

A NANO-ELECTRONIC APPROACH FOR EARLY DETECTION AND TREATMENT OF PROSTATE CANCER

¹DEEPTHI N, ²CLINTON LEWIS, ³A ARUNKUMAR

Department of Electronics and Communication Engineering, Bangalore Institute of Technology
Bangalore, India

Email: ¹dariondee@gmail.com, ²clintonlewis17@gmail.com, ³thenama101@gmail.com

Abstract—In recent years there has been an increasing interest in using nanotechnology for prostate cancer therapy. Conventional detection methods as well as treatments have significant side effects which makes them unpopular. Nanomaterials have unique physical, optical and electrical properties that have proven to be very useful in the medical electronics field. In this paper we discuss five major types of nanoparticles that have the potential to greatly improve the scope of detection and treatment of prostate cancer.

Keywords—Prostate Cancer; Nanotechnology; Prostate Specific Antigen; Gold Nanoparticle; Quantum Dots; Carbon Nanotube; Nanowire; Magnetic Nanoparticle

I. INTRODUCTION

Cancer is a generic term for a large group of diseases whose defining feature is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs [1]. Worldwide, one in seven deaths is due to cancer; cancer causes more deaths than AIDS, tuberculosis, and malaria combined. When countries are grouped according to income, cancer is the second leading cause of death in high-income countries (following cardiovascular diseases) and the third leading cause of death in low- and middle-income countries (following cardiovascular diseases and infectious and parasitic diseases) [2]. There are more than 100 different types of cancer. Most cancers are named for the organ or type of cell in which they start [3].

The prostate is an exocrine gland of the male reproductive system whose primary function is to secrete a fluid that constitutes around 30% of the volume of semen [4]. Worldwide, prostate cancer is the second most frequently diagnosed cancer in men after lung cancer, with around 1.1 million new cases estimated to have occurred in 2012. With an estimated 307,500 deaths in 2012, it is also the fifth leading cause of cancer death in men worldwide [2]. The only well-established risk factors for prostate cancer are older age, ethnicity, and a family history of the disease [5]. Symptoms of prostate cancer are increase in urinary frequency, difficulty in starting or stopping urination, interrupted, weak or slow urinary stream, blood in urine or in semen, intense pain in the low back, hips or thighs often present with aggressive or prostatic cancer spread to other organs. Figure 1 shows the location of the prostate gland in humans [31]. The highest estimated prostate cancer incidence rates occur in the developed areas of the world that include North America, Australia and New Zealand, and western and northern Europe. However, the

highest estimated prostate cancer mortality rates tend to be seen elsewhere, mainly in the areas of South America, the Caribbean, and sub-Saharan Africa [6]. In spite of its high incidence and prevalence, the progression of prostate cancer in most men is relatively slow. Most tumors remain organ confined allowing for potentially life-saving treatments to be instituted in such cases [7]. Figure 2 shows the international variation in prostate cancer incidence rates for 2012 [2].

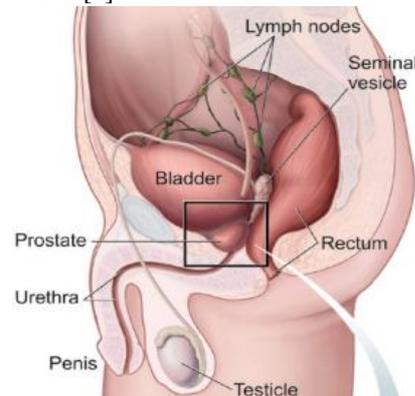


Fig. 1. Prostate gland in a human male

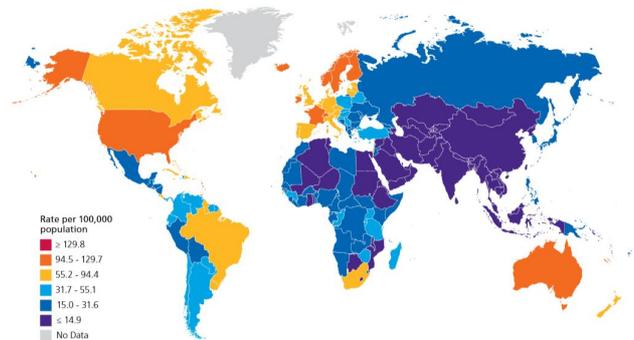


Fig. 2. International variation in prostate cancer incidence rates for 2012

In developing areas such as India, Africa and China, most men are not diagnosed with prostate cancer until

