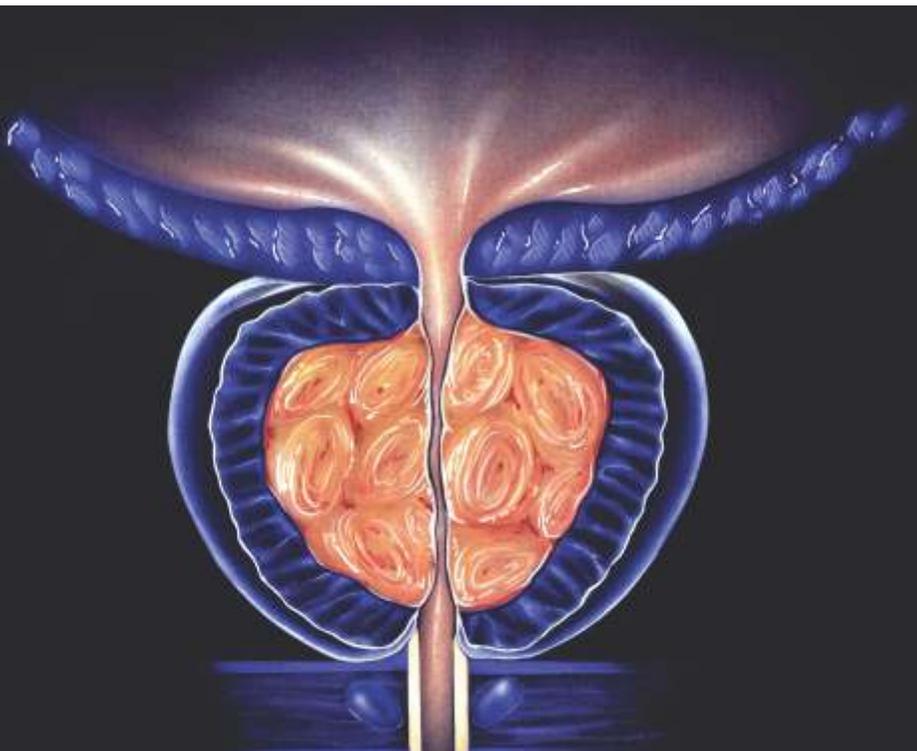# CANCER NEWS

PROSTATE CANCER

Highlights:

Screening for Prostate Cancer

Focal Therapy in Prostate Cancer

Diagnosis of Early and Clinically Significant Prostate Cancer

Rajiv Gandhi Cancer Institute and Research Centre

A Unit of Indraprastha Cancer Society
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EDITORIAL

Prostate cancer (PCa) is a disease which only affects men. As the second most common male cancer in the world, PCa affects roughly 1.1 million people and kills more than 300,000 people each year, which represents about 4% of all cancer deaths worldwide. Prostate is the second leading site of cancer among males in large Indian cities like Delhi, Kolkata, Pune, Thiruvananthapuram and third leading site of cancer in cities like Bangalore and Mumbai. It is among the top ten leading sites of cancers in the rest of the population as per cancer registries of India.

The risk factors include older age, ethnicity of African-American and Caribbean men of African ancestry, family history of PCa, nationality, of North America, Europe, the Caribbean, Australia; genetic factors and diet etc. The symptoms of PCa include urinary problems, erectile dysfunction, back pain and weight loss etc. The tests that examine prostate and blood to detect PCa include digital rectal examination, prostate-specific antigen (PSA), transrectal ultrasound, transrectal magnetic resonance imaging, biopsy, etc.

For men diagnosed with very early-stage PCa, treatment may not be necessary immediately. Some men may never need treatment. Instead, sometimes active surveillance is recommended. In active surveillance, regular follow-up blood tests, rectal exams and possibly biopsies may be performed to monitor the progression of cancer. However, if cancer is progressing, PCa treatment, such as surgery or radiation may be considered.

Surgery is a common choice of treatment if the PCa is not thought to have spread outside the prostate gland. Hormone therapy is most often used for late-stage, high-grade tumors or in patients with cancer that has spread outside the prostate. Chemotherapy may be a treatment option for metastatic PCa or for cancers that don't respond to hormone therapy. All treatment options carry the risk of significant side effects, including erectile dysfunction and urinary incontinence. However, newer treatments, such as HIFU or cryotherapy aim to reduce these side effects. But the long-term effectiveness of these treatments is not yet known. Additionally, PCa vaccines are designed to help treat and not prevent. An advantage of these types of treatments is that they seem to have very limited side effects. An example of such vaccines is sipuleucel-T (Provenge), which has received FDA approval.

In its early stages, PCa is highly treatable with 5-year survival rates close to 100%. However, the survival rate falls to less than 30% in metastatic PCa, highlighting a significant need for more effective treatment of advanced stage disease.

PCa screening is controversial as PSA testing increases cancer detection but does not decrease mortality. The United States Preventive Services Task Force recommends against screening using the PSA test, due to the risk of overdiagnosis and overtreatment, as most cancer diagnosed would remain asymptomatic.

The present issue of the Cancer News highlights the newer advances in the field of 'Prostate Cancer' and features the regular articles, such as Special Feature, Guest Article, Perspective, Outlook and In Focus. We are grateful to Dr Ganesh Bakshi, Professor and Convenor, Disease Management Group, Tata Memorial Hospital, Mumbai for contributing the Special Feature and Dr Raghunath S K, Director Robotic Surgery, Uro-oncologist, HCG-Bangalore Institute of Oncology, Bangalore for Guest Article.

Guest Editor: Dr S K Rawal

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SPECIAL FEATURE

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SCREENING FOR PROSTATE CANCER- RECENT UPDATES

Background

Population or mass screening for cancer is systematic examination of asymptomatic or at risk individuals or population and is usually initiated by health authorities with intention to reduce the mortality from the disease.[1] Screening is practiced in breast, cervical, colorectal and lung cancer.[2]

The variations of prostate cancer (PCa) incidence look to be directly related to the use of prostate specific antigen (PSA).[3] Asian incidence was always found to be less, as in a study of Japanese in Japan and those settled in the US, the predominant cause being the diet and the Asian races [4]. Due to refinements in treatment, prostate cancer specific mortality (PCSM) has started decreasing in most Western countries. The overall change in the scenario depended on the contemporary health policies. Till now, there is no uniform acceptability of prostate cancer screening (PCS) and doctors have their own policies. In Asia, there is no definite population screening policy. PCS trials have been done in Japan, China, Nepal, South Korea, Saudi Arabia and Vietnam with no definite conclusion on PCSM reduction.[5]

Screening in PCa is a topic of hot debate. For any screening program, the benefits have to be weighed against the harmful effects of early detection and finally the costs. The main harms of PCS are overdiagnosis and overtreatment, specially of indolent cancers. Men are exposed to invasive biopsies with potential side effects. Definitive therapies like surgery which may lead to incontinence and impotence or radiation which may cause bowel problems.[6] Before the randomized studies, the policy on PCS had no guiding literature. From 1993, major PCS studies were conducted. The long journey of various participants in these studies has given us a list of do's and don'ts, as regards PCS policy. We discuss in this article the studies, results and the updates on PCS.

