Flow of presentation

- Prostate cancer overview
- Staging
- Stratification of risk
- NCCN guidelines of management
- Various metaanalysis
- Take home message

Overview

Prostate Cancer

Worldwide:
- Second most common cause of cancer
- An estimated 161,360 new cases of prostate cancer will be diagnosed in 2017, accounting for 19% of new cancer cases in men.
- Researchers have estimated prostate cancer to account for 26,730 deaths in 2017, which represent 8% of male cancer deaths.

- Prostate cancer incidence
  - Lowest:
    - Asian populations 10.5 per 100,000
    - Eastern and South-Central Asia 4.5 per 100,000
  - Highest:
    - 111.6 Australia/New Zealand
    - 97.2 per 100,000 Northern America
In India

- Previously – thought - prevalence of prostate cancer in India is far lower compared to western countries
- increased migration rural to urban areas
- changing life styles
- increased awareness
- easy access to medical facility
- more cases of prostate cancer are being picked up
- we are not very far behind the rate from western countries.
- Current incidence rate of prostate cancer in India is ~ 10.66 per 100000 population
**GLEASON GRADING SYSTEM**

Core biopsies are measured for histologic aggressiveness using the above system, correlates with prognosis. 5 histologic patterns, where the primary and secondary grades are measured then added together to make Gleason score 2-10. Score <6 considered low grade.

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**Risk Stratification Systems**

- Based on tumor stage, pretreatment PSA, and biopsy Gleason score, several risk stratification models have developed.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle/Mskcc</td>
<td>PSA &lt;10 ng/mL and GS 2-6 and stage T1-T2b</td>
<td>PSA &gt;10 ng/mL or GS &gt;=7 or stage &gt;T2c</td>
<td></td>
</tr>
<tr>
<td>N. Sinc</td>
<td>PSA &lt;10 ng/mL and GS 2-6 and stage T1-T2a</td>
<td>PSA 10.1-20 ng/mL or GS 7 or stage T2b</td>
<td></td>
</tr>
<tr>
<td>Amico</td>
<td>PSA &lt;10 ng/mL and GS 2-6 and stage T1-T2a</td>
<td>PSA &gt;20 ng/mL and/or GS 8-10 and/or stage &gt;T2c</td>
<td></td>
</tr>
</tbody>
</table>

These systems are useful to provide a means to appropriately recommend treatment options and compare treatment results.

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**Low recurrence risk**

- T1-72a tumors, PSA level <10, and Gleason score 6
- <10 years: No treatment, start active surveillance
- >10 years: Radical prostatectomy, Adjuvant features: Radiotherapy, or Hormonal therapy or Ongoing monitoring
- PLND 2-5% chance of cancer in lymph nodes
- Cancer in lymph nodes: Ongoing monitoring, or Immune therapy

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Meta-Analysis in treatment of Carcinoma Prostate Dr. Preety Jain
Radiation therapy

- **RADICAL RADIOTHERAPY (MONOTHERAPY)**
- **SALVAGE RADIOTHERAPY**
  - PSA recurrence after surgery
  - No distant mets
  - Few months to years after RP
- **ADJUVANT RADIOTHERAPY**
  - Immediate post-Prostatectomy
  - High risk of recurrence
  - Adverse pathological features
- **PALLIATIVE RADIOTHERAPY**
  - Most effective in treating symptomatic bone mets
Radiotherapy Techniques

1. External Beam Radiation Therapy (EBRT)
   A) Conventional Techniques
   B) 3D-CRT/IMRT/VMAT/SBRT

2. Brachytherapy:
   A) Radioactive seed implants into prostate.
   B) HDR brachytherapy

3. Radioisotopes

Indications for radiotherapy

- Radical radiotherapy
  - T1, T2, T3, T4a
  - Irresectable
  - Elderly, frail, coexisting condition
  - Radical surgery
  - Prohibitive morbidity due to surgery
- Post op radiotherapy
  - pT3
  - Close to positive margins
  - Extracapsular extension
  - Invasion to
    - seminal vesicles
    - Extracapsular extension
  - multiple nodes
  - RT recurrence
  - Pre-op PSA >10 ng/ml
  - Pre-op PSA velocity >2 ng/ml/year
- Salvage radiotherapy
  - Post RP recurrent disease
  - Post RP early PSA failure

Metaanalysis

1. Surgery versus RT for clinically localized PCa: A systematic review and metaanalysis
2. Adjuvant RT following radical prostatectomy for pT3 or margin positive PCa: A systematic review and metaanalysis
3. Higher than conventional radiation doses in localised PCA treatment: A metaanalysis of RCT
4. Does hormone treatment added to RT improve outcome in locally advanced PCA
5. SBRT for primary PCa: A systematic review
6. Comparison of treatment related toxicities in men: IMRT versus 3D CRT
7. Comparison of HRQoL among surgery & RT for localised PCa: A systematic review and metaanalysis
Objective:
To conduct a systematic review and meta-analysis to compare efficacy data on overall and prostate cancer-specific survival among patients treated with radiotherapy or radical prostatectomy for clinically-localised prostate cancer. Nineteen studies of low to moderate risk of bias were included and up to 118,830 patients were pooled.

