. Harm to adjacent tissues is also expected to be minimized due to lower radiation dose.

As a result of this study, there is a possibility of local control of deep-seated small breast tumors using a combination of interstitial hyperthermia by using coaxial-slot antenna array to increase the temperature to over 42.5˚C and radiation brachytherapy by applying cumulative dose of 30 Gy.

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Chapter 1
Introduction

Cancer is a collection of related diseases in which some of the body's cells begin to divide without stopping, and spread into surrounding tissues [x]. It is a generic term for a large group of diseases that can affect any part of the body, which is made up of trillions of cells. Normally, human cells grow and divide to form new cells as the body needs them. When the cells grow old or become damaged, they die, and new cells take their place. This orderly process breaks down when cancer develops. Many cancers form solid tumors, which are masses of tissue. Cancerous tumors are malignant, which means they can spread into, or invade, nearby tissues. This latter process of cancerous cells invading adjoining parts of body is referred to as metastasizing. Metastases are a major cause of death from cancer.

Cancer is one of the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases in 2012 [1]. The number of new cases is expected to rise by about 70% over the next 2 decades. Cancer is the second leading cause of death globally, and was responsible for 8.8 million deaths in 2015. Globally, nearly 1 in 6 deaths is due to cancer [1].

Breast cancer is the formation of a malignant tumor that has developed cells in breast. Breast cancer continues to be one of the most common cancers and a major cause of death among women worldwide.

In Japan, the number of projected breast cancer incidence in 2016 is 90,000 [2].

Figure 1 shows the statistics of projected breast cancer incidence and other cancer incidence in Japan in the year of 2016 [2].

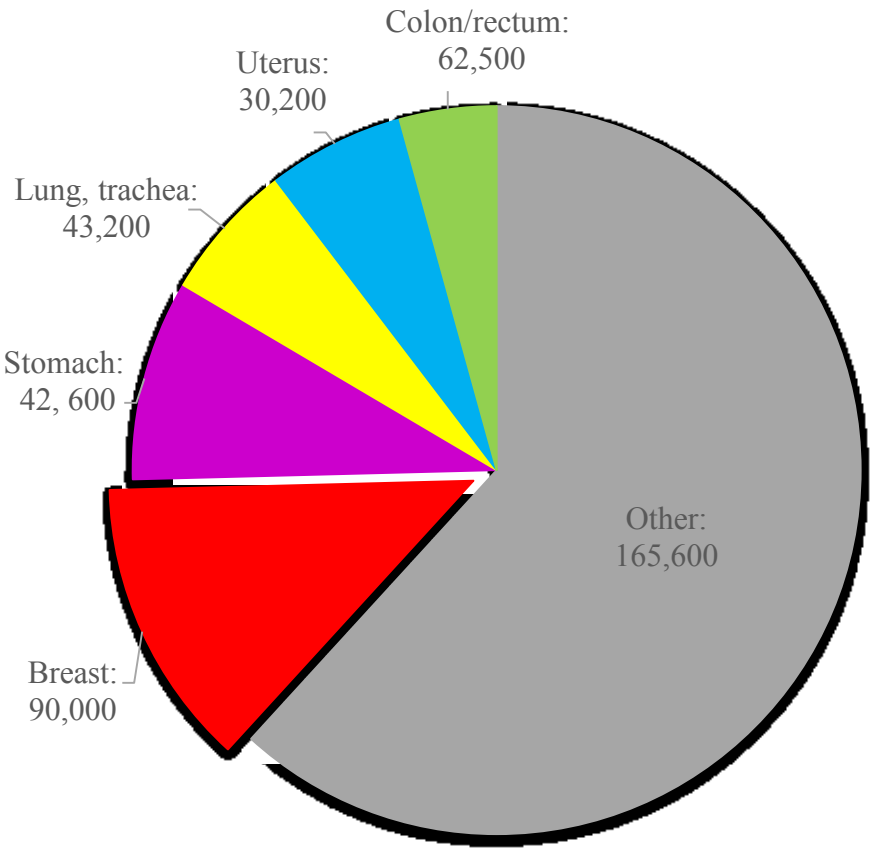


Figure 1.1 Projected cancer incidence in Japan in 2016

Figure 2 shows the statistics of projected number of cancer deaths due to breast cancer along with other major cancer deaths. Projected number of deaths due to breast cancer in 2016 is 14,000.

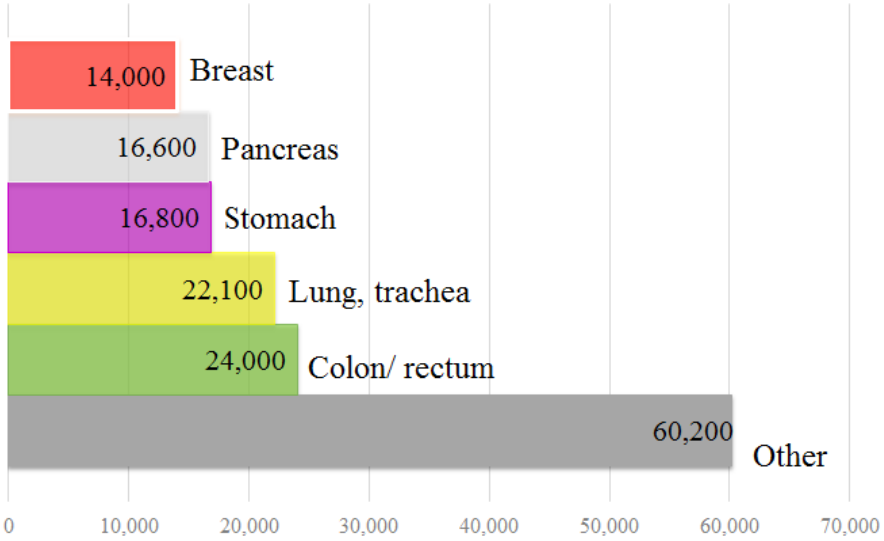


Figure 1.2 Projected number of cancer deaths in 2016

1.1 Composition of a Breast

Breast is composed of various tissues [3], such as fibro glandular, fat, muscle tissues. The shape, size and ratio of different tissues vary from person to person. A mass of glandular, fatty, and fibrous tissues over the pectoral muscles of the chest wall are attached by fibrous strands. A layer of fatty tissue surrounds the breast glands and gives the breast a soft consistency.

The glandular tissues of the breast house the lobules, which are milk producing glands, toward the nipple and the ducts which are milk passages. Toward the nipple, each duct widens to form a sac called ampulla. During lactation, the lobules produce milk. Once milk is produced, it is transferred through the ducts to the nipple.

To summarize, the breast is composed of:

- Lobules or Milk glands
- Ducts or milk passages
- Nipple
- Areola
- Fibro glandular tissue
- Fat
- Muscle

The content of fat and fibro glandular tissue varies from person to person. This makes the diagnosis or treatment of breast related illness difficult.

Figure 1.3 shows the image of a breast emphasizing different components of it.

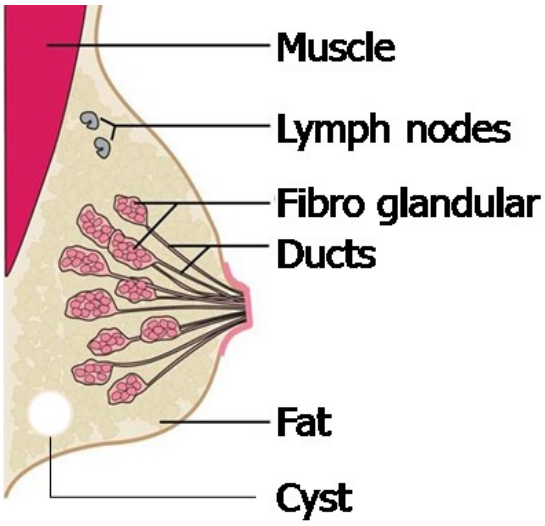


Figure 1.3 Image of a breast showing different parts [1]

In this research work, microwave is applied inside the breast. Microwaves are a form of electromagnetic radiation. A microwave's interaction with the tissues in human body cause the wave's amplitude to change its amplitude as it propagates through the tissues.

1.2 Electrical Properties of the Tissues Present in Breast

Research on the electrical properties of the human body tissues at microwave frequency range of 300MHz- 300GHz has been extensive. The electrical properties are represented in terms of relative permittivity and conductivity.

Studies revealed that the permittivity of the tissues are highly dependent on the water content [4]; tissues with low water content , such as fat have lower permittivity than tissues like muscle, skin and tumor tissues [4]. While permittivity gives us the indication of the tissue's ability to absorb microwave energy, conductivity on the other hand gives the indication of the loss or

attenuation of the microwave signal. Therefore, as the microwave signal travels through different tissues in the breast it suffers both attenuation and reflection as it encounters.

Understanding the electrical properties and heterogeneous nature of a female breast is important as it helps in the creation of a more realistic either numerical or physical breast phantom that can be used to assess the efficacy of any microwave technologies for treatment of cancer. Measurements of the tissue's electrical properties depend on a number of factors such as: tissue density, temperature, water content, location in the breast etc.

As this research work was conducted on a 2.45GHz frequency, the dielectric properties of the tissues were considered accordingly [5].

Table 1.1 shows the dielectric constants, namely the relative permittivity and conductivity of the tissues used for this research work.

Table 1.1. Dielectric constants of different tissue phantoms

Parameters	**Relative Permittivity**	**Conductivity (S/m)**
Skin	72.9	0.49
Fat	56.9	0.30
Muscle	66.0	0.71
Fibro glandular	68.8	0.79
Breast tumor	79.2	0.80

1.3 Breast Cancer Symptoms and Risks

In a patient suffering from bearing breast cancer, the cells surrounding the tumor are affected and in a span of time the tumor can damage the normal breast tissues of the human body. Major symptoms include an indication of red marks around the breast, discharge of blood from the nipples, nipple turning inward, formation of a lumpand pain in the breast. The following are the known risk factors and causes of breast cancer [1]:

- Risk of breast cancer is higher in women whose close relatives have (or have had) a breast cancer [1].

- Abortion- Risk of breast cancer is higher in women who have had an abortion at an young age [1].
- Age: Risk of breast cancer increases with age. Women at the age of 50-64 have a higher risk [1].
- Weight: Risk of breast cancer is higher in women who are overweight [1].

1.4 Types of Breast Cancer

Breast cancer can start in different areas of the breast- the ducts, the lobules or in the tissue in between. Following are few of the different types of breast cancer [6].

- Ductal carcinoma in situ: Carcinoma refers to any cancer that begins in the skin or other tissues that cover internal organs — such as breast tissue. In situ or "in its original place" means that the abnormal growth remains inside the lobule and does not spread to surrounding tissues. This is most invasive type of non-invasive breast cancer. This type of cancer starts inside the milk ducts that cover or line the internal organs, this does not spread beyond the milk ducts into any normal surrounding breast tissues.
- Invasive ductal carcinoma: This is a common type of breast cancer. This begins in the milk ducts and spreads to the surrounding breast tissues.
- Lobular carcinoma in situ: Lobular carcinoma in situ (LCIS) is an area (or areas) of abnormal cell growth that increases a person's risk of developing invasive breast cancer later on in life. Lobular means that the abnormal cells start growing in the lobules, the milk-producing glands at the end of breast ducts. People diagnosed with LCIS tend to have more than one lobule affected.
- Invasive lobular carcinoma: This type of cancer develops in milk-producing lobules, spreads into the ducts that carry milk to the nipple, and later also spreads to the surrounding breast tissues.
- Inflammatory breast cancer: This type of cancer normally starts with the reddening and swelling of the breast instead of a distinct lump. It tends to grow and spread faster than the other types of breast cancer.

- Male breast cancer: Breast cancer in men is a rare disease. When men bodies synthesize breast developing hormones and have abnormal hormone levels, breast cancer may occur.
- Molecular subtypes of breast cancer: There are five different molecular subtypes of breast cancer.
  (i) Luminal A: It is hormone-receptor positive, HER2 negative and has low levels of the protein Ki-67, which helps control how fast cancer cells grow.
  (ii) Luminal B: This type of breast cancer generally grow faster than luminal A and their prognosis is slightly worse than them. This is also hormone receptor and any extreme level of HER2 with high level of Ki-67.
  (iii) Triple-negative/Basal-like: This type of cancer is commonly seen in women with BRCA1 gene mutations. This type of breast cancer is hormone receptor negative and HER2 negative.
  (iv) HER2-enriched. As name suggest, this type of cancer is HER2 positive. This type of cancer is treated with targeted therapies aimed at HER2 proteins.
  (v) Normal-like: This type of cancer grows slowly. This cancer is hormone-receptor positive and HER2 negative.
- Paget's disease of the Nipple: Paget's disease of the nipple is a rare form of breast cancer in which the cancer cells collect in or around the nipple. The cancer usually affects the ducts of the nipple first (small milk-carrying tubes), then spreads to the nipple surface and the areola (the dark circle of skin around the nipple). The nipple and areola often become scaly, red and itchy, and irritated.
- Phyllodes tumors of the breast: This type of cancer tend to grow quickly but rarely spread outside the breast. Most of the cancer of this type are benign..
- Recurrent and metastatic breast cancer: Recurrent breast cancer is a type of cancer which comes back to another breast or chest wall after a period of time. On the other hand, metastatic breast cancer is a type of cancer which spreads to other parts of the body.

  Both these types of cancers are considered as advanced stage cancers.

1.5 Different Types of Treatment Modalities

Different types of modalities or the combination of two or three modalities are used to treat breast cancers [7]. Following are some of the modalities used commonly:

1.5.1 Surgery

Surgery is a common treatment for breast cancer, and its main purpose is to remove the cancer as much as possible. There are two main type of surgery is done.

Breast Conserving Surgery: In this kind of surgery, only a part of the breast containing the cancer is removed. Figure 3 shows the procedure to detect the area before breast conserving surgery.

The patients who opt for breast conserving surgeries, in most cases, opt for radiation therapy or chemotherapy after the surgery. .

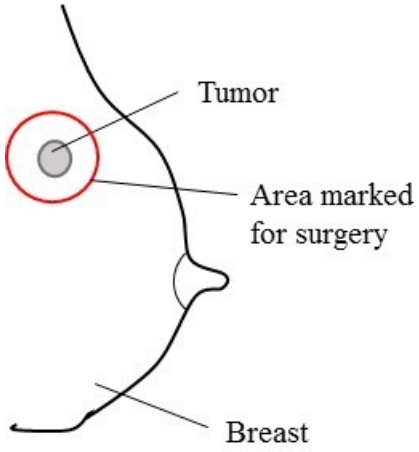


Figure 1.4 Breast Conserving Surgery- lumpectomy

Mastectomy: In this kind of surgery, the entire breast is removed, including all of the breast tissue and in some cases, other nearby tissues.

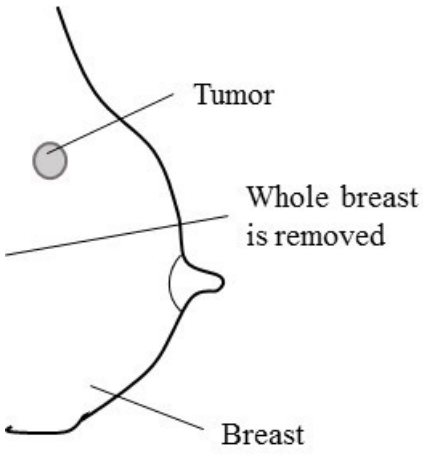


Figure 1.5 Breast mastectomy surgery

1.5.2 Chemotherapy

Chemotherapy is a treatment using cancer killing drugs that may be given intravenously or orally. In most of the cases, it travels through the blood stream and reaches the cancer cells to destroy them. Chemotherapy can be given before or surgery.

Before Surgery: Chemotherapy is done before the breast conserving therapy.

After Surgery: In most of the cases,, chemotherapy or a combination of chemotherapy and radiation therapy is given to the breast after surgery. After breast conserving surgery, few cells remain in the lymph node or other tissues, stay back. In order to kill those cells, chemotherapy or a combination of chemotherapy and radiation therapy is given.

1.5.3 Radiation Therapy

In radiation therapy, high energy particles are used in order to kill the cancer cells. Radiation therapy for breast tumor is done after surgery. Radiation therapy can be done in various ways:

External Beam Radiation Therapy: In this case, the whole breast gets irradiated with high energy particles. Radiation therapy is usually done after the surgery. External beam

radiation therapy is given in order to kill cancer cells which have spread in many different areas of the breast.

Figure 1.6 shows the procedure how the whole breast gets irradiated.

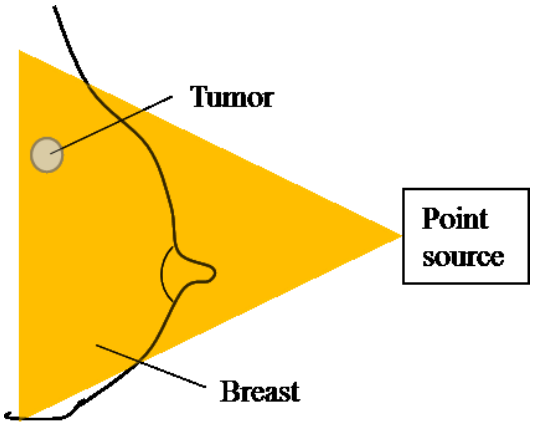


Figure 1.6. Breast tumor treated by external beam radiation therapy

Internal Beam Radiation Therapy: Internal radiation is a form of partial breast radiation. During the treatment, a radioactive liquid is injected using needles, catheters etc., in order to target the area.

Breast Brachytherapy: In breast brachytherapy, catheters are placed inside the breast to deliver the breast at the time of the surgery or shortly thereafter which carries targeted radiation to the tissue where the cancer originally grew.

Figure 1.7 shows the procedure for breast brachytherapy.

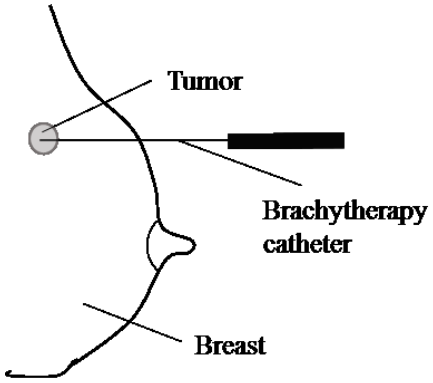


Figure 1.7 Brachytherapy procedure for breast with tumor

1.5.4 Hyperthermia

Microwave-hyperthermia is a method of treating cancer by heating the tumor. In this method, the tumor temperature is increased by an external means to over 42.5˚C. At this temperature, the cells behave cytotoxic and as a result, the cells die or become sensitive to radiation.

Many methods of hyperthermia treatment are available. Hyperthermia may be local, where only a small restricted area of the body is heated, or it can be regional, where an entire body part may be heated, or whole body may be heated. Techniques that have been used for production of hyperthermia include conduction through the skin, recirculation of externally heated blood, heated intravenous fluids, ultrasound, and electromagnetic coupling modalities. These electromagnetic methods may be invasive or non-invasive depending on the location of the tumor.

The main challenge in treating cancer with hyperthermia is the technologies used in different experiments, cannot deliver effective and homogenous heating of all sites, particularly the deep seated tumors.

1.5.5 Combination Therapy

Recently, different types of combination therapies are being practiced. for treating breast tumors.

Combination therapies are given in order to achieve better results in treatment of cancer cells, lesser use of radiation therapy, given and to prevent reoccurrence of cancer cells. Depending the breast cancer stage, tumor size, proliferation rate and other condition such as metastases, the combination of different modalities of breast cancers are chosen. For stage I and II breast cancer, combination of breast conserving therapy and radiotherapy is mostly used [7]. The highest percentage of the breast cancer are treated with mastectomy surgery, radiotherapy and chemotherapy [7]. This whole process takes long time and observation regularly. Radiotherapy can be delivered by either external beam radiation therapy or brachytherapy. Depending on the patient history, tumor size and metastases, the radiation dose gets decided. As discussed earlier, there are two types of surgery for breast cancer common. Depending on the type of surgery and metastases the radiation dose is decided. Most commonly breast cancer is stage II and the radiation dose for that is mostly given 50 Gy- 60 Gy [46].

In this research, the cumulative radiation dose is proposed 30 Gy which is comparatively lesser than the conventional dose

In this current research work, combination therapy of hyperthermia and breast brachytherapy is investigated. The detailed research work is described in the theses.

1.6 Literature Survey

Combination of microwave hyperthermia and radiation therapy has been a topic of interest for many researchers for the past several decades.

In 1977, Dewey et al, investigated the cellular responses of the combination of hyperthermia and radiation [8]. The main advantages of applying hyperthermia as a cancer therapy from cellular point of view are:

(a) During cell cycle, the cells are relatively radio-resistant in the S phase but they are sensitive to hyperthermia. So the cells in S phase can be radio-sensitized by combining hyperthermia and X-irradiation; the tumor cells which would normally survive radiation dose alone, can thus be killed by combining hyperthermia and radiation.

(b) Tumor hypoxia is the situation where tumor cells are deprived of oxygen under such hypoxic conditions, it has been shown that cell obtain radio resistance [x2]. Such relatively radio-resistant cells in the tumor may be destroyed by combination of hyperthermia and x-irradiation.

In 1980, Raymond et al, investigated about the microwave induced local hyperthermia in combination with radiotherapy particularly in human malignant tumors [9]. This study had shown microwave hyperthermia can be used in conjunction with radiation for clinical benefits. The results of the combination therapy were positive, and the harm to the surrounding tissues were less as the heating and radiation.

Simultaneous application of hyperthermia and radiation therapy has also examined by many researchers. In some cases, hyperthermia is applied before radiation therapy; sometimes it is applied along with the radiation therapy and sometimes it is applied after the radiation therapy. In 1978, Overgaard et al, examined the effect of applying the therapies sequentially. During the experiments, a temperature of 42.5˚C was achieved in 60 min [10]. The results were compared to the effect of applying the therapies simultaneously. A decrease in thermal enhancement ratio (The synergistic effect of heat and radiation is quantified by thermal enhancement ratio) with increasing interval between the treatment modalities. For hyperthermia given after radiation, there was a marked reduction in thermal enhancement ratio within the first hour. With hyperthermia given before radiation, the reduction in the thermal effect with increasing time interval was less pronounced, and there was an increase in thermal

sensitization The rapid recovery from excess thermal damage to the skin when radiation was given before hyperthermia has implications for the therapeutic ratio. But for all intervals tested except 24 hours, the thermal enhancement ratio for the skin was only slightly below that observed in the tumor and did not result in any significant improvement of the therapeutic ratio. With the 24 hours interval, the thermal enhancement ratio for tumor was significantly higher than that of normal tissue, and a slight therapeutic gain was obtained. However, the improvement in therapeutic gain was more impressive for radiation given before hyperthermia.

Research result had shown that increasing the interval between radiation and hyperthermia resulted in an improvement in the therapeutic gain reaching a maximum at an interval of 4 hours.

Patients with persistent and/or recurrent breast tumors or chest wall tumors have significantly benefited when hyperthermia has been added to their radiotherapy and/or chemotherapy regimens [10-19]. One of the reasons for the success of hyperthermia in this group of patients is the superficial location of the tumor. Superficial lesions are the least difficult to heat adequately because of their accessibility and proximity to external energy sources. The composition of the local anatomy may also contribute to better heating [20, 21]. Another possible reason may be that superficial lesions are more amenable to invasive thermometry and thermal mapping of temperature sensors, thus providing more temperature feedback data during the treatment, which can be used to improve heat delivery and ensure treatment quality [22, 23]. Clinical research efforts have demonstrated that the response of cancerous tumors to sequential thermoradiotherapy (i.e., sequentially combined radiotherapy and hyperthermia) is well correlated with power deposition coverage and/or thermal dose coverage [17, 23-33]. These studies have also pointed to the challenge of consistently achieving biologically meaningful thermal doses in 100% of the target volume (total tumor area) in routine clinical practice. Therefore, it is widely accepted that the benefits of hyperthermia as an adjunct to radiotherapy can be significantly augmented with improvements in treatment delivery techniques, better heating technology, advances in treatment planning and implementation of quality assurance guidelines [23-27]. Moreover, in vitro and animal studies have shown that when hyperthermia and radiation are administered simultaneously —rather than sequentially as it is conventionally done—heat induced radio sensitization is increased at thermal doses achievable in the clinic

[38-41]. For instance, mild hyperthermia—41°C maintained for ~60 minutes—produces heat induced radio sensitization if radiation and heat are delivered simultaneously, but not sequentially. This is significant because a minimum target temperature of 41°C is more clinically achievable than the > 42°C needed to produce heat induced radiationwith sequential treatment [39, 41-42]. In 1983, Ronald et al, reported clinical research study where hyperthermia in combination with radiotherapy was used for superficial tumors [43]. The heating was observed 3 cm deep under the skin layer. The tumor temperature was increased to around 43˚C-44˚C.

Although a phase III clinical trial conducted by Emami et al. (1996) had concluded that there are no beneficial effects of the combination of interstitial hyperthermia and radiation therapy as compared to radiation therapy alone, limitations in the quality of hyperthermia due to inadequacy of technologies available at that time, was mentioned to be a challenge [44].

