PROSTATE CANCER SCREENING AND TRUS BIOPSY

JAMIL MERICAN
PROSTATE CANCER SCREENING

• Introduction
  – started over a decade ago
  – significant experience and empirical evidence of effectiveness of modalities such as PSA, DRE and TRUS biopsies
  – the role of early detection as a means of prostate cancer control still remains CONTROVERSIAL
Definitions

• Screening
  – is the search for disease in persons for whom the only basis for suspicion is the expected rate of detectable disease for the population of which the individual is a member
  – the purpose is to detect the disease before it is brought to medical attention by signs or symptoms
– Testing done for individual with symptoms falls into the category of diagnosis.

– If once an individual has a positive screening test, all other further tests are considered diagnostic.

– For a screening intervention to be effective its application must change the course of disease in a favourable direction from that expected to occur in the absence of screening.
Criteria for Screening Program Evaluation

• WHO has identified 10 criteria by which the value of screening in all settings may be evaluated
  – 1. the disease under study should be an important health problem
  – 2. there must be effective treatment for patients suffering from early or localized disease
  – 3. facilities for further diagnosis and treatment must be available
Criteria for Screening Program Evaluation

– 4. there must be an identifiable latent or early symptomatic stage of the disease
– 5. the technique to be used for screening must be effective
– 6. the test must be acceptable to the screened population
– 7. the natural history of the disease, including the development of the latent phase to clinical disease must be sufficiently known
Criteria for Screening Program Evaluation

– 8. there must be a generally accepted strategy enabling determination of patients who should be treated and who should remain untreated
– 9. the expenses of the screening must be acceptable or cost effective
– 10. an effective program must be continuous and not a once and for all kind of project
Measures of Test Performance

- **Sensitivity**
  - the ability of a test to detect cancer whenever it is present

- **Specificity**
  - the accuracy of a test to demonstrate the absence of cancer when it is not present

- a test with low sensitivity will provide false reassurance and waste the resources to detect cancer
Measures of Test Performance

• A test with low specificity may cause alarm when there is no threat and lead to potentially costly and unnecessary further diagnostic evaluation

• Positive predictive value
  – is the likelihood that a result indicative of the presence of cancer will prove correct on further evaluation
Biases in screening

• Lead time bias
  – the interval between the moment a disease can be detected and the moment that disease would have been brought to attention by patient awareness of signs or symptoms
  – therefore if it is not accounted for comparisons of survival rate for screened and unscreened population will be misleading
Biases in screening

• Overdiagnosis
  – the purpose of early detection examination is to find the cancer at an early stage
  – however sometimes it is possible to find some tumours at so early a stage that their biological propensity to progress and cause death is uncertain
  – this might inflate the survival statistics for screening detected cancers
Research Designs for Screening Evaluation

• Descriptive Study
  – uncontrolled studies based on experience of individual physicians, hospitals and registries can yield important information about screening
  – however, descriptive studies do not establish efficacy because of the absence of an appropriate control group
Research Designs for Screening Evaluation

• Case control studies
  – retrospective case control studies can provide additional evidence on screening effectiveness
  – this method proves more cost effective that prospective studies when screening procedure is already in clinical use
Research Designs for Screening Evaluation

• Randomized controlled trial
  – the most rigorous assessment of screening, that measures cancer specific mortality reduction as a primary end point
  – randomization is useful to control the distorting effect of selection
  – although it is the most desirable form, the sample size required, the expenses and long duration for such trials are limitations for conducting it
Recent and Current Population Research

• Several clinical and cohort studies have already documented increased prostate cancer detection yield and earlier stage of disease at diagnosis using modalities like PSA

• Following several decades of gradually increasing death rates, prostate cancer mortality began to decline in the USA
Recent and Current Population Research

- Between 1991 and 1996 there was a clear decline of death rates of an average annual decline of 2.1%
- Olmstead County Minnesota age adjusted, community mortality rates from prostate cancer rose 34/100000 in 1989-1992 and declined 22% to 19.4/100000 in 1993-1997
• Similar trends were observed elsewhere in e.g. Canada
• In Quebec, overall age standardized prostate cancer mortality declined by 23% between 1991 and 1997 and 9.6% in Canada between 1991 and 1996 (Meyer F., Moore L., J.Urol 1999)
• Jacobsen et al conducted a population based case-control study on all men who died of prostate cancer in Olmstead County from 1976 to 1991, they found that men who died from prostate cancer were less likely to have received prostate cancer screening compared to men who did not die
• Quebec trials
  – Labrie el al, identified 46,193 men aged between 45 and 80 who were randomized for invitation to screening
  – screening included measuring PSA using 3ng/ml as upper limit of normal and DRE
  – TRUS was done when only if PSA and or DRE were abnormal
– 8 years follow-up, prostate cancer death rates were 48.7 and 155 per 100,000 man in the years in the screened and unscreened group respectively, suggesting 69% decrease in mortality