Text

The major studies include the prostate, lung, colorectal, ovarian screening trial (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC). PLCO was a multicenter US based study from 1993 to 2001, which randomly assigned 76,693 men in age group 55-74 years in screening and control arms. Screening was done by annual PSA for 6 years with DRE for 4 years. In 2009, when the first results were published, PLCO trial showed a 22% increased rate of PCa diagnosis. Study showed no reduction in PCSM in first 7 years in both arms. The various explanations for this included a PSA cut-off of >4ng/ml, PSA contamination in the control group, 44% participants in each group had a baseline PSA, thereby affecting the PCa diagnosis, change and improvisation in PCa therapy leading to increased survival, and the follow-up interval, which was hypothesized to be longer.[7]

ERSPC was a multicenter study which recruited 182,160 participants between the ages of 55-69 years. The study published in 2009 showed a relative risk reduction in PCSM by 20%.[8] The average screening interval was 4 years. To prevent one death, 48 additional men needed to be treated and 1068 needed to be screened. At 9 years of followup, the number needed to screen was similar to the mammographic screening in cancer breast and fecal occult blood screening test in colorectal cancers. The other age groups did not show conclusive results and the data appeared preliminary. The rates of overdiagnosis and overtreatment was almost reached 50% and these were vastly more common than those in breast, cervical, and colorectal cancer.

Later an update of Cochrane review meta-analysis was published in 2011. It included 5 largest studies – ERSPC, PLCO, Norrkoping, Quebec and Stockholm. As per the study quality, ERSPC and PLCO had a low bias whereas the other three had a high bias, mainly due to lack of concealment of allocation. 341,351 men were randomized in all with the same primary objective –PCSM. Secondary objectives were all-cause mortality (ACM), PCa diagnosis, stage at diagnosis and treatment follow up. PCSM reduction was not found statistically significant. ERSPC had already shown a PCSM risk reduction in a core subgroup of age 55 - 69 years. Furthermore, in this meta analysis, no significant PCSM was seen when the screening was considered from any specific age – 45 years, 50 years or 55 years. ACM from 2 ERSPC centers and Stockholm study showed no difference in any arms. Meta analysis showed a 35% rate of overdiagnosis of PCa. It concluded with negative routine screening. Those men who want to get screened should be offered it after an informed counseling session about the pros and cons. Also, it seemed that for those with a life expectancy < 10-15 years, the benefit is doubtful.[9]

Next Cochrane update was published in 2013, and it showed that only 2 of 7 trials from ERSPC contributed in major to achieve the PCSM relative risk reduction to 21%. It concluded that even though subgroup of years 55-69 showed benefit, the overall benefit was very small and that too would take years to sink in, with a high rate of overdiagnosis. Also, in the PLCO, only 4% were non-Hispanic black men, in whom PCa incidence is very high, thereby casting doubts on the actual benefits of screening in this population. In ERSPC study, there is no data on nonwhites and hence it was considered that non-whites were less.[10]

Out of the five main studies, ERSPC with its constituent trials managed to give the best results. However, wide variations were observed within the ERSPC centers. The reasons probably being the difference in screening protocol - PSA cut-off value, number of screenings and participation. Although Sweden and Finland had almost same population characteristics and PCSM rate, the impact was best in Sweden and smallest in Finland. Also, it seemed that the mortality reduction came with an obvious higher rate of overdiagnosis, but different centers fared differently.[11] It appeared that interventions to reduce overdiagnosis and how to target the specific populations at high risk and those who will benefit, need to be devised. The rising importance of multiparametric MRI to detect clinically significant PCa would be one of the solutions to leave out the indolent cancers.[12] Also, the discovery and validation of other novel gene based prognostic markers tests would also help in the identification of those who need to be treated. New risk stratification strategies would allow us to target at the higher risk PCa population, and then plan screening policy in such groups.

The Goteborg screening trial, initially designed independently, has later contributed to the Swedish arm of ERSPC. It was truly population based as men randomized were from the population register. 200,00 men were randomized and PSA levels were recorded biennially till the age of 70 years. The PSA threshold was 3.4 initially but in 1999 revised to 2.9 and in 2005 to 2.5 ng/Ml as per other centers in ERSPC. PCa was detected in 1138/9592 in the screening group and 718/9952 in the control arm. The advanced PCa was lower in screening group – 46 versus 87 in the control, p= 0.0003.It showed an absolute risk reduction in PCSM of 40%. Also, the screen detected cancers were of lower stage and grade. And hence, screening truly caused a stage migration. The benefits are attributed to a low PSA threshold, younger age of participants and a 2-year screening interval. This study had superb results, to prevent 1 death from PCa, 293 men needed to be screened [NNS] and 12 needed to be treated [NNT]. The NNT is quite low in comparison to the ERSPC publication. It seems that NNT might depend on the follow-up as also on the age subgroup of the population.[13] Goteborg late results also showed that starting screening at early age of 50 years did prepone PCa diagnosis but not caused overdiagnosis. And the chance of PCa diagnosis was higher near the age of termination of screening.[14] As the patients in Sweden have an average life of 80 years with PCa, it seemed that some men with less comorbidities would do well if screening continued till 74 years. The benefit of screening has been put to a modest 9 years. In general, for other men, it depends on the overall health, baseline PSA and life expectancy as to when to terminate screening.

Coming back to ERSPC after 13 years of follow-up, men were screened at an average of 2.3 times. To prevent one death, the NNS and NNT were 781 and 27 at 13 years, 979 and 35 at 11 years and 1410 and 48 at 9 years, giving a 21% reduction in PCSM in favor of screening. French data was included for the first time. Finland, one of the biggest arm in ERSP, had no great difference in PCSM at 13 years. Overdiagnosis was calculated at 41%.[15]

Yet, it looks that population based screening is not recommended. Any man seeking such test should be offered extensive and balanced information on the same and then proceed. Post publication of the 13 years of ERSPC study, US Preventive Services Task Force (USPSTF) has put forth a "D" recommendation against any screening of men" 70 years. A new draft guideline "C", says men of age 55-69 years be informed about the benefits and harms of screening, and offered PSA testing if they chose it.[16]

Future in Asia

We need to take note of the screening outcomes from western studies with mainly Caucasian participants and apply it to our regional population with respect to age at risk, comorbidities and life expectancy. The use of risk calculators to find men at high risk and in them, the use of mpMRI would also work towards reducing over diagnosis and morbidity.

Conclusion

Recent data analyses on screening have shown us that screening is a double edged sword. In the true sense, it helps us detect more early cancers and prevent cancer related mortality but we may still end up with a debilitating over treatment. In the Indian context, we need a restrained screening policy. One thing for sure, a more liberal screening in India will surely help the stage migration of cancer prostate seen in the Indian subcontinent but we don't yet know, if it will reduce the PCSM.

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(Dr Ganesh Bakshi, Professor and Convenor, Disease Management Group; Dr Mahendra Pal, Assistant Professor Uro Oncology, Tata Memorial Hospital, Mumbai)

RESEARCH & DEVELOPMENT

Genetic Linkage of Aggressive Prostate Cancer

The identification of the Kallikrein 6 gene region may change the course of prostate cancer care through a blood test developed by the Lunenfeld-Tanenbaum Research Institute, Toronto, Canada. To identify the relevant mutations, the scientists analyzed the blood samples of 1,858 men from three independent cohorts in Europe and North America. The Kallikrein 6 variants also independently predicted treatment failure after surgery or radiation for prostate cancer in an independent cohort of 130 men from the International Cancer Genome Consortium. Up until now, no single test could predict the severity of the cancer type, the current PSA test (Kallikrein 3), which is located near Kallikrein 6, only identifies the risk of prostate cancer, not the severity. These findings are important because it is well established that most men will die with prostate cancer, and not from the disease due to the unexpected high prevalence of indolent prostate cancer in men. Hence, diagnosing the aggressive form of the disease is an important unmet need.