It is also reported that the combination of hyperthermia and radiation therapy can reduce the tumor growth. In 2005, Clare et al, had concluded that combined hyperthermia and external beam radiation therapy increased animal survival compared with either of the treatments alone [46]. This study was done on rat breast models and was limited to tumors having a diameter of 2.5 cm or less. The study had shown the evidence of the histo-pathologic sections of the tumor after 7 days of the surgery. There was no other side effects observed. This research group had also noted that a radiation dose of 20 Gy or more along with hyperthermia increases the chances of end survival and/or local cure. These findings suggested a dose related effect of radiation therapy and possibility of optimization between the temperature rise and radiation therapy.

As the previous studies shown the difficulty in heating the human tissue properly and in monitoring the temperature rise, some researchers came up with different microwave antennas for hyperthermia.

There are normally two ways practiced by different researchers for hyperthermia:

(1) Ultrasound
(2) Microwave

In 1999, Chris et al, used ultrasound in order to increase the temperature inside the tissue in a focused area [47]. The attenuation coefficient of ultrasound energy loss in tissue is roughly proportional to frequency, thus penetration depth was controlled from less than a centimeter to approximately 10 cm or deeper, by varying the frequency or using focused beams, in order to verify the effect. Additionally, the transducer fabrication technology combined with wavelengths on the order of mm within this frequency range, facilitates practical applicator dimensions and multiple transducer configurations; thus, allowing a wide variety of shaping or control of the beam distributions. This includes focusing of beams using focused transducers or electronically phased arrays to increase localization, depth and control of heating.. As high intensity focused ultrasound, focuses on a small area and the control of temperature increase is less. In this research work, that challenge was tried to be solved.

In 2007, Florence et al, reported analytical modelling of microwave antenna-insulated dipole applicators for interstitial hyperthermia [48]. In that research work, a different design of antenna was emphasized. The electric field radiated, power distribution and energy absorbed depend on the frequency of the antenna and the type of material in which the antenna is used. The electromagnetic field radiated in the l dielectric medium surrounding the insulated antenna produces energy dissipation which converts into heat. This is the fundamental logic of using invasive antenna for the purpose of hyperthermia. The power absorption which is also known as Specific Absorption Rate (SAR), is related to the temperature rise at steady state. The higher dissipated power appears close to the feed point.

In 2011, Earl et al, proposed a new microwave hyperthermia approach that used time multiplexing of multiple beamformers [49]. Each patient-specific beamformer was designed to focus microwave energy at a target location while minimizing energy deposition in a normal tissue region was unique to each beamformer. In this paper, a simulation of a human brain was used. In this research work, with beam forming technique, the temperature was increased in the superficial layer.

In 2012, Teng Jiao has used invasive hyperthermia antenna on pork liver to increase the temperature [50]. The practical experiment was done for 240 second and was targeted around a range of 2.8 cm * 6.0 cm. In this research work, a coaxial-slot antenna was designed which successfully increase the temperature. Antennas were applied on a pork liver. But in this research work, no particular tumors were heated.

In all the studies mentioned, there were different observations from different point of views. Further studies and investigations were recommended in each of these studies for combination of hyperthermia and radiation therapy.

1.7 Objective of this Research

The purpose of this study was to identify the appropriate antenna array which can be effectively used on a deep-seated breast tumor to increase the temperature to more than 42.5˚C, and to examine the effect of a smaller cumulative radiation dose of 30 Gy.

The motivation was to adequately heat the deep seated tumor, with lesser harm to the surrounding normal tissues.

In this research work, a deep seated tumor about 5cm ~ 7 cm from the skin surface, radius of about 30 mm was assumed for design of different types of non-invasive and invasive antennas, the simulation and the experiments and analyzed heating this tumor.

In non-invasive antennas micro-strip patch antenna and spiral antennas were designed and simulations were conducted using phantoms similar to human tissues. A two micro-strip patch antenna array separated by a distance was applied on layers of phantoms to check the diffraction. During the experiment with spiral antenna array, similar phantoms were used to see the effect and heating penetration depth. After the experiment, with the application of antenna array separated by 0.5 mm, the heating depth was found to be 2 cm – 3 cm. The heating pattern was found to be more distributed close to skin surface and it did not penetrate deep seated tumor.

In invasive antennas coaxial-slot antenna was designed and simulations were conducted using phantoms which were used for the non-invasive antennas. The power generation, temperature elevation and few other parameters, namely duration of application of antennas, the depth of heating penetration were compared with each other. The temperature distributions were measured with a breast phantom, and specific absorption rate (SAR) distributions were calculated using a simulation software. A coaxial-slot antenna array, consisting of two coaxial-slot antennas, separated by a distance, and using a microwave power of 15 W increased the temperature of a tumor phantom, in an area of 40 mm in diameter, to over 42.5˚C in 30 min. The temperature as well as SAR were observed to have increased more in the tumor tissue than in the other types of tissues which were tested.

As per the initial objective of heating a deep seated tumor with lesser harm to the surrounding normal tissues, the coaxial-slot antenna array was found to be the most appropriate.

Thereafter, the radiation dose distribution of brachytherapy was examined using a treatment planning software. Simulations were conducted on the Computed Tomography image of an anonymous breast tumor patient; the tumor's dimensions were 40 mm (length) × 30 mm (width). A radiation dose of 30 Gy given in 5 fractions of 6 Gy each, which is lesser than the conventional radiation doses used in external beam radiation therapy [xx], was applied to the tumor. Harm to adjacent tissues is also expected to be minimized due to lower radiation dose.

In conclusion, there is a possibility of local control of deep-seated small breast tumors by using a combination of interstitial hyperthermia applied by a coaxial-slot antenna array, increasing the temperature to over 42.5˚C, and radiation brachytherapy, applying a cumulative radiation dose of 30 Gy.

1.8 Outline of this Thesis

This thesis consist of six chapters in total.

Chapter one is the general introduction background of the breast cancer and its different treatment modalities and, the basic motivation of starting this research.. It includes the extensive literature survey regarding cellular effect of hyperthermia and radiation brachytherapy individually and in combination, and clinical trials done in different stage of the tumors. In this chapter, objective of the research work is mentioned.

Chapter two describes the first part of this research work, i.e. hyperthermia, in details. The conventional ways of hyperthermia, different methods to implement etc., are discussed. The antenna design, experiments using the antenna on the phantoms, the results and the discussion on the results obtained are also covered in this chapter.

Chapter three describes the second part of this research work, i.e. radiation brachytherapy in details. The conventional way of brachytherapy, the different methods to implement, the simulation results and the discussion on the results obtained are also covered in this chapter.

Chapter four describes the steps towards optimizing the combination therapy. In order to get better results, the distance between the antennas were adjusted and similar experiments were conducted for hyperthermia and radiation therapies. The results obtained and discussion on the results obtained are covered in this chapter.

Chapter five describes a general discussion on various parameters such as blood flow and how that varies from tumors to normal tissues.

Chapter six describes the summary and conclusion of this research work. It discusses the potential next steps and future work.

Chapter 2
Hyperthermia

2.1 Introduction to Hyperthermia

Microwave-hyperthermia is a method of treating cancer by heating the tumor. This distinguishes it from normal fever of up to 40˚C and high fever which might occur as a result of some health related problem such as sunstroke.

Many methods of hyperthermia treatment are available. Hyperthermia may be local, where only a small restricted area of the body is heated, or it can be regional, where an entire body part may be heated, or whole body may be heated. Techniques that have been used for production of hyperthermia include conduction through the skin, recirculation of externally heated blood, heated intravenous fluids, ultrasound, and electromagnetic coupling modalities. These electromagnetic methods may be invasive or non-invasive depending on the location of the tumor.

The objective of this artificially induced temperature rise is the treatment of tumors, directly by introducing irreversible biological damage or indirectly by enhancing the effects of other treatment regimens such as X-irradiation or chemotherapy in a synergistic way.

Different Kinds of Hyperthermia:

Local Hyperthermia:

Superficial tumors can be heated by means of antennas or applicators emitting mostly microwaves or radio waves placed on their surfaces with a contacting medium. Several types of applicators have been used clinically, such as waveguide applicators, horn, spiral, current sheet, and compact applicators. The main components of such an invasive hyperthermia system are shown in figure 2.1.

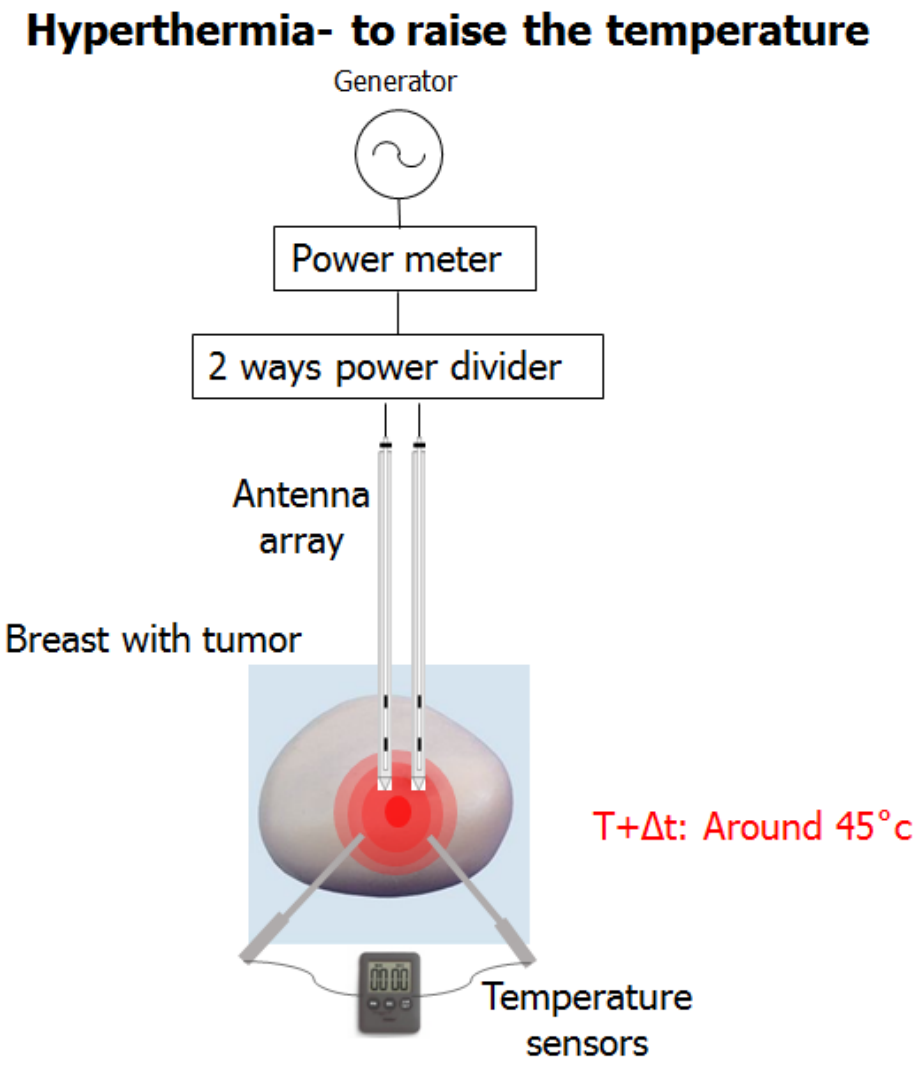


Figure 2.1 Hyperthermia by applying two antennas inside the tumor

For non-invasive antennas, there is a bolus material is required to be placed between the tissue and the antenna. The electromagnetic coupling of the applicator to the tissue is ensured by a water bolus (preceding water path). Intra-tumoral temperature can be controlled by the output of the power generator or by positioning the applicator. The resulting SAR distribution is subject to strong physical curtailment resulting in a therapeutic depth of only a few centimeters and is even further limited in regions with an irregular surface, such as the head and neck area, the supraclavicular region, or the axilla.

Whole Body Hyperthermia:

In whole body hyperthermia, a mild high temperature is maintained for long time.

The effects of hyperthermia are listed below [8,52]:

- Cell death due to high temperature and duration of application of high temperature: Due to high temperature cell death occurs. Temperature and duration of application of high temperature are also important to count the amount of cell death.
- Variations during the cell cycles in sensitivity to hyperthermia: Normally in S phase, the cells are radio resistant and temperature sensitive.
- Cell kinetics following the treatment:
- The time required to repair the heat induced lesions
- The effects of hypoxia and other physiological states due to increase in temperature

Biological effects of hyperthermia:

The effects of hyperthermia are listed below [8,52]: The cell killing property of hyperthermia depends on various cellular factors [53]:

Cell cycle: Synchronized cell cultures exhibit variations in their susceptibility to heat in accordance to their phase in the cell cycle. In general, the highest heat sensitivity can be observed during the mitotic phase. Microscopic examinations of M-phase cells exposed to hyperthermia show damage of their mitotic apparatus leading to insufficient mitosis. S-phase cells are also sensitive to hyperthermia, where chromosomal damage is observed. Both S and M-phase cells undergo a 'slow mode of cell death' after hyperthermia, whereas those exposed to heat during G1-phase are relatively heat resistant and do not show any microscopic damage. These variations existing between the different cell cycle phases indicate the possible diversity of molecular mechanisms of cell death following hyperthermia and is shown in figure 2.2.

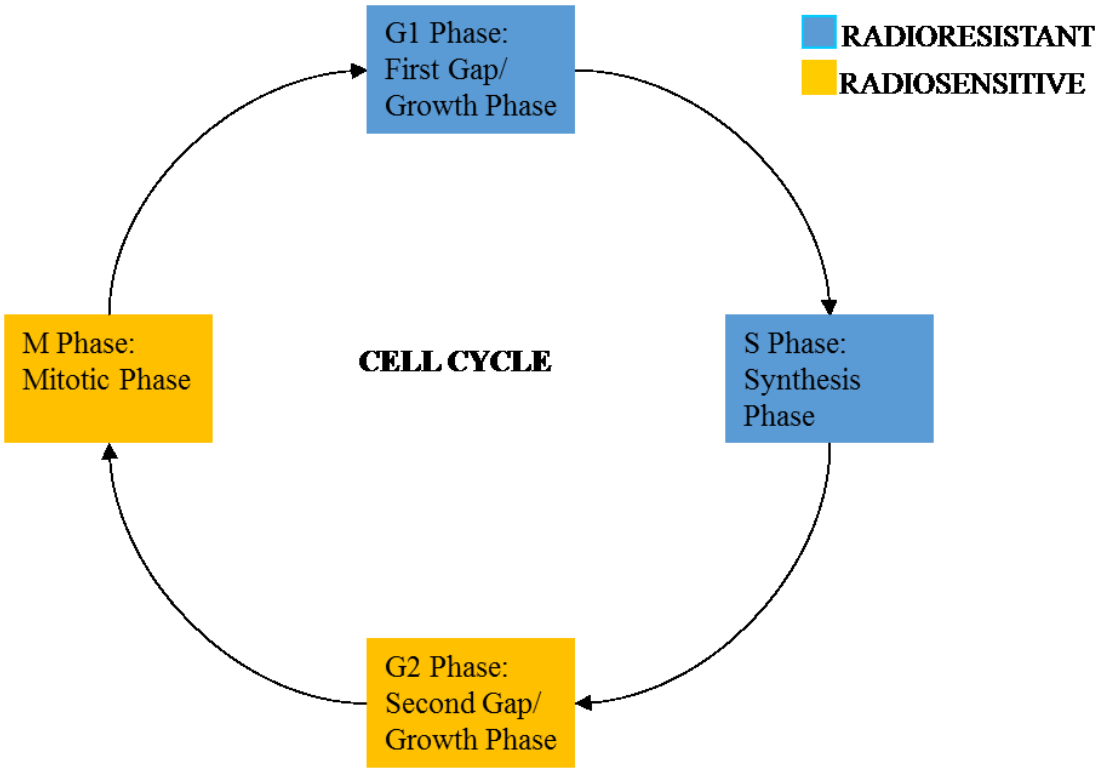


Figure 2.2 Cell cycle showing the cell sensitivity to radiation during each phase

Effects in DNA and RNA: Intracellular synthesis and polymerization of both RNA and DNA molecules as well as protein synthesis are decreased at temperatures over 42.5˚C. RNA and protein synthesis recover rapidly after hyperthermia, but DNA synthesis is inhibited for a longer period. Heat shock induces an aggregation of denatured proteins at the nuclear matrix. This is mainly due to insolubility of unfolding of heat induced protein, creating an enhancement of the nuclear protein concentration. Increase of the nuclear protein content due to heat consequently affects several molecular functions including DNA synthesis and repair when a certain thermal dose is exceeded. This threshold dose varies with different cell types.

Apoptosis Induction

Researchers have investigated about the behavior of cells after hyperthermia and after combination of hyperthermia and radiation therapy. The oxygen content in the tumor cells increase due to hyperthermia, and oxygen as a strong radio sensitizer helps in killing the cells with lesser dose of radiation.

Hyperthermia is a method of increasing temperature of tissue by an external means and it can be differentiated with fever. While hyperthermia has been used as a cancer therapy for over a hundred years, only now is equipment for physical hyperthermia has started emerging from the laboratory in recent years, being commercially produced, and gaining acceptance in the clinical arena.

The properties of hyperthermia, namely making the tumor cells sensitive to radiation or even killing them, makes it an interesting technique which should be further investigated in combination with other cancer therapies. The amount of cells killed depends on the thermal dose, which is a function of temperature and time. Hyperthermia is practiced for more than 100 years above. However, due to the complexity of heat induced changes, the accurate experimental set-up and optimum thermal dose is still under investigation. Here, several cellular effectors of hyperthermia are being described.

Methods to increase temperatures

To reach temperatures clearly above the systemic temperature of 37·5°C in a defined target volume is a technical challenge and still under development. The temperature increase is induced by applying a power-density specific absorption rate (SAR; measured in W/kg). Human basal metabolic rate (basal metabolism) is above 1 W/kg. Perfusion counteracts the temperature rise. Perfusion rates in tumors are around 5–15 mL per 100 g per min, but they vary widely. To reach therapeutic temperatures of about 42°C at least in some parts of such tumors necessitates power density of about 20–40 W/kg at the target region[5].

At present, the optimum temperature distribution for clinical purposes is unknown. Temperature distributions achieved to date have limited absolute values and homogeneity (minimum temperatures typically lie between 39·5°C and 40·5°C), mainly because of physical and physiological characteristics such as electrical tissue boundaries, local perfusion variations, and perfusion regulations. Only about 50% of deeply located tumors reach at least 42°C at one

particular measurement point. Clinical studies have shown that uncritical adoption of preclinical results into clinical guidelines for tumor temperatures is not justified. Nevertheless, many phase II clinical studies have shown associations between tumor response and characteristics of temperature distribution (minimum temperature or minimum thermal dose in the tumor area).

Even though the tumor temperatures that have to be reached for clinical efficacy are still unclear, we should achieve temperature distributions as high and homogeneous as possible. Technological potential for in vivo monitoring and control of temperature distribution has not yet been intensively scrutinized, at least for the regional hyperthermia approach.

2.2 Modalities of Hyperthermia

Hyperthermia can be achieved by different modalities using different waves. Following are some of them:

(i) Ultrasound: High intensity focused ultrasound can be used to achieve high temperature regions inside a patient without requiring any invasive interaction. A multitude of ultrasound transducers, i.e. up to two thousand, positioned in a phased array is used to produce a small, well defined pressure focus. As the pressure oscillates, microscopic movement is produced that translates heat due to friction. The heat focus can be used to coagulate tissue or to temporarily increase drug intake in certain cells by breaching the blood brain barrier. Sometimes MR guidance is used to safely steer and monitor the ablation process.

(ii) Microwave: Microwave ablation is used treat various kinds of tumors. Invasive or non-invasive antennas are used to increase the temperature. In various cases, one or multiple ablation antennas are inserted in a minimally invasive manner into the treatment region. The invasive catheters are inserted in a minimally invasive manner into the treatment region. Non-invasive antennas are able to increase the temperature of the superficial tumors lying within 2 cm under the skin layer.

In the experiments, hyperthermia was applied using the frequency 2.45 GHz as it comes under Industrial, Scientific, and Medical (ISM) band in Japan, the U.S., and some other countries.

2.3 Antenna design

There are two types of microwave antennas are used for hyperthermia:

(i) Non-invasive: Non-invasive antennas are those which are applied from outside of the body. Normally it is places in the skin just above the skin or focusing antennas effects towards a particular tumor.

During this research work, two types of non-invasive antennas were designed:

(a) Micro-strip patch antenna

(b) Spiral Antenna

(ii) Invasive: Invasive antennas are those minimally invasive antennas, light weight and easy to use.

In this research work, one type of invasive antenna was designed:

(a) Coaxial-slot antenna

Non-invasive micro-strip patch antenna

Micro-strip patch antenna is a common type of non-invasive antenna. It has a number of advantages over other antennas, such as: it is light weight, inexpensive and easy to make conformal structures. As it is a non-invasive antenna, it generates the far field when used.

Figure 2.2 shows the basic structure of a micro-strip patch antenna: a flat plate over a ground plane. This antenna is often built of printed circuit board material and the substrate makes up the patch antenna's dielectric. Antenna parameter diameters depends on the frequency on which it is operated.

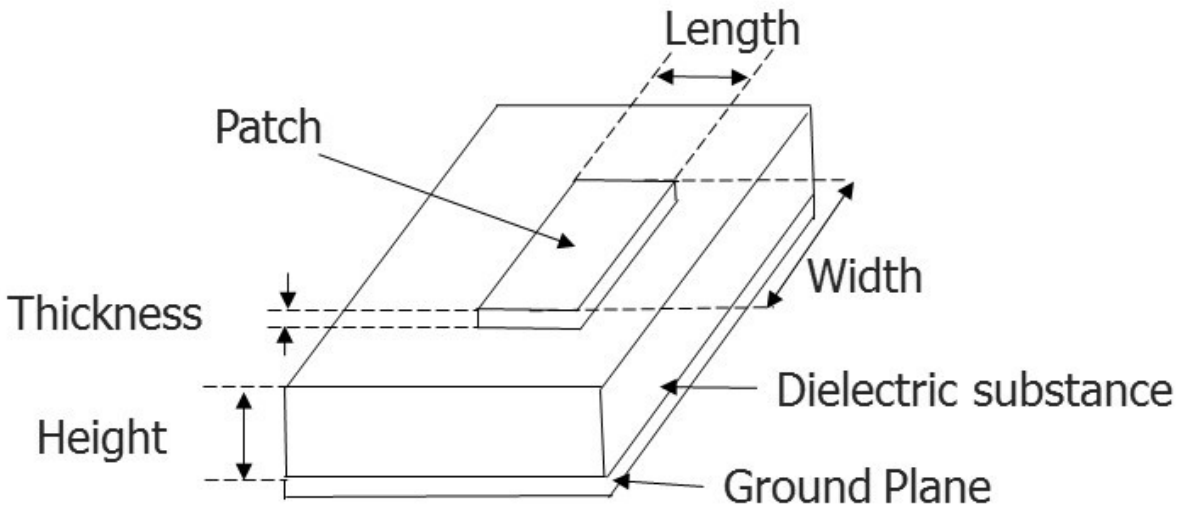


Figure 2.2 Basic structure of micro-strip patch antenna

A half wave long patch operates in what we call the fundamental mode: the electric field is zero at the center of the patch, maximum on two sides, and minimum on the other two sides. These minima and maxima continuously change side like the phase of the RF signal.

The electric field does not stop abruptly near the patch's edges like it would in a cavity: the field extends beyond the outer periphery. These field extensions are known as fringing field and cause the patch to radiate. Figure 2.3 explains the radiating sides and non-radiating sides.

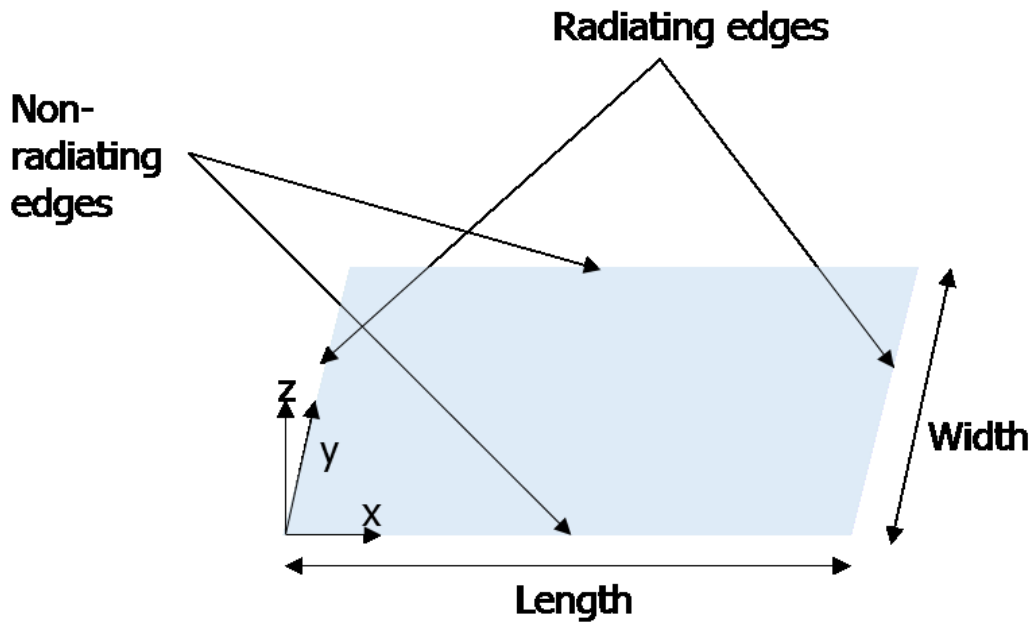


Figure 2.3 Working principle of micro-strip patch antenna

The distance to which the radiation pattern can be obtained is given by the equation [54]:

$$\text{Distance of far field} = \frac{2W^2}{\lambda}$$

Where, W: Width of the antenna

λ: Wavelength

As the frequency is fixed for this research work, wavelength is also a fixed amount. More the width of the antenna, greater is the distance covered by the antenna. As the antenna here is applicable on the human breast, the antenna parameter cannot be too big.

