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FACULDADE DE
MEDICINA DENTÁRIA
UNIVERSIDADE DO PORTO

APLICAÇÃO DE BIOMATERIAIS NO TRATAMENTO DE TUMORES SÓLIDOS POR TERMOTERAPIA: Revisão bibliográfica

MONOGRAFIA DE REVISÃO BIBLIOGRÁFICA

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA DA UNIVERSIDADE DO PORTO

MARIA JOÃO LOPES TAVARES

Aluna do 5º ano do Mestrado Integrado em Medicina Dentária da Faculdade de Medicina Dentária da Universidade do Porto

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Porto, 2018

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Aos incríveis amigos que a vida académica me proporcionou: Carol, Belisa, Filipa, Manuela, Mariana, Maria, Linda e Daniel. A todos os amigos que me acolheram de braços tão abertos e coração tão cheio em Bilbao: Evert, Jorge, Ashanti, Magda, Alice, Greta e Mariana. Às queridas Denise e Emilía, pelos seis mêses que pareceram cinco anos. Amigos espalhados pelos quatro cantos do mundo. Convosco tudo foi mais fácil. Pelos momentos inesquecíveis, pelas festas, passeios, tardes de estudo e muito mais. Nunca me deixaram esquecer que a felicidade adota outras proporções quando é partilhada. Foi uma honra partilhá-la convosco.

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Resumo

A termoterapia altamente focalizada apresenta-se como um método eficaz na indução da morte celular de células tumorais pelo aumento de temperatura e consequente destruição da rede vascular neoplásica. O desenvolvimento de biomateriais com nanopartículas ferrimagnéticas injetáveis diretamente na neoplasia, permitiu a produção controlada e localizada de calor aquando da aplicação de um campo magnético externo de alta frequência.

Pretendeu-se no presente trabalho referenciar o estado de arte deste tema verificando aspetos como o modo de atuação da termoterapia, as alterações que provoca nos tecidos e células, quais os princípios físicos da termoterapia magnética, o estudo dos biomateriais usados, e os avanços técnicos mais recentes na termoterapia magnética e as suas perspectivas futuras na melhoria do tratamento de pacientes oncológicos.

A revisão bibliográfica teve por base a pesquisa de artigos nas fontes de informação: PubMed, e Repositórios Científicos de Acesso Aberto de Portugal. As palavras-chave que orientaram a pesquisa foram: Hyperthermia induced, Biocompatible Materials (Mesh terms), Ferrimagnetic Cement, Highly Focalized Hyperthermia, Magnetic particles, High frequency magnetic field.

O objetivo da utilização de biomateriais na termoterapia é possibilitar o aumento da frequência de sessões de tratamento do tumor, diminuindo a ação nefasta do calor nas células sãs adjacentes e averiguar a aplicabilidade clínica desta metodologia, uma vez que os estudos *in vitro* e *in vivo*, em modelo animal e humano, corroboram a eficácia desta modalidade.

Os resultados revelam-se positivos uma vez que esta opção de tratamento é eficaz na destruição de células neoplásicas, o ritmo de crescimento das células tumorais diminui ao longo das sessões de termoterapia, existe mínima afetação dos tecidos adjacentes, não se verificam respostas inflatórias consideráveis aos biomateriais mais usados nem interferência significativa com os restantes órgãos. No entanto, verifica-se a falta de ensaios clínicos e de protocolos de tratamento.

Abstract

Highly focalized thermotherapy is an effective method in inducing cell death of tumor cells by increasing temperature and consequent destruction of the neoplastic vascular network. The development of biomaterials with ferrimagnetic nanoparticles injected directly into the neoplasia allowed the controlled and localized production of heat when applying a high frequency external magnetic field.

The aimd of this study was to analyze the state of the art of this subject by verifying aspects such as the mode of action of the thermotherapy, the changes it causes in the tissues and cells, what are the physical principles magnetic thermotherapy, the study of the biomaterials, and as its future prospects in improving the treatment of cancer patients.

The accomplishment of this bibliographic revision was based on the research of articles of the following sources of information: PubMed, and Scientific Repositories of Open Access of Portugal.

The keywords that guided this monograph were: Hyperthermia Induced, Biocompatible Materials (Mesh terms), Ferrimagnetic Cement, Highly Focalized Hyperthermia, Magnetic particles, High frequency magnetic field.

The objective of the use of biomaterials in thermotherapy is to increase the frequency of tumural treatment sessions, reducing the harmful action of heat on adjacent healthy cells, and to investigate the clinical applicability of this methodology, since *in vitro* and *in vivo* studies, in animal and human model, corroborate the efficacy of the treatment studied.

The results turn out to be positive as this treatment option is effective in the destruction of neoplastic cells, the growth rate of tumor cells decreases during the thermotherapy sessions, there is minimal affectation of the adjacent tissues, there are no significant inflammatory responses to the cells. biomaterials, nor significant interference with other organs. However, there is a lack of clinical trials as well as lack of treatment protocols.

Abbreviations

MHT – Magnetic Hiperthermia

MNP – Magnetic Nanoparticles

Co – Cobalt

Zn – Zinc

Ni – Nickel

Mn - Manganese

HSP – Heat Shock Protein

AMF – Alternative Magnetic Field

MRI – Magnetic Ressonace Imaging

PMMA – Poly(Methylmethacrylate)

AC – Alternative Camp

SLP – Specific Loss Power

Key-words

- Ferrimagnetic Cement;
- High frequency magnetic field;
- Highly Focalized Hyperthermia;
- Hyperthermia induced; Biocompatible Materials (Mesh terms);
- Magnetic particles;

Introduction

Cancer is a severe disease and currently is one of the leading causes of morbidity and mortality in the world, and so much research and investment have been made with the purpose to discover more effective treatments for this disease.(1-4) Currently, the most important approach in cancer treatment is surgery, then it comes chemotherapy and radiotherapy but with unpredictable tumor responses and also associated with high resistance.(1, 5, 6) There is a need for a new approach in cancer treatment, more effective, and capable of increasing the patient quality of life like the use of magnetic nanoparticles for the induction of intracellular hyperthermia.(1, 7-9) This kind of treatment could result in fewer side effects than chemo- or radiotherapy(2, 6, 10) and in synergetic effects when combined with these treatment modalities.(2, 4, 11, 12)

Magnetic particle hyperthermia is a highly specific and targetable method of localised remote heating of bodily tissue.(7, 12-14) Cancers are characterized by their unregulated growth and spread of cells to other parts of the body through the bloodstream or the lymphatic system.(6) As a consequence of the defective blood perfusion, tumours and the surrounding tissues present a low pH and hypoxia. In these conditions, radiotherapy is less effective and cytotoxic drugs reach the affected regions in a much lower concentration than the aimed therapeutic dose.(6, 13) In other and, these conditions improve the action of hyperthermia in the neoplasm, and a marked action on the core of the tumor.(3, 13)

Hyperthermia ($41°C<T<46°C$)(14) has various effects both at the cellular level (e.g., on the induction and regulation of apoptosis, signal transduction, multidrug resistance and heat-shock protein release)(15) and on tissues (e.g., changes in pH and in the perfusion and oxygenation of the tumor microenvironment).(16, 17)

Magnetic particle hyperthermia was introduced and tested by Gilchrist in 1957 as a means to heat lymph nodes in dogs.(3, 10, 13, 18, 19) His idea was to treat lymphatic metastases of large bowel cancer with heat by allowing microscopic ferromagnetic particles to embolize in lymph nodes draining the primary cancer site and then applying an external alternating magnetic field to cause hysteretic heating of the particles.(19)

In vivo experiments have indicated that magnetic nanoparticle-mediated hyperthermia can also distant metastatic tumors unexposed to heat(12-14, 20) thru the induction of an immunological and apoptotic response.(21) It has been reported that the cytotoxic effect of mild temperature hyperthermia alone, around 41ºC, is decreased due to the development of chronic thermotolerance(22), but most human tumour cell lines are more sensitive to that than rodent cells.(21) This causes an immunoresponse, where healthy cells are ignored and cancer cells are attacked.(13, 17, 23, 24)

The methods currently available to produce hyperthermia are generally limited by the inability to selectively target the neoplasm cells.(5, 9, 23, 25, 26)

It was assessed a new method of neoplasm treatment by hyperthermia, the Highly Focalized Thermotherapy, wich consists in the direct injection of a material into the tumor and the sunsequent exposition to na external high frequency magnetic field that will heat the magnetic particles and subsquently, the neoplasm cells.(7, 10, 17, 23, 24) This concept is based on the principle that under an alternating magnetic field a ferrimagnetic particle can generate heat by hysteresis loss while a superparamagnetic particle generates heat by relaxation of the magnetic moment.(1, 9, 17)

