Perspectives of Nanotechnology in Minimally Invasive Therapy of Breast Cancer

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ABSTRACT

Breast cancer, the most common type of cancer among women in the western world, affects approximately one out of every eight women over their lifetime. In recognition of the high invasiveness of surgical excision and severe side effects of chemical and radiation therapies, increasing efforts are made to seek minimally invasive modalities with fewer side effects. Nanoparticles (<100 nm in size) have shown promising capabilities for delivering targeted therapeutic drugs to cancer cells and confining the treatment mainly within tumors. Additionally, some nanoparticles exhibit distinct properties, such as conversion of photonic energy into heat, and these properties enable eradication of cancer cells. In this review, current utilization of nanostructures for cancer therapy, especially in minimally invasive therapy, is summarized with a particular interest in breast cancer.

Keywords: breast cancer, minimally invasive therapy, nanoparticles

1. INTRODUCTION

Breast cancer is the most common type of cancer among women in the western world, which affects approximately one out of every eight women over their lifetime. According to the most recent estimates for breast cancer from the American Cancer Society, about 226,870 women are diagnosed with invasive breast cancer, and more than 39,000 will die from it every year in the United States [1]. Despite tremendous efforts in search for alternative treatments, surgical excision, chemotherapy and radiation currently still remain the primary options for breast cancer, with surgical excision biopsy as the gold standard diagnostic modality [2]. However, these treatment practices are either invasive with a high risk of morbidity or accompanied with severe side effects (*e.g., hair loss, fatigue, etc.*) [3]. Recognition of these associated challenges has greatly motivated efforts in exploring other therapies with minimal invasion, which

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can not only shorten the patient recovery time but also cause less morbidity and fewer complications. With the continuous progress in mammography screening for early detection of small-sized breast cancer lumps, minimally invasive therapy has become more practical and popular than ever [4–6].

Recent progress in nanotechnology (referring to structures less than 100 nm in size) has shed exciting light on cancer therapy and diagnosis due to the large surface area, high surface reactivity and unique physicochemical properties of these nanostructures [7–9]. Cumulative evidence has shown the advantages of nanoparticles in cancer therapy, in which nanoparticles can be engineered to incorporate various chemotherapeutics and deliver them to a specific tumor site for better efficacy and less toxicity in chemotherapy [10–15]. Moreover, the tunable size and surface properties can prevent the opsonization of nanoparticles to prolong the circulation, thus increasing the opportunity to accumulate in cancer [16–20]. More details in nanoparticle-assisted drug delivery can be found in several seminal reviews [21–23].

The intrinsic features of nanoparticles hold tremendous promise for their application in minimally invasive therapies. As recognized, the major challenges of current minimally invasive therapy are the unsatisfactory treatment effectiveness and limited targeting capacity [4–6]. One way to address these challenges is to distinguish diseased tissue from healthy tissue while maintaining sufficient killing efficiency with the assistance of nanoparticles. Various nanoparticles, such as liposomes [24–26], dendrimer [27, 28], and magnetic [29, 30] and metallic nanoparticles [31, 32], are being evaluated for their potentials in minimally invasive therapies as they have been applied in other cancer therapies. These nanoparticles offer superior advantages, such as increased delivery of cytotoxic drugs, (*e.g.*, doxorubicin [33, 34], paclitaxel [35], oxaliplatin [36], etc.), contrasting agents (*e.g.*, gadolinium containing contrast agents [37] and iron platinum [38], *etc.*), or therapeutic gene sequence (*e.g.*, p53 gene [39] and small interfering RNA (siRNA) [40], *etc.*) to cancer cells (See Figure 1).

Figure 1. Applications of nanoparticles in cancer treatment.

Upon modification with tumor-specific ligands (*e.g.*, transferrin receptor [41], herceptin which binds to HER2/neu receptor [42, 43], and folic acid [44], *etc.*), nanoparticles could be selectively directed to cancer cells, resulting in accumulation of drugs/agents in cancer cells for targeted treatment. In addition to delivering cytotoxic or biologic agents, some nanoparticles themselves act as anticancer therapeutic agents as a result of their unique inherent optical and dielectric properties, magnetic susceptibility, thermal or electrical conductivity. With the continuous evolution of minimally invasive techniques and nanotechnology, their combination will become more intriguing toward future therapeutic interventions of various cancers.

