Evaluation of Nanoparticles-Based Thermotherapy for Cancer

by

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B.Eng. Materials Science and Engineering
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Abstract

Under alternating magnetic field, superparamagnetic iron oxide nanoparticles can be used to generate heat for the treatment of cancer. With suitable coating, these nanoparticles are biocompatible, stable in solution, and absorbed by tumor cells in good contrast. The mechanism of heating is mainly due to Néel relaxation process and a quantity called specific loss power (SLP) / specific absorption rate (SAR) is used to describe the heating effect. Past clinical studies have shown minimum side effects and proven the success of the new thermotherapy as a treatment modality in conjunction with chemo- or radiotherapy. Studies are in progress to improve the nanoparticles' heating power to enable treatment of small tumors and metastases, thermoablation as a monotherapy, and to achieve tumor-specific thermotherapy with the aid of tumor-finding molecules.

This paper evaluates the novel technology that is magnetic nanoparticles-based thermotherapy and explores its commercialization potential. It explains the medical need driving the innovation, examines the technology in comparison with existing cancer therapies, identifies the strategic position the technology has in the present state of market for cancer therapies, and explores opportunities and challenges in the introduction of the new therapy into the U.S. market.

Thesis Supervisor: Caroline Anne Ross
Title: Professor of Materials Science and Engineering

Acknowledgments

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1. Introduction

The past decade's surge in interest and research in nanotechnology has also taken root in the drug and medical device industry. Termed 'nanomedicine', these developments promise novel applications and innovative improvements in drug delivery, therapies, in vivo imaging, in vitro diagnostics, and biomaterials. This emerging field has attracted governmental agencies and various science administrations for funding. The European Science Foundation, in their report published in 2005, warns that without major investment and coordinated strategy to bring nanomedicine to market, the benefits will be lost [1]. It is therefore significant to conduct roadmaps and foresight studies to analyze the technological and commercial perspectives of this emerging field. This report specifically addresses how nanotechnology opens a new dimension in cancer therapy, the use of magnetic nanoparticles to treat cancer by hyperthermia and thermoablation. It covers the technology in detail: the properties of the nanoparticles that enable their function, how the nanoparticles are made, the advantages and disadvantages associated with the new therapy; as well as provides an insight on the steps and considerations to be taken to bring this technology to market: looking into the American market for medical device and cancer therapy, the regulations governing the commercialization of medical products, identifying major competitors, and other observations related to pricing and affordability.

2. Medical Need / Market

Based on the data on US mortality in 2004, cancer accounts for nearly one-quarter of deaths in the United States, exceeded only by heart diseases.

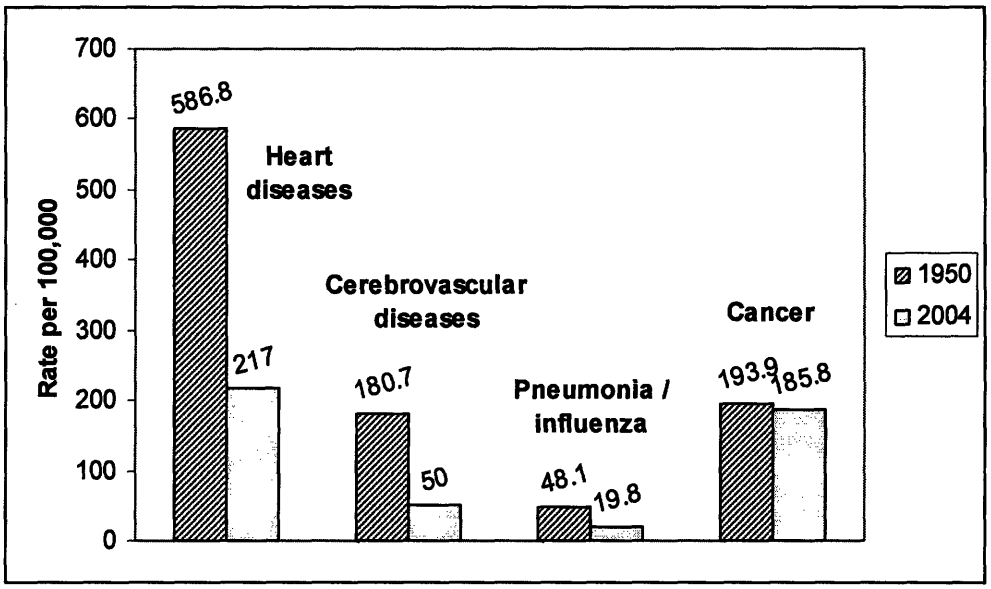
TABLE 1
U.S. Mortality, 2004
(from the American Cancer Society [2])

Rank	Cause of death	No. of deaths	% of all deaths
1	Heart diseases	652,486	27.2
2	Cancer	553,888	23.1
3	Cerebrovascular diseases	150,074	6.3
4	Chronic lower respiratory diseases	121,987	5.1
5	Accidents (Unintentional injuries)	112,987	4.7
6	Diabetes mellitus	73,138	3.1
7	Alzheimer disease	65,965	2.8
8	Influenza & pneumonia	59,664	2.5
Source: U.S. Mortality Public Use Data Tape 2004, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.			

The same trend is true worldwide, where over 6.7 million people die every year as a result of cureless cancer diseases.

Moreover, the following figure shows the change in the US death rates by cause, comparing the year 1950 and 2004. Observe how while rates for other major chronic diseases decreased substantially, that associated with cancer has only decreased slightly.

FIGURE 1
Change in the U.S. Death Rates by Cause, 1950 & 2004
(from the American Cancer Society [2])



Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2004 Mortality Data: US Mortality Public Use Data Tape, 2004, NCHS, Centers for Disease Control and Prevention, 2006

This says something about the different therapeutic approaches we have today, namely surgery, chemotherapy, and radiotherapy. In fact, roughly 25% of cancer patients experience failure of tumor control after these conventional therapies. Even when they are successful, they are known to have substantial side effects and dramatically reduce the quality of life.

And if the high number of deaths associated with cancer were not enough, there is another incentive. In the same year, the financial costs attributed to cancer treatments accounted for about $72 billion (5% of total US spending on medical

treatments), but the additional economic burden of cancer due to morbidity and premature mortality was estimated to be $120.4 billion, resulting in a total cost of cancer in 2004 to be $192.4 billion [3-5].

3. Technology

3.1 Thermotherapy, New Cancer Treatment

The most common methods of treating cancer are by surgery, chemotherapy, and radiotherapy. Surgery is the oldest known treatment of cancer, in which cancer is physically removed from the body. Like most surgery procedures, it carries the risk of pain, infection, bleeding, and altered bowel and bladder function. In chemotherapy, cytotoxic chemicals are used as drugs to kill rapidly dividing cells. These include cancer cells and healthy cells that also divide rapidly such as those in the bone marrow, gastrointestinal tract, reproductive system, and hair follicles. Its main advantage is that it treats the entire body, making sure cancer cells that may have broken away from the original cancer are affected. However, it is also its primary disadvantage, because side effects arising from healthy cells being destroyed are experienced by patients. These side effects might include hair loss, nausea, diarrhea, infertility, cognitive impairment, and go as far as to cause organ and nerve damage. Radiotherapy, on the other hand, uses radioactivity to kill cancer cells. It involves exposing cancer cells to beams of high-energy particles or waves such as gamma rays or X-rays which destroy the genetic material that controls how cells grow and divide. And while both healthy and cancerous cells are equally damaged by radiation, the goal of the treatment is to hurt as few normal, healthy cells as possible by good targeting.

For decades, numerous pre-clinical studies have shown that heat is largely effective against cancer [6]. This discovery is only natural, since the human body itself instinctively uses heat to fight disease. A fever, for example, is body's way of slowing the rapid multiplication of disease-causing agents, giving the body advantage while fighting the infection. There is a synergistic interaction between heat and radiation dose (in radiotherapy) or the cytotoxic drugs used (in chemotherapy) [7,8]. Raising the temperature of cancer tissues to 40-43° C (100-110° F) increases drug delivery and hence the efficacy of chemotherapy. When applied with radiotherapy, heat inhibits repair of sublethal radiation damage and induces increasing radiosensitivity [9,10]. Interestingly, an in vitro study also demonstrated that heat-treated cancer cells may undergo alterations of some cell surface receptor molecules which make them better recognized by the immune system [11]. This practice of heating organs or tissues for therapy purposes is called hyperthermia. When this approach is taken one step further, heating tissues above 46° C up to 70° C (158° F), tissues undergo extensive necrosis known as thermoablation. Putting it simply, they burn away and die.

The effect of heat on biological tissues can be quantified according to the method proposed by Sapareto and Dewey [12], which converts an arbitrary temperature-time curve to an equivalent time in minutes at 43°C. From the Arrhenius equation, an iso-effect relationship between different temperatures has been established [13] and is given by:

$$\text{Cumulative Equivalent Minutes (CEM) } 43°C = tR^{(43-T)} \qquad [14]$$

for temperature T and time t. R is 0.25 for T< 43°C or 0.5 for T > 43°C. For example, 60 minutes of heating at 43°C is equivalent to 30 minutes at 44°C but 1 hour at 41°C has the same effect with 4 hours at 40°C.

Typical survival curves have shown that by heating mechanism alone, 60 minutes at 43°C can reduce the tumor cell number by a factor of 10. When tumors are macroscopic, however, we need to destroy 10^9 cells or more, which requires 10 hour at the same temperature. Higher temperatures and small tumor volumes, therefore, are the conditions needed for thermoablation for it to be realistic in the clinical setting [15].

This type of cancer treatment is termed thermotherapy and not unlike other therapies, may be used in combination with them or as an option at different times during cancer treatment. This simple concept is much more complicated in practice because heating devices available on the market (whether using radio frequency, microwaves, or ultrasonic sound) have limitations [16]. High frequency electromagnetic waves have poor depth penetration and low frequency waves are difficult to focus on target areas. Ultrasound is good in both, but strong absorption by bone and high reflection by air filtered cavities (lungs, for example) render it difficult to heat up targets of high perfusion area to the desired temperature due to continuous dissipation of heat. These techniques are also limited by how their target region is defined according to contrast-enhanced imaging [17]. When the region matches the tumor volume, it is good, but in most

cases it does not. As a consequence, some tumor cells are spared from the heat treatment and normal cells located near or within the target region are damaged. Temperatures above 42°C in healthy tissues can cause burns, blisters, and discomfort. This means increased side effects, which is undesirable. These aforementioned issues especially prevent the treatments of deep-seated tumors including brain and pelvic tumors. Another problem lies in achieving a homogeneous heat distribution in the treated tumor tissue, because insufficient temperature rise in parts of the tumor enables tumor regrowth. These reasons are why the benefits of thermotherapy have not been well-established in clinical routine.

The use of magnetizable particles to perform heat therapies was first proposed in the early 1960s. The innovative system of combining magnetic fields and power absorbing materials can be classified as follows:

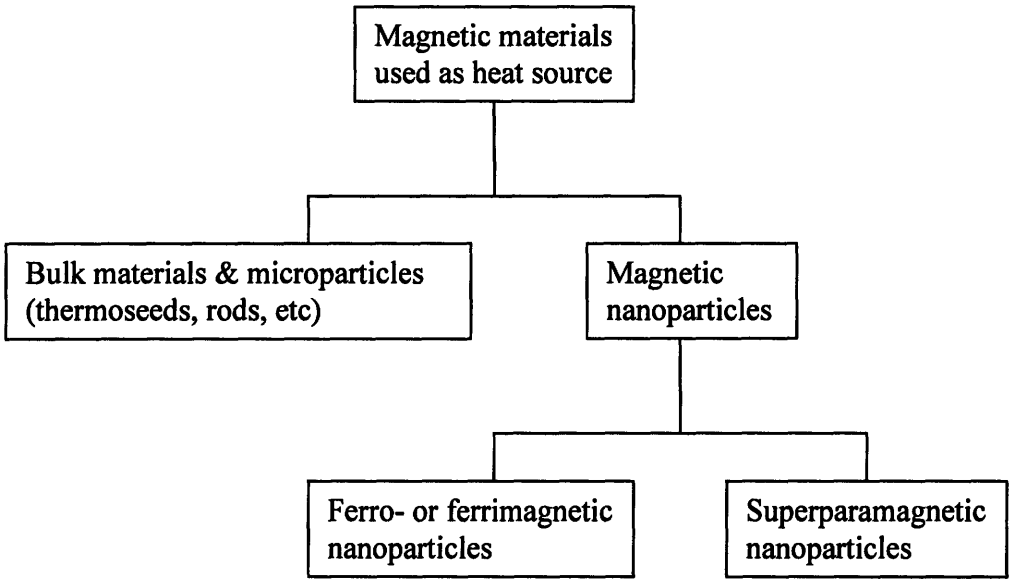


FIGURE 2
Classification of Magnetic Particles-based Hyperthermia
(adapted from Bahadur & Giri [16])

In this report we limit our discussion to only magnetic nanoparticles and more specifically, superparamagnetic nanoparticles.

3.2 Magnetic Nanoparticles

3.2.1 Physical Requirements

To serve the function of magnetic heat induction of particles localized in cancer [18], the particles must fulfill these requirements:

- Biocompatibility - particles must not have toxic or carcinogenic effects in the body.

