Overview Of Prostate Cancer

Prof. Prabir Kr. Sur

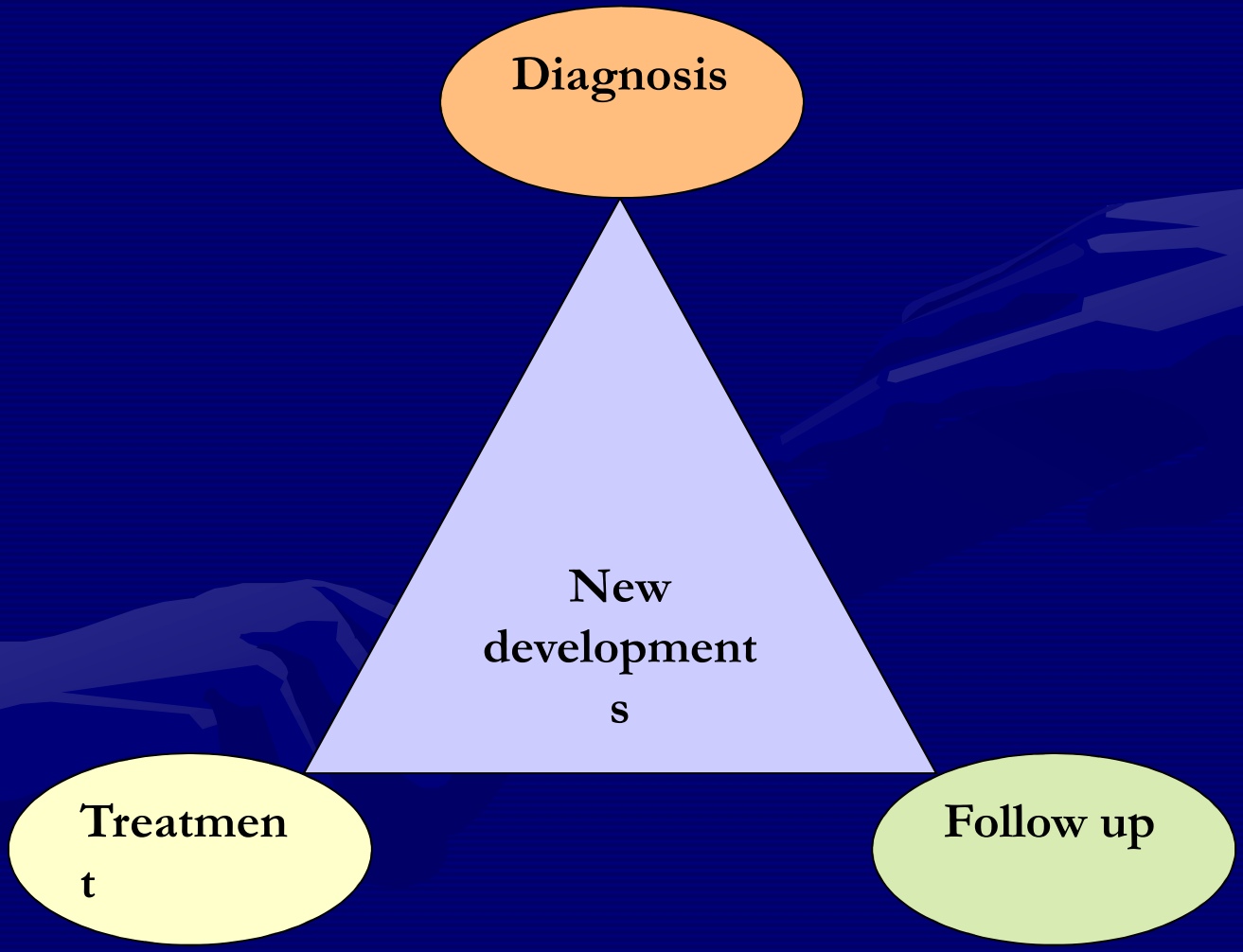
Department of Radiotherapy

Medical College, Kolkata

&

Chairman, ICRO

WHY THIS SUBJECT?
Prostate Cancer :



Diagnosis

- **Rapid changes in approach** to Prostate cancer diagnosis and treatment in recent times
- **New diagnostic** algorithms now available to identify the clinically significant subgroup
- **Better prognostic models** to determine patients who need treatment and those who do not, based on clinical and biologic determinants of an individual disease

