threshold of 3 mm for the prostate cancer length. The occurrence rate of no cancer in the RP specimen ('disappearing cancer') was 0.8%. The overall estimate of the risk that patients with microfocal prostate cancer would have extracapsular extension at RP was 17.6%. The combined estimate for a positive surgical margin among men with microfocal prostate cancer was 12%. The range of PSA recurrences among this population was 0–26%, with an estimated risk of 8.6%. Among studies of watchful waiting, an increasing PSA level was reported in nine of 15 patients who had a microfocus of prostate cancer. There was conversion to definitive therapy in 30%. The overall conclusion was that a small volume of prostate cancer in prostatic biopsies is not necessarily indicative of a good prognosis.

Further important questions about the promulgation of AS as a management strategy for prostate cancer are raised by a recent publication of a study of prostate cancer mortality in the USA and UK in 1975–2004 [6]. This report highlights the four-fold greater decline in prostate cancer mortality in the USA compared with the UK since 1992. This period coincides with a much greater uptake of PSA screening in the USA; in 2001, 57% of men in America aged ≥50 years reported having a PSA test within the previous year [6]; by contrast in the UK, only 6% of men aged 45–84 years were tested [7,8]. The result of this has been to produce a pronounced stage shift in men presenting with prostate cancer towards localized disease in the USA, where in general the disease is treated more aggressively. It could certainly be argued that this is the reason for the markedly different reductions in prostate cancer death rates on the two sides of the Atlantic.

AS is a still experimental option for men with 'indolent' prostate cancer; moreover, there is no reliable method at present to identify this disease with certainty. Low-risk prostate cancer is not necessarily 'indolent' disease, particularly in younger men with a long life-expectancy. Currently, there is no good evidence to inform us what the best treatment is for low-risk prostate cancer, and while we can identify disease which has already progressed, we have unreliable methods to determine which patients are progressing within the 'window of curability' and who will benefit from treatment. Patients need to be informed about both AS and active intervention, and their respective risks and benefits equally. The NICE panel has failed to highlight the fact that there is currently little or no evidence in this area to suggest best practice. Ongoing trials are addressing the uncertainties and controversies, and it is therefore premature to make strong recommendations about 'how best' to manage prostate cancer without highlighting these uncertainties. There is a risk that promoting AS as a management strategy with no firm evidence that it is safe and effective might serve only to increase the already four-fold divergence in death rates from prostate cancer in the UK as compared with the USA.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **NICE**, National Institute for Health and Clinical Excellence; **AS**, active surveillance; **RP**, radical prostatectomy.

NANOTECHNOLOGY IN THE MANAGEMENT OF PROSTATE CANCER

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INTRODUCTION

Nanotechnology is the study, design, creation, synthesis, manipulation and application of functional materials, devices, and systems through the control of matter at the nanometre scale. Nanomedicine is the monitoring, repair, construction and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures. Several recent reports have suggested that nanotechnology and nanomedicine will have a significant impact on urological research and clinical practice, allowing urologists to intervene at the cellular and molecular level [1,2]. In this comment we present an update on the use of nanotechnology in the minimally invasive

diagnosis and detection, and its role in the treatment of prostate cancer.

As in other fields of surgical oncology, nanotechnology has been used for the detection and diagnosis of urological cancer, in particular prostate cancer. There are many publications on the use of nanotests as tools to measure PSA. Using microcantilevers, which can be thought of as flexible beams, resembling a row of diving boards that can be coated with molecules capable of binding biomarkers, quantification of PSA at clinically significant concentrations was reported [1]. In 2002, the use of a PSA 'blotting paper' nanotest assay was reported, and there was a good correlation between the novel test and conventional PSA testing [2]. However, the reliability decreased inversely with the PSA value. Subsequently, a novel reagent consisting of gold nanoparticles and using biolyte-selective surface-enhanced Raman scattering responses detected free PSA levels of ≈1 pg/mL in human serum [1]. Further work showed that after recrystallization of the bacterial cell-surface layer fusion protein on gold chips pre-coated with thiolated secondary cell-wall polymer, a monomolecular protein lattice has been exploited as a sensing layer in surface plasmon resonance biochips to detect PSA [3]. More recently Shulga *et al.* [4] developed a new spectrophotometric method using covalently attached capture antibody labelled with alkaline phosphatase for the detection of free PSA, and Briman *et al.* [5] described the production and use of a novel electronic device architecture for the quantitative detection and measurement of PSA. Telomerase activity, which is often increased in malignancy, has also been investigated using nanoparticles that switch on their magnetic state by annealing with telomerase-synthesized TTAGGG sequences, which can then be detected by bench-top magnetic resonance relaxometers. In their study, Grimm *et al.* [6] stated that these nanoparticles were biocompatible and might be able to detect molecular lesions *in vivo*.

The mainstay of nanotechnology applications in imaging is the ability to confer *in vivo* localization and external detectability with high sensitivity and specificity. Angiogenesis in animal models using MRI and nanoparticles targeted to the avb3-integrin has been reported [7]. Furthermore, quantum dots, which are fluorescent semiconductor nanocrystals, have been shown to have possible applications in biomolecular and cellular imaging [8]. Although hydrophobic and toxic properties have until recently limited their use *in vivo*, by altering the surface structure and limiting the use of toxic semiconductors, such as selenium and cadmium, clinical potential might become a reality. Finally 'intelligent probes' have been studied to detect malignant lesions by examining the signature nanostructures and analysing physical properties of prostate tissue, such as electrical conductance, pH, oxygen content, carbon dioxide content and temperature changes [9].