Inclusion criteria:
• Men of any age with nonmetastatic prostate cancer treated with any commonly-utilized form of radiotherapy including conformal external beam (EBRT), intensity-modulated (IMRT), brachytherapy, or a combination of radiotherapy modalities with curative treatment intent.
• Irrespective of dose and duration of radiotherapy.
• Studies having a comparison group comprising patients treated with radical prostatectomy.

Exclusion criteria:
• Studies assessing adjuvant or salvage therapy as the specific objective.
• Studies assessing nonstandard treatments (such as cryotherapy).

Primary outcome: overall mortality
Secondary outcome: prostate cancer-specific mortality.

• Studies reporting surrogate endpoints such as biochemical recurrence only were excluded.
• Since age, comorbidity, and histologic factors such as grade and stage significantly impact overall and prostate cancer-specific mortality, we considered studies only reporting multivariable adjusted hazard ratios (aHR).
Absolute mortality rates for included studies

RP-PLND vs RT for clinically localised prostate cancer

Overall mortality:
- Ten studies reporting on 95,791 patients were aggregated to assess the effect of treatment modality on overall mortality. Patients treated with radiotherapy experienced an increased risk of overall mortality compared with those treated with radical prostatectomy (aHR 1.63, 95% CI 1.54–1.73, p < 0.00001; I² = 0%).
- Similar direction of effect was found in patients with low risk prostate cancer (aHR 1.47, 95% CI 1.19–1.83, p = 0.0004, I² = 59%), intermediate risk prostate cancer (aHR 1.50, 95% CI 1.24–1.82, p < 0.0001; I² = N/A), or high risk prostate cancer (aHR 1.88, 95% CI 1.64–2.16, p < 0.00001; I² = 0%).

RP-PLND vs RT for clinically localised prostate cancer

Prostate cancer-specific mortality:
- Fifteen studies reporting on 118,830 patients were aggregated to assess the effect of treatment modality on prostate cancer-specific mortality. Patients treated with radiotherapy had an increased risk of prostate cancer-specific mortality (aHR 2.08, 95% CI 1.76–2.47, p < 0.00001; I² = 48%) compared with those treated with surgery.
- Similar direction of effect was found in patients with low risk prostate cancer (aHR 1.70, 95% CI 1.36–2.13, p < 0.00001; I² = 0%), intermediate risk prostate cancer (aHR 1.80, 95% CI 1.45–2.25, p < 0.0001; I² = 0%), or high risk prostate cancer (aHR 1.83, 95% CI 1.51–2.22, p = 0.0001; I² = 42%).
Subgroup analysis assessing risk of overall mortality and prostate cancer-specific mortality following treatment with surgery or radiotherapy

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Overall mortality</th>
<th>Prostate cancer-specific mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Adjusted HR (95% CI)</td>
<td>$I^2$</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.47 (1.28 - 1.66, p&lt;0.0001)</td>
<td>29%</td>
</tr>
<tr>
<td>High risk</td>
<td>1.78 (1.61 - 1.95, p&lt;0.0001)</td>
<td>42%</td>
</tr>
<tr>
<td>Tumor volume</td>
<td>1.80 (1.63 - 2.00, p&lt;0.0001)</td>
<td>53%</td>
</tr>
<tr>
<td>Age (55-64 vs. &gt;65)</td>
<td>1.76 (1.59 - 2.00, p&lt;0.0001)</td>
<td>45%</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>0.5-yr</td>
<td>1.54 (1.40 - 1.70, p&lt;0.0001)</td>
</tr>
<tr>
<td>1-3 yr</td>
<td>1.71 (1.56 - 1.87, p&lt;0.0001)</td>
<td>50%</td>
</tr>
<tr>
<td>4-5 yr</td>
<td>1.54 (1.38 - 1.72, p&lt;0.0001)</td>
<td>51%</td>
</tr>
<tr>
<td>Type of cancer</td>
<td>Early</td>
<td>1.74 (1.57 - 1.93, p&lt;0.0001)</td>
</tr>
<tr>
<td>Later</td>
<td>1.78 (1.61 - 1.97, p&lt;0.0001)</td>
<td>53%</td>
</tr>
<tr>
<td>Geographic region</td>
<td>1.67 (1.48 - 1.86, p&lt;0.0001)</td>
<td>54%</td>
</tr>
<tr>
<td>Best of world</td>
<td>1.62 (1.43 - 1.82, p&lt;0.0001)</td>
<td>55%</td>
</tr>
</tbody>
</table>

Conclusions:

In this review and meta-analysis of 19 studies with low to moderate risk of bias, an increased overall and prostate cancer-specific mortality for patients treated with radiotherapy compared with those treated with surgery for clinically localized prostate cancer.