In this review, various minimally invasive therapies for breast cancer will be summarized, with insightful discussion of the advantages and shortcomings of each procedure. We will also discuss the state-of-the-art development of nanotechnology for a variety of minimally invasive modalities with a specific emphasis on their potential contributions.

2. MINIMALLY INVASIVE TREATMENT OF BREAST CANCER AND NANOTECHNOLOGY

In principle, compared to the standard therapy, minimally invasive therapy for breast cancer could achieve a similar outcome, if not better, with less morbidity, better cosmetic appearance, shorter and safer procedures, quicker recovery and reduced inpatient period for a better quality of life as well as considerable savings in healthcare costs [6]. The most exciting and successful demonstration is the use of percutaneous ablation (*i.e.*, through a small incision on the skin) to eradicate breast cancers instead of surgical excision [45]. To date, four major categories of minimally invasive techniques have been explored for breast cancer treatment, including direct removal (stereotactic excision), tumor ablation through heating or freezing (radiofrequency ablation (RFA), focused ultrasound (FUS) ablation, laser ablation and cryoablation), direct administration of anticancer drugs into tumor site through a catheter (chemoembolization), and light-based therapy (photodynamic and photothermal therapy). Besides removal of the primary tumors, these treatments also show promising results in eradicating residual tumors which still poses a significant recurrence risk to the patient [46]. At present, the main challenges associated with these treatments are to identify the exact tumor location, confine the treatment to tumor and completely destroy tumor cells inside the primary lesion. As noted, inadequate therapeutic efficacy of these minimally invasive approaches results in a high tendency for local recurrence of the cancer [47]. Although the possibility of damage to surrounding healthy tissues of these minimally invasive therapies is much lower than that of conventional therapies, accurately targeting the treatment to tumors is always highly desired to minimize unwanted side effects and improve treatment efficacy. In the following subsections of this review, we will discuss several minimally invasive ablative modalities, including radiofrequency ablation (RFA), focused ultrasound (FUS) ablation, cryoablation, photodynamic and photothermal therapy for breast cancer and potential utilization of nanoparticles in each procedure (see Table 1).

Table 1. Potential utilization of nanoparticles in minimally invasive techniques for cancer therapy

Treatment modality	General mechanism	Nanomaterials applied	Functions of nanomaterials
Radiofrequency ablation (RFA)	Heat generated by an alternating high-frequency electric current	<ul style="list-style-type: none"> • Au NPs [48, 49] 	<ul style="list-style-type: none"> • Targeting cancerous cells • Excellent conductor of thermal energy • Increased intracellular heat when exposed to the external RF field
Focused ultrasound (FUS) ablation	Heat converted from acoustic energy	<ul style="list-style-type: none"> • Magnetite (Fe_3O_4) nanoparticle agglomerates [50] • Fe_3O_4-containing PLGA microcapsules [51] 	<ul style="list-style-type: none"> • Enhanced inertial cavitation • Enhanced therapeutic efficacy • Imaging for guidance
Cryoablation	Rapid cooling achieved by liquid nitrogen or argon gas delivered to the cancer tissue	<ul style="list-style-type: none"> • Iron oxide magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$) [52] • TNF-$\alpha$ gold nanoparticles [53] 	<ul style="list-style-type: none"> • Enhanced heat conduction • Serving as nucleation seeds for ice-ball formation and orientation
Photodynamic therapy (PDT)	Light irradiation for photosensitizer activation and reactive oxygen species (ROS) production to destroy cancerous cells	<ul style="list-style-type: none"> • p-THPP loaded PLGA nanoparticles [54] • ZnPc loaded PLGA nanoparticles [55] • Ceramic-based nanoparticles [56] • Phthalocyanine-nanoparticle conjugates [57] • 5-ALA conjugated Au NPs [58, 59] 	<ul style="list-style-type: none"> • Selective and effective delivery of photosensitizer • Strong scattering light energy • Enhanced localized electromagnetic field
Photothermal therapy (PTT)	Electronic excitation under laser irradiation and energy relaxation leading to overheating the local environment	<ul style="list-style-type: none"> • EGFR-conjugated Au NPs [60] • gold-silica nanoshells [61] • anti-HER2-conjugated silica-gold nanoshells [62] • PEG-protected gold nanorods [63] • folate-single-walled carbon nanotubes [64] 	<ul style="list-style-type: none"> • Enhanced targeting specificity • Strong light absorption • High photostability • High optical absorbance in the near-infrared region

