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Tumor Ablation and Nanotechnology

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Abstract

Next to surgical resection, tumor ablation is a commonly used intervention in the treatment of solid tumors. Tumor ablation methods include thermal therapies, photodynamic therapy, and reactive oxygen species (ROS) producing agents. Thermal therapies induce tumor cell death via thermal energy and include radiofrequency, microwave, high intensity focused ultrasound, and cryoablation. Photodynamic therapy and ROS producing agents cause increased oxidative stress in tumor cells leading to apoptosis. While these therapies are safe and viable alternatives when resection of malignancies is not feasible, they do have associated limitations that prevent their widespread use in clinical applications. To improve the efficacy of these treatments, nanoparticles are being studied in combination with nonsurgical ablation regimens. In addition to better thermal effect on tumor ablation, nanoparticles can deliver anticancer therapeutics that show synergistic anti-tumor effect in the presence of heat and can also be imaged to achieve precision in therapy. Understanding the molecular mechanism of nanoparticle-mediated tumor ablation could further help engineer nanoparticles of appropriate composition and properties to synergize the ablation effect. This review aims to explore the various types of nonsurgical tumor ablation methods currently used in cancer treatment and potential improvements by nanotechnology applications.

Keywords

Theranostic; Microwave; Radiofrequency; Cryoablation; Photodynamic Therapy; High-Intensity Focused Ultrasound; Nanoparticles

Introduction

Surgical resection remains the standard treatment for many cancers. However, there are a large number of cases where surgical resection is not possible due to unfavorable location of the tumor, the presence of multiple tumors, or patient preference. Chemotherapy and radiation therapy are often used as substitutes for surgery, either alone or in combination.1 Nonetheless, typical chemotherapy regimens and radiation therapy require regular treatment for a number of weeks with high doses of anti-cancer therapeutics or high energy X-rays and can have side effects such as structural and functional morbidity, skin redness, cosmetic defects, vomiting, hair loss, and many others without guarantee of the tumor being fully eradicated.1–3

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Nonsurgical tumor ablation methods have been developed with the precision and immediacy of surgery without the associated pain, potential morbidity, long hospitalization time, and high cost.[3, 4] The term tumor ablation refers to the complete destruction of a tumor by the direct application of chemical or thermal therapies while sparing nearby vital and healthy structures.[5, 6] The ablation area often includes treatment of a 0.5-1 cm margin of normal tissues adjacent to the lesion.[7] Several local tumor ablation methods developed for the treatment of unresectable tumors in various organs include thermal therapies, photodynamic therapy (PDT), and agents that produce reactive oxygen species (ROS).[3, 8–10]

While nonsurgical tumor ablation therapies are minimally invasive options to conventional surgery, these therapies have their own challenges, such as achieving a balance between accurate targeting and minimizing damage to surrounding vital organs and structures. To eliminate some of the limitations and increase the efficacy of these ablative therapies for cancer treatment, nanomaterials, composed of metals, lipids, or polymers have emerged with promising applications and results.[11] Nanoparticles take advantage of the tumor's rapidly formed vasculature and the enhanced permeability and retention (EPR) effect to help target and advance the efficiency of these treatments. The tumor tissue is highly vascular and the ill-formed blood vessels are highly permeable to different macromolecules such as lipids, plasma proteins, and nanoparticles. The poor lymphatic clearance causes the increased retention of these compounds within the tumor tissue. This article will explore the various types of nonsurgical tumor ablation methods currently in use. An overview of these methods and a summary of their advantages and disadvantages are listed in Table 1 and will be discussed in greater detail throughout this article. For each technology, the basic principle, methodology, and equipment used will be explained, as well as the associated benefits and limitations. Improvements to these treatments through nanotechnology applications will also be analyzed and discussed. A brief overview of the mechanisms of tumor ablation provided by various types of nanoparticles is included in Table 2.

Thermal Therapies

Thermal therapies use radiofrequency, microwaves, cryoablation, or focused ultrasound for the delivery of thermal energy to destroy tumor tissue.[8, 9] All thermal therapies offer the advantage of flexible, low cost treatment approaches including percutaneous, laparoscopic, and open surgical access.[12] Thermal therapies are also minimally invasive outpatient procedures with repeatability and reproducibility of results between patients.[8, 9] These therapies have limited procedural pain with the patient usually under conscious sedation; however, if pain persists, general aesthetic can be administered.[8] The major disadvantage of thermal therapies is that they are local treatments and cannot be used to treat systemic ailments.

Radiofrequency

Radiofrequency (RF) ablation is currently the most popular and widely used thermal therapy for the treatment of solid malignancies of the liver, lung, bone, breast, kidney, and adrenals.[13–20] Radiofrequency works by creating a complete electrical circuit through the body of the patient.[5, 20] An RF probe is inserted directly into the treatment area using image-guided ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), or general surgical techniques. An RF generator then delivers a high frequency (375-500 kHz) alternating current, creating a voltage between the tip of the probe and one or more grounding pads placed on the patient within the vicinity of the treatment site (Figure 1A).[5] RF ablation initially produces a heating zone through the friction caused by rapid oscillation of ions present within the tissue. The heat from the friction then dissipates further out from the focal point at the probe tip via thermal conduction. The initial active heating zone can produce an effective and uniform ablation zone. However, thermal conduction is inversely

proportional to distance, and as you move further from the active heat produced from friction, lower temperatures result.

Ideally, the temperature achieved during RF ablation is around 60 °C, as temperatures in the range of 50-60 °C induce cellular death via coagulation necrosis, and temperatures in excess of 60 °C cause instantaneous cell death.[7, 20] Temperatures above 100 °C result in tissue boiling and charring, which actually decreases the ablation area.[7, 21] The boiling and charring of the tissue causes an increase the thermal resistance of the tissue which reduces the amount of heat dissipated through the charred tissue. Therefore, in order to maximize the results of RF, it is important to maintain an appropriate temperature level throughout the procedure. The power deposition in the ablation zone is strongly dependent on the electrical conductivity of the target tissue.[7] By increasing the ions present in the target tissue it is possible to increase the area of the ablation zone. Several techniques, such as injecting saline into the tissue prior to or during the RF procedure, can cause increased electrical conductivity and a larger active heating area.

The efficacy of RF ablation is also highly dependent on the probe design. Each RF probe usually comprises a metal shaft that is insulated except for an exposed conductive tip, which is in direct electrical contact with the desired target tissue.[7] Probes can range from single-tip monopolar probes to more complex multipolar cluster arrays, and include designs such as multitoned expandable probes, needle perfusion probes, and cool-tip probes. In general, mono-polar probes allow for a larger heating zone around the probe and limited invasiveness, while multi-polar arrays have more localized and effective heating in the area between the probes and no need for grounding pads (Figure 1B).[20] Multi-polar arrays require additional probe insertions and often saline infusion to improve results.[20] Overall, the choice of the probe depends largely on the size of the tissue to be ablated and the proximity to vital organs and structures. The size of the area heated is affected by the overall length and size of the probe tip; therefore, it is vital to use the correct probe for each procedure.[5]

RF is an effective and safe treatment for tumor ablation, but there are potential side effects. The grounding pads required to complete the electrical circuit through the patient can cause skin burns. Patients can exhibit post-ablation syndrome, characterized by flu-like symptoms including low-grade fever, depression, nausea, and/or vomiting that can last up to two weeks after the procedure. RF technology is also limited by the requirement for invasive needle placement, accuracy of image-guidance, and ablation size limits due to probe designs.[22] Moreover, RF is a relatively nonspecific treatment. Although the RF probe is positioned into the target ablation zone, the range of heating cannot be controlled and thermal damage occurs in both malignant and normal cells surrounding the RF probe. The other issue that arises with RF ablation is its power dissipation with distance away from the probe. Although it is possible to heat the target zone for long enough to destroy all malignant cells, because of the rapid dispersion of heat and lack of concentration, to destroy all malignant cells in one area a margin beyond that area is also affected. This may not destroy the cells within that margin; however, the damage can still leave a scar (Figure 2). This method of passive heating face the same common problem that is associated with many thermal therapies known as the heat-sink effect. The heat sink effect is tissue cooling by nearby vessels that carry away heat via thermal convection. This cooling effect of blood flow is most prominent within zones of conductive heat transfer as seen in RF.[23] Overall, the heat sink effect is detrimental to the RF procedure because it inhibits the dissipation of heat through the tissue and adequate ablation of perivascular tissue.[24]

