

THE USE OF NANOTECHNOLOGY WITHIN THE IDENTIFICATION AND TREATMENT OF MALIGNANT NEOPLASMS

BY

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PASS



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*"For us, the Holy Grail would be finding a way to selectively kill cancer cells and not
damage healthy ones."*

Hongjie Dai

March 2011

Abstract

Malignant neoplasms, more commonly referred to as cancers, are the third biggest killer in the world. In 2009 they killed over eight million people and the numbers are constantly increasing: by 2030, an estimated twelve million people will be killed each year by cancer alone. This dissertation examines the possibilities of using nanotechnology as a quicker, easier, more effective treatment without any of the side effects provided by the current methods, by combining the developing technologies allowing nanodevices to seek out and bond to cancerous cells with those which infiltrate the cells and physically eliminate them, using methods such as a gradual drug delivery or hyperthermia brought on by nanoparticles.

Introduction

In 2007, 7.9 million people died of cancer – 13% of all of the global human population deaths that year – and 30% of these tragedies were preventable. In less economically developed countries identification of the disease is less common and the treatment is less efficient, resulting in those who contract the disease having a

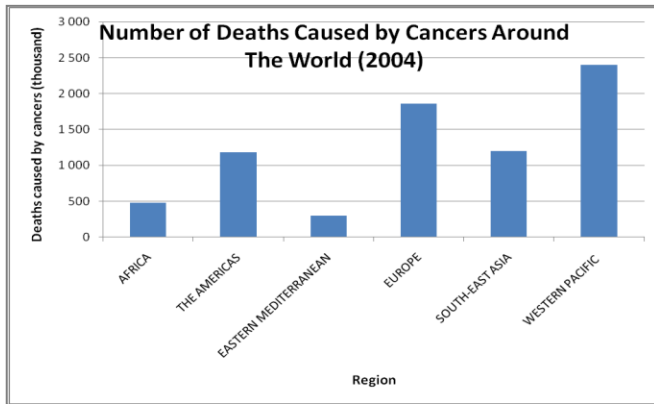


Figure 1 – Data from the World Health Organisation, 2004

lower chance of survival; however, many factors can contribute to the development of cancers, such as tobacco, obesity, radiation, stress, lack of physical activity and environmental pollutants; features which are normally associated with more developed nations, resulting in generally more deaths in the richer countries/continents due to lifestyle habits (Figure 1). Despite treatments being more effective and numerous, the amount of the population who succumb to the disease is higher because of the more lavish lifestyles which allow for ‘luxuries’ such as cigarettes and cheaper food, to name but a couple.

Current treatments, in spite of being improved constantly

over their lifespans, are still crude and often ineffective – radiotherapy and chemotherapy are often referred to as ‘carpet bomb treatments’ due to their nature of killing all cells in a specific area; inevitably it is not just the cancerous tumours but also the healthy tissue surrounding it that is affected. Radiotherapy consists of using high-energy radiation (either from an external source, or a temporarily implanted one) such as gamma rays and x-rays to damage the DNA of cancer cells, or create charged particles which subsequently damage the DNA, causing cell death. However, the science is not exact and normal tissue is also damaged, whilst side effects can be as serious as fibrosis, bowel damage, memory loss, infertility and even possibly causing a second tumour. Chemotherapy (using drugs) is not much better on that front; it can and relatively frequently does cause degradation of the immune system, anaemia, fatigue, hair loss, organ damage, nausea/vomiting, and potentially even brain damage, compared to drug treatments for other infections. Drugs such as liposomal amphotericin B are infamous for their severe and potentially lethal side effects, such as a high fever, shaking chills, hypotension, anorexia, nausea, vomiting, headache, dyspnea/tachypnea, drowsiness and generalised weakness. The success rate is also very variable, depending on both the sex of the patient