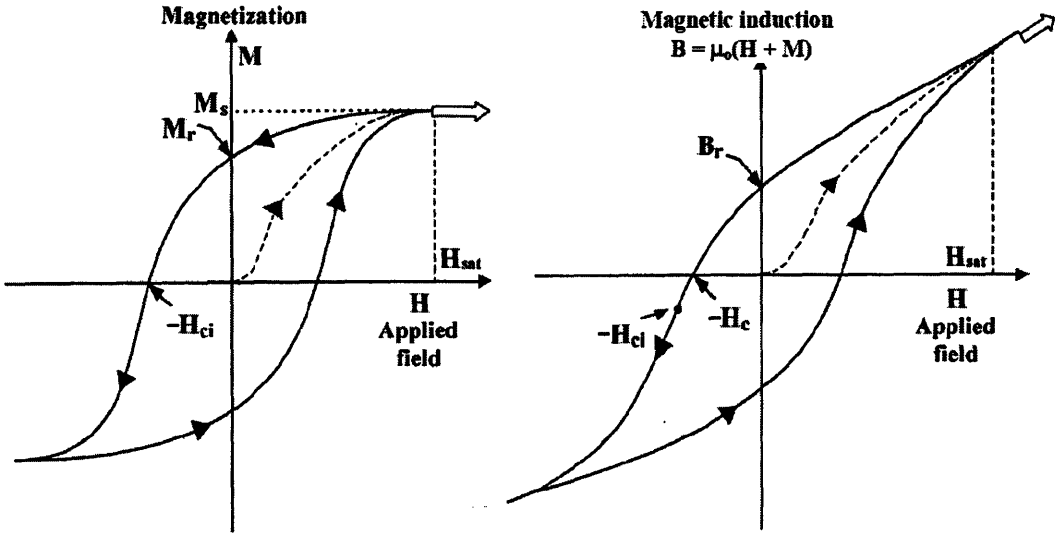
- Size – particles should be able to diffuse through intercellular space to achieve near-uniform distribution in a short amount of time.
- Colloidal stability – particles must be stable in solution. This also depends on size since particles must be small enough to avoid sedimentation due to gravity. They should also avoid segregation, which means their surface need to be engineered to give rise to steric or coulombic repulsions.
- Magnetic heat generation – particles must possess magnetic properties necessary to enable heat generation when alternating magnetic fields is applied
- Functionalization – particles need to be conjugated with chemical groups that allow preferential targeting to tumor cells in the case of intravascular injection that delivers the particles throughout the body

3.2.2 Magnetic Properties

Physically, materials exhibiting ferro- or ferrimagnetic properties can be used for heat generation in alternating magnetic field. Biocompatibility requirement, however, rules out good magnetic materials such as cobalt. To date, the perfect magnetic cores that satisfy those needs are composed of iron oxides, magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), mainly for their low toxicity and the advantage that our body is designed to process excess iron. Haemoglobin in our blood, for example, is an iron complex and is magnetic in nature. Ferro and ferrimagnetic particles display magnetism even in the absence of an applied magnetic field. They have permanent magnetic orientations or moments and by introducing a

stronger magnetic field than the internal field (coercive field), the internal field can be reoriented.

FIGURE 3
Hysteresis Curves: Magnetization (M) and Magnetic Induction (B) as Functions of Magnetic Field Strength (H)
(from Sung and Rudowicz [19])



For an initially unmagnetized sample (M=0 at H=0), M and B increases as H increases as shown by the dashed curves. This magnetization process is due to the motion and growth of the magnetic domains, areas with the same direction of the local magnetization. When the sample is fully magnetized with the direction of M along H, a saturation point is reached, and the magnetization curve will not retrace the original dashed curve when H is reduced because the domain wall displacements are irreversible. Instead, a degree of magnetization is retained as domains are still aligned in the original direction of applied magnetic field. In the

graphs, these values are shown as the remanent magnetization (M_r) and remanent induction (B_r), respectively. To reduce the magnetization M and magnetic induction B back to zero, a reverse field is required, known as coercive field or coercivity. To distinguish the notions of coercivity in the two graphs, we use the term intrinsic coercivity (H_{ci}) to denote the reverse field required to reduce M from M_r to zero and coercivity (H_c) to denote the reverse field required to reduce the magnetic induction to zero. In general, however, the values of B and M are much larger than H and hence if H is neglected in the equation for B, then $B \approx \mu_o M$ and H_c and H_{ci} can be considered equivalent. The coercivity values are determined by intrinsic magnetic properties (anisotropy and magnetization) as well as extrinsic (particles' size and shape). Size and shape dependence of internal or coercive field is well known. It is maximized when it reaches a critical low size (single domain particle) and is higher for acicular particles having large aspect ratios.

In cancer thermotherapy, the applied alternating magnetic field can provide the energy necessary to repeatedly reorient particles' magnetic moments. The energy loss associated to this periodic reversal, the hysteresis loss, when dissipated, is converted to thermal energy. Hysteresis loss per cycle is represented by the area inside the B-H loop.

In addition to causing changes in the magnetic moments, energy from the AC field can also cause the particles to physically rotate if they are in an environment

of sufficiently low viscosity. This is termed Brownian relaxation and the rotational motion causes Brownian losses. Brownian relaxation time for ferrofluids is related to the hydrodynamic particle volume V_h and viscosity η according to:

$$\tau_{\text{Brown}} \cong \frac{3\eta V_h}{k_B T} \qquad [20]$$

Inductive heating via eddy currents can be neglected here since the magnetic oxides have low electrical conductivity. Hyperthermia cancer treatment uses the heat generated by this conversion to raise the temperature of tissues.

For very small magnetic particles, heating in alternating magnetic fields occurs through slightly different mechanisms because particles change their magnetic properties when entering the size regime below approximately 20 nm [21]. These particles display superparamagnetism, a behavior similar to paramagnetism, except it occurs at temperatures below the Curie (for ferromagnets) or Néel (for ferrimagnets) temperature. All ferro- and ferrimagnets above their corresponding threshold temperatures turn to paramagnets because the thermal energy is sufficiently high to overcome the energy of the magnetic moments, causing random fluctuations and eliminating magnetic order. On the other hand, superparamagnetism is observed in particles that are so small they consist of only one magnetic domain and because energy barrier that must be overcome before a subdomain particle can reverse its magnetism (anisotropy energy barrier)

decreases linearly with volume, the thermal energy at moderate temperatures is sufficient to change their magnetization direction. In the absence of external magnetic field, they do not display magnetism while under alternating field, the magnetic moments fluctuate with the field and average to zero.

The size-dependent behavior of coercivity can also be the indication of superparamagnetism. As particle size decreases, coercivity increases to reach a maximum at a threshold particle size (typical values are 15 and 35 nm for Fe and Co metallic particles, respectively, while for $SmCo_5$ it is as large as 750 nm [22]) which characteristically describes the transformation from multi domain to single domain nature. In magnetic bulk materials, there exists a multidomain structure constituted by regions of uniform magnetization separated by domain walls that minimizes the sum of energy of external magnetic field (magnetostatic energy) and energy of the domain walls. As the volume of magnetic system decreases, the size of the domains and the width of the walls are reduced until the energy cost to produce a domain wall is greater than the corresponding reduction in magnetostatic energy. Consequently, the system no longer divides itself into smaller domains, maintaining the magnetic structure of a single domain instead. In a single domain particle, it is not possible for magnetization reversal to take place by means of the boundary displacement process, which requires relatively weaker fields. Instead the magnetization of the particle must rotate as a whole, a process that requires a large field, depending on the anisotropy energy of the

material. A further decrease of particle size, then, will cause the coercivity value to decrease rapidly to zero, marking the transition to superparamagnetic state.

Below the critical size, the corresponding rapid decrease in remanent magnetization due to this relaxation effect (Néel relaxation) can be expressed by the equation:

$$M_r = M_i e^{-t/\tau} \qquad [16]$$

where τ is magnetic relaxation time, M_i is remanence of particles not affected by relaxation. This phenomenon results in vanishing of hysteresis losses. Instead, power losses are only due to relaxational losses (both Brownian and Néel).

For Néel relaxation, magnetic relaxation time is determined by the ratio of anisotropy energy KV (K is magnetic anisotropy energy density, V is volume of magnetic particle core) to thermal energy kT (k is Boltzmann's constant and T is absolute temperature) and is expressed as:

$$\tau = f_o \exp[KV/kT] \qquad [16]$$

where f_o (frequency factor) ~ 10^9 s^{-1}.

Néel relaxation is actually very similar to Brownian. The two mechanisms are different in two aspects. Néel relaxation is due to reorientation of the magnetic moment inside a particle while Brownian relaxation is due to reorientation of

magnetic particle itself in the fluid. And while Néel relaxation time is controlled by the anisotropy barrier, Brownian's is determined by viscous friction.

For the identification of the contribution of Brownian and Néel losses in a ferrofluid, a method using the sol-gel transition can be applied where the ferrofluid is dispersed in an aqueous solution of gelatine (sol). When temperature is decreased, sol-gel transition is induced and this change is accompanied by an increase of the viscosity by many orders of magnitude. Essentially we do this to freeze the Brownian motion of the particles.

In a comparative study, Hiergeist et. al. observed the heating of superparamagnetic and ferromagnetic magnetite fluids and obtained these results:

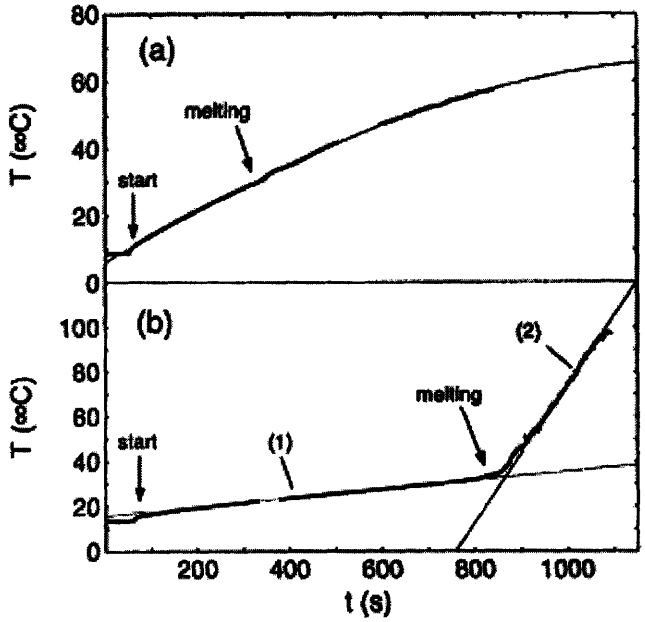


FIGURE 4
Temperature Increase due to Heating of (a) Superparamagnetic Iron Oxides and (b) Ferromagnetic Iron Oxides in Commercial Gel (with a melting point of above 30° C to model the heating of tissues) with Field Amplitude of 6.5 kA/m at 410 Hz
(from Hiergeist, et. al. [23])

In Figure 4, superparamagnetic particles were found to behave similarly in liquid sol and solid gel save a little wobbling in the curve while ferromagnetic particles showed a considerable loss power in liquid sol compared to solid gel. This means Brownian losses have negligible influence in the case of small particles. The transition appears for a characteristic value d_t of the particle core size where $\tau_N = \tau_B = \tau_t$ [k]. Assuming a relation $d_H = 3d_C$ between core diameter d_C and hydrodynamic diameter d_H, one gets d_t = 23 nm [20].

Additionally, these additional power losses are smaller when observed in high frequencies, implying that Brownian relaxation has more effect in low frequency because it has longer relaxation time. From figure 5, it was concluded that the specific loss power associated with superparamagnetic particles follows a H^2-law while for ferromagnetic particles, it is proportional to H^3.

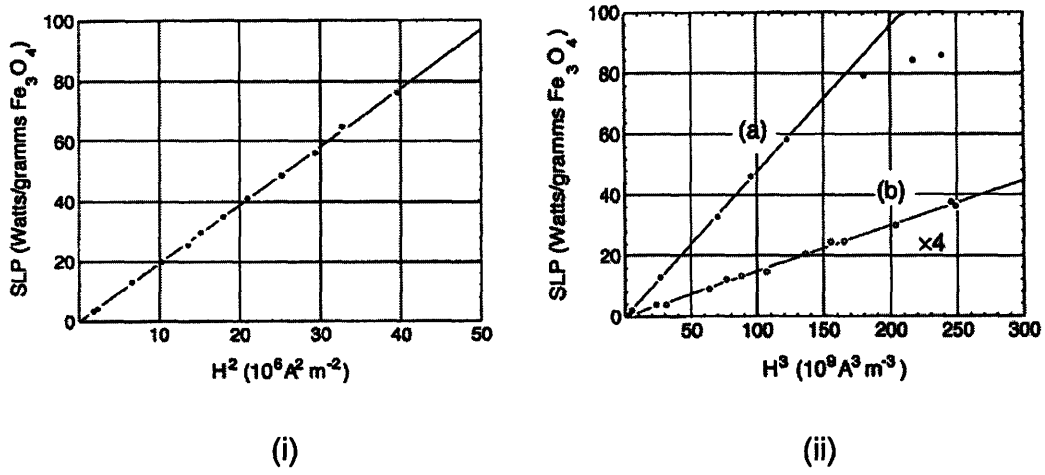


FIGURE 5
Specific Loss Power (SLP) for (i) Superparamagnetic Iron Oxides in Water and (ii) Ferromagnetic Iron Oxides (a) in Water and (b) Fixed in Solid Gel (SLP data of curve (b) is multiplied by a factor of 4)
(from Hiergeist et. al. [23])