Coagulation necrosis via RF treatment is the most widely accepted thermal ablative method currently in practice. Although it is useful to treat unresectable tumors, it is limited by its

inability to eliminate larger malignancies, and it can also cause damage to surrounding tissues. Because the heat diffuses so rapidly it is difficult to target a concentrated area and have it be large enough to eradicate the entire malignancy. Furthermore, it requires invasive needle placement to reach deeply set tumors. Also, tumors need to be treated to within 0.5-1 mm of the periphery to ensure that retreatment is not necessary, and often this is not feasible due to the heating range of a standard needle probe.25

Nanoparticles provide unique characteristics that can be combined with the existing effects of RF treatments. Gold nanoparticles and single-walled carbon nanotubes (SWNTs) generate heat in excess of 50 °C when subjected to RF radiation. It is possible that the high aspect ratio and resistive conductivity of these particles contributes to their acute heating capabilities.22, 26 This excess heat can be used in the same manner as a traditional RF treatment to cause coagulation necrosis in tumor tissues. Nanoparticles also do not require an electrical circuit to function. The nanoparticles produce heat by converting the energy from RF waves, rather than by friction in the tissue.5, 22 In addition, nanoparticles have the ability to be targeted to specific organs and even tissues with different receptors, ligands, and antibodies.27 Combining these two qualities, nanoparticle formulations can be made that selectively treat tumor cells without the need for invasive procedures or multiple treatments. Destruction of malignant cells in combination with RF therapy can be further enhanced with temperature responsive liposomes that carry various cytotoxic drugs.28 Such nanoparticles in combination with RF and hyperthermia are currently being evaluated in Phase I-III clinical trials for the treatment of both hepatocellular carcinomas and recurrent breast cancer at the chest wall. Combinations of drug and heat can destroy the entire tumor limiting cytotoxic effects to other tissue or organs.

Nanoparticles are a novel and developing subject in the research field. Their functionality can greatly enhance the efficacy of RF treatment. Nevertheless, they still have some problems. When entering the body, the nanoparticles need to make it to the target site to be effective. In most cases though, they are cleared by the reticuloendothelial system (RES) before they can reach the target site.29 Lack of clearance can also be an issue in nanoparticles that build up with multiple treatments, e.g. long-term effects of residual gold particles are not known. Overall the enhancements that nanoparticles provide to the existing RF method make it a very viable treatment option.

Microwaves

Microwave (MW) ablation is a thermal therapy for numerous malignancies. Similar to RF ablation, MW ablation induces cellular death via coagulation necrosis by generating heat. Conversely, while RF employs radiofrequency current to generate this heat, MW ablation produces an electromagnetic wave that is emitted from a 14.5 gauge microwave antenna placed directly within the treatment site. The electromagnetic wave produces 60 W of power at a frequency ranging from 900–2450 MHz, which generates frictional heat from the agitation of polar water molecules.8, 23, 30 As the electromagnetic wave passes through the tissue it causes polar water molecules to rapidly change their orientation in accordance with the magnetic field. The efficiency of MW therapy also depends heavily on the antenna design. Ablation zones need to extend 5–10 mm beyond the tumor.23 Thus, designs with longer antenna lengths capable of producing larger coagulation diameters are preferable.

Radiofrequency and microwave ablation share the benefits common to thermal therapies; however, MW ablation offers significant improvements over RF.31 The most important distinction between these two techniques is that RF heating is primarily passive and generally only produces an active heating zone of several millimeters around the probe tip. 20, 30 Conversely, the transmission of MW in tissue does not rely on the conduction of electricity and consequently is not reliant on thermal conduction (Figure 3).20, 31

Microwave ablation uses an active heating method, as its primary means of thermal ablation so there is a more uniform heating pattern allowing for a larger heating zone. Electromagnetic waves target polar ions such as water in the tissue so grounding pads are not required to create a circuit as in RF treatments. Nevertheless, MW ablation is only a local treatment and has side effects including post-ablation syndrome and pleural effusions.23 MW ablation is less affected by the perfusion-mediated "heat sink" effect commonly observed in RF.30, 31 Since MW ablation produces zones of active heating rather than conduction zones, MW ablation greatly eliminates the potential for the heat sink effect. As a result, MW therapy may also allow for more uniform and complete tumor kill in areas next to large vessels.23, 31

There are multiple methods that can employ MW heating for enhancing nanoparticle tumor ablation, from selectively increasing the heating at the site of the tumor to promoting drug release through deformations in nanoparticle capsules (Figure 4). Nanoparticles are just beginning to be used in combination with MW as an ablation technique. Nanoparticles such as SWNTs and iron oxide formulations have the advantages of generating additional heat and can be imaged to simultaneously guide and monitor the hyperthermia within malignant tissue. Active targeting with folic acid can further enhance the signal of iron oxide nanoparticles by up to 5-fold within the tumor compared to non-targeted particles, increasing the local thermoacoustic signal and thus temperature.32, 33 Non metal-based formulations can also provide additional therapies with MW application through modification of the particles with MW frequencies. Liposils, i.e. 100 nm silica shells (~10 nm thick) synthesized around intact liposomes, do not release their payload at temperatures below 260 °C, but triggered release occurs with short (<30 s) MW application possibly through fissures forming in the surface of the particles through steam build-up.34 These liposils, which are also coated with PEG phospholipids to reduce their aggregation, may better evade RES uptake *in vivo* and prevent systemic toxicity by only releasing their contents when heated with MW at the tumor.

High Intensity Focused Ultrasound

High intensity focused ultrasound (HIFU), also commonly known as focused ultrasound surgery, is a noninvasive treatment for deep tumors of the liver, kidney, pancreas, breast, prostate, and abdomen.4, 35-41 In this therapy, ultrasonic beams delivered from an extracorporeal source are focused into the target tissue.39, 42 The ultrasound source ranges from single-element transducers to phased arrays, and can be focused either mechanically, using a focusing lens, or electronically by phasing an array of transducers.43 As the HIFU beam is focused into the target tissue, acoustic energy is absorbed causing the temperature within the focus site to elevate above 60 °C.42 As a result, HIFU induces cellular death by thermal necrosis, apoptosis, and acoustic cavitation.42, 44 Acoustic cavitation occurs when ultrasonic waves form small cavities within the tissue. Additional ultrasonic excitation leads to volumetric pulsation of these cavities, also known as bubbles.44

Acoustic intensities of HIFU are several orders of magnitude greater than diagnostic ultrasound.39 Diagnostic ultrasound typically produces time averaged acoustic intensities around 100 mW/cm^2, whereas HIFU can deliver intensities at focus that is over 10 kW/cm^2.45 HIFU can produce peak compression pressures up to 30 MPa and peak rarefaction pressures up to 10 MPa.39, 45 By combining these high acoustic intensities with the focused nature of HIFU, the acoustic intensities are only high within the treatment site.36, 42 Outside the region the acoustic intensities remain low, which minimizes damage to the surrounding healthy tissue and helps preserve much of the tissue architecture.36, 42 This ability to generate a highly confined lesion is the main advantage of HIFU.44 However, the tight focus and high pressures of HIFU also makes adaptive focusing due to body movement extremely challenging and limits the wide application of this technology.44, 46 Compared to

the other thermal therapies, HIFU is truly a noninvasive procedure, and therefore does not require an incision or percutaneous insertion of a probe.

The noninvasiveness of the procedure allows HIFU to be less toxic than other ablation therapies.45 Nevertheless, HIFU does have associated procedural complications, including skin burns, soft tissue damage in adjacent organs, as well as organ system specific side effects.36, 44 Other disadvantages of HIFU include long procedural time, difficulty in targeting and monitoring moving organs, and relatively high procedural cost.36

One major limitation of HIFU is that the presence of bones and gas pockets in the region surrounding the ablation zone can lead to thermal damage due to the increase in delivered energy at the soft tissue boundaries with air or bone.43, 47 Both gas pockets and bone can interfere with the focusing ability of HIFU and hinder treatment success.43, 48, 49 Thus, targeting is extremely important to the HIFU procedure and advances in using MR-imaging guidance can help eradicate some of these problems.36, 50

In addition to inducing local hyperthermia and acoustic cavitation to cause tumor ablation, HIFU can also enhance drug release from drug delivery systems such as nanoparticles and liposomes through their destruction or degradation. Controlled drug release can be difficult when particles are in the nanometer size range, but this drug release can be enhanced with HIFU in the MHz range. HIFU generates fractures in the liposomes, resulting in rupture of liposomes >100 nm in size, or pore like defects in smaller liposomes <100 nm in size, both of which lead to release of the nanoparticle contents.51 In order to avoid rapid clearance, PEG is covalently attached to lipid liposomes. PEG and oligo(ethylene glycol) surfactants further increases the sensitivity of the liposomal membrane to break up by ultrasound enhancing drug-release up to 10-fold.52 Through sonoporation, cavitation can further facilitate drug delivery, though this only occurs at the cellular level where the membrane is open for seconds.53, 54