There are many approaches to finding the most effective vehicle to place the magnetic particle into the tumour.(13, 21) Most solid tumours are known to have a defective vascular architecture(15) which allow particles (with sizes as large as 150 nm) to accumulate and be retained inside tumours for longer times than in normal tissues. This phenomenon is known as the enhanced permeability and retention effect, and has been used to improve therapeutics efficiency using nanoparticles.(11) Current developments in nanotechnology are making it possible to use nanometric heat-generating ‘foci’ that can be activated by an external magnetic field.(10, 16, 24) Indeed, in order to successfully treat tumours one needs several properties such as large tumour accumulation, good tumour penetration (a challenging problem due to high interstitial pressures), and an efficient heat delivery system.(11) The monitoring of heat delivery is also a very important issue, since clinicians need to be sure that they are being able to focus and deposit the necessary heat for the planned treatment.(7, 9, 25) Progress in this field has been achieved by magnetic resonance imaging techniques.(10, 11)

The important properties of magnetic particles for inducing hyperthermia are: non-toxicity, biocompatibility, injectability, high-level accumulation in the target tumor and effective absorption of the energy of the alternating magnetic field.(1, 7) The magnetic properties of MNPs are very strongly correlated to several parameters such as their structure, method of synthesis, size, and dispersion media.(5, 10, 12, 27)

Over the past few years, many experiments have been performed to establish the bioactivity of bioceramic materials.(23, 28) All magnetic nanoparticles used so far are composed of the iron oxides magnetite and maghemite due to their low toxicity and their known pathways of metabolism(13, 29) and its low-level release should not produce any deleterious effects.(30)(27)

The use of a material that can carry the magnetic particles, be applied by injection into the tumour and remains locally, will prevent the damage of other tissues and allow the entire body to be exposed to a magnetic field. The possibility of repeated exposures without the need of new injections is also desirable.(7, 10, 15, 17, 21, 24)

The recent success of magnetic hyperthermia in cancer therapy is very promising but the method still needs further improvement before it can become a standard medical procedure. In particular, two main tasks need to be addressed: first, a safe, comfortable, and reproducible application of particles to the tumour region is needed.(13) Second, absorbing materials capable of reaching and maintaining therapeutic temperatures inside tumour tissue need to be improved.(7)

The objective of this study was to review the use of biomaterials in the treatment of solid tumor by termotherapy with regard to experimental or clinical results, advantages, limitations and current status.(7)

Methodology

The databases used for this revison were PubMed, and Scientific Repositories of Open Access of Portugal.

The keywords that guided this review were: Hyperthermia Induced, Biocompatible Materials (Mesh terms), Ferrimagnetic Cement, Highly Focalized Hyperthermia, Magnetic particles, High frequency magnetic field.

As we may see on attachment I, In the PubMed database, using the keywords "Ferrimagnetic Cement", using the filters ‘’full text’’, ‘’from 2000 to 2018’’ and "systematic review" 0 articles were found; changing the type of article to ''review'', 1 article was found, being used 1; changing the type of article to ''Evaluation studies'', 3 articles were found, being used 3; changing the type of article to ''Research Support'', 3 article were found, being used 1; at least, changing the type of article to ''Clinical trial'', 1 article was found, being used 1.

In the PubMed database, using the keywords ''Hyperthermia Induced AND high frequency magnetic field", using the filters ‘’full text’’, ‘’from 2000 to 2018’’ and "systematic review" 1 article was found, being used 0; changing the type of article to ''review'', 7 articles were found, being used 3.

In the PubMed database, using the keywords ''Hyperthermia Induced AND Magnetic Particles", using the filters ‘’full text’’, ‘’from 2000 to 2018’’ and ''Author Manuscript'' 1 article was found, being used 1; changing the type of article to ''Reasearch Support'', 33 articles were found, being used 10; changing the type of article to ''Review'', 41 articles were found, being used 10; using the filter ''1993'' and the type of article to ''Biography'', 1 article was found, being used 1.

In the PubMed database, using the keywords ''Highly Focalized Hyperthermia", using the filters ‘’full text’’, ‘’from 2000 to 2018’’ and "Systematic Review'' 4 articles were found, being used 0; changing the type of article to ''Review'' 78 articles were found, being used 1; changing the type of article to ''Research support'' 1079 articles were found, being used 3.

In the PubMed database, using the keywords "Biocompatible Materials AND Hyperthermia Induced", using the filters ''full text'', ''from 2000 to 2018'' and "Meta-analysis" 1 article was found, being used 0; changing the type of article to "Reasearch support" 170 articles were found, being used 51; changing the type of article to "Systematic Review" 3 articles were found, being used 0; changing the type of article t "Review" 18 articles were found, being used 18;

In the PubMed database, using the keywords "High Frequency Magnetic Field", using the filters ''full text'', ''from 2000 to 2018'' and "Communication Engineering" 1 article was found, being used 1.

In the Scientific Repositories of Open Access of Portugal, using the keywords ''Hyperthermia'', using the filter ''doctoral thesis'', 47 articles were found, being used 1.

Results and Discussion

Hyperthermia in tumor's treatment

In spite of improvements in the conventional therapies such as radiation, immunotherapy, surgery or chemotherapy, many cancers, particularly solid tumours, are still untreatable.(15, 31) Hyperthermia is a largely studied method in the tumour treatment, alone or in association with the conventional therapies.(32-35) The *in vivo* effect of hyperthermia on the malignant cells:

- 41-43ºC have potentials for selective destruction of malignant cells;(15)
- Acess to areas difficult to reach with other forms of treatment;(15, 35)
- effect on the non-proliferating tumour cells and may specially sensitize proliferating tumour cells to other treatment modalities, irradiation and chemotherapeutics agentes;(15)
- In combination with irradiation/chemotherapy, can also substantially reduce the doses of highly toxic chemotherapeutic agents.(15, 32-35)

Physical principles of magnetic hyperthermia

The process of heat generation by magnetic nanoparticles less than 20 nm in diameter has been attributed to a combination of Néel and Brownian relaxations, which are rotation of the magnetic moment within a nanoparticle or of the entire nanoparticle within its surroundings, respectively.(7, 36) In the presence of an alternating magnetic field, the magnetic moment of a particle changes orientation to align with the field. As the particle moment returns to its equilibrium position, the magnetic energy dissipates as thermal energy. Brownian heating is a result of frictional losses associated with particle movement in low-viscosity fluids.(36, 37) Experimentation has indicated that the heating power of ferrofluids depends on the particle size, surface coating, and strength of the applied field.(10) The heat generation mechanism can be attributed to two different phenomena: relaxation and hysteresis loss.

Hysteresis losses

If magnetic materials such as dry magnetic nanoparticles are exposed to an external magnetic field, their magnetisation undergoes a closed loop during reversal of orientation: the hysteresis loop.

The area within the loop measures the magnetic energy delivered in the form of heat to the material of the magnetic particles during reversal of magnetisation. The energy conversion to heat is caused by the coupling of the atomic magnetic moments to the crystal lattice.(7) For larger particles the energy loss per cycle is reduced while for smaller particles the energy loss is enhanced due to an enhancement of the anisotropy energy barriers separating the different orientation states, causing the blockage of the magnetisation in the case of superparamagnetic nanoparticles.(13, 38)

Relaxational losses

The relaxation is oftwo types: Néel and Brownian relaxations. Heat generation through Néel relaxation is due to rapidly occurring changes in the direction of magnetic moments relative to crystal lattice (internal dynamics). This is hindered by energy of anisotropy that tends to orient magnetic domain in a given direction relative to crystal lattice. Brownian relaxation is due to physical rotation of particles within a medium in which they are placed (external dynamics) and is hindered by the viscosity that tend to counter the movement of particles in the medium.(32)

Biocompatible magnetic colloids for hyperthermia

Many of the new articles published on magnetic hyperthermia are devoted to the synthesis of magnetic nanomaterials with enhanced heating properties and/or targeting capabilities.(13, 24, 39, 40) (41)There is a relatively wide range of materials being currently tested as candidates for magnetic hyperthermia, but ferrimagnetic iron oxides, maghemite and magnetite,(13, 42) have become the common choice, for the following reasons:

- Better chemical stability against oxidation than metal nanoparticles;
- High magnetisation;
- Produce less induced oxidative stress toxicity in vivo;
- Relatively well known metabolism;
- FDA approved for use in humans;
- Pharmacokinetics;(27)
- short and long term tolerability in the body;(27)
- therapeutic or diagnostic functionality in the desired organ.(27)

Biocompatible shell-coated iron oxide nanoparticles are generally less toxic compared with naked ones; and the biocompatibility depends on the type of coating.(24, 27) The magnetic properties of particles are affected by a plurality of factors but the main control elements are particle size and size distribution. When optimally adapting the particle diameter to the applied field amplitude and frequency, the highest hysteresis losses are obtained for monodisperse particles.(7)

The administration of the particles to the body is a very sensitive point of hyperthermia, and is important for the success of the therapy with respect to magnetic heating.(7, 24, 25) On the one hand, there are several medical risks due to toxic effects or embolization, and on the other hand, after a possible agglomeration of particles during administration the heating power of nanoparticles may decrease, due to magnetic interactions between them.(9)(25)

Unfortunately, according to the literature, magnetic properties are highly size dependent and may not extract the maximum potential from nanoparticles(24, 43), whose higher magnetic hyperthermia efficiency occurs at larger particle sizes (around 20 nm), while higher tumour accumulation and penetration are observed at lower particle sizes.(11)