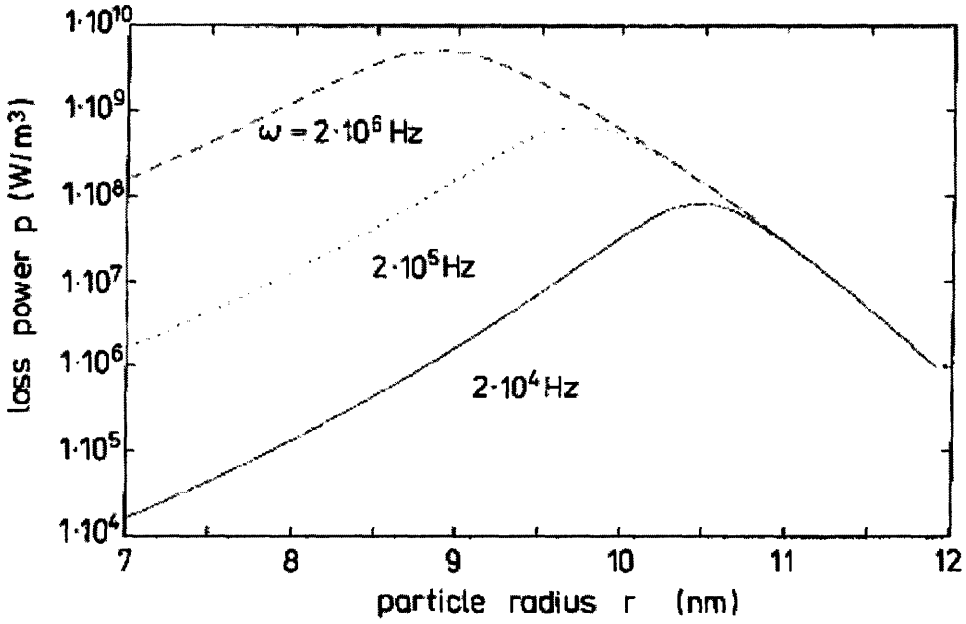
The results showed that superparamagnetic systems perform better than ferromagnetic systems, with higher SLP at a given field within tolerable range for this application. It should also be noted that Brownian losses must take place with hysteresis losses in order for ferromagnetic fluids to absorb the same power as superparamagnetic fluids undergoing only Néel relaxation. In body tissues or

within tumor cells, particle rotation might be limited or inhibited (nanoparticles may be immobilized on cell membranes [24]), and this is why subdomain particles are believed to result in more specific heating power at tolerable AC magnetic fields than is obtained by multidomain particles.

Another advantage to be derived from this phenomenon is that unlike ferro- and ferrimagnetic particles, superparamagnetic particles do not aggregate after exposure to external magnetic field [25]. As aggregation can hinder the body's efforts to remove the magnetic particles, superparamagnetic particles are more ideal candidates for biomedical applications.

Néel relaxation shows an extremely strong size dependence. The figure below clearly shows that there is a maximum loss power at a particular particle size.

FIGURE 6
Particle Size Dependence of Loss Power Density due to Néel Relaxation at Different Frequencies
(from Hergt et. al. [26])



The finding also implies that since for a given excitation frequency an ideal core size exists which yields maximum loss power, magnetic fluids with sharp core size distribution are preferable in order to minimize the therapeutic metal oxide mass required for a given target volume.

Losses are also frequency-dependent. For instance, for hysteresis losses, power increases linearly with frequency because one only has to multiply number of cycle per second (frequency) to loss per cycle (area in hysteresis loop). In the case of relaxational losses in superparamagnetic fluids, we can predict SLPs for different frequencies and amplitudes by employing the empirical equation:

$$\text{SAR (Specific Absorption Rate)} = \kappa H_0^2 f \quad [27]$$

where κ is a material constant for a given H_0 f combination. SAR is just another way to call SLP and is expressed in power/mass units. It may also be determined by the rate of temperature rise, which is how it is measured in most experiments:

$$\text{SAR} = c\mathrm{d}T/\mathrm{d}t \quad [16]$$

where c is the specific heat capacity and $\mathrm{d}T/\mathrm{d}t$ is temperature increase per time.

This is especially important because for clinical use, heating efficiency of particle systems cannot be raised simply by increasing magnetic field amplitude H and field frequency as eddy currents induced in healthy tissues may grow prohibitively high. Brezovich [28] found experimentally that there is an upper limit of the product $H \cdot f < C$ for hyperthermia because according to induction law the heating power is proportional to the square of $(H \cdot f \cdot D)$ where D is the induced current loop diameter. For a loop diameter of about 30 cm, test persons are able to withstand the treatment for more than one hour without major discomfort if $C = 4.85 \times 10^8\ \mathrm{A\,m^{-1}\,s^{-1}}$. For a smaller diameter of exposed body region and depending on the seriousness of the illness this critical product may be exceeded [29]. For breast tumor treatment, for example, the suitable limit is 4 x 10^9 A/ms, where a field amplitude of 10 kA/m would allow a maximum frequency of 400 kHz [30]. Further increase of the frequency combined with a reduction of field amplitude is not useful since SLP increases only linearly with f compared to its square dependence on H. On the other hand, a reduction of

frequency in favor of a higher amplitude would bring an increase in SLP only up to about 11 kA/m, above which SLP may be expected to have a weaker dependence on H.

SLP for superparamagnetic particles can be theoretically calculated by employing these equations:

$$\mathrm{SLP}(f, H) = \mu_0 \pi \chi''(f) H^2 f / \rho$$

$$\chi''(f) = \chi_0 \phi / (1 + \phi^2)$$

$$\phi = f \tau_R$$

$$\chi_0 = \mu_0 M_S^2 V / (kT) \qquad [29]$$

where ρ is mass density of the magnetic material, $\chi''(f)$ is imaginary susceptibility, M_S is saturation magnetization, and τ_R is relaxation time (Neel). Therefore, if we introduce the condition $f(H) = C/H$ into the dependence $\mathrm{SLP}(f, H)$, we can get:

$$\mathrm{SLP}_{max} = \mu_0 \pi C^2 \chi_0 \tau_R / \rho \qquad [29]$$

This further proves the SLP dependence on particle size since in superparamagnetic regime, SLP increases with increasing relaxation time (i.e. with increasing particle size) until the validity of the relaxation theory ceases near the superparamagnetic transition and hysteresis losses begin to arise.

SLP values for common ferrofluids to date are in the order of 100's W/g iron oxide. For thermotherapy, there is a necessity for further enhancing SLP because higher SLP allows for reduction of the ferrofluid dose in tumors.

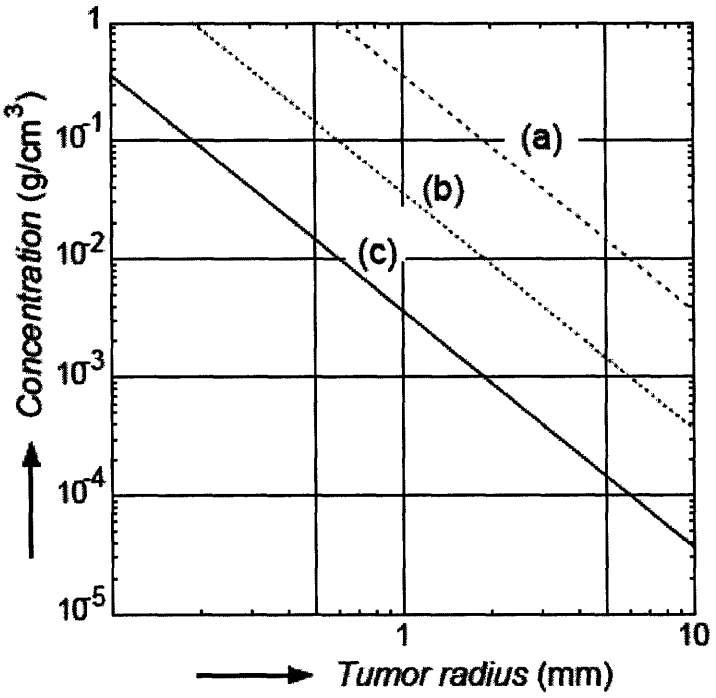
Systematic in vitro studies conducted in 1993 [31] and 1996 [32] consistently showed that the heating obtained with AC magnetic field excited nanoparticles is equal to the best homogeneous heating, i.e. water bath heating. A large number of single particles each acting in principle as a hot source surprisingly yield a temperature homogeneity comparable to water containing much more excited molecules than particles existing in a magnetic fluid. According to these encouraging results, a homogeneous temperature distribution in vivo is expected too, if the fluid could be administered homogeneously throughout the target region.

For this purpose one can model the heat conductivity problem for a ferrofluid enriched spherical tumor using the bio-heat equation [24] which neglects heat convection in comparison with conduction as proven experimentally [33]. In steady state, the following relation between the increase in temperature ΔT, concentration of c (particle mass per tissue volume), SLP, and the tumor radius R holds:

$$\Delta T = \mathrm{SLP} \cdot c \cdot R^2/(3\lambda) \qquad [29]$$

($\lambda = 0.64\,\mathrm{WK^{-1}\,m^{-1}}$ is the heat conductivity of tissue)

FIGURE 7
Ferrofluid Concentration Needed for Temperature Enhancement of 10 K in Dependence on Tumor Radius for Specific Loss Power of (a) 50, (b) 500, and (c) 5000 W/g
(from Hergt et. al. [20])



Considering that a tissue concentration of more than 0.1 g/cm^3 ferrofluid is hardly achievable, ferrofluids with a SLP of 50 W/g are only suitable for application of tumors not smaller than about 4 mm in diameter. In the case of present ferrofluids, this critical size is reduced to about 1 mm. For treatments of larger tissue regions, say with 20 mm diameter, only 10^{-3} g/cm^3 present ferrofluid concentration of the tissue is needed. A lower tissue concentration offers the possibility of ferrofluid application being more subtle and less invasive than intratumoral injection, for example using targeted blood transport.

3.2.3 Biocompatible Coating

There are generally two routes to administer magnetic particles to a particular site in the body. Particles may be injected intravenously to let the blood circulation transport them to the region of interest for treatment. Alternatively, particles suspension would be injected directly into the area where treatment was desired. Either one of these requires that the particles do not aggregate and block their own spread. Pure iron oxide particles have a high tendency to agglomerate and build larger structures even in the absence of magnetic field. Therefore to prepare these particles for biomedical applications, these particles are coated with a protecting shell that prevents agglomeration and is also responsible for the interaction of the particles with its surrounding, like provides binding sites to biomolecules or surfaces.

The use of nanoparticles instead of larger multidomain particles, as mentioned before, in addition to enabling fast homogeneous diffusion to the tissue spaces, partly removes concern for colloid stability after the magnetic field is removed. They do not retain magnetism and as such would not spontaneously aggregate due to magnetic interaction. However, their hydrophobic surfaces with a large surface area to volume ratio could cause them to form clusters, increasing particle size and exhibiting strong magnetic dipole-dipole attractions between them (ferromagnetic behavior) [34]. Once this happens, each particle is influenced by the magnetic field of their neighbors and can get further magnetized. The adherence of remanent magnetic particles then causes mutual

magnetization, resulting in worse aggregation [35]. Surface modification is therefore indispensable in the preparation and storage of nanoparticles in colloidal form, even for in-vitro uses.

Additionally, there are diverse biological events that need to be considered. Particles entering the bloodstream are rapidly coated by components of the circulation such as plasma proteins in a process known as opsonization. This is a critical process in determining what will happen to the particles next [36]. Normally opsonization renders the particles recognizable by the body's major defense system, the reticulo-endothelial system (RES). The RES is a diffuse system of specialized phagocytic cells (can engulf inert materials) associated with the connective tissue framework of the liver, spleen, and lymph nodes. They play a role of removing opsonized particles. As a result, surface modification for in vivo application needs to ensure particles are not only non-toxic and biocompatible, but also stable to the RES.

Numerous investigations have been aimed at reducing RES uptake to increase the concentration of the particles at the desired targets, the most promising is by reducing the particle size and sterically stabilizing the nanoparticles by coating the surface with nonionic surfactants or polymeric macromolecules [37]. This can be performed by physical adsorption, incorporation during the production of nanoparticles, or by covalent attachment to any reactive surface groups. The mechanism of stabilization involves an elastic as well as osmotic contribution.

The elastic contribution comes from loss of conformational entropy when two surfaces approach each other, caused by reduction in the available volume of each polymer. A positive heat of interfacial mixing may also be present. The loss of entropy and/or the increase in enthalpy translate to an increase in the free energy of mixing that causes particle separation to be favorable. The osmotic contribution arises from the increase in polymer concentration on compressing two surfaces, necessitating an influx of water into the region that forces particles apart. A similar thing happens when a protein molecule approaches the particle surface in both cases [38].

Past research came to the conclusion that particles with highly hydrophobic surface are efficiently coated with plasma components and thus rapidly removed from circulation whereas particles that are more hydrophilic can resist the coating process and therefore are cleared more slowly. The shell should also be thick enough and firmly anchored so as not to degrade with time in the fluid. Moreover, it should completely cover the particles and be as dense as possible in order to protect the iron oxide core against contact with blood protein and phagocytosis-associated receptors. Longer polymer chains were proven to be more effective, even at lower surface density, in suppressing opsonization. Presumably this is due to the steric hindrance effect generated by the surface-grafted polymer molecules providing a sort of shielding [39].