Adjuvant Radiotherapy after Radical Prostatectomy

Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: A systematic review and meta-analysis. doi:10.1016/j.radonc.2008.04.013

These RCTs representing 1743 patients were included.

Eligibility Criteria:
- Patients with prostate cancer treated initially with RP of any approach, and found to have either tumour extension beyond the prostate capsule (pT3a), seminal vesicle invasion (pT3b), positive resection margins (R1) or more than one of these features.
- They randomized patients to receive either adjuvant external beam RT to the prostatic bed in the immediate postoperative period or to observation with therapies (including RT, ADT, and other therapeutic modality in salvage for salvage).
- Trials in which the adjuvant RT arm included adjuvant treatment modalities in addition to RT (e.g., concurrent adjuvant ADT) were excluded.

Meta-Analysis in treatment of Carcinoma Prostate Dr. Preety Jain
Overall survival

- Survival data were available for the EORTC and SWOG trials.
- Neither trial detected a statistically significant difference in overall survival between adjuvant RT and observation groups.
- Pooling the mortality data in a meta-analysis (Fig.) also showed no difference (HR = 0.91, 95% CI 0.67–1.22, p = 0.52).
- It should be noted that, at the time of reporting, only 89 deaths had occurred in the EORTC trial, representing an event rate of only 8.9%.

Biochemical progression-free survival

All three trials provided data on this endpoint, and the definitions of biochemical failure used by the trials were similar.

All three trials detected a longer biochemical progression-free survival with adjuvant RT compared with observation that was statistically significant.

Pooling the results of the three trials in a meta-analysis (Fig.) produced an HR of 0.47 (95% CI 0.34–0.63, p = 0.0002), which represents a 53% decrease in biochemical progression with adjuvant RT compared to observation.

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>Biochemical progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survival data were available for the EORTC and SWOG trials.</td>
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<td></td>
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</tr>
</tbody>
</table>
Metastasis-free survival

- Only the SWOG trial reported on this outcome.
- The improvement in metastasis-free survival observed with adjuvant RT did not quite reach statistical significance (HR = 0.75, 95% CI 0.55–1.02, p = 0.06).
- The EORTC study reported 19 distant failures in the adjuvant RT treatment arm and 18 in the observation group; however, a time-to-event analysis was not provided.

Clinical progression-free survival

- Clinical progression was defined as clinical or imaging evidence of locoregional or distant recurrence irrespective of PSA.
- Clinical progression-free survival was significantly greater in patients treated with adjuvant RT compared with observation in the EORTC trial (HR = 0.61, 95% CI 0.43–0.87, p = 0.0001) and SWOG trial (HR = 0.62, 95% CI 0.46–0.82, p = 0.001). It should be noted that the SWOG trial refers to this endpoint as “recurrence-free survival.”

Conclusions

- Adjuvant RT following RP in patients with pathologic T3 or margin-positive prostate cancer reduces the risk of biochemical and locoregional failure compared to observation, and prolongs the time to initiation of ADT.
- Adjuvant RT is associated with a low rate of acute and late major toxicity.
- To date, an overall survival benefit has not been demonstrated with adjuvant RT.
- Longer follow-up is needed to ascertain whether such a benefit exists.
- Early referral following RP to a radiation oncologist for a discussion around the pros and cons of adjuvant RT is advisable.
The Role of Dose Escalation


The study enrolled 301 patients with T1-2 prostate cancer, of whom 150 were treated to 70 Gy (conventional EBRT) and 151 were treated to 78 Gy (conventional EBRT followed by a 3D boost).

Prostate-specific antigen relapse-free survival

Grade 2 or higher rectal toxicity rates at 6 years were 12% and 26% for the 70-Gy and 78-Gy arms, respectively (p = 0.001)

The Role of Dose Escalation


The study enrolled 393 patients with T1b-T2a/T2b prostate cancer with pretreatment PSA levels <15 ng/mL.

Patients were randomized: 70.2 Gy Vs 79.2 Gy.

Radiotherapy Technique: Prostate only RT using protons (19.8 GyE vs 29.8 GyE) f/b 50.4 Gy to pelvis using photons.

• The proportions of men free from biochemical failure at 5 years were 78.8% [corrected] (95% confidence interval, 73.1-84.5%) for conventional-dose vs 87.2% [corrected] (95% confidence interval, 81.4-92.0%) for high-dose therapy (P<.001), a 59% [corrected] reduction in the risk of failure.

• The advantage to high-dose therapy was statistically significant [corrected] in both the low-risk subgroup [corrected] (risk reduction, 84% [P<.001]) and the intermediate-risk group.