Specially designed temperature sensitive particles can be synthesized to rapidly release their payload in response to small increases in temperature (4-5 °C) generated from pulsed HIFU. Low temperature-sensitive liposomes stimulated to 42 °C for only 2 min can release 50% of their drug payload reducing tumor growth in murine adenocarcinomas, while no release is detected in nonthermosensitive liposomes under the same conditions.28 Interestingly, pulsed HIFU for only 2 minutes can significantly enhance polystyrene nanoparticle uptake when injected up to 24 h post treatment through a nondestructive reversible structural changes.53, 55 Because hyperthermia and acoustic cavitation are transient phenomena, this suggests that a third mechanism, such as weak mechanical forces like radiation or shear forces may also play a role in HIFU tissue interaction to further enhance nanoparticle uptake and drug delivery.55

Cryoablation

Cryoablation is used to treat benign and malignant lesions of the prostate, kidney, liver, lung, bone, and breast.56-61 The procedure can be performed either by a laparoscopic or percutaneous approach under US, CT, or MRI guidance.8, 62 Cryoablation involves a number of freeze-thaw-freeze cycles with argon and helium gas.8 Argon gas is used to remove heat from the target site and helium gas causes thawing.63 During the cryoablation procedure, a probe is inserted into the tumor tissue under image guidance and pressurized argon gas is released from the probe tip causing a rapid drop in temperature. As the tissue freezes, osmolarity increases and causes an imbalance of solutes between the intracellular and extracellular environments.62 Cellular death initially occurs through cellular dehydration and protein denaturation.62, 63 During the thawing process an “ice ball” is formed that further induces cell death by causing vascular damage (Figure 5).63 To achieve

sufficient cell death, a temperature of less than –40 °C must be reached.[5, 63] Adjusting the length of time and rate of the thawing step can also dramatically impact the effectiveness of the treatment.[64-66]

The main advantage of cryoablation is that the ice ball formation can be directly monitored with imaging (US, CT, MRI) throughout the procedure.[62, 63] This helps treat the tumor more effectively and diminishes the risk of healthy tissue damage.[62, 63] Compared to RF ablation, cryoablation can be used to treat larger tumors (> 3 cm), causes less procedural pain, and does not require the use of grounding pads.[8, 63] The development of catheter-based cryoablation therapies leads to an obvious adoption into percutaneous surgeries, and consequently cancer treatments. Yet, RF therapy is still more effective in its degree of treatment and effective disruption of cells.[67] Cryoablation is hindered by the same pitfalls experienced by RF and MW ablation; they lack the specificity needed to not harm healthy tissue and are also hindered by the heat sink effect.[68] Although cryoablation is much more effective near vasculature than RF or MW, the heat-sink effect remains a problem.

Nanoparticles are used as an indirect method of enhancing cryoablation, e.g. using cytokines to cause different immunological and inflammatory responses in the cell. As described previously nanoparticles have been effective methods of enhancing existing treatments to enable specificity and increased range for RF and MW therapies. The difference, though, is that RF and MW ablation generate heat and cause coagulation necrosis, whereas cryoablation uses extremely cold temperatures to stop cells from functioning.

The drug TNF-α increases neutrophil and cytokine localization to induce an inflammatory response as well as direct endothelial injury in solid tumors playing an important part in enhancing cryotherapy.[69, 70] The increased damage to the vascular region, or the periphery of the tumor, causes a synergistic response with the cryotherapy. This allows the ablation zone to reach closer to the edge of the tumor tissue without harming surrounding tissues.[68, 70, 71] Still, systemic delivery of enough TNF-α to enhance therapies is a major obstacle in its widespread use. The drug needs to be effectively delivered to only the target tissue, as it has many harmful effects to normal tissue as well.[71] Nanoparticles have the unique ability to carry drugs, as well as target different cell and tissue types. Gold nanoparticles are used to carry TNF-α and target tumor cells with antibodies. By using targeted nanoparticles for drug delivery, the systemic side-effects of cryoablation can be significantly decreased.[69]

Cryoablation is an extremely promising method because it allows for the real-time monitoring of the treatment. This allows the surgeon to ensure that the entirety of the tumor is removed with the ice-ball. In conjunction with the nanoparticle therapy described above, it is very possible to destroy a tumor fully without disruption to surrounding organs and tissue. However, the treatment can be rather painful and enduring, and the effects of the drug TNF-α are not fully understood in this setting. For these reasons, RF and MW ablation are currently much more viable clinical options.

Other Nanoparticle Thermal Therapies

Many nanoparticles have the ability to absorb different sources of energy such as NIR light, electromagnetic waves, RF waves, and HIFU pulses. Their ability to convert the energy they gain to thermal energy allows them to be used for thermal ablation separately from existing methods. Nanoparticles such as SWNTs release heat with continuous exposure to NIR light, while magnetic nanoparticles (MNPs) produce heat after exposure to an alternating magnetic field.[72-74] The heat released by these methods can produce significant tumor necrosis, making these methods promising therapies for minimally invasive tumor ablation.

Nanoparticles in the tissue produce heat strong enough for thermal ablation in both tumors and surrounding cells. Thus, it is critical to increase the intratumoral localization of the nanoparticles to protect the surrounding tissue and so that there is sufficiently high concentration of particles present to produce enough heat to effectively ablate the tumor. Alternate delivery methods, such as subcutaneous or intratumoral injections can increase the local concentration of nanoparticles.74 These methods are not always possible with deep tissue tumors, so increasing the intratumoral localization of nanoparticles for thermal therapy can also be achieved through antibody targeting, actively targeting a wide variety of cancer specific markers.72, 75, 76 Antibody conjugated nanoparticles increase the local nanoparticle concentration; however, if the particles specifically target the surface receptor the particles may not be internalized. Without internalization of the particles, the dissipation of heat through thermal conduction is not enough to directly destroy the cells, though the radiated heat could destroy different adjacent cellular structures consequently leading to cell death.76

There are limitations that prevent these nanoparticle therapies from providing a completely specific method of thermal ablation without any cytotoxic effects. SWNT ablation is limited by the penetration depth of the NIR wavelengths; the NIR spectrum does not penetrate deep enough to effectively excite nanoparticles beyond the surface, somewhat limiting this therapy to more superficial tumors.73, 76 However, in addition to applications in thermal therapy, SWNTs and MNPs can be used for drug delivery and visualized in different magnetic imaging systems. The multifunctional applications of these particles in tumor ablation through multiple mechanisms and the potential to monitor their distribution and effect will likely provide wide clinical application in the future.

ROS Inducing Agents

Oxidative stress is characterized by an imbalance in redox state resulting from excessive production of ROS and a reduction in cellular antioxidant agents.10, 77 The role of oxidative stress in cancer initiation, progression, and metastasis has been known for many years.78 Cancer itself is characterized by increased generation of ROS. If levels of ROS are high enough, there can be significant cellular damage including damage to DNA, proteins, and lipid membranes, as well as apoptosis.78 By taking advantage of the high amounts of ROS in tumor cells, further increasing these levels could provide an opportunity to kill cancer cells.78

Many non-surgical methods currently used to treat cancer such as thermal therapies, PDT, and radiation already rely on the production of ROS to induce cellular death.10 ROS molecules have unpaired electrons that make them highly reactive when formed *in vivo* via oxidation-reduction reactions and include free radicals such as hydroxyl ($HO^{\bullet}$) and superoxide radicals ($^{\bullet}O_2^-$), and nonradicals including hydrogen peroxide (H_2O_2) and singlet oxygen $^1O_2$.79 There are both endogenous and exogenous sources of ROS generation including NADPH oxidase, P-450 metabolism, peroxisomes, activation of inflammatory cells, transition metals, and radiation.77, 78 Mitochondria are major producers of free radicals and superoxides, and are involved in cell death by controlling apoptosis. Many ROS inducing agents work by targeting mitochondria and disrupting the electron transport chain, which increases ROS production.80 Therefore, ROS are not only inducers of cell death due to their high toxicity but they also act as signaling molecules in apoptosis.80

