



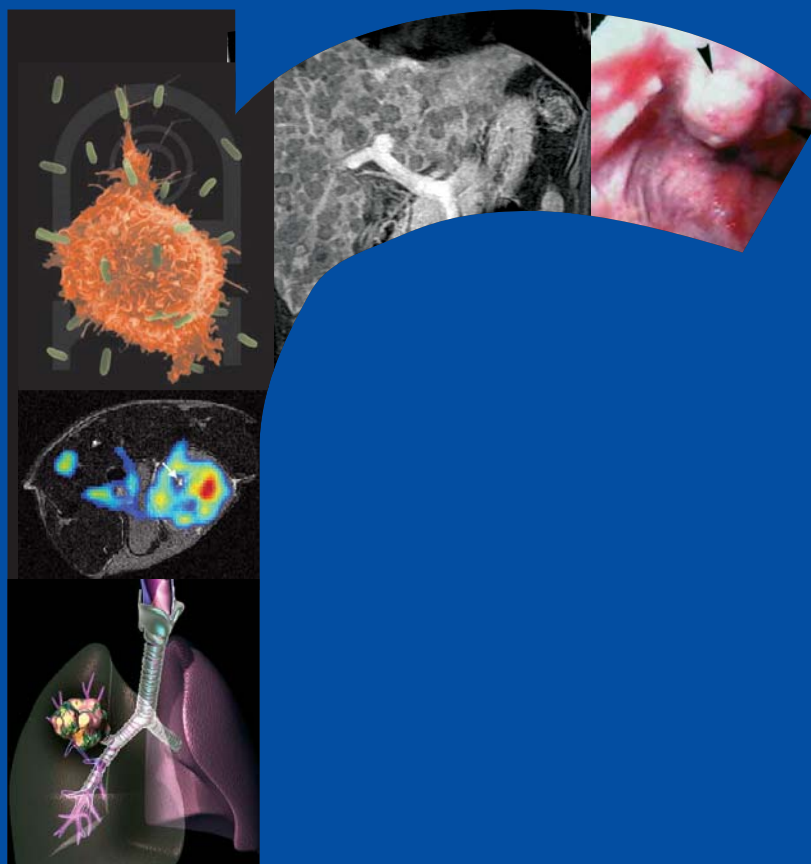
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CANCER NEWS

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From the Desk of Director Research

Prostate cancer is one of the most common type of cancer in men, generally affecting men over the age of 50. Worldwide, around 910,000 cases of prostate cancer were recorded in 2008, accounting for around 14% of all new cancer cases in men. According to the World Cancer Research Fund International, it is predicted the number of prostate cancer cases will almost double (1.7 million) by 2030. For reasons not fully understood, African American men have the highest frequency of prostate cancer in the world and the highest death rate from the disease. In other parts of the world, notably Asia, Africa and Latin America, the frequency of prostate cancer is low. The risk factors include age, race, nationality, diet, family history, genes, exercise, obesity and smoking. Nevertheless, after age and ethnic background, the strongest epidemiological risk factor for the disease is a positive family history. Men consuming large amount of fat, particularly from red meat and other sources of animal fat, are most likely to develop advanced prostate cancer.

Prostate cancer is generally diagnosed due to an elevated level of prostate-specific antigen (PSA) level or abnormal digital rectal exam. Unfortunately, PSA does not distinguish the type of prostate cancer a man may have in his gland – a microscopic cancer that will never cause a problem, a clinically relevant cancer that will cause morbidity and mortality if left in place, or a cancer that is lethal and hence incurable with localized therapy because it has already metastasized to distant organs. Research is being done to figure out whether early tests for prostate cancer in large groups of men will lower the prostate cancer death rate and help men live longer. The current challenge is to identify patients that may be cured with treatment and who do not require treatment and, therefore, must not be exposed to the morbidities related to the therapy.

Some prostate cancers become a serious threat to health by growing quickly, spreading beyond the prostate gland to other parts of the body and cause death while other prostate cancers grow slowly and never become a serious threat to the lives. The management of men diagnosed with prostate cancer remains predicated on a combination of clinical and pathological characteristics of the individual and the cancer. All prostate cancer treatments can cause side effects. The most common side effects are sexual, urinary and bowel problems. Some of these problems happen soon after treatment and others develop over time. However, the dramatic response of metastatic prostate cancer to castration shows the profound impact of effective molecular targeted therapy and the increasing insight into the molecular pathogenesis of prostate cancer certainly holds the further therapeutic promise.

This issue of Cancer News includes regular articles under the section “Special Feature”, “Perspective”, “Research & Development”, “New Technologies”, “Clinical Trials”, “Watch-Out”, “Globe Scan”, “Cancer Control” and “In Focus”.

We appreciate the contribution made by Dr Raghunath SK, Uro-oncologist, HCG - Bangalore Institute of Oncology, Bengaluru, for providing the “Guest Article” on ‘Insights on Biology of Prostate Cancer’.

Dr D C Doval

CONTENTS

- **Special Feature:** Robotic Surgery: A Perspective [3-5]
- **Guest Article:** Insights on Biology of Prostate Cancer [6-9]
- **Perspective:** Role of Radiotherapy in Prostate Carcinoma [10-11]
- **Research & Development:** Autoantibody Signatures as Biomarkers; Common Prostate Cancer Treatments; Mutation & Hereditary Prostate Cancer Risk; New Prostate Cancer Drug Target [12]
- **New Technologies:** Dutasteride for Low-Risk Prostate Cancer; New Ultrasound Technologies for Prostate Cancer; Prostate HistoScanning™; Targeted Nanoparticles for Prostate Cancer Therapy [13]
- **Clinical Trials:** Combined ADT and RT Therapy; Hormonal Treatment for Prostate Cancer [14]
- **Watch-Out:** Prostate Cancer Diagnosis & Treatment; Relapse of Prostate Cancer [14]
- **Globe Scan:** Starving Prostate Cancer Cells (Australia); Contraceptive Pill and Prostate Cancer (France); More Radionuclide Therapy (Germany); Heart Disease and Prostate Cancer (USA) [15]
- **Cancer Control:** Dietary Calcium and Prostate Cancer; High-Dose-Rate Prostate Brachytherapy Guidelines; Prostate Serum Antigen to Save Lives; Urine-Based Biomarkers for Aggressive Prostate Cancer [16]
- **In Focus:** Recent Advances in Management of Castration-Resistant Prostate Cancer [17-19]

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SPECIAL FEATURE

ROBOTIC SURGERY: A PERSPECTIVE

Diseases that harm require treatments that harm less – William Osler

Introduction

Robotic surgery is an emerging new and exciting new technology that is taking the surgical profession by storm. A robot taken from the Czech 'Robota', meaning forced labor, is a machine that resembles a human and does mechanical tasks on command. Robots are microprocessors used in computers, and routinely used to explore the deep sea and work in hazardous environment to name a few. Robotics, however, has been slow to enter the field of medicine.

History and Development of Surgical Robots

From their inception, surgical robots have been envisioned to extend the capabilities of surgeons beyond the limits of conventional surgery. In the late 1980s researchers at the National Aeronautic and Space Administration (NASA), Ames Research Center and Stanford Research Institute (SRI) became interested in virtual reality and robotic technologies. Their joint efforts culminated in the development of a telepresence surgical system to improve dexterity in microscopic hand surgery. The original idea soon evolved from microscopic to macroscopic surgery. The definitive event was the development of surgical laparoscopy which was ideal for the development of this new technology.

The US Department of Defence based upon the tele-surgery idea developed a new device-SRI Green telepresence Surgery System. It was a mobile, armored, operating room vehicle equipped with robotic surgical manipulators controlled remotely by a surgeon at a rear area mobile surgical hospital unit. Although it was intended to facilitate remotely performed surgery in battlefield and other remote environments, it turned out to be more useful for minimally invasive on-site surgery.

In 1985, a robot, the PUMA 560, was used to place a needle for a brain biopsy using CT guidance. In 1988, the PROBOT was used to perform transurethral resection of the prostate. The ROBODOC was introduced in 1992 to mill out precise fittings in the femur for hip replacement.

Later the AESOP (Automated Endoscopic System for Optimal Positioning) was successfully applied to hold the endoscopic during laparoscopy. Further development of robotic systems was carried out by Intuitive Surgical with the introduction of the da Vinci Surgical System and Computer Motion with the ZEUS Robotic Surgical System.

Types of Robotic Systems

There are three different classes of robotic systems.

1. Precise path systems: These are pre-programmed mechanical devices to perform systematically repetitive and predefined movements. They require no direct guidance from the surgeon. These include: the Surgeon Robot for Prostatectomies (Probot), designed to perform prostate transurethral resections, and the PAKY device to puncture the renal calyx during the percutaneous kidney procedures.

2. Intern replacement surgical robots: They substitute the surgical assistant to perform tasks that require dexterity without tiring. These include: the AESOP and Endoassist. They function as endoscopic holders that can be directed by commands from the surgeon.

3. The master-slave device: It is the least automatic of all systems as the robotic device never moves independently without guidance from the surgeon. The arms mimic the surgeon's movements at the console within the patient's body. Devices that meet these characteristics include the da Vinci Surgical System and the Zeus Robotic Surgical System.