it is too late for treatment. The causes for this vary, but are generally due to a lack of awareness about the same as well as the social stigma associated with the diagnosis. The existing diagnosis methods including the very widely used prostate specific antigen (PSA) test carry with them the risk of over treatment and over diagnosis [7]. Thus there is a need for an early and accurate diagnosis technique for prostate cancer.

This paper discusses the use of nanotechnology as an aid for diagnosis and treatment and is organized as follows. Section 1 provides an introduction to prostate cancer and the need for nanotechnology based diagnosis approach. Section 2 mentions the existing screening procedures for prostate cancer. Section 3 gives an overview of nanotechnology while Section 4 explains how nanotechnology can be used in the detection and treatment of prostate cancer. This is followed by conclusions and references.

II. EXISTING SCREENING PROCEDURES

The existing methods adopted for diagnosis of prostate cancer are Digital Rectal Examination (DRE), Prostate Specific Antigen (PSA) test, Transrectal Ultrasound, Transrectal Magnetic Resonance Imaging (MRI) and Prostate Biopsy.

A. Digital Rectal Examination (DRE)

Digital rectal Examination, also called as a prostate exam, is an internal examination of the rectum by a doctor. The prostate is felt through the rectal wall for lumps or abnormal areas. However, the proportion of potentially diagnosable cancers, diagnosed by DRE, remains very low, perhaps because many of the tumors are too small to be palpable by DRE [8]. DRE is also affected by interexaminer variability, irrespective of experience, and is limited to assessment of peripheral zone tumors. DRE remains a fundamental part of screening owing to its being part of the clinical examination without additional cost and its ubiquitous availability [12].

B. Prostate Specific Antigen (PSA) test

PSA is the protein secreted almost exclusively by a normal prostate gland to help nourish sperm. The theory is that elevated levels of PSA detected by a blood test suggest something is wrong with the prostate. This includes prostate cancer, but elevated PSA can also be caused by benign disease such as benign prostatic hyperplasia and prostatitis. PSA testing has been shown to increase prostate cancer detection by 81% compared to digital rectal examination alone; however its use remains debated due to a lack of sensitivity and specificity for the presence of the lethal variety of prostate cancer at an early stage [10]. Notwithstanding, it appears to be arguably one of the best screening markers available [9]. Use of the PSA in combination with DRE

increases detection of organ confined disease by 78% over DRE alone [11].

C. Transrectal Ultrasound

Ultrasound is widely used in the form of transrectal ultrasound, nearly always with the primary intent for transrectal biopsy to be performed in the same session. Transrectal ultrasound alone is not recommended for initial screening owing to a lack of supportive data on sufficient specificity or ability to significantly increase the detection rate of prostate cancer and its significant cost when used as a screening tool. Transrectal ultrasound is thus mainly used to provide visual guidance for biopsy. As a confirmatory test for patients suspected of having prostate cancer on the basis of DRE result and PSA level, transrectal ultrasound guided biopsy provides a sufficiently high specificity for diagnosis; however, it has limited sensitivity [13].

D. Transrectal Magnetic Resonance Imaging (MRI)

Transrectal Magnetic Resonance Imaging is used similarly to transrectal ultrasound, however it has better soft tissue contrast. It provides more detailed anatomic images of the prostate than does transrectal ultrasound and because it has been shown to be the most accurate imaging modality for localization of prostate cancer; MRI based guidance offers the possibility of more precise targeting, which may be crucial to the success of modern diagnostic and local therapeutic interventions in the prostate [13]. A major drawback of MRI is that it cannot detect entities that are smaller than a few centimeters. Thus transrectal MRI is usually not used as the primary diagnostic tool for prostate cancer; instead it functions as a visual aide during prostate biopsy.