Methods for staging prostate cancers have improved with the advent of gadolinium- and iron oxide-based nanotechnology for over 5 years. However, the clinical uptake of these imaging techniques has been slow. The technique relies on extravasation of ultra-small supermagnetic iron oxide nanoparticles into the interstitial space and uptake by macrophages in lymph nodes. Harisinghani *et al.* [10] reported complete detection of patients with positive lymph nodes before radical prostatectomy, compared with only 45% using current size criteria on unenhanced MRI scans alone. Further approaches have used dendritic nanoparticles, which have multiple arms that can complex with targeting moieties, such as antibodies or enzyme substrates, permitting both magnetic and optical detection properties. Sentinel lymph nodes have been mapped using intraprostatic injections of nanocolloid and lymph node scintigraphy. In a recent study, Warncke *et al.* [11] showed that the location of lymph nodes was highly variable and included the common iliac artery (16%), external iliac artery (33%), internal iliac artery (19%), obturator fossa (26%), presacral region (1%), inguinal fossa or lacuna vasorum (1%), and para aortic region (4%). That report concluded that the lymphatic drainage of the prostate might be more extensive than previously described, and hence further work is needed to verify these findings.

Ironically, many urologists will encounter nanotechnology daily, as nanotechnology treatment of prostate cancer is well established in the form of sustained release of the GnRH analogue leuprorelin-conjugated poly(lactic-coglycolic acid) liposome microspheres in metastatic prostate cancer. However, more contemporary research approaches are concentrating on energy delivery to the prostate using targeted nanotechnology or using nanoparticles to deliver chemotherapeutic agents specifically to prostate cancer within the gland. Kam *et al.* [12] used near-infrared light at 700–1100 nm to optically stimulate single-walled carbon nanotubes (SWNTs). The transparency of biological tissues to this wavelength of light and the strong absorption of SWNTs in this spectrum, make SWNTs uniquely suited to the delivery of olignucleotides. In addition, near-infrared targeting can cause localized heating of the SWNTs to cause cell destruction *in vitro*. Folate labelling has further enabled the internalization of nanotubes into folate receptor-expressing cancer cells rather than the folate receptor-negative benign tissue. These SWNTs have been shown to have limited cytotoxicity when used *in vitro*. More recently, Johanssen *et al.* [13] investigated the use of magnetic nanoparticles to heat prostatic tissue in an alternating-current magnetic-field applicator. Invasive thermometry was used to monitor heating to 39.4–48.5 °C. This novel interstitial treatment was applied for six weekly hyperthermia sessions of 60 min duration. Several interesting concepts can be extrapolated from this investigation. Injected nanoparticles remained within the prostate for the 6-week treatment duration and could be detected on CT, to ensure adequate prostate distribution with rectal and urethral sparing. In addition, the authors initiated the first clinical application of interstitial hyperthermia with magnetic nanoparticles in a phase I study to evaluate the treatment of local recurrence after radiotherapy with curative intent. Finally, as the folate receptor is often over-expressed in a multitude of cancers, folate receptor-mediated drug delivery is therefore an attractive option to target cancer cells rather than benign folate-receptor negative cells, and the effectiveness of folate-linked, lipid-based nanoparticles as a vector for DNA transfection and for suicide gene therapy to treat prostate cancer, has been reported [1]. Further progress has been made in manufacturing nanoparticles with an oleic acid shell that can be loaded with hydrophobic drugs for the sustained release of chemotherapy. *In vitro*, these approaches have shown dose-dependent antiproliferative effects compared to controls. This vehicle can also be labelled with antibodies for use in imaging [14]. In prostate cancer cell lines, polypropylenimine dendrimers have been used to deliver c-myc triplex-forming oligonucleotides to inhibit transcription of this oncogene *in vitro* [2]. These 130–280 nm

nanoparticles caused a 65% decrease in c-myc expression, making them useful candidates for gene transfer in malignancy. Finally, *in vitro* targeting of synthesized antibody against prostate-specific membrane antigen with conjugated dendrimer nanoparticles has also been shown to be a suitable platform for targeted molecule delivery into appropriate antigen-expressing cells [1]. This approach could target cancer cells specifically and spare noncancerous normal cells.

With regards surgical treatment itself, the Enseal™ (Surgrx, Redwood City, CA, USA) device has been used in laparoscopic radical retropubic prostatectomy to seal the dorsal venous complex. Using millions of nanoparticles embedded into the instrument, the temperature regulation of the bipolar diathermy can be optimally controlled, minimizing collateral thermal spread and tissue damage, with effective sealing of vessels up to 7 mm in diameter. The safe use of the Enseal system has been reported in sealing the dorsal venous complex during robot-assisted laparoscopic prostatectomy [15].

With the introduction of nanodevices, a highly intensive debate can be expected, and indeed, the impact of nanotechnology on human health has been assessed by the Office of Science and Technology in the UK. An independent review raises concerns that nanoparticles, because of their size and ability to pass across cellular membranes, represent a potential biohazard. Stringent attention to safety and exhaustive research into the toxicology of nanoparticles will be mandatory before the widespread clinical use of nanotechnology.

Exciting *in vitro* and *in vivo* applications of nanotechnology have been reported in the diagnosis and treatment of prostate cancer, but at least at present, there is a paucity of clinical studies to verify its potential use. As prostate cancer has one of the greatest potentials to benefit from nanotechnology, urologists should be encouraged to actively participate with basic science researchers working in this field. Commencement of phase 1 and phase 2 trials incorporating nanotechnology to evaluate novel diagnostic and therapeutic approaches for the benefit of patients with prostate cancer should be encouraged.

CONFLICT OF INTEREST

None declared.

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Abbreviation: **SWCNT**, single-walled carbon nanotube.