As an effective cancer treatment, ROS producing agents can either directly induce the generation of ROS in tumor cells, or inhibit their antioxidative defense system.78 Moreover, ROS producing agents can be used either alone or in combination with anti-cancer drugs or therapies. Hydrogen peroxide effectively induces ROS, but other agents and treatments that stimulate ROS generation in tumor cells are being investigated since hydrogen peroxide is

extremely toxic to humans. ROS producing agents used as a single anti-cancer drug include procarbazine, doxorubicin, buthionine sulfoximine, motexafin gadolinium, and rituximab.[10, 81] Furthermore, the thioredoxin system and the glutathione system are important targets in inhibiting cells' antioxidative defense system.[10]

The exact amount of ROS required to cause tumor cell death is not exactly known. ROS are required by both cancer and normal cells, and are essential for life because of their role in many vital processes such as signal transduction.[78] However, ROS can lead to carcinogenesis in healthy cells.[10] Excessive apoptosis can also cause cardiovascular and neurodegenerative diseases, ischemia-reperfusion injury, and autoimmune disorders.[10, 78] Therefore, the primary concern for using ROS inducing therapies is how to effectively and selectively kill cancer cells without producing toxic effects in normal cells.[10] *Wang et al.* describe a method to discriminate between normal and malignant cells by their differential capabilities in maintaining redox homeostasis.[10]

In general, mild increases in ROS cause cell proliferation, whereas large amount of ROS induce the lethal effects desired in cancer treatment.[80] Some cancer cells do result in growth arrest or death by eliminating ROS.[10] In addition, some tumors utilize an enhanced antioxidant system to adapt to increased oxidative stress that might be affected by a low level of ROS in combination with another anticancer therapy instead. Both ROS elevating and depleting approaches are effective therapies, and therefore, the best strategy employed will depend on the specific cell line.

Generally, nanoparticles can cause tumor ablation by several different mechanisms involving ROS. First, nanoparticles themselves can generate ROS in the biological environment; second, nanoparticles can be loaded with ROS promoting agents; and finally nanoparticles can perturb the normal oxidative stress levels by directly scavenging and depleting ROS or by scavenging antioxidants and enhancing ROS production. Each of these mechanisms of nanoparticle tumor ablation in combination with ROS is discussed below, however, there are interesting limitations. Similar to the paradox of ROS both causing and acting as a therapeutic for cancer, nanoparticles can either decrease or promote tumor growth depending on the conditions and tumor type. It is therefore necessary to carefully examine the roles of nanoparticles in various carcinomas to ensure that they act as a therapeutic agent.

One mechanism of ROS mediated cytotoxicity is the direct production of ROS from nanoparticle interactions in the biological environment. Concerns for human toxicity and environmental impact of nanoparticles has grown in recent years due to their widespread use for both consumer products and industrial applications. There is a growing body of literature examining the effects of nanoparticles composed of TiO_2, silver, silica, and other metal particles suggesting that these nanoparticles generate ROS and deplete the antioxidant glutathione in healthy cells *in vitro* and penetrate cell membranes to cause toxicity in healthy lung, liver, spleen, and kidney tissue *in vivo*.[82-86] However, when applied to the field of nanomedicine, nanoparticles are often coated with polymers to reduce their rapid clearance, and consequently are more biocompatible and often considered non-toxic *in vivo*. The altered environment of cancerous cells may be more susceptible to changes in oxidative stress than healthy cells as plain silica and chitosan nanoparticles have recently been shown to induce ROS and LPO acting as tumor suppressors in lung and liver carcinomas.[87, 88]

Nanoparticles can be loaded with ROS producing anti-cancer agents to improve their bioavailability, or to act synergistically with an agent to produce ROS once in the tumor vicinity. Drugs conjugated to the surface of particles, or loaded within particles are released via diffusion or degradation of the particles and can produce ROS. Block copolymers can

entrap water insoluble drugs such as tetrandrine, resveratrol, or ferrocenyl tamoxifen derivatives within a hydrophobic polymer core, exposing a hydrophilic surface to form a nanoparticle sized drug delivery system.89-91 Once released the drugs can enhance tumor effect by activating ROS dependent apoptotic pathways. Nanoparticles may also act synergistically with anti-cancer agents greatly increasing ROS production that can that affect tumor proliferation.92

Finally, nanoparticles can perturb normal oxidative stress levels by scavenging ROS directly. Endohedral metallofullerenol nanoparticles are a unique class of particles known as a 'radical sponge' that directly scavenge ROS such as $^{\bullet}O_2^-$, $HO^{\bullet}$, and singlet oxygen ($^1O_2$).93 These particles, originally designed as an MRI contrast agent, encapsulate the transition medal gadolinium within a fullerene cage. Interestingly, the fullerene cage is not destroyed during metabolism or when converting free radicals allowing the nanoparticles to continue to scavenge ROS.93, 94 Scavenging ROS is an indirect mechanism of tumor ablation, leading to significant tumor inhibition in mouse hepatomas.93, 95 Elevated levels of antioxidants detected in response to the tumors are further returned to more normal levels after treatment.94

While the nanoparticle therapies above generate or interact with ROS to cause cytotoxicity, it is worth mentioning that nanoparticles may actually lead to further tumor proliferation *in vivo*. For example, mesoporous silica nanoparticles internalized by malignant melanoma cells then implanted in mice increase the antioxidant glutathione, decreasing endogenous ROS required to inhibit NF-κB activation, thus promoting cell proliferation and increasing tumor growth.96 It is currently unclear whether this response is due specifically to the particles, cell type, dose, or mechanism of delivery. Thus nanoparticles as a cancer therapeutic must continue to be carefully studied to determine mechanisms and most efficacious treatments for cancer therapy.

Photodynamic Therapy

Photodynamic therapy is a minimally invasive, outpatient procedure gaining popularity for the treatment of numerous cancers including malignancies of the head and neck, esophagus, bladder, skin, lung, and brain.97-102 The basic principle of PDT involves the administration of a photosensitizing agent followed by local illumination of the target tissue with a light source of an appropriate wavelength (635–760 nm).103 For PDT to be an effective treatment, a sufficient amount of molecular oxygen (normally present in the tumor) is required.104 The combined action of the photosensitizer and molecular oxygen results in the formation of $^1O_2$ that causes oxidative damage to cellular components.105 PDT also damages the vasculature of the tumor thereby inducing cell death via hypoxia and starvation.3 Inflammation responses that follow post-PDT further assist in removing any remaining tumor cells.3, 105, 106 In addition to cancer, PDT can treat nonmalignant diseases including macular degeneration and infections.107, 108

The efficacy of PDT is affected by a number of factors including photosensitizer type, photobleaching, light delivery, blood flow, oxygen availability, and tumor interstitial pressure.3, 109 The most important factor is the type of photosensitizer used in the procedure. An ideal photosensitizer is easily synthesized, stable in water, activated with light of a longer wavelength, non-toxic in the absence of light exposure, and has target specificity.3, 103 Several drugs can be used for PDT with such characteristics. Porfimer sodium, the first and most commonly used photosensitizing drug, is used in thousands of patients and demonstrates the advantages of PDT as a cancer treatment option. Depending on the photosensitizing agent, it can be administered either topically or systemically.104

Over the past 20–25 years that PDT has been used clinically, no long-term side effects have emerged, and PDT can be used repeatedly without cumulative toxicity. However, PDT is a painful procedure for some patients and skin photosensitivity can occur at the treatment site.[3, 104] To improve the efficacy of PDT and reduce the amount of photosensitivity, new photosensitizing agents that incorporate more ideal properties and better target selectivity are in development.[3] Numerous formulations of drug-encapsulated nanoparticles are also being studied as potential PDT agents.[110-112]

PDT is used only for superficial tumors and deeper tumors accessible by endoscopies.[113] PDT cannot treat systemic diseases because an appropriate dose of the photosensitizing agent combined with whole body irradiation is not currently feasible.[104] Advancements in drug targeting, limiting light delivery, and using combination regimens improves the efficacy of this localized treatment.[3, 114] With the development of lasers, light emitting diodes (LEDs), and optical fibers, light of adequate dose and power can now be delivered directly to tumor sites. Compared to other tumor ablation methods such as surgery and radiotherapy, the controlled light penetration of PDT protects healthy tissue around the treatment area.[3] PDT also provides a matrix for regeneration of normal tissue by preserving the non–cellular supporting elements and basic tissue structure.[102] These factors allow functional recovery, superior healing, and positive cosmetic outcome (no scarring) after treatment.[3, 102]

A few major challenges currently limit PDT from more widespread clinical practice. High cost and the lack of a standardized protocol resulting from various randomized published trials deter untrained physicians from reaching to this relatively new treatment. The efficacy of the treatment as well as the inaccessibility of tumors deeper beneath the skin makes it less effective when compared to conventional therapies.[115] Also, the lack of specialization of the drug leads to prolonged photosensitivity. The first two issues are less of a problem and deal mainly with the popularity of the treatment, which is set back only by the effectiveness of the treatment. If the efficacy of the treatment, determined by the efficiency $^1O_2$ production and the specialization of the photosensitizer to the target site can be improved, then the cost and standardization will become a non-issue.[115]

Nanoparticles are emerging as a popular delivery method to address issues associated with photosensitizers including their hydrophobicity, cytotoxicity, and rapid degradation and consequent inactivity under irradiation. A wide range of nanoparticles are being used as vehicles for photosensitizers including polymeric nanoparticles, liposomes, silica, and gold nanoparticles.[116-120] In addition to protecting the healthy tissue from potential cytotoxicity from the photosensitizers, nanoparticles prevent the photosensitizer from leaking, minimizing degradation and consequent inactivity of the photosensitizer in the biological environment. The nanoparticles are then able to localize to the tumor via the EPR effect or active targeting further improving bioavailability at the tumor compared to free photosensitizers.