(Science Daily, March 16, 2017)

New Blood Test Discovered

A study conducted by Moffitt Cancer Center, Florida, USA, researchers found that a newly discovered epigenetic mechanism may lead to the development of castration-resistant prostate cancer. The research team also identified a novel drug that targets this epigenetic mechanism and may be able to combat the deadly form of the disease. An extensive set of experiments in prostate tumor cells and mice was performed. A protein, called ACK1, also known as TNK2, activates a pathway which causes the DNA-bound proteins called histones to undergo epigenetic modification. This modification was specifically accomplished by androgen receptor protein with the help of ACK1 and resulted in high activity of the androgen receptor even when prostate cancer cells had been treated with anti-androgen therapy. Following this discovery, the researchers developed a novel drug called (R)-9bMS that targets ACK1. This discovery is highly relevant because almost two-thirds of castration-resistant prostate cancer patients do not respond to enzalutamide.

(Cancer Cell, June 2017)

FOCAL THERAPY IN PROSTATE CANCER, WHERE ARE WE NOW?

Background

Due to widespread serum PSA testing, access to medical insurance and availability of advanced imaging, more men are being recently diagnosed of low risk prostate cancer (Pca). Focal therapy (FT) is emerging as an alternative tool in this subset of patients. The main purpose of FT is to ablate tumors selectively and limiting toxicity by sparing neurovascular bundles, urethral sphincter and urethra.

Some clinicians argue that focal therapy is an alternative to active surveillance for men with low-risk disease, while others claim that FT should be an alternative to radical therapy (radical prostatectomy / radiotherapy) for those men likely to benefit from definitive treatment.

The prerequisites for successful FT are to accurately identify, localize and completely ablate the cancer within the prostate. There are a number of ablative procedures that could potentially offer FT: cryotherapy, high intensity focussed ultrasound (HIFU), radiofrequency ablation, photodynamic therapy, photothermal therapy, stereotactic radiotherapy and irreversible electroporation.

Focal therapy (FT) in prostate cancer (PCa) is based on the concept of treating an index lesion,[1] which is generally defined as the largest-volume lesion with the highest grade. FT offers men the opportunity to achieve oncological control while preserving sexual and urinary function. Indeed, men may be willing to accept higher rates of genitourinary functional preservation with lower rates of survival.[2] Tissue / organ preserving approaches target the cancer and not the entire organ whenever possible to do so and thus reduce damage to collateral tissues. To balance the unfavourable risk-benefit ratio of current standard treatments, new approaches and novel technologies are being explored.

FT has been seen by many, predominantly in the United States, as an alternative to active surveillance, whereas others, predominantly in Europe, have argued that FT should also be regarded as an alternative to radical therapies.[3] The outcomes of cryotherapy and high intensity focussed ultrasound (HIFU) are established, but other options, such as radiofrequency ablation, photodynamic therapy, photothermal therapy, stereotactic radiotherapy and irreversible electroporation, are still in the early phases of evaluation.

How to Select Patients for FT?

Delphi consensus project 2017 suggested FT can be recommended in D'Amico low-/intermediate-risk cancer, including Gleason 4+3. Gleason 3+4 cancer, where localized, discrete and of favourable size represents the ideal case for FT. Tumor foci <1.5 ml on mpMRI or <20% of the prostate are suitable for FT, or up to 3 ml or 25% if localized to one hemi-gland.[4]

Fifteen experts in FT from USA and Europe followed a modified two-stage RAND/University of California, Los Angeles (UCLA) Appropriateness Methodology process to formulate expert opinion in June 2013 at the Royal Society of Medicine, London, and were supported by the Wellcome Trust and the UK Department of Health.[5] The following selection criteria were finalised:

- Prostate volume should not be a primary determinant of eligibility for FT.

- Age should not be a primary determinant of FT, although the panel was uncertain about whether FT should be recommended for patients <40 yr or >80 yr.

- Confirmatory tissue diagnosis of cancer should be available prior to performing FT.

- For patients who have not had a multiparametric MRI (mpMRI) because of lack of availability or physician preference, it was agreed that only a full transperineal template mapping biopsy was sufficient to perform FT.

- FT can be applied in patients who have already undergone one FT and in patients who have had previous whole-gland treatment.

Will TRUS Suffice to Deliver Focal Therapy?

FT requires accurate localization of disease to drive precision ablation. Several studies have reported on the limitations of transrectal ultrasonography (TRUS) biopsy that hinder its ability to guide FT. TRUS biopsy may miss up to 30% of clinically significant PCa. 30% of cancers reside in anterior regions of the prostate which is frequently overlooked by TRUS biopsy.[6]

Advances in ultrasound imaging have been explored based on the increased vascularity or changes in blood flow in PCa. Contrast-enhanced TRUS involves detecting the difference in acoustic impedance between the contrast agent and adjacent tissue.[7] Elastography demonstrates the higher cell and vessel density in prostate cancer based on increased stiffness in comparison to the surrounding normal tissue.[8]

Prostate Histo Scanning works by extracting and quantifying statistical features from back-scattered ultrasound data to detect specific changes in tissue morphology and therefore distinguish between benign and cancerous tissue.[9]

Recent innovations in mpMRI are also a further attempt to accurately localize PCa extent without the need for invasive procedures and associated morbidity. Delphi consensus project 2017 suggests that mpMRI is a standard imaging tool for patient selection for FT. In the presence of an mpMRI-suspicious lesion, histological confirmation is necessary prior to FT.[4]

Several studies have reported on MRI-Ultrasound fusion, which involves combining a prebiopsy magnetic resonance image with a live ultrasound image at the time of biopsy to guide more accurate biopsies.

Cryotherapy

Cryotherapy exerts its effects via a number of pathways[10]:

- Direct cytolysis through extracellular and intracellular ice crystal formation

- Intracellular dehydration and pH changes

- Ischemic necrosis via vascular injury

- Cryoactivation of antitumor immune responses

- Induction of apoptosis

- Endothelial damage leading to platelet aggregation and microthrombosis

- Injury that occurs during warming as a result of osmotic cellular swelling and vascular hyperpermeability

Currently, third and fourth generation cryosurgery devices are mainly used. Freezing of the prostate to -40°C is ensured by the placement of 12-15 x 17 gauge cryoneedles under TRUS guidance, placement of thermosensors at the level of the external urethral sphincter and bladder neck, and insertion of a urethral warmer. Two freeze-thaw cycles are done.

The largest published experience and outcomes with focal cryotherapy comes from the Cryo On-Line Data (COLD) registry. In its latest update of 1160 patients that had been treated with focal cryoablation, the biochemical recurrence-free rate (ASTRO definition) at 3 years was 75.7%. Prostate biopsy was performed in 14.1%, and positive in 26.3% of these patients, which comprised only 3.7% (43/1160) of all treated patients.[11]

High-Intensity Focused Ultrasound (HIFU)

The goal of HIFU is to heat malignant tissues to above 65°C so that it is destroyed by coagulative necrosis. The two predominant mechanisms of tissue damage are the conversion of mechanical energy into heat, and inertial cavitation. HIFU is performed under general or spinal anaesthesia, with the patient lying in the lateral position.

In the past, some groups systematically performed transurethral resection of the prostate (TURP), considering the risk of urinary retention to be high; but when HIFU is delivered in a focal manner, this risk is low and TURP should not be part of the standard procedure anymore.10 Certain groups, however, recommend TURP following HIFU as a part of necrosectomy which reduces the probability of infection and probability of prostatic urethral stenosis in the post-operative period.

HIFU uses frequencies of 0.8 to 3.5/ MHz. Prostatic tissue calcification leads to reverberation and shielding of the targeted area from parts of the HIFU pulse, leading to inadequate heating of the tissue. Hence further advancements are being carried out.