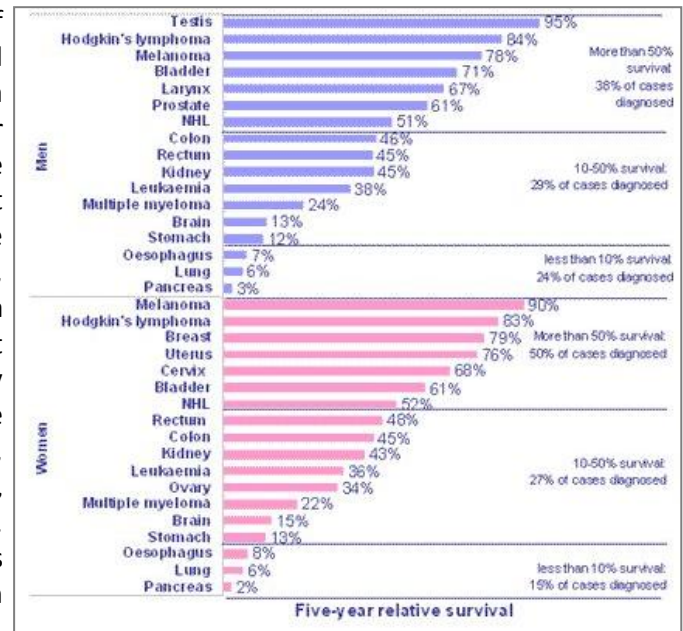


Figure 2 – Relative five-year survival estimates based on survival probabilities observed during 2000-2001, by sex and site, England and Wales – Data from Cancer Research^[7]

and the type of cancer, ranging from a relative 2.5% average survival rate for pancreatic cancer across both genders, to 95% for testicular cancer in men or 90% for melanocytic cancer (melanoma) in women, as demonstrated in Figure 2.

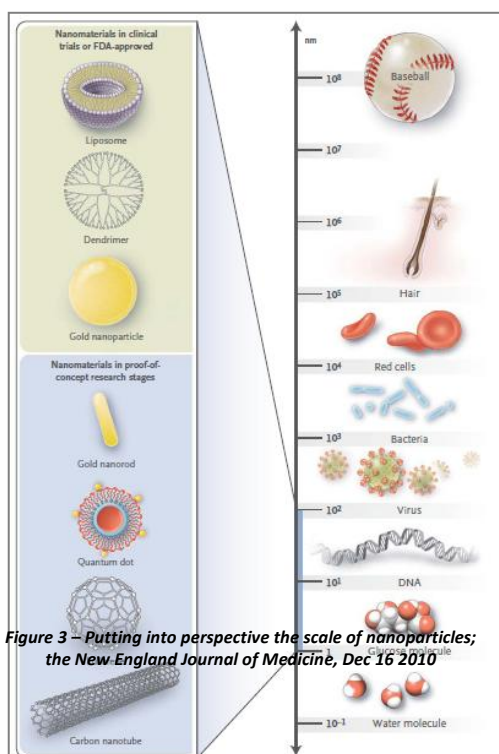
At current, when one is diagnosed by a doctor with cancer, it is as if a life sentence has been declared. The amount of people in which it is fatal is terrifying; the treatment is unreliable; and the emotional and physical stress for the patients, their families and friends and their doctor and carers is unquantifiable. However, if a new, safer, more effective, cheaper and easier method was to be created it would have the potential to save millions of lives – and this is where nanotechnology comes in.

This dissertation looks at how nanotechnology could provide the possibility of an on-the-spot injection, possibly – but not necessarily - with one short session inside a specialised treatment room, which would completely eradicate all tumours with potentially no side effects. Nanotechnology, derived from the Greek word ‘nano’ meaning ‘dwarf’, refers to the science of manipulating matter that is less than 100 nanometres wide (10^{-7} m, 0.0000001m) – it is defined as the “intentional design, characterization, production, and applications of materials, structures, devices, and systems by controlling their size and shape in the nanoscale range (1 to 100 nm).” Nanodevices are currently being engineered to assist to transport and actions of indicative and therapeutic agents around the body, focussing especially on gaining access into specific molecules and detecting changes in a sensitive manner. Contrastingly from macroscopic materials, nanomaterials have a high surface area to volume ratio and different features which can be manipulated in different, more complicated manners; biological, optical, magnetic and electronic properties are all different and are still being discovered in this relatively new field. The main presenting factor is also the most attractive one: the size is minute, and manipulating matter at this level opens up a world of possibilities.

Figure 3 shows the size of devices that are being used in the field of nanomedicine, compared to natural bodily substances and a baseball for perspective. The carbon nanodevices used by a team at Stanford^[1] are only half the width of a DNA molecule, and thousands can easily fit inside a typical cell, providing a wealth of opportunities which are being developed all the time.