• There has been no significant difference in overall survival rates between the treatment groups.
The Role of Dose Escalation

Meta-Analysis in treatment of Carcinoma Prostate  Dr. Preety Jain

Table 1. Role of dose escalation in localized prostate cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Dose</th>
<th>Acute Urinary Incontinence</th>
<th>Acute Rectal Incontinence</th>
<th>Late Urinary Incontinence</th>
<th>Late Rectal Incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDRT</td>
<td>66-74 Gy</td>
<td>16%</td>
<td>5%</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>HDRT</td>
<td>78-84 Gy</td>
<td>9%</td>
<td>2%</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Only 1% of patients receiving conventional-dose and 2% receiving high-dose radiation experienced acute urinary or rectal toxicity at a median follow-up of 34 months. Grade 3 or 4 acute toxicity was 2% of patients receiving conventional-dose and 1% of patients receiving high-dose radiation. This advantage was achieved without any associated increase in RTOG grade 3 or 4 late toxicity or mortality.

The Role of Dose Escalation


Purpose:

To determine in a meta-analysis whether the outcomes in men with localized prostate cancer treated with higher-than-conventional radiation doses are better than those in men treated with conventional-dose radiotherapy (CDRT), by quantifying the effect of the total dose of radiotherapy on biochemical control (BC).

Seven RCTs with a total patient population of 2812 were identified.

Eligibility Criteria:

- The men in the studies had to have histologically confirmed localized prostate cancer and to have undergone no previous treatment with pelvic radiotherapy, radical prostatectomy, or androgen deprivation therapy.

- Studies that included patients with evidence of metastatic disease were excluded.

Characteristics of studies of high-dose radiotherapy for localized prostate cancer

- Higher-than-conventional radiation doses were associated with improved biochemical control, especially for patients with high-risk disease.

- The results were consistent across different study populations and treatment modalities.

- The risk of progression and death was also reduced with high-dose radiation.

Meta-Analysis in treatment of Carcinoma Prostate  Dr. Preety Jain
Biochemical failure

- Six studies, with a total population of 2506 patients, analyzed biochemical failure as one of the outcomes.
- The biochemical failure rates were less in the HDRT arm (312 of 1255, 24.8%) than in the CDRT arm (434 of 1251, 34.6%).
- The overall odds ratio suggests that there was a statistically significant difference between the HDRT and CDRT arms in terms of the biochemical failure rate, with a p value of <0.0001, as shown in Fig.

Mortality rate

- Five studies, with a total patient population of 1663, examined mortality as one of the outcomes.
- The overall mortality rates were not decreased in the HDRT arm (120 of 833, 14.4%) compared with the CDRT arm (117 of 830, 14%).
- The overall odds ratio for all the trials was 1.02 (99% CI 0.7–1.4). The result of the test for heterogeneity was not statistically significant (p = 0.69).
- The overall odds ratio suggested that there was no difference between the HDRT and CDRT arms in terms of the overall mortality rate, with a p value of 0.88, as shown in Fig.
Prostate cancer–specific mortality
- Five studies with a total patient population of 1663 patients evaluated prostate cancer–specific mortality.
- The prostate cancer–specific mortality rates were 4.9% (41 of 833) in the HDRT arm and 6.1% (51 of 830) in the CDRT arm.
- The individual odds ratios varied from 0.45 to 1.44. The result of the test for heterogeneity was not statistically significant (p = 0.41), which allowed the results to be pooled.
- The overall odds ratio was 0.81 (99% CI 0.45–1.44), as shown in Fig.

Late Grade 2 GI and GU toxicity
- Six trials consisting of a total patient population of 2708, evaluated GI and GU toxicity.
- High-dose radiotherapy was associated with late Grade 2 GI toxicity, with an OR of 1.58 (99% CI 1.36–2.36, p = 0.006), without heterogeneity (p = 0.084).
- No significant difference was observed between the treatment arms with regard to late Grade 2 GU toxicity, with an OR of 1.2 (99% CI 0.9–1.5, p = 0.054), as shown in Figs.

CONCLUSIONS
- This meta-analysis provides evidence that HDRT is superior to CDRT in terms of preventing biochemical failure in low-, intermediate-, and high-risk prostate cancer patients, suggesting that HDRT should be offered to all patients regardless of their risk status.
- Across a range of total radiotherapy doses from 64 to 79.2 Gy, biochemical control in men with localized prostate cancer, according to regression analysis, was essentially uniform.
- The presence of a dose–response relationship supports the use of HDRT, because CDRT may increase the recurrence risk.
- Although the highest effective radiotherapy dose has not yet been identified, it could be higher than 90 Gy.
- However, because significant differences in late Grade 2 rectal toxicity were seen between the HDRT and CDRT groups, further trials of IGRT and IMRT to deliver doses higher than 80 Gy should be conducted with the goal to maintain the therapeutic index at a satisfactory level.
**ADT with RT vs RT alone in locally advanced prostate cancer**

**Does hormone treatment added to radiotherapy improve outcome in locally advanced prostate cancer?: meta-analysis of randomized trials. DOI: 10.1002/cncr.24392**

- Seven trials (4387 patients) were gathered. 
- The combination of HT and RT was considered as the experimental arm, and exclusive RT as the standard comparator.