The majority of published results using HIFU have investigated its efficacy as a whole-gland treatment, not many studies have used HIFU as focal therapy.[12]

Photodynamic Therapy (PDT)

PDT involves activation of a photosensitizer (PS) by appropriate wavelength of light, generating transient levels of reactive oxygen species (ROS). PDT involves three main components: a photosensitizer, light, and tissue oxygen. Several photosensitizers that have been studied include hematoporphyrin derivatives (Photofrin), aminolevulinic acid (5-ALA), verteporfin (visudyne), chlorophyll derivatives (pheophorbide a) and more.[13] Since the first use of PDT for PCa in a clinical setting in 1990, several advances in photosensitizer design and light delivery have been achieved. Heterogeneity of response, tissue light penetration and tissue oxygenation are current limitations, which can be overcome with further studies.

Focal Photothermal Therapy

Photothermal therapy uses laser technology to increase the temperature directly in the treatment region. No photosensitizing agent or oxygen tissue supply is needed. The therapy is delivered through a transperineal approach under general anesthesia or sedation.

Focal Electroporation

Irreversible electroporation uses low-energy direct current to induce nanopores in the cellular membrane leading to cell death. Advantages are tissue specificity and quick procedure (5 minutes). The electrode needles are placed at the boundaries of the lesion to preserve the surrounding structures.

Table 1: Summary of Available Outcomes of Focal Therapy in Published Literature[18]

Study	Patients	Treatment	Median Follow-up (months)	Potency	Continence	Positive biopsy, total gland	Positive biopsy, treated zone
Lambert et al[14]	25	Cryotherapy	28	71%	100%	12%	4%
Bahn et al[15]	73	Cryotherapy	44	86%	100%	15%	1%
Ahmed et al[16]	20	HIFU	12	100%	95%	11%	NA
El Fegon et al[17]	12	HIFU	120	NA	100%	9%	NA

Outcomes

Residual Cancer: When using FT to treat localized PCa, there is potential for cancer to remain within the intended treatment zone. The expert panel[5] agreed that cancer in the treatment zone of Gleason grade 3 + 3 with a cancer core length d3 mm is clinically acceptable, but only if there is a decrease from the original cancer burden. Remaining lesions of Gleason grade 3 + 4 or 4 + 3 are never clinically acceptable, regardless of cancer core length.

Follow-Up After FT: There are no standardized criteria to define tumour persistence or progression and no standardized tools or follow-up schedules to monitor patients after focal therapy. The Delphi consensus project[19] 2015 suggested follow-up of 5 years and following are the modalities: mpMRI, biopsies, and assessment of erectile function, quality of life, urinary symptoms and incontinence. A systematic 12-core TRUS biopsy combined with 4-6 targeted biopsy cores of the treated area and any suspicious lesion(s) should be performed after 1 year, and thereafter only when there is suspicion on imaging. The ideal way to perform targeted biopsies is to use TRUS-MRI fusion technology.

PSA should be performed for research purposes, in the first 2 years, every 3 months, and after 2 years, once in 6 months. mpMRI is currently the optimal imaging modality for follow-up after focal therapy. It is widely available and cost effective. MR-PSMA PET Fusion scans are superior to mpMRI and will eventually replace the latter with wider availability. Imaging should be performed at 6 months and at 1 year following treatment; after the first year post-treatment, it should be performed every year until 5 years following treatment. Any doubtful areas on mpMRI should be confirmed with PSMA PET Scan and in presence of doubtful disease recurrence, guided TRUS biopsies taken by standard techniques.

Retreatment: Biochemical relapse was defined as a PSA nadir + 1.2 ng/mL (Stuttgart definition). The expert panel[5] agreed that retreatment rates of $\leq$ 20% with focal therapy were clinically acceptable.

How Risky Focal Therapy is?

The side effect profile of focal therapies has consistently improved with time given the better understanding of the technology and anticipation of set complications. As with any technology, understanding the risks has facilitated relevant changes in delivery of therapy to improve outcomes and to minimize side effects. A recent review reported a 2.6% risk of urinary retention, a 2.3% risk of urinary infections, and 0.4% risk of urethral strictures.[20] Regarding functional outcomes, it is generally assumed that urinary continence and potency are preserved by FT. Long-term effects on sexual function remain undetermined. Similarly, long-term effects of FT on men with lower urinary tract symptoms (LUTS) are unknown. This is important given the high prevalence of LUTS in elderly patients diagnosed with PCa.[21]

How Much Does it Burn Your Pocket (Cost-Effectiveness)?

This remains an unanswered territory. There are no data analyzing the costs of treatment and treatment-related follow-up. We should not underestimate the potential costs associated with FT as these include initial mpMRI, template prostate mapping biopsy, and repeat mpMRI for treatment planning, conduct, and monitoring. The time has come to acknowledge that not all concepts and principles of organ preservation, common to several malignancies, can be translated to PCa.[21]

How Good or Feasible is Salvage - RARP After Focal Therapy?

Igor Nunes-Silva et al assessed the impact of FT on perioperative, oncologic, and functional outcomes in men who underwent salvage robotic-assisted radical prostatectomy (S-RARP) compared to primary RARP (P-RARP). They concluded that S-RARP following FT failure is feasible, with acceptable complication rates. However, patients assigned to primary FT should be advised about a poorer prognosis in terms of oncological control and lower erectile recovery rates in case of a future salvage surgery. Furthermore, S-RARP presented significantly increased risk of BCR (HR 4.8, 95% CI 1.67-13.76, p=0.004).[22]

Focal Therapy a "Lesser Evil" or "Attractive Illusion "or "Alternative Less Morbid Solution"?

Only time has to answer this question.

Giannarin G et al[21] questioned "Will Focal Therapy Remain Only an Attractive Illusion for the Primary Treatment of Prostate Cancer." He re-emphasized that it is time to realise that not all concepts and principles of organ preservation, common to several malignancies, can be translated to PCa. Ignoring this simple fact may lead to inadequate management of this highly heterogeneous disease entity. Tsivian M et al[18] called FT a "lesser evil" in low risk PCa as the contemporary practice of over-treatment of low-risk PCa is well documented and most men undergo whole gland treatment.

Conclusion

Despite a dramatically increasing interest among clinicians and investigators, focal therapy is still in its infancy and should be regarded as an experimental approach in the present context. Various modalities of FT are showing promising short-term results with acceptable failure and complication rates. As long-term oncological data for focal therapies are lacking, formal recommendations for its use cannot be made at present and FT should ideally be attempted in a clinical trial setting until availability of mature data (Grade A Recommendation).

There is level 3 evidence to conclude that focal therapy of any sort appears promising but remains investigational, with uncertainties surrounding outcome definitions, identification of early failures, follow-up and re-treatment criteria.

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Dr Pramod Krishnappa, Registrar, Dept of Urology, NU Hospitals; Dr Srivatsa N, Consultant; Dr Nagaraj H, Fellow; Dr Raghunath SK, Director, Department of Urooncology and Robotic Surgery, HCG, Bangalore.

PERSPECTIVE

CAN WE IMPROVE URINARY CONTINENCE AFTER ROBOT ASSISTED LAPAROSCOPIC PROSTATECTOMY?