The da Vinci Surgical System is a comprehensive master-slave robot with multiple arms operated remotely from a console with video assisted visualization and computer enhancement. There are essentially 3



Fig1: The da Vinci robotic surgical system consol



Fig2: The da Vinci robotic surgical system

components: a surgeon's console, a patient side robotic cart with 4 arms manipulated by the surgeon (one to control the camera and three to manipulate instruments), and a high definition 3D vision system. Articulating surgical instruments are mounted on the robotic arms which are introduced into the body through cannulas.

The camera arm contains dual cameras (a combination of two 5-mm optical channels one for each eye) and the image generated is 3-dimensional providing depth perception. The master console consists of an image processing computer that generates a true 3-dimensional image, the view port where the surgeon views the image, tool pedals to control electrocautery, camera arm/instrument clutches and master control grips that drive the servant robotic arms at the patients' side. The robotic instruments have articulated tips, which permit 7 degrees of freedom. The movements of the robotic system are intuitive i.e. a movement of the master control to the right causes the instrument to move to the right. The robotic systems provide increased precision by filtering hand tremors, providing magnification and providing scaling for surgeon's movements.

Advantages of Robotic System

The motivation to develop surgical robots rooted from the desire to overcome the limitations of current laparoscopic technologies and to expand the benefits of minimally invasive surgery. It offers all the advantages of

minimally invasive surgery like less pain and use of narcotics, less blood loss and transfusion rate, shorter hospital stay, smaller incision and earlier return to normal activity. It shortens the learning curve facilitating and hastening mastery of the procedure. It increases dexterity, restores proper hand-eye coordination and an ergonomic position. It provides better 3D visualization and a ten times image magnification. It offers the possibility for the surgeon to operate while sitting and eliminates the surgeon tremors. In addition, this system makes surgeries that were technically difficult easy to perform.

Disadvantages of Robotic System

The main disadvantage of this system is the cost, both for initial set up and maintenance. Its size is large requiring bigger operation theatres and requires specialized instruments and trained staff. Another disadvantage is its absolute lack of sensitivity making it impossible to interpret force or any tactile feedback.

Spectrum of Robotic Surgeries

Urology: Robotic Radical Prostatectomy- The complexity and morbidity associated with pelvic urological surgeries has been obviated with the advent of robotic surgery. Ever since Walsh et al popularized the technique of anatomic nerve-sparing radical prostatectomy, open radical prostate surgery has become a more desirable treatment for organ confined prostate cancer.

Though the first successful laparoscopic radical prostatectomies were performed in 1992 and 1997 and further modified by 2 French groups in 1999 and 2000, the extreme technical difficulty prevented its widespread use by the average urologist and thus limited penetration. The first reported robot assisted laparoscopic prostatectomy using the da Vinci system was described by Abbou et al in 2001. Menon et al from the Vattikuti Urology Institute are responsible for the development and popularization of robotic radical prostatectomy making it the largest performed robotic surgery in the world.

Radical cystectomy with urinary diversion, radical/partial nephrectomy, adrenalectomy, pyeloplasty and ureteric reimplantation have found wide usage and acceptance amongst urologists worldwide.

Gynecology: Robotic surgery in gynecology is one of the fastest growing fields of robotic surgery. Robotic myomectomy, radical Hysterectomies and surgery for pelvic prolapse can virtually obviate morbidity associated with open procedures.

Gastrointestinal Surgery: Whipple's procedure, liver resections, liver harvest for transplantation, oesophagectomy, fundoplication and Bariatric surgery have been performed with similar outcomes to the open procedure with significantly less morbidity.

Cardiothoracic Surgery: Robot assisted MIDCAB and Endoscopic Coronary Artery Bypass (TECAB) operations are being performed with the da Vinci system. Mitral valve repairs and replacements and ASD repairs have been performed. Hybrid CABG is being evolved and will soon be perfected. Lung resections and tumor resections have also been performed.

Neurosurgery: Neuroarm, the first MRI compatible stereotactic robotic system can perform complex brain tumor resection within a precision of 1mm.

Orthopedics: Total hip replacements, knee replacement and complex reconstruction of anterior cruciate ligament injuries have been found beneficial with the use of robotics.

Pediatrics: Surgical robots have been used in many pediatric surgical procedures, including tracheoesophageal fistula repair, portoenterostomy, congenital diaphragmatic hernia repair and others.

Head and Neck Surgery: Difficult to access areas like base of tongue and laryngeal resections are being done using the surgical robots.

Robotic Surgery at RGC&RC

Rajiv Gandhi Cancer Institute & Research Center (RGC&RC) acquired the da Vinci Surgical System in February 2011. So far, about 178 surgeries have been performed with this technique.

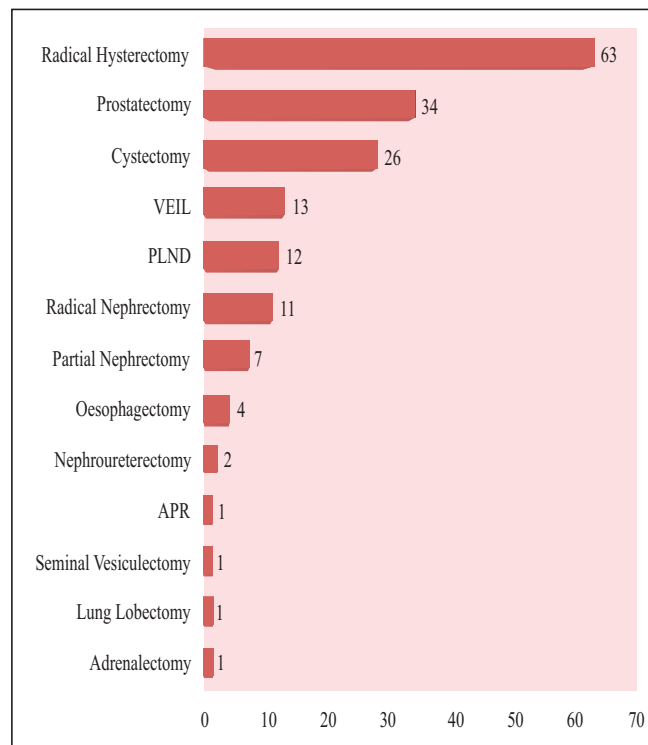


Fig 3: Robotic surgeries performed at RGC&RC

Future of Robotic Surgery

Many of the current advantages in robot assisted surgery ensure its continued development and expansion. Robotic surgery can be extended into the realm of advanced diagnostic testing with the development and use of ultrasonography and near infrared. One possibility is expanding the use of preoperative and intraoperative video image fusion to better guide the surgeon in dissection and identifying pathology. Some laboratories are working on systems to relay touch sensation from robotic instruments back to the surgeon. The possibility of automating some tasks is both exciting and controversial. Future systems might include the ability for a surgeon to program the surgery and merely supervise as the robot performs most of the tasks. The possibilities for improvement and advancement are only limited by imagination and cost.

(Dr Samir Khanna, Consultant; Dr Srivatsa N, Clinical Assistant; Dept of Genito-Uro Oncology; Dr Sudhir Rawal, Director of Surgical Oncology and Chief Genito-Uro Surgical Oncology)

GUEST ARTICLE

INSIGHTS ON BIOLOGY OF PROSTATE CANCER

Introduction

The statistics for prostate cancer make alarming reading and set undoubted challenges for research [1]. World wide incidence of prostate cancer is rising annually by 2-3% [1]. It is predominantly a disease of elderly men, its incidence is caused by ageing of the population, but the age adjusted incidence has also increased. Lately, a reversal may have set in, perhaps as a consequence of improved detection by screening for prostate-specific antigen (PSA) and better treatment [2]. The rise will be most pronounced in those countries with the greatest increase in life expectancy- France, Germany and Spain and will be further exacerbated as the post-war baby-boomers reach their fifties [1]. In patients with long life expectancy, carcinoma of prostate may be an aggressive and fatal disease [3]. Early disease is clinically heterogeneous because many patients have an indolent course that does not significantly affect an individual patient's survival [4]. It is important to understand how the life style, pathophysiology, development of a neoplasm and its progression involves in prostatic cancer for a better therapeutic intervention.

Anatomy

The prostate sits in the pelvis, surrounded by the rectum posteriorly and the bladder superiorly [5]. The base of the prostate is at the bladder neck and the apex at the urogenital diaphragm.

Normal Histology

The prostate is composed of branching glands, with ducts that are lined with secretory epithelial cells and basal

cells. Secretory epithelial cells are androgen-dependent for growth, and produce PSA and prostatic acid phosphatase. Surrounding the gland is a stroma. Stromal-epithelial interactions remain poorly understood, but recent insights suggest that the stroma produces multiple growth factors important for growth and development of normal prostate as well as prostate cancer [5].

Aetiology

Aetiology is insufficiently understood. Several risk factors have been identified. Risk factors for prostate cancer appear to include age, race, positive family history and dietary fat intake [6]. Positive family history is a risk factor but does not affect the prognosis [3]. High fat [6], dairy products and red meat consumption have emerged as risk factors in epidemiological studies.