2.1. Radiofrequency Ablation

RFA involves the procedure to insert a radiofrequency (RF) probe with needle-like electrodes to apply alternating electrical current into the breast tumor under imaging guidance such as ultrasound, computed tomography (CT), or magnetic resonance (MR). Heat generated by the alternating high-frequency (*e.g.*, 400~500 kHz) electric current between the electrodes can destroy breast tumor tissue through coagulative necrosis of cancer cells (Figure 2a). Tumor tissue is killed immediately at a temperature exceeding 50–60°C, while an adequate period of time is needed to kill the tumor if the temperature is just above approximately 40°C [65]. The sustainability of the heat depends on the tumor size. During the procedure, the temperature can be monitored by thermometers installed on the electrodes.

RFA ablation is well studied for ablative treatment of breast cancer. Mirza *et al.* [66] have shown the efficiency of RFA as a local treatment option for breast cancers smaller than 2 cm, that up to 87% ablation was achieved among 30 breast cancer patients without major complications. Similarly, Izzo *et al.* [67] also demonstrated a complete ablation and necrosis of breast tumors up to 3 cm for 25 out of 26 patients after ultrasound-guided RFA.

It appears that RFA is oncologically safe in the short term and yields satisfactory cosmetic outcomes. However, several limitations are also identified in RFA [49], including 1) the need to insert needle electrodes directly into the tumor site for the treatment, indicating their applicability only to those visible tumors; 2) the 3–3.5 cm maximum tumor size for complete tumor destruction, leading to 5–40% incomplete destruction for those tumors larger than 4–5 cm; and 3) the nondifferential treatment between malignant and normal tissues by the RF current around the needle electrode, increasing the risk of complications as a result of the thermal injury to normal tissue. Increasing the voltage of RF can enlarge the treatment area; however, it also produces extra heat inducing more complications. To address the last two limitations, the RF-to-heat conversion needs to be more efficient with RF-induced heating preferably limited to tumor cells.

Further improvement of the RF-to-heat conversion and confinement of the RFA only to tumors require the assistance of agents that can increase the thermal effects under RF radiation and be directed to the malignant cells. Among various agents, nanoparticles

Figure 2. Diagrammatic illustration of a) radiofrequency ablation (RFA) and b) focused ultrasound (FUS) ablation.

are considered as promising candidates to achieve the multifunctions, and gold nanoparticles (Au NPs) are of particular interest due to their easy modification with binding molecules to target cancer cells and outstanding electrical and thermal conductivity besides the superior biocompatibility and physical/chemical/biological stability [68–71]. Au NPs internalized by cells can significantly elevate the intracellular heat level upon exposure to an external RF field as evidenced in various settings. For example, Gannon *et al.* [49] demonstrated that Au NPs (~5 nm) released substantial heat after exposure to a high-voltage focused RF field (13.56 MHz) and its dose-dependent lethal injury to human cancer cells (Hep3B cells and Panc-1 cells) was more than 96%. Cardinal *et al.* [48] also found that the presence of 13 nm Au NPs in HepG2 liver cancer cells induced adequate heat to raise the temperature (>50°C) and caused approximately 80% cell death upon exposure to 13.56 MHz RF field (35 W for 7 min). Additional evidence was also shown in their *in vivo* experiments of the same study, in which the injection of Au NPs into JM-1 hepatoma nodule-bearing Fisher rats resulted in a significant increase of local temperature and thermal injury to the subcutaneous injection sites upon exposure to 35 W RF field compared to the sham controls without Au NPs. To better guide the Au NPs into breast cancer cells, an appealing approach is to modify the Au NPs with breast-cancer-specific ligand, HER-2, and then via the ligand-receptor interaction, Au NPs could be endocytosed by HER-2-expressing breast cancer cells [72, 73].