E. Prostate Biopsy

Prostate Biopsy is a procedure to remove small samples of prostate tissue using a hollow needle. The pathologist will then check the tissue sample to see if there are cancer cells and find out the Gleason score. The Gleason score ranges from 2-10 and describes how likely it is that a tumor will spread. The lower the number, the less likely the tumor is to spread. While it is currently the most accurate way to diagnose prostate cancer, it has significant side effects including small amounts of blood in urine and stools and the possibility of contracting an infection after the procedure. Prostatic biopsy should be considered if either the PSA level is greater than 4 micrograms/l or digital rectal examination is suspicious for cancer, even in the absence of abnormal transrectal ultrasonography findings [11].

III. NANOTECHNOLOGY

Nanoparticles are defined as particles on the scale of 1–100 nm in diameter. Materials reduced to the nanoscale can show different properties compared to

what they exhibit on a macroscale, enabling unique applications. The small size of nanoparticles allows for a greater surface to volume ratio. This increase in ratio allows for better detection, imaging, and prognosis methods and improved drug delivery to tumor sites that were previously not accessible [14].

IV. NANOTECHNOLOGY FOR EARLY DETECTION AND TREATMENT

A biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker can be a protein, a fragment of a protein, DNA, or RNA-based. Biomarkers, specifically cancer biomarkers, are an indication of cancer and by detecting them the existence of that specific cancer can be verified [15]. The use of nanomaterials as imaging agents allows for more sensitive and precise measurement of cancerous tissues. Additionally, the use of nanotechnology means smaller sensors, which translates into better access to and detection of cancer biomarkers, as well as more powerful and specific signal enhancements, reduced cost, and high throughput detection [16]. Nanomaterials that have been applied to sensing cancer biomarkers vary from gold nanoparticles, quantum dots, magnetic nanoparticles to carbon nanotubes and nanowires.

F. Gold Nanoparticles(GNP)

Gold nanoparticles (GNPs) have strong surface-plasmon-enhanced absorption and scattering which has allowed them to emerge as powerful imaging labels and contrast agents. They have better absorption and scattering bands than conventional organic dyes, the cross section of the bands going up to four to five orders of magnitude higher [17]. According to their size and shape, gold nanoparticles can absorb and scatter light from the visible to near-infrared (NIR) region [18]. A combination of GNPs and gold nanorods conjugated with anti-Prostate Specific Antigen (PSA) antibody is used as a one-step homogeneous immunoassay for cancer biomarker detection. Through Dynamic light scattering (DLS) analysis, the relative ratio of nanoparticle aggregate versus nonaggregated nanoparticles can be measured quantitatively. The relative ratio should therefore increase according to the amount of antigen in sample solution and this relationship is the basis of the homogeneous immunoassay (Figure 3) [32].

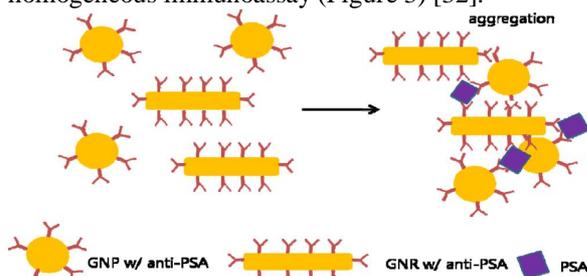


Fig. 3. Aggregation of GNPs and gold nanorods in the presence of PSA, leading to DLS analysis for the immunoassay [15].

Gold nanoparticles are especially appealing due to bioinertness and biocompatibility for biomedical use. For thermal therapy of prostate cancer, Stern et al. [19] used laser activated gold nanoshells for selective prostate cancer thermal ablation. Gobin et al. [20] demonstrated elective photo-thermal destruction of prostate cancer upon application of prostate-specific EphrinA1- conjugated gold nanoshells with the NIR laser irradiation. Normally, the size of gold nanoshells is more than 100 nm which is not suitable for in vivo application. Therefore, a gold nanorod is more attractive to researchers due to small size, easily surface function and with tunable surface plasmon resonance (SPR) in NIR region.