Atypical Small Acinar Proliferation (ASAP): It is defined as atypical foci suspicious for but not diagnostic of malignancy [7]. The presence of atypical small acinar proliferation in a needle biopsy is a strong risk factor for prostate cancer; 42% of men with biopsies containing lesions suspicious, but not diagnostic, of carcinoma have adenocarcinoma on follow-up biopsy [8]. Studies have shown that presence of ASAP or prostatic intraepithelial neoplasia (PIN) and ASAP in a biopsy, indicates a repeat biopsy [9]. Predictive factors for prostate cancer detection in patients diagnosed with ASAP are uncertain. Kyoung et al performed a study to evaluate the prostate cancer detection rates of initial ASAP patients with strict diagnostic criteria of ASAP as follows: (i) total loss of basal cells confirmed by immunohistochemistry and inconspicuous nucleoli; or (ii) a minute ($d'500$ micrometer in length) focus of atypical glands with total loss of basal cells and prominent nucleoli. Absence of the basal cell layer as evidenced by immunohistochemical staining is a very important clue in the diagnosis of prostate cancer. Several studies demonstrated that immunohistochemical stains, such as p63 and HMWCK (34 β E12), can aid in prostate cancer diagnosis in a needle biopsy by staining basal cells. ASAP was associated with prostate cancer in 24.7% of initial ASAP patients. All initial ASAP lesions were smaller than 500 μ m in maximal diameter, 81.2% of radical prostatectomy specimens were significant, clinically and pathologically. Therefore, performing a repeated prostate needle biopsy in ASAP cases is recommended [7].

The disease is thought to arise from high-grade prostatic intraepithelial neoplasia (PIN) in the peripheral zone of the prostate, present in 4-16.5% of needle biopsies.

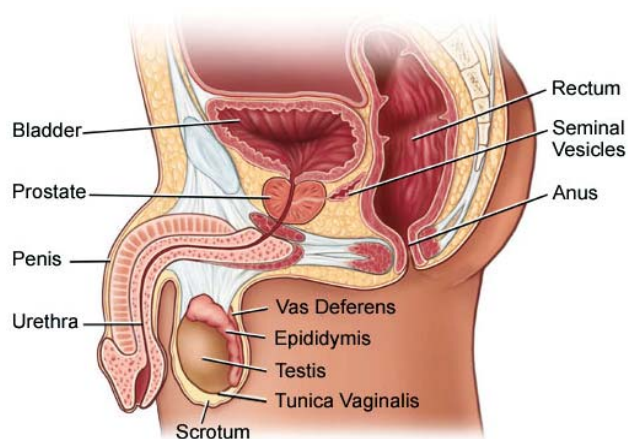


Figure: Male Reproductive Tract

Like any other development of carcinomas, even in prostate carcinomas, oncogenes play an important role in progression of the disease, but it is found that premalignant lesions may precede to malignancy by many years.

PIN appears to be a premalignant lesion that is associated with progressive abnormalities and this represents an intermediate step between the benign and invasive (malignant) state indicative of the early stages of release from normal growth control [10]. Two grades of PIN are identified (low grade and high grade). PIN is defined as the presence of cytologically atypical or dysplastic cells with architecturally benign appearing glands and acini [1]. PIN, like prostate carcinoma, is more frequently located in the peripheral zone of the prostate gland [11]. There is now convincing evidence that PIN is a precursor of prostate carcinoma [12], and that it precedes prostate cancer by 10 years or more [13].

Surgical Pathology

Over 95% of prostate cancers are adenocarcinomas that arise from prostatic epithelial cells. Other rare histologies have been described, including mucinous or signet-ring cell carcinomas, adenoid cystic carcinomas, carcinoid tumors, large prostatic duct carcinomas (including the endometrioid type adenocarcinomas), and small-cell undifferentiated cancers. It is important to recognize these unusual variants of prostate cancer since standard hormonal therapies may be less effective with some of them [5].

Systematic prostate biopsy labeling provides additional clinical information of value in the risk assessment of the patient. Anatomic, site specific, biopsy labeling or “**prostate biopsy mapping**” allow for (i) determination of the total percentage of separate biopsy samples involved by cancer (i.e. often referred to as “the percentage of positive cores”); (ii) the measurement in mm’s of the amount (or the percentage) of linear involvement by prostate cancer present in each positive biopsy core at a particular biopsy site; and (iii) the anatomic region or zone of origin (transitional zone vs. peripheral zone) of prostate cancer involvement [14].

Grading: Gleason’s grading system has found most wide spread acceptance and accounts for tumor heterogeneity by summing the grades assigned for the dominant and secondary architectural patterns [3]. The limitations of Gleason’s score (GS) indicate the clinical need to avoid under-grading GS 6 and to substratify GS 7 tumors in some clinically useful way. Undergrading will

specially affect the success of “watchful waiting”, and the observed efficacy of some of the newer treatment modalities like brachytherapy, and it also will conceal the need for adjuvant therapy in high risk patients who need it the most [14].

A quantitative interpretation of today’s biopsies should also include the *percentage of positive biopsy samples*, the *zonal origin* of the biopsy specimen with cancer if possible (transition zone vs peripheral zone), the notation of the presence or absence of invasion of the pericapsular fat (fatty tissue around the capsule of the prostate) and the perineural invasion by the cancer. It should also include the quantitative amount of cancer present on each positive tissue core presented in the biopsy.

In addition, many other predictors of clinical behavior have been explored, including PSA, clinical stage, tumor volume, deoxyribonucleic acid (DNA) ploidy, and nuclear morphometry. Many molecular markers have also been explored, but currently the Gleason score remains the most broadly applicable and prognostically useful histologic grading system [5].

Molecular Pathology

Some of the important oncogenes involved in development of prostatic cancer are:

Bcl-2 Protooncogene: produces Bcl-2 protein which regulates the apoptosis with other protein BAX [1]. Altered expression contributes to prostate cancer development and progression. It is overexpressed in half of all prostatic cancers particularly androgen-independent cases [2].

c-myc Oncogene: Overexpression of myc is a consistent finding in metastatic cancers.

C-ERB-B2 (HER-2): Although the C-ERB-B2 oncogene has been studied in prostate cancer, its clinical utility as a tumor marker or therapeutic target remains unclear.

P53: It regulates cell cycle inhibition and apoptosis in response to cellular stress [3]. Loss of one allele is accompanied by point mutations in the remaining copy of p53 leading to its functional inactivation [2]. p53 protein can be detected immunohistochemically in 8-64% of prostate cancers [3]. When p53 over-expression is identified in prostatic cancers, it is also seen in associated PIN, suggesting that p53 alterations may be an early event in prostate tumorigenesis [15]. The study of p53 is of interest in prostate cancer because over-expression is

associated with an androgen independent phenotype [16]. Locally recurrent prostate cancers after radical prostatectomy or radiotherapy have a significantly higher rate of p53 over-expression than have tumors before treatment [17]; the reason for this remains obscure.

PTEN: It is the most widely mutated tumor suppressor gene in prostatic cancer [3]. Most mutations were found in metastatic prostatic carcinomas [18,3]. PTEN is a marker for metastatic progression [18].

TMPRSS2: TMPRSS2 is a membrane-bound serine protease. It is localized in human prostate luminal epithelium and is regulated by androgens. Due to its high expression in prostate and prostate cancer, TMPRSS2 is a potential new marker of the disease [19]. Recurrent gene fusions between the androgen-regulated gene TMPRSS2 and the ETS family members ERG, ETV1, or ETV4 have been recently identified as a common molecular event in prostate cancer development [20,21]. TMPRSS2:ERG rearranged prostate cancers have been associated with a greater likelihood of lethal prostate cancer, moderate to poor differentiated tumors and higher stage diseases with pelvic lymphnode metastases [21]. TMPRSS2:ERG fusion and PTEN loss together are a predictor of earlier biochemical recurrence of the disease.

KAI-1 gene: Is a metastatic suppressor gene which is downregulated in metastatic prostatic carcinoma. It could be involved epigenetic silencing by promoter methylation or via polycomb activation [18]. Expression KAI-1 is correlated strongly with p53, loss of p53 may lead to downregulation of KAI-1 and ultimately result in metastasis [18].

CD44: Expression of this transmembrane glycoprotein is downregulated during prostate cancer progression, this being correlated with higher tumour grade, aneuploidy and metastases. Downregulation of CD44s and its CD44v6 isoform is related to an unfavourable prognosis in prostate cancer. [18]

NM23: Over-expression of the NM23 gene occurs frequently in adenocarcinoma of the prostate and may even be an early event of prostate cancer tumorigenesis. Levels of NM23 mRNA and protein were both increased in metastatic prostate cancer lymph nodes compared to normal prostate tissue [18].

Mismatched Repair Genes: Deficiency causes microsatellite instability (MSI) and increased mutation rates [18]. MSI has been described in high-grade and lymph node positive prostate cancer specimens. MSI

has been described in high-grade and lymph node positive prostate cancer specimens.