2.2. Focused Ultrasound Ablation

Minimally invasive tumor ablation through thermal effects can also be achieved by Focused Ultrasound (FUS). After localization of the tumor within the breast, ultrasound can be focused to rapidly generate substantial heat by converting the acoustic energy from an ultrasonic source. The slow heat dissipation leads to the increase of local temperatures up to 90°C, which can cook the tumor and cause the necrosis of cells and ablation of tumors [74] (Figure 2b). Temperature is monitored by probes during the FUS-induced tumor ablation process. It is possible to focus the ablation on a small lesion with high-resolution imaging techniques such as MRI for accurate detection and monitoring [75, 76]. For breast cancer treatment, Gianfelice *et al.* [77] used MRI-guided FUS to treat 12 patients with metastatic breast tumors smaller than 3.5 cm. Up to 88.3% of the tumor tissue was ablated with no major complications.

The major advantage of FUS is that no skin incision is required during the treatment. However, the difficulty for ultrasound to penetrate through air and bone results in its relatively low therapeutic efficiency for deep tumor lesions. Since ultrasound energy attenuates with the depth of the tissue, high power ultrasounds are needed for those deep tumors, which could cause severe side effects such as skin burns and nerve injury [78, 79]. Achieving a high therapeutic efficiency at a low acoustic power remains to be an unmet challenge in FUS therapy [51]. Magnetite nanoparticles have held great promise to address this challenge in consideration of their capability of enhancing inertial cavitation induced by high-intensity focused ultrasound (HIFU). Ho *et al.* [50] reported that with the presence of Fe₃O₄ nanoparticle agglomerates, 50% duty cycle of focused ultrasound was sufficient to cause cell lysis and to disintegrate the whole HeLa spheroid. Instead of using pure magnetite particles, Sun *et al.* [51] introduced an

organic/inorganic hybrid system based on Fe_3O_4 -containing poly(lactic-co-glycolic acid) (PLGA) microcapsules ($\text{Fe}_3\text{O}_4/\text{PLGA}$) to enhance the HIFU therapeutic efficacy with a simultaneous MRI/ultrasound dual biological imaging modality for HIFU guidance. The experimental results demonstrated that utilization of these composite microcapsules could efficiently improve ultrasonography and magnetic resonance imaging of cancer both *in vitro* and *in vivo*, and significantly enhance the HIFU ablation of breast cancer in tumor-bearing rabbits. Besides magnetite nanoparticles, Choi *et al.* [80] recently designed Gd-C5F12-phospholipid nanobubbles (PLNs, 30–100 nm in diameter) to enhance the hyperthermal effect of HIFU. The Gd-C5F12-PLNs have a prolonged plasma half-life in mice (longer than 1.5 hrs, about three times longer than that of SonoVue), and consequently extend the circulation time of PLNs-encapsulated HIFU agents. The long circulation time provides a window for the agent to accumulate in tumor tissues that have highly permeable, angiogenic microvessels. Indeed, Gd-C5F12-PLNs monitored by T1-weighted MR imaging continuously increased in the tumor tissues (colon cancer cell line CT-26) of BALB/c nude mice until at least 4 hrs after intravenous injection via the tail vein. HIFU treatment with Gd-C5F12-PLNs ablated a significantly larger tumor area than no HIFU or HIFU alone. The results suggest that Gd-C5F12-PLNs exhibit theragnostic potential for MR-guided HIFU ablation. Despite the advantages of Gd-C5F12-PLNs in enhancing HIFU ablation, some issues need to be carefully addressed prior to clinical application: 1) inertial cavitation due to combining HIFU and gas-filled Gd-C5F12-PLNs is unpredictable and may cause complications; 2) the effect of HIFU-induced hyperthermia on Gd chelation of the nanobubbles needs to be well studied to assure no release of free Gd with toxicity.