The most common routes are wet chemical methods, but there are many other methods including laser evaporation, milling of larger particles, or biomineralization in bacteria.(9) Cespedes et al. have demonstrated the potential for MH applications using biogenic MNP innovatively prepared by cultures of the bacterium *Geobacter sulfurreducens*. The successful doping of these particles with Co or Zn enabled the variation of the magnetic anisotropy, saturation magnetization and nanoparticle sizes, which leads to variations in the heating properties at different frequencies and in different environments.(12)

Despite the biocompatibility of iron oxide it self, depending on the preparation route, MNP may have surface modifications which result in toxic behaviour and thus prove to be unfavourable for medical application. Biocompatibility of such particles can be increased considerably by coating the core with a dense biocompatible layer which masks the toxicity of the core.(9, 44) Surface coating also retards a quick opsonisation (protein binding) after entering into the bloodstream.(13) These coatings include dextran, polyetyleneglycol, chitosan, aminosilane, glucuronic acid or citric acid, among others, but more and more frequently they include cytotoxic drugs, antibodies and other markers to target malignant cells more efficiently.(9)

Laurent et al found a clear correlation between composition of protein corona and cellular uptake and toxicity of particles. Investigation of protein corona formed during cellular uptake and the resulting biological fate of the incorporated MNP is a novel promising research field, which may lead to new and fundamental findings useful for the development of biocompatible MNP(45).

Hyperthermia in tumour's destruction

The appropriate physiologic response to heat is vasodilatation and the response of tumour vasculature is distinct from healthy vessels(15). Although higher temperatures can cause vascular shutdown and necrosis with reduced perfusion and increased hypoxia, milder temperatures (below ≈ 42ºC) will typically stimulate perfusion in the tumour and improve oxygenation (15). In addition, temperature elevation will reduce the oxygen binding of haemoglobin, contributing to increased delivery of oxygen within a region of localized hyperthermia. The tumour treatment by hyperthermia consist in the temperature increase in the tumour and a vascular collapse ensues due to a preferential:

- increase in red blood cell rigidity;
- endothelial cell swelling;
- haemorrhage into capillary lumens;
- leukocyte adherence to vessel walls;(15)

This process is first seen in tissues at approximately 42ºC.

The most probable mechanism of delivering heat to the surrounding medium is due to heat conduction. During field application a balance between heat generation in the particles and the flow of heat into the surrounding tissue must be established. Particles with smaller diameter generate more heat, as we can see in table I. It is this balance which determines the attainable temperature in the particle-containing tissue. They considered a spherical region of internal constant heat production—irrespective of whether the heat in that region originates from many homogeneously distributed small particles or is only due to one large object. The transport in the medium outside of that spherical heat production zone may be characterized by the well-known heat conductivity of water.(9)

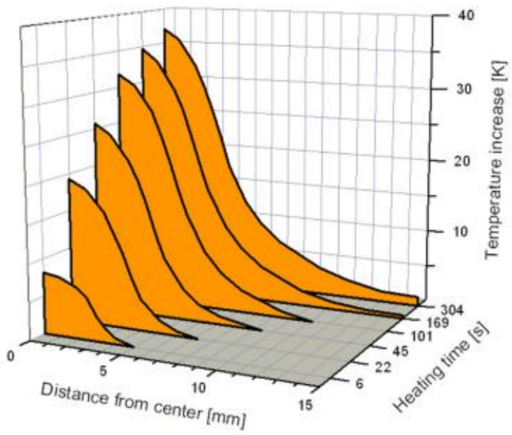

FIGURA 1 TEMPORAL EVOLUTION OF THE TEMPERATURE DISTRIBUTION AROUND A SPHERICAL REGION OF HEAT GENERATION (RADIUS 3,15 MM) CALCULATED BY SOLVING THE HEAT CONDUCTION PROBLEM. DUTZ S. ET AL (UNAUTHORIZED)

Celular response

The acidic, hypoxic, and nutrient poor condition within a cancer(17), subsequently exacerbated by hyperthermia, makes an otherwise survivable condition incompatible with cell life(15). The establishment of the neovascular supply is an attempt to overcome the hypoxia, but this is inefficient and irregular.(15) The result is the persistence within the tumour mass of heterogeneous micro-regions of nonproliferating hypoxic cells, which are surrounded by vital, well nourished, and proliferating cells.(15) The hypoxic microenvironments are characterized by low oxygen tension, low extracellular pH, high interstitial fluid pressure, glucose deficiency, increased extracellular lactate concentration and tendency to metastasization.(15) These tumour cells, chronically exposed to low extracellular pH, are relatively resistant to ionizing radiation and multidrug resistant, but they tend to be markedly sensitive to the thermal damage.(7)

Cells thermal damage will occur when the amount of heat delivered provides energy in the range of 100–150 kcal/mole, the range of that necessary for protein denaturation.(15) The rate-limiting step in thermal damage is likely to be this proteins denaturation and DNA damage repair, resulting in disruption of cellular structure and function.(15, 17) Heated cells show inactivation of membrane receptors, altered enzyme activity, altered cellular structures, and chromosomal damage and miss-repair.(15)

Immunity induction

The heat produced during MHT not only destroys the tumor cells but also boosts the activity of the majority of cytostatic drugs and activates the immunological response of the body.(10, 24) Immunocytochemical assay revealed that both CD8-positive and CD4 positive T cells migrated in the tumours after the hyperthermia treatment.(15) These results suggest that these therapeutic magnetic particles are potentially effective tools for hyperthermic treatment of tumours, because in addition to the killing of tumour cells by heat, a host immune response is induced.(15)

Heat Shock Proteins – HSPs

HSPs appear to be related to the heat effect on tumour cells essentially by different mechanisms(17):

- Correlation between induction of HSPs and development of tolerance to subsequent thermal shock. As the expression of HSPs protects cells from heat induced apoptosis, it can be considered a complicating factor in hyperthermia.(15)
- Use of HSPs in immunotherapy for the cancer treatment.(15, 17)

These facts are apparently in contrast each other, but, tacking in to account their different mechanisms of action, a possible concatenation can exist.(15)

It has been demonstrated that tumour-derived HSPs, such as HSP70, HSP90 and glucose-regulated protein 96 (gp96), can elicit cancer immunity.(15)

Thermotholerance refers to the adaptive responses of cells exposed to elevated temperatures.(17) In this regard, a mild heat shock treatment conditions, induces cells to withstand to the effects of a subsequent temperature insult, which would otherwise be lethal(15). Thermotholerance is at least partially based on the induction of heat-shock proteins (HSP) and other post-transitional adaptation processes.(15) The induction of HSPs in response to stress and the subsequente thermotholerance is transient.(15) When the stress element (heat) is removed, these cells continue to function normally and the levels of HSPs drop back to basal levels with time(15). When a cell experiences low level stress, it activates the stress response, which involves rapid induction of HSPs. Accumulation of HSPs accompanies thermotholerance and resistance to cells death.(15) When the stress element is removed, the cells return to their normal activities. As the stress level increases, the injured cells activate their own demise and undergo apoptosis.(15)

Magnetically mediated hyperthermia

The magnetically mediated hyperthermia technique consists of localizing magnetic particles or seeds within tumour tissue and then applying an external AMF(24) - that is generated by external coils situated outside of the patient's body(9). This heat then conducts into the surrounding cancerous tissue.(15) Magnetic particle heating for thermal tumour therapy is based on several loss mechanisms that occur during reversal of magnetisation when magnetic nanoparticles are exposed to an external alternating field.(7) The effectiveness of a hyperthermia treatment apparatus depends crucially on the following technical parameters, namely the amplitude and frequency of the magnetic field.(9) Is very importante having a coil with big current because, producing a localized hyperthermia dose to deep-seated tumors is still very difficult and the magnetic field decreases very quickly when apart from the current source It was found that in addition to the absolute value of temperature, the duration of the exposure to the elevated temperature plays a crucial role.(46) Dewhirst et al found a greater reduction in tumour volume when using a few large thermal doses with higher temperatures than when using a larger number of doses with lower temperatures.(25) This has led to suggestions that a 'thermal dose' may be defined, in analogy to what is usually done for irradiation damage. In a series of first therapeutic trials of hyperthermia, the authors report that a treatment time of 60 min at 43 °C may be halved to 30 min at 44 °C, but the treatment time has to be increased four times to 240 min at 42 °C, as can be seen in figure II.(9)

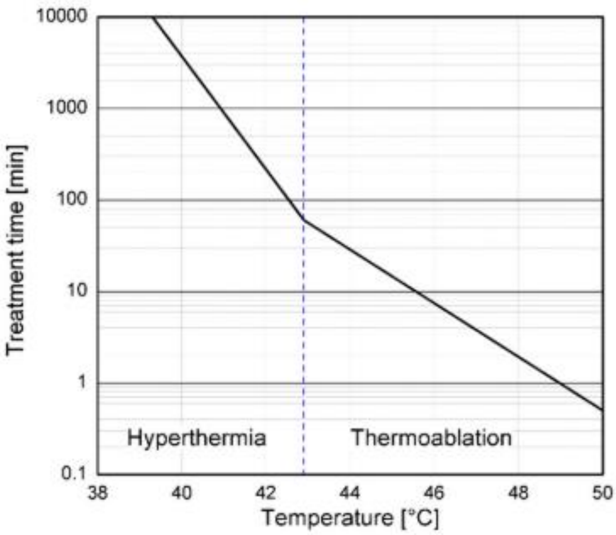

Figura 2 ''Isoeffect time'' in dependence on treatment temperature for hyperthermia and thermoablation. Johannson et al (unauthorised)