Growth factors and their receptors also play an important role in the growth regulation of normal and cancerous cells. Although the mechanisms of the progression of prostate cancer are poorly understood, many of these growth factor genes can be amplified in this setting. Growth factors implicated in prostate cancer are: insulin-like growth factors I and II (IGF-I and -II), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF)- α and has been shown to be dysregulated in the development of prostate cancer. Chan and colleagues reported on the relationship between plasma IGF-1 levels and prostate cancer, citing a relative risk of 4.3 for men in the highest quartile compared to men in the lowest quartile. This association was independent of PSA levels. Further, IGF levels increased the detection rate of prostate cancer over PSA alone [5].

The alteration of a normal cell into the malignant state represents its escape from normal regulatory controls, and a new set of cellular capabilities develop. The

Table 1: Molecular Progression in Prostate Cancer [18]

Normal prostate cells

Presence of predisposing alleles (e.g. RNASEL, R462Q)
Methylation of TSG promoters leading to epigenetic gene silencing
Chromosome 8p loss
AR CAG repeat alterations
Vit D Receptor reduced activity
5 α reductase (SRD5A2) increased activity
CAPB (1p36) mutation
HPC1 (1q24-25) mutation
PCAP (1q42.2-43) mutation
MSR1 (8p22-23) mutation
KLF6 (10p15) mutation
ELAC2 (17p11.2) mutation
HPC20 (20q13) mutation
HPCX mutation

Localised prostate cancer

Chromosome 16q loss
Altered E-cadherin expression (16q)
RB1 (13q) loss
p53 (17p) inactivation
GSTP1 (11q13) inactivation

Metastatic prostate cancer

Over expression of EZH2 polycomb protein
Transcriptional silencing of many genes by histone deacetylation
Increased BCL-2 expression
Increased availability of adrenal steroids
Loss of KAI-1 (11p)
PTEN mutation
AR gene amplification
AR mutation
Abnormal phosphorylation of AR by 2nd messenger systems

Androgen-independent Prostate Cancer

enormity of these changes that enable a cancer cell to move, leave its original organ, invade new tissue and develop, cannot be underestimated [10], the route of which is shown in the Table 1.

Progression of Prostate Cancer

Normal prostate and early stage prostate cancers depend on androgens for growth and survival [22]. Over time, the prostate cancer cells overcome the need for androgen as a survival, growth, and differentiating factor and become androgen-independent (AI) [23]. Most metastatic androgen-independent prostate cancers express high levels of androgen-receptor gene transcripts. Mutations in androgen-receptor genes are not uncommon and may provide a selective growth advantage after androgen ablation [24]. Other cases activation of androgen receptors occurs in the absence of androgens due to crosstalk via other signaling pathway or sensitivity to low levels of androgen is increased by amplification, and/or elevated levels or broadened specificity of co-activators of the androgen receptors [22, 25]. Tumor cell genotype and phenotype have been considered the only determinants supporting cancer growth and metastasis [26]. Chung et al have shown that permanent genetic and phenotypic changes occur in prostate cancer cells after 3-dimensional co-culture in vitro or when co-inoculated and grown with inductive stroma cells in vivo which supports the intercellular communication between prostate cancer cells and organ specific stroma, including prostate and marrow stroma, leading to the development of metastasis [26]. Studies related to gene expression analysis of tumor samples has shown that phenotypes MTA1 and MYBL2 were over-expressed in metastatic prostatic cancer, HOXC6 and PDGFRA in recurrent cases and SIAT1 in nonrecurrent cases indicating the biology of prostate cancer progression [4].

Conclusion

The pathogenesis and molecular biology remains complex and poorly understood in prostatic carcinoma. Histopathologists play an important role in diagnosis and grading of the tumor [3]. Identifying the function of gene products and its cellular pathway will suggest better approach for treatment of prostatic carcinoma [18].

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PERSPECTIVE**ROLE OF RADIOTHERAPY IN PROSTATE CARCINOMA**

Radiation may be used as the primary method of treatment or as an adjuvant, or as additional treatment to increase the effectiveness of another primary therapy, such as radical prostatectomy. In advanced cancers, hormone therapy may be used as an adjuvant to radiation. Radiation therapy used to be reserved for older men (over age 70) with locally advanced prostate cancer who had a life expectancy of 15 years or less. However, it is now being used more frequently in younger and healthier men. The two main radiation treatments for prostate cancer are: External beam radiation and Brachytherapy (internal radiation).

History

External beam radiation therapy (EBRT) is one of the primary treatment modalities for patients with localized or locally advanced prostate cancer. Radiation therapy for prostate cancer was first introduced in the United States in 1915 in the form of radium applicators. This did offer a good treatment to the prostate but was associated with considerable reactions. Over the next 3 decades, EBRT started being used more and more but unfortunately, the limitations of these low-energy radiation beams which were in use, greatly restricted the use of radiotherapy in advanced prostate cancer throughout the first half of the 20th century. But with the discovery of megavoltage (energy >1000 kV) radiations after World War II, x-ray beams penetrated deeper and were associated with significantly less skin and subcutaneous morbidity.

During the 1950s and 1960s, megavoltage radiation was more commonly available but the linear accelerator, as the most common form of EBRT, was established by the early 1980s. In addition to allowing for deeper penetration into tissue, linear accelerators provided a beam with more sharply delineated borders. In turn, this allowed higher doses of radiation to be directed at the clinical target (prostate, seminal vesicles, regional lymph nodes).

With the evolution of improved computer-based treatment planning, modern radiotherapy techniques have essentially replaced conventional radiotherapy treatments with 3-dimensional conformal radiotherapy (3D-CRT),

intensity-modulated radiotherapy (IMRT), and image-guided radiotherapy (IGRT). By the mid-1990s, further developments of treatment planning software, coupled with the integration of multileaf collimators (mechanized radiation beam shaping devices), allowed for the introduction of a more conformal treatment modality intensity-modulated radiation therapy (IMRT). With this technique, the radiation beam is divided into individual beamlets so that differences in position of tumor and normal tissue can be exploited with varying doses. Planning is facilitated by assigning maximal doses to the targets at risk and assigning minimized doses to normal tissue volumes. With the introduction of more conformal radiation therapy techniques, it became apparent that daily prostate movement could result in inaccuracies with treatment delivery, thus producing geographical target misses. Prostate motion necessitated investigations into different imaging modalities for daily prostate localization now known as image-guided radiation therapy (IGRT).

Over the past 10 years, IGRT has largely replaced conventional conformal radiation therapy as the main radiation technique for prostate cancer. Today image-guided radiotherapy has become a current standard of care. Whether image guidance will allow for more successful dose escalation is uncertain. Doses previously considered unsafe for clinical use have become current standards. Patients with early-stage prostate carcinoma typically receive doses in the range of 72-78 Gy. Those with more advanced disease are commonly offered doses that approach 80-82 Gy. Prospective data suggest that certain groups of patients have improved disease control with increasing dose.

Image-guided radiotherapy (IGRT) makes use of additional verification tools to ensure proper target localization during the course of radiotherapy. The term IGRT has been widely used to refer to imaging techniques as simple as daily port films to those as complicated as computer-assisted patient repositioning devices. Regardless, as highly conformal radiotherapy is administered with increasing frequency, accurate target localization becomes mandatory. As radiotherapy for prostate cancer has become increasingly conformal, dose escalation has become a standard approach and accurate target and normal tissue localization has become increasingly important.

When patients are selected for primary radiotherapy treatment, simulation is performed with CT-based imaging or MRI technology. Accurate delineation of normal tissues in relation to the prostatic target is equally

important. Following identification of the prostatic target (GTV), a clinical target volume (CTV) and planning target volume (PTV) are created. Although this phase of treatment planning allows for accurate target localization based on the gland's location at the time of CT imaging, it does not address organ motion subsequent to that date. Kilo voltage imaging devices have been successfully added to linear accelerators. They are normally mounted at 90° to the treatment head of the machine and are opposed by digital image detectors. These x-ray cameras can be used to generate axial images representative of the target area of interest, which are then compared with CT scans obtained previously during treatment planning. Coordinated shifts can be made if positioning inaccuracies are detected in patient setup.

Brachytherapy

Brachytherapy is a technique that implants radioactive “seeds” directly into the prostate. Implants can be temporary or permanent. It is mainly used in early stage prostate cancer that is relatively slow growing. It is also used in combination with external beam radiation to treat intermediate-risk localized prostate cancer. Poorer candidates for brachytherapy include men who have had transurethral resection of the prostate (TURP) and patients with advanced cancer, high-grade tumors, or very enlarged prostate glands.