Table 2.1 shows the dimension of parameters of the micro-strip patch antenna.

Table 2.1 Dimension of micro-strip patch antenna

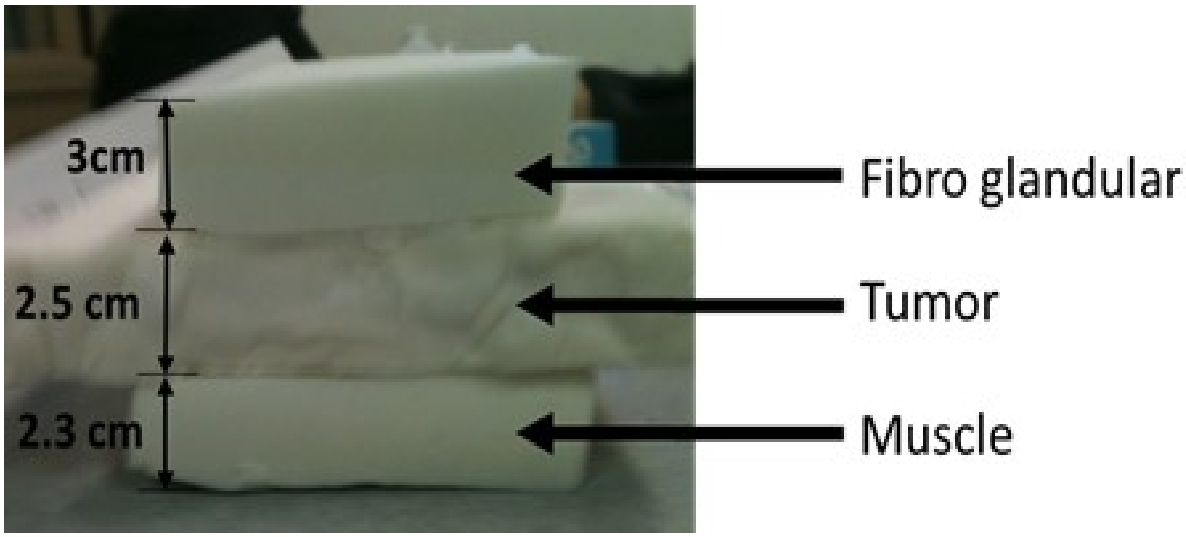
Description	Value
Height	1.54 (in mm)
Width	48.6 (in mm)
Length	40.76 (in mm)
Small thickness	0.02 (in mm)
Dielectric material	2.17

Experiments with Micro-strip patch antenna

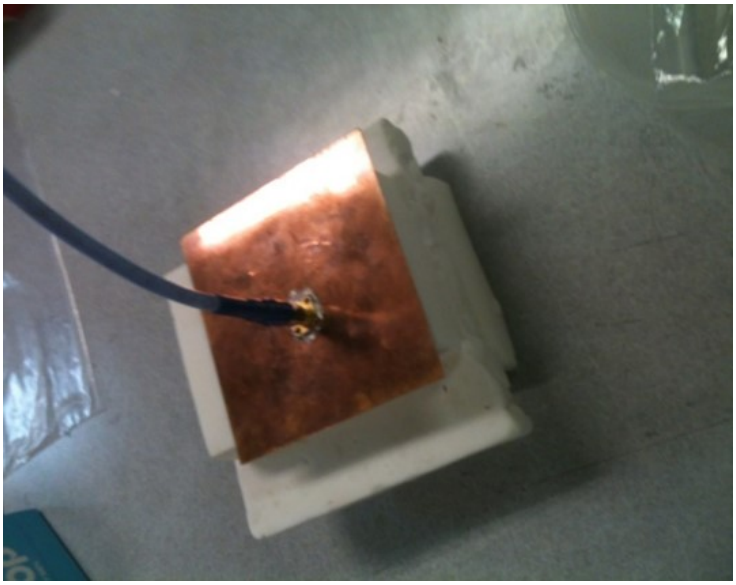
At first, layers of different tissue phantom are made. The dielectric properties of the phantoms used are described in table 1.1.

The micro-strip patch antenna was applied on the layers of tissue for some time to increase the temperature. Infra-red images were taken after heating the layers of phantoms. To get a better heating, two antennas were applied.

Figure 2.4 (a) shows the different layers of phantoms used. Figure 2.4 (b) and (c) shows the application of one micro-strip patch antenna and two micro-strip patch antennas.



(a)



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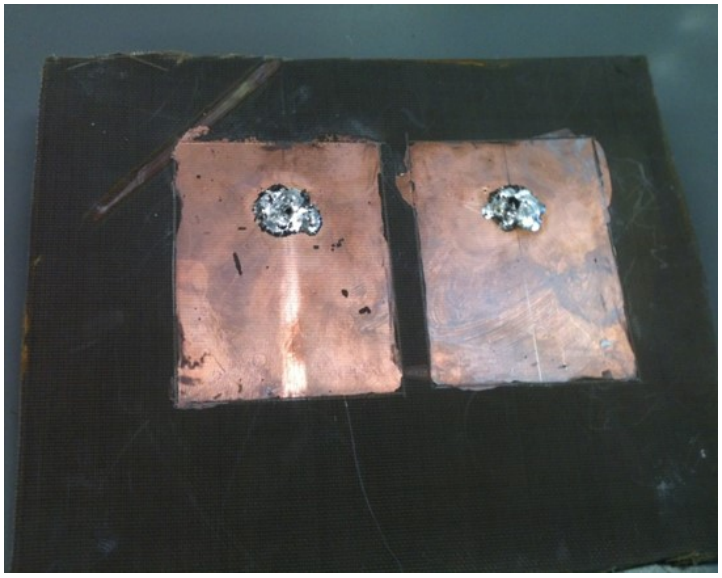


(c)

Figure 2.4 (a) Layers of different phantoms on which the antenna was applied; (b) Application of one micro-strip patch antenna; (c) Application of two micro-strip patch antennas

Further it was applied on a more realistic breast phantom. The temperature rise was recorded.

Figure 2.5 shows the different layers of tissue phantoms used to make a realistic breast structure

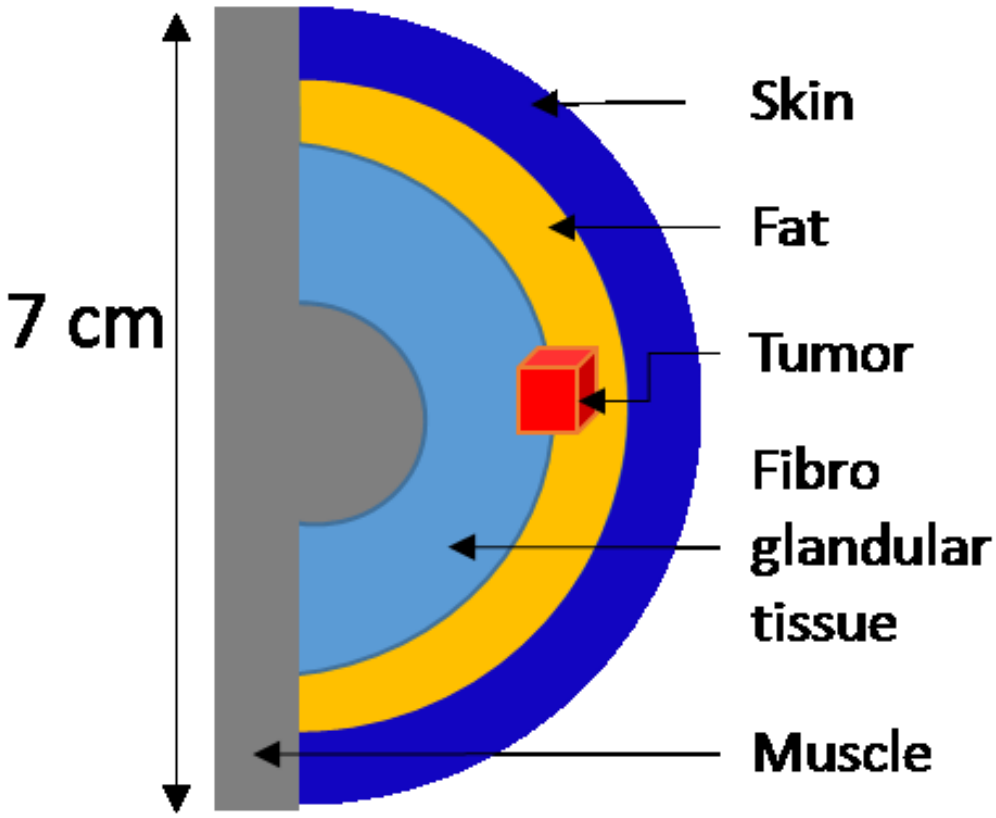


Figure 2.5 Different layers of phantoms

Non-invasive spiral antenna

If the arms of a dipole antenna is wrapped, it becomes a spiral antenna. Spiral antennas are also known as frequency independent antennas. These antennas are characterized as having a large bandwidth. Thus, these antennas are efficient in a wider range of frequency. Spiral antennas are usually polarized. The spiral antennas radiation pattern typically has a peak radiation direction perpendicular to the plane of the spiral.

Figure 2 shows the basic structure of the spiral antenna.

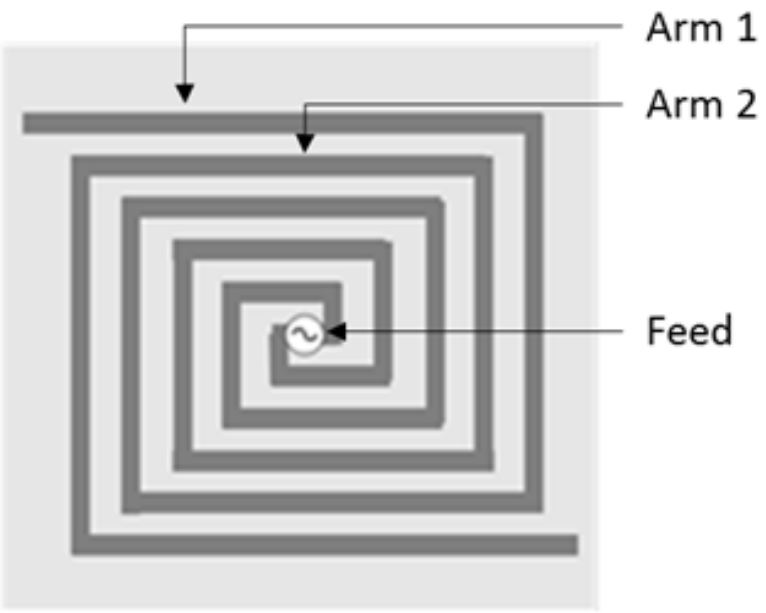
In this research work, the spiral antennas were used on the different layers of phantoms used which is described in table 1.1. Spiral antenna was applied on layers of different tissue phantoms to get the temperature rise.

The specifications of the spiral antenna are given in table 2.2.

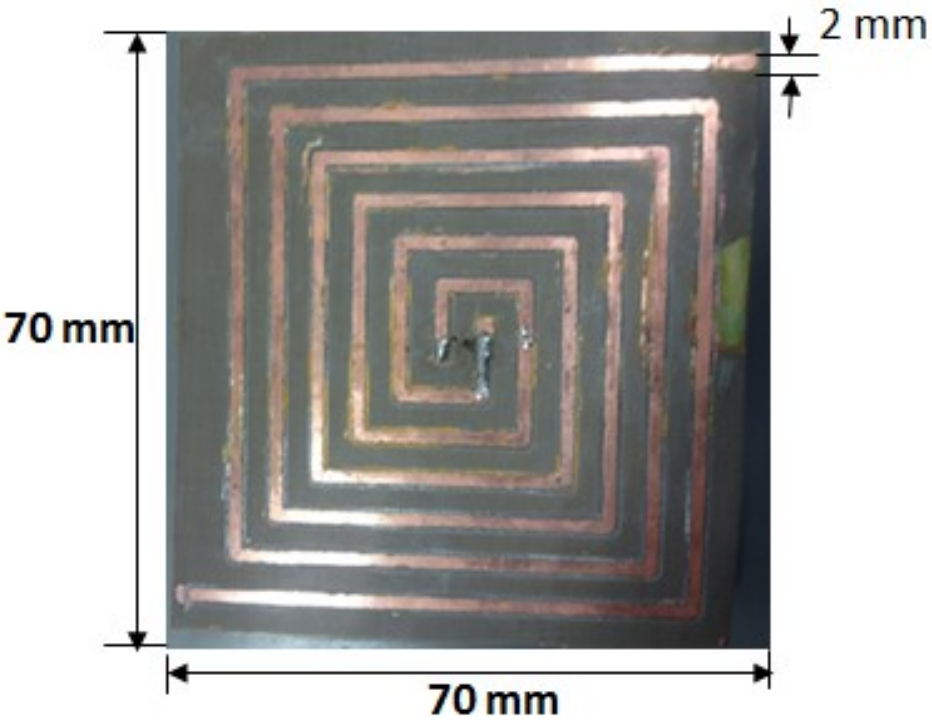
Table 2.2 Specifications of Spiral antenna

Angle maintained	90˚
Number of arms	3
Width of each arm	2 mm

Figure 2.6 (a) shows the basic structure of the spiral antenna and (b) shows the dimension of the spiral antenna respectively.



(a)



(b)

Figure 2.6 (a) Basic structure of spiral antenna; (b) Dimension of the spiral antenna

Experiments with Spiral antenna

The spiral antennas were applied on the layers of tissue for some time to increase the temperature. Infra-red images were taken after heating the layers of phantoms. Figure 2.7 shows the application of spiral antenna on a breast phantom of diameter 7 cm as shown in figure 2.5.

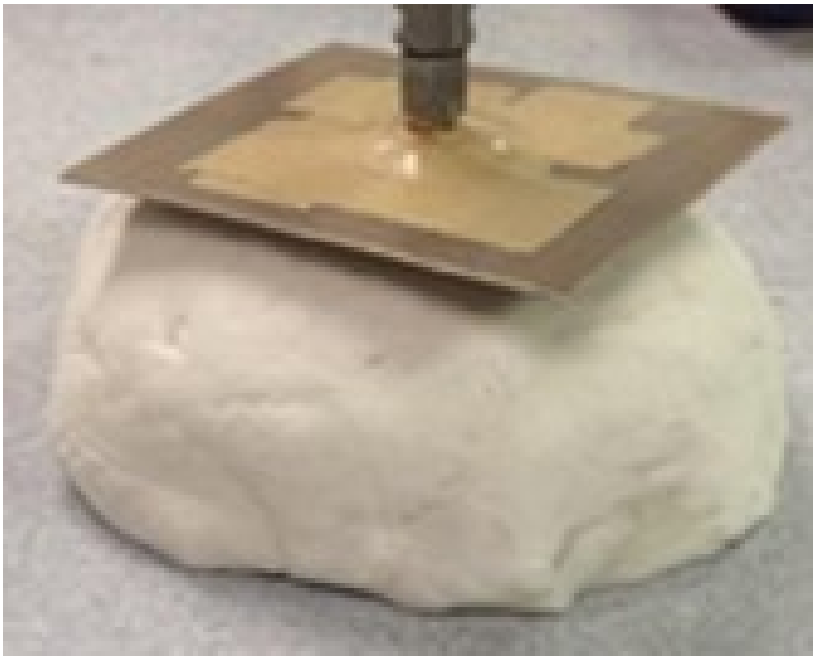


Figure 2.7 Application of spiral antenna on a breast phantom

Infra-red images were recorded using an infra-red camera.

Invasive coaxial-slot antenna

In this research work, coaxial-slot antenna is a type of invasive antenna which was designed and applied to get a desired results for tumor phantoms.

Figure 2.8 shows the basic structure of the coaxial-slot antenna.

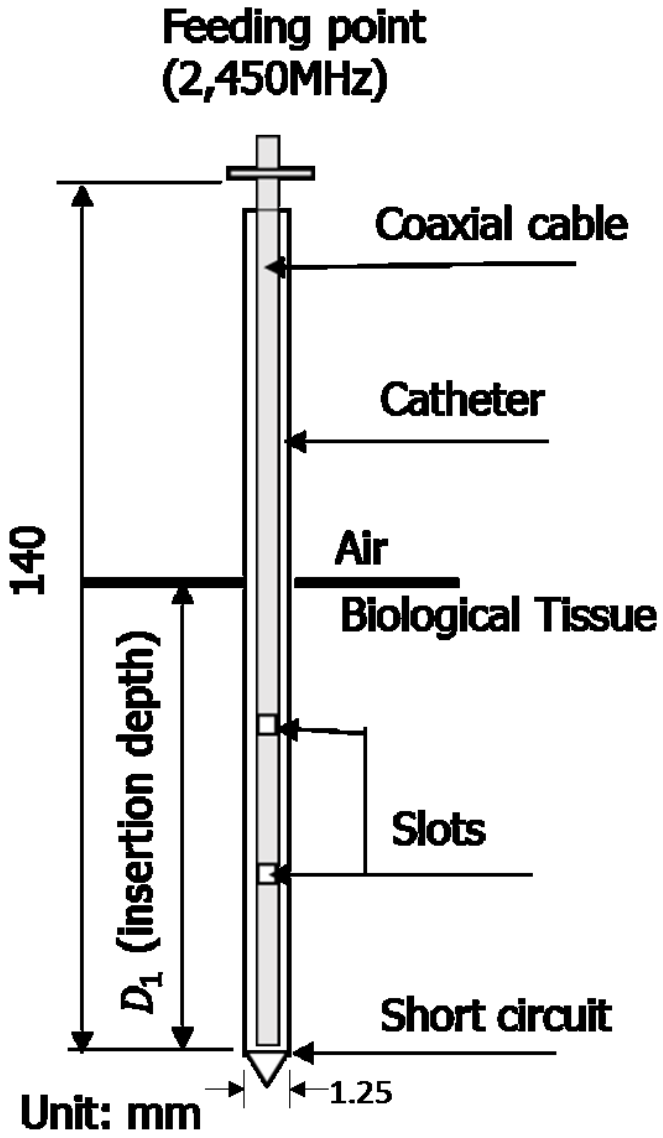


Figure 2.8 Basic structure of coaxial-slot antenna

In the experiments conducted, interstitial hyperthermia was applied on breast tumor phantoms. A coaxial-slot antenna was used to localize the heating effect. Advantage of using coaxial-slot antenna is the ability to heat deep seated tumors, with minimum diffraction.

Antenna parameters and the spacing between the slots for coaxial-slot antennas were calculated for the frequency of 2.45 GHz. The antenna was designed particularly for breast tumor. The coaxial-slot antenna is shown in Figure 7. The parameters used for designing the antenna are listed in Table 2.3.

Two coaxial-slot antennas, separated by 5 mm, were used in the array in order to get the maximum heating effect in the intermediate zone between the two antennas.

Table 2.3. Dimensions of coaxial-slot antenna

Parameters	**Value**
Diameter of antenna	1.19 mm
External diameter of the catheter	1.79 mm
Thickness of the catheter	0.30 mm
Distance from the tip to the center of the slot close to the feeding point	20.00 mm
Distance from the tip to the center of the slot close to the tip	10.00 mm
Width of the slot	1.00 mm
Relative permittivity of the catheter	2.6

In order to see the exact temperature elevation inside the phantoms, the phantoms were cut into halves and after the application of antennas, one half was taken away. Infra-red camera was used to record images thereafter. Fiber optic sensors were used during the experiments to record the temperature rise.

Figure 2.9 shows the steps followed during the experiments.

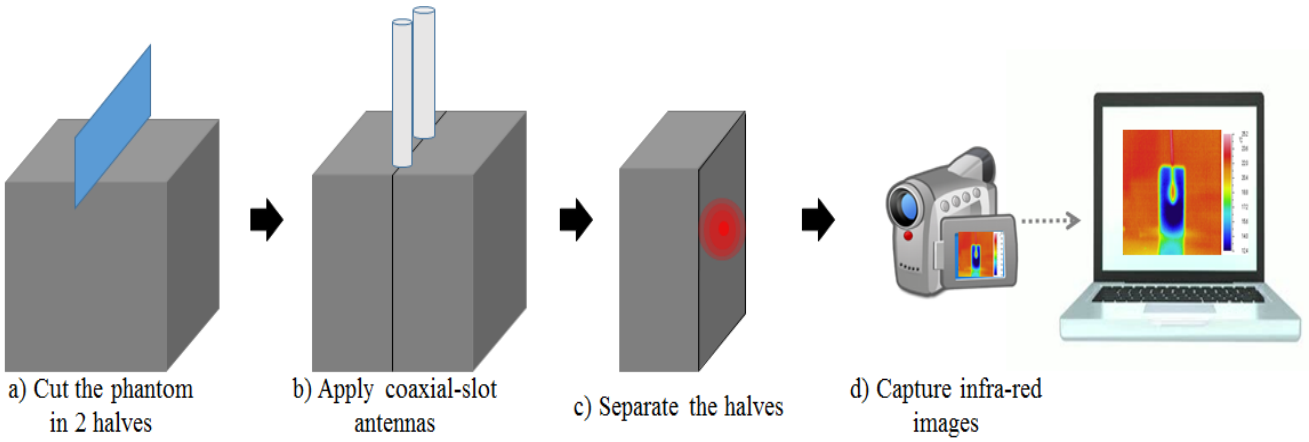


Figure 2.9 Steps followed during the experiments

2.4 Results

2.4.1 SAR Calculation

The basic concept of SAR is that a tissue exposed to the electromagnetic radio waves absorbs power from these waves, and this power gets distributed throughout the tissue [54]. The equation for SAR is shown in Equation (1).

$$|\mathrm{SAR}| = \sigma \frac{|\mathrm{E}|^2}{\rho} \quad (2)$$

Where σ : conductivity of the tissue (S/m),

ρ : density of the tissue (kg/m^3),

|E|: electric field (V/m).

SAR Distribution of Micro-strip Patch Antenna

SAR distribution of the micro-strip patch antenna was calculated. Figure 2.10 shows the SAR distribution of the micro-strip patch antenna.

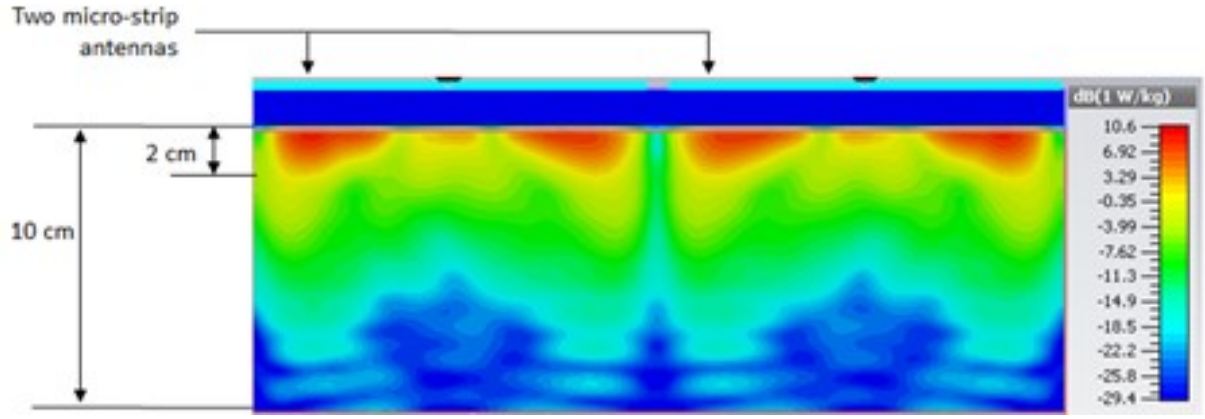


Figure 2.10 SAR distribution of micro-strip patch antenna in breast tissue phantom

The electromagnetic field around the antenna was calculated using the Finite Integration Technique (FIT) [55]. For FIT calculations, a mesh structure of the antenna was created and boundary conditions were applied. Figure 2.11 shows the port created inside the micro-strip patch antenna for SAR distribution and temperature distribution.