Photosensitizers do not have to be released from nanoparticles to generate $^1O_2$ to cause cytotoxicity, unlike some nanoparticle drug carriers that must release their drug payload to effectively ablate the tumor.[118, 121] Singlet oxygen is generated within the nanoparticle and diffuses out into the surrounding environment, though nanoparticles must be carefully designed to allow diffusion out through the nanoparticle shell.[121] To improve availability of $^1O_2$, photosensitizers such as phthalocyanine can be attached as a monolayer coating on gold nanoparticles.[117] When delivered in a cremophor emulsion, such nanoparticles generate more $^1O_2$ than free phthalocyanine for tumor ablation.[117, 119]

In addition to simply delivering photosensitizers to produce $^1O_2$, nanoparticles can simultaneously deliver chemotherapeutic agents or contain contrast agents for image guided PDT. Nanoparticles with combination drug and photosensitizers can significantly enhance ROS production and cytotxicity compared to single drug treatment to overcome resistance in drug resistant tumor cells.122 Nanoparticles can also be loaded with magnetic or fluorescent contrast agents to visualize tumor uptake of the therapy, and in some cases, the photosensitizer itself can be excited and visualized for optically guided therapy.121 Quantum Dots (QDs) are nano-size particles that act as a photosensitizer as well as a fluorophore.79 QDs generate $^1O_2$ at a much lower yield than photosensitizers (1-5% compared to 30-50% respectively); however they may exert toxicity after irradiation *via* production of ROS other than $^1O_2$.123-125

Nanoparticle-Mediated Drug Delivery and Tumor Ablation

Although the various methods described above are used in practice for tumor ablation, each method has its own problem and is not completely effective. These treatments are beginning to be increasingly effective with the help of nanoparticles, yet none have presented to be particularly better than chemotherapy or radiation therapy. In many cases, the potential side effects of these treatments are overlooked due to their familiarity. Nanoparticles have been developed to carry different drugs, dyes, or targeting ligands. This unique ability allows the use of multiple methods in conjugation to produce a synergistic effect.

Drugs have the ability to suppress tumor growth and proliferation; however, they are nonspecific and can be harmful to all tissue. Different commercial drugs can be loaded within or attached to a wide variety of nanoparticle formulations, and there are dozens of on-going clinical trials that are combining nanoparticles as delivery agents with currently approved chemotherapeutics for the improved treatment of many types of cancers.126 Nanoparticles can target these drugs to prevent proliferation for tumor cells in difficult to treat carcinomas, limiting the systemic cytotoxicity of the drug.127 With that advantage, a thermal or other noninvasive therapy can be administered allowing for destruction of the majority of the malignant cells. The drug released can then prevent recurrence of the tumor by preventing cell proliferation. However, there are only a handful of clinical trials that currently combine nanoparticles for drug delivery with thermal therapies such as RF and HIFU.128

As combined therapies are enhanced with drugs, it becomes necessary to ensure the proper delivery of nanoparticles and drugs to the appropriate tissue in the correct dosage. To ensure delivery, visualization of nanoparticles and the consequent treatments are necessary *in vivo*, and accurate diagnosis and translational data are needed to make effective treatment regimens.

Nanoparticles and Imaging in Tumor Ablation

Many nanoparticles can be visualized inherently, or through the attachment of a fluorescent dye. As new tumor ablation methods are being developed it is necessary to determine effective treatment regimens with accurate knowledge of the tumor boundaries. Modifying contrast agents or dyes to differentiate between malignant tissues and healthy tissues before, during, and after treatment, can enhance the clinical application of therapies.

Magnetic resonance imaging and fluorescence imaging are two very common methods of visualization each with their own advantages. The use of MRI for pre-surgical and diagnostic purposes is very common with all tumors. MRI provides high resolution images that are very useful in determining size, location, and the shape of a tumor. Our laboratory has created a formulation of nanoparticles that can be used for such purposes (Figure 6). The

nanoparticles are made of an iron oxide core, which is then coated with oleic acid, and finally a layer of Pluronic F127. The coating of Pluronic F127 makes the nanoparticle dispersible in water; however, it retains a hydrophobic region that can carry different hydrophobic anti-cancer agents. We have shown that this particle has the capability to delineate tumor margins, and serve as a prolonged contrast agent using MRI due to its iron oxide core.129 This is a very important advancement, as it is necessary to monitor the tumor size and shape after delivery of any anti-cancer drug to determine the treatment efficacy. The nanoparticle also can provide sustained drug delivery of multiple drugs alone or in combination to allow for a synergistic effect with certain drugs.130 Further, particles can be used to induce hyperthermia to enhance the drug effect

The images provided through MRI enhance the ability of a surgeon to locate and remove the entire tumor. However, this equipment can only be used as a reference, and cannot be compared to what is actually seen in surgery. Nanoparticles can be targeted to specific tissues and carry a dye or auto-fluoresce as described in many methods above. Using this ability and surgical probes, nanoparticles can delineate tumor margins intraoperatively.131 Since the same particles delineate the tumor margin in a pre-operative MRI image and during surgery, these particles provide accurate visualization of tumor margins for effective removal of tumor tissue.132

Alternatively, nanoparticles can be modified to increase retention time and provide a much longer period to monitor uptake by cells than common markers used for MRI.129 They can also be used in determining the success of tumor therapies and surgeries post ablation. The enhanced resolution provided by using nanoparticles as a target specific contrast agent in MR images can ensure complete eradication of tumors post surgery. With treatments like RF ablation and MW ablation where the only visualization of the tumor may be through fluorescence or MRI, nanoparticles can provide an accurate comparison of pre- to post-treatment images by eliminating variables such as auto-fluorescence, time, and noise.133 In recent years, imaging with fluorescent dye has progressed well and is useful particularly in monitoring the efficacy of treatment options for superficial cancers such as breast, because dyes can be imaged ~10 cm through tissue, an ideal penetration depth for breast cancer imaging.134 Magnetic nanoparticles can be simultaneously loaded with fluorophores in the NIR region to study the dynamics of biodistribution, targeting, and as an intraoperative technique to define tumor margins.133, 135 Fluorescent images are thus useful in determining what should be resected during surgery and what tissue is healthy, the level of tumor regression, and reducing the chance of recurrence. In general, nanoparticles with multifunctional properties such as drug delivery and imaging in combination with ablation techniques could improve cancer treatment.

Molecular Mechanisms of Nanoparticle-Mediated Tumor Ablation

The properties of nanoparticles alone can impact many biological processes within cells. Understanding the molecular mechanisms of nanoparticle-mediated tumor inhibition will be important to further optimizing and controlling their properties, and identifying synergies with specific drugs, ablation techniques, and other cancer treatment modalities. This section highlights some of the mechanisms by which nanoparticles affect cell functions, and how these may be applied to tumor ablation.