**Primary outcomes were:**
1. biochemical failure (time between randomization and prostate-specific antigen increases) 
2. clinical PFS (clinical progression-free survival, time between randomization and clinical evidence of local and/or distant relapse or death by any cause).

**Secondary endpoints were:**
1) cancer-specific survival (time between randomization and death for prostate cancer), 
2) OS (time between randomization and death by any cause), 
3) local failure rate, 
4) distant metastases rate (DM), 
5) overall grade 3-4 toxicities, 
6) genitourinary grade 3-4 toxicity (GI), 
7) gastrointestinal grade 3-4 toxicities (GI), and 
8) cardiac deaths.

**TRIAL CHARACTERISTICS**

**Primary outcomes**
- HT significantly decreased biochemical and clinical failure over exclusive RT by 24% and 19%, respectively. 
- The absolute benefit was 18% for biochemical failure and 7.7% for clinical progression-free survival, corresponding to 10 and 13 NNT (number needed to treat), respectively. 
- The benefit was obtained regardless of HT duration.

**Secondary outcomes**
- HT significantly reduced the risk of death for prostate cancer by 24%, without significant heterogeneity. This corresponds to an absolute benefit of 5.5%, with 19 NNT. 
- In the sensitivity analysis, the absolute benefit in cancer-specific survival ranges from 5.0% in the long-term trials to 7.2% in the short-term trials. 
- HT significantly decreased the risk of death by any cause by 14%, regardless of treatment duration, with an absolute benefit of 4.9%, corresponding to 20 NNT. 
- With regard to recurrence, both local relapses (2.4%) and DM were significantly decreased (36% and 28%, respectively) by the addition of HT to RT, with a 0.9% and 0.9% absolute benefit, corresponding to 19 NNT.
ADT with RT vs RT alone in locally advanced prostate cancer

Secondary outcomes
- No significant differences in toxicities and cardiac deaths were observed by comparing the 2 arms, without heterogeneity.
- According to the meta-regression analysis, none of the considered predictors significantly affected outcome, with the exception of lymph node positivity and Gleason score, which significantly influenced clinical progression-free survival.

Conclusion:
- The present meta-analysis demonstrates that the administration of hormone-suppressive therapy in patients affected by prostate cancer who are candidates to receive exclusive RT significantly improves all investigated outcomes.
- Although with significant heterogeneity in many of the endpoints, the overall absolute benefit is in the range of 7.5% to 10% in favor of HT for both primary outcomes, biochemical failure and clinical progression-free survival.
- Although no statistically significant differences in toxicity were observed, the 31% to 34% reduction in the RR and GI toxicities observed for patients receiving the combined treatment suggests that the addition of HT to RT may actually prove beneficial in a larger population.
- According to the results reported herein, no significant difference in terms of cardiac deaths was observed when comparing exclusive RT with HT & RT.
IMRT vs 3D-CRT for Prostate cancer


PURPOSE:
To assess whether IMRT can provide better clinical outcomes in comparison with 3D-CRT in patients diagnosed with prostate cancer.

A total of 23 studies containing 9556 patients were included.

INCLUSION CRITERIA:
1) Studies with GI, GU toxicity or other clinical outcomes, including RFS or OS
2) Late Grade ≥ Grade 2 toxicity were scored according to the Fox Chase (TC) modification of the Radiation Therapy Oncology Group (RTOG) and Late Effects Normal Tissue Task Force (LENT) toxicity criteria (RTOG/<{RTOG}/LENT late toxicity criteria/CTCAE version 2.0, 3.0, or 4.0)
3) Late rectal bleeding was scored based on RTOG criteria
4) Biochemical failure was defined as a rise in prostate-specific antigen (PSA) level of ≥ 2 ng/ml above the nadir, with no backdating (ASTROPhoenix definition)

Summary of the studies included in the meta-analysis:

The total number of the included patients was 9556, ranging from 27 to 1571 per study.

The prescribed doses to the primary tumor were 70–85.3 Gy in IMRT group and 55.8–84.8 Gy in 3D-CRT group.

Stage III comprised 71.3% of the patients, and the remaining 22.7% were in stage I+II.