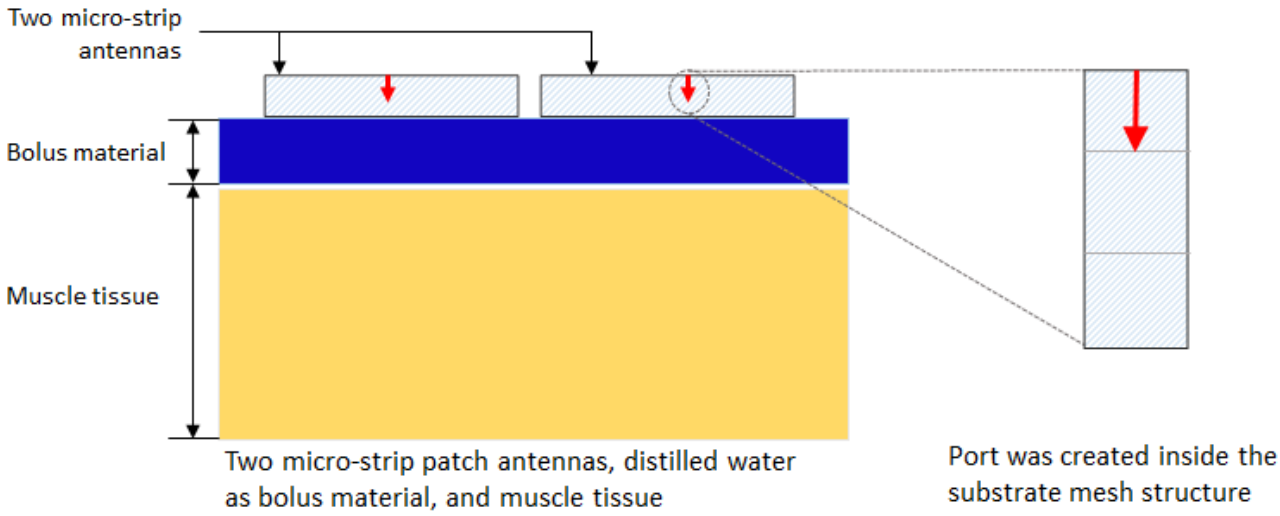


Figure 2.11 Finite Integration Technique Calculation inside Phantom

SAR Distribution of Spiral Antenna

SAR distribution was measured in different phantoms using spiral antenna array. Figure 2.12 shows the SAR distribution of spiral antenna inside the breast tissue.

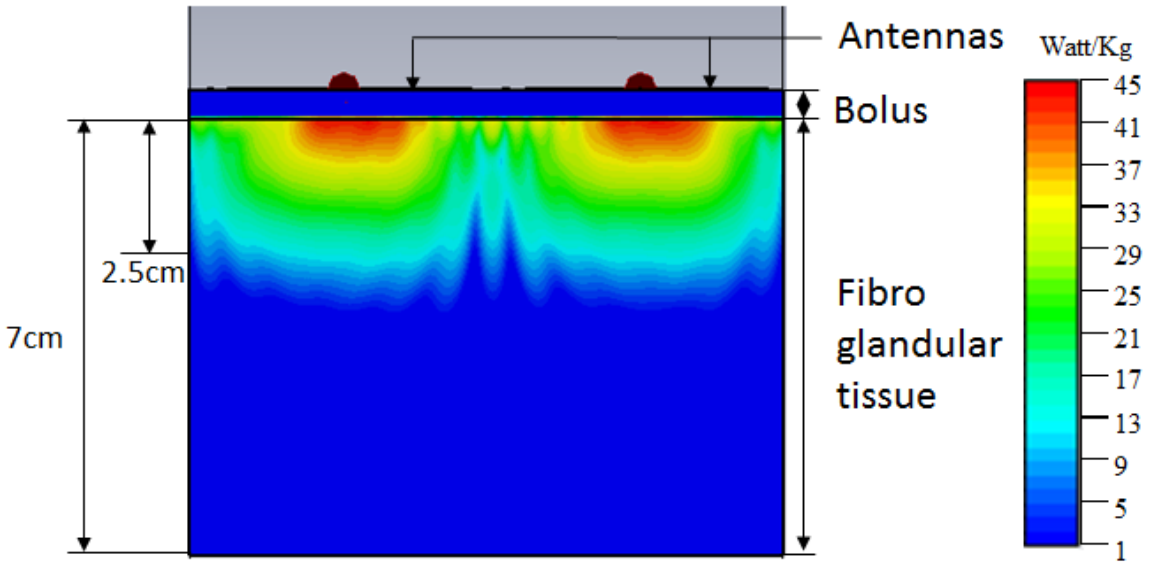


Figure 2.12 SAR Distribution of Spiral Antenna array in breast tissue

SAR Distribution of Coaxial-slot Antenna

As coaxial-slot antenna is an invasive type of antenna and it can be inserted exactly the desired location.

During this research work, deep seated tumors were targeted by coaxial-slot antenna array and it was inserted 7cm inside the phantom. Figure 2.13 shows the SAR distribution of coaxial-slot antenna array inside the tumor phantom.

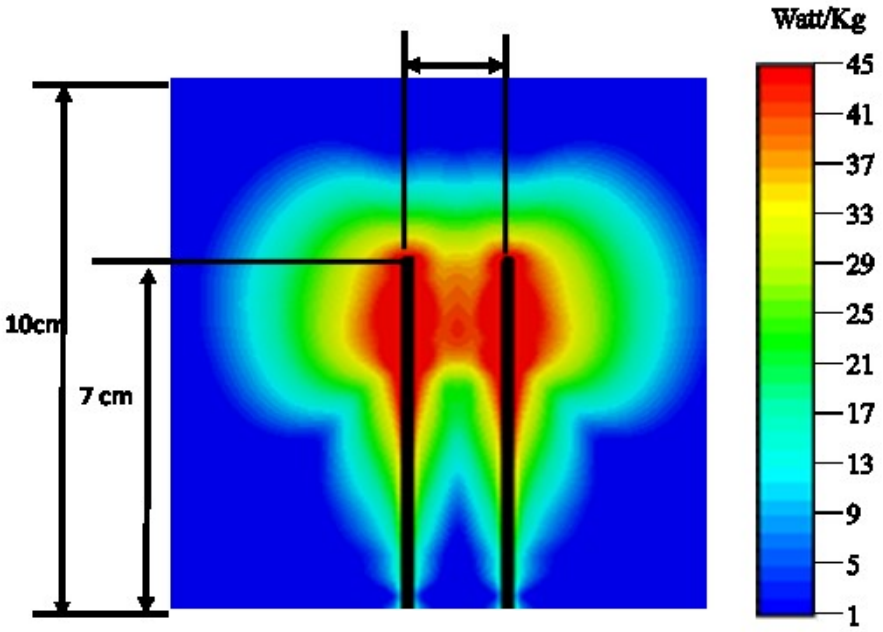


Figure 2.13 SAR distribution of coaxial-slot antenna array in tumor phantom

The cross-sectional view of antenna and catheter, and boundary conditions are shown in Figure 2.14. The length of antenna used was 140 mm and the depth of penetration of this antenna in the phantom was 70 mm. The length of the boundary was considered to be 180 mm.

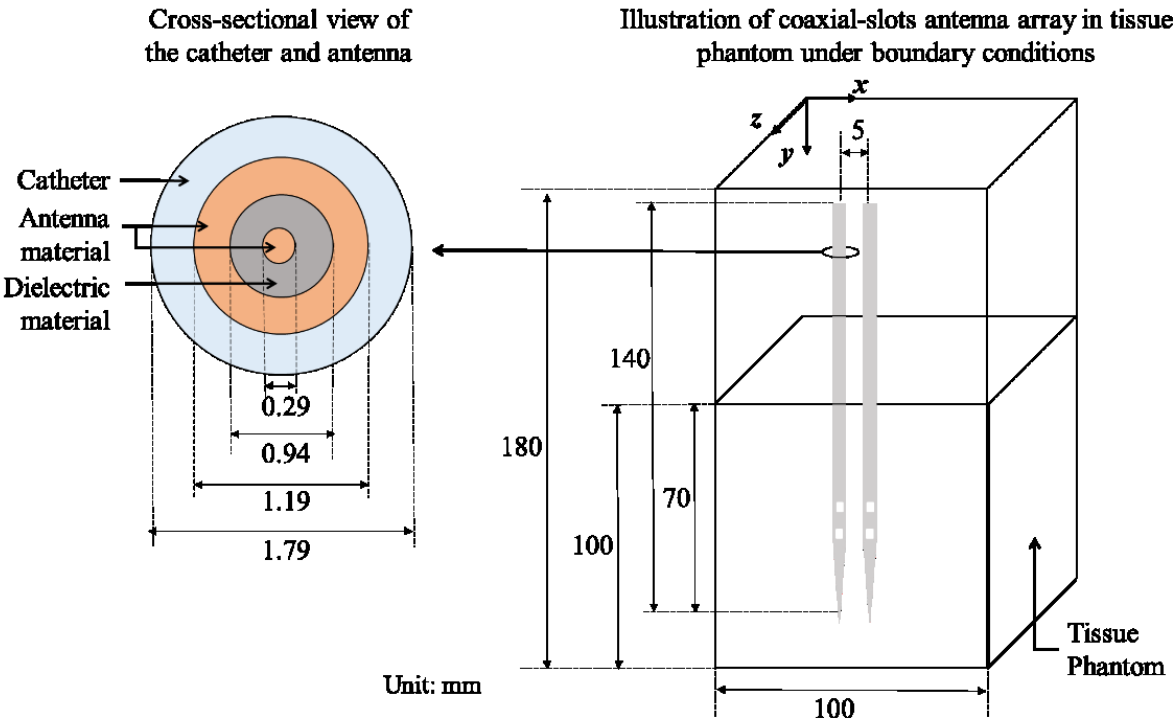


Figure 2.14 Cross sectional view of Coaxial-slot antenna

Temperature Calculation

Temperature calculation for all the antennas were done on the tumor phantom. The temperature calculation

Table 2.4 shows the comparative study between the temperature increases by all antennas used in this study.

Table 2.4 Temperature obtained by different antennas

Name of the antenna	**Microwave Power**	**Duration**	**Temperature**
Micro-strip patch antenna	25 Watt	30 Minutes	9˚C
Spiral antenna	15 Watt	30 Minutes	10.5˚C
Coaxial-slot antenna	15 Watt	30 Minutes	12˚C

The increase in temperature [57,58] due to application of the antenna was calculated using Penne's bio-heat transfer equation, shown in Equation (2). Body temperature was considered to be 37˚C.

$$(\rho\, c_p)_t \frac{\partial T_t}{\partial t} = \nabla\,(k_t\, \nabla T_t) + q_p + q_m + \rho\, SAR \qquad (3)$$

where ρ: tissue density

c_p : tissue-specific heat

T_t,: tissue temperature

k_t: tissue thermal conductivity

q_p: heat transfer from blood to tissue

q_m: uniform rate of metabolic heat generation in the tissue layer per unit volume

SAR: Specific Absorption Rate

For the calculations in this research work, tissue density (ρ) was considered to be 916 kg/m^3, tissue specific heat (c_p) to be 2,300 J/Kg·K, tissue temperature (T_t) to be 37℃, tissue thermal conductivity (k_t) to be 0.33 W/m·K, and uniform rate of metabolic heat generation (q_m) to be 4.7 X 10^3 Watt/m^3. The heat transfer from blood to tissue (q_p) was disregarded—the temperature of blood and tissue were assumed to be the same in the experiments. The SAR varies; the value of SAR decreases when the distance from the catheters increases, which is shown later in this chapter.

Temperature at the surface of the phantom was calculated using Equation (3). This equation gives the heat lost from the surface of a phantom due to lower ambient temperature.

$$k\frac{\partial T}{\partial n} = -h\,(T - T_a) \tag{4}$$

where k: thermal conductivity,

$\partial T/\partial n$: rate of change in temperature to unit vector normal to the surface of the phantom,

h: convective heat transfer coefficient from the surface of the phantom to the outside air (W/m^2 K),

T: temperature,

T_a: ambient temperature (˚C).

In the experiments, h was considered to be 10.5 W/m^2 K and T_a to be 27˚C.

Use of Bolus Material for non-invasive antenna

Bolus material is used for getting resonance at desired frequency and also used for avoiding skin ablation.

During this research work, different types of bolus materials were used such as normal water, distilled water and saline water. Distilled water gave the best result among these.

Figure 2.15 shows the difference between the temperature of the phantom using bolus material and not using bolus material.

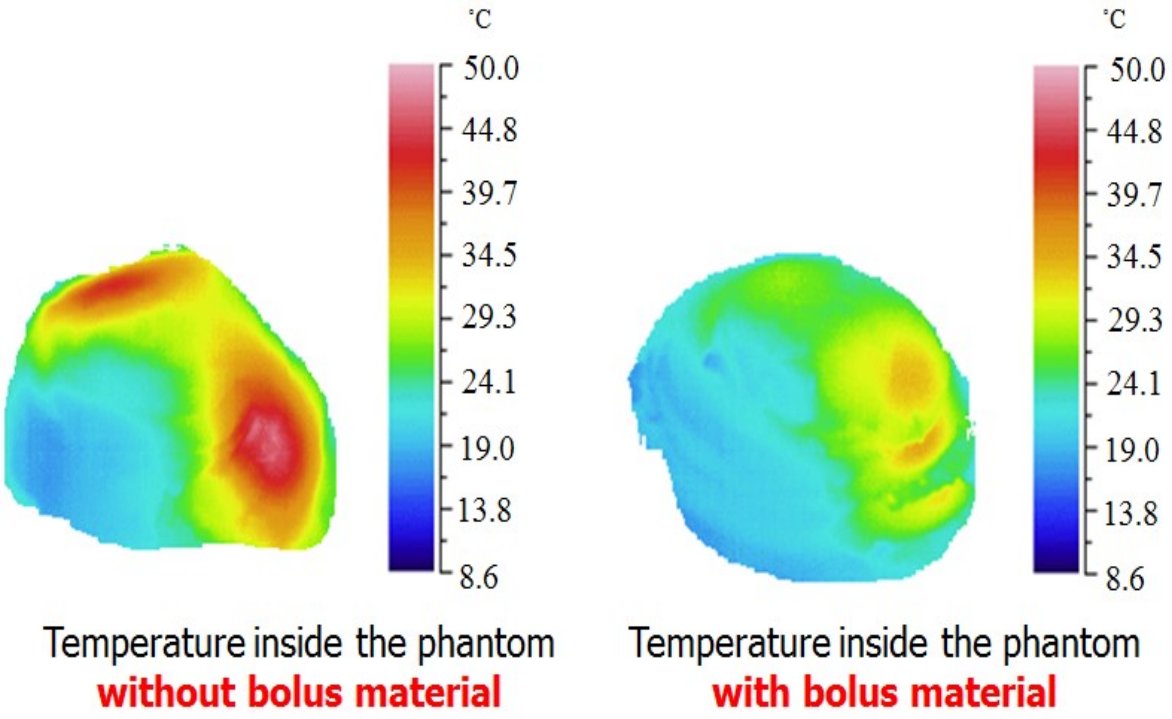


Figure 2.15 Difference between the temperature of the surface using and not using bolus material

In the experiments, the temperatures were measured using a fiber optic temperature sensor inserted in the tumor phantom. Infrared images were also recorded using an infrared camera.

Figure 2.16 (a) shows the experiment set up with the coaxial-slot antenna array applied on a phantom and Figure 2.16 (b) shows the infrared images after application of the antenna array. Due to different dielectric properties, the rate of increase in temperature is different for different types of tissue phantoms.

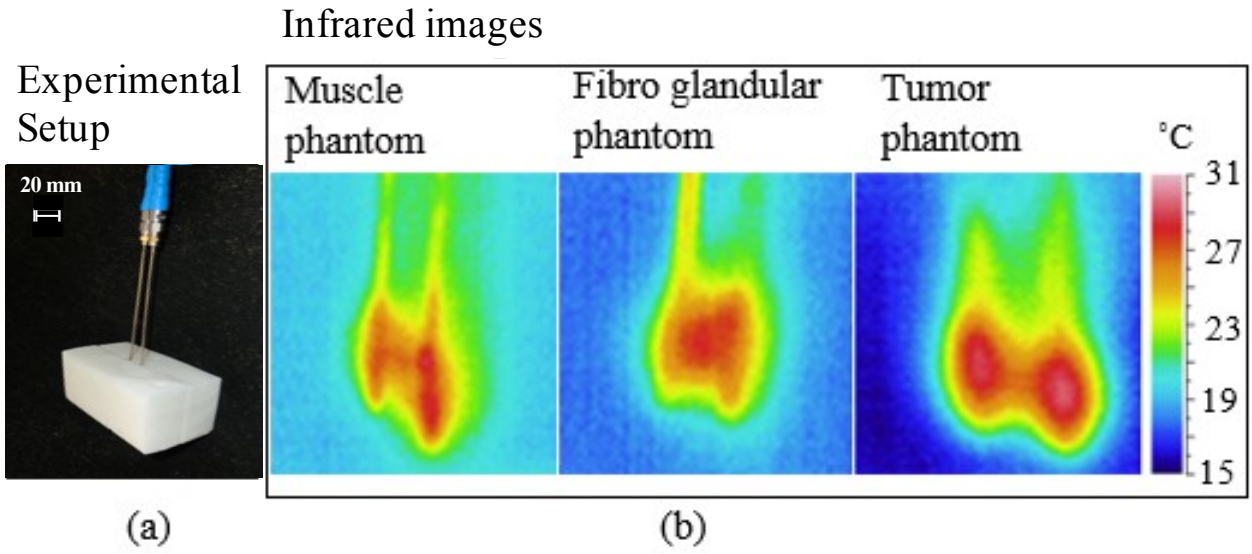


Figure 2.16 (a) Coaxial-slot antenna array applied on a phantom; (b) Infrared images of different types of phantoms after applying coaxial-slot antenna array.

Figure 2.17 shows the increase of temperature of different phantoms over the time. This difference was obtained due to different dielectric properties of the tissues.

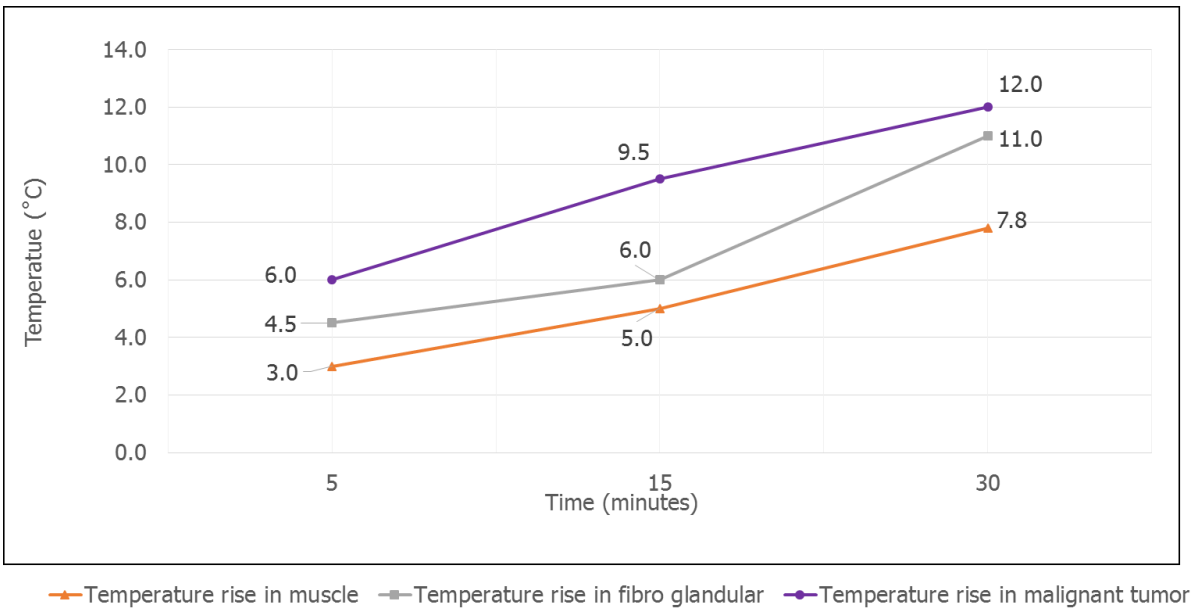


Figure 2.17 Temperature rise in different homogenous phantoms over 30 minutes of time.

Difference between the temperature obtained in experiments and simulation

In both experiments and simulations, the dielectric constants of the phantoms were maintained the same as shown in chapter 1, Table I. However, there were differences between the results of practical experiments and those of simulations. The increase in temperature was calculated in simulation as well as in phantoms. Figure 2.18 shows the difference between the temperatures achieved in experiments and simulations. With the same microwave power, the difference in temperature was found to be around 6˚C to 9˚C. This difference is because of the different boundary conditions in experiments and simulations.

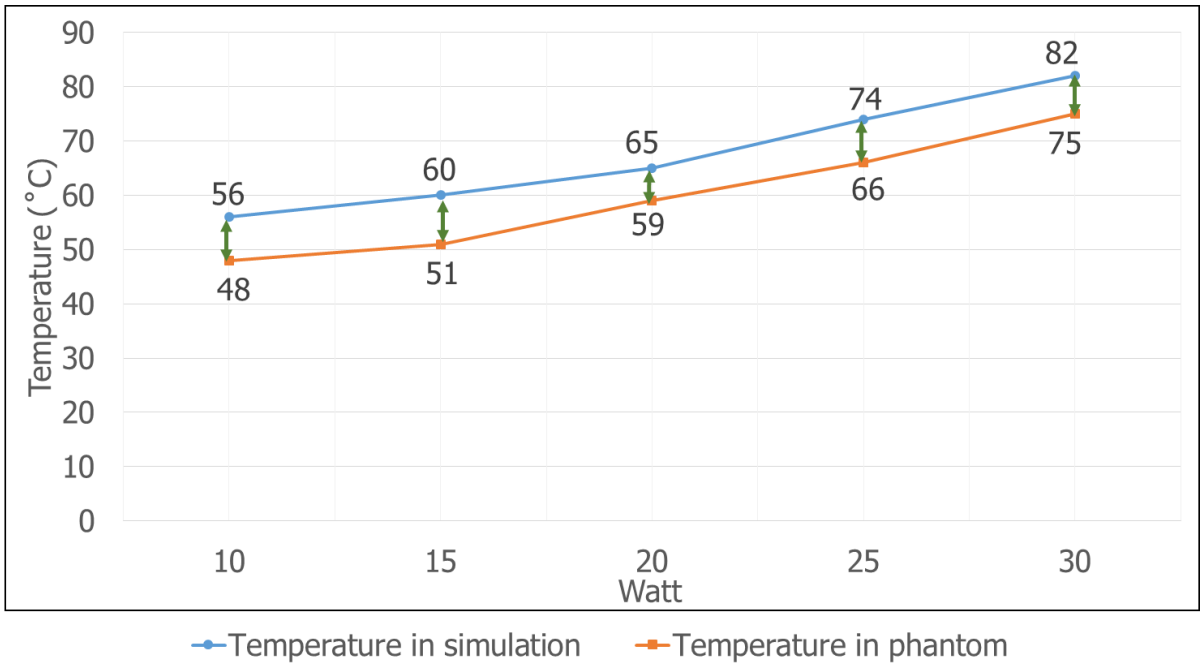


Figure 2.18. Temperature difference between the experimental results and simulation results

Temperature dependency on RF Power

Radio Frequency (RF) power and time are two interdependent factors that can be adjusted to increase the temperature in hyperthermia. The experiments were conducted keeping the time constant at 30 minutes. Figure 2.19 shows the dependency of temperature on RF power keeping the time constant at 30 minutes. This result is from the experiment conducted on homogenous fibro glandular tissue phantom.

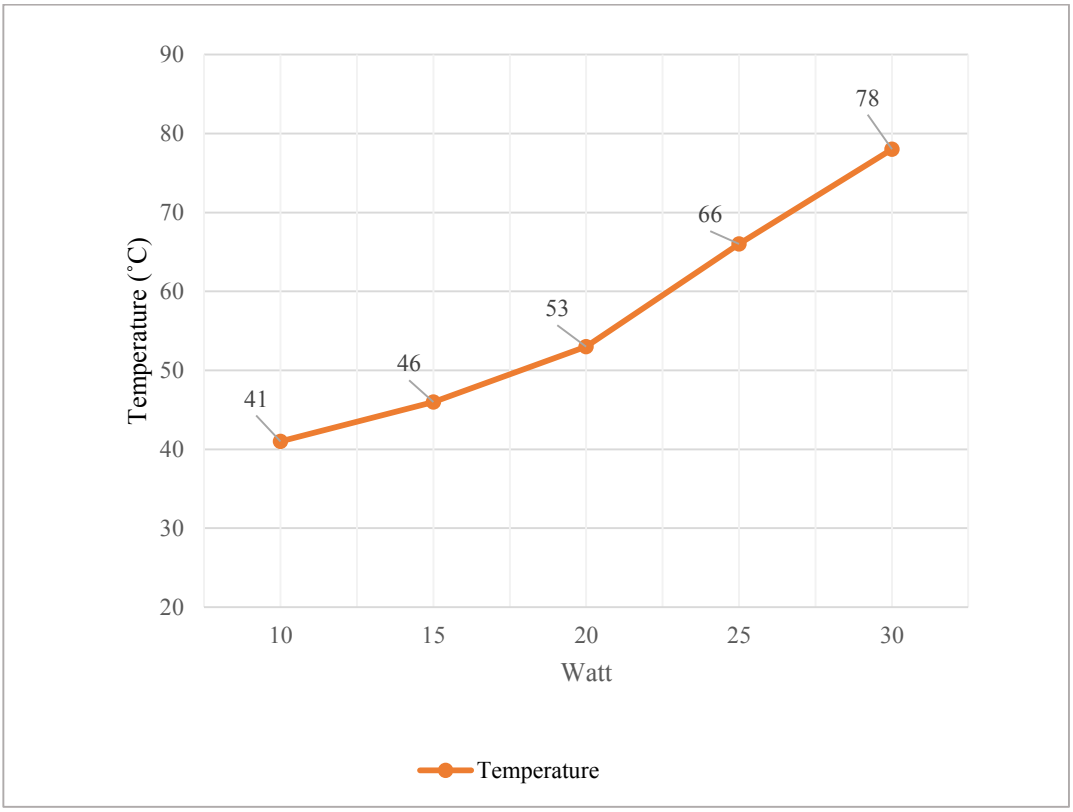


Figure 2.19. Temperature dependency on microwave power

2.5 Discussion

Two major categories of antenna are available in hyperthermia to heat the tumor: non-invasive and invasive. In the early phases of this research work, non-invasive antennas, namely, micro strip patch antenna and spiral antenna, were designed and tested on different types of phantom. The heating and depth of penetration were better in the case of spiral antenna as compared to micro-strip patch antenna. While both the non-invasive antennas gave good results for heating of a superficial tumor few centimeters beneath the skin, there was limited or no impact on deep-seated tumors. There was also a possibility of ablation of skin and other tissues adjacent to the tumor.