2.3. Cryoablation

In contrast to the above thermal-based ablation, cryoablation (cryosurgery) is another approach to achieve minimally invasive, controlled destruction of tumor tissues through a specifically administered freezing procedure (Figure 3). During this procedure, one or

Figure 3. Diagrammatic illustration of cryoablation.

more small needles, called cryoprobe, deliver either liquid nitrogen or argon gas directly to the cancer tissue. Cellular damage is believed to result from the disruption of cell membrane during the freeze/thaw cycles. Imaging guidance based on ultrasound, CT, or MRI is needed to direct the cryoprobes to the right location. The ablated area can be easily visualized under the ultrasound since the ice ball formed during the therapy is hypoechoic [81]. For more details in probes, cryogens, major mechanisms of cellular, vascular injury and possible immunological effects due to freeze-thaw treatment, Goel *et al.* [82] have made a fascinating summary.

Currently, cryoablation is still in its experimental stage for breast cancer treatment. Its long-term effectiveness remains to be determined and is now under investigation. Sabel *et al.* [83] reported the only clinical trial on cryoablation of breast cancer, in which twenty-seven patients with ultrasound-visible primary invasive breast cancer (≤ 2.0 cm) successfully underwent ultrasound-guided cryoablation with a double freeze/thaw cycle using a tabletop argon-gas-based cryoablation system under local anesthesia. Complete ablation was successfully achieved for tumors less than 1 cm, but only 63% of tumors larger than 1 cm were completely ablated, indicating suitability of cryoablation for early-stage breast cancer.

There are several practical concerns regarding cryosurgery for breast tumor treatment. The most important one is that insufficient or inappropriate freezing may not completely destroy the tumor and lead to tumor regrowth, thus failing treatment. Meanwhile, the surrounding healthy tissue may suffer from freezing injury. Cryoablation is a localized therapy and only treats the disease at a single site. Sonographic monitoring may be inaccurate to estimate the exact dimensions of the iceball and some microscopic cancer may be missed during the treatment [83].

With enhanced thermal conductivity and capability to serve as nucleation seeds, certain nanoparticles can be combined with cryosurgical procedures to increase treatment efficacy [52, 84]. Moreover, nanoparticles modified with tumor-specific ligands can target tumor tissues for treatment accuracy [52, 84]. It is expected that the presence of nanoparticles in cryoablation can maximize the freezing heat transfer process, regulate freezing scale, modify the orientation of iceball formation and prevent the surrounding healthy tissues from being frozen. In addition, the introduction of nanoparticles during cryosurgery could also help to visualize the edge of a tumor as well as the margin of the iceball for better positioning of the treatment [52].

Nanoparticles suitable for cryoablation can be made from a variety of materials including inorganic metals, biodegradable polymers, liposomes, micelles, semiconductors, etc. [52]. Yan *et al.* [52] claimed that iron oxide, magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$), nanoparticles with high thermal conductivity and good biological compatibility might be a popular and appropriate choice for enhancing freezing rate with controllable iceball formation. In cryosurgery, the destruction of cancer within the iceball is normally incomplete. To solve this issue, Goel *et al.* [82] have tried to deliver tumor necrosis factor- α (TNF- α) to the human prostate carcinoma xenografts in nude mice using 30-nm Au NPs for enhancing the destruction within an iceball. The results suggest that pre-incubation with TNF- α conjugated Au NPs can efficiently destroy tumor cells within the iceball and cause more shrinkage of the tumor without systemic toxicity. Although

comprehensive studies are needed to further elaborate the effects of nanomaterials on cryosurgery, it is believed that the nanoparticle-enabled maximization of the freezing rate as well as *in vivo* medical imaging could be the promising future of cryosurgery [84].

2.4. Photodynamic Therapy

Photodynamic therapy (PDT) has been developed as a modality for cancer treatment, which combines the use of low energy light with a photosensitizer. A photosensitizer is a chemical compound that can be excited by visible or near-infrared (NIR) light of a specific wavelength. Usually, the photosensitizer is activated from a ground singlet state to an excited singlet state and is followed by a longer-lived triplet state. When the photosensitizer and an oxygen molecule are in proximity, energy can be transferred to the oxygen molecule, leading to the generation of reactive singlet oxygen species. Singlet oxygen species will ultimately cause the apoptosis or necrosis of tumor cells [85, 86] (Figure 4a).