The preservation of urinary continence after radical prostatectomy has been garnering much interest and attention given that it represents one of the most feared complications for men, potentially even more than erectile dysfunction. Thus, postoperative urinary incontinence has a relevant negative effect on the satisfaction and health-related quality of life of patients who undergo radical prostatectomy for prostate cancer.[1-3] The prevalence of urinary incontinence after RALP ranges from 4% to 31%.[4] In the era of robotic surgery, improved three-dimensional imaging and the instrument's endo-wrist capability of movement has led urologists to attempt different techniques to improve surgical outcomes of robot-assisted laparoscopic radical prostatectomy (RALP).[5]

Not only surgical technique and surgeon's skill, but also patient characteristics can affect continence status after RALP. These include increasing age, prostate volume, BMI and preoperative LUTS. Increasing age is an important predictor of incontinence because atrophy of the rhabdosphincter and neural pathway degeneration would occur with increasing age. Studies have shown that continence rates were significantly lower in older men (70 years of age) at 6 months after surgery, although rates returned to levels equivalent to those in younger men (70 years of age) within 12 months after surgery.[5] BMI is associated with poor post-prostatectomy continence outcome. Ahlering et al reported that at 6 months followup, just 47% of obese patients (BMI³ 30) versus 91.4% of non-obese patients had achieved pad-free urinary continence (P<0.001).[6] Wiltz et al showed that urinary continence outcomes were significantly lower for obese men at both 12 and 24 months.[7] Prostate volume is also an important factor for post - prostatectomy incontinence. Boczko et al reported that the 6-month continence rate in patients with a prostate <75 g was 97% versus 84% in patients with larger prostates (P<0.05).[8] Link et al reported that increasing prostate size was associated with more postoperative urinary leakage, but overall continence recovery was not affected.[9] Although different values were used in the literature to define a large prostate, a cut-off value between 70 and 80 cm3 could be correlated with a significant risk of urinary incontinence after RALP.[9,10] Preoperative LUTS is one of the most critical factors for incontinence after RALP. Rodriguez et al reported that IPSS and bother scores are associated with occasional urinary leak after pad-free status has been achieved after RALP.[11] Lee et al found that increased LUTS severity are associated with decreased odds of achieving continence 6 weeks after RALP.[12]

Rocco et al described the range of continence after RALP as being from 2% to 87%.[13] One of the reasons for these differences among reports appears to be a lack of homogeneity in the definition of continence, and differences in the methods used to evaluate it among the reports. The definition of continence after RALP in most reports is a "pad-free" status. However, there are discrepancies in the perception of urinary incontinence between doctor and patient.[13,14] Lee et al investigated the differences in perception of post RALP urinary incontinence acquired through doctor's interviews about the number of pads used and patient-reported questionnaires (ICIQ). They reported that physicians reported that 51.5% had obtained complete continence, whereas just 14.7% of patients had never leaked during the previous 4 weeks according to the analysis of the questionnaires, indicating that there are discrepancies in the perception of urinary incontinence between doctor and patient after RALP.[14] Therefore, use of only "the number of pads used" is not a good measure to determine the status of complete urinary continence. Various measures have been used for evaluation of urinary incontinence, ranging from urodynamic study to pad tests and self-reporting.[15] Questionnaires including IPSS, QOL index, OABSS, OAB, ICIQ-SF and the EPIC urinary domain are useful tools to gauge the patients' perception, because they enable us to obtain information about voiding and storage status, kinds of incontinence, such as urge and stress incontinence, and QOL status. Furthermore, the pad test is viewed as a credible, non - invasive, effective test for quantifying urine loss, and is commonly used in research as well as clinical practice.[15] Currently, a combination of both self-administered questionnaires and objective assessment might be accurate measures to assess postoperative continence and QOL. Although many intraoperative technical modifications to prevent postoperative urinary incontinence have been reported, the establishment of an accurate measure to assess postoperative continence and QOL, as well as validation of the usefulness of these modifications by prospective, randomized and controlled studies carried out at multiple centres are required.

More controversial is the impact of surgeon experience and learning curve on the prevalence of urinary incontinence after RALP. Two prospective studies showed a significant increase of the continence rate after 500 cases.[16,17] Conversely, excellent results were also reported in several clinical series, including <500 cases.[18-22]

The basic concept of the intraoperative technique to improve early return of urinary continence after RALP is to maintain normal anatomical and functional structures in the pelvis as much as possible. The anatomical structure to maintain continence includes two systems: a sphincteric system and a supportive system.[23,24] The action of the urethral sphincteric mechanisms consists of an inner smooth muscle layer (longitudinal and circular smooth muscle) and a striated urogenital sphincter muscle (rhabdosphincter), which contribute to the maintenance of urethral closure pressure above the bladder pressure. These layers are intermingled and cooperate to maintain sphincteric activity.[25]

A supportive hammock under the urethra and bladder neck provides a firm backstop against which the urethra is compressed during increases in abdominal pressure to maintain urethral closure pressures above the rapidly increasing bladder pressure.[23,24,26] Any damage to this mechanism will result in urinary incontinence. The major components of this supporting system in males include Denonvilliers' fascia, puboprostatic ligament, endopelvic fascia, levator ani muscle and arcus tendineus fascia pelvis. These components might not play a significant role in determining continence in healthy males, because the prostate itself can prevent stress urinary incontinence. However, as the prostate is removed by radical prostatectomy, these components might be impaired. Therefore, preservation, reconstruction and reinforcement of these components can recreate a new supporting system and ensure urethrovesical pressure dynamics, and thus improve recovery of urinary continence after radical prostatectomy.

Preservation of anatomical structure in the pelvis includes bladder neck preservation, nerve preservation (nerve fibers from the pelvic nerve, intrapelvic branch and a perineal branch of the pudendal nerve), preservation of the puboprostatic ligament, pubovesical complex and preservation of urethral length.Reconstruction of the supporting system in the pelvis can be done by various techniques which include posterior reconstruction of the rhabdosphincter, anterior retropubic suspension, reattachment of the arcus tendinous to the bladder neck and total reconstruction of the vesicourethral junction. In addition to preservation and reconstruction, reinforcement of the anatomical and functional structures in the pelvis might provide additional support to avoid postoperative urinary incontinence, which includes bladder neck plication or bladder neck sling suspension.[27] Only a few comparative studies have evaluated the impact of different surgical techniques on urinary continence recovery after RALP. Posterior reconstruction, with or without anterior reconstruction, seems to be associated with a small advantage in urinary continence recovery one month after the procedure. Bocciardi et al demonstrated Retzius-sparing RARP to be oncologically safe and to result in high early continence and potency rates.[28] A study done by Tewari et al concluded that anatomical retro-apical technique of synchronous (posterior and anterior) urethral transection has ameliorated apical positive surgical margin rates in patients undergoing RALP.[29]

To summarize, radical prostatectomy is the most commonly recommended treatment for patients diagnosed with localized prostate cancer who have a sufficiently long-life expectancy. On the whole, radical prostatectomy can be considered in need for improvements in postoperative urinary continence and erectile function preservation and recovery. Of all the techniques of robotic radical prostatectomy, Retzius sparing RALP has shown the more promising results in terms of post-operative urinary continence rates. In terms of urinary continence expectations, a number of a priori patient characteristics must be carefully considered, including patient age, BMI and prostate volume. Hence, despite numerous aspects which cannot be modified or even adequately ameliorated, others such as those which can be handled differently during surgery (i.e., conservative and precise surgical techniques), pelvic floor exercises and adequate drug support, must be taken into careful consideration as they can lead to significant differences in terms of postoperative urinary continence preservation.

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(Dr. Saroj Lal Baidya, Fellow, Dept of Surgical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Rohini, Delhi)

OUTLOOK

DIAGNOSIS OF EARLY AND CLINICALLY SIGNIFICANT PROSTATE CANCER: A STEP AHEAD

Introduction

Prostate cancer is among the most common cancers in men across the world. Annual incidence of prostate cancer is approximately 16,00,000, and annual deaths are 3,66,000.