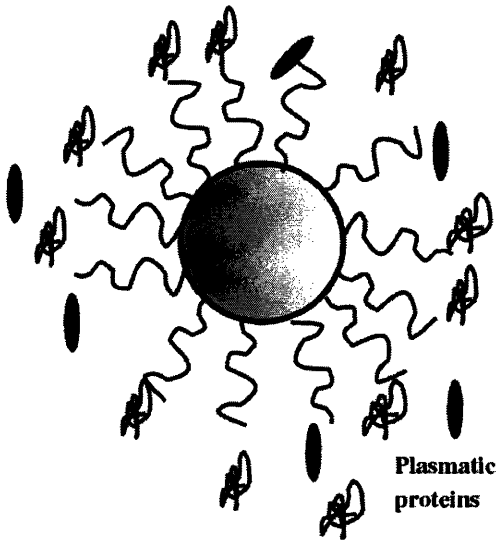


FIGURE 8
Schematic Representation Showing Steric Repulsion of Plasma Proteins When Nanoparticles are Decorated with Hydrophilic and Flexible Polymers
(from Couvreur et. al. [39])

Ensuring sufficiently long residence time of magnetic nanoparticles in the blood stream is particularly important for intravenous administration. While it is true that tumor blood vessels have several abnormalities compared to normal physiological vessels that result in enhanced permeability of the tumor vasculature, allowing diffusion of nanoparticles into the tumoral tissue, it is crucial that the particles stay long enough in circulation to reach said region.

Most common shell materials are biopolymers or synthetic organic polymers [40] such as described in the table below.

TABLE 2
Some Useful Polymers for Nanoparticles Coating for Biomedical Applications
(from Gupta [41])

Polymers	Biomedical use
Polyethylene glycol (PEG)	Improves biocompatibility, blood circulation time, and internalization efficiency
Dextran	Enhances circulation time, stabilizes colloidal solution
Polyvinylpyrrolidone (PVP)	Enhances circulation time, stabilizes colloidal solution
Fatty acids	Colloidal stability, functional carboxyl groups
Polyvinyl alcohol (PVA)	Prevents coagulation for monodisperse particles
Polyacrylic acid	Increases stability and biocompatibility, helps in bioadhesion
Polypeptides	Good for cell biology, eg. cell targeting
Poly (D,L-lactide)	Biocompatible, low toxicity
Poly (N-isopropylacryl-amide) (PolyNIPAAM)	Thermosensitive drug delivery and cell separation
Chitosan	Natural hydrophilic & cationic linear polymer widely used as non-viral gene delivery system, biocompatible
Gelatin	Natural polymer used as gelling agent, hydrophilic emulsifier, biocompatible

Of all these, dextran is dominant in studies on hyperthermia application as it has proven to be long circulating with no measurable reported toxicity index. Dextran is a polymer $(C_6H_{10}O_5)_n$ of anhydroglucose having mainly alpha-D(1-6) linkages with some unusual 1,3 glucosidic linkages at branching points. In aqueous solutions, dextran interacts with metals and covers its surface yielding aggregates between 20 and 150 nm in hydrodynamic diameters. Dextran-coated particles have negative surface charge in the pH range between 4 and 10 and therefore will

be stable at the physiological pH (about 7), one of the minimum prerequisites for their in vivo use [42].

Another function served by the coating layer of nanoparticles is to enable binding of various biological molecules such as antibodies, proteins, targeting ligands, etc. via amide or ester bonds. These molecules are what make the nanoparticles target specific and may further improve their cellular uptake. Transferrin-coupled dextran-coated nanoparticles, for example, were captured by cells two or four times higher compared to dextran-coated only. Some applications of this derivation are presented here.

TABLE 3
Selected Proteins / Ligands for Nanoparticles Functionalization for Biomedical Applications
(from Gupta [41])

Protein/Ligand	**Functional activity**
Transferrin	Active targeting ligand of anticancer agents, proteins, & genes to primary proliferating cells via transferrin receptors
Lactoferrin	Structurally similar to transferrin, anti-infective, a modulator of inflammatory response, iron absorption, an immuno-regulatory protein
Pullulan	High water solubility, no toxicity, non-immunogenic, non-antigenic, for receptor-mediated hepatic uptake in rats
Tat-peptide	Membrane-permeating peptide, enhances intracellular delivery
Folic acid	Preferentially target cancer cells, poorly immunogenic, folate receptor facilitates internalization of particles
Ceruloplasmin	Principal carrier of copper in plasma, plays important role in

	iron homeostasis, effective anti-oxidant, binds to fibroblasts

These, and many more types of targeting agents are also widely used for cellular labeling or separation. Furthermore, they can be coupled with viruses (20-450 nm), proteins (5-50 nm), and genes (10-100 nm long) [32], an interesting area of research for future gene therapy.

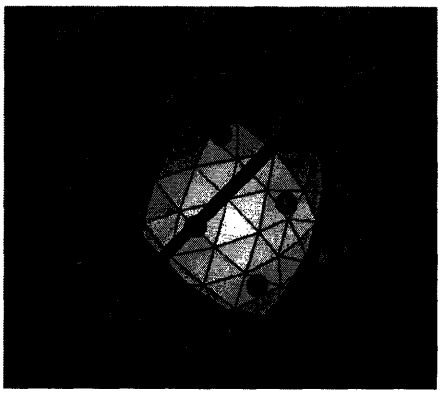


FIGURE 9
Schematic of a Nanoparticle, Coated and Functionalized
(from MagForce [43])

In summary, the coating of magnetic nanoparticles for thermotherapy have these tasks to fulfill:

- stabilizing nanoparticles of 20 nm or less in size in a biological suspension of pH around 7.4
- improving monodispersity
- avoiding immediate uptake by the RES
- providing functional groups at the surface for further derivation, when necessary

and effectively-coated superparamagnetic nanoparticles have the following interesting features:

- are able to absorb energy from highly alternating magnetic field to generate heat due to their magnetic behavior
- have a great number of binding sites for cancer cells due to their enormous surface
- are able to infiltrate deeply into tumor tissues due to their size, and
- with the suitable coating:
  - form a homogeneous, finely dispersed fluid of low viscosity and neutral pH suitable for biological application
  - are detected late by the immune system so they can reach their target
  - can be absorbed by tumor cells in great quantities to optimize dose

3.2.4 Biophysical Limitations

This technology works because just like what happens in an MRI or a CAT-scan, the human body is "transparent" to magnetic field while particle-loaded tumors are excessively and high-selectively heated on the cellular level, or so it is claimed. The cornerstone of this method is using the nanoparticles to reach the necessary contrast level in the treatment.

As discussed in earlier section, presently the magnetic nanoparticles having SLPs in the order of 100 W/g is only capable of achieving temperature increase of 10 K in tumors no smaller than a few millimeters in radius. Application of particles

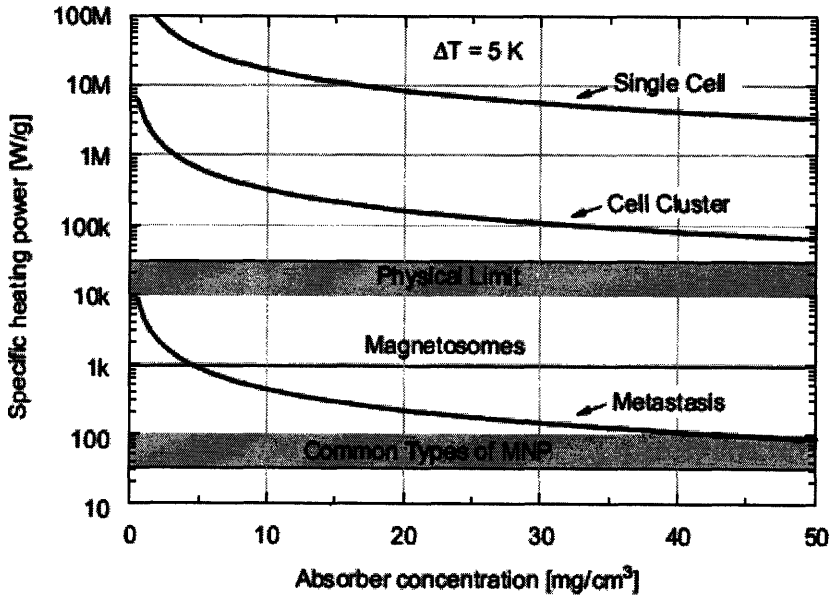
with low SLPs needs to be compensated by larger particle covered volume to reach therapy temperatures, which in turn results in large necrosis volume with known medical complications related to it. This can be improved by either considerably increasing SLP or delivering adequate supply of magnetic nanoparticles to the tumor. SLP can be increased by optimizing the nanoparticles in terms of size, shape, size distribution, and reduced clustering. Roughly enhancement of half an order of magnitude from present data for magnetic iron oxides may be expected from this route. Further potential is doubtless present if instead of iron oxides other magnetic particles are taken into consideration too. In relaxation theory, the maximum SLP is proportional to susceptibility, the main parameter of which is saturation magnetization of the particles. Co has higher saturation magnetization than Fe, for example, and Co nanoparticles were investigated recently and measured up to 770 W/g [44]. One of the highest saturation magnetization of 2 MA/m (five times higher than maghemite) is shown by Fe_2Co, nanoparticles of which are under development now [45]. Of course biocompatibility issues associated with these nanoparticles will also have to be resolved.

The well known problem of homogeneous injection, the way of injecting homogeneously high particle concentration suspension into the tumor without it spreading out to nearby tissues under external pressure, on the other hand, people have tried to solve by very slow infusion or multiple site injection. But still, injected liquid of very high concentration will tend to spread along the weak

links of the tissue. To avoid insufficient heating of some tumor parts, one has to increase the particle concentration to an amount that might result in very hot temperature spots. In this way, conventional intratumoral injection makes the differentiation between hyperthermia and thermoablation hard to achieve. While relatively large tumors may be addressed efficiently, surgery may as well do the trick. The answer to another unsolved problem of cancer, the proliferation of cancer cells with formation of small, yet undetectable metastases, in the meantime is still questionable. Antibody targeting that allows one to successfully attack these small cancerous objects is an idea optimistically reported in media, but up to now, no data regarding targeting efficiency in vivo are available despite many papers detailing in vitro experiments.

For the following illustration, let's assume that tumor-specific targeting is achievable. The demand for SLP is presented below, with dependence on particle concentration for targets of different sizes: a metastasis of 3 mm in diameter, a cell cluster of 0.1 mm diameter, and a single tumor cell (10 μm diameter) [35]. A metastasis is an important stage when a tumor starts to build its own supply system by angiogenesis, the limit of tumor diagnostics at present.

FIGURE 10
Specific Heating Power Needed for Hyperthermia in Dependence on Particle Concentration Achieved in Tumor Tissue for a Metastasis (3 mm diameter), a Cell Cluster (0.1 mm), and a Single Cell (15 μm)
(from Hergt [29])



Though chances exist to treat metastases, the treatment of single tumor cells by thermotherapy is physically impossible. An unrealistic amount of power would be needed to heat a single cell in human body, a concept mentioned as intracellular hyperthermia in literature.

3.2.5 Synthesis of Biocompatible Iron Oxide Nanoparticles

Synthesis methods for nanoparticles focus on generating particles of uniform size and shape. For the application we are interested in, it is generally desired to synthesize iron oxide nanoparticles smaller than 20 nm in diameter and having a narrow size distribution.

The most common approach is solution chemistry. Generally, the wet chemical routes are considered simpler, more tractable, and more efficient with appreciable control over size and composition of the nanoparticles when compared to physical methods such as gas phase deposition or electron beam lithography. Homogeneous precipitation can be used to prepare nanoparticles from solutions, with the reaction occurring in two stages: particle nucleation and growth. In an ideal case, a single group of particles form when the solution exceeds the critical saturation point. The particles then grow as solutes adhere to their surfaces. To get monodisperse nanoparticles, these two stages should be separated, i.e. nucleation should be avoided during the period of growth [46].

Spherical iron oxides (magnetite or maghemite) can also be synthesized through the co-precipitation of Fe^{2+} and Fe^{3+} aqueous salt solutions by adding a base. The control of size, shape, and composition depends on the type of salts used (chlorides, sulphates, nitrates, etc.), Fe^{2+} and Fe^{3+} ratio, temperature, reaction time, pH, and ionic strength (electrolyte concentration) of the media. We can obtain nanoparticles with diameter ranging from 2-30 nm, with smaller particles sizes resulting from coprecipitation in dilute solutions, lower temperatures, and shorter reaction time [47].

The reaction for a conventional preparation of magnetite may be written as follows:

$$Fe^{2+} + Fe^{3+} + OH^- \rightarrow Fe_3O_4 + H_2O \qquad [41]$$

The law of thermodynamics expects a complete precipitation of magnetite between pH 9 and 14 if the molar ratio of Fe^{3+}: Fe^{2+} is 2:1. The reaction should be done under a non-oxidizing environment or the resulting Fe_3O_4 will be oxidized and give $Fe(OH)_3$. To prevent from possible oxidation and from agglomeration, during the precipitation process the nanoparticles are usually coated with organic or inorganic molecules. To do this, the synthesis can simply be performed in an organic solvent. Dextran coating, for example, can simply be done by shaking the aqueous suspension of the magnetic nanoparticles containing 1% dextran for a few hours [20]. Modifications of this method that allow for synthesis in the presence of dextran or other substances that render the magnetic nanoparticles biocompatible make this method especially appropriate for our application.

To further improve the monodispersity of iron oxide nanoparticles synthesized by chemical means, many researchers used the help of ultrasonic radiation [48,49]. Zhang et. al. [49] found that ultrasonic irradiation could greatly enhance the crystallization rate of iron oxide nucleus. Nanoparticles with size of 9.6 ± 0.2 nm were successfully prepared at relatively low temperature of 190°C (The reported temperature for crystallization of iron oxide particles is about 220°C -250°C). Another proposed method was to use magnetic fractionation to separate post-synthesis nanoparticles based on their magnetic properties, giving rise to magnetic fractions that have distinctly better magnetic properties than the original magnetic fluid [50].