The initial clinical application of PDT was mainly in the treatment of superficial lesions such as skin cancer, superficial epidermal lesions, and superficial mucosal lesions *etc.* in consideration of the limited penetration of light and photosensitizer [87, 88]. Currently, efforts are underway to extend the PDT to other types of cancers including breast cancer. Various photosensitizers (*e.g.*, 5-aminolaevulinic acid and mitoxantrone) have been assessed for their effectiveness in mediating the destruction of breast cancer cells under light irradiation [89, 90]. Ahn *et al.* [89] reported an *in vivo* PDT study using BALB/c mouse models with subcutaneous EMT6 mammary carcinomas. Their findings confirmed that PDT with a moderate energy of 90 J/cm² could be used to treat breast cancers less than 10 mm.

PDT has shown multifaceted advantages like low morbidity, minimum functional disturbance, good tolerance, and the ability to be applied to the same site repeatedly. However, the major limitation of PDT comes from the shortcomings of conventional photosensitizers, *e.g.*, high lipophilicity, poor selectivity, and the need for a large amount to obtain sufficient killing efficiency. In addition, the limited penetration of laser to tumor tissue also impacts the efficacy of PDT, especially in the situation of breast cancer. In general, the efficiency of PDT is largely determined by 1) the

Figure 4. a) Photodynamic therapy (PDT) and b) photothermal therapy (PTT).

therapeutic concentration of photosensitizer that is delivered to the diseased site, 2) the light dose that is absorbed, 3) the oxygen level in the tissue, and 4) the specificity of singlet oxygen formation in targeted tissues. While much attention has been paid to improve light sources, selectively enhancing the light absorbance by photosensitizers in the cancerous cells can be another interesting approach to increasing PDT efficiency.

In search for possible improvement of PDT efficiency, nanoparticles hold favorable solutions to address at least one of the aforementioned issues. Various strategies have been tried to use nanoparticles as the photosensitizer carrier for passively or actively delivering the photosensitizers to tumor tissues by converting the hydrophobic photosensitizer into cell-permeable hydrophilic format or choosing the appropriate size. In a review from Chatterjee *et al.* [90], the emerging application of various nanoparticles for PDT has been comprehensively summarized. Functionally, nanoparticles can be used as a passive carrier in PDT to simply carry the photosensitizer around. Both polymer-based and non-polymer-based nanoparticles have been tested for this purpose [91–94]. Selective accumulation of the photosensitizer-loaded nanoparticles in cancer cells can be achieved via surface modification of the nanoparticles with those molecules (*e.g.*, monoclonal antibodies [95, 96]) targeting cancer cells. Instead of merely serving as a carriage for photosensitizer, some nanoparticles participate in the actual PDT process. For instance, Au NPs, which are widely used in cancer detection and treatment, can enhance PDT as a result of their unique optical properties (*i.e.*, surface plasmonic resonance). As shown in Figure 5, briefly, upon electromagnetic enhancement, the light absorbed onto the surface of Au NPs is scattered and transferred to the neighboring photosensitizer molecule. Due to the plasmonic enhancement by Au NPs, more photosensitizer molecules are activated, consequently increasing the formation of singlet oxygen species. Therefore, Au NPs can enhance the PDT killing efficiency. In our previous study, elevated formation of

Figure 5. Basic mechanism underlying Au-NP-assisted photodynamic and photothermal reactions.

reactive oxygen species (ROS) was detected on fibrosarcoma tumor cells treated with 5-aminolevulinic acid (ALA)-conjugated Au NPs, leading to 50% more cell death compared to those treated with 5-ALA alone [58]. Recently, we have further demonstrated that Au NPs can significantly promote ROS formation with protoporphyrin IX (PpIX) photosensitizer upon light irradiation. The convergence of experimental findings and theoretical simulation on size-dependent ROS formation and plasmonic enhancement suggests that elevated generation of ROS in the presence of Au NPs is attributed to highly localized plasmonic resonance fields on Au NP surface, which increased with particle size [59]. Following the similar mechanism, other gold nanostructures such as nanorods [97–99] and nanoshells [100] can also be used in PDT to enhance ROS formation.