Table 2.5 shows the comparative study between the non-invasive antennas and invasive antennas.

Table 2.5 Comparative study between the non-invasive antennas and invasive antennas

Factors	**Non-invasive antenna**	**Invasive antenna**
Depth of tumor	Cannot heat a deep-seated tumor	Possible to heat a tumor located at any depth
Effect on adjacent tissue	Temperature increases in adjacent tissues– higher chances of skin ablation	Less harm on adjacent tissues
Bolus material	Needed	Not needed

As mentioned in the above table, non-invasive antennas were used for heating the superficial tumors which were located around 2-3 cm below the skin layer. During the experiments, non-invasive antennas were used to add their effects and then focus on a tumor which is located deeper than 3cm, but it was not effective due to high diffraction from human tissue.

As this research work was focused on deep seated tumors, coaxial-slot antenna was chosen for further analysis. For coaxial-slot antenna the risk of effects on normal tissue due to high temperature such as skin ablation, can be avoided. Another advantage of using coaxial-slot antenna is, there is no requirement of using bolus material for coaxial-slot antenna.

Blood flow inside the breast is an important factor which impacts the temperature [59]. There may be some changes in the duration required to reach the desired temperature once blood flow is considered. While blood flow was not taken into account in the experiments conducted on the phantoms as part of this research work, it was considered in the simulations. As the blood flow is understood to significantly impact temperature, the effects of blood flow—both in the tumor and normal tissue—is an important field to study further.

At this point in time, despite a strong rationale for combining interstitial hyperthermia and radiation brachytherapy, interstitial hyperthermia is still an out of routine clinical practice. One of the reasons for hyperthermia's slow adoption is understood to be a need for high quality equipment, which in turn have to be operated by well-trained personnel. Based on the results from the studies hitherto and from this research work, we assert the need for further investigation on the effectiveness of combination therapy using interstitial hyperthermia and brachytherapy on deep-seated breast tumors.

Chapter 3
Radiation Brachytherapy

3.1 Introduction to Radiation Brachytherapy

Brachytherapy is a method of delivering radiation to tumors by placing radioactive sources either within or immediately adjacent to tumor tissue. Because the radiation source is very close to the tumor, it can affect the tumor while minimally affecting normal tissue surrounding the tumor. Brachytherapy can be provided using Low Dose Rate (LDR) or High Dose rate (HDR) techniques, depending on the length of time the radioactive sources remain in place.

Radiation Effects on Cancerous Cells:

Years of experiments have shown the impact on in cells due to radiation exposure [xx].

There are two commonly known effects:

(i) Direct Effect: If an X-ray or radiation interacts with the DNA , this is considered a direct effect. The direct effect of radiation causes more damage to the DNA.

(ii) Indirect Effect: When X-rays enter a cell, they are much more likely to hit the water molecules and ionize these water molecules which in return produces ions and free radicals. These ions and free radicals in turn bond with the DNA molecules and change its structure.

Brachytherapy can be provided alone or in combination with other therapies such as surgery, external beam radiation therapy and chemotherapy.

Depending on the type of the cancers, and the treatment plan, course of brachytherapy can be completed in lesser time than that required for other radiotherapy techniques. This can help reduce the opportunities for surviving cancer cells to divide and grow in the intervals between radiotherapy doses. With brachytherapy, patients typically make fewer visits to the radiotherapy clinic compared with external beam radiation therapy, and the treatment is often performed on an outpatient basis. This makes treatment accessible and convenient for many patients. Brachytherapy

is also associated with a low risk of serious adverse side effects. These features of brachytherapy mean that most patients are able to tolerate the procedure very well.

Breast brachytherapy is in that matter is a promising alternative to surgery or external beam radiation therapy, in terms of improved patient cure, organ preservation, and cost of efficiency of the treatment.

Breast Brachytherapy

Radiation therapy is the standard of care for women who have undergone breast lumpectomy or mastectomy surgery, and it is an integral component of breast conserving therapy [55]. Brachytherapy can be used after surgery, before chemotherapy or in the case of advanced forms of the disease [55]. Brachytherapy to treat breast cancer is usually performed with high dose rate using temporary implants. Post-surgery, breast brachytherapy can also be used as a 'boost' following the irradiation of the whole breast using external beam radiation therapy [61,62]. More recently brachytherapy alone is applied in a technique called APBI (accelerated partial breast irradiation), which involves delivery of radiation to only the immediate region surrounding the tumor [61-63].

The main benefit of breast brachytherapy compared to external beam radiation therapy is that a high dose of radiation can be precisely applied to the tumor while minimizing radiation exposure to the healthy breast tissues and underlying structures such as ribs and lungs [60]. Accelerated partial breast irradiation can typically be completed over the course of a week [63]. The option of brachytherapy may be particularly important in ensuring that working women, the elderly or the women without an easy access to a treatment center, are able to benefit from breast-conserving therapy due to the short treatment course as compared with external beam radiation therapy [59]. Brachytherapy has demonstrated excellent local control of breast cancer at a follow-up of up to 6 years post treatment [60, 65, 66]. A study is underway to compare patient outcomes of APBI in comparison to external beam radiation therapy at a follow-up of up to 10 years after the treatment [67].

Breast Brachytherapy as a Boost: This section describe the combination of surgery and brachytherapy as a radiation therapy for treating breast tumors. The goal of irradiation is to minimize the risk of a local relapse in the treated breast, especially in the area of a tumorThere are many methods of increasing the dose to the tumor area [52, 68-69]. The best approach is chosen depending on clinical and morphological criteria, patient's will and institutional resources and protocols. Modern interstitial multi-catheter high-dose rate (HDR) brachytherapy offers local and accurate irradiation of the target tumor. Randomized "boost vs. no boost" trials revealed that there is an evident advantage from administering an additional dose to the tumor area. A boost reduces the local recurrence rates [72-74]. Polgár et al. also summarized the results of many different high dose rate brachytherapy series worldwide, in which , a 5-year local recurrence rate of 0-9% (mean 5.5%) was achieved in 1776 patients [52]. Brachytherapy is appropriate to deliver an additional conformal boost dose to the surgical area plus margin following standard whole breast radiation therapy. Choice of brachytherapy would be dependent on the size, shape, and location of the lumpectomy cavity in relation to the size and shape of the breast [57]. While an external electron beam boost usually includes the skin and subcutaneous vessels, the interstitial implant represents a more local treatment technique, which offers the advantage of lower rates of side effects, in particular of skin telangiectasia and skin fibrosis [75-77]. Clinical trials showed an increase in local control and an increase in survival among patients with boost as compared to patients with no boost [74, 78-80]. In the European Organization for Research and Treatment of Cancer (EORTC), a "boost versus no boost" randomized trial , 2661 patients enrolled in the boost arm were analyzed. All the patients received 50 Gy whole breast radiation therapy and a boost dose of 16 Gy to the primary tumor area after microscopically complete tumorectomy. 63% of the patients received a boost dose with electrons, 28% with photon beams, and 9% with interstitial brachytherapy. At 5 years of follow-up, local recurrences were seen in 4.8% of patients who received an electron boost, in 4% of cases with a photon boost received, and in 2.5% of patients who underwent brachytherapy [81-82]. From the above result obtained from tumors treated by different modalities, brachytherapy gave a lesser recurrence rate of tumor as it is given locally and more targeted to the tumor.

3.2 Conventional Brachytherapy

There are few methods that are used to deliver breast brachytherapy:

(1) **Interstitial breast brachytherapy**- Brachytherapy using interstitial applicators can be delivered in two ways. Perioperative brachytherapy involves the usage of flexible applicators during surgery at the place of the tumor. In this method, brachytherapy is applied during the breast conserving surgery. The advantage of the perioperative technique is the need for only one general anesthesia (implantation of the applicators takes place during surgery), resulting in a reduction of overall treatment time, and the ability to precisely determine the location of the tumor visually during the surgery. During a lumpectomy/ mastectomy the surgeon attaches surgical clips to determine the tumor boundary, later these surgical clips are helpful in treatment planning. Insertion of the applicators requires precision, experience and knowledge in the field of radiation. The irradiated area is limited to the surgical area with a margin of 1-1.5 cm.

In another way, applicators are often implanted after the healing of the surgical scar and after receiving the final histo-pathological diagnosis in 2-4 weeks after the surgery. The radiation oncologist inserts applicators after visualization of the tumor area (the location of surgical clips) using X-ray and ultrasound. After determining the shape and position of the tumor area, a correct template is selected; the number of tumors, the distance between the applicators is proposed. The number of implanted applicators has to be determined individually, depending on the breast size, location of the tumor area, and type of surgery. Usually there are from seven to over a dozen applicators.

(2) **Intra cavitary breast brachytherapy**- This technique was intended to reduce the technical difficulties associated with external beam radiation therapy treatment planning and application of many interstitial applicators [85-86]. The balloon applicator consists of a silicone balloon catheter containing a channel for filling the balloon and 1 to 8 channels to introduce radioisotope. Strut adjusted volume implant applicator does not include a balloon but only applicators to adapt to the shape of the box. Balloon technique is in principle applicable in accelerated partial breast irradiation with resignation of whole breast radiation therapy after surgery. High-dose-rate sources are used in this technique. Balloon applicators may be placed near the tumor during the breast conserving surgery (rarely) or

2-4 weeks after surgery with the help of ultrasound. Previously published results suggest a satisfactory treatment outcome (as measured by the percentage of local failure), and good cosmetic results (80% to 93% of patients) [87-90]. The results of Phase III Trial (NSABP B-39/RTOG 0413) conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Radiation Therapy Oncology Group (RTOG) had shown a comparative study between different treatment methods. Whole breast radiation therapy, Accelerated partial breast irradiation with MammoSite or multi catheter interstitial BT 3D EBRT in stage 0, I and II of breast cancer [91]. Balloon brachytherapy was developed as an alternative to interstitial brachytherapy. Interstitial brachytherapy requires the experience in setting up many interstitial applicators, while using balloon brachytherapy is simpler in application. Cosmetic results after balloon brachytherapy techniques seem to be very satisfactory. A high rate of satisfactory or excellent results is worth noting. To achieve such results the proper selection of patients (large breasts, the central location of the primary tumor) is important.

The balloon applicator consists of a silicone balloon with a catheter to fill the balloon with fluid and 1 to 8 channels where a radioactive source is placed. For greater precision in most centers using this method, the balloon is fixed in the operating room under ultrasonography. Then, the applicator is fluid-filled to a volume strictly adhering to the walls of the tumor boundary. Then a cross-section CT is made in order to prepare a treatment plan. Clinical target volume (CTV) includes the volume of the balloon with a margin of 1 cm. Critical organs include the skin and lungs. In this technique HDR sources are used.

Literature Survey on Clinical Studies for Radiotherapy

Various reports have shown almost equivalent results between short and standard radiotherapy schedules [76-79]. In a randomized trial conducted in Canada, Whelan et al [92] reported equivalent results (regarding local-regional tumor control, survival, and post-radiation effects) between the standard fractionation schedule of 50 Gy in 25 fractions of 2 Gy each, and a hypo fractionated scheme of 42.5 Gy in 16 fractions of 2.6 Gy each over 22 days for women with early stage breast cancer. This study has been updated recently and, most importantly, results have not changed after a 10-year follow-up [93]. However, the potential limitations of this study are as follows: The trial was restricted to women who had node negative, invasive breast cancer with clear margins of excision after lumpectomy; women with large breasts were not included; few women received adjuvant chemotherapy and we should bear in mind that those patients can be at a higher risk for acute and late post-radiation effects; boost irradiation was not used, as by the time the study was initiated, the efficacy of boost irradiation had not been demonstrated [93] and was later shown in studies conducted in Europe[73-74]. However, boost irradiation was used in Standardization of Breast Radiotherapy trials, and adjuvant chemotherapy was used more widely than in this trial. In addition, a broader spectrum of tumors and patients (node-positive, larger tumors, no limitation of breast size) were included, but no differences have been noted in tumor control and side-effects between standard and another treatment in those trials so far.

Another short RT schedule, 40 Gy in 15 fractions of 2.6 Gy each, has been used traditionally at Christie Hospital in Manchester, UK; the reported results of 2,159 treated patients are comparable to those reported from other treatment centers [94-95]. This schedule is now becoming the "standard" in the UK, especially after the publication of the START trials. The START A trial randomized 2236 patients from 17 treatment centers across the UK and reported that 41.6 Gy in13 fractions or 39 Gy in13 fractions are similar to 50 Gy in 25 fractions in terms of local-regional tumor control and late normal tissue effects, same as post-radiation effects. The initial trial [96] showed that after a median follow-up of 5.1 years, the rate of local-regional tumor relapse was 3.6% after 50 Gy, 3.5% after 41.6 Gy, and 5.2% after 39 Gy. The estimated absolute differences in 5-year local-regional tumor relapse rates compared with after 50 Gy were 0.2% after 41.6 Gy and 0.9% after 39 Gy. Clinical assessments suggested lower rates of late adverse effects after cumulative effect of 39 Gy than cumulative effect of 50 Gy. Lesser radiation dose gave lesser late adverse effects. The results have shown that breast cancer and late reacting normal tissues respond similarly to

change in radiotherapy fraction size. 41.6 Gy in 13 fractions was similar to the control regimen of 50 Gy in 25 fractions in terms of local-regional tumor control and late normal tissue effects. The START B trial [97] randomized 2215 patients from 23 centers across the UK and reported that a radiotherapy schedule of 40 Gyin15 fractions offers equivalent results to the standard schedule of 50 Gy in 25 fractions. After a median follow-up of 6.0 years, the rate of local-regional tumor relapse at 5 years was 2.2% in the 40 Gy group and 3.3% in the 50 Gy group. Clinical assessments indicated lower rates of late adverse effects after 40 Gy than after 50 Gy. Although the START trials had a relatively limited follow-up time and differences in their design (inclusion criteria) compared with the Canadian trial, their results were similar.

Other non-randomized studies have also reported similar results, such as fujii et al [98] reported acceptable results in terms of local control and toxicity a short fractionation schedule of 42.5-47.8 Gy in 16-20 fractions.

3.3 Proposed Method

In this research work, a combination of hyperthermia and brachytherapy is proposed as an effective treatment for deep-seated breast tumors of size 30mm~40mm. In the conventional way of treating breast tumor, a combination of surgery, radiation therapy and chemotherapy is commonly tried. In such cases, normal cells in the breast also get irradiated by a high dose of radiation. As a result, chances of side-effects are high.

Normally brachytherapy is applied on a localized area by inserting a radioactive source in a catheter [62]. This study focuses on method of sequentially applying brachytherapy after applying hyperthermia. In this study, a method of introducing the radioisotopes in the same catheters as those that were used in hyperthermia is proposed. After the application of hyperthermia, the coaxial-slot antennas will be removed whereas the catheters will be maintained in the same place. The radioactive sources will then be introduced in the same catheters as shown in figure 3.1. Iridium-192 is assumed to be the radioactive source.

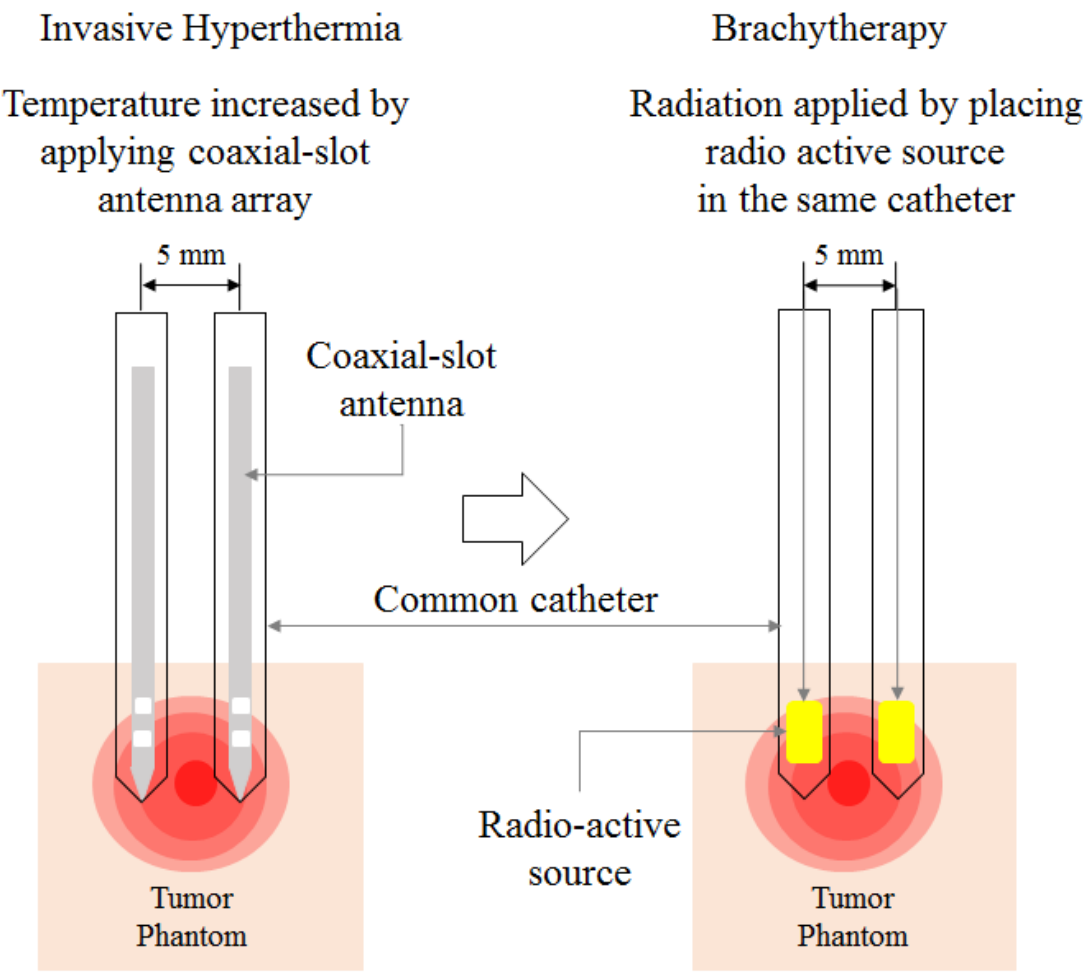


Figure 3.1 Combination of two methods: hyperthermia and radiation dose distribution for breast tumor.

3.4 Calculation of Radiation Dose

A treatment planning simulation software based on the Monte Carlo method was used to observe the effect of radiation doses applied using brachytherapy. A CT image of an anonymous patient's breast tumor, which had dimensions of 40 mm x 30 mm, was used to conduct the simulations. Firstly, a Region of Interest (ROI) was drawn. Then a radiation treatment planning was conducted according to the spread of the tumor. In the experiments for hyperthermia, which were conducted using a coaxial-slot antenna array, the maximum increase in temperature was observed in an area of 30 mm around the catheters. In the simulations conducted for radiation brachytherapy, the same area of 30 mm around the catheters was targeted. The effect of radiation dose outside this target area was also observed.

In the conventional external beam radiation therapy, generally a high cumulative radiation dose of 50 Gy to 60 Gy is applied [99]. There is a possibility that the radiation dose can be reduced if applied in combination with hyperthermia. Further investigations are required to accurately measure the reduction possible.

Figure 3.2 illustrates the concept of applying interstitial brachytherapy in combination with invasive hyperthermia on a breast tumor. The tumor is shown in black color. The maximum effect of the combination, an increase in temperature to over 42.5˚C and a cumulative radiation dose of 30 Gy, is shown using dark color. Lighter shades are used to illustrate that as the distance from the catheter increases, the effect of the combination decreases.

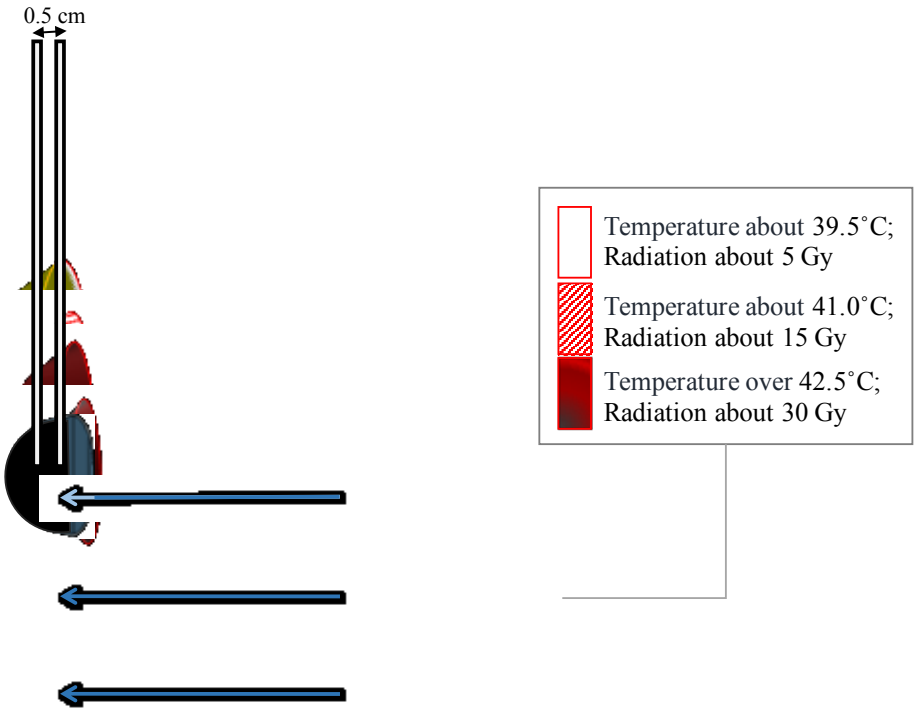


Figure 3.2 Concept of combining temperature and radiation dose distribution.

Figure 3.3 shows the result of a simulation of radiation distribution after applying radiation sources using two catheters. The effects of various radiation doses were observed using simulations conducted for a breast tumor having the dimensions 40 mm x 30 mm. A cumulative radiation dose of 30 Gy was determined to be effective, with minimal harm to the adjacent tissues, for such a tumor.

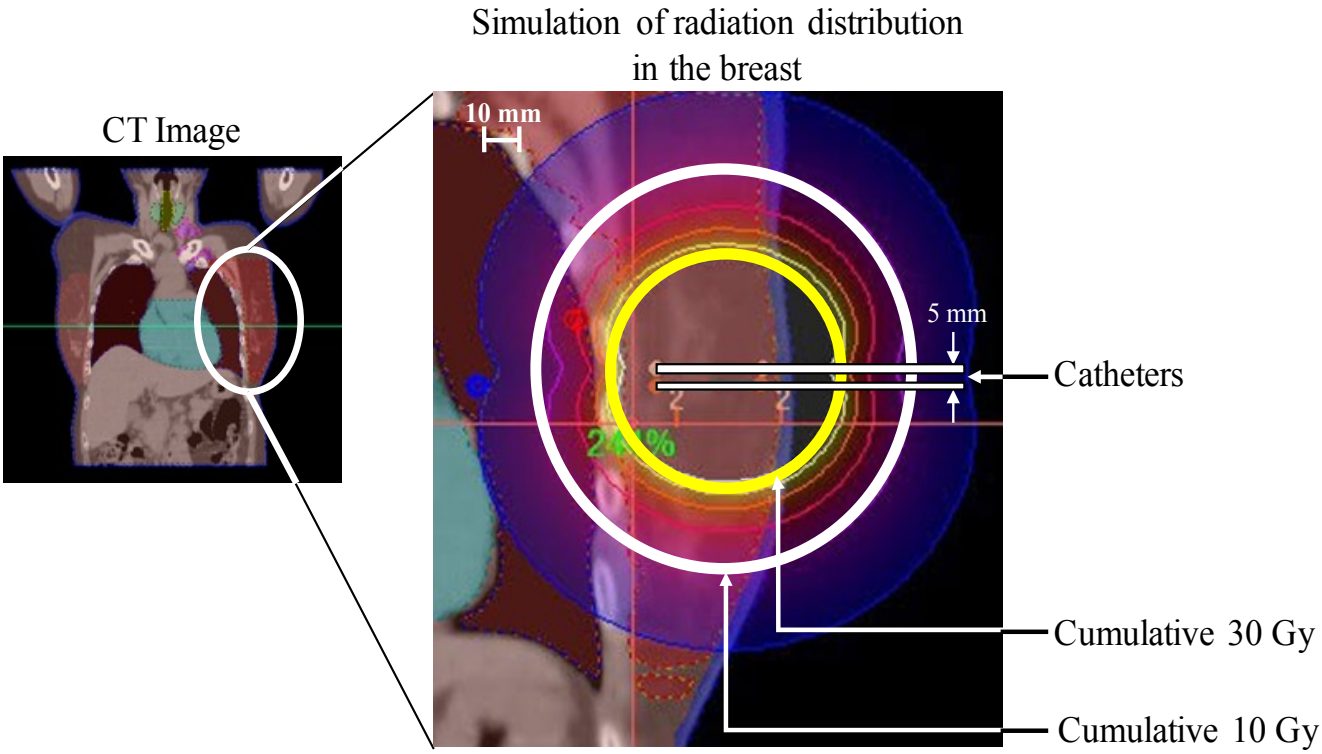


Figure 3.3 Radiation distribution after applying radioactive source.