Originally, the idea of nanotechnology was proposed by famous physicist Dr. Richard Feynman (1918-1988), one of the most famous scientists of his time, in lectures such as ‘There’s Plenty of Room at the Bottom’^[2] in which he contemplated the possibility of manipulating matter at the atomic level. He theorised that it would be possible to “arrange the atoms the way we want” – something that has been realised and is the basis for all nanotechnology. He brought up the changing conditions; gravity would become insignificant, whilst surface tension and Van der Waals forces would become far more important. He even suggested the possibility of ‘swallowing the doctor’ – orally ingesting a surgical robot with quarter-scale surgical tools, which would construct ten other robots, which in turn would construct their own in a repeating pattern as numbers grow, resulting in billions of nanoscale robots working in parallel to combat disease/infection within the body; this idea was accredited by Feynman to his friend and colleague, mathematician Albert Hibbs. This paper does not look specifically at that idea, but as a by-product of it; engineering molecular-sized devices which can help to combat cancer.

All of the information in this report was gathered via personal sources, correspondence with scientists working in the field and the internet, and the ideas being developed have been compiled into one, ultimate end product which has the potential to cure cancer very quickly and easily. It is, however, only a gedanken experiment, and the presented idea has not been tested thus far – though one could assume that it is a valid possibility in the near future.



“The long term prospects are substantial and limited only by the creativity of individuals involved in this area of investigation.” –

Steve Rosen, Director of the Robert H. Lurie Comprehensive Cancer Centre, on using nanotechnology against cancer

Discussion

Combining the different types of nanotechnology to create one end result which could detect, treat and remove a tumour could soon become a possibility. Current technologies have created contrast agents: nanoparticles (often carbon) containing iron oxide molecules which attach themselves to cancerous cells – the high density of iron oxide, which provides a high contrast, makes the tumour effectively ‘glow’ on a magnetic resonance imaging (MRI) scan, which detects magnetic fields. An MRI scanner is consisted of mainly a large, powerful magnet of strength ranging from 0.5-2.0 tesla (the Earth’s magnetic field is 0.00005 tesla, for comparison^[3]), along with resistive magnets with strength of approximately 0.3 tesla. Because such a high current is required for this main superconducting magnet, the temperature of the wires is reduced to almost zero degrees Kelvin (-273.2°C) by being bathed in liquid helium at 4.1K (-269.1°C), which gives them superconductive properties and makes the resistance in the wires infinitely small, thus allowing for more current and a stronger electromagnet. Three other ‘gradient magnets’ inside the scanner range from 0.018 to 0.027 tesla, which create a variable field and allow for different parts of the body to be scanned. The magnetic field produced causes most hydrogen atoms (about 999,998 in every 1,000,000) to align themselves along field lines, travelling from north to south or vice-versa. This is because hydrogen only has one proton so reacts strongly to magnetic fields – it has a strong magnetic moment; however some atoms remain unattached to any direction (approximately two in every million), travelling randomly, until a radio frequency pulse is emitted from the scanner. These loose hydrogen atoms then pick up the signal, causing them to spin at a particular frequency in a different direction, whilst the gradient magnets alter the field – and once the pulse ends, the atoms release their energy which is detected by the magnets, resulting in the forming of a detailed image using smart computer software. Using standard contrast in MRI scans can produce up to 250 different shades of grey for different tissues as different concentrations of magnetic fields are picked up, and nanotechnology can provide even more than this. This is because within iron oxide nanoparticles (<20nm), for example, all electrons spin in the same direction, whereas the macromolecules of the same iron oxide compound spin in opposite directions to each other. The combined spinning effect when electrons are aligned and are spinning in the same direction creates a larger, localised magnetic field, whilst having electrons spinning in different directions cancels it out. This larger magnetic field increases the contrast on MRI scans, making tumours easier to detect.

The current approach consists of injecting contrast intravenously, in which a monoclonal antibody is attached to a single molecule of an MRI contrasting agent; and hundreds or even thousands of this structure are required for this to reach the cancer for it to show up strongly enough to be detected. However, if this monoclonal antibody was attached to a nanoparticle that contains tens of thousands of the same contrast agent on a nanoscale, only one such construction would be required to reach the tumour for it to be detectable; ultimately it could result in a ‘smart’, oral, targeting contrast agent which improves the resolution of the MRI scans of cancers to the cellular level.