Highly Focalized Thermotherapy

This method consist in the direct injection of a material into the tumour and the subsequent exposition to an external high frequency magnetic field.(17, 24) The magnetic energy supplied by the external alternating magnetic field is converted into heat within the magnetic nanoparticles, which is depleted into the surrounding medium.(7, 10) that will heat the magnetic particles and subsequently, the tumour cells.(15) For this purpose, Cavalheiro et al. developed a material in the form of an injectable paste.(15) Successful *in vitro* studies were performed to assess the biocompatibility of this material, which was later *used in vivo* to treat solid tumours.(15) Treatments were effective in small tumours, with a significant reduction of the tumour, but the injection of larger quantities in larger tumours was lethal to some animals, because of the material toxicity.(15)

There are serious practical difficulties for achieving an adequate particle distribution.(9) Of course, the nanoparticle suspension is not homogeneously soluble in organic tissue.(24) During injection it rather displaces the organic matter while distributing itself along of weakest links of the structurally inhomogeneous tissue. Nevertheless, under the therapy, the real 3D temperature distribution in the tumour has to be controlled carefully.(47) The adequate filling of a tumour with nanoparticles remains one of the most serious problems of the MPH therapy. Since the particle distribution cannot fit a complicate tumour shape properly, the elimination has to consider keeping a security fringe in healthy tissue. In this case the situation is similar to tumour elimination by surgery. The temperature pattern under magnetic field excitation reflects the actual concentration distribution of nanoparticles.(9)

Biodistribution and toxicity

Iron oxide nanoparticles are usually taken up by macrophages in the mononuclear phagocytic system of the liver, spleen, lymphatics, and bone marrow.(13) The associated blood half-lives depend on particle size and coating; smaller nanoparticles have generally longer half-lives and are taken up by lymph nodes, whereas the bigger ones have shorter half-lives and are taken up by the liver and spleen.(13) Magnetite in vivo degradation is believed to induce oxidative stress through the formation of hydroxyl radicals, which could potentially affect DNA bases; nevertheless, recent in vitro studies have discarded any mutagenic effects caused by iron oxide nanoparticles.(13, 48)

In a study of Almeida T. et al it was studied the Silicon and iron levels in tissues of animals treated with a ferrimagnetic ceramic with oncotherapeutic potential (anti-tumor) value – a glass powder. The experimental model was the rat, and organs (liver, kidney, spleen, lung, heart, and brain) of the implanted and control animals were collected for quantification of these elements by electrothermal atomization atomic absorption spectrometry methods. The release of silicon and iron, if any, is not significant as demonstrated by analysis of the principal organs.(49) Although there is the uncertainty of extrapolation of these results to human beings, the material studied seems to pose no additional health risk for patients to be implanted with the bioceramic, although clinical trials have to be performed.(50)

One of the approaches for delivering therapeutic agents to tumours is passive targeting.(13) This takes advantage of both the high permeability associated to the tumour vasculature and the fluid retention caused by its defective lymphatic system, which leads to particle accumulation over time in the affected tissue.(13) This implies that the concentration of nanoparticles and other macromolecules can be 100 times higher than in normal tissues – albeit that even this is usually not enough to ensure a therapeutic dose at the tumour site.(13)

The other approach is active targeting, which makes use of either locally or systemically administered nanoparticles functionalised with antibodies that specifically bind to the targeted tumour, constituting a first step towards tailored treatments.(10, 13) There has been a burgeoning activity around this concept during the past ten years but it has been lately taken to a higher level with the design of multifunctional nanocarriers.(13) Cho et al. succeeded in synthesising magnetic nanospheres integrating fluorescent superparamagnetic nanoparticles for multimodal imaging and hyperthermia, specific antibodies for cell targeting and anticancer drugs for localised treatment.(13)

Biomaterials Classification (composition)

Varied materials, as can be seen in figure 3, proceeding from the world of metals, ceramics, polymers and the composites, have been determining new methodologies and alternative treatments, in the fight against many diseases or in the development of new generations of soft or hard tissues implants.(15)

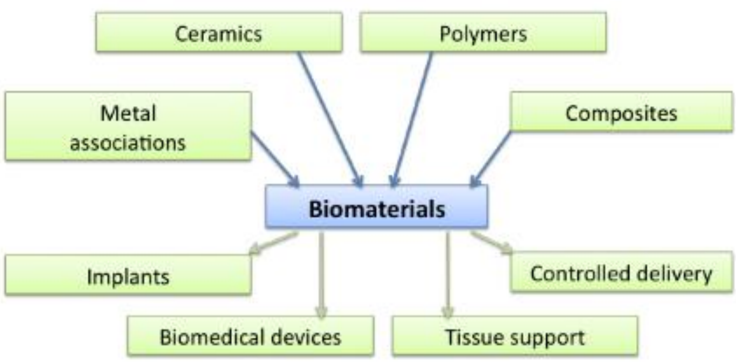

FIGURA 3 BIOMATERIALS COMPONENTS AND FREQUENT APPLICATIONS IN THE BIOMEDICAL FIELD. PORTELA. A (UNAUTHORIZED)

Magnetic nanoparticles have been a subject of great interest in recent years due to their unique physio-chemical properties and potential biomedical applications such as magnetic separation, magnetic resonance imaging (MRI)(11, 32), targeted drug delivery and thermotherapy of cancer (so-called hyperthermia)(51) immunoassay, detoxification of biological fluids, hyperthermia, drug delivery, cell separation, etc.(10, 52) MNPs) are typically single or multiple inorganic crystals of a magnetic material coated with or embedded within a biocompatible polymer, or a gold or silica shell enabling functionalisation.(53-56)

The nanoparticles extract high energy per applied mass from a magnetic field. Due to their enormous surface the nanoparticles are:

- able to carry a huge number of binding sites for cancer cells/ target molecules;
- able to intrude deeply into tumor tissue.(5)

With special coatings, the nanoparticles are recognized delayed by the immune system and thus reach their targets.(5, 57) The nanoparticles can be ingested in great quantities by tumor cells and they can form a homogeneous fluid of low viscosity in water.(5) The morphological properties of the nanoparticles, including their size, structure and shape are mainly responsible for heat transmission.(5, 10, 12) The type and thickness of functional layers used for stabilizing nanoparticles can significantly influence heating ability.(24, 26) However, unprotected nanoparticles can easily form aggregates when they are directly exposed to biological systems and react with oxygen in the air.(27) The specific absorption rate, which actually controls the heating of the tumour cells is pronounced as the heating potential of the nanoparticles (the amount of heating delivered per unit mass and time as a consequence of the exposure of the nanoparticles to an alternating magnetic field).(5) This important parameter actually dictates the dosages which have to be applied to the tumour region, in order to achieve an inactivation of target cells.(5, 26)

The most popular magnetic silica nanocomposites have a core/shell structure. The shell is silica that coats a magnetic core. Different magnetic nanoparticles could be encapsulated into these magnetic nanocomposites.(10, 27)

The most common parameter for measurement of the heating rate is specific absorption rate (SAR), also called specific loss power (SLP)(58). A high SAR is a required factor for nanoparticles in magnetic hyperthermia.(12) This factor is the amount of heat dissipated per unit mass of the magnetic material in an AMF (1)(32), and the SLP of different particle types may vary by orders of magnitude in dependence on structural and magnetic particle properties as well as magnetic field amplitude.(37, 58)

Different types of nanoparticles

Different types of biocompatible nanoparticles have been used in the literature. Such particles are directly injected into the tumor tissue, where they are stimulated by an alternating magnetic field to produce heat due to Brownian and Néel relaxation processes.(5) Iron-oxide nanoparticles are directly injected into the tumor and release heat after inductively induced activation by an alternating magnetic field.(5) Superparamagnetic iron oxide nanoparticles (SPIONs) have excellent biocompatibility as well as multi-purpose biomedical potential.(5, 59, 60) Even though the presence of Mn, Co, Ni in SPIONs composition significantly enhancing the SLP, the oxidative instability and free radical induced toxic mechanisms (apoptosis mostly) with these elements are still a concern.(32, 61) Iron oxides can be synthesized through the co-precipitation of Fe^{2+} and Fe^{3+} aqueous salt solutions by addition of a base.(5) The control of size, shape and composition of nanoparticles depends on the type of salts used (e.g. chlorides, sulphates, nitrates, perchlorates, etc.), Fe^{2+} and Fe^{3+} ratio, pH and ionic strength of the media.(5)