The median follow-up time ranged from 5.3 months to 120 months.
IMRT vs 3D-CRT for Prostate cancer

Summary of the outcomes presented in this meta-analysis:

- 14 studies compared the effects of acute toxicity of an IMRT group to that of a 3DCRT group, including acute GI toxicity (n = 12), acute GU toxicity (n = 12) and acute rectal toxicity (n = 4).
- 21 studies compared the late toxicity effects of IMRT group to that of 3DCRT group, including late GI toxicity (n = 13), late GU toxicity (n = 12) and late rectal bleeding (n = 6).
- 6 studies compared the biochemical control between IMRT group and 3DCRT group,
- 3 studies compared the OS between IMRT group and 3DCRT group.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of studies</th>
<th>No. of total patients</th>
<th>RR (95% CI) (IMRT vs 3DCRT)</th>
<th>P for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GI toxicity (grade 2–4)</td>
<td>12</td>
<td>4142</td>
<td>0.53 (0.44, 0.63)</td>
<td>0.000</td>
</tr>
<tr>
<td>Acute GU toxicity (grade 2–4)</td>
<td>14</td>
<td>9936</td>
<td>1.00 (1.00, 1.17)</td>
<td>0.366</td>
</tr>
<tr>
<td>Acute rectal toxicity (grade 2–4)</td>
<td>4</td>
<td>2188</td>
<td>1.03 (0.65, 1.63)</td>
<td>0.000</td>
</tr>
<tr>
<td>Late GI toxicity (grade 2–4)</td>
<td>1 year</td>
<td>4</td>
<td>0.26 (0.15, 0.46)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>3 years</td>
<td>7</td>
<td>0.70 (0.46, 1.08)</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>5–9 years</td>
<td>8</td>
<td>0.55 (0.31, 0.98)</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>11</td>
<td>0.54 (0.30, 0.97)</td>
<td>0.030</td>
</tr>
<tr>
<td>Late GU toxicity (grade 2–4)</td>
<td>1 year</td>
<td>4</td>
<td>0.63 (0.46, 0.88)</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>3 years</td>
<td>5</td>
<td>0.78 (0.74, 1.29)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>5–9 years</td>
<td>7</td>
<td>1.09 (0.69, 1.71)</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>12</td>
<td>1.03 (0.62, 1.70)</td>
<td>0.000</td>
</tr>
<tr>
<td>Late rectal bleeding (grade 2–4)</td>
<td>1 year</td>
<td>5</td>
<td>0.48 (0.27, 0.85)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>3 years</td>
<td>5</td>
<td>0.49 (0.27, 0.89)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>5–9 years</td>
<td>9</td>
<td>0.97 (0.54, 1.77)</td>
<td>0.000</td>
</tr>
<tr>
<td>Biochemical control</td>
<td>6</td>
<td>2416</td>
<td>1.17 (1.05, 1.31)</td>
<td>0.010</td>
</tr>
<tr>
<td>OS</td>
<td>3</td>
<td>424</td>
<td>1.67 (0.96, 1.18)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Meta-Analysis in treatment of Carcinoma Prostate Dr. Preety Jain
IMRT vs 3D-CRT for Prostate cancer

OUTCOME:

- IMRT significantly decreased grade 2–4 acute GI toxicity compared with 3D-CRT [RR = 0.59, 95% CI (0.44, 0.78)].
- Incidence of grade 2–4 acute GU toxicity was only 1.08-fold higher in IMRT than that in 3D-CRT, which showed modest effect [RR = 1.08, 95% CI (1.00, 1.17)].
- There was no significant difference between IMRT and 3D-CRT in grade 2–4 acute rectal toxicity [RR = 1.03, 95% CI (0.45, 2.36)].
- A significant overall benefit of grade 2–4 late GI toxicity in favor of IMRT was found for all studies with a RR of 0.54 [95% CI (0.38, 0.76)].
- IMRT was with comparable grade 2–4 late GU toxicity with 3D-CRT [RR = 1.03, 95% CI (0.82, 1.28)]. The results clearly favor IMRT over 3D-CRT in grade 2–4 late rectal bleeding [RR = 0.48, 95% CI (0.27, 0.85)].
- There was a significant difference in biochemical control favoring IMRT [RR = 1.17, 95% CI (1.08, 1.27)]. IMRT showed modest increase in biochemical control compared with 3D-CRT.
- A non-significant increase in overall survival favoring IMRT [RR = 1.07, 95% CI (0.96, 1.19)].
IMRT vs 3D-CRT for Prostate cancer

Conclusion:
• IMRT significantly decreases the occurrence of 2–4 grade acute GI toxicity, late GI toxicity, late rectal bleeding, and achieves better PSA relapse free survival in comparison with 3D CRT.
• IMRT and 3D CRT remain the same in regard of acute rectal toxicity, late GU toxicity and overall survival, while IMRT increases the morbidity of acute GU toxicity.
• In general, based on the above results, IMRT should be considered as a better choice for the treatment of prostate cancer.

Stereotactic body radiotherapy for primary prostate cancer: A systemic review

• The relatively slow proliferation rate of prostate cancer is reflected in a low α/β ratio, most commonly reported between 1 and 4.
• These values are similar to that for the rectal mucosa.
• Since the α/β ratio for prostate cancer is similar to or lower than the surrounding tissues, hypo fractionated regimens are feasible. Based on the patients' clinical features, extremely hypo fractionated regimens should result in similar cancer control rates without increased risk of late toxicity.
• Center researchers found insufficient evidence to indicate that SBRT is an effective treatment for prostate cancer.
• One systematic review of case series looked at outcomes from SBRT (Tan, Siva, Foroudi, & Gill, 2014)
• Fourteen phase I–II trials and retrospective studies using SBRT for the treatment of prostate cancer were used.
  Three studies were identified which addressed cost.
### Stereotactic body radiotherapy for primary prostate cancer:

- Dose fractionation, radiotherapy procedures, biochemical progression-free survival, toxicity, cost and quality of life were critically appraised.