Other more complicated, therefore less-established techniques to produce biocompatible iron oxide nanoparticles include the use of various surfactants for synthesis by microemulsions, the glass crystallization method [51], hydrothermal synthesis [52,53], and thermal decomposition [54].

3.3 MagForce Nanotechnologies

Most techniques established so far concerning the use of magnetic nanoparticles for thermotherapy are basically based on direct instillation of magnetic fluids containing the nanoparticles into the tumor tissue followed by exposure to an externally applied alternating magnetic field. The first animal trial was reported in 1997 [55] where a group of researcher studied thermotherapy on mice. Other animal trials followed, all with encouraging results (suppressed tumor growth and killing of the tumor cells) observed in most of the animals [56-62]. Hyperthermia and thermoablative intratumoral temperatures were achieved.

MagForce Nanotechnologies in Berlin, Germany is the only start-up company currently on the path of commercializing the nanoparticles-based thermotherapy technology. They are well in clinical trials for treatments of brain, prostate, esophagus, ovarian, and cervical cancer and expecting to obtain European approval before releasing their products over the next year. MagForce has 10 international patent families (Europe, USA, China, Japan, Australia) with another 2 new applications filed in 2006 protecting the invention of their

nanoparticles and their magnetic field applicator system, MFH300F. Some of these are: DE 102005039579; DE 102005016873; WO 2006108405; WO 2007019845. They develop their own magnetic nanoparticles and treatment planning software and collaborate with Siemens for the production of the magnetic field applicator.

Clinical trials began in 2003 to investigate the feasibility of the approach on different tumor entities. Developed by MagForce over the last 15 years, the magnetic fluid used was MFL 082 AS, consisting of proprietary aminosilan-coated iron oxide cores 15 nm in diameter in aqueous solution with the iron concentration of 2 mol/l (112 mg/ml). For this magnetic fluid, power density of 50 W/kg is achieved if 1 ml of it is distributed in 10 ml of tumor tissue (in a 100 kHz magnetic field of 5 kA/m field strength, continuous wave, peak value). This relation enables an estimation of the SAR for any volume v (ml) of such magnetic fluid homogeneously distributed in the target volume V (ml) in a magnetic field H (kA/m) of a frequency f (kHz):

$$\text{SAR (W/kg)} = 10\,(v/V)\,(H/5)^2\,(f/100)^2\,50\ \text{W/kg} \qquad [63]$$

An alternating magnetic field of 100 kHz and a variable field strength of 0-18 kA/m were established with a magnetic field applicator also developed by MagForce, MFH 300F [64]. Before starting thermotherapy, all patients' treatments were planned by specially-designed software (MagForce NanoPlan) that allows calculation of the expected heat distribution within the treatment area

in relation to the magnetic field strength. The distribution of the nanoparticles in the target volume after instillation can be quantitatively determined via computed tomography (CT) by the relationship between nanoparticle amount (iron mass) and CT density (Hounsfield unit HU) elevation above the HU of tissue of interest. From the magnetic field strength applied during treatment, the amount of nanoparticles in the specific region calculated from the density distribution in the CT, and the perfusion level in the body area, temperatures can be measured and temperature distribution mapped by finite element method. The data showed good agreement with the temperatures obtained by calculation using the bioheat equation.

The first clinical trial conducted by MagForce was performed from March 2003 to June 2004 with 14 glioblastoma multiforme patients. This type of brain cancer has an incidence of approximately 5 in 100,000 per year and represents approximately 40% of primary brain tumors in adults. They are clinically problematic due to their treatment resistance and invasive nature into the surrounding brain tissue which makes complete resection almost impossible. Median overall survival after first-line therapy does not exceed 12-15 months and no significant increase has been achieved over the last decade with modern treatments [65].

Presented below is the illustration of a thermotherapy treatment employed to a patient with a glioblastoma (a type of malignant brain tumor). At the beginning

of the procedure, the magnetic fluid containing the nanoparticles with pre-calculated dosage is injected into the tumor. The nanoparticles will diffuse in the tumor, achieving homogenous composition in a relatively short time. The patient then enters the therapy device, in which an alternating magnetic field is produced which is of no danger to humans. The particles will start to generate heat which can be precisely regulated and monitored from the outside with millimeter precision.

FIGURE 11
MagForce Nano Cancer Therapy
(from MagForce [43])

Of 14 patients enrolled in the study, 2 suffered from non-resectable primary tumors and 12 from recurrences. All received a combination of thermotherapy

and radiotherapy (2 heat treatments for each week of irradiation). Instillation of the nanoparticles was tolerated without any complication or side effect. After the treatments, one patient is still in remission and others displayed the median survival of 14.5 months, a good improvement over the prognosis of 2.7-11.5 months [66]. The efficacy of thermotherapy is currently being further evaluated in a phase II study on 65 patients suffering from recurrences of glioblastoma multiforme.

Another phase I trial started in February 2004 with 22 patients suffering from non-resectable and pre-treated local relapses of different tumors (rectum, ovarian, prostate, cervix, soft tissue sarcoma). Again, patients received thermotherapy in combination with radio- or chemotherapy. Nanofluid concentration in the target area was claimed to be as high as possible. Different H-fields were used, taking account of the limitations posed by the anatomical regions and hot spots arising from skin folds where current path narrows and current density therefore increases.

While the SAR of the area covered by the nanoparticles achieved the median of 130 W/kg, the median SAR for the whole target area was lower (51 W/kg), indicating heterogeneity and incomplete coverage [63]. Because increasing the magnetic field tolerance would improve heat coverage considerably (note the quadratic dependency of SAR on H), different technical design of the magnetic field applicator was suggested to maximize H in the target area, such as a chair-

like design for prostrate or a dome-shaped one for the head. Another result obtained from the study is that due to the stability of the nanoparticle deposits in the tumor, treatments can be repeated over weeks without additional injection of the magnetic fluid. Only a 10% decrease of nanoparticle mass in 100 days was shown, corresponding to only 3% loss of heating power in a month if other parameters remain constant. Efficacy will be evaluated in time and with phase II studies.

Another study was performed on patients with locally recurrent, radioresistant prostate cancer. Only 5 kA/m magnetic field strength was used since discomfort in the perineum and groin was experienced beyond that. This was because the pelvis area has a large cross sectional volume. Preliminary clinical results suggested that thermoablation might be suitable since prostate intratumoral temperatures could reach above 44°C at low magnetic field strengths [67].

Because of the use of alternating magnetic field, before all heat treatments, metallic implants near the treated area have to be removed unless they are sufficiently small (a millimeter in length and less than that in diameter) and thus have negligible power absorption.

3.4 Comparison with Conventional Therapies

TABLE 4
Surgery, Radiation, Drugs and Thermotherapy in Comparison

	Surgery	Radiation	Drugs	Thermotherapy
Patient's exposure	high	high	high	low
Selective targeting	medium	medium	low	high
Repeatability	low	low	low	high
Side-effects	medium	high	high	low

The qualitative comparison table shows that if executed correctly and effectively as a monotherapy, thermotherapy is superior to surgery, chemotherapy, and radiotherapy. The selective targeting capability can dramatically reduce side effects. It can be easily repeated because once injected, the particles remain in place for an extended period of time (a few weeks) before being completely metabolized by the body. In addition, it can serve as an adjunctive therapy, to be implemented with radio- or chemotherapy, as well as a sole treatment, which makes it a non-disruptive technology.

4. Competition

4.1 Other Hyperthermia Systems

Presently, machines that can perform both hyperthermia and thermoablation do not exist in the market but commercial systems capable of performing non-magnetic nanoparticles-based hyperthermia have been engineered. Below are information on the companies and systems they develop. The list should not be considered comprehensive as numerous companies have been assigned patents for various systems or apparatus performing some type of hyperthermia treatment but have not been known to develop their systems in the aim of marketing them and therefore not included here.

4.1.1 BSD Medical (BSM) Corporation

BSD Medical is a Salt Lake City-based company that develops, manufactures, markets, and services hyperthermia systems operating by focused radio frequency and microwave energy [68]. Their major products, BSD-500 and BSD-2000 are capable of creating hyperthermia in body tissues and measuring temperature distributions within the treated volumes during the course of treatment. While BSD-500 treat cancer on or near the body surface, BSD-2000 can treat cancers located deeper in the body. In the hyperthermia subsystem, a high frequency energy source (above 300MHz with a preference for 915 MHz, as approved by the Federal Communications Commission for medical devices) is

coupled to and controlled by the CPU. A power splitter divides the energy into a plurality of lines having the same phase and power, a phase adjuster, and applicator connecting switches. The output of each phase shifter is coupled to one individual applicator or a group of applicators, the actual delivery of which is controlled by switches. Figure 12 only shows four phase shifters, applicators and switches but an actual system may employ more of each to provide steering in several directions.

FIGURE 12
Block Diagram Showing BSM's Hyperthermia Apparatus (the numbers 34, 36, 37 represent phase shifters, applicators, and switches, respectively)
(from US Patent 4,798,215)

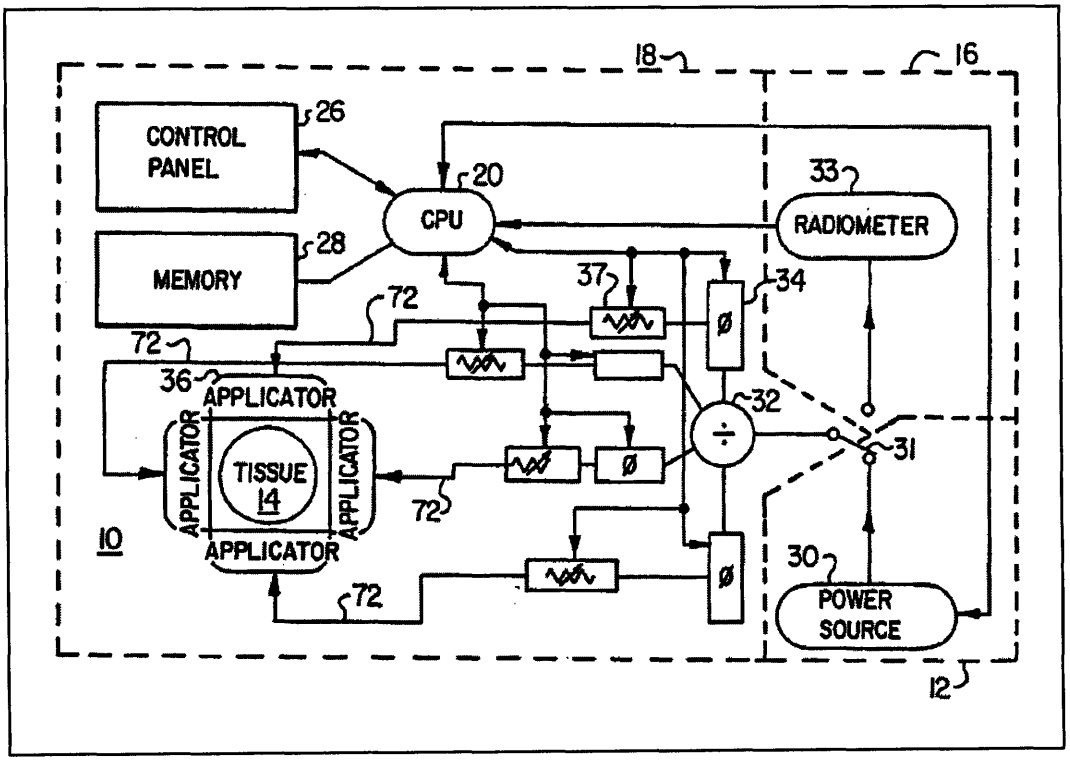
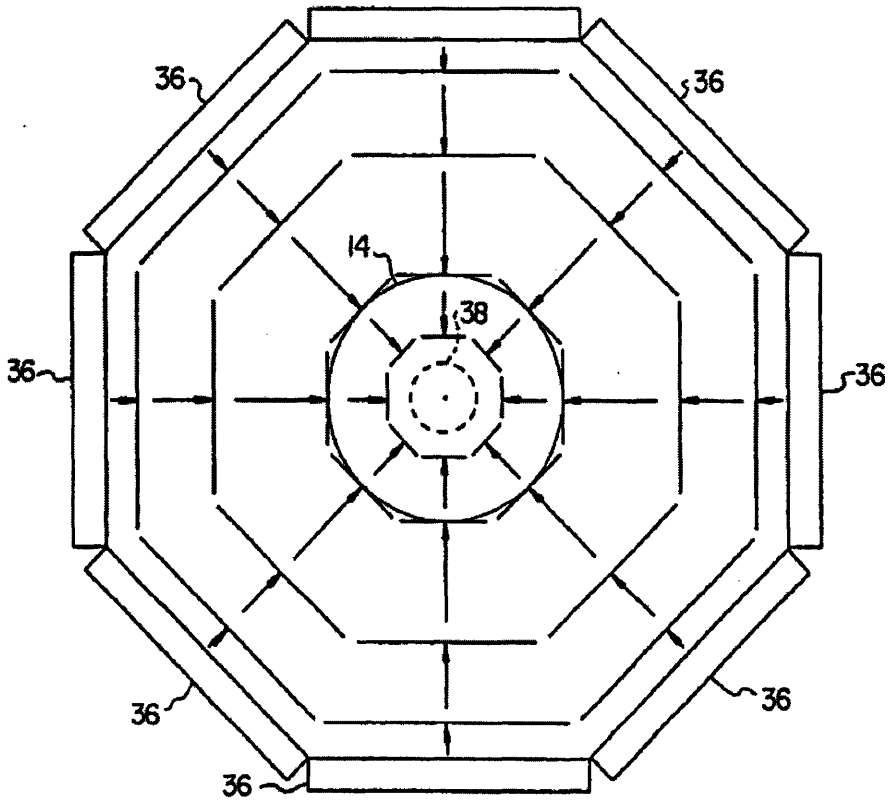


FIGURE 13
2D Diagram of Microwave-Based Hyperthermia
(from US Patent 4,798,215)



In Figure 13, eight individual applicators are shown coupled together in an octagonal arrangement surrounding a circular target. It should be noted that it is a two-dimensional representation of a three-dimensional phenomena. As the microwave radiation is emitted from each applicator (the arrows illustrating the wavefronts of the electromagnetic radiation, which are perpendicular to the electric and magnetic field components), it converges on the target where the electric field adds constructively and heats the center region of the target to a greater degree than that caused by any one of the applicators alone. This is how

internal heating is induced without dangerously increasing the temperature at the surface of the target. Changes in amplitude and phase can displace the central energy focus to better heat a non-central target. The constant phase relationship of the radiation from each applicator creates a synergistic result whereby the center is heated to more than a simple sum of the energy of the various applicators.