Ceramic coated magnetic metal-oxide nanoparticles as MNPs have been of interest in the medical field for use in magnetic hyperthermia. Examples of different nanoparticles developed for magnetic hyperthermia are Si glass ceramics or FeSi microspheres. Bioactive glasses are a promising group of biomaterials and have a wide range of applications.(62) They exhibit unique properties like osteoinductive behaviour, ability to bond to soft and hard tissues and formation of a carbonated hydroxyapatite layer when exposed to biological fluid. The porosity of bioactive glasses makes it an excellent candidate for protein delivery. Bioactive glass can be made magnetic by incorporating magnetic materials into the core of the glass matrix and it could be widely used for magnetic hyperthermia treatment for tumour targeted drug delivery.(62-64)

Arcos D. et al studied three biphasic materials that have been synthesized from a magnetic glass–ceramic (Si-Ca-Fe) and a bioactive sol–gel glass (Si-P-Ca), to replace bone on surgical bone tumors removal. Biphasic materials are attractive potential candidates for hyperthermia treatment. The glass–ceramic provides magnetic properties to produce heat, whereas the sol–gel glass ensures the bioactive behavior of the material.(28) Bruno, M et al propose a composite formed with a PMMA matrix in which a ferrimagnetic biocompatible/bioactive glass ceramic is dispersed, to treat cancers in bone. The structural ones are conferred by PMMA which acts as filler for the bone defect or its damaged area. Bioactivity is conferred by the composition of the residual amorphous phase of the glass-ceramic and magnetic properties are conferred by magnetite crystals embedded in the bioactive glass-ceramic.(14, 65, 66)

Once implanted or injected in the body, magnetic materials can behave as thermoseeds under the effect of AC magnetic fields. Metallic thermoseeds commonly consist of sections of wire and are oriented parallel to their axes in the oscillating magnetic field. Among the different metals and alloys tested, nickel–silicon, nickel–copper, nickel–palladium and iron–platinum have shown very interesting properties but different *in vivo* studies have demonstrated biocompatibility problems related to corrosion. Magnetic thermoseeds based on magnetite and maghemite, have attracted the attention of many research groups for their use in hyperthermia treatment of cancer, an excellent alternative that overcomes the biocompatibility drawbacks of metallic alloys.(67, 68)

Gold nanoparticles have been extensively used in the literature for the hyperthermia treatment.(10, 69) While gold has many favorable properties as a bulk metal (such as high electrical conductivity, reflectivity, malleability, and resistance to corrosion and oxidation), new properties and potential applications emerge when it is finely divided into the nanoscale.(24) Gold has high atomic number which enhances the effect of radiotherapy which is further induced by laser hypothermia.(5) One of the recent development is the use of colloidal solutions of bifunctional luminescent neodymium ions doped a-NaYF4 colloidal nanoparticles.(5) These particles may be excited in visible or near infrared range. The infrared excitation is compatible with the windows of biological tissues and achieve sufficient penetration depths compared either visible or UV-range.(5) This characteristic is also coupled with long luminescence times. Optimisation at 95ºF was achieved in 25% Nd^{3+}: NaYF4 solution. (5)The work reported has the potential to develop therapeutic agents which could be deducted by molecular agents.(5) Though strides have been made in this direction, the greatest challenge now is to continue to enhance our understanding of the behavior and fate of gold nanostructures in complex *in vivo* environments, and truly make these techniques clinically relevant.(69) Gold nanoparticles coated with biological agents permeate the tumour cells and localize with endosomes.(5, 10) The lower pH within the endosome allows an easy passage for the drug release into the target area.(5)

Magnetite cationic liposomes magnetite cationic liposomes (MCLs), one of the groups of cationic magnetic particles (with improved adsorption and accumulation properties within tumors and demonstrated the efficacy of their technique in several animal tumor models(29)) , can be used as carriers to introduce magnetite nanoparticles into target cells since their positively charged surface interacts with the negatively charged cell surface; furthermore, they find applications to hyperthermic treatments.

Magnetite nanoparticles conjugated with antibodies (antibodyconjugated magnetoliposomes, AMLs) have enabled tumor-specific contrast enhancement in MRI (11)via systemic administration.(5, 9) Since magnetic nanoparticles are attracted to a high magnetic flux density, it is possible to manipulate cells labeled with magnetic nanoparticles using magnets.(5) The applications of these functionalized magnetic nanoparticles with their unique features will further improve medical techniques.(5, 26)

Carbon or polymeric nanoparticles labeled with fluorine-18 deoxyglucose have been studied in preclinical models to enhance tumor diagnosis and detection rates using positron emission tomography.(5) Ludwig et al. proposed a functional cover made up of core-shell nanofibers with a unique combination of thermoresponsive polymeric shell and stretchable polymeric core (poly-(NIPAAm-co-HMAAm)/polyurethane core-shell nanofiber) for non-vascular nitinol stents that uses an alternating magnetic field to induce heat in the stent for hyperthermia therapy and simultaneously release 5-fluorouracil and/or paclitaxel, combinig effective synergy between thermoterapy and chemotherapy in cancer treatment.(70)

Single walled carbon nanotubes (SWNTs) have a wide dynamic range of electromagnetic absorptions that arise from their one dimensional structure which consists of a honeycomb pattern of carbon that is rolled into a seamless cylinder forming a thin cylindrical form of carbon.(5) The conductivity of carbon nanotubes is determined by the crystalline arrangement of carbon of the cylindrical wall.(5) Several popular methods including co-precipitation, microemulsion, thermal decomposition, solvothermal, sonochemical, microwave-assisted, chemical vapor deposition, combustion, carbon arc, and laser pyrolysis, for the synthesis of magnetic nanoparticles have been discussed with detailed references.(5) Nanotubes are either metallic or semiconducting depending on the twist in the graphitic carbon wall.(5)

Green nanotechnology has attracted a lot of attention and includes various processes which reduced toxicity.(5, 71) The biosynthesis of metal nanoparticles by plants is currently under development.(5) Biological methods of nanoparticle preparation using microorganisms, enzymes, fungi and plants or plant extracts are the possible substitutes to chemical and physical methods and remarkable work to date.(5) The green synthesis has many advantageous features for the synthesis of magnetic nanoparticles.(5) Remarkably, magnetite nanocrystals synthesized in magnetosomes by magnetotactic bacteria, exhibit among the largest reported SAR values.(12)

Conclusions

The MHT used in tumours treatment has led to significant advances. The increased understanding has highlighted the complexity of the problem, and future successes will be dictated by the development of tailored protocols for a given type of cancer, rather than find a generic multipurpose method. However, despite the promising results, hyperthermia has not yet been established in clinical routine.

Another important point requiring well-focused efforts is in reducing the concentration of magnetic fluid to be administered. This may be possible through the incorporation of new materials with better heating properties than iron oxides, the most studied system so far. Moreover, the fate of the iron oxide nanoparticles once injected in the body (elimination route, biodegradability, toxicity of the metabolites, etc) and their tissue distribution must be clearly elucidated. In addition, clearance mechanisms have to be taken into account in designing new nanoparticles for MHT.

Thermal therapies are attractive for cancer therapy as this physical approach avoids concerns with drug resistance and biological variability between tumor types. Nanoparticles can offer the opportunity to develop multifunctional platforms for integrated imaging (to reach a well-controlled temperature distribution in tumor tissue) and therapy.

Finally, despite many open questions and restrictions, it can be stated without a doubt that research on magnetic hyperthermia in the past decade has led to a much more profound understanding of the whole topic, and significant progress has occurred in all related aspects of this promising cancer therapy. The complexity of hyperthermia is obvious and demands a careful and comprehensive interpretation of the results and correlation of the findings to find strategies for further improvement of the present state of the art in hyperthermia.

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Attachments

Attachment I - Methodology

Electronic Search in PubMed database							
Key-word	Years	Type of Studie	Articles (nº)	Elected Articles (nº)	Selected Articles (nº)	Excluded	Included
Ferrimagnetic Cement	2000-2018	systematic review	0	-	-	-	-
		review	1	1	Composite bone cements loaded with a bioactive and ferrimagnetic glass-ceramic.	-	x
		Evaluation studies	3	3	''Highly focalised thermotherapy using a ferrimagnetic cement in the treatment of a melanoma mouse model by low temperature hyperthermia.'', '' An in vitro and in vivo investigation of the biological behavior of a ferrimagnetic cement for highly focalized thermotherapy.'', '' Silicon and iron levels in tissues of animals treated with a "ferrimagnetic ceramic" with oncotherapeutic potential (anti-tumor) value''	-	x
		Research Support	3	1	'' In vitro biocompatibility of a novel Fe2O3 based glass ionomer cement''	-	x
		Clinical trial	1	1	'' A rat osteoporotic spine model for the evaluation of bioresorbable bone cements''	x	-
Hyperthermia, high frequency magnetic field	2000-2018	Systematic Review	1	0	-	-	-
		Review	7	3	'' Developing Antitumor Magnetic Hyperthermia: Principles, Materials and Devices. '', '' Magnetic resonance temperature imaging for guidance of thermotherapy. ''	x	-
					'' Magnetically mediated hyperthermia: current status and future directions''	-	x
Hyperthermia, magnetic particles	2000-2018	Author Manuscript	1	1	''MAGNETIC NANOPARTICLE HYPERTHERMIA IN CANCER TREATMENT''	-	x
		Research Support	33	10	'' Bacterially synthesized ferrite nanoparticles for magnetic hyperthermia applications'', '' The role of hyperthermia in the battle against cancer'', '' RGD-conjugated iron oxide magnetic nanoparticles for magnetic resonance imaging contrast enhancement and hyperthermia', "Inhibition of heat shock protein 90 sensitizes melanoma cells to thermosensitive ferromagnetic particle-mediated hyperthermia with low Curie temperature","Tumor regression by combined immunotherapy and hyperthermia using magnetic nanoparticles in an experimental subcutaneous murine melanoma", "PMMA-based bone cements containing magnetite particles for the hyperthermia of cancer", "Magnetic particle hyperthermia: nanoparticle magnetism and materials development for cancer therapy", "Focused RF hyperthermia using magnetic fluids", "Self-regulating hyperthermia induced using thermosensitive ferromagnetic material with a low Curie temperature", "Real-time infrared thermography detection of magnetic nanoparticle hyperthermia in a murine model under a non-uniform field configuration"	-	x