A total of 1472 patients were examined across studies.

Median follow-up ranged from 11 to 60 months.

- The most common dose fractionation was 34–36.25 Gy in five fractions, used in nine out of 14 studies.
- Ten of 14 studies used CyberKnife.

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Dose (Gy)</th>
<th>Biochemical Progression-Free Survival (%)</th>
<th>Hormone Therapy Use</th>
<th>Cost-effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al. 2017</td>
<td>Rationale</td>
<td>34-36.25</td>
<td>Biochemical progression-free survival 81-100%</td>
<td>Yes</td>
<td>IMRT more cost-effective than SBRT</td>
</tr>
<tr>
<td>Kim et al. 2015</td>
<td>Rationale</td>
<td>34-36.25</td>
<td>Biochemical progression-free survival 81-100%</td>
<td>Yes</td>
<td>IMRT more cost-effective than SBRT</td>
</tr>
<tr>
<td>Lee et al. 2016</td>
<td>Rationale</td>
<td>34-36.25</td>
<td>Biochemical progression-free survival 81-100%</td>
<td>Yes</td>
<td>IMRT more cost-effective than SBRT</td>
</tr>
</tbody>
</table>

Summary of dose given, use of hormone therapy and corresponding bPFS for each respective study

- The overall biochemical progression-free survival ranged 81–100%.
- When bPFS was analysed according to total dose received, no difference was observed for the dose range studied in this analysis (34–40.5 Gy in five fractions).
- The most common planning CTV-PTV expansion used was a 3-mm margin posteriorly and 5-mm expansion in all other dimensions.
- Luong et al. assessed intra-fraction motion in 17 patients with electromagnetic transponders implanted in the prostate; on average, the prostate displaced by +3 mm and +5 mm approximately 14% and 5% of the time, respectively.
- Lifetime costs and QALY for hypothetical cohorts of SBRT-treated patients were simulated in a parameter including assumed mortality, bPFS and toxicity and compared with similar parameters from SBRT-treated patients for prostate cancer through the Markov model of analysis.

It was consistently seen that SBRT overall was more cost-effective than IMRT and PT in the treatment of prostate cancer.

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**Meta-Analysis in treatment of Carcinoma Prostate Dr. Preety Jain**
Stereotactic body radiotherapy for primary prostate cancer:

Toxicities:
- Acute grade 2 urinary and rectal toxicities were reported in 5–42% and 0–27% of patients, respectively.
- Acute grade 3 or more urinary and rectal toxicity were 0.5% and 0%, respectively.
- Late grade 2 urinary toxicity was reported in 0–26% of patients, while 1.3% had a late grade 3 urinary toxicity.
- There were no late grade 4 urinary toxicities seen.
- Late grade 2 rectal toxicity was reported in 0–11%, while 0.5% had a late grade 3 rectal toxicity.
- Late grade 4 rectal toxicity was reported in 0.2% of patients.

IMRT vs 3D-CRT for Prostate cancer toxicities

National Population-Based Study Comparing Treatment-Related Toxicity in Men Who Received Intensity Modulated Versus 3-Dimensional Conformal Radical Radiation Therapy for Prostate Cancer

A.Sujenthiran, MRCS  doi.org/10.1016/j.ijrobp.2017.07.040

Purpose:
To compare, severe genitourinary (GU) and gastrointestinal (GI) toxicity in patients with prostate cancer who were treated with radical intensity modulated radiation therapy (IMRT) or 3-dimensional conformal radiation therapy (3D-CRT), in a national population-based study.

Data sources and patient population:
Patients treated with IMRT (n=6933) or 3D-CRT (n=16,289) between January 1, 2010 and December 31, 2013 in the English National Health Service were identified using cancer registry data, the National Radiotherapy Dataset, and Hospital Episodes Statistics, the administrative databases of data episodes in National Health Service hospitals.
Inclusion and exclusion criteria

Included Treatment categories:
- IMRT
- 3D-CRT

Exclusion criteria:
- Did not include any of the above
- Underwent adjuvant hormonal therapy
- Underwent modified radical prostatectomy
- Underwent neoadjuvant hormonal therapy
- Underwent previous radiation therapy

Table: Patient Population

<table>
<thead>
<tr>
<th>Region (area in cm²)</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1233</td>
</tr>
<tr>
<td>2</td>
<td>1234</td>
</tr>
<tr>
<td>3</td>
<td>1235</td>
</tr>
</tbody>
</table>