2.5. Photothermal Therapy

An alternative to PDT is photothermal therapy (PTT), in which photothermal agents are employed to achieve a selective heating of the local tissue (Figure 4b). Upon absorbing photons, PTT agents are excited from their ground state to an excited state. Different from PDT where energy is transferred to oxygen molecule, excited PTT agents release vibrational energy (*i.e.*, heat) (Figure 4b), consequently increasing the local temperature. Ideally, PTT should induce an elevated temperature within cancerous tissue while avoiding overheating the surrounding healthy tissue. However, currently available hyperthermia modalities are often unable to selectively target the tumor tissue without collateral organ damage [101]. In this regard, photoabsorbing nanostructures have been developed in order to enhance both photothermal effects and improved specificity in cancer treatment in conjunction with lasers in the NIR region [102]. These nanostructure agents include noble metal nanoparticles (*e.g.*, hollow gold nanoshells, gold nanorods, gold nanocages), titanium nanotubes, photothermal-based nanobubbles, polymeric nanoparticles and copper-based nanocrystals, *etc.*

Noble metal nanoparticles have become widely adopted agents for PTT on account of their enhanced absorption cross sections, usually four to five orders of magnitude larger than those of conventional photoabsorbing dyes. The strong absorption ensures effective laser therapy at a relatively lower power to render a minimal invasion. Additionally, the high photostability of metal nanostructures warrants no photobleaching. Currently, gold nanospheres, gold nanorods and gold nanoshells have been demonstrated as photothermal therapeutics for their strong absorption in the visible and NIR regions from the surface plasmon resonance (SPR) oscillations [61]. In addition to the localized SPR properties, the highly functionalizable surface of gold nanostructures can be conjugated with versatile molecules such as antibodies, polymers, or DNA to increase the targeting specificity [91–93].

Various studies have revealed that gold-silica nanoshells release a significant amount of heat when exposed to NIR light (650–950 nm) and have been used to produce thermal cytotoxicity both *in vitro* and *in vivo* [54, 103, 104]. Recently, El-Sayed *et al.* [60] demonstrated the use of epidermal growth factor receptor (EGFR)-conjugated Au NPs as a photothermal agent, which can specifically target cancer cells overexpressing EGFR. It was found that malignant cells required less than half the laser energy to be

killed than benign cells under the same exposure conditions. This Au NP-mediated photothermal cancer therapy presents a promising treatment option for chemotherapy resistant cancers. For example, Carpin *et al.* [62] demonstrated that anti-HER2-conjugated silica-gold nanoshells can mediate the effective targeting and photothermal ablation of two HER2-expressing breast cancer cell lines, which are both resistant to treatment with trastuzumab. Besides nanoshells, efforts were also made to use Au NPs or nanorods in PTT [63, 105, 106]. Maltzahn *et al.* [63] synthesized polyethylene glycol (PEG)-protected gold nanorods (PEG-NR) that exhibited better spectral bandwidth and photothermal heat generation than gold-silica nanoshells, showing great potential for ultrasensitive tumor ablation. They found that PEG-NR rapidly generated more than 6 times of heat generated by PEG-gold nanoshells under identical experimental conditions, and can cause more efficient destruction of human tumor cells (MDA-MB-435) after light irradiation. *In vivo* study showed that intravenous injection of PEG-NRs enabled destruction of human xenograft tumors in mice upon irradiation. Besides noble metal nanoparticles, Hong *et al.* [107] demonstrated the potential therapeutic effect of titanium oxide nanotubes (TiO₂ NTs) for cancer therapy with both *in vitro* cell and *in vivo* animal (CT-26 murine colon carcinoma tumor bearing mice) tests. They found that TiO₂ NTs in combination with NIR laser could destroy all tumor cells without damaging surrounding healthy tissue under optimized the treatment conditions in terms of laser intensity, laser exposure time, amount of TiO₂ NTs suspension and TiO₂ NTs concentration. Single-walled carbon nanotubes (SWNTs) with a high optical absorbance in the NIR region were also investigated for selective photothermal therapy of cancer [64, 108]. Zhou *et al.* [64] found that folate-SWNTs effectively enhanced the photothermal destruction of tumor cells by 980-nm laser irradiation while noticeably sparing non-targeted normal cells in both *in vitro* and *in vivo* experiments. However, negative reports on the biosafety of SWNT raise some concerns on their clinical application [109, 110].