Clinically prostate cancer is a very diverse disease, varying from clinically insignificant disease which never metastasis to clinically significant state and which may progress and lead to death. Prostate specific antigen (PSA) screening for prostate cancer has always been discussed for its potential benefits and drawbacks. Though, there are conflicting results for survival benefit from two large randomized control trials: European Randomized Study of Screening for Prostate Cancer (ERSPC); and Prostate, Lung, Colorectal, and Ovarian (PCLO) cancer, but screening resulted into increase in prostate biopsy and increase in incidence of early prostate cancer. Therefore, concerns of biopsy related side effect and overtreatment of clinically insignificant disease have also increased. Several markers from serum, urine, prostate tissue, radiology imaging have been investigated to detect only clinically significant prostate cancer to prevent unnecessary biopsy and overtreatment of prostate cancer. Here, we have discussed some important markers which are useful in diagnosing early significant prostate cancer.

Blood Markers

Free Prostate-Specific Antigen: A lower percentage of free PSA (%fPSA) is suggestive of increased risk of prostate cancer. The test is approved by the US Food and Drug Administration (FDA) for men with normal digital rectal examination (DRE) and total PSA between 4 and 10ng/ml. In a study of men with PSA between 4 and 10 ng/ml and normal DRE, prostate cancer (any grade) was found in 56% of men with a % f PSA less than 10%, in contrast to 8% cancer among men with %fPSA more than 25%. NCCN 2016 thus recommends less than 10% as an informative cut-off for patients who have never undergone biopsy (or after negative biopsy) [1]. Like total PSA levels, fluctuations of %fPSA are common, particularly among men never diagnosed with prostate cancer. Therefore, some suggest repeating a %fPSA for men with PSA less than 4ng/ml so that a spurious value does not prompt unnecessary biopsy.

Prostate Health Index

FDA approved Prostate Health Index (PHI) in 2012 for patients over the age of 50 with a PSA in the range 2 – 10 ng/ml and negative DRE. It is based on a mathematical formula of the measured biomarkers [PHI = ([-2]pro-PSA/free PSA)x √total PSA]. Similar to %fPSA, it is intended as a secondary aid to PSA to distinguish any prostate cancer from benign prostatic condition, as cancer releases more pro-PSA and free PSA than benign prostatic hyperplasia. NCCN considers a PHI more than 35 as potentially informative in men who have never undergone biopsy (or after negative biopsy) [1]. In a large, prospective, multicenter study in the United States on 892 men with a PSA 2 – 10 ng/ml, PHI improved the detection of any prostate cancer and Gleason score at least 4 + 3 = 7 compared with free PSA and total PSA. A PHI cut-off of at least 25 for biopsy could avoid 36 to 41% of unnecessary biopsies and 17 to 24% of over diagnosis, while missing 5% of tumors with Gleason score 7 or higher.

4-Kallikrein Score

The 4Kscore is a combination of free, total, intact PSA and Human Kallikrein 2 (hK2) with age, DRE, and prior biopsy information. The test predicts risk of aggressive prostate cancer. It has recently been shown to be associated with long- term risk of metastasis among unscreened men with elevated PSA at least 3 ng/ml at age 60. Among men with a 'low' 4Kscore below 7.5% (38% of men), the 10-year risk of metastasis was 0.2%. It is not FDA approved, but a Clinical Laboratory Improvement Amendments (CLIA) accredited laboratory developed test. It is included in the 2016 NCCN guideline as a secondary testing option after PSA and prior to initial or repeat biopsy [1]. In a recent 2016 study conducted within a multi-ethnic cohort in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, the 4K-panel improved the prediction of high-grade prostate cancer over total PSA.

Urinary Marker

Select MDx: Select MDx is performed on post-DRE, first-void urine and measures the mRNA levels of the HOXC6 and DLX1 biomarkers, using KLK3 expression as internal reference.

The first evaluation resulted in AUC of 0.86 for significant prostate cancer on multivariable analysis, and a 42% reduction in biopsies with 2% high-grade cancers missed. The test is not FDA approved but performed in a CLIA-accredited laboratory.

Michigan Prostate Score

The MiPS is a multiplex urine analysis of Prostate Cancer Antigen 3 (PCA3) and TMPRSS2:ERG combined with serum PSA. Test is designed to detect high-grade prostate cancer (Gleason score 7 or higher) on biopsy after initial PSA testing. The test is not FDA approved. A first evaluation, using a 30% risk threshold for biopsy, showed a halving of the number of biopsies [16% of biopsies avoided with the Prostate Cancer Prevention Trial (PCPT) risk calculator vs 35% with PCPT-risk calculator and MiPS] whereas missing, or delaying 1% of high-grade cancers.

PCA3

PCA3 is a non-coding mRNA that is overexpressed in prostate cancer and can be measured in urine after DRE. Numerous studies show that PCA3 can better predict any prostate cancer on repeat biopsy compared with PSA and clinical models. However, the reason the test is FDA approved only for men at least 50 years with previous negative biopsy and other indications for repeat biopsy, is because there is conflicting data regarding the relationship between PCA3 and prostate cancer aggressiveness and a risk of 13% high-grade prostate cancer missed among men with low PCA3 scores less than 20 in the initial setting in the US validation study (compared with 3% in the repeat setting).

ConfirmMDx

ConfirmMDx is a tissue-based epigenetic test that can help decrease unnecessary repeat biopsy. The negative predictive value was 88% in a study of 350 men with negative biopsy and repeat biopsy within 2 years. The test builds on a "field effect" phenomenon, that is, benign prostatic tissue adjacent to a cancer focus showing distinct epigenetic alterations. Because of limited available data, there is no recommendation regarding the routine clinical application. The test is not FDA approved but performed in a CLIA-accredited laboratory.

Risk Calculator

Nomograms, or risk calculators, have the advantage of incorporating and easy to retrieve clinical variables, such as age, family history, DRE, PSA density, with or without biomarkers. In a recent meta-analysis of six nomograms predicting risk of any prostate cancer on biopsy (Prostaclass, Finne, Karakiewicz, PCPT, Chun, ERSPC-risk calculator3), most risk calculators performed better than PSA alone in terms of discrimination. However, guidelines leave the decision to the physician's discretion which risk calculator to use. It is important to utilize a risk calculator in the clinical setting and the population in which it was developed.

Multiplex Test

Stockholm-3: Recently, Gronberg et al reported results from the STHLM3 study, a large-scale study comprising 58 818 men between ages 50–69. The study was innovative in testing a multiplex 'next generation' screening strategy, in which men received a battery of protein biomarkers combined with genetic markers and clinical information: total, free, intact PSA, hK2, Microseminoprotein Beta, Macro-phage Inhibitory Cytokine-1, DRE, prostate volume, age, family history, and previous biopsy information. Consistent with prior observations (PHI, 4K-panel), adding Kallikrein markers to the STHLM3 model improved prediction of high-grade prostate cancer over PSA alone (from 0.56 to 0.74), with excellent calibration. As compared with PSA only with a cut-off of 3ng/ml to determine biopsy, use of the STHLM3 test in all men with PSA more than 1 ng/ml decreased overdiagnosis by 17% and reduced the number of unnecessary biopsies by 32%.

Multiplex Test: 'Liquid Biopsy'

A recent 2016 study on 319 patients with indication for prostate biopsy measured a panel of gene expression levels (liquid biopsy) in plasma and urine (UAP1, PDLIM5, IMPDH2, HSPD1, PCA3, PSA, TMPRSS2, ERG, GAPDH, B2M, AR, and PTEN), along with serum PSA and age, to screen for best biomarker combinations to predict high-grade prostate cancer in a multivariable logistic model. The AUC for the 13 variables was 0.85, and 0.80 if only eight were included. Whether this model improves predictions over clinical base models and reduces the number of biopsies is yet unknown.