Mechanisms of ROS Generation—The hydroxyl radical is considered the most toxic free radical, and is generated in biological systems primarily by the iron-catalyzed Haber-Weiss reaction (also referred to as Fenton Reaction).136 In this reaction, hydroxyl radicals ($^{\bullet}OH$) are formed from hydrogen peroxide (H_2O_2) and superoxide ($^{\bullet}O_2^-$) via the following reactions:

1. $Fe^{3+} + {}^{\bullet}O_2^{-} \rightarrow {}_{Fe}^{2+} + O_2$ (Reduction of ferric iron to ferrous iron)
2. $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{-} + {}^{\bullet}OH$ (Fenton Reaction)
3. ${}^{\bullet}O_2^{-} + H_2O_2 \rightarrow {}^{\bullet}OH + OH^{-} + O_2$ (Net Reaction)

Nanoparticles made from transition metals may break down within the cell to provide the metal ions that catalyze ROS (hydroxyl radical) generation via the Haber-Weiss reaction. Iron oxide based nanoparticles are particularly well suited for this mechanism. The coatings typically used on the nanoparticles can be degraded by lysosomal enzymes, exposing the redox-active iron oxide core. Copper, as well as other metals, may also be capable of ROS generation via the Fenton reaction.137-139

Cancer cells are generally deficient in the antioxidative enzymes present in normal cells, making them particularly vulnerable to an oxidative assault. In addition, differences in iron metabolism between cancer cells and normal cells suggest an iron-mediated oxidative assault may be a mechanism for selectively targeting cancer cells while leaving normal cells unharmed. In cells of the RES, iron oxide nanoparticles are broken down with majority of iron stored as ferritin and or hemosiderin,140 and excess iron is then removed from these cells *via* ferroportin. The metabolic demands of cancer cells manifest in increased levels of transferrin receptors to facilitate iron uptake, and decreased levels of ferroportin.141 Therefore, when iron levels are increased in the blood as well as *via* direct uptake of iron-oxide nanoparticles, this may result in acutely elevated intracellular iron concentrations in cancer cells and subsequent ROS generation *via* the Fenton reaction.

Silver nanoparticles have been linked to ROS generation via disruption of calcium homeostasis.142 Silver ions may act on the same sites as calcium ions, which could affect calcium flux in and out of the mitochondria. Consequently, mitochondrial membrane damage results in ROS production, inhibition of ATP synthesis, and initiation of apoptotic signaling pathways. Another mechanism by which some nanoparticles can generate ROS is related to their semiconductor properties, as is the case with zinc oxide (ZnO) nanoparticles. Electrons and holes within the ZnO nanoparticle can migrate to the particle surface and react with oxygen or with hydroxyl ions or water to form superoxide and hydroxyl radicals, respectively.143 UV light further enhances electron conduction and ROS generation. The combination of ZnO nanoparticles and the anti-cancer drug daunorubicin with UV irradiation has synergistic cytotoxic effects on leukemia cells. 144

Nanoparticles Induce Cytoskeletal Alterations and Anti-Proliferative Effects— The presence or accumulation of nanoparticles within cells may affect or interfere with cell functions. Cellular uptake of nanoparticles results in changes to the cytoskeleton, which can affect numerous biological processes such as cell spreading and adhesion, cell growth, viability, and ECM production. Iron-oxide, gold, and silver nanoparticles alter the cellular cytoskeleton of various cell types, including fibroblasts, endothelial cells, neural progenitor cells, and glioblastoma cells, which is correlated with a decrease in cell proliferation. 142, 145-148 After nanoparticle exposure, cells became condensed (decreased cell area), more polarized (larger aspect ratio) and cell proliferation was reduced. Cytoskeletal changes included remodeling of microtubules,147 disruption of actin filaments,148 down-regulation of filamin,142 decrease in focal adhesion complexes,145 and decreased levels of focal adhesion kinase signaling.146 These observations were often dependent on dose, exposure time, nanoparticle properties (size, roughness), as well as cell line. The accumulation of nanoparticles in the cytoplasm may result in physical interactions/interferences with the cytoskeleton, or an increase in size and/or number of endosomes associated with nanoparticle uptake, and may cause rearrangement of cytoskeletal components in order to form new trafficking routes.145, 149 One study showed nanoparticle exposure caused a

decrease in ECM production and changes in ECM properties, which may also impact the cytoskeletal organization of the cell.149 The morphological changes can subsequently affect signaling pathways that lead to decreased proliferation. Normal cells could eventually recover from the nanoparticle-mediated anti-proliferative effects. As the cells divided, albeit at a slower rate, the nanoparticles redistributed among the daughter cells, thus reducing the intracellular concentration of nanoparticles. Interestingly, cancer cells were not able to recover and ceased to proliferate.142 Facilitating the transport of nanoparticles from the cytoplasm to the nucleus of the cell may further enhance the anti-proliferative effects. Gold nanoparticles tagged with nuclear targeting ligands localized within the nucleus of cancer cells where they disrupted cytokinesis and prevented the completion of cell division, ultimately leading to apoptosis.150

Altering the Tumor Microenvironment—Tumors comprise not only the malignant cells, but also the supporting stroma. The tumor stroma includes fibroblasts, immune cells, vascular/endothelial cells, and progenitor cells, which regulate the tumor microenvironment and impact tumor growth and disease progression. Increasing interest has developed in cancer therapies that target the tumor stroma in order to create a less favorable microenvironment for cancer cells to thrive. This approach, in combination with other therapeutic agents, may be important for preventing recurrence and overcoming drug resistance. In addition to controlling the biochemical environment, the cells and extracellular matrix of the tumor stroma also form physical barriers for drug delivery to cancer cells. Nanotechnology may provide new opportunities for targeting components of the tumor microenvironment and improving clinical outcomes of tumor ablation techniques.

The tumor endothelium has been targeted by a number of anti-angiogenic agents, including nanoparticle-mediated approaches, with the aim of reducing the blood and nutrient supply to tumor cells.151, 152 The tumor vasculature is also a barrier that must be crossed in order to delivery therapeutics to the tumor parenchyma. Iron oxide nanoparticles induced ROS-mediated remodeling of microtubules in endothelial cells which ultimately resulted in increased endothelial cell permeability.147 In this case, exposure to the iron oxide nanoparticles resulted in inhibition of GSK-3β via the PI3K/Akt signaling pathway. Nanoparticles that target the tumor endothelium and act to increase its permeability may serve to facilitate extravasation of drugs, macromolecules, or the nanoparticles themselves into surrounding tumor tissue.

Macrophages are inherently phagocytic and may preferentially uptake nanoparticles either within the tumor or in the circulation (as circulating monocytes) and subsequently migrate to the tumor. Macrophages are being studied as carriers for nanoparticles to tumors,153 but may also be therapeutic targets themselves. Tumor associated macrophages (TAMs) are generally associated with the M2 phenotype, and therefore play a pro-tumorigenic role including the promotion of angiogenesis, matrix remodeling, and suppression of adaptive immune responses.154, 155 The number of M2 macrophages and proliferating macrophages within tumors has been correlated with poor clinical outcome in certain cancers.156, 157 The development of nanoparticles to track and image TAMs is being studied as a tool to monitor tumor progression.158 Nanoparticles engineered to deplete TAMs, decrease their recruitment to the tumor, or alter their pro-tumoral phenotype/behavior could be effective in stopping or slowing the progression of cancer. The role of macrophages in iron metabolism within the tumor may be exploited with nanoparticles made from iron oxide. Macrophages are specialized in storing of iron, and under conditions that favor accumulation; they may acquire an amount of iron sufficient to induce cytotoxic effects on themselves and surrounding cells.159, 160 Iron oxide nanoparticles caused apoptosis in human macrophages via ROS-mediated activation of the c-Jun N-terminal kinase (JNK) pathway.160

The physicochemical properties of nanoparticles can impact various biological processes within cancer and stromal cells of the tumor. Many cytotoxity and mechanistic studies are performed *in vitro*, and a better understanding of how these correlate *in vivo* is needed. Ultimately, optimization of nanoparticle properties for a given therapeutic target will be combined with therapeutic agents that act synergistically to yield more effective tumor ablation techniques.

Concluding Remarks

Tumor ablation could become the most effective non-surgical method of treating certain types of cancers. Nanotechnology can add to the improvement in the outcome of different tumor ablation techniques by delivering drugs for synergistic effects to prevent recurrence and enhance tumor imaging for precision of treatment. Strategies to synergize the ablation effect in combination with drugs, ROS generating agents specifically in tumor cells, and optimal energy source, could further improve the outcome of ablation techniques. In this regard, new nanomaterials that can potentiate the thermal effect and with imaging capability could certainly play a critical role. Nonsurgical tumor ablation techniques with advancements in nanotechnology will continue to develop and thrive as an effective and preferred approach to treat local cancers over surgical resection or convention drug therapy.