3. DISCUSSION AND PERSPECTIVES

The advent and advancement of nanotechnology has shed promising light on both cancer therapy and diagnostics. In particular, the high surface/volume ratios, deep tissue penetration, versatile surface chemistry for modification, and distinct optical and magnetic properties have empowered nanoparticles with potentials to enhance the efficacy of many minimally invasive therapies for breast cancer. It is envisioned that if nanoparticles can be directed only to cancer cells, treatment efficacy would be more pronounced and specific. This is especially crucial for those therapies with detrimental side effects. For example, in nanoparticle-assisted PTT, one critical challenge is to control the extent of thermal intervention only necessary to kill the tumor [111]. Unfortunately, thus far, there are no available strategies that are effective enough to guide nanoparticles only into cancer cells, even with the conjugation of cancer cell specific ligands like HER-2 [112]. Addition of excess targeting ligands also increases the clearance rate by mononuclear phagocyte system. Therefore, it is still uncertain how active targeting affects nanoparticle accumulation in targeted tissues. The effect of nanoparticle size and ligand density on cellular uptake and tumor targeting remains to

be further established in order to improve the nanoparticle design for optimal tumor accumulation [113]. In pursuing a better targeting strategy, limited understanding of the interactions between cells and nanoparticles has left several key questions unanswered and targeting unsolved. The questions include, *e.g.*, What is the system distribution of nanoparticles through different administration routes? What is the fate of the nanoparticles following therapy? How fast can nanoparticles travel into cells? All these questions may be complicated by the versatility of nanoparticles in size, surface properties, and shape on one hand, and the presence of various molecules and self-protecting filtration systems *in vivo* on the other hand. The proper answers to these questions are essential to address the targeting issue [114].

Besides the properties of nanoparticles, more attention should be paid to their biodistribution and biosafety prior to clinical application. Although many of the materials are safe in bulk with known interaction profile with biological system, such information may not be directly applicable to the nanoscale. As a matter of fact, the small size of nanoparticles allows them to penetrate into tissue and accumulate inside cells, and the large surface area would lead to more interactions between nanoparticles and cells as well as the intracellular organelles [115]. To this end, the evaluation of biosafety and cell/nanoparticle interaction becomes highly demanded and it needs to be investigated in a physiologically relevant setting. For example, Au NPs are known for their biocompatibility without adverse effects [116, 117]. This finding is, however, only valid under low concentration. It was found that Au NPs at high concentrations could significantly slow down cell proliferation with certain cytotoxicity [118]. Obviously, the studies on the interaction between biological system and nanoparticles as well as comprehensive understanding of 1) the cellular uptake mechanism and intracellular destination, 2) biological distribution and clearance, and 3) short- and long-term toxicity of nanomaterials, can help to better design the therapeutic strategy appropriate for minimally invasive therapy. In addition, the insightful understanding of cell and nanoparticle interactions will also formulate the basis to develop new biomarker-probe systems and targeting strategies with optimal particle compositions, geometries, activation, and high payload delivery, which can facilitate the combination of diagnostics with therapeutics in the future.

4. CONCLUSION

With concerns of morbidity and severe side effects from established breast cancer therapies, minimally invasive therapy is highly desirable and will continue to evolve at an ever-faster pace as a result of the rapid progress in early diagnosis and the emergence of new technology. The application of nanotechnology in healthcare, though still in its early stage, introduces many potentially exciting and revolutionary solutions to address the unmet challenges confronting current minimally invasive therapy and may lead to the development of new modalities. Besides promising experimental findings in minimally invasive techniques (RFA, FUS, cryoablation, PDT and PTT, etc.), extensive efforts in clinically relevant tests must be conducted prior to their adoption for routine practice especially in breast cancer management. In addition, it remains elusive how various nanostructures are ingested via various

entry routes (*e.g.*, intravenous injection, inhalation), transported through biological barriers (*e.g.*, the blood barrier), preferentially accumulated in targeted tissues (tumors) and removed from the biological system (*e.g.*, kidney filtration). In this regard, comprehensive understanding of these issues in a physiologic system is crucial for their further clinical utility. Once these issues are solved, multifunctional nanostructures will significantly elevate our capability of diagnosing and yield next-generation minimally invasive oncological interventions with high efficiency and specificity.

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CONFLICT OF INTEREST

The authors indicated no potential conflicts of interest.

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