Multiparametric MRI (mpMRI)

mpMRI has evolved as a promising tool in the diagnostic arsenal, mainly to guide biopsies toward suspicious lesions, to maximize the detection of high-risk disease (Gleason at least 4+3) and limit the detection of insignificant (Gleason 6 or

lower volume 3+ 4) [1]. Several diagnostic strategies incorporating mpMRI are now undergoing, for example, the PROMIS study comparing mpMRI against TRUS biopsy [2] and a prospective screening trial utilizing PSA and mpMRI, the 'Goteborg-2' trial, ongoing in Sweden. In a pilot study of 384 men within the Goteborg-1 screening trial, mpMRI with targeted biopsies for men with suspicious lesions and a PSA level in the 'gray zone' improved the detection of significant disease while reducing over-diagnosis (defined as T1c, PSA density <0.15, Gleason Score <7, 2 positive cores, unilateral cancer) compared with systematic biopsy [3].

The recent 2016 NCCN guideline recommends consideration of 'refined prostate biopsy techniques' (in addition to, or in spite of, biomarkers) for men with negative prostate biopsy, including MRI/ ultrasound fused-guided biopsies, trans-perineal biopsies, or saturation biopsy [1].

Conclusion

Screening for prostate cancer is not recommended as it may lead to over diagnosis and overtreatment. Moreover, there are also concerns of missing high risk prostate cancer which may lead to significant morbidity in absence of screening for prostate cancer. So, it is a need of the day to have certain markers which can guide us to detect high risk cancer at early stage. At present, we have many promising markers from urine, blood, and prostate tissue, but still our search for most sensitive and specific marker is on. We hope that we will find it very soon in the near future.

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(Dr Amitabh Singh, Consultant, Uro Oncology, Dept of Surgical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Rohini, Delhi)

Image Analytics for Evaluating Cancer Treatment Response

Dr Anant Madabhushi, professor of biomedical engineering and director of the Center for Computational Imaging and Personalized Diagnostics, and colleagues were recently awarded US patent: 9,262,583, titled "Image similarity-based finite element model registration. "The patent relates to a method and apparatus associated with evaluating global deformations and local deformations in a prostate following cancer treatment.One example of the application of this technology is in capturing changes within prostate following treatment for prostate cancer via pre-external beam radiation treatment (EBRT) where the prostate has been imaged via three-dimensional magnetic resonance image before and after radiotherapy.The technology involves extracting image texture information from the pre-EBRT and post-EBRT images and employing it to construct a finite element model in order to co-register and hence capture the differences between the deformed pre-EBRT image and the post-EBRT image.

(USPTO: Sep, 2016)

Patent for ProscaVax in Japan and Mexico

OncBioMune headquartered in Baton Rouge, LA, announced that patent No. 6118730 entitled " Composition and Method for Treating Cancer," has been granted by the Japan Patent Office to ProscaVax. The patent, protects the intellectual rights of Onc Bio Mune's Prosca Vax in Japan until January 8, 2032. ProscaVax is a clinical-stage protein therapeutic cancer vaccine that combines tumor-associated antigens with biological adjuvants to selectively target tumor cells without damage to healthy cells. OncBioMune's intellectual property portfolio protecting ProscaVax and other technologies consists of 16 patents spanning approximately 50 countries worldwide. Mexican Institute of Industrial Property has issued patent No. 343266, titled "Composition and Method for Treating Cancer," protecting the intellectual rights of Onc Bio Mune's Prosca Vax throughout Mexico until January 8, 2032.

(marketinsider.com, Jun 20, 2017)

IN FOCUS

IS PSMA PET-CT BETTER THAN BONE SCAN? WHEN AND WHY?

Introduction

Prostate cancer (PCa) is the second most common cancer and sixth leading cause of cancer deaths in man worldwide [1]. In India, though the incidence is less than the western world, it is showing a rising trend now. Indeed in many metro-cities like Delhi, it has become the runner-up with age-adjusted incidence of 10.9/105 person-years [2]. A large number of patients diagnosed with early stage PCa got cured with definitive local therapy, ie, Radical Prostatectomy or Radiotherapy. However many developed metastatic disease. PCa has a unique exquisite tropism to spread in bone [3]. Haematogenous spread in red bone marrow of axial and proximal appendicular skeleton leads to development of bone metastases (BMs). BMs are the most frequent and main distant metastatic site in about 80% of PCas patients and is therefore one of the most important determinants of treatment and outcome [4,5]. Skeletal complications known as 'skeletal-related events (SREs)' account for most of the PCa's morbidity and mortality [6]. Bone marrow replacement by PCa cells leads to anaemia while involvement of cortical bone can lead to pain, fractures, and spinal cord compression. Once bone metastasis is diagnosed, local definitive treatment goes out of the picture and the intent of treatment becomes palliative. Hence timely diagnosis of bone metastasis is important for correct treatment planning and prevention of SREs.

Bone scintigraphy/scan (BS) with 99mTc-Methylene diphosphonate (MDP) is the most favoured investigation for detecting BMs. This is due to physiological adsorption of this radiopharmaceutical at the site of osteoblastic activity. In PCa BMs, there is predominant upregulation of osteoblasts that lead to formation of characteristic sclerotic lesions. Hence, this method has high sensitivity (range 62-89%) for BMs in PCa [7]. Briganti has showed risk on BMs in low (Gleason d≤7, T_{2-3} and PSA <10ng/ml), intermediate (Gleason d≤7, T_{2-3} and PSA >10ng/ml), and high risk (Gleason >7) PCa of 1.8%, 8.5% and 16.4% respectively [8]. Therefore, most guidelines suggest BS to be performed in patients with high risk PCa or those presenting with bone symptoms [9,10,11].

BS has been associated with a number of limitations as well. It is a wellknown fact that BM begins in bone marrow, hence it is predicted that BS will not be able to detect bone marrow lesions or early lesion with insufficient osteoblastic activity. In addition, it is a non-specific tracer and many a time it is hard to differentiate between degenerative bone disease and BMs, hence frequently requiring additional imaging modality for characterization [12]. With modern hybrid imaging SPECT-CT (Single Photon Emission Computed Tomography - Computed Tomography), MDP BS has largely addressed this issue of low specificity and has been able to correctly characterize planner imaging equivocal lesions. It has been reported that the number of equivocal lesions dropped from 61 to 8% with addition of SPECT-CT [13]. Flare response is another known fact in BS [14]. Post-treatment increase in tracer activity or new lesion is tricky in interpretation. Whether this is due to reparative response or due to disease progression is a matter of concern. Nonetheless this phenomenon has been assumed as response by most physicians and presumed to have better outcome.

Despite these limitations, bone scan has been recommended as standard for BMs in clinical trials by prostate cancer working group, reason being it is widely available, low cost, time tested and whole body imaging. In addition, it has been reported superior to X-Ray and CT [15], roughly equivalent to 11C-Choline-positron emission tomography (PET) [16] as well. Though it isinferior to whole body MRI [17] and 18F-Fluoride PET [18], but these imagings have still not been able to find their way in clinical practice and associated with few limitations as well.