		Review	41	10	"Relationship between physico-chemical properties of magnetic fluids and their heating capacity", "Nanoparticles for cancer therapy using magnetic forces", "Nanomedicine : Magnetic nanoparticles for drug delivery and hyperthermia - new chances for cancer therapy].", "Nanomedicine: magnetic nanoparticles and their biomedical applications", "Research progress on application of gold magnetic nanocomposite in biomedicine"	x	-
					"Magnetic nanoparticle heating and heat transfer on a microscale: Basic principles, realities and physical limitations of hyperthermia for tumour therapy", "Application of hyperthermia for cancer treatment: recent patents review", "Medical applications of magnetic nanoparticles", "Magnetic iron oxide nanoparticles for tumor-targeted therapy", "Magnetic nanoparticles adapted for specific biomedical applications", "Effects of size distribution on hysteresis losses of magnetic nanoparticles for hyperthermia", "Magnetic particle hyperthermia--a promising tumour therapy?", "Cancer hyperthermia using magnetic nanoparticles", "Antitumor immunity by magnetic nanoparticle-mediated hyperthermia"	-	x
	1993	Biography	1	1	''Inductive heating of ferrimagnetic particles and magnetic fluids: physical evaluation of their potential for hyperthermia''	x	-
Highly Focalized Hyperthermia	2000-2018	Systematic Review	4	0	-	-	-
		Review	78	1	'' Clinical applications of magnetic nanoparticles for hyperthermia''	-	x
		Research Support	1079	3	'' Significance of cell ''observer'' and protein source in nanobiosciences'', '' Therapeutic mechanism of treating SMMC-7721 liver cancer cells with magnetic fluid hyperthermia using Fe_2O_3 nanoparticles'', '' In vitro assessment of poly(methylmethacrylate)-based bone cement containing magnetite nanoparticles for hyperthermia treatment of bone tumor''	-	x
Biocompatible Materials, Hyperthermia	2000	Meta-analysis	1	0	-	-	-
		Research support	170	51	'' Practical aspects of ferromagnetic thermoseed hyperthermia'', '' Investigation on Tc tuned nano particles of magnetic oxides for hyperthermia applications.''	x	-

	- 2018				"In vitro study on apoptotic cell death by effective magnetic hyperthermia with chitosan-coated $MnFe_2O_4$-", "Chitosan-coated triangular silver nanoparticles as a novel class of biocompatible, highly effective photothermal transducers for in vitro cancer cell therapy", "Biocompatibility of Fe_3O_4@Au composite magnetic nanoparticles in vitro and in vivo", "Plasmonic nanodiamonds: targeted core-shell type nanoparticles for cancer cell thermoablation", "Biocompatibility of Mn0.4Zn0.6Fe2O4 Magnetic Nanoparticles and Their Thermotherapy on VX2-Carcinoma-Induced Liver Tumors", "Magnetic and degradable polymer/bioactive glass composite nanoparticles for biomedical applications", "Calculation of heating power generated from ferromagnetic thermal seed (PdCo-PdNi-CuNi) alloys used as interstitial hyperthermia implants", "Magnetic Hyperthermia Ablation of Tumors Using Injectable Fe_3O_4/Calcium Phosphate Cement", "Synthesis and characterization of PEG-iron oxide core-shell composite nanoparticles for thermal therapy", "Silica coated gold nanorods for imaging and photo-thermal therapy of cancer cells", "In vitro heat generation by ferrimagnetic maghemite microspheres for hyperthermic treatment of cancer under an alternating magnetic field", "Preparation of ferrimagnetic magnetite microspheres for in situ hyperthermic treatment of cancer.", "Optimizing magnetic nanoparticle design for nanothermotherapy", "Synthesis, characterization and in vitro study of biocompatible cinnamaldehyde functionalized magnetite nanoparticles (CPGF Nps) for hyperthermia and drug delivery applications in breast cancer.", "Bioactive magnetic nanoparticles of Fe-Ga synthesized by sol-gel for their potential use in hyperthermia treatment.", "Carboxyl decorated Fe3O4 nanoparticles for MRI diagnosis and localized hyperthermia", "'Smart' gold nanoshells for combined cancer chemotherapy and hyperthermia", "Carboxymethyldextran/magnetite hybrid microspheres designed for hyperthermia.", "Surface chemistry and entrapment of magnesium nanoparticles into polymeric micelles: a highly biocompatible tool for photothermal therapy", "Magnetic bioactive glass ceramic in the system CaO-P2O5-SiO2-MgO-CaF2-MnO2-Fe2O3 for hyperthermia treatment of bone tumor", "Preparation of magnetic and bioactive calcium zinc iron silicon oxide composite for hyperthermiatreatment of bone cancer and repair of bone defects", "Evaluation of CaO-SiO2-P2O5-Na2O-Fe2O3 bioglass-ceramics for hyperthermia application", "Targeting to carcinoma cells with chitosan- and starch-coated magnetic nanoparticles for magnetic hyperthermia", "TC-tuned biocompatible suspension of La0.73Sr0.27MnO3 for magnetic hyperthermia", "Magnetic mesoporous silica spheres for hyperthermia therapy", "Determining iron oxide nanoparticle heating efficiency and elucidating local nanoparticle temperature for application in agarose gel-based tumor model", "Comparative evaluation of heating ability and biocompatibility of different ferrite-based magnetic fluids for hyperthermia application.", "Ag-doped manganite nanoparticles: new materials for temperature-controlled medical hyperthermia", "Silica encapsulated manganese perovskite nanoparticles for magnetically induced hyperthermiawithout the risk of overheating", "Sr-hexaferrite/maghemite composite nanoparticles-possible new mediators for magnetichyperthermia", "Magnetic silica nanocomposites for magnetic hyperthermia applications", "TC-tuned biocompatible suspension of La0.73Sr0.27MnO3 for magnetic hyperthermia", "Inductive heat property of Fe3O4/polymer composite nanoparticles in an ac magnetic field for localized hyperthermia", "Preparation of ferrimagnetic magnetite microspheres for in situ hyperthermic treatment of cancer.", "Investigation on Tc tuned nano particles of magnetic oxides for hyperthermia applications.", "Biocompatible magnetic microspheres for Use in PDT and hyperthermia", "Nanosized As2O3/Fe2O3 complexes combined with magnetic fluid hyperthermia selectively target liver cancer cells.", "Functionalization of strongly interacting magnetic nanocubes with (thermo)responsive coating and their application in hyperthermia and heat-triggered drug delivery", "Magnetically induced hyperthermia: size-dependent heating power of γ-Fe(2)O(3) nanoparticles", "Biphasic materials for bone grafting and hyperthermia treatment of cancer", "Enzymatic preparation of hollow magnetite microspheres for hyperthermic treatment of cancer","Multimodality treatment of cancer with herceptin conjugated, thermomagnetic iron oxides and docetaxel loaded nanoparticles of biodegradable polymers.", "In vitro positive biocompatibility evaluation of glass-glass ceramic thermoseeds for hyperthermic treatment of bone tumors", "Magnetic multicore nanoparticles for hyperthermia--influence of particle immobilization in tumour tissue on magnetic properties", "Size-sorted anionic iron oxide nanomagnets as colloidal mediators for magnetic hyperthermia", "A smart, phase transitional and injectable DOX/PLGA-Fe implant for magnetic-hyperthermia-induced synergistic tumor eradication", "In vitro biocompatibility of a ferrimagnetic glass-ceramic for hyperthermia application", "Multifunctional magnetic nanostructured hardystonite scaffold for hyperthermia, drug delivery and tissue engineering applications", "On-demand drug release and hyperthermia therapy applications of thermoresponsive poly-(NIPAAm-co-HMAAm)/polyurethane core-shell nanofiber mat on non-vascular nitinol stents.", "Sol-gel synthesis, characterization, and in vitro compatibility of iron nanoparticle-encapsulating silica microspheres for hyperthermia in cancer therapy"	-	x
		Systematic Review	3	0	-	-	-