Treatment

- Highly improved **cure rates** and decreased morbidity in early prostate cancer, by advancements in surgery and radiotherapy
- Improvements in **systemic treatment** of metastatic disease
- More **effective chemotherapy** for Hormone refractory patients

Epidemiology

- Second leading cause of cancer death in men from western countries
- Surpasses Lung as the commonest male cancer in North America (29% of all male cancers)
- Significant ethnic, geographic and racial differences in incidence and mortality rates

Epidemiology….contd

- Enormous differences in incidence over the world.
- Age-adjusted annual incidence 176 per 100,000 in USA, whereas only 7.1 in Mumbai and 4.3 in Bangalore (NCRP 1990-96)
- Still one of the 10 leading cancer sites in males in India, accounting for about 4 % all male cancers

Etiology

- **Family history:** 2-3 fold increased risk in men with a first degree relative
- **Hereditary association:** Early onset of disease and a Mendelian autosomal dominant inheritance– accounting for <10 % of all cases but 40 % in younger men <55 yrs
- **Racial Factors:** Striking differences in incidence and mortality between the Black and White population

Etiology….contd

- **Environmental Factors:** also responsible for ethnic differences, as Asians migrating to USA have higher incidence of prostate cancer
- **Diet:** one of the most important modifiable risk factors--high fat intake increases risk whereas diets rich in carotenoids (tomatoe based products) and vitamin-E are protective

Etiology….contd

- No association with cigarette smoking, alcohol use, height and weight and blood group
- No data regarding viral origin
- No convincing evidence that Vasectomy increases risk of prostate cancer

Diagnostics procedure

- Signs and symptoms of Prostatism
- Abnormal DRE: although correlates poorly with the volume and extent of cancer, an integral part of the algorithm, used as the 'prognostic model'
- Serum PSA: usually > 4 ng/ml (20% 2.5-4 ng/ml) With increasing PSA level, chance of getting cancer increases, but less likely to be organ confined
- TRUS guided Biopsy: 1) to establish the diagnosis
  2) to report extent and grade of cancer in each core
  3) to document presence of PNI or ECE

Advances in Imaging

	Commonly used method	Newer technique
A) For diagnosis:	TRUS (with biopsy)	CECD US, MRS
B) For staging in: localised disease	Pelvic CT	Endorectal MRI MRS, LNMRI
C) Rising PSA	Whole body bone scan	ERMRI
(To look for mets)	Pelvic CT, SPECT	SPECT BS PETScan
D) Clinical Mets	Bone Scan	PET, MRI

Presentation

Prostate cancer, not just a single entity but viewed as a spectrum of diseases and patients may present in any state of this spectrum as follows