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Abbreviations

CT	computed tomography
ECM	extracellular matrix
EPR	enhanced permeability and retention
HIFU	high-intensity focused ultrasound
LED	light emitting diode
MNP	magnetic nanoparticle
MRI	magnetic resonance imaging
MW	microwave
PDT	photodynamic therapy
QDs	Quantum dots
RF	radiofrequency
RES	reticuloendothelial system
ROS	reactive oxygen species
SWNT	single wall carbon nanotube
TAMs	tumor associated macrophages
US	ultrasound

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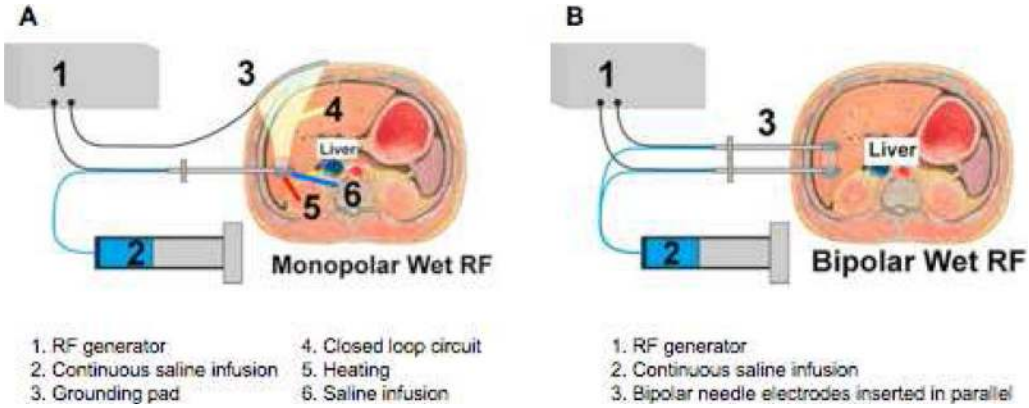

Figure 1.
Comparison of monopolar wet RF (A) with bipolar wet RF (B). The bipolar method does not require a grounding pad and has two saline infusions in the tissue which requires two separate probe insertions. Images courtesy of Dr Afshin Gangi.

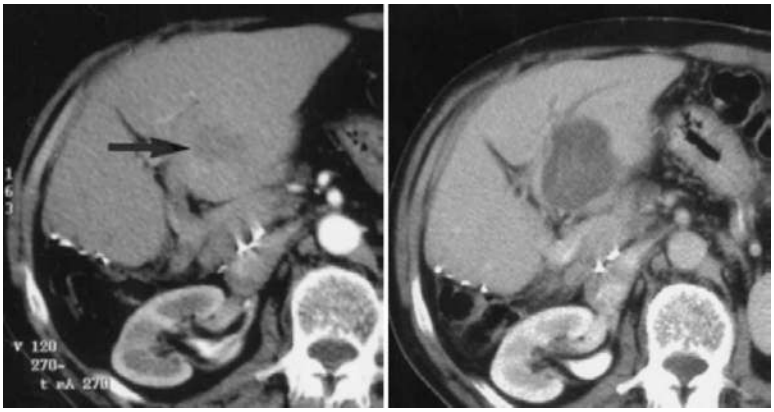

Figure 2.
A 54-year-old man with colon cancer. A CT scan was obtained 3 months after right hepatectomy (left) shows hepatic 3-cm-diameter metastasis (arrow). A CT scan obtained at the same level 2 months after radiofrequency ablation of tumor (right) shows hypodense "scar." The scarred area is completely covering the site of the metastasis. Reprinted from de Baere, *et al.*,161 with permission from the American Roentgen Ray Society.

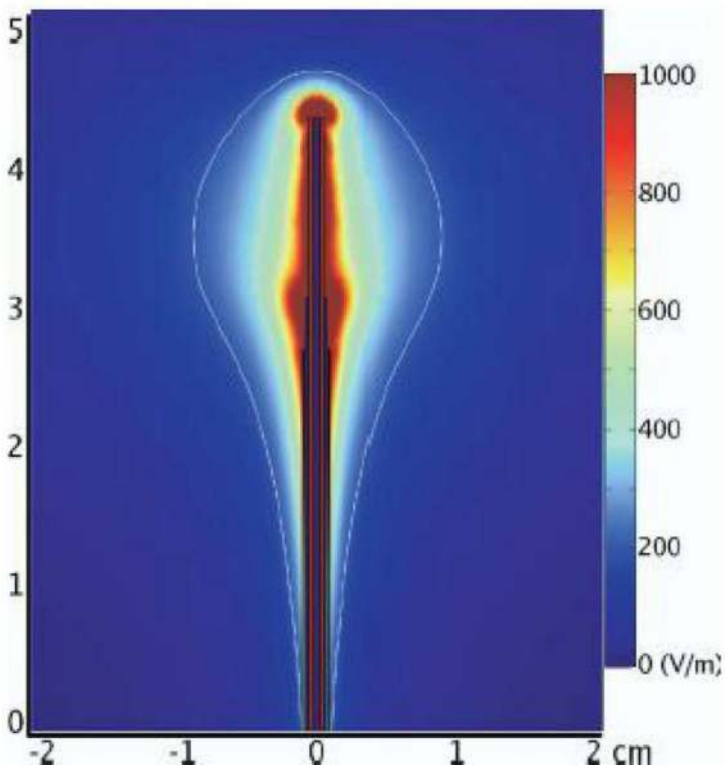

Figure 3.
Heating pattern around a microwave antennae probe where the active heating range extends almost to 2 cm in diameter. A larger active heating range provides a more effective tumor kill, as well as greater efficacy near vasculature. Reprinted from Brace, C.L.20 with permission from Elsevier.

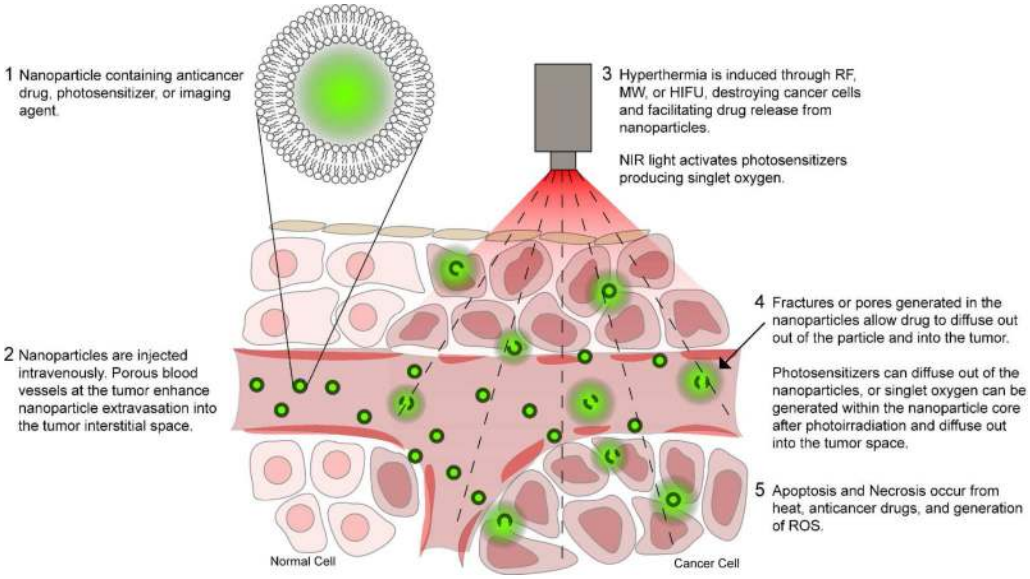

Figure 4.

Illustration of nanoparticle mediated tumor ablation. Nanoparticles containing drug or dye (1) are intravenously injected and extravasate into tumor tissue through the leaky vasculature by the EPR effect (2). Photoirradiation or hyperthermia (3) generate singlet oxygen or facilitates drug release from nanoparticles within the tumor (4) leading to tumor apoptosis and necrosis (5). Radiofrequency (RF), microwave (MW), high intensity focused ultrasound (HIFU), reactive oxygen species (ROS).

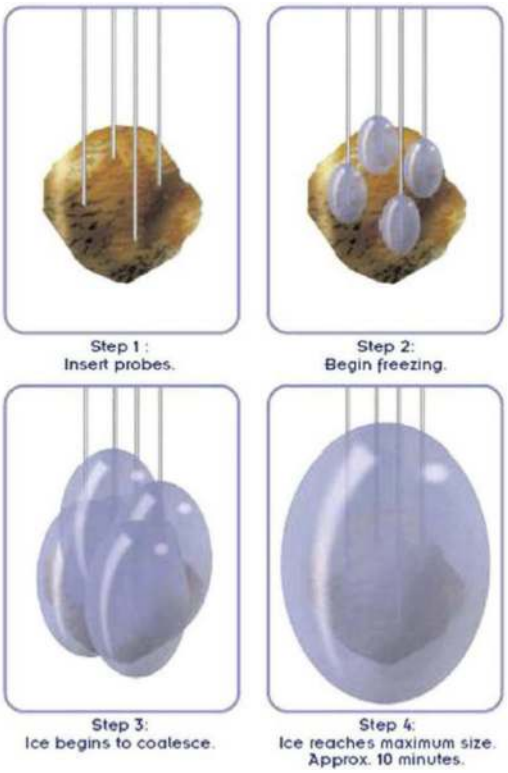

Figure 5.
Multiple cryoablation probes create a uniform “ice-ball” for full tumor eradication. Illustration courtesy of HealthTronics, Inc, Austin, TX; with permission.