		Review	18	18	‘’ In vivo applications of magnetic nanoparticle hyperthermia’’, ‘’ Practical aspects of ferromagnetic thermoseed hyperthermia’’, ‘’ Applications of magnetic nanoparticles in medicine: magnetic fluid hyperthermia’’	x	-
					‘’ "Magnetic hydroxyapatite: a promising multifunctional platform for nanomedicine application", "Hybrid biomaterials based on calcium carbonate and polyaniline nanoparticles for application in photothermal therapy.", "Physics of heat generation using magnetic nanoparticles for hyperthermia", "Nanoparticles for thermal cancer therapy", "Oxide and hybrid nanostructures for therapeutic applications", "Structured superparamagnetic nanoparticles for high performance mediator of magnetic fluid hyperthermia: Synthesis, colloidal stability and biocompatibility evaluation", "Recent advances in nanosized Mn-Zn ferrite magnetic fluid hyperthermia for cancer treatment.", "Cell death induced by AC magnetic fields and magnetic nanoparticles: current state and perspectives.", "Magnetic fluid hyperthermia: advances, challenges, and opportunity", "Recent advances in nanosized Mn-Zn ferrite magnetic fluid hyperthermia for cancer treatment", "Magnetic fluid hyperthermia: Focus on superparamagnetic iron oxide nanoparticles", "Gold nanostructures: a class of multifunctional materials for biomedical applications", "A review on hyperthermia via nanoparticle-mediated therapy", "Physics of heat generation using magnetic nanoparticles for hyperthermia.", "Thermoseeds for interstitial magnetic hyperthermia: from bioceramics to nanoparticles"	-	x
high frequency magnetic field	2000-2018	Communication Engineering	1	1	‘’Design and construction of a hyperthermia system with improved interaction of magnetic induction-heating’’	-	x

Attachment II – Biomatherials Table

Author	Year	Title	Biomatherial Name	Class	Conclusions
Almeida, T. et al(50)	2002	Silicon and iron levels in tissues of animals treated with a "ferrimagnetic ceramic" with oncotherapeutic potential (anti-tumor) value	SiO 2 (35.6%), CaO (42.4%), P~O 5 (17%), Na20 (5%) and 30% of its weight of Fe304 dissolved in (NH4)2HPO 4 plus NH~H2PO	Glass powder - ceramic	The material of the bioceramic implant is stable. The release of silicon and iron, if any, is not significant as demonstrated by analysis of the principal organs.
Aguilar, L. et al(70)	2017	On-demand drug release and hyperthermia therapy applications of thermoresponsive poly-(NIPAAm-co-HMAAm)/polyurethane core-shell nanofiber mat on non-vascular nitinol stents	thermoresponsive poly-(NIPAAm-co-HMAAm)/polyurethane core-shell nanofiber	Polymer - composite	Appropriate temperature response of the p-NP-HM componente; the co-polymer can be used in multiple cycles, crosslinking process must be observed; 45 °C hyperthermia adjunct with dual chemotherapy drug release is beneficial for treating this kind of cancer
Ansari, et al.(27)	2016	Magnetic silica nanocomposites for magnetic hyperthermia applications	- Fe3O4-polymer Core/ silica shell with atherosclerotic plaque-specific peptide-1 (AP-1) as targeting ligand - n situ forming implants (ISFI) entraps superparamagnetic iron oxide nanoparticle (SPION) embedded in silica microparticles -Biphasic suspension of mesoporous silica encapsulated with YVO4:Eu3C and Fe3O4 - Core/ shell: Fe3O4@mSiO2 with polymer as a gatekeeper -Zinc-doped iron oxide nanocrystals (ZnNCs) containing MSNs, which have been surface-decorated with valves - MagneticNanoAssemble@D ye-SiO2@SiO2	composite	-The size of magnetic agent is of particular importance -The optimal amount of silica should be the minimum necessary to keep the nanocomposites stable in water as well as does not reduce the heat generation ability -Another important point is the dispersion médium -the temperature of the initial synthesis of magnetic nanoparticles affects its heat generation properties.

			-Maghemite @ mesoporous silica microspheres -Silica coated La0.56(SrCa)0.22MnO3 -Silica coated La1-xSrxMnO3 -Fe3O4–SiO2		
Arcos, D. et al(28)	2003	Biphasic materials for bone grafting and hyperthermia treatment of cancer	glass–ceramic (Si-Ca-Fe) and sol–gel glass (Si-P-Ca)	Ceramic	The biphasic materials are attractive potential candidates for hyperthermia treatment. The glass–ceramic provides magnetic properties to produce heat, whereas the sol–gel glass ensures the bioactive behavior of the material.
Baeza, A. Et al(67)	2013	Thermoseeds for interstitial magnetic hyperthermia: from bioceramics to nanoparticles	bioactive SiO2–CaO–P2O5 sol–gel glass with the magnetic glass-ceramic The new biphasic material was prepared by mixing the finely ground iron-containing parent glass with the bioactive sol–gel glass	Thermoseeds	The use of iron oxide based magnetic thermoseeds for interstitial hyperthermia treatment of tumors is already well established and can improve the range of tools available for the clinician

Barick, K C et al(51)	2014	Carboxyl decorated Fe_3O_4 nanoparticles for MRI diagnosis and localized hyperthermia	Glycine functionalized iron oxide nanoparticles (GIONs)	Superparamagnetic nanoparticles Carbon nanoparticles	They showed high r2 relaxivity and excellent self-heating efficacy under AC magnetic field, and have no adverse toxic effect for further in vivo use new class of Fe_3O_4 colloidal nanoparticles has been fabricated by conjugating glycine at the interface, which can be used as a contrast agent in MRI and heating source in localized hyperthermia therapy.
Boca, S. C et al(47)	2011	Chitosan-coated triangular silver nanoparticles as a novel class of biocompatible, highly effective photothermal transducers for in vitro cancer cell therapy	-chitosan-coated silver nanotriangles (Chit-AgNTs → tested -poly(ethylene) glycol capped gold nanorods (PEG-AuNRs)	silver nanoparticles	The optical properties, chemical stability and biocompatibility of newly synthesized agents have been carefully assessed and compared with that of other plasmonic-active nanoparticles already described in literature
Bretcanu, O. Et al(52)	2017	In vitro biocompatibility of a ferrimagnetic glass-ceramic for hyperthermia application	$24.7SiO_2–13.5Na_2O–13.5CaO–3.3P_2O_5–14FeO–31Fe_2O_3$ → SC45	Ferrimagnetic glass-caramic	simulated body fluid pre-treatment (a surface activation process - induces the formation of a silica-gel layer on the materials surface) can contribute to an increase of the biocompatibility of SC45 glass-ceramics by modifying their surface reactivity
Bruno, M. et al(14)	2014	Composite bone cements loaded with a bioactive and ferrimagnetic glass-ceramic. Part I: Morphological, mechanical and calorimetric characterization	polymethylmethacrylate (PMMA) matrix and $SiO_2–Na_2O–CaO–P_2O_5–FeO–Fe_2O_3$	composite	The calorimetric analysis demonstrated the cements ability to generate heat in an alternate magnetic field.

Cespedes, E et al(12)	2014	Bacterially synthesized ferrite nanoparticles for magnetic hyperthermia applications	nanoparticles extracellularly produced by the bacteria Geobacter sulfurreducen that contain Co or Zn dopants	Green nanotechnolo gy	We have demonstrated the potential for magnetic hyperthermia applications using biogenic magnetic nanoparticles inno vatively prepared by cultures of the bacterium Geobacter sulfurreducens
Chandra, S. et al(24)	2011	Oxide and hybrid nanostructures for therapeutic applications	Poly(NIPAAm)chitosan (CS) based nanohydrogels (NHGs) and iron oxide (Fe_3O_4) magnetic nanoparticles encapsulated magnetic nanohydrogels (MNHGs) hydrogel nanocomposites containing magnetic nanoparticles	Iron-oxide nanoparticles	Thermoresponsive polymer-coated magnetic nanoparticles can be used for magnetic drug targeting followed by simultaneous hyperthermia and drug release
Cobley, C. M. et al(69)	2011	Gold nanostructures: a class of multifunctional materials for biomedical applications	Gold nanostructures	Gold nanostructure s	The tunable surface chemistry, morphology, and optical properties of gold nanostructures make them ideal for a variety of biomedical applications
El-Sayed et al(72)	2007	Calculation of heating power generated from ferromagnetic thermal seed (PdCo-PdNi-CuNi) alloys used as interstitial hyperthermia implants	PdNi, PdCo and NiCu ferromagnetic thermoseeds	Thermoseeds	These seeds are clinically useful in treating localized tumors
Farzin A. Et al(32)	2017	Multifunctional magnetic nanostructured hardystonite scaffold for hyperthermia, drug delivery and tissue engineering applications	Magnetic Fe- Hardystonite scaffolds	Bioceramic	This newclass of multifunctional scaffolds can be a good candidate for the regeneration ofbone defects due tomalignant bone disease by a combination of hyperthermia therapy and local drug delivery.