G. Quantum Dots(QD)

Quantum dots (QD) are luminescent nanocrystals that have many of the same properties as optical biosensors [21]. Quantum dots are able to track molecules and entire cells as they move through an environment. Quantum dots are also capable of delivering therapeutic agents to specific target sites to improve pharmaceutical effectiveness while minimizing side effects [16]. Highly sensitive QD based probes have been reported for multicolor fluorescence imaging of cancer cells in vivo [22]. Shi et al. [23] showed the superior quality of Quantum Dot immunohistochemistry (QD-IHC) compared with conventional immunohistochemistry (IHC) and also successfully realized simultaneous detection of androgen receptor and PSA in prostate cancer cells based on multiplexing QDs. The detection sensitivity of QD-based prostate cancer biomarkers can be enhanced by surface plasmon-coupled emission which has been introduced as a novel biosensing technology for detecting biosensors and biochips [24].

H. Magnetic Nanoparticles

Magnetic nanoparticles have been widely used in cancer cell imaging. By using the principle of decrease in transverse relaxation time due to aggregation of magnetic nanoparticles in presence of target molecules, concentration of cancer biomarkers could be measured [27]. This device allowed in vivo, local environment monitoring for cancer biomarkers and could be left implanted after tumor surgery. This exciting new method is expected to be convenient for continuous monitoring since biopsies do not have to be performed for each screening. Johannsen et al. [25] analyzed the effects of thermotherapy using magnetic nanoparticles combined with external radiation on prostate cancer and demonstrated this technique was feasible for prostate cancer treatment. Further, morbidity and quality of life were investigated during thermotherapy using magnetic nanoparticles in locally recurrent prostate cancer, the results showed interstitial heating using magnetic nanoparticles was feasible and well tolerated in patients [26].

I. Carbon nanotubes (CNT)

Carbon nanotubes (CNT) as a class of nanomaterials holds great potential for various biomedical applications including extrinsically activated hyperthermia for prostate cancer therapy. Multiwalled carbon nanotubes (MWNTs) coupled with laser irradiation can be used to enhance treatment of human prostate cancer [28]. DNA-encased multiwalled carbon nanotubes (MWNTs) were shown to safely eradicate prostate cancer in vivo following NIR irradiation of MWNTs [29]. Despite these promising results, the toxicity of carbon nanotubes has been an important question in nanotechnology. CNTs from manufactured and combustion sources in the environment could have adverse effects on human health [30].

J. Nanowires (NW)

Chao Li et al. demonstrated complementary biosensing using In_2O_3 nanowire and single-walled carbon nanotubes (SWNT) devices for the detection of PSA (Figure 4). Specificity was gained via proper surface functionalization, including a novel approach developed to covalently attach PSA antibodies to In_2O_3 NW surfaces. In addition, electronic characterization revealed enhanced conduction for In_2O_3 nanowire devices and suppressed conduction for SWNT devices upon PSA exposure, with sensitivity demonstrated down to 5 ng/mL for real-time detection in a buffer at physiological concentration [33].

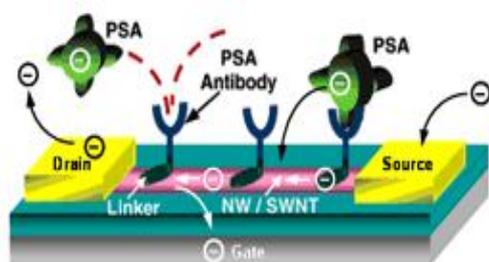


Fig. 4. Schematic diagram of field-effect transistor nanosensor. Electrons flow from right to left through the channel formed by nanowires (NWs) and single-walled carbon nanotubes (SWNTs) [33].

CONCLUSIONS

The various conventional methods used for diagnosis of prostate cancer have been discussed along with their limitations. An overview of different types of nanomaterials that are relevant to the diagnosis and treatment of prostate cancer is provided. While the development of various nanomaterials and nanotechnology has enabled detection of cancer biomarkers with great precision and sensitivity that could not be achieved before, factors such as probability of getting false positive/negative and impact of nanomaterials on humans and the environment should be fully understood before applying them for clinical diagnosis.

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