- Localised disease
- Rising PSA
- Non castrate Metastatic
- Castrate Metastatic

Prostate cancer management

Concept

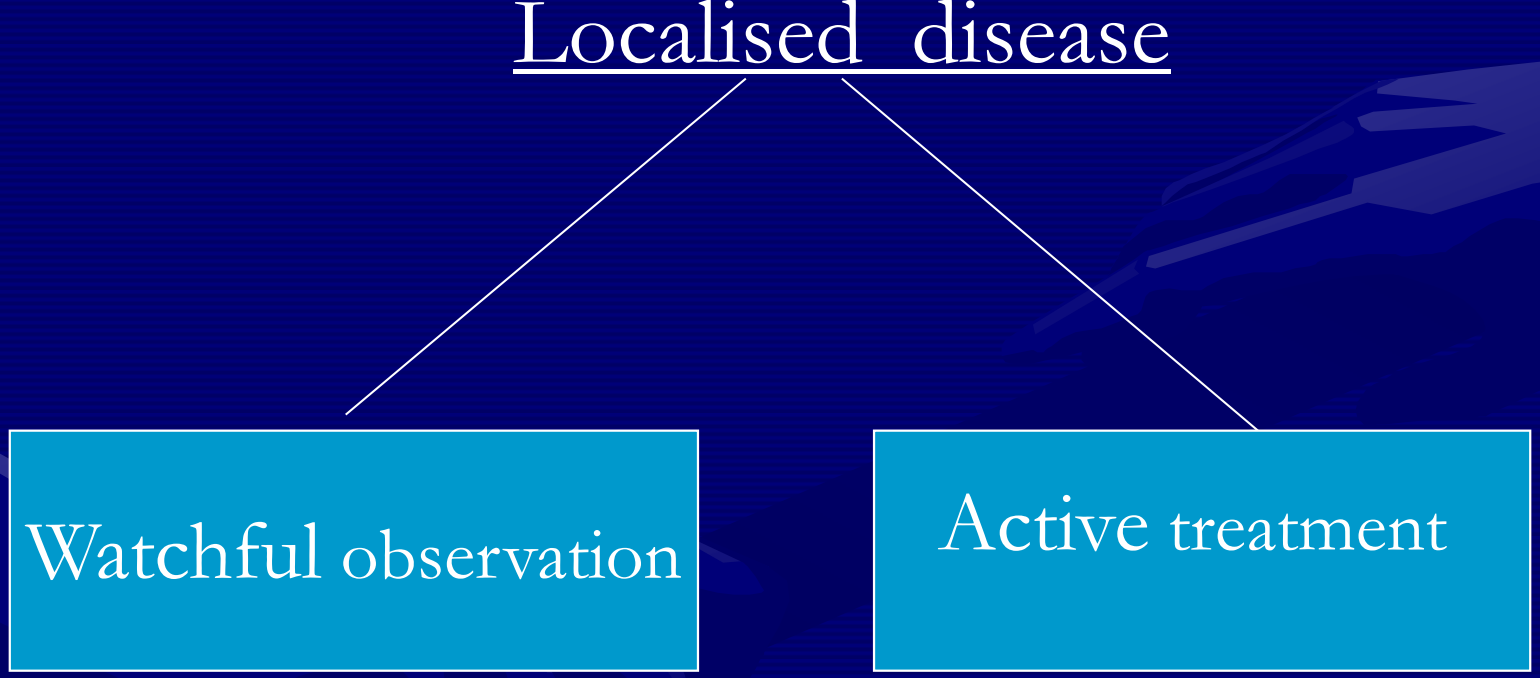
- Prognostic assessments, therapeutic objectives and treatment outcomes vary according to the state at which the patient presents
- Determination of patient's state by clinical assessment, physical exam, imaging and testosterone estimation

Therapeutic Objectives

For those who do not have cancer diagnosis but are at risk of developing it or harboring occult disease:

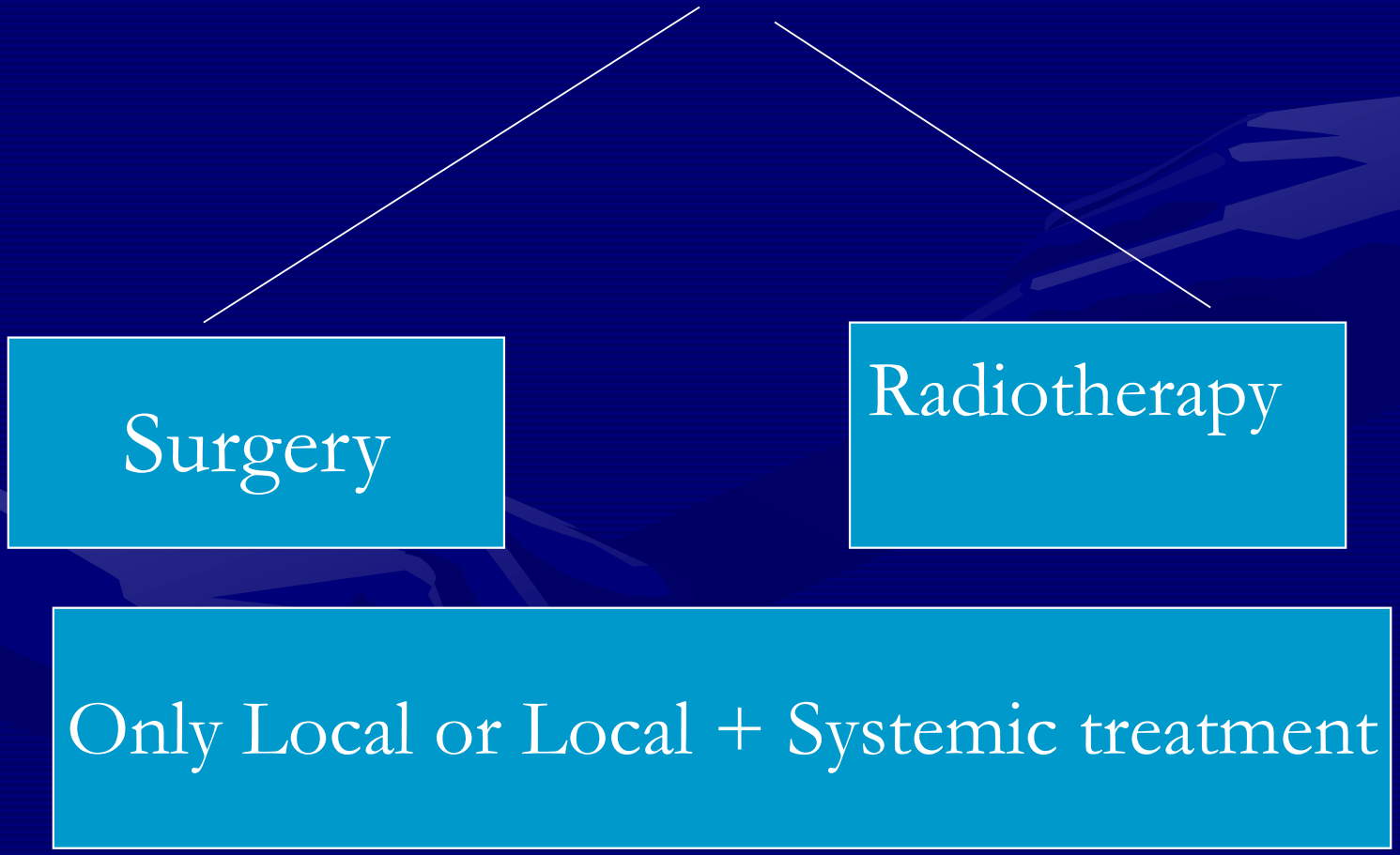
Prevention & early detection

Therapeutic Objectives



Therapeutic Objectives

Those who need active treatment:



Therapeutic Objectives

Those with rising PSA

- Local
- Systemic disease

If systemic, what is the probability of developing clinical features of metastasis and in what time ?

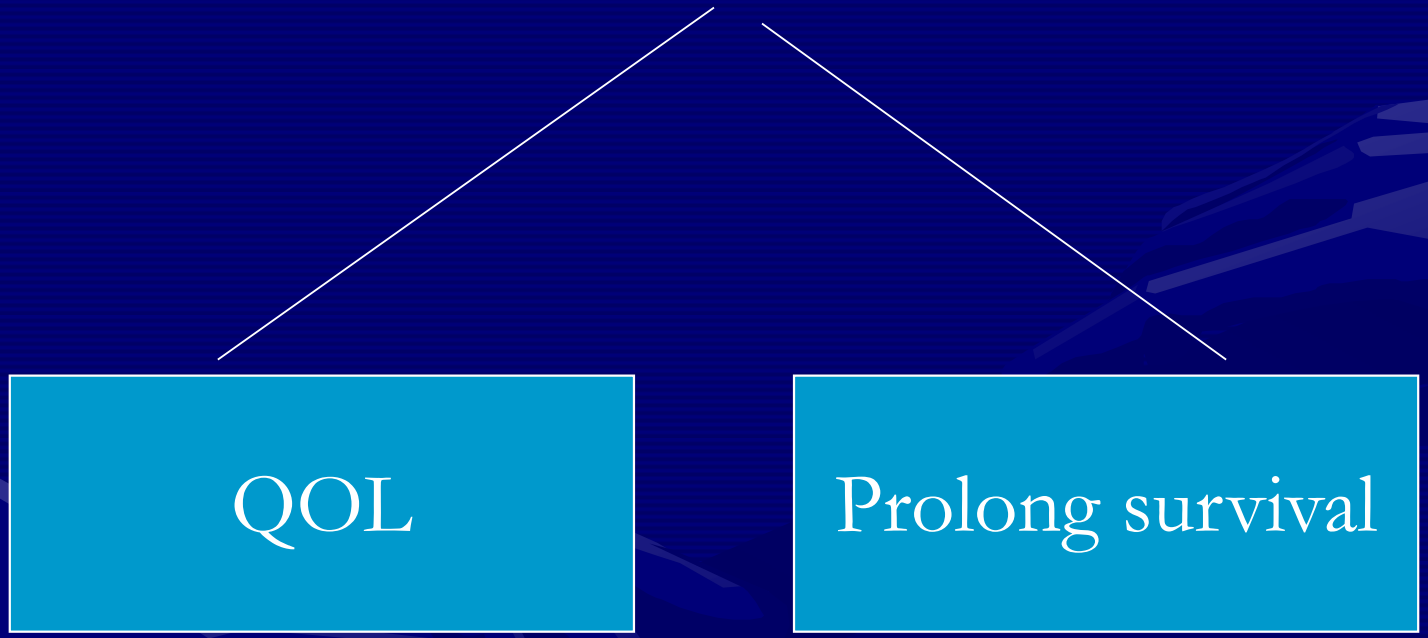
Therapeutic Objectives

For those with detectable metastasis:

- Delay progression?
- Response to castration?