Possible Side Effects of External Beam Radiation Therapy

The numbers used to describe the possible side effects below relate to conventional external radiation therapy, which is now used much less often than in the past. The **risks of the newer treatment methods described above are likely to be lower.**

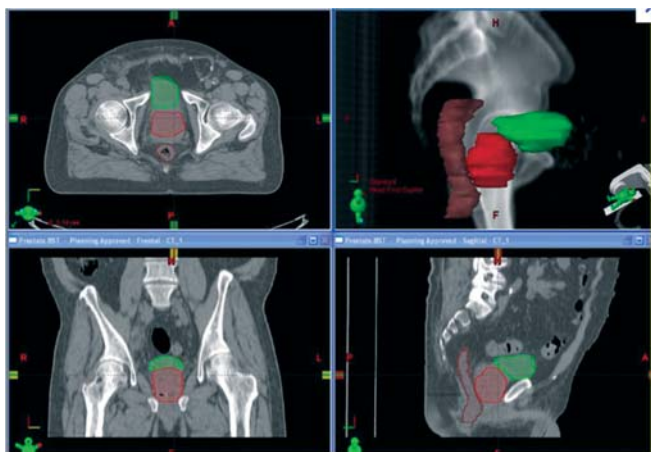


Figure: Conformal radiation planning in prostate carcinoma

Bowel Problems: During and after treatment with external beam radiation therapy, one may have diarrhoea, sometimes with blood in the stool, rectal leakage, and an irritated large intestine. Most of these problems go away over time, but in rare cases normal bowel function does not return after treatment ends. In the past, about 10% to 20% of men reported bowel problems after external beam radiation therapy, but the newer conformal radiation techniques are less likely to cause these problems.

Bladder Problems: There may be increased frequency of urination and burning in urine. These problems usually improve over time. Urinary incontinence is less common than after surgery.

Impotence: After a few years, the impotence rate after radiation is about the same as that of surgery. It usually does not occur right after radiation therapy but slowly develops over a year or more. This is different from surgery, where impotence occurs immediately and may improve over time.

Feeling Tired: Radiation therapy may also cause fatigue that may not disappear until a few months after treatment stops.

Lymphedema: Fluid build up in the legs or genitals is possible if the lymph nodes receive radiation.

Urethral Stricture: The urethra may, rarely, be scarred and narrowed by radiation, and require further treatments to open it up again.

Newer Advances

Conformal proton beam radiation therapy related to 3D-CRT and uses a similar approach. But instead of using x-rays, this technique focuses proton beams on the cancer. Protons are positive parts of atoms. Unlike x-rays, which release energy both before and after they hit their target, protons cause little damage to tissues they pass through and then release their energy after travelling a certain distance. This means that proton beam radiation may be able to deliver more radiation to the prostate and do less damage to nearby normal tissues. Although early results are promising, studies are needed to see if proton beam therapy is better in the long-run than other types of external beam radiation. Right now, proton beam therapy is not widely available. The machines needed to make protons are expensive, and there are only a handful of them in use in the United States.

(Dr Swarupa Mitra, Consultant, Department of Radiation Oncology)

RESEARCH & DEVELOPMENT

Autoantibody Signatures as Biomarkers

Researchers at Harvard Medical School, United States, have identified 5 autoantibody signatures (TARDBP, TLN1, PARK7, LEDGF/PSIP1, and CALD1) to distinguish prostate cancer from benign prostatic hyperplasia (BPH) in patients with increased serum prostate specific antigen (PSA) using a native antigen reverse capture microarray platform. Prostate cancer patient serum samples (n=41) and BPH patient samples (collected starting at the time of initial diagnosis) with a mean follow-up of 6.56y without the diagnosis of cancer (n=39) were obtained. Combining these signatures resulted in an area under curve (AUC) of 0.95 (sensitivity of 95% at 80% specificity) compared to AUC of 0.5 for serum concentration PSA (sensitivity of 12.2% at 80% specificity). This may result in the reduction of unnecessary biopsies in patients with increased serum PSA.

(Clin Chim Acta, Mar 22, 2012)

Common Prostate Cancer Treatments

Experts comparing three leading prostate cancer therapies find external beam radiation therapy (EBRT) to be more toxic and expensive than either surgery or brachytherapy. Researchers examined treatment outcomes among more than 137,000 men who received EBRT, prostatectomy or brachytherapy. The study revealed that just over 7% of the men needed some type of follow-up treatment for a problem related to their prostate cancer therapy. Brachytherapy resulted in the fewest number of toxicities involving their genital or urinary organs and only 3.4% patients experienced problems such as narrowing of urethra or bladder bleeding. 6.7% patients treated with prostatectomy experienced problems with their genital or urinary organs. Over 7% of patients who received EBRT had these adverse effects. Only 0.1% of prostatectomy patients and 0.3% of brachytherapy patients experienced these issues. The researchers were unable to determine how far the disease had progressed in each patient and the study was limited to patients older than 65 whose only diagnosed condition was prostate cancer. Findings are preliminary and more research is needed to investigate why the three prostate cancer therapies produce different results and whether or not certain types of patients are more vulnerable to long-term effects of a particular treatment.

(Health Day News, Jan 31, 2012)

Mutation & Hereditary Prostate Cancer Risk

Investigators have identified a rare, inherited mutation linked to a significantly higher risk of the prostate cancer that strikes men at younger ages and runs in families. Men who inherit this mutation have a 10 to 20 times higher risk of developing prostate cancer. Researchers started with samples from the youngest patients with prostate cancer in 94 families with multiple cases of the disease among close relatives. Members of four different families were found to have the same mutation in the HOXB13 gene, which plays an important role in the development of the prostate during fetal stage and its function later in life. The mutation was carried by all 18 men with prostate cancer in these four families. The study also looked for the same HOXB13 gene mutation among 5,100 men who had been treated for prostate cancer. The mutation was found in 72 of the men. The researchers also looked for the mutation in a control group of 1,400 men without prostate cancer, and only 1 of those men carried the mutation. The mutation was significantly more common in men with a family history and early diagnosis compared with men diagnosed later, after age 55, without a family history. With further study, it may be possible to have genetic test for inherited prostate cancer.

(NEJM, Jan 12, 2012)

New Prostate Cancer Drug Target

Research at LSU Health Sciences Center, New Orleans, has identified a new protein (ARD1) critical to the development and growth of prostate cancer. ARD1 is involved with the male hormone, androgen, and its receptor. Androgen deprivation therapy has been a standard treatment for advanced prostate cancer. They determined that ARD1 is overproduced in the majority of prostate cancer samples, that it activates the androgen receptor, and that it is an essential component of prostate cancer cell growth. Inactivation of ARD1 inhibits the function of androgen receptors, resulting in complete suppression of prostate cancer cell growth in tissue culture and prostate tumor growth in mice. Furthermore, the role of ARD1 in the development of prostate cancer to modify the androgen receptor to enhance its activity was revealed. The study provides a novel avenue for controlling AR-mediated prostate tumor development by directly inhibiting the function of ARD1 or AR-ARD1 interaction. Developing an ARD1-specific inhibitor or an AR-ARD1 interaction-disrupting compound may be of therapeutic benefit in the treatment of prostate cancer.

(PNAS, Feb 6, 2012)

NEW TECHNOLOGIES

Dutasteride for Low-Risk Prostate Cancer

A team of scientists from Canada and USA have shown that dutasteride used to treat enlargement of the prostate, may also reduce the need for treatments that pose risks of incontinence and impotence and delay growth of early-stage prostate cancer. Dutasteride is a 5 α -reductase inhibitor that works by preventing testosterone from converting to dihydrotestosterone. The drug has been approved for treating benign prostatic hyperplasia. In a multicentric trial, 302 men age between 48 and 82 years undergoing active surveillance for low-risk localized prostate cancer were randomly assigned to two groups; one group received 0.5 mg dutasteride once daily for 3 years, while the other group received placebo for the same duration. Drug-related adverse effects were experienced by more participants in the dutasteride group than those given placebo. Those who received dutasteride also reported considerably lower cancer-related anxiety compared with the placebo group. The researchers found that dutasteride considerably delayed disease progression in comparison with placebo. It could provide a beneficial adjunct to active surveillance for men with low-risk prostate cancer.

(The Lancet, Jan 24, 2012)

New Ultrasound Technologies for Prostate Cancer

Researchers from Medizinische Universität Innsbruck, Austria, have concluded that new ultrasound technologies, including color and power doppler ultrasound, contrast enhanced US and real-time sonoelastography, have shown improved prostate cancer diagnosis. Contrast-enhanced ultrasound has shown a sensitivity of 100% (95% CI, 95%), a negative predictive value (NPV) of 99.8% and a positive predictive value (PPV) of 88.8% for prostate cancer detection. Real-time sonoelastography has shown a sensitivity of 86%, a specificity of 81% and NPV of 91% for prostate cancer diagnosis. Most studies show that these new ultrasound modalities demonstrate 1.5 to 2.5 times higher detection of prostate cancer per biopsy specimen compared with systematic biopsy. In patients with suspected prostate cancer, these new ultrasound techniques should be used. These techniques can detect prostate cancer and allow a targeted biopsy approach.

(Radiologe, Nov 2011)

Prostate HistoScanning™

Prostate HistoScanning™ (PHS), an ultrasound-based tissue characterization application has the potential to benefit the prostate cancer detection and staging pathway with increased cancer detection and tumour localization. In a multicentric study conducted in 6 European centers to evaluate the ability of PHS, 31 organ-confined prostate cancer patients diagnosed on transrectal biopsies were included. Three patients were excluded from analysis due to inadequate scan acquisition and one patient had withdrawn from the study. Results established a strong correlation between the total cancer volume detected in each of the 27 glands by PHS and by histopathology. At the level of individual cancer lesions, PHS detected 25 of the 27 foci (91% sensitivity) that were greater than 0.20cc in volume. More detailed analysis by prostate sextant examined the ability of PHS not only to detect and size, but also to accurately locate significant lesions and indicated that PHS showed a sensitivity of 90% and a specificity of 72% for the localisation of prostate cancer foci within the 162 sextants. PHS has the ability to identify and locate prostate cancer and consequently may aid in pre-treatment and pre-surgical planning.