This obviously has the bonus of allowing for the early detection of cancers which would be harder, possibly even near impossible using the conventional methods of visually analysing the appearance of computerised scans without any definitive marker or contrast of a cancer – even more modern and advanced methods would not be as detailed as those produced using nanotechnology. Other nanodevices allow for the detection of cancers in different ways: some are being developed which can detect changes in a cell’s DNA that is a forerunner of the development of cancers; whilst others can detect ‘biomarkers’ in a sample of blood far

earlier than current tests allow. The advantage of this is enormous – it is in general agreement that detecting a cancer early is ‘winning half the battle’, and nanotechnology could make this earlier than ever before. Present imaging methods can only detect cancers once they have made a visible change to a tissue, by which time thousands upon thousands of these abnormal cells would have been produced and are attacking vital organs; mammography requires more than a million cells for accurate clinical diagnosis, and each one of these cells is meanwhile having a detrimental effect on the body. Nanotechnology produces a simple way in which cancer can be detected and exterminated before it has the chance to develop and take a hold; this technology, once it is inevitably mass-produced and made cheaper, even has the potential of becoming a house-hold item which could be bought over the counter and could test for cancer at home, much like a pregnancy or smear test. Ideally spot checks would be recommended biannually, or annually for those deemed to be at a particular risk due to lifestyle habits or a history of cancer in his/her genetics.

Although the detection of cancers can be done in several different ways, this paper is looking at mainly two: using iron oxide molecules as a contrast in MRI scans, and quantum dots. The former was discussed earlier, and is relatively simple compared to the latter. Quantum dots, sometimes known as Qdots, are a nanotechnology which illuminates in different colours merely because of different size particles by taking advantage of the photoelectric effect: for example, in cadmium selenium quantum dots, electrons can jump between two different energy levels. When they are given sufficient energy the electrons become excited and move from the ground state to an excited state, but once there they are more unstable and thus they are attracted to the ground state, becoming de-excited and falling back down. It is this transition that is important – as the electron becomes de-excited it releases energy in the form of electromagnetic radiation (often light). The frequency of the wave produced depends on the size of the transition, which consequently depends on the size of the molecule – for example, a larger molecule produces a wave that has a higher frequency, proportional to that of a smaller size by the equation $E=hf$ where E is the energy input (joules), f is the frequency (hertz) and h is Planck’s constant (6.626×10^{-34}). This mechanism can be maximised in the medical industry by using it to analyse which kind of tumour(s) is/are present – theoretically, if all nanoparticles containing quantum dots of a certain size were covered in the same substrate, whilst nanoparticles of a different size were covered in a different substrate etc, different quantum dots would bond to different types of cancer and thus would illuminate them in different ways, identifying the cancers and thus advising on the best treatment. The patient would be placed under an infra-red emitter to provide the energy for the quantum dots which would illuminate the cancers, whilst a detailed electromagnetic scanner detects the frequency of waves being produced and pinpoint their origin to particular cells. An advantage of this is that it allows for non-intrusive, in vivo detection which is impossible in current methods because traditional molecular counterparts do not produce a strong enough signal; nanotechnology produces an optical and magnetic signal that is at least ten times more powerful.

Despite all of the strengths of this technology, it relies on one main factor – actually being able to ‘seek out’ tumours – being able to locate them in the body, bond to them and not interfere with any other living cell. This is especially hard because, as George Whiteside once said, “cancer cells are abnormal cells, but they’re still us.”^[4] This presents a massive problem, as it can be hard to distinguish the cancerous cell types from healthy tissue – attempts by scientists at Harvard have shown that without proper targeting, nanoparticles have been dissolving in the liver and spleen, releasing toxic amounts of therapeutic drugs to healthy tissue. Indeed, the immune system can recognise particles in the range which most therapeutic and imaging technologies use; so it is a real struggle to design and create nanotechnologies which will either avoid immune cells or use them to achieve their goals without activating or crippling the immune system.

Research done by scientists in Harvard University^[5] has analysed attempts and utilised the different chemicals found on the surface of tumours to develop antibodies which react only to these and not any normal cells. To understand this, it is important to understand what a cancer is. The National Cancer Institute defines it as “a term used for diseases in which abnormal cells divide without control and are able to invade other tissues”, but it is important to note that there are more than a hundred different types, both malignant (cancerous, and can spread) and benign (non-cancerous, does not spread), and can form anywhere in the body; they can be categorised into five main groups: carcinoma, which begins in the skin/tissues that cover internal organs; sarcoma, which begins in bone, cartilage, fat, muscle, blood vessels or other connective/supportive

tissue; leukaemia, which begins in tissue such as bone marrow which forms blood; lymphoma and myeloma, which begin in the immune system; and central nervous system cancers, which begin in the brain or spinal cord. Figure 2 shows that the survival rate for different cancers can vary enormously; though their formation is fundamentally similar. Cells in the body grow, live and die, so that they can be replaced by new cells – however mutations in the DNA can cause the cell to not go through the process of cell death, thus replicating without dying. These cancers replicate again and again over time, forming a mass of tissue called a tumour. The different types of cancers have different characteristics, such as chemicals which are over-expressed in cancerous cells which make them able to be detected.