Fortin J. et al(33)	2007	Size-Sorted Anionic Iron Oxide Nanomagnets as Colloidal Mediators for Magnetic Hyperthermia	anionic iron oxide nanoparticles (Maghemite particles, cobalt ferrite particles)	Colloidal nanocrystals	Potential of iron oxide nanomagnets with well-characterized particle size distributions, magnetic anisotropy, and carrier fluids for their efficiency as heat mediators
Gao W. et al (34)	2016	A smart, phase transitional and injectable DOX/PLGA-Fe implant for magnetic-hyperthermia-induced synergistic tumor eradication	poly lactic-co-glycolic acid (PLGA) implant incorporating magnetic material (Fe powder) and anti-cancer drug (doxorubicin (DOX)	Polymer	imaging-guided chemo-hyperthermal synergistic therapy
Jayalekshmi A. Et al(22)	2013	Magnetic and degradable polymer/bioactive glass composite nanoparticles for biomedical applications	iron oxide incorporated chitosan-gelatin bioglass composite nanoparticle	bioglass composite	The results reveal that these iron oxide incorporated composite nanoparticle with good biocompatibility is applicable for drug delivery and other clinical applications.
Jiang Y. et al (73)	2011	Preparation of magnetic and bioactive calcium zinc iron silicon oxide composite for hyperthermia treatment of bone cancer and repair of bone defects	calcium zinc iron silicon oxide composite	composite	promising material for hyperthermia treatment of bone cancer and repair of bone defects.
Kakwerw H. et al(74)	2015	Functionalization of Strongly Interacting Magnetic Nanocubes with (Thermo)responsive Coating and their Application in Hyperthermia and Heat-Triggered Drug Delivery	cubic-IONPs with a polymer coat (PNIPAAM-co-PEGA)	IONPs	Such materials may provide a synergistic therapeutic effect in cancer treatment via hyperthermia and chemotherapy with triggered drug release while not displaying the side effects of standard chemotherapy
Kaman O. Et al(75)	2009	Silica encapsulated manganese perovskite nanoparticles for magnetically induced hyperthermia without the risk of overheating	Nanoparticles of manganese perovskite coated with silica	composite	enhancement of the heating efficiency of the silica encapsulated nanoparticles in comparison with the raw nanoparticles due to the removal of the smallest magnetic cores and probably due to the better dispersion of stabilized particles

Kawaahita M. et al(76)	2008	In vitro heat generation by ferrimagnetic maghemite microspheres for hyperthermic treatment of cancer under an alternating magnetic field	Ferrimagnetic microspheres	Thermosseds	The microspheres showed in vitro heat generation when they were dispersed in an agar phantom and placed under an alternating magnetic field
Kawashita W. et al(77)	2010	PMMA-based bone cements containing magnetite particles for the hyperthermia of cancer	Fe3O4-containing calcium phosphate-based cement	Cement	The cement samples containing magnetite nanoparticles generated enough heat for clinical application even in an alternating magnetic field
Kawashita M. et al (78)	2006	Enzymatic preparation of hollow magnetite microspheres for hyperthermic treatment of cancer	silica glass microspheres coated with ferrimagnetic maghemite	Thermosseds	Microspheres are believed to be promising thermoseeds for hyperthermic treatment of cancer
Kawashita M. et al (79)	2005	Preparation of ferrimagnetic magnetite microspheres for in situ hyperthermic treatment of cancer	Fe3O4 microspheres	Thermosseds	microspheres are believed to be promising thermoseeds for hyperthermic treatment of cancer
Kim D. et al(80)	2009	Targeting to carcinoma cells with chitosan- and starch-coated magnetic nanoparticles for magnetic hyperthermia	chitosan-coated magnetic nanoparticles starch-coated magnetic nanoparticles	Thermosseds	Chitosan-coated magnetic nanoparticles expect to be promising materials in magnetic targeted hyperthermia, rader than the starch-coated ones
Li G. et al(81)	2011	Magnetic bioactive glass ceramic in the system CaO–P2O5–SiO2– MgO–CaF2–MnO2–Fe2O3 for hyperthermia treatment of bone tumor	CaO–SiO2–P2O5–MgO–CaF2–MnO2–Fe2O3	Magnetic bioactive glass ceramic	The material has the potential to be used as thermoseeds for hyperthermia
Li Y. et al(82)	2011	Biocompatibility of Fe3O4@Au composite magnetic nanoparticles in vitro and in vivo	core–shell Fe3 O4 @ Au composite magnetic nanoparticles	Composite	Highly biocompatible and safe nanoparticles that are suitable for further application in tumor hyperthermia
Li Z. et al(83)	2012	In vitro assessment of poly(methylmethacrylate)-based bone cement containing magnetite nanoparticles for hyperthermia treatment of bone tumor	Poly(methylmethacrylate) (PMMA)-based cements containing magnetite (C-PMMA/Fe3O4)	Cements	Without scientifically conclusive results

Li Z. et al(84)	2012	Sol–gel synthesis, characterization, and in vitro compatibility of iron nanoparticle-encapsulating silica microspheres for hyperthermia in cancer therapy	iron nanoparticle-encapsulating silica (FeSi) microspheres	Thermoseeds	Further investigations are needed to improve the heating efficiency of the microspheres by optimizing their magnetic properties
Liang Z. et al(85)	2014	‘Smart’ gold nanoshells for combined cancer chemotherapy and hyperthermia	Multifunctionalized GNs containing the drug doxorubicin and a targeting peptide	Gold nanoshells	Multifunctional GNs show promise for combined chemotherapeutic and thermal therapy for tumorselective treatment
Lin M. et al (86)	2014	Recent Advances in Nanosized Mn–Zn Ferrite Magnetic Fluid Hyperthermia for Cancer Treatment	Nanosized Mn–Zn Ferrite	Iron-oxide nanoparticles	Beside its own antitumor effect, it also can improve the sensitivity of chemotherapy and radiotherapy.
Martin S. et al(87)	2010	Magnetic mesoporous silica spheres for hyperthermia therapy	Magnetic mesoporous silica (MMS) spheres	Composite	Magnetic hyperthermia experiments show the ability to control the temperature rise in the cell culture environment upon MMS treatment and AMF exposure, thus generating heat treatments that severely compromise cell survival.
Melnikov O. Et al (88)	2009	Ag-doped manganite nanoparticles: New materials for temperature-controlled medical hyperthermia	silver-doped manganites Ag-doped perovskite manganites particles	Metal associations	The magnetic relaxation properties of the particles are comparable with that of SPIO, and so we were able to monitor the particle movement and retention by MRI
Miyazaki T. et al(89)	2013	Carboxymethyldextran/magnetite hybrid microspheres designed for hyperthermia	Carboxymethyldextran/magnetite hybrid microspheres	Thermosseeds	These microspheres have potential as thermoseeds for cancer treatments using hyperthermia with embolization
Mondal S. et al(90)	2017	Magnetic hydroxyapatite: a promising multifunctional platform for nanomedicine application	Magnetic hydroxyapatite		Coating over magnetic nanoparticles offers several advantages such as excellent biocompatibility and high stability in a broad pH and temperature

					range; moreover, it protects nanoparticles such as polymers from agglomeration

Attachment III – Declaração de Parecer da Orientadora

U.PORTO
FACULDADE DE MEDICINA DENTÁRIA
UNIVERSIDADE DO PORTO

APPLICATION OF BIOMATERIALS IN THE TREATMENT OF SOLID TUMORS BY
THERMOTHERAPY: bibliographical review

PARECER DA ORIENTADORA PARA ENTREGA DEFINITIVA DO TRABALHO APRESENTADO

Informo que o trabalho de Monografia desenvolvido pela estudante Maria João Lopes Tavares com o título "Application of biomaterials in the treatment of solid tumors by thermotherapy: bibliographical review" está de acordo com as regras estipuladas na Faculdade de Medicina Dentária da Universidade do Porto, foi por mim conferido e encontra-se em condições de ser apresentado em provas públicas.

A orientadora,

____

Porto, 17 de Maio de 2018

Attachment IV – Declaração de Autoria do Trabalho Apresentado

DECLARAÇÃO DE AUTORIA DO TRABALHO APRESENTADO

MONOGRAFIA DE REVISÃO BIBLIOGRÁFICA

Declaro que o presente trabalho, no âmbito da Monografia de Revisão Bibliográfica integrado no MIMD, da FMDUP, é da minha autoria e todas as fontes foram devidamente referenciados.

_______/________/___________

A investigadora,

____

Attachment V

Declaração
Mestrado Integrado em Medicina Dentária

Declaro que o presente trabalho, no âmbito da Monografia de Investigação, integrado no Mestrado Integrado em Medicina Dentária, da Faculdade de Medicina Dentária da Universidade do Porto, com o título "Application of biomaterials in the treatment of solid tumors by thermotherapy", apresenta-se traduzida na totalidade em inglês.

A transcrição, por mim conferida, encontra-se fidedignamente traduzida, não existindo nenhuma alteração ao conteúdo.

Porto, 17 de Maio de 2018

(Professora Doutora Ana Isabel Pereira Portela)

(A aluna Maria João Lopes Tavares)