(BJU International, Nov 17, 2011)

Targeted Nanoparticles for Prostate Cancer Therapy

Scientists from Massachusetts Institute of Technology and Massachusetts General Hospital, USA, have created a drug delivery system that is able to effectively deliver chemotherapeutic drugs to prostate cancer cells. Using prostate cancer (PCa) as a model disease, researchers developed a cell-uptake selection strategy to isolate PCa-specific internalizing 2'-O-methyl RNA aptamers (Apts) for nanoparticle (NP) incorporation which can distinguish PCa cells from nonprostate and normal prostate cells. When docetaxel, a chemotherapeutic agent used for the treatment of PCa, was encapsulated within the NP-Apt, a significant improvement in cytotoxicity was achieved in targeted PCa cells. Moreover, the ability for a ligand to intentionally be engulfed by a cell is crucial in drug delivery since it enables a significant amount of drug to enter the cancer cell, as opposed to remaining outside on the cell surface. This is a more effective method for cancer therapy. This strategy simplifies the development process of targeted nanoparticles and broadens their applications in cancer therapy.

(ACS Nano, Jan 3, 2012)

CLINICAL TRIALS

Combined ADT and RT Therapy

Result of a multicentric randomized phase III trial reported that Radiotherapy (RT) in combination with androgen deprivation therapy (ADT) improves overall survival in men with locally advanced disease or organ confined disease. Researchers recruited 1205 patients in the study and it was found that 1057 patients had locally advanced (T3 or T4) and organ-confined (T2) prostate cancer with either prostate-specific antigen (PSA) concentration more than 40 ng/ml (n=119) or 20 ng/ml and Gleason Score of 8 or higher (n=25). These patients were randomly assigned into two groups, first group of 602 patients received ADT only and second group of 603 patients received ADT as well as RT. At the time of analysis total 175 patients died in ADT only group and 145 in the ADT and RT group. The overall survival rate was 74% in the ADT and the RT group compared with 66% in the only ADT group. Serious long-term toxicity from RT was very less with few serious adverse events. This trial provides convincing evidence that local control of disease in the prostate improves survival in patients with locally advanced prostate cancer.

(The Lancet, Nov 3, 2011)

Hormonal Treatment for Prostate Cancer

According to the complete analysis of Phase III trial, advanced stage prostate cancer patients receiving a new type of hormonal treatment, MDV3100, lived extra for 4.8 months compared to men taking a placebo. A randomized, multinational placebo controlled trial was conducted which included 1999 men with advanced prostate cancer who had already received docetaxel based chemotherapy. MDV 3100 is the first new class of medicines called androgen receptor signaling inhibitors (ARSI); this drug binds to the receptor of testosterone on prostate cancer cells. Final analysis of data showed that men taking MDV 3100 lived for 18.4 months compared with 13.6 months for men taking placebo. Patients receiving MDV 3100 had drop of at least 50 percent in their prostate specific antigen (PSA) levels and showed mean time until tumor growth for 8.3 months whereas other group showed 2.9 months. Over the recent years there has been a significant increase in number of drugs for advanced cancer patients and MDV 3100 has shown impressive results. It can also be offered to very ill patients as a life prolonging option.

(The Institute of Cancer Research UK, Feb 1, 2012)

WATCH-OUT

Prostate Cancer Diagnosis & Treatment

Scientists Claudio Cuello et al of Proscan RX Pharma Inc. Montréal, Canada, have been awarded United States patent (No. 8101713) on 24th January 2012 for the invention "Prostate cancer diagnosis and treatment". The prostate gland is affected by various significant pathological conditions as benign growth (BPH), infection (prostatitis), and neoplasia (prostate cancer). Prostate cancer is the second most frequently diagnosed cancer in Canadian and American men, after non-melanoma skin cancer, which is rarely fatal. More importantly, after lung cancer, prostate cancer is the most common cause of cancer-related deaths. The present invention relates to novel antibodies and their use for detecting, imaging, staging, treating and monitoring of prostate cancer, and/or metastasis thereof. It also relates to novel pharmaceutical compositions for the treatment of prostate cancer.

(www.freepatentsonline.com, Feb 4, 2012)

Relapse of Prostate Cancer

Illumina Inc. San Diego, USA, has been awarded US Patent No. 8,110,363 on Feb 7, 2012 for their invention entitled "Expression profiles to predict the relapse of prostate cancer". The invention relates generally to gene expression profiling and, more specifically to relapse prediction and clinical management of prostate cancer. It provides a method for preparing a reference model for cancer relapse prediction that provides higher resolution grading than Gleason score alone. The method encompasses obtaining from different individuals a plurality of prostate carcinoma tissue samples of known clinical outcome, representing different Gleason scores; selecting a set of signature genes having an expression pattern that correlates positively or negatively in a statistically significant manner with the Gleason scores; independently deriving a prediction score that correlates gene expression of each individual signature gene with Gleason score for each signature gene in said plurality of prostate carcinoma tissue samples; deriving a prostate cancer gene expression (GEX) score that correlates gene expression of said set of signature genes with the Gleason score based on the combination of independently derived prediction scores in the plurality of prostate cancer tissue samples; and correlating said GEX score with the clinical outcome for each prostate carcinoma tissue sample.

(USPTO, Feb 07, 2012)

GLOBE SCAN

Starving Prostate Cancer Cells

Researchers have discovered a potential future treatment for prostate cancer through starving the tumor cells of an essential nutrient they need to grow rapidly. Their work, with human cells grown in the lab, reveals targets for drugs that could slow the progress of early and late stage prostate cancer. Growing cells need an essential nutrient, the amino acid called leucine, which is pumped into the cell by specialized proteins. And this could be prostate cancer's weak link. It was found that prostate cancer cells have more pumps than normal. This allows the cancer cells to take in more leucine and outgrow normal cells. This information allowed the researchers to target the pumps. They found that they could disrupt the uptake of leucine firstly by reducing the expression amount of the proteins pumps, and secondly by introducing a drug that competes with leucine. This fundamental research tells us more about how prostate and other cancers grow, and will open the way for new treatments in the long term.

(Australia: Science Daily, Nov 2, 2011)

Contraceptive Pill and Prostate Cancer

Data from the International Agency for Research on Cancer (IARC) and the United Nations World Contraceptive Use report was used to pinpoint rates of prostate cancer and associated deaths and the proportion of women using common methods of contraception for 2007. Use of the contraceptive pill in the population as a whole was significantly associated with both the number of new cases of and deaths from prostate cancer in individual countries around the world, the analysis showed. These findings were not affected by a nation's wealth. Excess oestrogen exposure is known to cause cancer, and it is thought that widespread use of the pill might raise environmental levels of endocrine disruptive compounds (EDC's) which include byproducts of oral contraceptive metabolism. These don't break down easily, so can be passed into the urine and end up in the drinking water supply or the food chain, exposing the general population. Temporal increases in the incidence of certain cancers (breast, endometrial, thyroid, testis and prostate) in hormonally sensitive tissues in many parts of the industrialized world are often cited as evidence that widespread exposure of

the general population to EDC's has had adverse impact on human health.

(France: BMJ Open, Nov 14, 2011)

More Radionuclide Therapy

For prostate cancer patients with bone metastases, repeated administration of radionuclide therapy with ¹⁸⁸Re-HEDP is shown to improve overall survival rates and reduce pain. The retrospective study reviewed cases of 60 patients with hormone-refractory prostate cancer. Radionuclide therapy of bone metastases has been used for several decades for those with prostate cancer. However, for this study the authors developed ¹⁸⁸Re-HEDP as a novel radiopharmaceutical which, due to its short half life of 19 hours, makes sequential therapy possible. The researchers found that post-treatment survival increased with the number of radionuclide therapies administered. Pain reduction was achieved in 89.5 percent of those receiving one therapy, in 94.7 percent of those receiving two therapies and in 90.9 in percent of those receiving three or more therapies. For patients failing chemotherapy or hormone treatments, ¹⁸⁸Re-HEDP is a promising therapy that can both extend the number of survival years and help relieve pain from bone metastases. The findings support and expand the role of molecular therapy with radioisotopes in oncology.

(Germany: J Nuclear Med, Nov 1, 2011)

Heart Disease and Prostate Cancer

In a large analysis of men participating in a prostate drug trial, researchers have found a significant correlation between coronary artery disease and prostate cancer, suggesting that the two conditions may have shared causes. In the current study, data from 6,390 men enrolled in a large four year study called REDUCE, randomized trial to test the prostate cancer risk reduction benefits of a drug called dutasteride was used. All the study participants had a prostate biopsy at the two- and four-year marks, regardless of their PSA levels. Among the men in the study, 547 reported a pre-enrollment history of coronary artery disease. This group of men tended to be older, heavier and less healthy, with higher baseline PSA levels, plus more diabetes, hypertension and high cholesterol. The men were also much more likely to develop prostate cancer, even after accounting for all the baseline differences. It was found that having coronary artery disease increased the men's risk of prostate cancer by 35 percent, with the risk rising over time.