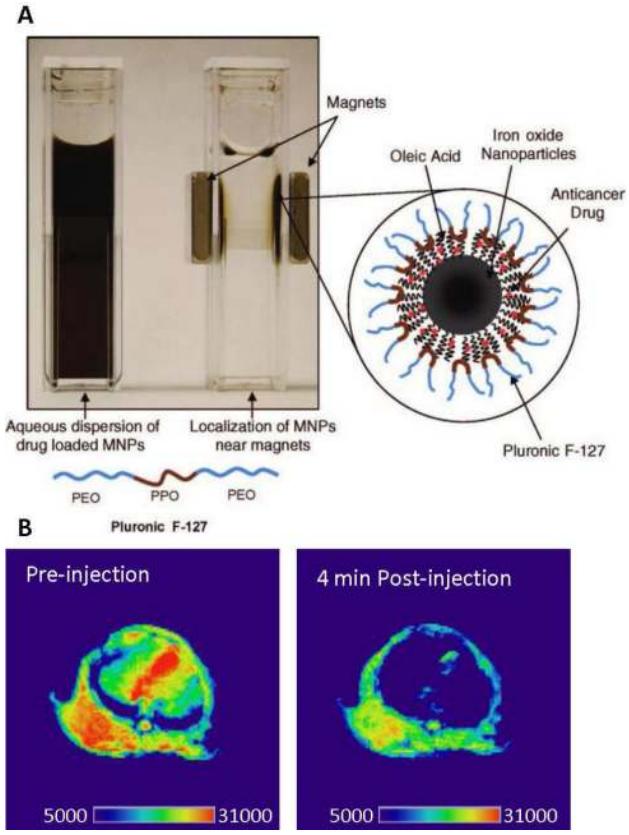

Figure 6.

(A) The F-127 magnetic nanoparticle formulation has the ability to be localized using a magnetic field. F-127 Pluronic works to provide a hydrophobic region to carry anti-cancer drugs while still being dispersible in water. (B) The magnetic nanoparticles serve as an effective contrast agent in delineating tumor margins in an MR image. Figure 6B is reprinted from Jain, *et al.*,129 with permission from Elsevier.

Table 1

A summary of current tumor ablation therapies.

Radiofrequency (RF)	Liver, lung, bone, breast, kidney, adrenals	Minimal Side effects, Relatively safe, inexpensive efficient procedure	Small heating range, requires grounding pads, heat sink effect	Post-ablation syndrome, skin burns
Microwave (MW)	Liver, lung, bone, breast, kidney, adrenals	Less heat sink effect, no grounding pads, larger area of ablation	Local treatment, non-specific	Post-ablation syndrome
Cryoablation	Prostate, kidney, liver, lung, bone, breast	Can be done with US, CT, MRI guidance, same day procedure	Heat-sink effect, recurrence more often than RF or MW	Cryo-shock
Photodynamic Therapy (PDT)	Head, neck, esophagus, bladder, skin, lung, brain	Minimal long-term side effects, superior healing, no scarring	Painful procedure, skin photosensitivity, cannot treat deeply set tumors	Prolonged light sensitivity
High Intensity Focused Ultrasound (HIFU)	Liver, kidney, pancreas, breast, prostate, abdomen	Confined accurate lesion, completely noninvasive, non toxic	Difficult to focus US wave, expensive, long procedure time, difficult to maneuver near air pockets, or bone	Skin burns, organ system specific side effects
Chemotherapy/Radiation Therapy	All	Well-known, most used and effective	Recurrence, long procedure, multiple dose regimen, many side effects	Hair loss, vomiting, cosmetic defects, functional morbidity

Table 2

Nanoparticle formulations and mechanisms of tumor ablation.

Iron oxide NPs coated with polyaniline	MW	30 – 50 nm		Targeting: folic acid imaging: thermoacoustic imaging	*in vivo*	S180 mouse tumor sarcoma	Nie, *et al.*33
SWNTs	MW hyperthermia	d: 1 – 2 nm × l: 5 – 30 μm				tissue mimicking mixtures	Mashal, *et al.*32
Fe_3O_4, Fe_2O_3 NPs	MW hyperthermia	3.2 – 5.3 nm					Janmaleki, *et al.*162
AuNPs	drug-NP-ROS	15 nm		combination therapy: 5-aminolevulinic acid + citrate AuNPs	*in vitro*	human MCF7 breast cancer and HepG2 hepatocellular carcinoma	Ito, *et al.*92
PVP coated AgNPs	ROS	118 – 121 nm	-21.8 mV		*in vitro*	BRL3A rat liver cells and rat alveolar macrophages	Foldbjerg, *et al.*83
polymer nanosphere, vesicular nanocapsules	drug-ROS	52 – 56 nm, 130 – 180 nm	(-7.9) – (-2.9) mV, (-57.8) – (-44.0) mV	drug: ferrocenyl tamoxifen derivatives	*in vitro*	human MELN (MCF 7 breast cancer)	Nguyen, *et al.*91
mPEG-PCL polymer	drug-ROS	87.5 nm	-5.6 mV	drug: resveratrol	*in vitro*	rat C6 glioma cells	Shao, *et al.*90
mPEG-PCL polymer	drug-ROS	75.3 nm	-6.1 mV	drug: tetrandrine	*in vitro*	human colorectal cancer cells (LOVO)	Li, *et al.*89
chitosan nanoparticles	ROS	40 – 100 nm	+50 mV		*in vitro, in vivo*	human hepatoma BEL7402	Qi, *et al.*88
mesoporous silica NPs	AO increase, ROS depletion	110 nm	(-35.6) – (+27.5) mV	Promote tumor growth	*in vitro, in vivo*	A375 human malignant melanoma	Huang, *et al.*96
silica Nps	ROS	15 – 46 nm			*in vitro*	A549 human bronchoalveolar carcinomas	Lin, *et al.*87
'liposils': hollow ceramic silica spheres	MW, US	100 nm	-40 mV	encapsulate: congo red and other dyes			Steinberg34
polystyrene nanospheres	HIFU	100 – 200 nm		encapsulate: dyes	*in vivo*	muscle	Hancock55
temperature sensitive liposomes	US hyperthermia	140 nm		drug: doxorubicin	*in vivo*	human squamous cell carcinoma xenograft in mice	Kong, *et al.*163
temperature sensitive liposomes ThermoDox	HIFU hyperthermia, RF, US			drug: doxorubicin	*in vitro, in vivo* Phase I, II, III clinical trials	murine adenocarcinoma hepatocellular carcinoma, recurrent breast cancer at chest wall	Dromi, *et al.*28 and ClinicalTrials.gov126, 128
liposomes	HIFU	210 nm		encapsulate: FITC			Chen, *et al.*51

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Aerosol OT (AOT)-alginate nanoparticles	PDT, ROS	62 nm	-25.1 mV	encapsulate: methylene blue drug: doxorubicin	*in vitro*	drug resistant NCI/ADR RES	Khdair, *et al.*122
Polyacrylamide, Sol-gel silica, or Organically modified silicate (ORMOSIL)	PDT	20 – 30 nm, 190 nm, 160 nm		encapsulate: methylene blue	*in vitro*	rat C6 glioma cells	Tang, *et al.*118
gold nanoparticles in Cremophor emulsion	PDT			Zn(II)-phthalocyanine disulphide	*in vivo*	amelanotic melanoma	Camerin, *et al.*119
ZnO nanoparticles	PDT			drug: daunorubicin	*in vitro*	drug resistant leukemia K562/A02	Guo, *et al.*144

Abbreviations: AgNPs – silver nanoparticles, AO – antioxidant, AuNPs – gold nanoparticles, NPs – nanoparticles, mPEG-PCL – methoxy poly(ethylene glycol)-poly(caprolactone) , PVP – poly vinyl pyrrolidone, ZnO – Zinc Oxide

[a]Size may be core diameter determined by electron microscopy or hydrodynamic diameter determined by dynamic light scattering.