Therapeutic Objectives

For those having progressed on castration:



Management of early localised disease

Watchful waiting

Treatment

Still a contentious issue and decision making involves balancing the immediate risks of treatment with ongoing risks of recurrence or metastasis from cancer, if left untreated

Wathcful waiting / Treatment?

Scandinavian Prostate Cancer Group Trial-4

10 yr follow-up study after randomization between Radical Prostatectomy and Watchful Waiting

- Clear benefit from surgery over watchful waiting
- Benefit in all subgroups except in men >65 yrs
- Extent of benefit differs by gleason score, stage or PSA

Decision to treat or not to treat

Depends upon:

- life expectancy of the patient
- Probability of metastasis or death from prostate cancer over time, if left untreated
- Prognostic features of the primary tumour
  (**gleason score, serum PSA, tumour stage**)
- Complications and side effects of treatment and
- Patient's own preferences after being informed of the risks and benefits of treatment

Surgery or Radiotherapy ?

- No prospective randomized trial
- Level II evidence shows that , Stage for stage, survival outcome are comparable, upto 15 yr Follow- up

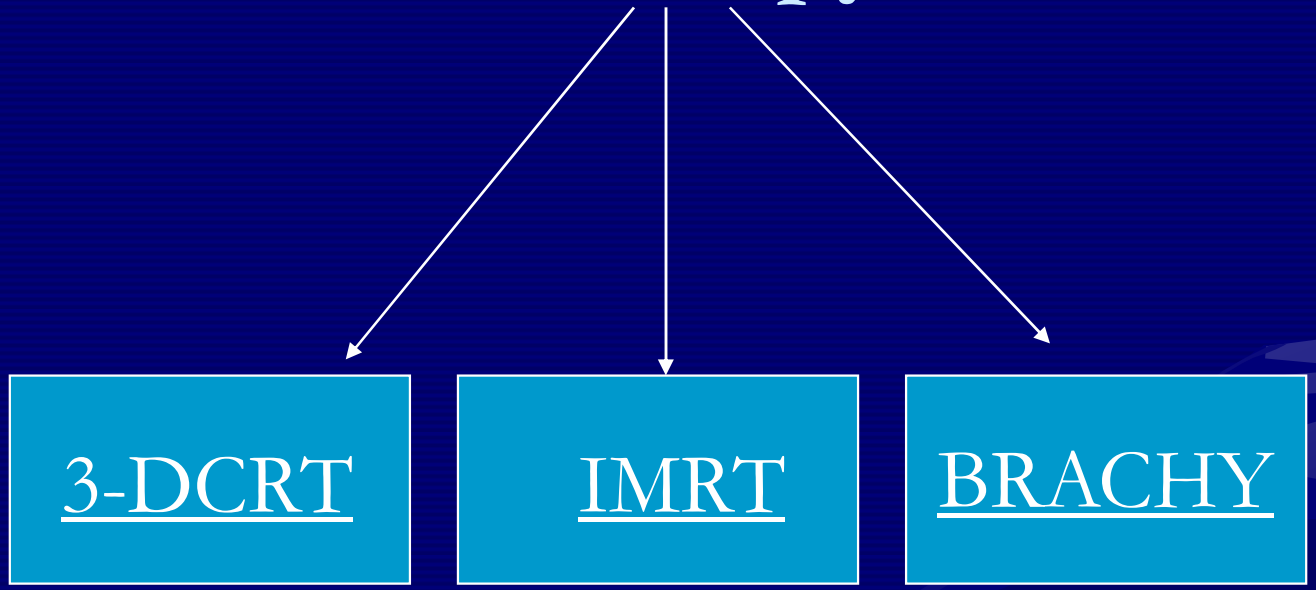
PSA free survival better with surgery ?

- Low risk pts (pretreatment PSA <=10 ng/ml & gleason score <7) show similar 5 yr PSA free survival
- High risk pts (PSA >10 & gleason >=7) better with S

Situation changed after arrival of High dose conformal RT & IMRT

Results comparable to Surgery when dose > 72 Gy

Radiotherapy How?