(USA: Can Epid Biomarkers and Prev, Feb 8, 2012)

CANCER CONTROL

Dietary Calcium and Prostate Cancer

According to a study conducted at the Durham Veterans Affairs Medical Center, Durham, North Carolina, the higher levels of calcium in a man's normal diet may be associated with a lower risk for diagnosis of prostate cancer. This study carried out during 2007-2009 among US veterans included 506 men which consisted of 108 biopsy-positive prostate cancer patients, 161 biopsy-negative controls and 273 healthy controls. The Harvard food frequency questionnaire was used to assess diet and estimate calcium intake, and a separate questionnaire to obtain information on potential prostate cancer risk factors, including smoking and alcohol use, physical activity and family history of prostate cancer. It was observed that the men in the highest tertile of calcium from food was associated with lower risk of high-grade prostate cancer when men with high-grade cancer were compared to biopsy-negative controls (OR=0.37) and when men with high-grade cancer were compared to healthy controls (OR=0.38; 95% confidence interval). The study concluded that the calcium from food is associated with lower risk for prostate cancer, particularly among black men and lower risk for high-grade prostate cancer among all men.

(Preventing Chronic Disease, Jan 12, 2012)

High-Dose-Rate Prostate Brachytherapy Guidelines

The American Brachytherapy Society recommends the use of high-dose-rate (HDR) brachytherapy as definitive treatment for localized prostate cancer. A group of expert practitioners and physicists had been organized by the American Brachytherapy Society to develop the guidelines for use of HDR in management of prostate cancer which involved an extensive literature review and contribution from an expert team. It was observed that in spite of wide variation in doses and fractionation, HDR brachytherapy provides biochemical control rates of 85-100%, 81-100% and 43-93% for low, intermediate and high-risk prostate cancers respectively. Rare severe toxicity i.e. less than 5% Grade 3 was reported by most of the authors. It has been concluded that the clinical outcomes for HDR are excellent with high rates of biochemical control, even for high-risk disease, with low morbidity.

(Brachytherapy, Jan 11, 2012)

Prostate Serum Antigen to Save Lives

According to a study conducted by an European group, the extensive use of Prostate Specific Antigen (PSA) blood test can save around 700 Australian lives annually. The long term study included 162,000 men from eight countries who underwent screening for prostate cancer using PSA blood test. It was found that there was 21 percent fall in prostate cancer deaths after the follow-up of 11 years. The mortality difference between the men screened and those who did not undergo screening was found to be larger corresponding to the longer duration of follow up after the screening began. It was found that about eighty percent of Australian men aged 45 to 74 did not undergo the PSA testing and 3,300 men died annually from the disease in Australia. The statistics suggest that screening all those men would save almost 700 lives per year. The reason behind no improvement in prostate cancer mortality found in a US study may be the period of only seven years which seems not to be long enough for the benefits of screening to become evident.

(www.theaustralian.com, Mar 1, 2012)

Urine-Based Biomarkers for Aggressive Prostate Cancer

Initial results of the Canary Prostate Active Surveillance Study, an 8-institution consortium show that two investigational urine-based biomarkers, PCA3 and T2-ERG, are associated with prostate cancers that are likely to be aggressive and potentially life-threatening among men who take a 'watchful waiting' or active surveillance to manage their disease. The study was conducted by researchers from the Fred Hutchinson Cancer Research Center, Stanford University, USA, and Beth Israel Deaconess Medical Center, Boston, USA. PCA3 is a noncoding RNA and T2-ERG is a fusion of *TMPRSS2* gene and ERG, an oncogene. The two markers correlate well with two indicators of aggressive prostate cancer, tumor volume and Gleason score. The biomarkers were identified in an interim analysis of data from 401 men who preferred active surveillance for their prostate cancer. The odds ratio for a positive biopsy in comparison to a negative biopsy was 1.37 for PCA3 ($P=0.02$) and 1.30 for T2-ERG ($P=0.0006$). The study is still continuing; if confirmed through a longer-term, large-scale study, a biomarker urine test could be developed that would decrease unnecessary treatment, lower the cost and improve the quality of life for some cancer patients.

(CancerNetwork, Feb 6, 2012)

IN FOCUS

RECENT ADVANCES IN MANAGEMENT OF CASTRATION-RESISTANT PROSTATE CANCER

Introduction

Prostate cancer is the most common malignancy, and the second leading cause of cancer mortality among men. Approximately 70% of patients with prostate cancer progress to castration-resistant prostate cancer (CRPC), which has a poor prognosis and is a therapeutic challenge. Strategies developed to counteract androgen-deprivation therapy (ADT) resistance have had only modest clinical benefit. Indeed, before 2010, only docetaxel-based chemotherapy improved overall survival in patients with CRPC compared with mitoxantrone. Improved understanding of the biology underlying CRPC has heralded a new era in chemotherapy and molecular-targeted anticancer drug development.

Chemotherapy in Prostate Cancer

Mitoxantrone: In a Phase III CALGB 9182 study, the combination of type II topoisomerase inhibitor mitoxantrone with prednisone was significantly more efficacious than prednisone alone for palliative symptom management. It gained regulatory approval but prostate cancer was considered to be predominately insensitive

to chemotherapy until results from two key Phase III clinical trials, assessing docetaxel chemotherapy (TAX327 and SWOG9916), were published in 2004.

Docetaxel and Docetaxel Combinations: The TAX327 Phase III clinical trial enrolled 1,006 men with chemotherapy; naive metastatic CRPC were randomly assigned to receive prednisone (5 mg twice daily) with mitoxantrone or docetaxel every 3 weeks. Patients in the 3-weekly docetaxel group had an increased overall survival of 18.9 months with a hazard ratio (HR) for death of 0.76 (95% CI 0.62–0.94; $P = 0.009$). A total of 45% patients had a $\geq 50\%$ decline in their serum PSA levels ($P < 0.001$); 35% had predefined reductions in pain ($P = 0.01$), and 22% had improvements in their quality of life ($P = 0.009$). The updated extended follow-up survival data from this study showed an absolute median overall survival of 19.2 months (95% CI 17.5–21.3 months) in the 3-weekly docetaxel arm versus 16.3 months (95% CI 14.3–17.9 months) in the mitoxantrone arm.

A key challenge in CRPC is the management of patients with disease progression during or following docetaxel-based chemotherapy.

Satraplatin: The SPARC Phase III trial was conducted in patients with metastatic CRPC who had received at least one line of chemotherapy, to evaluate satraplatin, the first orally available platinum compound. A total of 950 patients with CRPC were randomly assigned to receive prednisone (5 mg twice daily) with or without

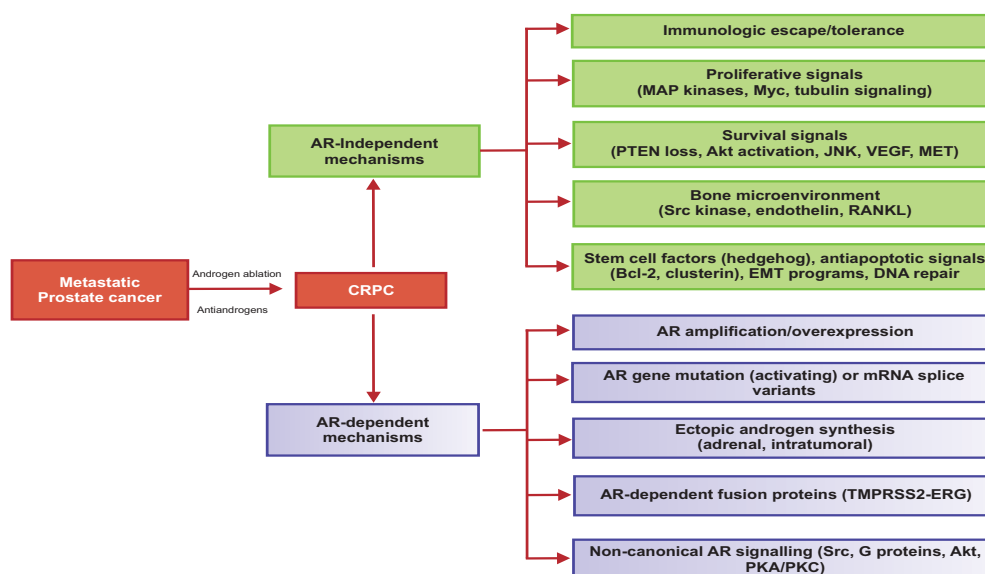


Figure: Mechanisms of Castration Resistance in Prostate Cancer

AR, androgen receptor; CRPC, castration-resistant prostate cancer; EMT, epithelial to mesenchymal transition; JNK, Jun N-terminal kinase; MAP, mitogen activated protein; MEK, MAP kinase kinase; PKA/PKC, protein kinase A/ protein kinase C; PTEN, phosphatase and tensin homolog deleted on chromosome 10; RANKL, receptor activator of nuclear factor- κ B ligand; Src, signal-regulated kinase; VEGF, vascular endothelial growth factor

(Fig Reference: Clinclinal Oncology News, June 2011)

satraplatin (80 mg/m²) for 5 days every 4 weeks. Despite significantly higher PSA declines ($P < 0.001$), pain responses ($P < 0.005$), time-to-pain progression ($P < 0.001$) and median progression-free survival (PFS; $P < 0.001$) in the satraplatin arm, the primary end point of significantly improved overall survival was not achieved (HR = 0.98) and the drug was not approved. Despite this result, satraplatin might have a role in patients with *BRCA1* and/or *BRCA2* mutated CRPC or in those who display a 'BRCAness' phenotype since *BRCA*-mutated tumors are exquisitely sensitive to platinum-based chemotherapies.

