# From Diagnosis to Treatment

## Clinical Applications of Nanotechnology in Thoracic Surgery

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• Nanotechnology • Nanotheranostics • Lung cancer • Thoracic surgery

**KEY POINTS**

- Nanotechnology is an exciting field of medicine that is rapidly evolving from in vitro and in vivo testing to the clinical arena.
- Through targeted drug delivery, nanoparticles (NPs) are able to deliver therapeutics at increased local concentrations with minimal systemic toxicity.
- A variety of material platforms are currently available with specific advantages and disadvantages.
- With more research into the mechanisms of action and safety profiles, NPs promise to be a major part of medicine and surgery moving forward.
- Thoracic surgery may benefit from improved diagnostic imaging, advancements in image-guided surgery, and the enhanced efficacy profile of targeted and stimuli-responsive drug delivery.

## INTRODUCTION

Nanotechnology is a rapidly evolving field that offers novel opportunities for the treatment and diagnosis of oncologic disease, specifically in thoracic surgery. The use of nanoparticles (NPs), materials generally ranging in size from 1 to 1000 nm, has emerged from the desire to achieve targeted drug delivery that maximizes treatment efficacy, while minimizing toxicity.[1–3] To achieve

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this goal, NPs are being engineered with varying characteristics and increasing complexity. Researchers leverage the chemical and physical characteristics of small molecule drugs, peptides, proteins, nucleic acids, lipids, polymers, and elemental metals to form a number of unique NPs. These NPs can be enhanced further through a variety of approaches, such as surface modification and responsiveness to the tumor microenvironment, leading to improved pharmacology and active intracellular function.[4]

Nanotechnology has broad application in the field of oncology; however, thoracic oncology is uniquely poised to benefit given the relatively poor prognosis of thoracic malignancies, such as lung and esophageal cancers, as well as the intricacy of the thoracic cavity, which requires careful navigation. Lung cancer is among the most common malignancies and is the number one cause of cancer-related death in the United States.[5] With recent guidelines for lung cancer screening from the National Lung Screening Trial, it is anticipated that the incidence of lung cancer will increase dramatically, and thus the number of patients requiring treatment.[6] Nanotechnology will change the way we approach lung cancer in the future, both as an adjunct to thoracic surgery by improving preoperative diagnosis, intraoperative tumor localization, and image-guided lymphatic mapping, as well as to thoracic oncology through improved systemic therapy of more advanced disease. For example, traditional chemotherapeutics such as paclitaxel and doxorubicin, which are typically used to treat lung cancer, are being packaged within the various nanotechnologies to enhance the pharmacokinetics and biodistribution of drug resulting in improved local concentration. Traditional contrast agents used for computed tomography (CT) and MRI are being delivered via novel nanostructures to provide improved imaging and diagnostic capabilities, and fluorescent nanomarkers are guiding surgeons to the exact tumor location and associated lymphatics.[7–9] Clearly, nanotechnology has the potential to impact each stage from the diagnosis to the treatment of thoracic malignancy as researchers are able to tailor composition, structure, and properties to meet the challenges of clinical application.

## MATERIAL PLATFORMS FOR NANOTECHNOLOGY

Nanotechnology comprises a variety of platforms, including nanocrystals, polymeric NPs, liposomes, quantum dots, micelles, dendrimers, and carbon nanotubes (CNTs; Fig. 1). Each platform possesses distinctive properties such as size, shape, charge, and surface characteristics that can be strategically altered to overcome the physiologic challenges faced by traditional chemotherapeutics. Commonly used antineoplastic agents in lung cancer, such as paclitaxel or docetaxel, are often difficult to solubilize with nonspecific targeting leading to a vast array of unwanted side effects; however, encapsulation of drugs in NPs facilitates improved biocompatibility and biodistribution, protects against acidic or enzymatic breakdown, and importantly allows for targeted delivery of drug to tumor-laden tissue.[10–12] Tumor neovascularization leads to increased permeability allowing NPs to passively accumulate and remain within tumor tissue through the enhanced permeability and retention effect, a key mechanism driving NP-mediated tumor targeting (Fig. 2).[4] In addition, NPs can be engineered with a variety of targeting moieties (ie, ligands, aptamers, or antibodies) that allow active targeting of specific tumors.[13] NPs are modified to provide diagnostic and therapeutic capabilities tailored to specific clinical applications through drug or gene loading, endogenous or exogenous stimuli, contrast or dye loading, or even a combination of these. The distinct advantages and disadvantages of common material platforms are outlined elsewhere in this paper, with a focus on specific innovations that are certain to impact the field of thoracic oncology.

### *Nanocrystals*

Nanocrystals are pure drugs that have been processed down to nanometer size, typically 100 to 1000 nm. Drug processing is achieved using a variety of methods including ‘bottom-up’ (precipitation) or ‘top-down’ (high-pressure homogenization) approaches.[14,15] The advantages of nanocrystal drug delivery stem from high saturation solubility owing to a small size and an amorphous state.[16] Nanocrystals can be altered using surface modifiers such as polyethylene glycol to avoid opsonization and consumption by the reticuloendothelial system, allowing for passive tumor accumulation via the enhanced permeability and retention effect.[14] Traditional chemotherapeutics such as paclitaxel are being processed into nanocrystal formulations to take advantage of these properties. For example, paclitaxel is traditionally delivered using a Cremophor EL (polyethoxylated castor oil and ethanol mixture) carrier that is responsible for many of the clinical side effects associated with paclitaxel.[17] Promisingly, paclitaxel-loaded nanocrystals demonstrate significantly less toxicity in preclinical studies using