To generate a real time thermal profile for monitoring purposes, both invasive (using temperature probes) and noninvasive (based on blackbody radiation) thermography method are used in the system. It has been found that warm living tissue emits black body radiation at depth indicating frequencies. Thus, a receiver subsystem (radiometer) is used to measure this radiation by setting the receive frequency of the radiometer depending on the zone of the sensed thermal energy.

BSD Medical also invented a microwave hyperthermia apparatus that can be inserted into the body which includes a hollow central tube for the insertion of radioactive therapy sources. This form of radiotherapy is also known as brachytherapy and commonly used to treat localized prostrate cancer and cancers of the head and neck. The device provides a special microwave interstitial antenna applicator with a hollow center conductor large enough to permit insertion of a standard 0.9 mm brachytherapy source.

A search through online patent databases [69-71] reveals that BSD Medical holds the following patents protecting their invention:

US 4,638,813; US 4,672,980; US 4,658,836; US 4,712,559; US 4,798,215; US 4,448,198; US 4,669,475; US 4,860,752; US 4,974,587; US 4,967,765; US 4,672,980; US 5,249,585; US 5,097,844; US 5,344,435; US 5,220,927; US 6,957,108; WO 8,803,823; WO 9,207,622; WO 9,207,621; WO 9,308,875; AU 1,320,492; AU 1,269,692; EP 0207729; EP 0612260; AT 58065T; AT 39327T.

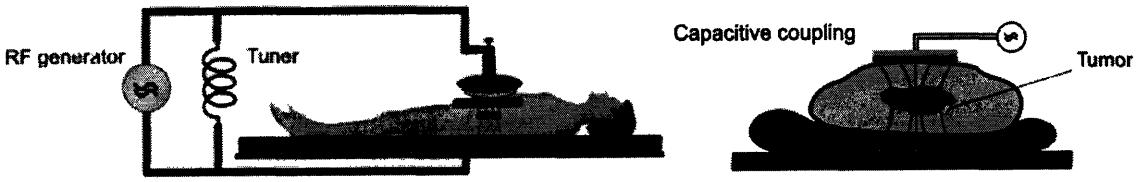
BSD Medical has obtained FDA approval to market BSD-500. In March 2006, they completed a submission for FDA approval to sell BSD-2000. Clinical studies using BSD's systems to deliver hyperthermia in conjunction with radiotherapy have shown that 83.7% of patients had tumor regression, and 37.4% of patients had a complete tumor regression. Approximately 10% of patients experienced burns and blistering from heating, 8% experienced pain, 4% experienced ulceration from rapid tumor necrosis, and 2% experienced ulceration from placement of temperature sensors and rapid tumor necrosis. Most recently, they conducted a phase III clinical trial with 340 patients suffering from soft tissue cancers and it showed an approximate doubling of disease-free survival or local progression-free survival when hyperthermia therapy was added to chemotherapy, as compared to results for patients treated with chemotherapy alone [72]. A new system, MicroThermX 100, is currently being developed to treat cancers that can be destroyed with heat alone. Submission for FDA approval is expected in 2007.

In the three months ended February 2007, BSD Medical's revenues were $660,657, showing an approximately 50% increase compared to the three months ended February 2006. The revenues came from sales of a small number of medical products.

4.1.2 Oncotherm

Oncotherm's EHY-2000 device utilizes the principle of capacitive coupling of radio waves of 13.56 MHz to specifically heat the near-membrane extracellular liquid of tumors. Because tumor tissue has lower impedance than the surrounding tissues, most of the energy is absorbed by the cancerous lesion and external focusing is unnecessary. This therapy is used in combination with radiotherapy and chemotherapy when the common therapy regimens show little chance for success.

FIGURE 14
Oncotherm's Hyperthermia Apparatus
(from Oncotherm [73])



EHY-2000 got a market approval according to European Medical Device Directive. The systems are distributed in Europe, several Asian countries, and

Russia. Patent owned by Oncotherm protecting this technology is HU 0401772 [69].

4.1.3 Labthermics Technologies, Inc.

Labthermics' commercial therapy product, the SONOTHERM 1000, uses ultrasound energy to treat tumors [74]. Depth of energy penetration is chosen by adjusting frequency, 1 or 3.4 MHz for deep (8-10 cm below surface) or superficial (up to 3 cm below surface) tumor. It utilizes a sixteen sector applicator to vary the pattern of energy deposition in tissue, allowing the beam shape to be tailored to tumor size and shape. The applicator generates ultrasonic wave energy by applying a high voltage radio frequency signal to one side of a piezoelectric crystal grounded on a second side of the crystal.

The change in temperature of the treatment area is detected by a thermometry unit consisting of multiply thermocouple temperature sensors disposed within the patient's body. Plastic catheters are used to contained the sensors upon insertion but withdrawn before treatment in order to avoid disruption of the ultrasound heating pattern. Labthermics is also developing a microwave hyperthermia probe for more direct and exact invasive hyperthermia treatment.

Patents granted to Labthermics are: US 5,190,054; US 5,097,845; US 4,945,318; US 4,638,436; WO 8,601,919; EP 0195073 [69-71].

4.2 Comparison of Hyperthermia Methods

TABLE 5
Nanoparticles and Non Nanoparticles-Based Thermotherapy In Comparison

Nanoparticles-based thermotherapy	Electromagnetic waves (ultrasound, RF, microwaves)-based thermotherapy
Interstitial treatment	Locoregional treatment
Magnetic field used depends on target location (tolerance of pelvis < thorax < head)	Frequency used depends on target location (better penetration at low frequencies, better focusing at high)
SAR distribution depends on distribution of nanoparticles	SAR distribution more homogeneous at lower frequencies
Realistic SAR of 50-380 W/kg	Realistic SAR of 35 W/kg in abdomen
Improved SAR can be achieved by optimizing the magnetic fluid	Very large SAR of 2500 W/kg can be achieved by high intensity ultrasound only in focus of 1 – 3 ml
Instillation of nanoparticles done by injection, highly dependent on therapists' skill	Water load required to direct radiation to patients
Further therapy steps done contact-less	Antenna arrays must be optimized for control and efficiency
Same magnetic field applicator can be used for all clinical cases, but modifications can improve H-tolerance	Different number and arrangements of antennas/applicators needed for different clinical applications
Minimum side effects	May have minor side effects
	High ohmic losses
Suitable for all solid tumors	Suitable for pelvic tumors (prostate, cervix, rectum, bladder)

Aside from the above, nanoparticles-based thermotherapy has a competitive advantage in its versatility and adaptability to new emerging technologies. It is not only suitable for use with conventional therapies but also presents great potential in the near future. As the properties of nanoparticles are enhanced, thermotherapy can be established as a monotherapy for all kinds of cancer. Nanoparticles coupled with specific targeting molecules and drugs which can be released in a temperature-dependent manner can enable chemotherapy and thermotherapy to be performed at once, free of side-effects. In short, it is a non-disruptive technology that will perform well in the ever-evolving market of cancer treatments.

4.3 The Impact of Biotechnology Revolution, Emerging Anti-Cancer Drugs

When it comes to curing cancer, while thermotherapy is promising, we must also take note of other solutions being offered. The Researchers have come up with experimental new drugs to treat cancer that promise fewer side effects [75]. Few examples are Velcade & Revlimid, drugs developed by Boston's Dana-Farber Cancer Ins. for myeloma, a cancer in which white blood cells invade bone marrow, Gleevec, a drug for adults and children with chronic leukemia, Avastin & Tarceva, complementary drugs for colorectal and lung cancer by Anderson Cancer Center in Houston, and Abraxane, a modified older drug (Taxol) for breast cancer developed by Northwestern University. These drugs battle cancer

by various mechanisms. Some find cancer cells by recognizing specific markers or attach a specific chemical pathway necessary for malignant cells to live and multiply, some use large molecules to block growth-promoting proteins from attaching to receptors on cell surfaces, the first step to uncontrollable cell growth, some use small molecules to get inside cancer cells and block chemical signals that drive cells to multiply intensively, and others target blood vessels that supply oxygen and nutrients to cancer cells.

At the same time, researchers also continue to develop new methods to improve on the existing therapies [76]. In radiotherapy alone, there are several improvements currently tried, always with the goal of directing a high dose of radiation to the tumor while protecting surrounding tissues. The use of drugs that protect healthy cells (radioprotectors) from radiation has been proposed. The intravenous drug amifostine, for example, is an antioxidant which can successfully protect salivary glands from damage during radiation to the head and neck and more studies are being conducted to see if it and other drugs might protect healthy tissues in other areas of the body that receive radiation treatment.

The opposite can also be done where drugs that make cancer cells more sensitive to treatments (radiosensitizers) are used. Several chemotherapy drugs including fluorouracil and cisplatin are being studied as sensitizers as they modify the cancerous cells to make them more susceptible to the radiation.

Yet another approach is coined radioimmunotherapy. In it, radiation is targeted directly to the cancer by means of attaching radioactive substances to special antibodies that find and bind to cancer cells. When they have reached their targets, radiation is released, killing the cancer cells. Two radioimmunotherapy drugs, ibritumomab tiuxetan and tositumomab, have already been approved for use in advanced non-Hodgkin's lymphoma.

A few of these evolving therapies have been approved by the US Food and Drug Administration (FDA) while many others are in various stages of clinical trials and their results will set apart which may be the next big answer to the battle against cancer. The uncertainty arising from many technological developments in progress, and the fact that data gathering on scientific and business activities in the field is enormously challenging, the market share to be expected by each solution is almost impossible to predict and discussions up until now have been largely qualitative.

Despite the hype surrounding the 'magic bullet' therapy associated with drugs with tumor-selective monoclonal antibodies, however, the technology has a number of limitations. These drugs are large molecules that cannot enter or penetrate deeply into target tissues. They cannot be administered orally and must be given in very high concentrations in order to be effective. Furthermore, they must be produced in cell culture, making them expensive to manufacture [77].

5. Regulatory Environment

Before new patented technologies can enter the marketplace, there are regulations that need to be followed to ensure their safety and effectiveness. All medical devices manufactured and sold in United States, for this purpose, are subjects to premarketing and postmarketing regulatory controls by the Food and Drug Administration (FDA). A medical device, according to section 201(h) of the Federal Food, Drug, and Cosmetic (FD&C) Act, is:

"an instrument, apparatus, implement, machine, contrivance, implant, in-vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of a disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes." [78]

This definition is meant to provide a clear distinction between a medical device and other FDA regulated products such as drugs. FDA has many Centers as its components, each regulating a specific type of products. Some products are regulated by more than one Center. Medical devices generally fall under the jurisdiction of the Center for Devices and Radiological Health (CDRH).

There are three steps to obtaining marketing clearance from CDRH. Step one is making sure that the product is indeed a medical device and whether or not it is regulated by other FDA components. Step two is to determine the classification of the medical device. Devices are allocated into 3 classes depending on the amount of control necessary to ensure their safety, class I being the least rigorous. Hyperthermia systems are Class III devices, the most stringent classification. Generally, Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Step three is the development of data and/or information necessary to submit a marketing application to obtain FDA's clearance.