– this study had an important impact as a demonstration of community screening

– only 23.1% of men invited to screening were actually screened and this study has been difficult to evaluate as a randomized controlled trial
The European Randomized Study of Screening for Prostate cancer (ERSPC)

- this was a study initiated in 1994 in Antwerp
- the study was to demonstrate the effectiveness of screening to reduce mortality
- identify best screening method
- identify risk groups who will benefit from screening
- to evaluate the quality of life and its cost effectiveness
- 7 countries participated Belgium, Finland, Italy, Portugal, Spain, Sweden and Netherlands
- The age of participants enrolled were between 50-74 years
- consents were obtained from some from certain countries
- most centres applied a 4 year screening interval
- in the Finnish arm, 106 cancers were detected among 399 men biopsied with elevated PSA
- prostate cancer detection rate based on a serum PSA concentration of 4 ng/ml or higher was 2.1%
- 9 out of 10 screen detected prostate cancer were localized and well or mod-diff cancer
• In Rotterdam trials
  – men were screened between 55 - 74, by PSA, DRE and TRUS
  – the trial also evaluated DRE as a stand alone screening test and found detection rate as 2.5% compared to PSA, DRE and TRUS was 4.5%
• The American Cancer National Prostate Cancer Detection Project (ACS-NPCDP)
  – was established in 1987
  – a non random cohort of 2999 men aged between 55-70 were tested annually in ten clinical centres by PSA, DRE and TRUS
  – this study showed that a combined modality approach to prostate cancer detection yield high levels of early detection
  – by using PSA, DRE and TRUS 229 cases were diagnosed in 1709 men
• Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Overview (PLCO)
  – large scale randomized study
  – was to determine whether certain screening tests will reduce the number of deaths from these cancers
  – for prostate cancers, DRE and PSA were evaluated at initial visit and once every year for next 5 years
– Secondary objective included assessment of screening variables including specificity, sensitivity and positive predictive values
– this trial is still ongoing
• TYROL County Trial
  – PSA based screening, considered to be the most effective screening method for men with signs and symptoms of the disease
  – not known how effective it is on asymptomatic men
  – mass screening project was performed in Tyrol County, Austria
– 21,078 volunteers, 8% had elevated PSA and of which 48% had biopsies
– 25% were positive and 135 had radical prostatectomy
– of this 135, 70% were organ confined
– Psa cutoff used was 2.5ng/ml for 45-49 and 3.5ng/ml for 50-59
– concluded that detection rate of clinically significant and organ confined cancers increased with PSA screening
Screening Frequency

• Carter et al from the Baltimore Longitudinal Study of Aging (BLSA) suggested a 2 years PSA testing interval was not likely to miss curable prostate cancer among men with no palpable suspicion of cancer on DRE and a PSA level of less than 2ng/ml
Screening Frequency

- Prostate Cancer Awareness Week by Leewansangtong et al (J.Urol 1998) concluded that borderline PSA of 2.0ng/ml or less, cancer detection rates were 6% or less 3 years later, whereas for men with PSA of 2.1-4.0ng/ml was 17% 3 years later.
Screening Frequency

• The Washington University Screening Project demonstrated that after 4 years of testing 8662 men at 6 months interval the rate of PSA conversion to more than 4.0ng/ml was 4% when base PSA was less than 2.5ng/ml and 48% when base PSA was between 2.5ng/ml to 4.0ng/ml
Age to Begin Screening

- American Cancer Society recommends PSA testing begin at age of 50 and 45 for African-American men
- Ross et al (J.Urol 1999) compared different screening strategies using computer simulation of natural history of prostate cancer progression in a population of men followed from 40 to 80 years old
- He found that using 4.0ng/ml cutoff beginning at 50, a 2 year PSA interval beginning at 40 reduced prostate cancer deaths
- Lowering the PSA cutoff to 3.0ng/ml or 2.5ng/ml did not prevent more prostate cancer deaths but doubled the number of biopsies required to detect a curable cancer
Age To Stop Screening