Moreover, while in the immediate vicinity of the catheters, a cumulative radiation dose of 30 Gy was observed, as the distance from the catheter increased, the effect of radiation dose was reduced. In the region inside the inner circle colored in yellow—up to a distance of 30 mm from the catheter—a cumulative radiation dose of 30 Gy was observed; in the region between the inner circle colored in yellow and the outer circle colored in white—at a distance between 30mm and 50 mm from the catheter—a cumulative radiation dose between 30 Gy and 10 Gy was observed; in the region over a distance of 50 mm from the catheter, a cumulative radiation dose of less than 10 Gy was observed.

3.5 Discussion

The research conducted for part was using Oncentra Workstation which is a treatment planning simulation software based on Monte Carlo Simulation, in The University of Tokyo Hospital. To accurately measure the positive effects of the proposed method , further deeper study and experiments are needed.

In conventional treatment of breast tumor, usually a combination of breast conserving surgery and external beam radiation therapy is used. A high radiation dose is given post-surgery and it covers a wider region. This method increases the impact on the normal tissues adjacent to the tumor.

Harry et al. (2007) had shown the results of a cumulative radiation dose of 50 Gy applied by external beam radiation therapy, with and without a radiation boost of 16 Gy, on stage I and II breast cancer in 5,318 patients [73]. The conclusion after a median follow up period of 10.8 years was that a boost of 16 Gy to the standard 50 Gy breast radiation therapy significantly lowers the risk of local recurrence rates.

In this research work, while the effect of a lower cumulative radiation dose of 30 Gy applied by brachytherapy was simulated using a CT image of an anonymous breast cancer patient, further investigations are needed to establish the effectiveness of this combination treatment.

In 1981, Miller et al had reported an extensive study on results of application of different modalities for cancer treatment [100]. This report gave a summary of the conclusions and recommendations resulting from combinations of different modalities used for treating tumors. This study was initiated by the World Health Organization. For the combined treatment modality, the study suggested to clearly establish the time relationship of the different forms of therapies i.e., whether given concurrently, sequentially, during the primary therapy, maintenance, or any other way.

As in the previous chapter it was mentioned that invasive antenna was selected for further analysis and brachytherapy was a selection for delivering radiation due to the same purpose. Brachytherapy also has the advantage of delivering higher doses of radiation therapy with less dose to the surrounding normal tissues, thus minimizing toxicity in patients. Early studies have revealed that survival is proportional to the dose of radiation delivered.

However brachytherapy may not be sufficient to combat all types of breast tumors. Tumor cells have their own strategy to resist radiation. Few of the strategies are:

1. Tumor Burden: In some cases, the tumor mass is huge. Due to inhomogeneity in blood flow and oxygen supply in that mass, radiation alone cannot uniformly destroy the full mass of the tumor.
2. Tumor Microenvironment: Hypoxia, i.e. lack of oxygen supply inside the tumor makes the tumor radio resistant.
3. Inherent or acquired treatment resistance: Due to pre irradiation or inherent genetic structure the tumor tissue may be radiation resistant.
4. Repopulation during the treatment: Mostly radiation treatment is fractionated in many doses and there is a time gap between two fraction doses. As growth of tumor is faster than that of normal cells, during this gaps, repopulation of the tumor calls occur.

So, to combat with some of these strategies, combination of hyperthermia and radiation therapy is proposed in this research work. Figure 3.4 shows the effect of combination therapy.

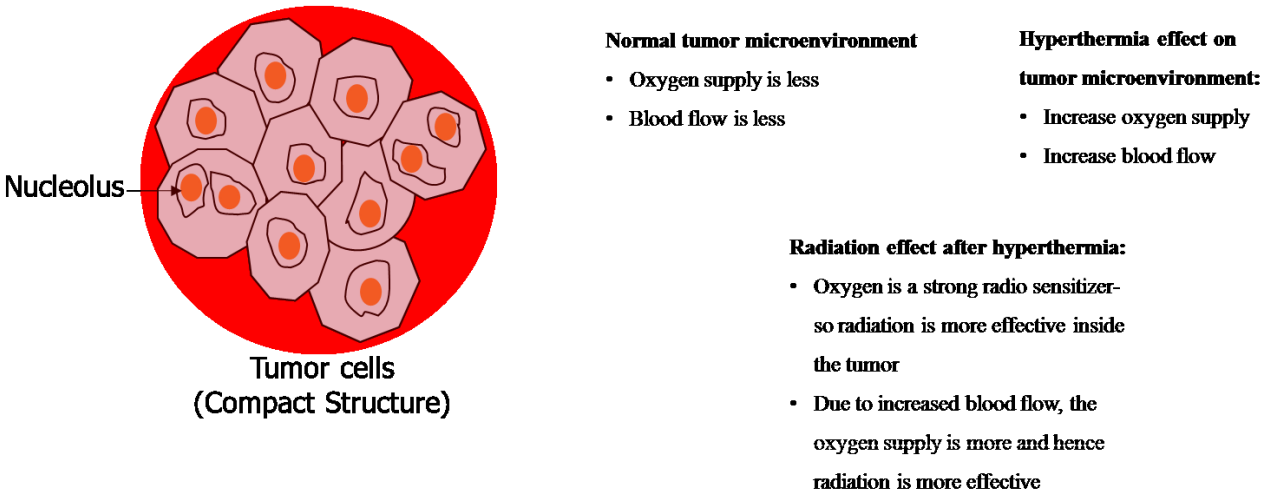


Figure 3.4 Effect of tumor microenvironment due to the combination

This study has some unavoidable limitations. There is no information about combination of hyperthermia and how much radiation dose is possible to reduce actually for a tumor of radius 4 cm. There are other factors which are important such as determining the time gap between two therapies and how that affect the combination therapy. Such factors are important to investigate further.

Many clinical studies were conducted in order to find the advantages of implementing combination of radiation therapy with hyperthermia. Dewey et al had concluded the cellular effects happens due to high temperature [8]. So it can be expected that the radiation dose required would be lesser than the required. Refaat et al, in a recent study of 2015 had performed a randomized trial of mostly breast cancer patients included rigorous and thermal dosimetry [100]. 109 patients were randomized to radiation and combination of radiation and hyperthermia. Patients treated with hyperthermia, were planned for at least a dose of 10 cumulative equivalent minutes at 43˚C for 90% of measured points. This was in additional to conventionally fractionated external beam radiation therapy of 60-70 Gy. For the patients who were previously irradiated, they received 30-66 Gy radiation dose. The proportion of patients receiving systemic treatment at the time did not differ between both arms. The complete response rate was significantly higher in patients treated with hyperthermia as opposed to radiation dose alone. Local control was also more accessible for hyperthermia, as the tumor only was heated.

The studies shows the rationale of choosing 30 Gy radiation dose for a small tumor of 4cm, when combined with hyperthermia. This suggest further investigation on this radiation application.

Chapter 4:

Optimization of the Combination

The literal meaning of the word optimization means choosing the best element over the available set of elements.

The practitioner who adds hyperthermia to radiotherapy and/or chemotherapy, electromagnetic fields are used for heating. Loco-regional deep hyperthermia is usually applied by an antenna array using constructive interference to deposit sufficient energy at depth, for example for tumors located in the lower pelvis [102] or the head and neck region [103]. Control of the electromagnetic heating of the tumor is realized by changing amplitudes, phases of the signal on pairs of antennas, distance between the antennas. There exists a broad consensus that the clinical efficacy of a hyperthermia treatment is correlated to the applied thermal dose [8-10].

Hyperthermia treatment planning is considered an essential tool to guide SAR steering and to increase the thermal dose [104-105]. In a recently published patient study on the effectiveness of hyperthermia treatment planning in deep hyperthermia treatments, Franckena et al. showed that the use of hyperthermia treatment planning as an objective guide for SAR steering during patient treatments leads to temperature results comparable to the conventional, i.e. subjective, method to control SAR steering during the treatment [106-107].

Optimization of the SAR distribution in hyperthermia treatment planning guided steering essentially consists of maximizing SAR in the tumor, and minimizing SAR peaks in the healthy tissue, in the expectation that this leads to maximization of the tumor temperature. Deep hyperthermia treatments are often limited by hotspots [105,108]. The treatment strategy lies always to heat up to the discomfort limit, and keeping the RF power as high as possible. Therefore, heat induced discomfort in patients is common. Accurate prediction of SAR peaks that would lead to patient complaints would offer an elegant method to prevent the occurrence of such complaints. This requires however, that a high correlation exists between the predicted SAR peaks and the location of patient complaints. Therefore, this study aims at assessing whether predicted SAR peak

locations correlate with the locations of the patient complaints. If so, this enables us to use hyperthermia treatment planning predicted SAR peak locations as a-priori indicators for the occurrence of patient complaints during treatment. This study is a logical follow-up of the previously mentioned study of [106]. Further, the translation from model to clinic is very important when using hyperthermia treatment planning models. Hence, a sensitivity analysis of the hyperthermia treatment planning predictions is performed for factors that may determine the quality of this translation: patient positioning, signal of the antennas, dielectric properties, and water bolus shape. Water bolus shape is expected to influence SAR patterns [109], but is not included in this study.

Mutual Coupling

Mutual coupling is an electromagnetic phenomenon which exists in many antenna arrays when they are placed too close to each other. In most of the usual cases it is detrimental to the antenna operation, although there are some examples in which its presence can be beneficial.
By its nature, mutual coupling exhibits differently in transmitting and receiving antenna arrays and therefore has to be treated differently.
The effect of mutual coupling is serious if the element spacing is small. It will affect the antenna array mainly in the following ways [110]:

- Change the array radiation pattern
- Change the array manifold (the received element voltages)
- Change the matching characteristic of the antenna elements

The amount of mutual coupling depends primarily on the following points [111,112]:

(a) Radiation characteristics of each
(b) Relative separation between them
(c) Relative orientation of each

In figure 4.1, change in radiation pattern is explained.

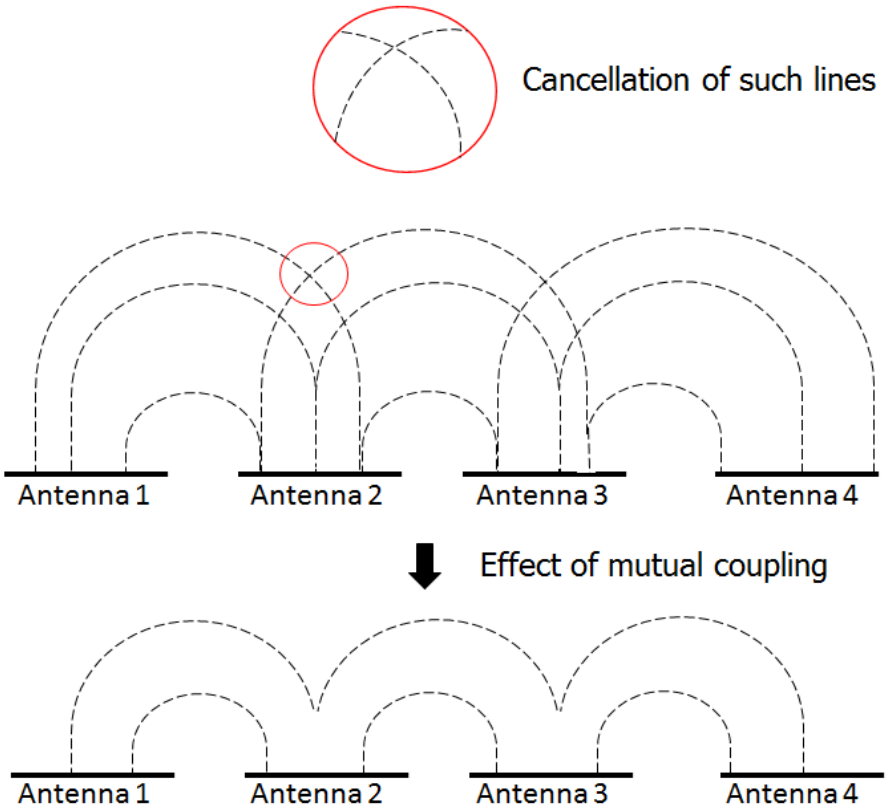


Figure 4.1 Change in radiation pattern due to mutual coupling

Two of the most important characteristics of an antenna are its input impedance and its radiation pattern, both being frequency-dependent quantities. Mutual coupling simply corresponds to the fact that, in view of the presence of another object in the vicinity of the antenna, its near-field radiation pattern is different from the one found when the antenna is isolated in unbounded free space. As a result of the change in boundary conditions, new currents (or different equivalent currents) appear on the neighboring objects. The currents on the antenna itself, including its port current, are also modified. As a result, both the antenna radiation pattern and its input impedance change.

When the neighboring element is another antenna, even passively terminated, currents may flow through its termination, such that energy is being dissipated in it. This will, for instance, impose constraints on the efficiency of an antenna located in a dense array [112]. When considering an array with only one element excited, the neighboring elements may also be regarded as an extension of

the excited antenna. The impedance of the resulting antenna is sometimes called the "passive" impedance and its radiation pattern is called the "embedded element pattern."

A simple approximation to finite array effects on embedded patterns is presented by Kelley and Stutzman [113], where a distinction is made between edge and core elements in the array. An N-element array can also be regarded as an N-port device with its own impedance matrix (or, equivalently, admittance or scattering matrix). The elements of the N-port scattering matrix are sometimes called the "coupling coefficients." However, it is important consider, except for special cases, the knowledge of the "coupling coefficients" does not provide a complete picture of the effects of mutual coupling. This means that, in general, the knowledge of the radiation pattern of the isolated element and of the N-port scattering matrix is not sufficient to obtain all the embedded element patterns.

This was the basic need for making the changes in the distance between the antennas.

4.1 Distance between the Antennas

Initially in this research work, the distance between two antennas were considered to be 0.5 centimeters but due to the mutual SAR and temperature effect.

After checking other distances, 0.5 centimeters distance was found to give a good amount of cumulative amount of SAR and temperature generation.

But in later experiments, it was found that considering 0.5 cm distance between two antennas causes mutual coupling. Henceforth, the distance between the catheters were recalculated to get rid of mutual coupling effect and at the same time, to get a considerably good amount of mutual SAR and temperature effect inside the tumor.

In chapter 2, the reason behind choosing invasive coaxial-slot antenna over other non-invasive antennas was explained and justified. So, it is important to consider the input impedance factor as well. If the input impedance factor varies, it becomes difficult for impedance matching and hence proper delivery of the current.

Thus further calculations were required to consider the mutual coupling factor here and hence re-calculation.

After calculating the SAR and temperature, a comparative study was done in varying distance between two antennas and effect in mutual coupling, mutual SAR and mutual temperature.

Here an important thing to note is: More the mutual SAR and temperature effect, it is better. With increasing the distance we could see that there is a reduction in mutual SAR and temperature effect. On the other hand, more the mutual coupling, it is worse. With increasing distance the mutual coupling between the antennas decrease. At 2 cm, the mutual coupling between the antennas was not seen.

2 cm distance was found to be suitable as mutual coupling factor was not affecting the cumulative power of the antennas. Though the mutual effect of SAR and temperature was reduced than before, but a considerable amount of heating was found.

Discussion on Coherent and Non-coherent system

Normally in electromagnetics, when an antenna array is used, coherent or non-coherent system arises.

(i) Coherent System: When the antennas are used with same power source in an antenna array, they emit power with a fixed phase relationship.

(ii) Non-coherent System: When the antennas are used with different power source in an antenna array, they emit power in different phase and they have a phase difference relationship.

For Non-coherent system, mutual coupling factor does not reduce the power. In that case, the distance between the antennas in an antenna array can be adjusted to 0.5 cm as it is mentioned earlier. In that case, the mutual SAR and mutual temperature effect can be found.

Some research previously done by Denman et al had shown while arranging a four square array, heating effect was found in the periphery of the array structure [114]. If such a heating zone can be generated by using an array of invasive antenna, then it can be considered beneficial and further can be considered.

As this research work is done by simulating the effects of the antenna inside human like tissue. But human tissue has varying characteristics of dielectric properties. Presence of different tissue and their lossy characteristics diffracts the signal in between [115].

The characterizing quantities are radiation pattern and input impedance. As per the experiments, the input impedance is 50 ohm and it did not change due to variation in distance between the

catheters. This happened due to the dielectric properties of the human tissue. For human tissue, mutual coupling factor is not as dominant as mutual coupling factor observed when antennas are placed in free space or air.

In figure 4.2 and 4.3 the mutual SAR and mutual temperature effect of 0.5 cm and 2 cm is shown individually.

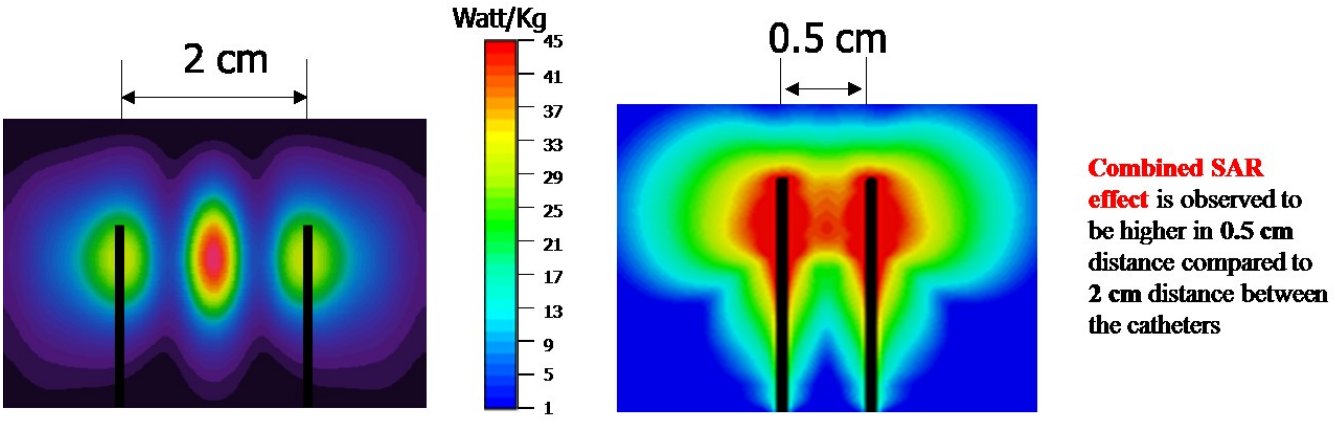


Figure 4.2 SAR effect from antennas placed in 2 cm and 0.5 cm

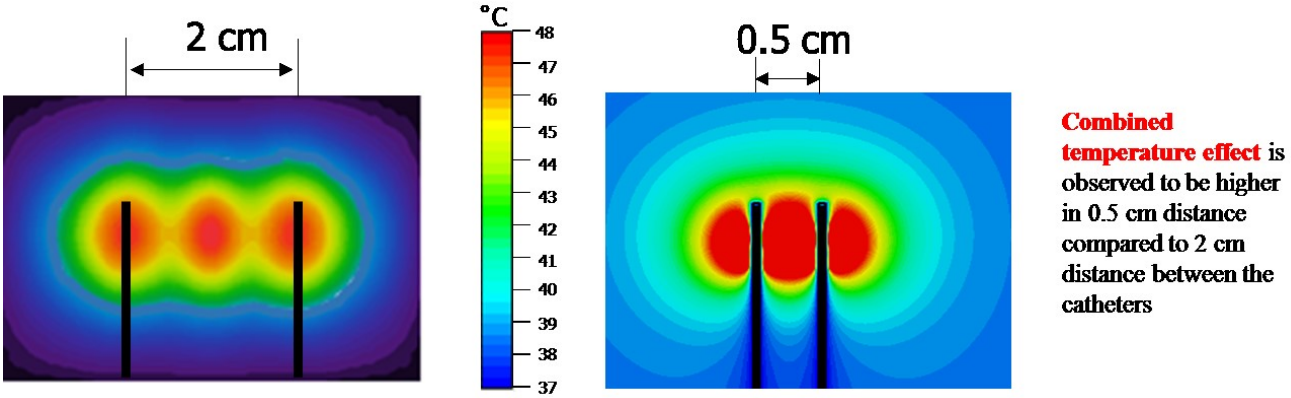


Figure 4.3 Temperature effect from antennas placed in 2 cm and 0.5 cm

4.2 Effect of 2 cm distance in radiation calculation

In this research work, the distance between the catheters were optimized to 2 cm in order to avoid mutual coupling effect and also to get a considerable amount of SAR and temperature effect.

In conventional brachytherapy the radiation dose is the cumulative dose of all the probes used for brachytherapy.

As mentioned in chapter 3, about the radiation dose, it is proposed that radio-isotopes would be introduced inside the catheter. Thus if the distance between the catheter is changed, that factor would also affect radiation dose distribution.

Radiation dose delivered by conventional brachytherapy machine, the probes are placed near to each other. Radiation dose would therefore cumulatively distributed to the adjacent tissues.

If the distance between the probes which are responsible to distribute the radiation dose are placed more distance than each other, the cumulative dose distribution would cover a lesser area. In that case, the lesser area would have higher dose of radiation and the harm could be more.

On the other hand, if the probes or the catheters distributing radiation dose are placed at 0.5 cm from each other, then the cumulative radiation dose distribution would cover 4cm area around the catheters which is a desired area to be covered by radiation dose.

Henceforth, the catheters distance which were optimized to 2 cm in order to avoid mutual coupling in hyperthermia, is not applicable for radiation dose distribution. Distance between the catheters are not therefor optimized for radiation dose distribution. Figure 4.4 shows the effect of radiation dose when the catheters are placed 0.5 cm away.

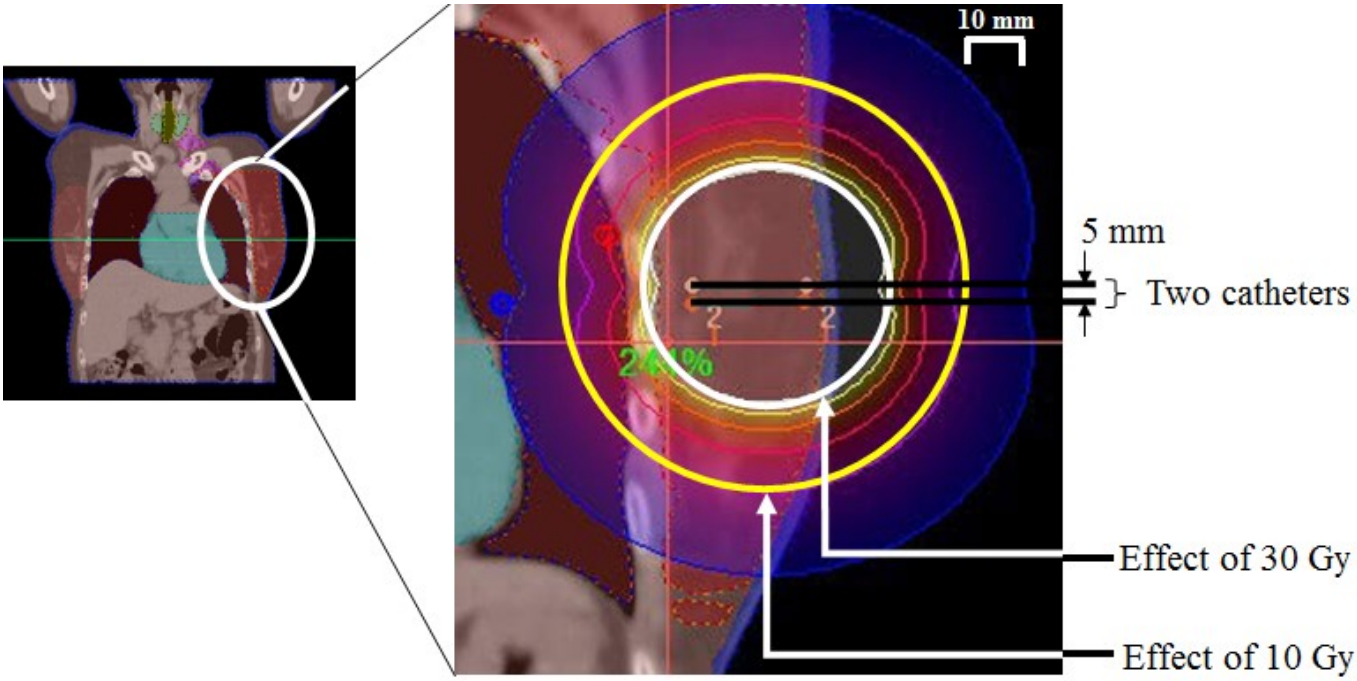


Figure 4.4 Effects of 30 Gy radiation dose when catheters are 0.5 cm apart

Another case of right breast where the tumor spread was found to be around 5 cm X 3 cm, was targeted and 30 Gy radiation dose was applied. Figure 4.5 shows the radiation dose effect.
In this later case, the radiation dose effect of 10 Gy was seen to be effective in 5 cm X 3 cm area.

