Surgical Innovation

# Applications of Nanotechnology in the Management of Cancer

## Miniature Technology, Great Potential

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### What Is the Innovation?

Nanotechnology refers to the applications of science at the nanoscale between 1 and 100 nm. To put it into context, if you have printed this article, 1 nm is 1/100 000 of the thickness of the sheet of paper you are holding. The ability to produce and investigate materials at this scale has provided applications in most scientific fields including engineering, chemistry, and materials science. The concept was first described by physicist Richard Feynman in a talk entitled "There's Plenty of Room at the Bottom" at the California Institute of Technology in 1959. He envisioned the creation of objects so small that they could be controlled at the cellular level. Over the last few years, there have been a surge of applications arising from nanotechnology for therapeutic and diagnostic use in cancer.

### What Are the Key Advantages Over Existing Approaches?

The unique properties of nanoparticles are being used in various ways to overcome the current dilemmas in cancer imaging, diagnostics, and therapeutics. In imaging, modalities such as computed tomographic and magnetic resonance imaging (MRI) scans are useful for tumor detection but their ability to detect precancerous lesions and early cancers is limited. Magnetic nanoparticles can be manipulated by an external magnetic field and have been used in conjunction with MRI for enhanced sensitivity. Quantum dots are nanoparticles with fluorescent properties that have also been evaluated for their use in imaging. In contrast to conventional fluorescent molecules, the wavelength of light emission is size dependent and they are excited by a broad range of wavelengths. This allows multiplexing by probing to several different targets to increase their sensitivity and specificity. Similar techniques are being developed to guide the surgeon by intraoperative imaging.

For diagnostics, metal-enhanced fluorescence is a phenomenon only displayed by metal nanoparticles. Currently, fluorescent molecules attached to antibodies that target certain protein biomarkers are used in fluorescent immunoassays. However, one of the limiting factors with their use is that background autofluorescence from biological samples increases the noise to signal ratio. This affects the ability of this technique to detect ultralow levels of potentially useful biomarkers. These problems are being overcome by coupling of fluorophores to metal nanoparticles, which greatly amplify the fluorescence signal.

The small size and relatively large surface of nanoparticles allow intracellular uptake and functionalization with multiple ligands for binding. Targeted drug delivery avoids the need for large systemic doses to increase the local tumor drug concentration. Nanoparticles promote the use of both targeted and nontargeted entry to tumor cells. Known as the enhanced permeability and retention effect, extravasion of nontargeted nanoparticles occurs through "leaky" tumor vasculature with increased permeability. In addition, the potential for multiple receptor binding on target cells has resulted in greater and more specific uptake of drugs by cancer cells, which in turn results in greater efficacy and lower toxicity. Dual functionalization of nanoparticles for both imaging and drug delivery is being evaluated in a new modality termed *theranostics* and will allow real-time monitoring of treatment response, which is currently unavailable.

Irreversible electroporation is a process delivered by the NanoKnife (AngioDynamics) for the treatment of solid tumors. High-voltage electrical current is delivered to tissue by insertion of electrodes. This creates tiny nanopores in the cell membranes, which brings about apoptosis. There is no thermal effect seen as in current available treatments such as radiofrequency ablation.[1] The high temperature here causes damage to surrounding structures such as blood vessels and bile ducts. This also overcomes the problems of the "heat-sink" effect. This is when the buildup of thermal energy is dissipated around structures such as large vessels. This leads to incomplete ablation of perivascular cells, which in turn increases recurrence rates.

### How Will This Impact Clinical Care?

Tumor size is one of the strongest prognostic factors. The 5-year survival rate of pancreatic tumors 10 mm or less is 80% compared with 4% for advanced stage IV disease.[2] The ability to achieve diagnosis at an earlier stage with more sensitive detection of biomarkers and enhanced imaging should therefore have a positive impact on patient survival. Equally, resection margin status is a risk factor for local recurrence and this has an impact on survival for some types of cancer. For adequate resection, the surgeon must remove the primary tumor and small satellite tumor deposits while preserving adjacent unaffected structures with or without lymph node resection. The ability to detect these intraoperatively will improve the rate of R0 resections. Therapy will be more targeted with reduction in adverse effects and toxicity and better treatment response. NanoKnife has a major advantage in treating tumors close to major vascular pedicles where other modalities are contraindicated to avoid inadvertent damage to key vessels while achieving its therapeutic effects of tumor destruction.