Cabazitaxel: Cabazitaxel is a taxane that is as potent as docetaxel in tumor cell lines, and exhibits antitumor activity in preclinical models resistant to paclitaxel and docetaxel. A Phase I clinical study established neutropenia as the dose limiting toxicity and 20 mg/m² as the recommended dose. A higher dose (25 mg/m²) was examined in the Phase II trial of cabazitaxel in patients with taxane resistant metastatic breast cancer who did not experience significant toxicity during the first cycle.

Cabazitaxel was progressed from Phase I directly to a randomized open-label Phase III trial (EFC6193; TROPIC); 755 patients with docetaxel-treated metastatic CRPC were treated with prednisone (5 mg twice daily) and either mitoxantrone (12 mg/m²; $n = 377$) or cabazitaxel (25 mg/m²; $n = 378$). The median overall survival was 15.1 months (95% CI 14.1–16.3) in the cabazitaxel group and 12.7 months (95% CI 11.6–13.7) in the mitoxantrone group. The HR for death of men treated with cabazitaxel compared with those taking mitoxantrone was 0.70 (95% CI 0.59–0.83; $P < 0.0001$). The most common grade 3 or worse toxic effects included neutropenia and diarrhea. Cabazitaxel is the first drug to improve overall survival in patients with metastatic CRPC who had developed disease progression during and after docetaxel-based therapy. As a result of these data, cabazitaxel was recently approved by the FDA as the new standard of care for the second-line treatment of CRPC following failure of docetaxel chemotherapy.

Although the cabazitaxel Phase III trial was a 'success', several criticisms have been made against this study. For example, one is the reasonableness to bypass conducting a Phase II trial with a potentially toxic agent. In addition, despite exclusion of patients who had extensive prior radiotherapy or concurrent serious illness, the treatment-related death rate was 5%, with no data demonstrating improved quality of life. Further studies

evaluating drug safety in this patient population and assessing the quality-of-life benefits imparted by cabazitaxel are warranted.

Other Novel Chemotherapies

Apart from cabazitaxel, other microtubule stabilizers, including third generation taxanes (TPI-287 [Tapestry Pharmaceuticals, CO, USA]) and the epothilones (ixabepilone and patupilone) are currently in Phase II clinical trials in patients with CRPC and are showing promising antitumor activity. It is likely that they will need to be compared head to head with cabazitaxel in a Phase III post-docetaxel trial setting.

Targeting the AR

The development of CRPC is characterized by a rise in prostate specific antigen (PSA) and subsequent progression of disease despite castrate blood levels of testosterone (<50 ng/dl or 1.7 nmol/l). There is a growing body of evidence of the continued dependence of CRPC on androgen receptor (AR) signaling and related underlying mechanisms. Androgens from the adrenal glands account for 10–30% of serum androgens and are an important source of continued AR activation. Importantly, dehydroepiandrosterone (DHEA) and other precursor steroids secreted by the adrenal glands can be converted into potent androgens. Recurrent prostate cancer might be able to synthesize testicular androgens through intracrine production.

Available AR antagonists have agonistic properties in advanced-stage CRPC, either by increased sensitivity and activity caused by AR mutation, or through AR overexpression. They have variable levels of androgenic activity; therefore, they are not frequently used for CRPC treatment.

AR Antagonists in Development

In preclinical studies, the second generation AR antagonist MDV3100 (Medivation, CA, USA) had five-fold to eight-fold increased affinity for the AR compared with bicalutamide, reduced the efficiency of AR nuclear translocation and prevented co-activator recruitment of the ligand–receptor complex. In a multicenter Phase I–II trials, 140 patients with metastatic CRPC received daily oral MDV3100 (30–600 mg). This trial established a maximum-tolerated dose of 240 mg daily. Antitumor activity was observed at all doses, and included PSA responses of $\geq 50\%$ in 56% of patients.

MDV3100 is being assessed in multinational Phase III, randomized double-blind placebo controlled studies

in chemotherapy-naïve patients with CRPC (PREVAIL) and patients with CRPC who have been previously treated with docetaxel-based chemotherapy (AFFIRM). Other novel AR inhibitors currently in early-phase clinical trials include the small molecules ARN-509 (Aragon Pharmaceuticals, CA, USA) and BMS-641988 (Bristol-Myers Squibb, NY, USA).

CYP17 Inhibitors

Abiraterone: Abiraterone acetate is a small-molecule inhibitor of cytochrome P450 (CYP)17.34–37 CYP17, is a key enzyme with dual functions of 17 α -hydroxylase and C17,20-lyase activity, which are necessary for both adrenal and intratumoral *de novo* biosynthesis of androgen hormones. It is highly potent and selective and is 10-30 fold more potent against CYP17 than ketoconazole. A Phase II clinical trial in patients with CRPC in both chemotherapy-naïve and post docetaxel settings reported a PSA response of $\geq 50\%$ in 67% and 51% of patients and a median time- to-PSA progression of 225 days and 169 days, respectively.

A Phase III multinational, multicenter, randomized, double-blind, placebo-controlled study of 1,000 mg of abiraterone plus 5 mg twice daily of prednisone versus placebo plus prednisone was conducted in 1,195 patients with docetaxel-treated CRPC. Abiraterone improved median overall survival compared with the placebo arm (14.8 months versus 10.9 months; $P < 0.001$). Importantly, the survival benefit was similar between patients who had received one or two previous lines of chemotherapy and across all patient subgroups studied, including age, performance status and the presence of visceral disease. All secondary endpoints achieved significance in favor of abiraterone, including time-to-PSA progression ($P < 0.001$), radiological progression-free survival ($P < 0.001$) and confirmed PSA response rate ($P < 0.001$). Adverse events were similar in both arms of treatment. Of note, grade 3 or 4 mineralocorticoid toxic effects were only seen in less than 4% of patients. Based on this trial, abiraterone was approved by the FDA for the treatment of CRPC in the post-docetaxel setting.

A separate Phase III trial of abiraterone plus prednisone in patients with chemotherapy-naïve and ketoconazole-naïve CRPC has completed patient accrual (NCT00887198); abiraterone has the highest chance of having an impact by increasing cure rates in

high-risk disease. However, the potential adverse effects associated with long term administration of prednisone and the castrating effects of abiraterone, especially with regards to potential increased cardiovascular effects and bone health effects of protracted ADT, will need to be considered.

Orteronel: In a Phase I–II trial, 26 patients with CRPC received the selective 17,20-lyase inhibitor orteronel (100–600 mg twice daily) as monotherapy and six patients received orteronel (400 mg twice daily) in combination with prednisone (5 mg twice daily). Drug-related toxic effects included fatigue (including three patients with grade ≥ 3 fatigue at 600 mg) and gastrointestinal symptoms. A randomized, double-blind, Phase III study evaluating orteronel plus prednisone versus placebo plus prednisone in both chemotherapy-naïve patients and post-docetaxel patients with CRPC is ongoing.

TOK-001: TOK-001 (Tokai Pharmaceuticals, MA, USA) is an oral small-molecule inhibitor of AR and CYP17. It is being assessed in a Phase I–II study (ARMOR) and results are expected soon.

Immunotherapy

The most promising immunotherapies are sipuleucel-T and ipilimumab and antibodies to the immune checkpoint programmed death-1 (PD-1) protein, of which only sipuleucel-T has received FDA approval for CRPC.

Alpharadin: Alpharadin (Bayer Schering Pharma, Berlin, Germany) is a radioisotope containing an α -particle emitting nuclide, which was recently assessed in a randomized, placebo controlled Phase III trial (ALSYMPCA) in 922 patients with symptomatic CRPC with bone metastases. The primary end point of the study, overall survival, was significantly increased in the alpharadin arm (two-sided $P = 0.0022$, HR = 0.699); the median overall survival was 14 months for patients in the alpharadin arm and 11.2 months for those receiving placebo.

Conclusion

These are exciting times for the treatment of advanced stage prostate cancer, but much remains to be done, particularly in the introduction of novel treatments in the adjuvant setting where it is envisioned that higher cure rates may be achievable. Overall, we are entering a new era in CRPC management.

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The Armamentarium of Surgical Facilities

Robotic Surgical Suite

Robotic surgical suite has been added to the armamentarium of surgical facilities in the year 2010-11. The da Vinci, state-of-the-art robotic surgical equipment is the first of its kind in an exclusive cancer hospital in India. This Robotics system is being used for radical prostatectomy, cystectomy, nephrectomy and radical hysterectomy etc.



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- Cutting-edge solutions
- Highly qualified professionals
- State-of-the-art equipment
- Evidence-based decisions



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