Depending on the classification, the FDA approval process may begin with the 510(k) submission. It is a required premarket notification that demonstrates that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device. Submitters must compare their device to one or more similar legally marketed devices and make and support their

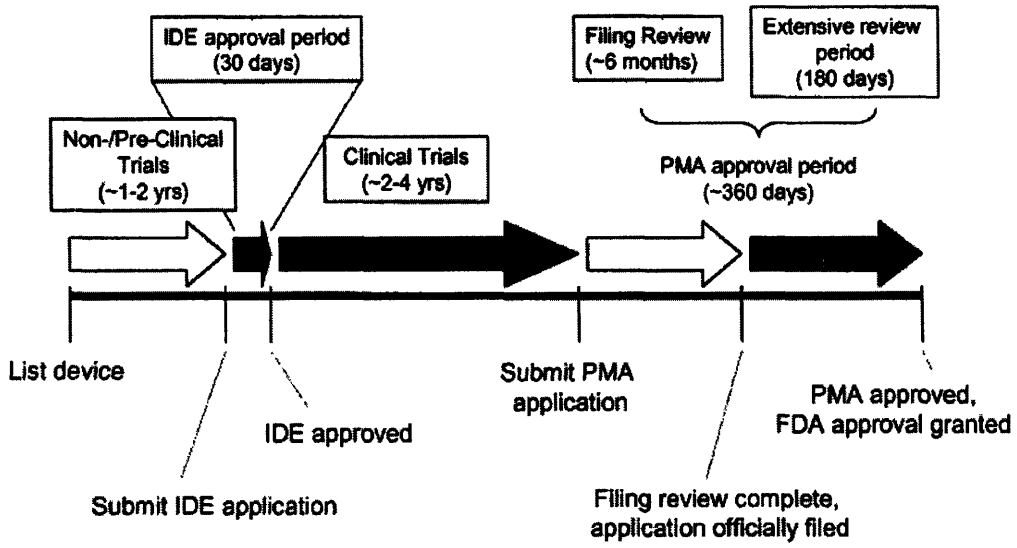
substantial equivalency claims. This is to inform the FDA of "new" devices, those that are ready for first time distribution or reintroduction of modified devices to the extent that may affect safety and effectiveness. After a letter declaring the device substantially equivalent (SE) has been issued by the FDA, submitters may market the device immediately. SE determination is usually made within 90 days. Manufacturers should be prepared for an FDA quality system inspection at any time after 510(k) clearance as FDA does not perform pre-clearance facility inspection.

Premarket Approval is another FDA process of scientific and regulatory review for the evaluation of Class III medical devices. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to ensure their safety and effectiveness. FDA regulations provide 180 days to review the PMA and make a determination. In reality, the review time is normally longer, with an average of 411 days [79]. PMA requires all Class III devices to file a full report of investigation containing data from both non-clinical and clinical studies. Additionally, the components and principle of operations are to be described in detail. Manufacturing and quality control procedures, proposed labeling, and actual sample of the device are also required. It is a highly extensive process. An approved PMA is, in effect, a private license granting the applicant to market the device.

In order for the investigational device to be allowed for use in clinical trials to in turn collect safety and effectiveness data required to support a Premarket Approval (PMA) application in the U.S., an Investigational Device Exemption (IDE) is needed. This is because there are regulations and requirements that must be complied while conducting a clinical study with human subjects. IDE applications therefore include complete reports of previous studies (in-vitro studies, animal trials), a full investigational plan for the clinical study to be conducted, and a list of committees to be involved in the study. After IDE is granted, the first phase of clinical trials may be performed, beginning with a small group of volunteers to assess the safety and tolerability of the therapy. Once safety has been established, phase II trials can be performed on larger groups to evaluate efficacy. Next, phase III trials are aimed at being the definitive assessment of the efficacy of the new therapy, in comparison with current 'gold standard' treatment. They are usually the most expensive, time-consuming, and difficult trials to design and run. Phase IV trials involve the post-launch safety surveillance and ongoing technical support and though not a condition for approval, may be mandated by regulatory authorities or undertaken by sponsoring company for competitive or other reasons (for example, test a therapy on certain population groups who are unlikely to subject themselves to trials). They are designed to detect any rare or long-term adverse effects over a much larger patient population and timescale than was possible during the initial clinical trials. Such adverse effects may result in withdrawal or restriction of a product.

The entire process, from IDE to PMA approval may take from three to six years or more, as illustrated below.

FIGURE 15
Timeline of FDA Approval Process
(from Wu [80])

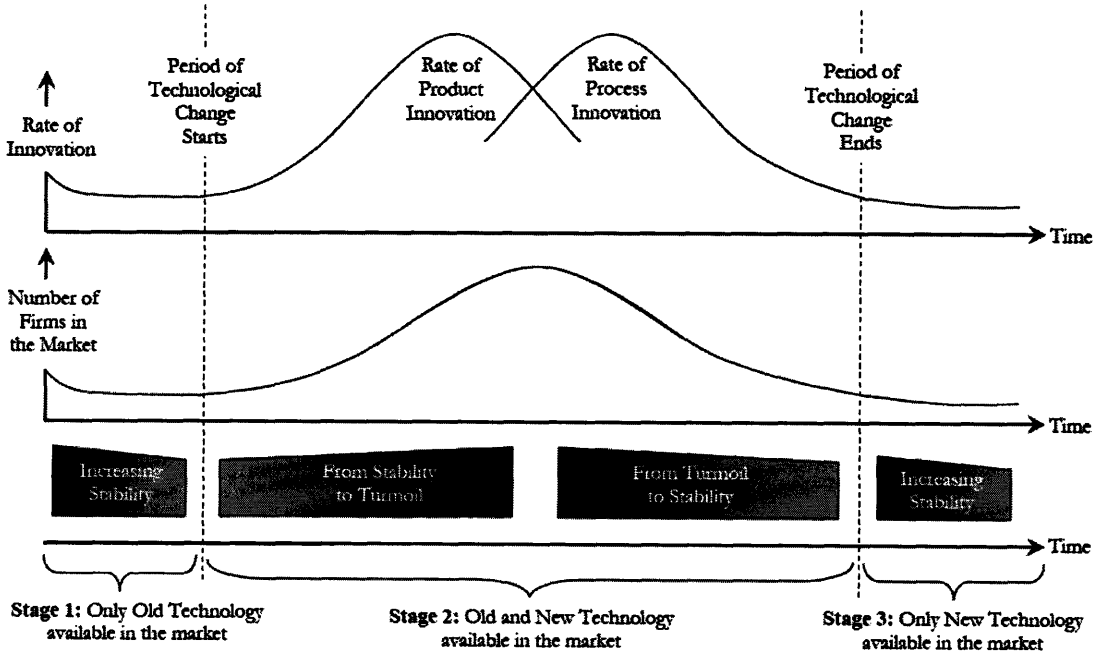


6. Market Assessment

6.1 Overview

In a market disrupted by technological change, there is a phenomenon called creative destruction. Characteristically, the market undergoes a turmoil period of transition during which the old and new technologies compete. As a result, the barrier to entry is lowered and for some time, the old and new technologies can coexist and remain profitable. Entrants to the market can usually gain an advantage by investing in the old technology simultaneously with the new.

FIGURE 16
The Dynamics of Creative Destruction
(from Sosa [81])



The market for cancer therapies is currently at the fluid, emerging phase of technological disruption brought forth by nanotechnology (eg. nanoparticles-based thermotherapy, nanoparticles as drug carriers), and bioengineering (eg. the discovery of monoclonal antibodies, vaccines, modified protein-based products, stem cells). This phase is characterized by broad R&D focus and high performance uncertainty. Market tolerates frequent changes in products and market share due to rapid entry in response to market opportunities. Cancer currently has the most new drugs in development and displays an extremely large boom in commercial activity. PhRMA estimates that there are approximately 683 drugs currently in clinical development for cancer despite high attrition rate (For every 5,000 to 10,000 compounds screened for drug approval, 250 will reach preclinical development, 5 will reach clinical development, and only 1 will eventually be approved) [82].

In this setting, technical performance and product differentiation determine the competition more than price or cost [83]. Only when the new technology matures and market settles down is competition for market share driven by cost reductions and economies of scale. By that reasoning, instead of doing a rigorous cost analysis, we will look into the size of market that can be addressed by our technology and hopefully, seeing how big an impact it can deliver, be convinced of its potential.

6.2 Potential Target Market

In determining the available market for nanoparticle-based cancer thermotherapy, different cancer types are investigated to generate an estimate of the number of people who will benefit from the new treatment. All solid tumors (cancer of body tissues other than blood, bone marrow, or the lymphatic system) are considered with special attention on malignant, difficult-to-treat cases. The following few paragraphs describe how the number of cases is estimated for brain cancer. In the same way, other cancer types are analyzed and summarized in a table.

The American Brain Tumor Association stated that 14 person out of 100,000 are diagnosed with new cases of primary brain tumors in 2004 [84]. This statistics include both malignant and benign tumors but exclude brain metastases, tumors that begin as cancer elsewhere in the body and spread to the brain. Brain tumors are the leading cause of cancer-related deaths in males ages 20-39 and fifth leading cause in women of the same age group.

There are two widely-cited methods to express the survival rate of cancer patients and one of them is prevalence, the total number of people still living following the diagnosis of cancer. For primary malignant brain tumors, this prevalence rate is 29.5 per 100,000 (based on year 2000 prevalence rate, the most recent available)

while for primary benign tumors, it is 97.5 per 100,000. Prevalence does not give us any indication on whether these people still have active disease or are cured, though, since it includes everyone who is still alive on the day the statistics are taken, who has been diagnosed with cancer at any point prior to that date. The other is five-year survival rates, which are often used to complement the aforementioned figure and measure the percentage of cancer patients who survive 5 years after diagnosis of the disease. The overall 5-year relative survival rate (normalized to the general population to isolate the effect of cancer) for 1996-2003 from National Cancer Institute's SEER was 33.9% [85].

For the rest of the analysis, we will use this statistics to estimate the number of cases unsolved by the conventional therapies and therefore the new thermotherapy may be applicable for. In this case, for example, we will take the 66.1% (100% - 33.9%) of the total diagnosed brain cancer cases as potential candidates for thermotherapy. This is a good enough estimation as low-grade tumors do not often recur after first treatment and for all cancer, if recurrence happens, it usually is within 2 years. People surviving 5 years of cancer, therefore, are likely to have been cured or displaying good tumor control after conventional therapies.

By that assumption, the number of brain cancer patients that conventional therapies fail to save is calculated to be 13,550 (66.1% of 20,500, projected incidence in 2007). Employing the same calculation to different types of solid

tumors (chosen are the ones with high estimated cancer deaths in 2007 and those to which hyperthermia clinical trials have proven feasible and improved) gives us the table below. When statistical stage distribution for a type of cancer is known, the 5-year relative survival rate is averaged accordingly.

TABLE 6
Calculation of Unsolved Cases for Major Solid Tumors Diagnosed in U.S., 2007
(Based on SEER Statistics [85])

Cancer	Incidence (in 2007)	5-year relative survival rate	Unsolved cases
Brain	20,500	33.9%	**13,550**
Breast			
- localized (61%)	108,873	98%	2,177
- regional (31%)	55,329	83.5%	9,129
- distant (6%)	10,709	26.7%	7,850
- unstaged (2%)	3,569	56.9%	1,538
Overall	178,480	88.4%	**20,694**
Lung			
- localized (16%)	34,141	49.1%	17,378
- regional (35%)	74,683	15.2%	63,331
- distant (41%)	87,486	3%	84,861
- unstaged (8%)	17,070	8.1%	15,687
Overall	213,380	15.05%	**181,257**
Esophagus			
- localized (24%)	3,734	33.7%	2,476
- regional (30%)	4,668	16.9%	3,879
- distant (30%)	4,668	2.9%	4,533
- unstaged (16%)	2,490	10.8%	2,221
Overall	15,560	15.76%	**13,109**
Pancreas			
- localized (7%)	2,602	20.3%	2,074
- regional (26%)	9,664	8%	8,891
- distant (52%)	19,328	1.7%	18,999
- unstaged (15%)	5,576	4.1%	5,347
Overall	37,170	5%	**35,311**
Ovary			
- localized (19%)	4,262	92.4%	324
- regional (7%)	1,570	71.4%	449
- distant (68%)	15,252	29.8%	10,707
- unstaged (6%)	1,346	24.8%	1,012

Overall	22,430	44.3%	**12,492**
Cervix			
- localized (51%)	5,686	92%	455
- regional (34%)	3,791	55.7%	1679
- distant (9%)	1,004	16.5%	838
- unstaged (6%)	669	60.1%	267
Overall	11,150	71%	**3,239**
Urinary bladder			
- localized (75%)	50,370	92.1%	3,979
- regional (19%)	12,760	44.6%	7,069
- distant (4%)	2,687	6.4%	2,515
- unstaged (2%)	1,343	59.3%	546
Overall	67,160	79%	**14,109**
Prostate			
- localized or regional (91%)	199,190	100%	0
- distant (5%)	10,944	31.9%	7,453
- unstaged (4%)	8,756	79.1%	1,830
Overall	218,890	95.7%	**9,283**
Colon & rectum			
- localized (39%)	59,966	89.8%	6,117
- regional (36%)	55,354	67.7%	17,879
- distant (19%)	29,214	10.3%	26,205
- unstaged (6%)	9,226	35.8%	5,923
Overall	153,760	63.5%	**56,124**
Total	468,824		34,980
	217,819		112,306
	181,292		163,961
	50,045		34,371
	938,480		**359,168**

Based on this calculation, there are approximately 359,168 new cancer cases in 2007 that still elude existing therapies and are therefore potential targets for thermotherapy. In the future, when the technology is established, the non-invasive and free of side effects nature of thermotherapy might make it attractive even to cases the conventional therapies can address effectively and broadening of target market can be expected. Considering the state the technology is in now, we can confidently say treatment of localized tumors is guaranteed to be

improved. This means at least 48,530 new cases yearly. What about the existing cases? Below prevalence is used for a rough estimate.

TABLE 7
Estimated U.S. Cancer Prevalence, 2002
(from American Cancer Society [86])

Cancer	**No. of patients living in 2002 (rounded to the nearest 1,000)**
Brain	106,000
Breast	2,290,000
Lung	351,000
Esophagus	23,000
Pancreas	26,000
Ovary	170,000
Cervix	223,000
Urinary bladder	499,000
Prostate	1,832,000
Colon & rectum	1,052,000
Total	**6,572,000**

These figures are not accurate because in addition to the unavailability of a more recent prevalence statistics (cancer data are always 'late'), as mentioned before, prevalence includes people who have been 'cured' as well as the recently diagnosed. Even so, 'cured' cases can sometimes come back. Taking that in mind, prevalence does give us a ballpark figure of the size of preexisting market. In reality, both the size of the preexisting and ongoing market will have considerable contribution from cancer in other sites not yet mentioned above.