Receptors for chemicals such as the vitamin folate have been discovered to be common on cancers, and so antibodies are being developed that have these specific receptors and are then being coated in nanodevices for the identification/treatment of cancers. The idea is that the nanoparticles will travel around the body, and will not react with any normal, healthy cells as the active site and substrate of the cancers and nanoparticles do not match, but once the nanoparticles reach a cancer their active site will bond with the cancer's substrate due to the chemically identical receptors. Due to the high surface area to volume ratio of nanoparticles, a large number of receptors/therapeutic agents can be attached to the surface of the molecule.

Getting to the desired cell is another feature of nanotechnology which cannot be exploited using macroparticles – as every cell requires a constant flow of oxygen to survive, every cell is attached to a blood vessel. The holes in the walls of blood vessels between molecules are too small for even nanoparticles to fit through – which is in essence a good thing. Cancers cause blood vessels around them to leak, creating bigger holes than is natural which are of a large enough diameter for nanoparticles of 40nm to fit through. The nanoparticle will of course have to be in the blood stream, which could be done intravenously, or possibly orally as its small size and robustness means that it can be absorbed by the digestive system but not disintegrated.

Once the nanoparticle reaches the cancer, treatment can begin, and this paper looks at three different technologies which are currently being developed: toxic drugs encased in nanoparticles; nanoshells which react to infra-red; and nanoparticulates which react to a rapidly alternating magnetic field. In the case of the former, a hollow core of a spherical nanoparticle allows for the encapsulation of hundreds of drug molecules within a single particle, which are released slowly as the carrier (often made of carbon and hydrogen) is broken down over time. An advantage of this technique is that the composition of the particle can be altered to change the rate of decomposition, or coated with polymers such as polyethylene glycol which increases the longevity of the particle within the body and prevents the removal/breaking down of the particle by the body. The chemicals used are the same as in current chemotherapy, but as with the contrast agent, many drug molecules can be placed inside one targeting carrier particle which releases them at a set rate, thus preventing the need for constant injections whilst removing the damage to other cells and requiring a smaller dosage to be taken. This was experimented on by scientists at Harvard Medical School and the Massachusetts Institute of Technology, when they tested five lots of mice implanted with human prostate cancer with different methods of this; the first received ineffective saltwater, the second fatal empty nanoparticles, the third a shot of the drug which was too sudden and proved deadly, the fourth a nanoparticle-encased toxic drug which was not targeted, and thus not successful, and the final group which received the full, targeted treatment being worked on. There was a full success for this final group, whilst those who did not receive any treatment were euthanized in 12 days because of the large growth rates of their cancers. Of course there are many ethical issues involved in this style of experiment, but overall it has enabled us to envisage the possibility of this type of nanoscale chemotherapy being used in humans.

The latter two methods, involving infra-red and a rapidly alternating magnetic field, are fairly similar; a targeted nanodevice attaches itself to the cancer using the methods stated earlier, and rely on causing hyperthermia to kill the cell. Once it has been ingested into the cell, the patient is placed into the corresponding field, which causes the device to heat up to high temperatures, killing the cancer instantly, whilst leaving all other cells unaffected. The advantage of using nanoparticles for this is that they can entrap more than ten thousand molecules of, say, iron oxide, whilst concentrating them into a small area – this provides enough thermal mass to eliminate the tumour yet affect no other tissues. Experiments have shown

that carbon nanotubes under an infra-red beam can heat up to 70°C in under two minutes^[6], which is primarily because of their small size.

After treatment, the nanotechnology should be removed from the body, which can be done completely naturally. The chemotherapeutic capsule deteriorates by itself, whilst the latter two methods would either result in the nanoparticles being destroyed by the heat, or being washed out of the body in the urine (if less than 8nm); yet another advantage of the small scale that nanotechnology provides. If no cancer was discovered, the nanoparticle would pass out of the body in the urine; the particle containing drugs would not bond to a tumour so would pass out of the urine before it has time to dissolve and release any toxins.

Despite all of these scientific wonders, there is no current mechanism which can both detect and treat a cell (possibly because this is all relatively new); though it is a technology which is almost certainly possible and should be explored to the fullest extent. It should be relatively simple to pair these technologies together once they have been fully developed, and a flow chart of how this process would work (Figure 4) follows.