Pollack et al: **First prospective randomized study: conventional 70 Gy vs 3DCRT 78 Gy (dose escalated) At 5 yrs, significantly better outcome (L.Control & FFF) in the 78 gy arm, in high risk pts (PSA > 10 ng/ml)**

3DCRT vs IMRT

Dose escalation study at MSKCC:

907 pts with 3DCRT vs 777 pts with IMRT

- Established role of dose escalation in long term cure
- Data showed that 81 Gy required for maximal control
- Showed that IMRT better than 3DCRT in achieving this dose escalation with much less rectal toxicity(3%)

3DCRT vs Brachytherapy

No prospective randomized study

One study compared 3DCRT 64 -81 Gy vs Interstitial implantation at dose of 150 Gy median

- 5yr PSA relapse-free survival were similar, but
- Incidence of late bladder toxicity and urethral stricture significantly higher in Implant arm
- Rectal toxicity were not significantly different
- Post RT erectile dysfunction more in implant arm

So treatment toxicity is the deciding factor in choice between 3DCRT / IMRT and Brachytherapy

Local RT alone or combined with Androgen deprivation ?

4 Multi-institutional Randomized trials

(3 RTOG & 1 EORTC):

- Significant in local control, distant mets free survival and PSA failure free surv with combined therapy in all studies
- Maximal benefit in locally advanced, high risk category
- Overall survival not affected except EORTC study

Local RT alone or combined with Androgen deprivation ?

2 relevant questions?

Is this benefit still present if RT dose escalated (3DCRT/IMRT)?

Can we avoid high dose RT if we combine systemic treatment ?

MSKCC study to answer these questions.
However, Quality of life also matters in deciding finally on combined treat.

New Inventions: Minimally invasive approach in localised Ca Prostate

- **Cryotherapy**: Tissue ablative approach by freezing and destroying target tissue or organ—still evolving
  As alternative to radical prostatectomy and
  Treatment of local recurrence after EBRT and Brachy
- **High intensity focused ultrasound** (HIFU): – still in clinical trial as i) primary treatment of localised cancer
  and ii) treatment of recurrence following EBRT
- **Laparoscopic and Robotic Radical Prostatectomy**
  Initial results promising

Management of the patient with Rising PSA alone

- A challenging and practical problem
- Following definitive therapy (RP or RT) 20-40% of pts will have PSA failure in the next 10 yrs
- Poor correlation between PSA failure and clinical recurrence
- 1/3 rd of those with PSA failures progress to clinical disease
- PSA doubling time more predictive than single PSA value

Management of the patient with Rising PSA alone

Therapeutic options

- Salvage RT: after surgical failure- impact on survival unknown
- Salvage RP: after failed RT
- Hormone therapy: Castration with/without antiandrogens

  Early HT: better survival , but at the cost of quality of life

Management of metastatic disease: Role of Hormone therapy

- Surgical Orchiectomy– the Gold Standard
- Medical options:

A) Testosterone lowering agents: a) Estrogens (DES)

b) LHRH analogues: Leuprolide, Zoladex

c) Progestational agents: Megestral acetate, cyproterone, : not as 1st line of treatment

d) Antifungal: Ketoconazole

B) Androgen receptor blockers: Flutamide, Bicalutamide, Nilutamide

Some questions in Androgen therapy

- Is one form of monotherapy superior to another ?
- Is there an optimal form of therapy ?
- Does androgen therapy prolong survival ?
- Is combined androgen blockade better than monotherapy ?
- When should it start : Early or Late ?
- Do attempts to reduce the toxicities of androgen therapy compromise the outcomes ?
- Does addition of androgen therapy with Surgery or RT improves the outcome ?

Management of Clinical metastasis Castrate

To ensure first that testosterone is in castrate level

- Options are a) 2nd and 3rd line hormonal therapy
  b) Androgen withdrwal
  c) Cytotoxic drugs:
  Mitoxantrone & Prednisolone
  Estramustine & Vinca alkaloids
  Taxanes (Docetaxel, Paclitaxel)
- At present, Docetaxel q 3 wks standard treatment
- Established that Chemotherapy can prolong life

5 yr Survival in Prostate Cancer

PSA relapse free survival (%) (5 yrs)	RTOG 86-10	RTOG 85-31	EORTC
I. RT + Hormones	28	54	76
II. RT alone	10	21	42
Overall Survival (5yrs)			
I . RT + Hormones	72	75	78
II. RT alone	68	71	62

I hope all of you will actively participate in this teaching programme and will definitely gain from it

Thank you