- While no upper limit has been established over which PSA testing is not recommended, there is a general agreement that men with less than a 10 year life expectancy are unlikely to gain years of life from early detection because of the long natural history of untreated localized prostate cancer.
- Pearson et al (J.Urol 1998) using data from the BLSA had serial PSA measured at age 60, 65 and 70 to the time of diagnosis with cancer, suggested that by the age of 65, men with very low PSA (0.5 < or < 1.0 ng/ml) are not likely to be diagnosed with prostate cancer over the next decade.
• Since early diagnosis of prostate cancer is not likely to extend life when made after 75 years, the target population is below 75
Race Specific

- Black men with newly diagnosed prostate cancer have been shown to have higher PSA than white men after the adjustment for age at diagnosis
Family History

• Early detection and screening will benefit patient with increased risk such as strong family history
• Rodriguez et al computed a relative risk of fatal cancer prostate of 1.6 times for patients with one affected relative and 3.2 for two or more affected relatives
TRUS BIOPSY

• Prostate imaging with endorectal sonography started as early as 1968
• gained popularity only in 1980s
• PSA testing stimulated the need for early detection of prostate cancer
• 3 advances made TRUS preferred approach for biopsy, the high frequency transducer, spring driven biopsy device and sextant biopsy (Hodge et al 1989)
• TRUS Biopsy is indicated in men with life expectancy greater than 10 years who have an abnormal DRE or raised PSA
Instrumentation and Technique

- Images are displayed in two planes, transverse and sagittal.
- Color doppler has created a lot of enthusiasm due to neovascularity seen when increased blood flow in malignancy.
- But increased blood flow also occurred in inflammation and BPH.
Biopsy Instrument

• Spring driven biopsy device
• sample tissue with Tru-Cut type needle, 18gauze
• biopsy needles take 1.5cm core
Patient Preparation

• Consent
• medication e.g. Aspirin, NSAID stopped at least 7-10 days before
• but not absolute contraindication
Antibiotic Prophylaxis

- I/v, I/m or oral
- Shandera et al. 1998, antibiotic use significantly reduced the incidence of infectious complications but no significant difference in a single dose and 3 days use.
- Fluroquinolones are recommended for uncomplicated patients.
Bowel Preparations

• Phosphate enemas
  – effective
  – inexpensive

• enemas reduce the rate of bactereamia
  – 38%-76% when no enemas given
  – 17%-19% when povidine iodine enema given
Anesthesia

• Usually unnecessary for TRUS
• Rodriguez 1998, 20-30% of patients reported significant discomfort but not related to no. of biopsies
• Issa 2000, significant decrease in discomfort with 2% lignocaine jelly
• periprostatic nerve block has been used but results were similar to lignocaine jelly
• nerve block is given at the space between the seminal vesicle and prostatic capsule, visualized on TRUS as hypoechoic area
Complications

- Infection
  - most serious is bacterial sepsis
  - bacteuria ranges from 20-53%
  - bacteraemia 16-73%
  - most infections are E.coli, Kleb, Bact.fragilis and Clost. (Enlund 1997)
• Bleeding
  – most common, usually haematuria
  – at least 50% last for 7 days
  – haematospermia 30%, can last for 1 month
  – amount of bleeding is related to the no. of biopsies
• Urinary obstruction
• Vasovagal reaction
Biopsy Techniques

• Directed biopsy
  – taken from suspicious areas
  – superior to digital guided bx
  – Hodge 1989, reported 53% found cancer in TRUS bx compared to digital bx

• Sextant Biopsy
  – originally described as taken from midlobe at apex, midgland and base bilaterally
  – false negative of 15-34%
  – cancer > 2cm² or PZ the sensitivity is 83.3%
  – TZ 33%
• Anterior Biopsies
  – TZ cancers are generally non palpable and diagnosed on TURP
  – this technique is used to sample TZ for pts diagnosed to have cancer from TURP
  – most studies show that TZ biopsies are useful for pts undergoing repeat bx after prior negative sextant bx
  – TZ bx should be taken near the midline as close as possible to the urethra
• Lateral biopsies
  – pathology specimens of radical prostatectomy specimen suggest that small prostate cancers occur at the posterolat portion of prostate
  – this area is referred to as the anterior horn
  – Naughton 2000, found no added benefit of lat bx even when startified by race, PSA, prostate vol. But highest rate of positivity in patients with palpable nodule
• Extended field Biopsy
  – varies methods have been described
  – this method involves taking combination of sextant bx, lateral, anterior and midline prostatic sampling
  – cancer detection was higher compared to sextant (Babaian 2000)

• Repeat Biopsies
  – recommended for pts where initial biopsies were negative but where suspicion was high e.g high PSA, African American men, family history and PIN changes on initial biopsies
  – should include sextant plus TZ and or lateral biopsies in an extended field biopsies