### Is There Evidence Supporting the Benefits of the Innovation?

For imaging, administering magnetic nanoparticles increased the sensitivity and specificity of MRI for the detection of lymph node metastases from 65% and 75% to 93% and 96%, respectively, in 75

patients with bladder and prostate cancer.[3] In vivo imaging in mouse models has been successfully achieved using nanoparticles conjugated to RGD peptide.[4] This binds to integrin receptors that are upregulated in solid tumor cells and tumor vasculature. This would be used clinically to guide resection intraoperatively with enhanced sensitivity and the ability to detect microdeposits. Applying metal-enhanced fluorescence for the detection of biomarkers using gold nanoparticles on a biosensor chip, a 5000-fold increase in the sensitivity of carcinoembryonic antigen detection in the serum of colon cancer mouse models has been demonstrated.[5] Aggregation of nanoparticles alters their light emission properties so that they change color. This has been used to develop aggregation-based enzyme-linked immunoassays, or plasmonic enzyme-linked immunosorbent assay, to detect ultralow levels of prostate-specific antigen in human serum.[6] The color changes were detectable with the naked eye, circumventing the need for expensive detection equipment. Nanoparticles containing the chemotherapeutic agent docetaxel and targeting solid tumor cells led to complete resolution of cholangiocarcinoma lung metastases at 20% of the typical clinical dose.[7] Treatment of 74 patients with locally advanced and metastatic pancreatic cancer with NanoKnife has shown to significantly increase progression-free survival from 6 months to 14 months and overall survival from 11 to 20 months.[8]

## What Are the Barriers to Implementing This Innovation More Broadly?

Limitations to applying this to clinical practice include issues with cytotoxicity. Because of the unusual properties of nanoparticles, the dose-toxicity relationships are unpredictable. Another setback has been the immune-mediated destruction of these particles in vivo. Immune-resistant coating is being used to protect against this but this may compromise uptake by target cells.

## In What Time Frame Will This Innovation Likely Be Applied Routinely?

It is difficult to say when nanotechnology will routinely be used; although early clinical trials are showing positive results, its introduction to clinical use has been delayed by uncertainties around prolonged retention and toxicity of certain particles. However, it is clear that nanotechnology has the potential to provide solutions in a multidisciplinary fashion and brings us the ability to explore cancer science at a much finer scale than ever before.


### ARTICLE INFORMATION

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### REFERENCES


1. Lee EW, Thai S, Kee ST. Irreversible electroporation: a novel image-guided cancer therapy. *Gut Liver*. 2010;4(suppl 1):S99-S104.

2. Egawa S, Toma H, Ohigashi H, et al. Japan Pancreatic Cancer Registry: 30th year anniversary. Japan Pancreas Society. *Pancreas*. 2012;41(7):985-992.

3. Birkhäuser FD, Studer UE, Froehlich JM, et al. Combined ultrasmall superparamagnetic particles of iron oxide-enhanced and diffusion-weighted magnetic resonance imaging facilitates detection of metastases in normal-sized pelvic lymph nodes of patients with bladder and prostate cancer. *Eur Urol*. 2013;64(6):953-960.

4. Liu Z, Tabakman S, Welsher K, Dai H. Carbon nanotubes in biology and medicine: in vitro and in vivo detection, imaging and drug delivery. *Nano Res*. 2009;2(2):85-120.

5. Tabakman SM, Lau L, Robinson JT, et al. Plasmonic substrates for multiplexed protein microarrays with femtomolar sensitivity and broad dynamic range. *Nat Commun*. 2011;2(6):466.

6. de la Rica R, Stevens MM. Plasmonic ELISA for the detection of analytes at ultralow concentrations with the naked eye. *Nat Protoc*. 2013;8(9):1759-1764.

7. Hrkach J, Von Hoff D, Mukkaram Ali M, et al. Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. *Sci Transl Med*. 2012;4(128):128ra39.

8. Moir J, White SA, French JJ, Littler P, Manas DM. Systematic review of irreversible electroporation in the treatment of advanced pancreatic cancer. *Eur J Surg Oncol*. 2014;40(12):1598-1604.