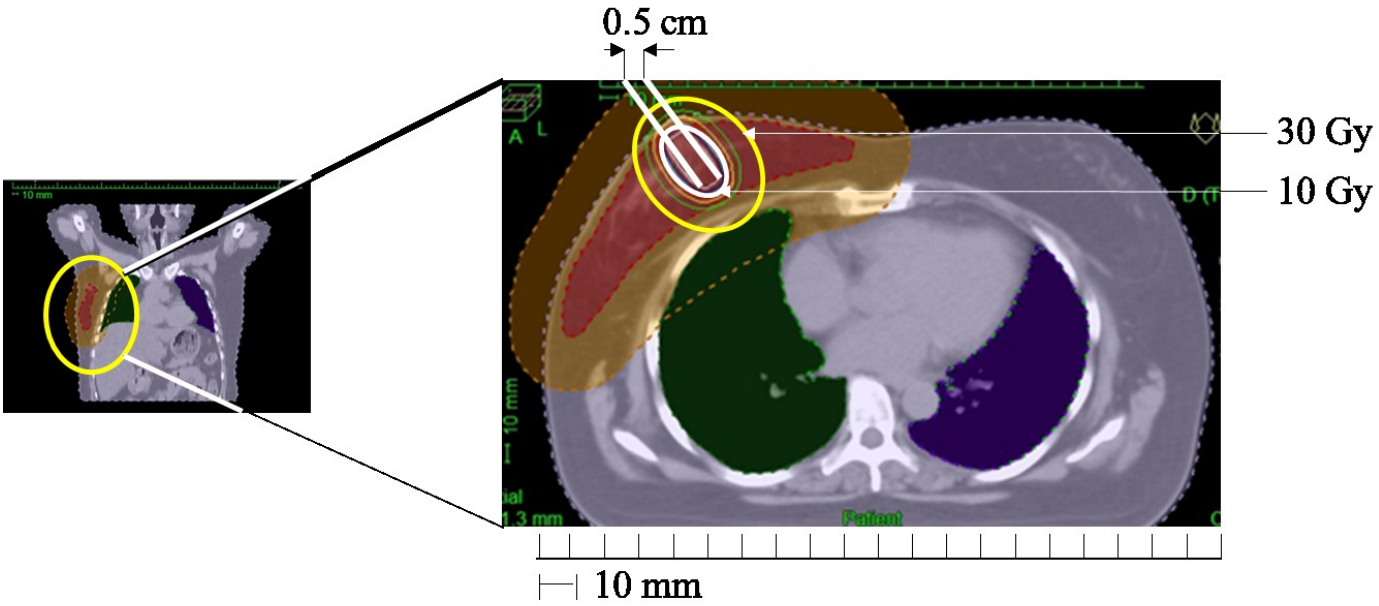


Figure 4.5 Effect of 30 Gy radiation dose in right breast tumor of spread 5 cm X 3 cm

Chapter 5
General Discussion

In this chapter, the entire research work is concluded and general discussion part is provided in terms of looking up to the future investigation.

The initial motivation of starting this research work was to treat breast tumors with less harm to surrounding normal tissue. In the initial phase of the research work, an extensive research on previous study was done. The combination treatment was selected for the further application.

5.1 Advantages of Combination of Microwave Hyperthermia and Radiation Brachytherapy

There has been considerable interest in the possible applications of hyperthermia to radiation therapy [8]. First, the effects of hyperthermia by itself will be considered in terms of:

(a) Cell killing as a function of temperature and duration of thermal treatment;

(b) The thermodynamics of heat inactivation;

(c) Evidence pertaining to the molecular lesions and particular structures inactivated within the cell;

(d) Variations during the cell cycle in sensitivity to hyperthermia;

(e) Cell recovery following treatment;

(f) The time required for repair of heat-induced lesions;

(g) The effects of hypoxia and other physiological states on the hyperthermia response.

(h) The cell membrane becomes more watery and permeable- the objects which were not able to

Secondly, the effects of hyperthermia in combination with x-irradiation will be considered in relation to:

(a) The effects of heat on the shape of the x-ray survival curve when cells are irradiated either as asynchronous populations or in different phases of the cell cycle;

(b) The effects of different temperature and durations of thermal treatment in relation to the time that the heat is applied relative to the x-ray dose;

(c) The repair kinetics both for the heat damage interacting with the subsequent x-ray dose and for radiation damage interacting with the subsequent heat dose; and
(d) The effects of hypoxia on combination of hyperthermia and radiation.

These considerations should allow us to define the possible advantages of hyperthermia in cancer therapy, and to delineate the specific problems to be resolved in order to determine if hyperthermia should be used in such therapy, and if so, most effective use of its protocol.
An additional advantage of using the combination of interstitial hyperthermia and brachytherapy is that the adverse effect on the other tissues adjacent to the breast tumor is minimized because the heat and radiation are focused on the breast tumor.

Though in past, the combination of invasive hyperthermia and brachytherapy was tried for cancer treatment. But the heating module and non-homogeneity of the heating region made it conclude in a quantitative way.
The temperature over 42.5˚C was examined to be cytotoxic for the tumor region [8]. But the exact temperature and amount of radiation was not been optimized till now. The rationale is every human and its thermal tolerance differs from each other.
Even for the computer simulation, during this research work, some difference was found due to the boundary conditions applied.
Figure 5.1 shows the effect of temperature in normal cells and tumor cells.

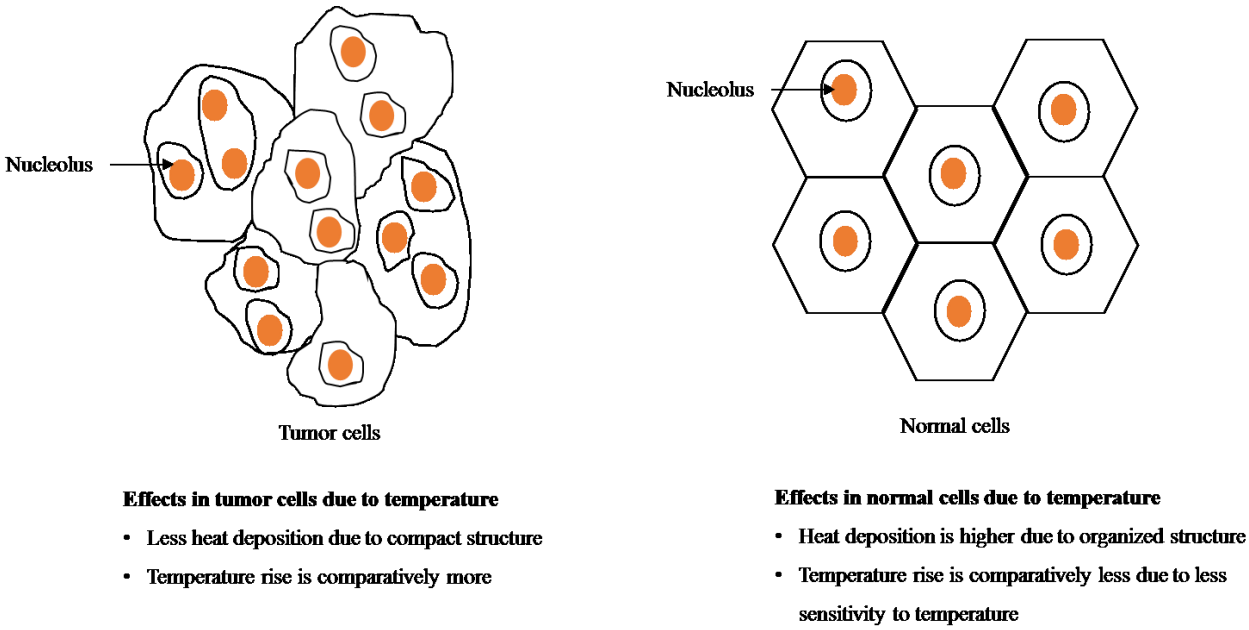


Figure 5.1 Comparative results between tumor cells and normal cells due to temperature

There could be several conditions where combination shows to be effective on cancerous cells.

Another advantage of this proposed method is the thermal sensor. The introduction of thermal sensor is added advantage as temperature can be monitored from outside and according to patient's need, the temperature can be increased.

Even during the time lag between two therapies, the amount of temperature decrease can be monitored by the thermal sensors.

In figure 5.2, the whole set up for hyperthermia is shown.

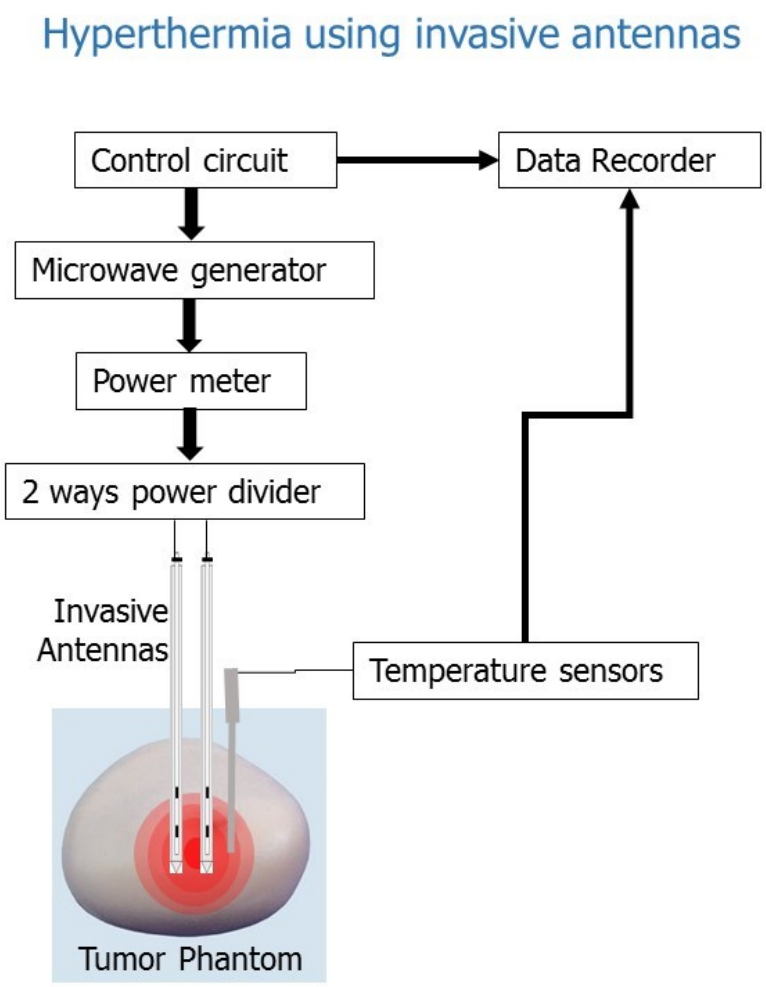


Figure 5.2 Whole experimental set up for hyperthermia using invasive antenna arrays

5.2 Advantages of Microwave Hyperthermia

Cancer hyperthermia is a treatment to raise the tissue temperature either locally or whole body to a therapeutic level to eradicate tumors. Over the last three decades, much has been learned about the effects of heat on cells and the interactions between heat and radiation and chemotherapeutic agents [8-14]. The scientific rationale for its use either alone or combined with other methods is multifactorial, and new justifications for its use are continuously being identified. For example, heat may be directly cytotoxic to tumor cells or inhibit repair of both sublethal and potentially lethal damage after radiation. Hyperthermia has been used in combination with chemotherapy because heating increases membrane permeability and the potency of some drugs. The synergism of radiation and hyperthermia is accomplished by the thermal killing of hypoxic and S phase (DNA syntheses) cells which are resistive to radiation alone. Although the biologic rationale is strong, and hyperthermia has been studied in phase I-III trials, the results of phase III clinical trials are controversial and the use of hyperthermia is still a developing project in all over the world.

Numerous factors could affect the results of hyperthermia. The foremost problem in hyperthermia, however, is the generation and control of heat in tumors. Current heating methods include whole body heating, using hot wax, hot air, hot water suits, or infrared radiation, and partial body heating, utilizing ultrasound, heated blood, fluid perfusion, radio frequency (RF) fields, or microwaves. The effective temperature range of hyperthermia is very small: 42 to 45°C. At lower temperatures, the effect is minimal. At temperatures higher than 45°C, normal cells are damaged. Due to this narrow temperature range, the response rate of the tumor is highly dependent on how much of it is heated to a therapeutic level. The clinical use of hyperthermia has been hampered by a lack of adequate equipment to effectively deliver heat to deep-seated and even large superficial lesions and by a lack of thermometry techniques that provide reliable information on heat distribution in the target tissues. In RF hyperthermia, the final temperature of tumors is mainly dependent on energy deposition. When electromagnetic (EM) heating methods are used, the energy deposition is a complex function of the frequency, intensity, and polarization of the applied fields, the applicator's size and geometry, as well as the size, depth, geometry, and dielectric property of the tumor [9,10]. The material, thickness, and construction of a cooling bolus also influence the amount of energy deposition. In this chapter, the main methods of RF hyperthermia will be reviewed.

Microwave:

The EM energy used in hyperthermia is usually classified by frequency as either microwave energy or RF energy. Microwaves occupy the EM frequency band between 300 MHz and 300 GHz. Strictly speaking, RF is between 3 kHz and 300 GHz, but for hyperthermia it generally refers to frequencies below the microwave range. The most commonly used microwave frequencies in hyperthermia are 433, 915, and 2450 MHz, which are the designated ISM (industrial, scientific, and medical) frequencies in the Japan, U. S. and Europe. Common RF frequencies are 13.56 and 27.12 MHz, which have also been widely used in diathermy. Frequencies higher than 2450 MHz have no practical value due to their limited penetrations. At lower frequencies field penetration is deeper, but the applicator must be larger and focusing is difficult. Despite these limitations, EM heating methods have been developed for local, regional, and whole body hyperthermia.

Interstitial Hyperthermia:

Interstitial techniques for radiation implants as primary or boost treatments have been practiced successfully by radiation oncologists for many years. When hyperthermia was learned to be cytotoxic and synergistic with radiation, it was natural to consider this combination with conventional interstitial radioactive implantation. The advantages of this technique over external hyperthermia include confined treatment volume, better sparing of normal tissue, and accessibility of deeper tumors, more homogeneous therapeutic temperature distribution, and better control and evaluation of thermal parameters. Interstitial hyperthermia has been used for various site tumors; however, a phase III study of interstitial thermo-radiotherapy for recurrent or persistent human tumors did not show any additional beneficial effects over interstitial radiation alone. The delivery of hyperthermia remains a major obstacle [46, 113-116]. Methods such as resistive heating, the microwave technique, or ferromagnetic seed implants can be used for interstitial hyperthermia.

With resistive heating, multi-electrodes inserted in plastic tubes were implanted in the treatment volume. The mean power deposition of the individual electrodes was controlled by varying the duty cycle of the RF signal applied to the electrodes [117]. To prevent excitation of nerve action potentials, an operating frequency greater than 100 kHz should be used. The microwave technique utilizes small microwave antennas inserted into hollow plastic tubing to produce interstitial heat.

In the U. S., 915 MHz is a commonly used frequency for this technique. However, satisfactory heating patterns can be produced between 300 and 2450 MHz [118]. A small coaxial antenna can irradiate a volume of approximately 60 cc. In a brain hyperthermia study, the array of four dipole antennas spaced 2.0 cm apart were capable of heating a volume of 5.9 cm x 2.8 cm x 2.8 cm [119]. As in RF resistive hyperthermia, the degree of control of microwave power radiating from these antennas is important in order to achieve homogeneous heating. Since the antennas couple to each other, the spacing, phasing, and insertion depth affect the heating patterns of array applicators [120-121].

Interstitial heat can also be produced by using ferromagnetic seed implants. This technique is applicable for delivering thermal energy to deep-seated tumors. The seed characteristics and implant geometry must be determined prior to the treatment [122]. When exposed to RF magnetic fields (~100 kHz), the implants absorb power and become heated until they reach the Curie point. Here, the implants become non ferromagnetic and no longer produce heat. The surrounding tissues are then heated by thermal conduction. The influence of blood flow and tissue inhomogeneity of the tumor, which may affect the temperature distribution, can be compensated by the self-regulation of the implants. It is therefore possible to maintain a temperature close to the Curie point [123-124]. Another method, which exposes magnetic fluid in a tumor to an RF magnetic field (0.3 to 80 MHz), has also been shown to be feasible for inducing selective heating [125]. Cetas et al. [126] developed an alternative form of ferromagnetic seed. A nearly lossless ceramic ferrite core (FC) is surrounded by an electrically conductive metallic sheath (MS).

5.3 Advantages of Brachytherapy

Brachytherapy is a method of delivering radiation to tumors by placing radioactive sources either within or immediately adjacent to tumor tissue. Because the radiation source is very close to the tumor, therapeutic radiation can affect the tumor directly while minimally affecting normal tissue. Brachytherapy can be provided using low dose rate (LDR) or high dose rate (HDR) techniques, depending on the length of time the radioactive sources remain in place.

During this research work, in the initial phase different antennas, namely micro-strip patch antenna, spiral antenna and coaxial-slot antenna was designed and applied on human tissues to check the accessibility and also the temperature achieved. As coaxial-slot antenna was chosen for heating deep seated tumors with less heating of surrounding normal tissues, consequently brachytherapy was also chosen for further calculations.

A huge research work has undergone for treating breast tumors and doses are always considered to be high in order to treat the tumor.

During this research work, there were discussions with medical doctors who are specialized in radiation therapy and according to them, the medical doctors prioritize treating the tumor than counting the hazard of high radiation dose. In many cases, secondary tumors occurs due to the previously irradiated with high radiation dose.

Whelan et al [92] reported prominent results (regarding local control, survival, and post-radiation effects) between the standard fractionation schedule of 50 Gy in 25 fractions and a hypo fractionated scheme of 42.5 Gy in 16 fractions over 22 d for women with node-negative early breast cancer.

Though it is an extensive area to look upon. For this research work, 30 Gy divided in 5 fractions, each having 6 Gy was decided. Further calculations and simulations were done on that basis.

Because during this research work, the whole work was done on simulation only, thus the harm or hazards could not be concluded.

5.4 Effects of Blood Flow

Blood flow is an important parameter in this research work which was not considered in the phantom experiments.

There are two dependencies are found.

(i) Hyperthermia's effect on blood flow

(ii) Blood flow's effect on hyperthermia

For the first case of hyperthermia's effect on blood flow, the characteristics are found to vary from normal tissue to tumors [134]. The variation is characterized in table 5.1.

Table 5.1 Variation of blood flow in different tissue due to hyperthermia

Tissue Type	**Hyperthermia's Effect on Blood Flow**
Tumor	Blood flow initially increases with increase in temperature, but later returns to normal [134]
Normal tissue	Blood flow increases with temperature [134]

For the second case mentioned above, every tissue inside the human body are enriched with blood vessels and normally blood is known as a thermo regulator. Previous research had shown that due to the equilibrium created by blood flow, it becomes more difficult to increase up to desirable temperature [93].

Blood flow term is a scalar property. In fact, blood flow in a tissue usually has a direction from the artery to vein passing through the capillary bed. Furthermore, the blood and its surrounding tissues are not in thermal equilibrium when the blood vessel diameter is larger than 200 μ meter. This means the equation for tissue and blood large vessels must be treated individually. Equation (1) gives the equation for tissue and equation (2) gives the equation for blood vessels.

$$\rho_t C_t \frac{\partial T_t}{\partial t} = K_t \left[\frac{1}{r}\frac{\partial\left(r\frac{\partial T_t}{\partial r}\right)}{\partial r} + \frac{\partial^2 T_t}{\partial z^2}\right] - w_b C_b (T_t - T_a) + Q_t(r,z,t) \quad (1)$$

$$\rho_b C_b \left(\frac{\partial T_b}{\partial t} + \omega \frac{\partial T_b}{\partial z}\right) = K_t \left[\frac{1}{r}\frac{\partial\left(r\frac{\partial T_b}{\partial r}\right)}{\partial r} + \frac{\partial^2 T_b}{\partial z^2}\right] + Q_b(r,z,t) \quad (2)$$

Where, T(r,z,t) = temperature that is distributed axis symmetrically

$\rho =$ density

$K =$ thermal conductivity

$c =$ specific heat

$Q(r,z,t) =$ power of heat added axis symmetrically

$\omega_b =$ perfusion mass flow rate

$T_a =$ ambient temperature (37°C)

$\omega(r,t) =$ axial velocity of bloof flow

$Q_m =$ neglected

The heat sink in equation (1) is used to describe the perfusion effect by the microvascular network of blood flow, while the heat transfer due to thermally significant large blood vessels has to be separately described in equation (2).

One of the key issues in thermal treatment is blood flow usually drains out the heat from the heating region, which causes insufficient thermal dose in the targeted volume. More the volume of the target, more will be difficult to increase the desired temperature. The differential therapeutic effect of thermal treatments between malignant and normal tissue may primarily depend on vascular characteristics of the tumor.

It is of interest to not only consider simple steady uniform or parabolic blood velocity profile, but also the pulsatile blood flow in thermally significant blood vessels, (larger than 200 μ meter in diameter) with the assumptions that the blood vessel segment is straight, the vessel wall is rigid and impermeable and the flow is incompressible and Newtonian.

Considering the steady blood flow passing through a rigid vessel of inner radius r0, the axial Hagen-Poiseuille velocity profile can be expressed as equation (3):

$$\omega(r) = -\frac{1}{4\mu}(r_0{}^2 - r^2)\frac{dp}{dz} \qquad (3)$$

Where, μ = dynamic viscosity

r_0 = inner radius

r = outer radius

dp/dz = constant pressure gradient along the axial z direction

Whether the tumors are preferentially heated and thus preferentially damaged by hyperthermia depends largely on the relative rate of heat dissipation by blood perfusion in the tumors and normal tissues. In some experimental tumors, the blood flow increases before vascular collapse occurs upon heating. Usually, the increase in tumor blood flow is less than 2-fold.

The clinical observations that temperatures in human tumors rise higher than that in the surrounding normal tissues may also be attributed to sluggish blood flow in the tumors relative to that in the normal tissues. However, blood flow in certain tumors would remain greater than that in the normal tissue, despite the greater degree of increase in normal tissue blood flow during heating. It would be difficult to raise the temperatures in such tumors higher than that in the normal tissues. It is conceivable that certain areas in a tumor are poorly vascularized, and thus the temperature in such areas rises higher than in the surrounding well-vascularized areas or normal tissues. The tumor cells in such poorly vascularized areas might be radio biologically hypoxic, and thus radio resistant, while these cells may be selectively killed by hyperthermia owing to the preferential rise in temperature and also to the acidic environment associated with the hypoxic condition. Changes in blood flow rate during the course of fractionated heating as well as the effect of combined use of radiation or drugs with heat on the blood flow rate remain to be elucidated.

In this research work, this parameter was not considered thoroughly and it can be understood that it plays a major role in the holistic approach of hyperthermia. Thus in future, this parameter needs to be considered for conclude more substantially.

Chapter 6
Conclusion and Future Work

6.1 Summary

This study was started in order to treat breast tumor with the combination therapy and possible less harm to the surrounding tissues. Despite of extensive research work on this combination in the past, there was no quantitative and conclusive results for breast tumors. That is why this study was initiated.

These phantoms were made of agar material, polyethylene powder, Sodium chloride and distilled water. These phantoms were mostly made planar and oval shaped for making it realistic like breast structure.

Hyperthermia:

Biological effect of hyperthermia:

The cell killing property of hyperthermia depends on various cellular factors [53]:

Cell cycle: Synchronized cell cultures exhibit variations in their susceptibility to heat in accordance to their phase in the cell cycle. In general, the highest heat sensitivity can be observed during the mitotic phase. Microscopic examinations of M-phase cells exposed to hyperthermia show damage of their mitotic apparatus leading to insufficient mitosis. S-phase cells are also sensitive to hyperthermia, where chromosomal damage is observed. Both S and M-phase cells undergo a 'slow mode of cell death' after hyperthermia, whereas those exposed to heat during G1-phase are relatively heat resistant and do not show any microscopic damage. These variations existing between the different cell cycle phases indicate the possible diversity of molecular mechanisms of cell death following hyperthermia.

Effects in DNA and RNA: Intracellular synthesis and polymerization of both RNA and DNA molecules as well as protein synthesis are decreased in vitro at temperatures over 42.5˚C in a dose dependent manner. Whereas RNA and protein synthesis recover rapidly after termination of heat exposure, DNA synthesis is inhibited for a longer period. Heat shock induces an aggregation of denatured proteins at the nuclear matrix. This is mainly due to insolubility of cellular proteins after

heat induced protein unfolding, entailing an enhancement of the nuclear protein concentration. Increase of the nuclear protein concentration. Increase of the nuclear protein content by heat consequently affects several molecular function (including DNA synthesis and repair) when a certain thermal dose is exceeded. This threshold dose varies with different cell lines.