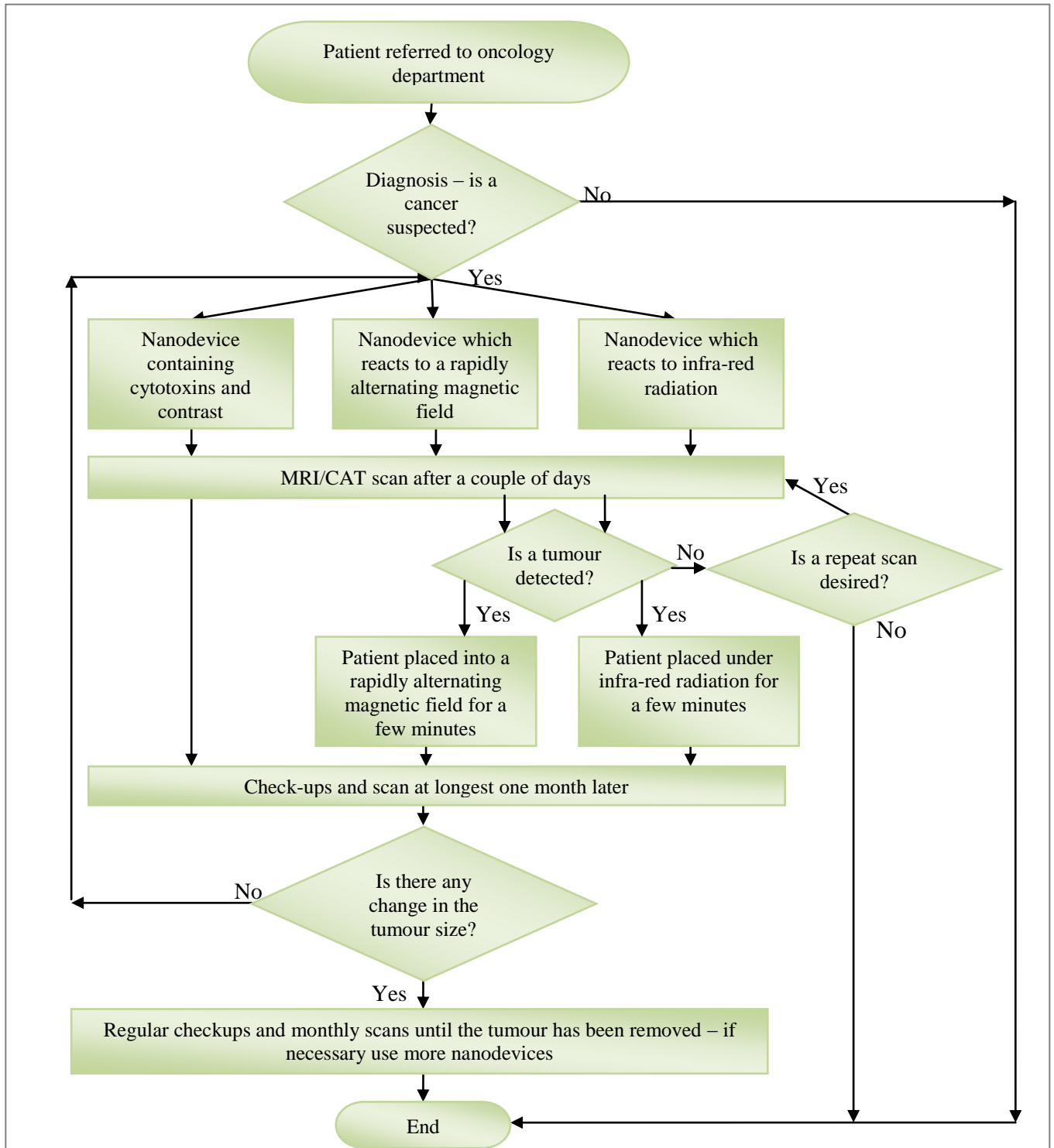


Figure 4

Conclusion

Fifty, forty, maybe even thirty years ago this technology would have not even have been dreamed of – but now it is fast becoming a life-saving reality, and constant further advances will inevitably save yet more lives, until hopefully cancer becomes a disease ‘of the past’, similar to smallpox and the plague. The creation of a single, mass-produced, cheaper nanodevice which uses quantum dots to illustrate where a cancer is, a coating which lets it seek out and attach itself to cancerous cells, and then eliminates the tumour and itself – all in one type of nanoparticle – is a genuine possibility which could soon become a fully fledged medical reality.

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