Recently, prostate-specific membrane antigen (PSMA) has been acclaimed as a distinct target in PCa. Its expression is 100-1000 times more in PCa cells [19] and level of expression is directly proportional to Gleason score, androgen independence, metastasis and progression [20]. Many monoclonal antibodies and small molecule inhibitors have been developed to target PSMA. Out of these, a small molecule inhibitor Glu-NH - CO - NH - Lys - (Axe) - [68Ga(HBED-CC)] (68Ga-PSMA-11) is being most investigated. It has shown to be of high clinical value for lymph node staging [21] and detection of local recurrence [22, 23]. For BMs PSMA PET has unique distinction of being positive in bone marrow metastasis and not being positive in degenerative bone disease. In a direct comparison, PSMA PET outperformed planner BS for detection of affected bone regions as well as overall bone disease volume [24, 25]. Overall 17.6% of affected bone regions were exclusively recognized only by PSMA PET, while only 1.2% of bony regions exclusively detected by BS.
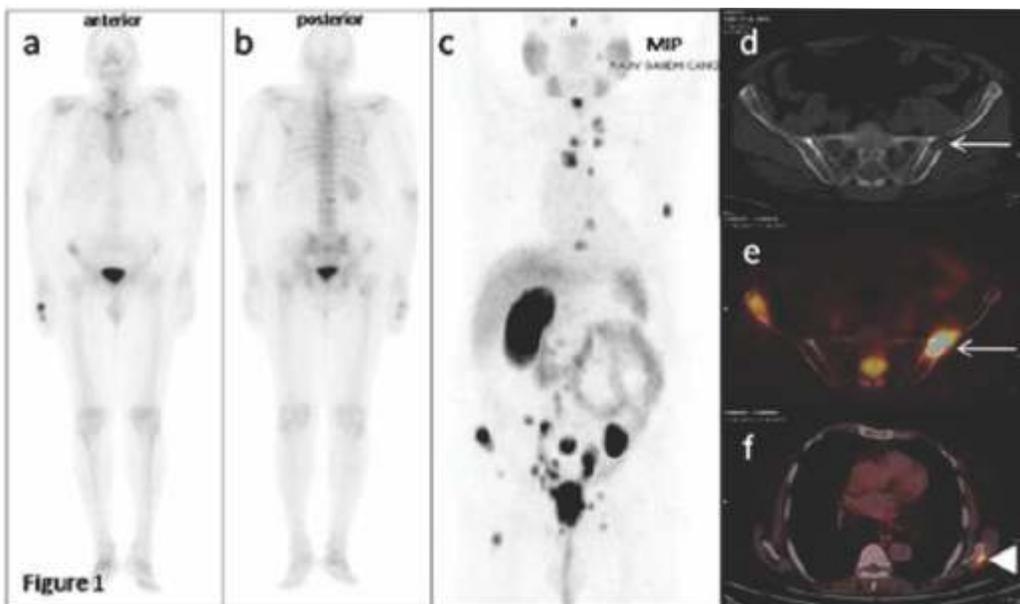
Figure 1: 68 years male with adenocarcinoma prostate, Gleason score 4+5, PSA 121.5ng/ml underwent MDP bone scan (image a and b) and 68GaPSMA PET-CT (image c, d, e, f). MDP bone scan shows doubtful lesions in right iliac crest, D3 and L2 vertebrae. PSMA PET-CT showed locally infiltrating prostate lesion with pelvic lymphnodes, multiple osteolytic bony lesions (arrow) and a left infraspinatus muscle deposit (arrow head).

PSMA-PET showed significantly higher sensitivity and accuracy than BS (90.5% vs 73.68%, and 97.0% vs 86%) for BMs [26]. In our experience of 97 staging PSMA PET studies, we found that only 57.41% of patients with BMs had pure sclerotic lesions. Mixed (33.33%), marrow (7.14%) and lytic (2.3%) types of lesions constitute the rest and thus BS alone in these patients may leads to underestimation of bony disease burden (In-press data). We reported that overall the PSMA PET allows envisioning an all-in-one metastatic work up (both visceral and bone) in high risk prostate cancer (Figures 1, 2). In addition, we believe PSMA PET will have upper hand in response evaluation of BMs than BS, however, data is deficient in the literature.
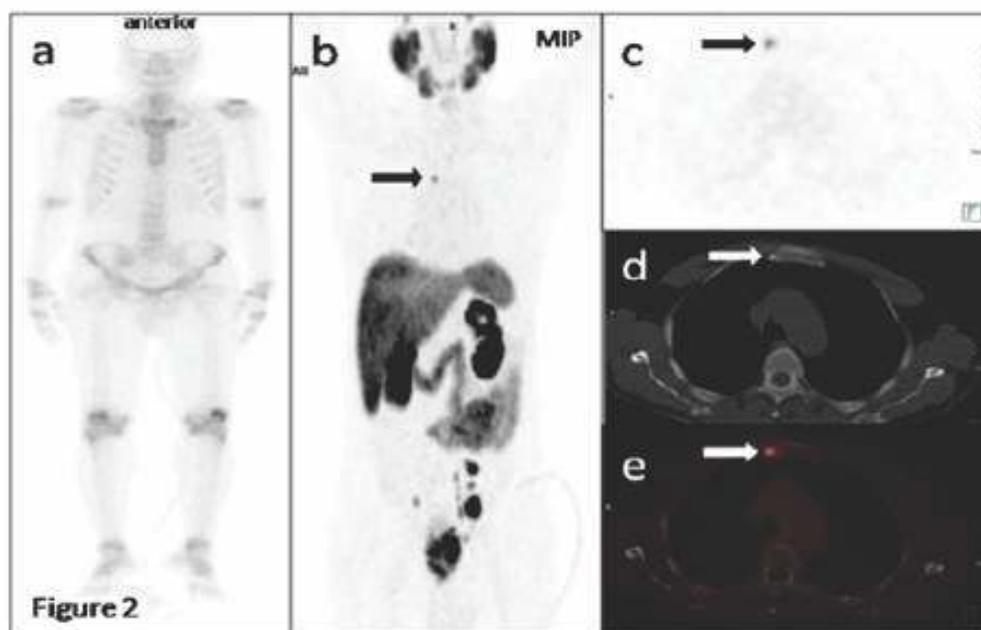

Figure 2: 62years male with adenocarcinoma prostate, Gleason score 5+4, PSA 17.5ng/ml underwent MDP bone scan (image a) and 68GaPSMA PET-CT (image b, c, d, e). MDP bone scan was reported normal while PSMA PET-CT showed locally infiltrating prostate lesion with pelvic lymphnodes and a solitary bony lesion in sternum (block arrows)

Nevertheless we need to understand that PSMA PET is still in infancy stage and no prospective data is available for its role in BMs. Availability limited to few tertiary care cancer institutes is a big challenge for PSMA PET to come in main stream. Cost and reimbursement are other critical points here for PSMA PET as BS is often covered in heath insurance. Growing availability of SPECT-CT makes BS specific and a strong contender to PSMA PET in BMs, especially in advanced diseases. It has been noticed that PSMA expression is inversely related to androgens level, hence, its expression will increase in androgen deprivation state [27]. This influence of anti-androgens on PSMA expression is requiring attention in interpretation of response as initial flare up to 3 months can be expected [28, 29]. Further studies might be interested in order to disentangle this treatment dependency of PSMA in response assessment of BMs.

Conclusion

We concluded PSMA PET has better sensitivity and specificity than BS and a unique distinction for detecting non-sclerotic metastases. Its role in response evaluation to anti-androgens needs caution and further studies. We presumed that if PSMA has been performed for staging workup then there is limited role of BS except in clinical trial patient.Overall PSMA PET may become one-stop-shop for PCa workup.

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(Dr Manoj Gupta, Consultant, Dr P S Choudhury, Director, Department of Nuclear Medicine, RGCIRC)