In the first phase of research work, hyperthermia was the main objective where heating the tumor and finding the appropriate set of antenna with optimum parameters were main challenge. For hyperthermia, different antennas and different phantoms having similar dielectric values to human tissue were designed. After conducting the experiments in phantoms and simulations, the results were emphasized. In chapter 3 and 4 had shown the comparative and quantitative results. From there, invasive antenna was found to be suitable for this research work and also serve the initial objective. Interstitial hyperthermia applied using a coaxial-slot antenna increases the temperature of the tumor tissues to over 42.5˚C in 30 min of heating. A coaxial-slot antenna array was used in such a way that the temperature increase takes place in a localized area with minimal effect on the adjacent tissues. After increasing the temperature of the breast tumor to over 42.5˚C, a lower dose of radiation is expected to be effective for treatment.

The Initial motive was to find the antenna and setting the array structure. Initially 0.5 cm distance was found to be decisive as it was giving a cumulative SAR effect and temperature elevation. During that work, mutual coupling factor was not considered.

One of the important factor which was not considered during the experiments in simulation was blood flow in the tumor during hyperthermia and effects of blood flow for hyperthermia. Considering that, the calculation, time required and power mentioned in this research may vary to some extent [60].

Song et al, investigated the effect in blood flow in tumors and concluded that, the blood flow in tumors varies considerably among different tumor types [127]. Even in the same tumor, the distribution of vasculature and blood flow is quite heterogeneous. The tumor blood flow generally decreases as the tumors grow larger, owing partially to progressive deterioration of vascular beds and to the rapid growth of tumor cell population relative to vascular beds. Contrary to the general notion that blood flow is less in tumors than in normal tissues, blood flow in many tumors, particularly in small tumors, is actually greater than that in surrounding normal tissues at normal thermal conditions. Compared to the normal tissue blood flow, however, the capacity of tumor

blood flow to increase upon heating appears to be rather limited. Consequently, the heat dissipation by blood flow in tumors is slower than that in normal tissues, and thus the temperature of tumor rises higher than that in normal tissue during heating. Preferential heating of tumors, however, may not be achieved all the time because the relative blood perfusion in some tumors remains greater than that in the surrounding normal tissues despite the profound increase in normal tissue blood flow during heating. The vasculature in tumor can be significantly damaged at temperatures which may alter but do not damage the vasculature of normal tissue. Upon heating, the inside the tumor environment becomes acidic, hypoxic, and nutritionally deprived due probably to vascular damage. Such a suboptimal environment in the heated tumors potentiates the response of tumor cells to hyperthermia, inhibits the repair of thermal damage, and also interferes with the development of thermal tolerance. The acidic environment also appears to potentiate the response of tumor cells to certain drugs at elevated temperatures. The changes in oxygenation of tumors and normal tissues caused by the changes in blood flow may have significant implications in the effectiveness of different sequences of hyperthermia and radiotherapy in the combined use of these two modalities. Changes in the distribution of drugs in tumors and normal tissues due to changes in blood flow will also determine the optimal use of hyperthermia in conjunction with chemotherapy.

It is a well-known fact that heat induces a prompt increase in blood flow accompanied by dilation of vessels and an increase in permeability of the vascular wall in normal tissues [126]. The degree of pathophysiological changes in the vascular system in normal tissue is, of course, dependent on temperature and duration of heating. An excess exposure of tissues to heat results in a breakdown of vasculature followed by necrosis of the tissues. Information on the vascular changes in normal tissues at temperatures commonly used in clinical hyperthermia, i.e., 41-45˚C.

Hyperthermia is a complicated technique and should be applied only by individuals well trained in its use. Due to the complexity of EM energy coupling to human tumors, careful heating pattern studies should be performed on all exposure geometries and contingencies prior to treatment to assure the best treatment conditions for the patient. Since hyperthermia in combination with high energy radiotherapy cannot be repeated after the tumor receives a maximal dosage of ionizing radiation, the physician must try to reach the critical tumor temperatures in optimal conjunction with radiotherapy. Accurate thermometry is particularly important in all phases of clinical hyperthermia, especially when the patient is anesthetized. The benefit of a good treatment outweighs minor risks. If there is no other choice, it would be more beneficial for the patient to

have an effective treatment with a few blisters rather than a safe but ineffective treatment. It is easier to treat the burns than the cancer.

In this research work, two major categories of antenna are designed in hyperthermia to heat the tumor: non-invasive and invasive. In the early phases of this research work, non-invasive antennas, namely, micro strip patch antenna and spiral antenna, were designed and tested on different types of phantom. The heating and depth of penetration were better in the case of spiral antenna as compared to micro-strip patch antenna. While both the non-invasive antennas gave good results for heating of a superficial tumor few centimeters beneath the skin, there was limited or no impact on deep-seated tumors. There was also a possibility of ablation of skin and other tissues adjacent to the tumor.

As mentioned in the chapter 2, non-invasive antennas were used for heating the superficial tumors which were located around 2-3 cm below the skin layer. During the experiments, non-invasive antennas were used to add their effects and then focus on a tumor which is located deeper than 3cm, but it was not effective due to high diffraction from human tissue.

As this research work was focused on deep seated tumors, coaxial-slot antenna was chosen for further analysis. For coaxial-slot antenna the risk of effects on normal tissue due to high temperature such as skin ablation, can be avoided. Another advantage of using coaxial-slot antenna is, there is no requirement of using bolus material for coaxial-slot antenna.

Radiation Biology:

Radiation biology, or radiobiology, is the study of the effects of radiation on living systems. Absorbed radiation dose is an important quantity when predicting the biological effect. However, there are many factors that affect the biological response to a given dose: the inherent radio-sensitivity of the biological system studied, the degree of oxygenation, the dose distribution within the irradiated volume, the way dose is fractionated, e.g. dose per fraction, the time between fractions, overall treatment time, etc.

On the other hand, brachytherapy is well practiced by many doctors for treating cancers. Though it is an invasive way to treat the tumors but locally given radiation dose harms comparatively lesser to the surrounding normal tissues than external beam radiation therapy in which the whole breast is irradiated. Evidences of brachytherapy and its catheters are well researched and commercialized.

Organ and tumor response to radiation

Clinical radiation biology often focuses on the relationship between the absorbed dose and resulting response, and on factors influencing this relation. The response in often described as a probability of a specific outcome for the normal tissue or the tumor, typically showing a sigmoid dose-response curve. Tissues can be classified as serial or parallel, or somewhere in between, based on how their functional subunits are organized. Serial tissues, such as the spinal cord and brain stem, may lose their function even if only a small proportion is severely damaged. Parallel tissues, such as lung and liver, can function even when substantial parts are damaged. Tumors are always assumed to have a parallel function since all clonogenic cells need to be eradicated in order to achieve tumor control. The response of normal tissues can also be divided into early and late occurring damage, reflecting the time of occurrence of side effects. Rapidly dividing tissues such as skin, bone-marrow, and intestinal epithelium respond early to radiation. Late-responding tissues are for example spinal cord, lung, and kidney.

Dose fractionation

Dose fractionation is the practice of dividing the therapeutic dose into smaller doses delivered over a period of time. It is a key determinant of the therapeutic response. The rational of fractionation is that normal tissues are well-organized and have well-functioning repair systems and may therefore repair radiation-induced damage to some extent between the fractions, whereas tumors are more chaotic in their structure and generally less capable of repair. Another reason is that the fast and poorly organized tumor growth often leads to poor vascular networks resulting in insufficient oxygen levels. Poor oxygenation results in radio resistant cells [8]. After the delivery of dose fractions, the oxygen supply may be improved by hypoxic cells turning toxic due to eradication of the more toxic, radiosensitive, tumor cells or through the reopening of previously closed blood vessels [128]. The main biological processes that affect the fractionation effect are summarized by the five R's of radiobiology:

1. Repair: Repair is one of the primary reasons for fractionation. The smaller dose fractions separated in time allow normal tissue to recover, and normal tissue with intact repair capacity generally has a better ability to repair damage than tumors.
2. Redistribution: Cells in some phases of the cell cycle (M and G2) are more radiosensitive than in other (S). Dose delivery over time allows for redistribution so that tumor cells in a resistant phase continue to cycle into a more sensitive phase.
3. Re oxygenation: Tumor hypoxia is a condition where tumor cells are deprived of oxygen making them more radio resistant than well oxygenated cells. The oxygenation status may change during treatment and dividing the dose may allow more tumor cells to be eradicated.
4. Repopulation: A prolonged treatment allows normal cells to proliferate which is beneficial. However, also tumor cells proliferate and, especially for fast growing tumors, a too long treatment time may lead to tumor regrowth.
5. Radio sensitivity: There is also an intrinsic radio sensitivity depending on cell type. Late-responding tissues are more sensitive to changes in fractionation patterns than early-responding tissues. The difference between these tissues in their response to changes in fractionation could be understood from the differences in their dose-response relations. The cell survival curve for late-responding tissues, with its more curved shape compared to early-responding tissues after photon irradiation, show more sparing when the dose is fractionated. Fewer and larger dose fractions result in more severe late effects even when the total dose is adjusted to produce equal early effects. The response following high-LET radiation, with generally straighter cell survival curves, is consequently less affected by fractionation.

Table 6.1 shows the comparative results of alone radiation dose required and combination of hyperthermia and radiation dose

Table 6.1 Comparative result of radiation dose with or without hyperthermia

	Radiation Dose Effect alone	Combination of Hyperthermia and Radiation Dose Effect
Breast Tumor	50-60 Gy	30 Gy (proposed)
Duration	Longer	Comparatively shorter
Cost	Expensive Linac	Comparatively cheaper (RF machine and commercial brachytherapy)

Dewey et al had concluded the cellular effects happens due to high temperature [8]. So it can be expected that the radiation dose required would be lesser than the required. Refaat et al, in a recent study of 2015 had performed a randomized trial of mostly breast cancer patients included rigorous and thermal dosimetry [100]. 109 patients were randomized to radiation and combination of radiation and hyperthermia. Patients treated with hyperthermia, were planned for at least a dose of 10 cumulative equivalent minutes at 43˚C for 90% of measured points. This was in additional to conventionally fractionated external beam radiation therapy of 60-70 Gy. For the patients who were previously irradiated, they received 30-66 Gy radiation dose. The proportion of patients receiving systemic treatment at the time did not differ between both arms. The complete response rate was significantly higher in patients treated with hyperthermia as opposed to radiation dose alone. Local control was also more accessible for hyperthermia, as the tumor only was heated.

The studies shows the rationale of choosing 30 Gy radiation dose for a small tumor of 4cm, when combined with hyperthermia. This suggest further investigation on this radiation application.

The whole realization of this project is emphasized in figure 6.2.

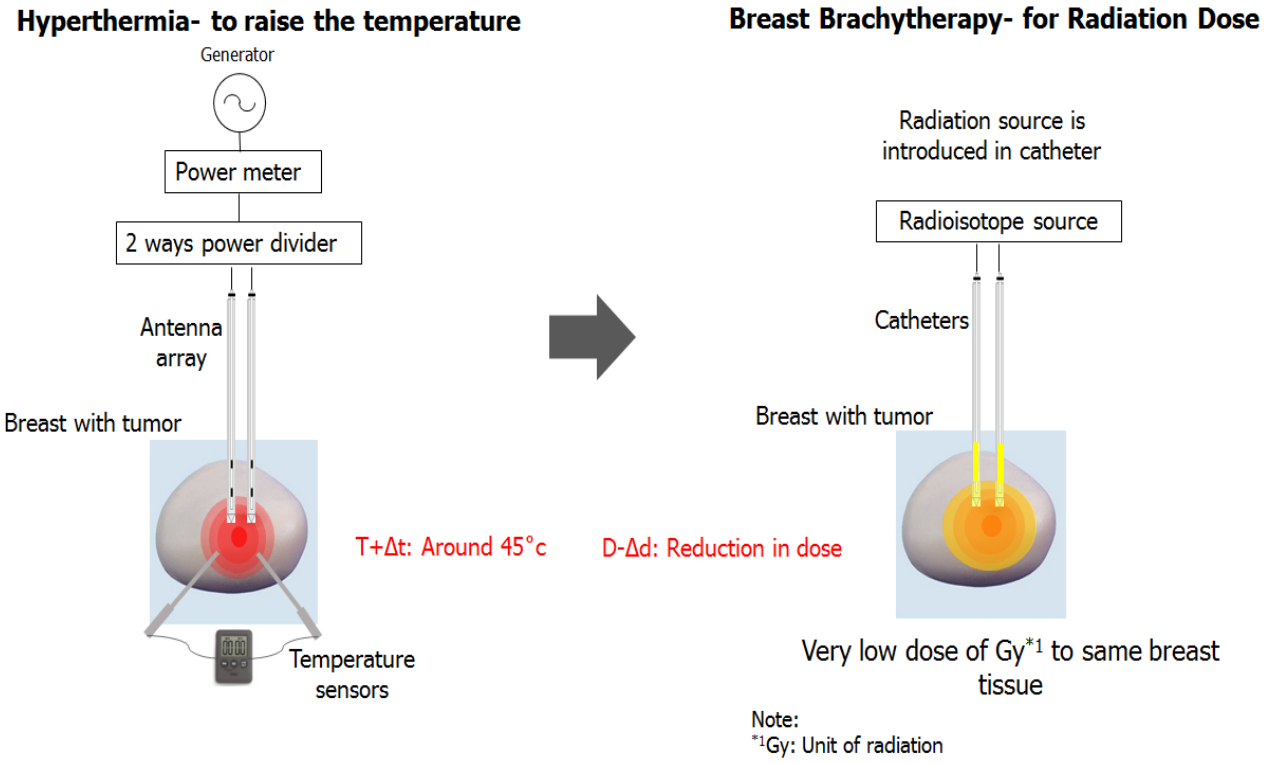


Figure 6.2 Realization of the holistic approach on this research

6.2 Conclusion

For Hyperthermia, invasive and non-invasive antenna was initially designed and human tissue like phantoms.

For this research work, three types of antenna were designed. Among which coaxial-slot antenna gave the best result for heating deep seated tumors.

After application of the coaxial-slot antenna array, the temperature rise was found to be around 12˚C, after 30 minutes.

Among all mentioned, as the research work was focused on the deep seated tumors, coaxial-slot antenna was chosen. Subsequently radiation brachytherapy was chosen in order to use the same catheter.

The advantage of using same catheter for both hyperthermia and radiation brachytherapy was to avoid many penetration which cause to medical practitioner and also avoidable by the patient. After hyperthermia, the antenna could be withdrawn and the catheter remain in the same place. Then, the radio-isotopes are introduced in the same catheters.

The distance between the antenna array was optimized to 0.5 cm, which gave the best mutual SAR and temperature effect as mentioned in chapter 4. This distance was maintained for radiation brachytherapy application as well.

In radiation therapy, a CT image of anonymous patient of breast tumor was used for the simulation calculation. After verifying with different radiation dose, 30 Gy radiation dose was found to be effective in the area of 4cm X 3 cm which is also target area for hyperthermia. The dose is fractionated in 5 fractions and each having 6 Gy radiation dose.

The radiation dose was found to be effective in the tumor area. The initial objective of the research work was to treat the deep seated tumors with lesser radiation dose than conventional radiation dose. Also, with possibly lesser effect to the adjacent tissues. At the end of this research work, the radiation dose was reduced comparatively to the radiation dose used in external beam radiation therapy.

This reduction was possible as the temperature of the tissue is increased and whole combination treatment was done locally.

6.2 Conclusion

(i) For Hyperthermia, invasive and non-invasive antenna was initially designed and human tissue like phantoms.

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(ii) In radiation therapy, a CT image of anonymous patient of breast tumor was used for the simulation calculation. After verifying with different radiation dose, 30 Gy radiation dose was found to be effective in the area of 4cm X 3 cm which is also target area for hyperthermia. The dose is fractionated in 5 fractions and each having 6 Gy radiation dose. The radiation dose was found to be effective in the tumor area. The initial objective of the research work was to treat the deep seated tumors with lesser radiation dose than conventional radiation dose. Also, with possibly lesser effect to the adjacent tissues. At the end of this research work, the radiation dose was reduced comparatively to the radiation dose used in external beam radiation therapy. This reduction was possible as the temperature of the tissue is increased and whole combination treatment was done locally.

(iii) For combination of both the therapies, it is proposed to use the same catheter for hyperthermia and radiation brachytherapy. The advantage of using same catheter for both hyperthermia and radiation brachytherapy was to avoid many penetration which cause to medical practitioner and also avoidable by the patient. After hyperthermia, the antenna could be withdrawn and the catheter remain in the same place. Then, the radio-isotopes are introduced in the same catheters.

The distance between the antenna array was optimized to 0.5 cm, which gave the best mutual SAR and temperature effect as mentioned in chapter 4. This distance was maintained for radiation brachytherapy application as well.

6.3 Future Prospects of this Research Work

For this work, there is much requirement to continue this work.

- Real experiments (e.g. on phantoms) of radiation brachytherapy with hyperthermia
- Study the effect of blood flow in hyperthermia
- Optimize the combination of hyperthermia and radiation brachytherapy
- Study the effect of applying hyperthermia and brachytherapy simultaneously and effect of time lag between application of the two treatments
- Conduct experiments on real animals and tumor cells
- Extend the study of the combination treatment to other type of tumors

First of all, the experiments in phantoms, need to be performed in animals, to see the practical effects and also the blood flow effect during hyperthermia.

Once the experiments are conducted, there could be some requirements of optimizing the antenna parameters.

The second part of this research work is only limited to radiation simulation only. To verify and see the actual cellular effects of 30 Gy on a tumor cell along with hyperthermia and without hyperthermia- it is essential do to some further experiments.

Till now the some fundamental background study and antenna and radiation cumulative dose is decided, but it needs further work to conclude more quantitatively to conclude this results.

One of the important parameter is to find the material which could be used for catheters making which can withstand the temperature rise and radiation dose inside the human body.

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Appendix A
Finite integration Method

The computational time-domain modeling of different types of wave-field problems is utilized in various disciplines of engineering and science: in increasingly challenging problems in remote sensing, communications, optics, geophysical exploration, ground-penetrating radar, medical diagnosis, and nondestructive evaluation.

Various numerical techniques are applied today to model transient wave fields in electromagnetics, for instance,

(1) Finite-Difference (FD),
(2) Finite-Element (FE),
(3) Finite Volume (FV),
(4) Finite-Difference Time-Domain (FDTD),
(5) Finite-Integration (FI), and
(6) Finite Volume Time-Domain (FVTD)
(7) Microcell Time Domain (MCTD)

For this research work, Finite Integration Technique was used in CST software for calculation of SAR and temperature when electromagnetic wave was applied.

In time-domain electromagnetics, the resulting discrete grid equations of FIT are, at least in "some" cases, identical to the discrete equations derived with the classical Yee method. This was introduced in the mid-1960s [129], and uses a coordinate-based staggered grid system and the famous Yee cell. In general, FIT includes the Yee method as a subset. In contrast to FIT, which is applied to the integral form of the field equations, the original Yee method is applied to the differential form of the governing equations: in electromagnetism, to the Maxwell curl equations [55].

The governing field equations of electromagnetics in differential form:

$$\frac{\partial B(R,t)}{\partial t} = -\nabla \times E(R,t) - J_m(R,t) \quad (1)$$

$$\frac{\partial D(R,t)}{\partial t} = \nabla \times H(R,t) - J_e(R,t) \quad (2)$$

Where, B (Vs/m^2): Magnetic Flux vector

E (V/m): Electric field strength vector

J_m(V/m^2): Magnetic current density vector

D (As/m^2): Electric flux density vector

H (A/m): Magnetic field strength vector

J_e (A/m^2): Electric current density vector

These are Maxwell's equation for electromagnetic waves.

The next equations are characterizing properties of the underlying materials.

$$D(R,t) = \varepsilon(R).E(R,t) \quad (3)$$

$$H(R,t) = \vartheta(R).B(R,t) \quad (4)$$

Where

Ɛ (As/Vm): Permittivity

ϑ(Am/Vs): Reluctivity

For inhomogeneous materials with interfaces or for boundary-value problems, it is essential that the underlying transition/continuity or boundary conditions are insured.

Suppose two media, with different materials are separated by an interface, I, with unit-normal n pointing from medium 1 into medium 2; then, for I∈R, for such situation [129,130]:

$$n \times E^2(R,t) - n \times E^1(R,t) = \begin{cases} -K_m(R,t) & \text{With interface sources} \\ 0 & \text{Source free} \end{cases} \quad (5)$$

$$n \times H^2(R,t) - n \times H^1(R,t) = \begin{cases} K_e(R,t) & \text{With interface sources} \\ 0 & \text{Source free} \end{cases} \quad (6)$$

K_m (V/m): Magnetic surface current density vector

K_e (A/m): Surface density of electric current vector

In general, these surface sources on the right hand side equations are field independent sources. If medium (1) is replaced by a medium that is field-free, boundary conditions are needed for the fields, which are directly obtained from above equations by deleting all field quantities with a superscript (1) and dropping the superscript (2). Then, the interface sources on the right-hand side of above equations vanish or define field-dependent sources.

For the utilization of the Finite Integration Technique, the governing field equations, Equations (1) and (2) in integral form by making use of Gauss' and Stokes' integral theorem, and insert the constitutive equations, Equations (3)-(4), as well as adding time-integration schemes:

$$\iint_S B(R,t)\,.\,ds = \oint_{C=\partial S} E(R,t).\,dR - \iint_S J_m(R,t)\,.\,ds \tag{7}$$

$$B(R,t) = B(R,t_0) + \int_{t_0}^{t} B(R,t^\star)dt^\star \tag{8}$$

$$\iint_S \varepsilon(R).B(R,t)\,.\,ds = \oint_{C=\partial S} \vartheta(R).B(R,t).\,dR - \iint_S J_e(R,t)\,.\,ds \tag{9}$$

$$E(R,t) = E(R,t_0) + \int_{t_0}^{t} E(R,t^\star)dt^\star \tag{10}$$

This is the basic of the calculation of CST simulation software which was used in this research work to calculate SAR and temperature.

Paper:

1. "**Interstitial Hyperthermia in Combination with Radiation Brachytherapy for Treatment of Breast Tumor**", Oiendrila Bhowmik Debnath, Kazuyuki Saito, Koichi Ito and Mitsuru Uesaka (Accepted in Journal of Thermal Medicine)

International Conference and proceedings:

1. **International symposium on Biotech and Global Warming, 2012 (Oral Presentation)** Oiendrila Bhowmik , "Detection of early symptoms of Alzheimer's disease from EEG signals"

2. **International Microwave Workshop Series on RF and Wireless Technologies for Biomedical and Healthcare Applications, 2015 (Oral Presentation)** Oiendrila Bhowmik Debnath, Kazuyuki Saito, Koichi Ito and Mitsuru Uesaka, "Design of invasive and non-invasive antennas for the combination of microwave-hyperthermia with radiation therapy".

3. **International Symposium on Antennas and Propagation, ISAP 2016 (Poster Presentation)** Oiendrila Bhowmik Debnath, Kazuyuki Saito, Koichi Ito and Mitsuru Uesaka, "Breast cancer treatment using Microwave hyperthermia and Radiation brachytherapy"

Domestic Conference and Proceedings:

1. **National symposium on Advanced Medical Imaging,** held in India **(Poster Presentation) October 2009**, Oiendrila Bhowmik, Anburajan "Detection of Breast Cancer by Medical Thermography"

2. **19th West Bengal State Science and Technology Congress (WBSSTC)**, held in India **(Oral Presentation), March 2012**, Oiendrila Bhowmik, Venkatraman Balasubramaniam "Detection of Breast cancer from Contra-lateral images"

3. **Todai-Seika University (China) Workshop , (Poster Presentation) June, 2015** Oiendrila Bhowmik Debnath, Kotarou Ushida, Kazuyuki Saito, Koichi Ito and Mitsuru Uesaka "SAR Patterns of Invasive and Non-invasive Antenna Array in Combination of Hyperthermia and Radiation Brachytherapy"

4. **Japan Society of Maintenology (JSM), (Oral Presentation) July 2016,** Oiendrila Bhowmik Debnath, Kazuyuki Saito, Koichi Ito and Mitsuru Uesaka "SAR Patterns of Invasive and Non-invasive Antenna Array in Combination of Hyperthermia and Radiation Brachytherapy"

5. **21st Annual Meeting of Kantō District Hyperthermia Study Group, March 2017:** Oiendrila Bhowmik Debnath, Kazuyuki Saito, Koichi Ito and Mitsuru Uesaka "Treatment

Planning of Combination of Microwave Hyperthermia and Radiation Brachytherapy for Bresat Tumor"

Awards

1. **Best Programmer in Matlab at Bioyantra- National Technical Symposium, August 2009, held at India**

2. **Best Paper Award, National symposium on Advanced Medical Imaging, October 2009, held at India**

3. **Second Best Paper Award at International symposium on Biotech and Global Warming, 2012**

4. **Best Original Paper Award (JSM, 2016)**

5. **Superior research Award (21st Annual Meeting of Kantō District Hyperthermia Study Group, 2017)**