The U.S. numbers, and not global statistics are used in this analysis based on the following considerations. The American Cancer Society states that a new report on global cancer trends finds men and women in North America have the highest cancer incidence rates worldwide. In 2002, the 1.6 million cancers accounted for 14.5% of the world's total. While this may partly be due to relatively good diagnosis, it is surprising that the chance of a man dying from cancer before age 65 is 18 percent higher in developed than developing countries. It is also far easier to gather U.S. data as even in the most recent and comprehensive database, GLOBOCAN 2002, data from a number of countries are not available. Global cancer statistics are therefore crude and worldwide study only emphasizes three major estimated measures: incidence, mortality, and prevalence. The study estimates that in 2002 there were 10.9 million new cases of cancer worldwide, 6.7 million deaths, and 24.6 million persons who had been diagnosed with cancer in the previous five years.

To treat these cases, in the United States there are at least 63 cancer centers listed under the National Cancer Institute and over 1,400 cancer hospitals that meet the guidelines and standards of the American College of Surgeons' Commission on Cancer (CoC) the new thermotherapy can be made available in.

6.3 Medical Device Market Opportunities

The U.S. medical device market is of a strategic importance as it is the largest and most sophisticated in the world with $71.3 billion in sales for 2002 [79]. As a rule of thumb, it represents about half of the world market and is expected to grow to $97.8 billion in 2007. This positive outlook is based on the observation that the economy of the United States is likely to continue to grow at a rate of between 3.5% and 4.3% and the fact that the U.S. population is aging. In 2004, the number of people aged 65 and over stood at 35 million. In 2020, this figure will be 55 million. This trend in demographics is relevant and important because the average yearly spending for healthcare increases with age: a man between 30 and 34 years of age spends an average of $1,528 while a man between 50 and 54 spends $ 4,454, nearly three times as much. Older people are also wealthier on average: according to the Wall Street Journal, the 78 million Americans that are 50 years and above control 67% of the country's wealth.

There are approximately 6,000 medical device manufacturers in the U.S., 80% of which are small companies employing fewer than 50 people. According to Charles Walen, a senior analyst with Frost and Sullivan in a comment delivered during a teleconference titled 2003 Industry Outlook on Medical Devices, the high diversity of the medical device market is the reason why it outperforms many other U.S. business segments. He also asserts that this is why medium and small companies offering specialized products can still be highly profitable [87].

Whelan also further predicted that prices for products with proprietary technology in the coming years could increase even though hospitals and group purchasing organizations are putting pressure on manufacturers to reduce prices.

6.4 Cost of Cancer Therapies

In chapter 2, it is mentioned that cancer's direct medical costs in 2004 are $72 billion, a substantial amount. But what does this mean for a cancer patient? How much money does a cancer patient have to pay for treatment of his/her disease?

Each cancer patient receives treatments that are customized depending upon the type and stage of cancer, and the patient's condition. It is most common to use several treatment modalities together or in sequence with the goal of preventing recurrence. For example, doctors may use radiation to shrink the size of the cancer before surgery, or they may use radiation after surgery to kill any remaining cancer cells. Sometimes intraoperative radiation is given, where radiation therapy is carried out during the surgery so that it goes straight into the cancer without passing through the skin. Chemotherapy and radiation therapy can be given before or after each other too. Sometimes hospitalization is required and other drugs or treatments prescribed to alleviate side-effects resulting from cancer treatments. This makes analyzing general cost of each specific cancer treatment especially difficult.

A study attempted to calculate the health care costs for seven selected cancer based on insurance claims throughout the United States [88] was able to conclude that mean monthly health care costs ranged from $2,187 for prostate cancer to $7,616 for pancreatic cancer, most often driven by hospitalization (Inpatient care accounted for approximately 58% of direct medical costs). Indirect morbidity costs to employees with cancer averaged $945.

TABLE 8
Mean Monthly Cancer-Related Costs (US $) by Cancer Treatment
(from Chang et. al. [88])

Types of Cancer	No. of Patients	Office-Visit Drug Treatment		Radiation Treatment		Surgical Treatment	
		Mean	SD	Mean	SD	Mean	SD
Brain	653	105	606	658	1,436	365	1,684
Colorectal	2,860	140	617	138	685	1,986	12,942
Lung	2,040	553	1,566	694	1,801	153	1,098
Ovarian	440	749	1,435	32	196	2,590	8,235
Pancreatic	412	360	1,104	391	1,130	1,574	19,296
Prostate	5,250	10	132	461	1,168	332	1,579

Notice that in all cases, the values for standard deviation are large, indicating high variability of costs even for one treatment type. The same study also reported that cancer costs vary by age because younger patients may receive more aggressive therapies. In other words, treatment costs can vary even for two

people with identical site and stage of cancer. The way subsequent treatments are planned also depends on the patient's response to the previous ones.

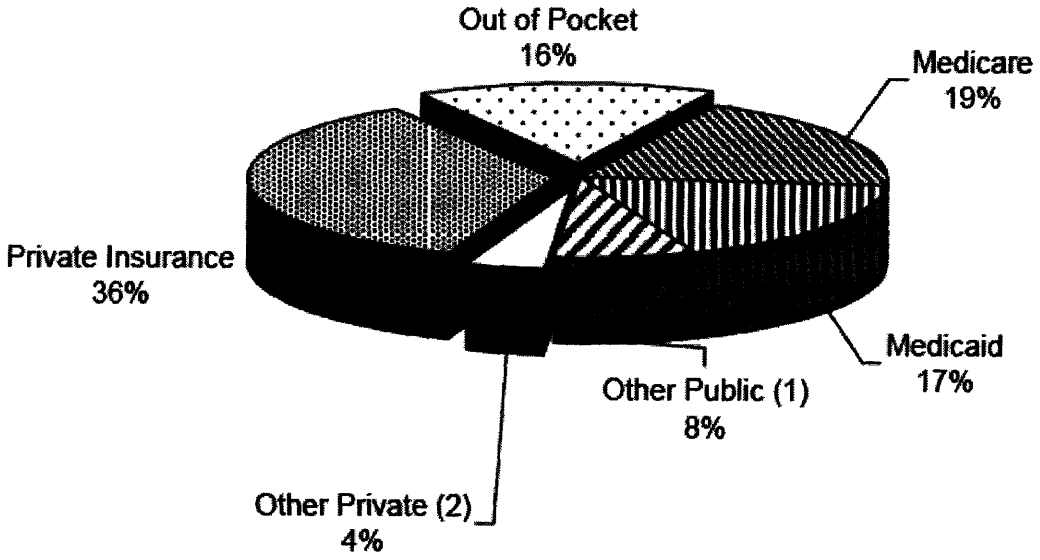
When we want to estimate cost for thermotherapy, we must take into consideration the various aspects of the treatment: the magnetic nanoparticles, the magnetic field applicator, and the imaging devices. Because we can be certain that hospitals and cancer centers have CT scanners for imaging purposes, we can focus on the incremental cost they will incur by introducing this new therapy. 100 ml of magnetic iron oxide nanoparticles are priced at $158.60 by Sigma-Aldrich [89]. These nanoparticles are stabilized by oleic acid, an organic fatty acid. If we assume that dextran- or aminosilan-stabilized nanoparticles are similarly priced, one treatment using 3 ml of the magnetic fluid, the median amount needed in the clinical trials by MagForce [67], utilizes less than $5's worth of magnetic fluid. This value may be lowered still if hospitals and cancer centers purchase magnetic fluid through a contract agreement. The cost driver for the treatment, therefore, lies in the magnetic field applicator and specialists' fee.

The complexity of high-end medical device pricing is a result of the large expense associated to research and product development. As is the case with drugs, the considerable investment in device development is a sunk cost at the time the product is launched and price is negotiated, and thus in strong contrast with the marginal cost of producing additional units, which is generally low [90]. If a

similar product is already on the market, its price serves as a limiting factor for the new product to have economic advantage.

Reimbursement by public and/or private insurance is one of the primary drivers that can affect the successful introduction of new medical devices in the U.S. market. Most patients rely on insurance to pay for medical procedures as they cannot afford them on their own. In 2002, the U.S. health expenditures totaled $1.55 trillion, a 38.8% share of an estimated $4 trillion global healthcare industry. The pie chart below shows where the nation's health dollar came from.

FIGURE 17
Breakdown of U.S. Health Expenditure in 2002
(from Swiss Medtech [79])



The public sector, comprising of 44% of health payments in the U.S. is made up of two primary components: Medicare, the national health insurance program which provides coverage to approximately 40 million Americans (people age 65 or older, people under 65 with disabilities, and people with End-Stage Renal Disease) and Medicaid, a program that pays for medical assistance for certain individuals and families with low incomes and resources who meet the eligibility requirements. The third component, Other Public, includes government health spending for veterans, military personnel, injured workers and schoolchildren and for general public health activities.

Public and private insurance companies, then, have a major voice in deciding which medical devices and procedures they agree to pay for, and how much they are willing to pay. The two sectors operate independently, however, each making its own decisions. On the public side, The Center for Medicare and Medicaid Services (CMS) take the role while on the private side, a large number of private insurance companies conduct their own cost-effectiveness reviews to make their own decisions. These commercial payers, covering approximately 200 million individuals in the U.S. often follow the lead set by CMS when determining their own coverage and payment guidelines though. That being the case, healthcare providers generally contract with both public and private payers to provide services at a specified maximum amount, and the patients are usually required to bear a part of the total cost through deductible and/or co-payment amount though considerable amount is covered by insurance.

A practical market indicator would be BSD-500, BSD Medical's commercial hyperthermia system which was quoted at a contract price of $282,575 to the American Society for Therapeutic Radiology and Oncology (ASTRO) at the end of 2005 [91]. BSD's outpatient hyperthermia procedure costs $205.68 in 2007, according to reimbursement claim data. Of this amount, co-pay is $60.88. Local hyperthermia is currently covered under Medicare when used in connection with radiation therapy for the treatment of primary or metastatic superficial malignancies. It is not covered when used alone or in connection with chemotherapy [92]. For a comparison, Medicare's reimbursement rates for an MRI scan of the breasts in 2007 range from $348.80 to $498.84 [93].

Because in the U.S. approval of a medical device marketing by the FDA does not automatically guarantee that a third party payer will provide coverage and reimbursement for that device, it is recommended that a medical device manufacturer make direct contact with the entities directly involved in the evaluation and decision process, namely the Center for Medicare and Medicaid Services, the National Blue Cross / Blue Shield Technology Evaluation Center, the American Association of Health Plans (representing many U.S. private insurers and health plans), and ECRI (an independent, nonprofit health services research agency performing many technology assessments for the insurance industry).

Generally, it is believed that thermotherapy is going to be cheaper than other cancer therapies and therefore will reduce the cost of cancer therapies if

collaborations with the right entities can be established [94]. This is because in addition to being relatively cheaper compared to other therapies, thermotherapy has almost no side effects and is given in an outpatient basis, eliminating the need for inpatient care, the major element in cancer treatment costs.

7. Conclusion

Despite advances made in the war against cancer, cancer remains the second leading cause of death in the United States and the world. This shows a significant need for novel therapeutics for the treatment of cancer. In this study, technological and market analysis are performed to evaluate the potential of the new magnetic nanoparticles-based thermotherapy to answer the challenge.

It is shown that magnetic nanoparticles-based thermotherapy may be used as an adjunctive therapy, complimenting the more established radiation and chemotherapy by the mechanism of hyperthermia, but also carries the potential of enabling thermoablation as a monotherapy. Clinical trials performed along with chemo- and radiotherapy to recurrent local tumors have showed considerable improvements of survival and proven the new therapy free of side-effects. The former is due to the synergistic action of heat with drugs and radiation, made possible by the magnetic properties of the nanoparticles while the latter is attributed to the size and selectivity of the nanoparticles. It is clear that the magnetic nanoparticles play the key role in this therapy. Among the limitations are the inability of magnetic nanoparticles with the quality we can fabricate them today to generate enough heat for treatment of tumors only a few millimeters in size and the fact that patients with metal implants near the cancer site are not eligible for the treatment at all unless the implants can be removed prior to the procedure.

This new cancer therapy also has a strategic position in anticipating future developments of the biomedical field. The nanoparticles can be conjugated with various biomolecules that may enable very precise and specific targeting of certain cells in the body. They can also be coated with drugs dissolved in polymer matrix, assuring the release happens at the desired site in a timely, temperature-dependent manner. Gene therapy may also be made possible. All these ensure the technology's long term value in the market.

Although the study has also shown that there is a need and therefore a sizable market for a novel effective cancer therapy, there are several things to consider when we wish to commercialize this technology. Specifically in the United States, the first requirement is to get FDA approval to market the medical devices used in this therapy. When this is done, the price at which the technology will be made available must be determined. In the medical device industry, this is a complex process that takes into account the large sunk cost, the competing technologies, and the relationship between healthcare providers, patients and third-party payers. Although the medical device market is currently in the turmoil state brought about by technological change, lowering the barrier of entry and rendering cost to be of secondary importance next to efficacy, the last factor is still particularly important as reimbursement for new technology is a major concern for all parties involved: providers, patients, the physician community and medical technology innovators. It may very well be the determining factor to the success of a new technology introduction to the market.

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