Mean and median values:
- Mean AFT (9.1) ± 1.9
- Median AFT (9.1) ± 1.9

IMRT vs 3D-CRT for Prostate cancer

Patient population:
- Among patients who received radical RT (n=23,222), the use of IMRT increased from 3.1% in 2010 to 64.7% in 2013.
- Approximately 60% of men included were between 65 and 74 years old.
- Approximately 1 in 5 men had at least 1 recorded comorbidity.
- Nearly 60% of patients were staged with locally advanced disease.
- The median dose per fraction and total dose received were the same in both groups (2 Gy per fraction and 74.4 Gy, respectively).
- Men in the 3D-CRT group were more likely to be older and have an RCS Charlson score 1 but were less likely to have locally advanced disease and receive radiation to the prostate and nodal compared with the IMRT group.
- Median (interquartile range) follow-up was 3.6 (1.9) years for all men in the study, 2.7 (1.1) years for the IMRT group, and 4.1 (1.6) years for the 3D-CRT group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3D-CRT (n=13,389)</th>
<th>IMRT (n=9,833)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of radiation therapy</td>
<td></td>
<td></td>
<td>&lt;.05</td>
</tr>
<tr>
<td>1</td>
<td>2445 (18.4)</td>
<td>216 (2.1)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3669 (27.2)</td>
<td>623 (6.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1069 (7.9)</td>
<td>897 (9.1)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3031 (22.5)</td>
<td>369 (3.8)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2397 (17.9)</td>
<td>206 (2.1)</td>
<td></td>
</tr>
<tr>
<td>RCS Charlson comorbidity score</td>
<td></td>
<td></td>
<td>&gt;.05</td>
</tr>
<tr>
<td>0</td>
<td>12,697 (92.2)</td>
<td>9842 (79.8)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1209 (8.7)</td>
<td>948 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Race (Black)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (lowest deprived)</td>
<td>3983 (29.6)</td>
<td>3049 (25.6)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4308 (32.3)</td>
<td>1720 (13.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1025 (7.8)</td>
<td>1071 (8.7)</td>
<td></td>
</tr>
<tr>
<td>RCS Charlson score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2397 (17.9)</td>
<td>206 (2.1)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>1</td>
<td>2035 (15.1)</td>
<td>212 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Race (Asian)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (lowest deprived)</td>
<td>2226 (16.8)</td>
<td>215 (2.2)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>RCS Charlson score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2397 (17.9)</td>
<td>206 (2.1)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2035 (15.1)</td>
<td>212 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Treatment region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>3841 (28.8)</td>
<td>2830 (29.4)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Pelvis</td>
<td>3425 (25.6)</td>
<td>2231 (23.4)</td>
<td></td>
</tr>
<tr>
<td>IMRT vs 3D-CRT treatment</td>
<td>11,272 (85.3)</td>
<td>4786 (49.5)</td>
<td></td>
</tr>
<tr>
<td>Local vs non-local</td>
<td>295 (2.1)</td>
<td>101 (1.1)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Missing</td>
<td>1037 (7.8)</td>
<td>234 (2.4)</td>
<td></td>
</tr>
</tbody>
</table>

P-values: < .05.
IMRT vs 3D-CRT for Prostate cancer

Timing and frequency of occurrence of toxicity

- Patients experienced 4.9 GI events per 100 person years of follow-up in the IMRT group, compared with 6.5 in the 3D-CRT group.
- Patients who received IMRT experienced 2.3 GU events per 100 person years of follow-up, compared with 2.4 in the 3D-CRT group.
- Men treated with IMRT were less likely to experience GI toxicity (HR 0.68; 95% CI 0.61-0.77; P<0.01) than those who received 3D-CRT.
- There was no significant difference in GU toxicity between the groups (HR 0.94; 95% CI 0.84-1.06; P=0.31).

<table>
<thead>
<tr>
<th>GI toxicity</th>
<th>5-year cumulative incidence (%)</th>
<th>Rate (per 100 person years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td>5.4 (5.3-5.5)</td>
<td>6.5</td>
</tr>
<tr>
<td>3D-CRT</td>
<td>6.6 (6.5-6.7)</td>
<td>8.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GU toxicity</th>
<th>5-year cumulative incidence (%)</th>
<th>Rate (per 100 person years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td>11.3 (10.3-11.3)</td>
<td>5.4</td>
</tr>
<tr>
<td>3D-CRT</td>
<td>10.5 (9.5-11.5)</td>
<td>5.5</td>
</tr>
</tbody>
</table>

**Conclusion**

This national population-based study of patients with nonmetastatic prostate cancer, shown that men who received radical RT using IMRT were less likely to experience severe GI toxicity and similar or severe GU toxicity compared with those who received 3D-CRT.
Health-related quality of life (QOL) outcome comparison between RP and EBRT for localized prostate cancer


Objective
To compare health-related quality of life (QOL) outcomes between radical prostatectomy (RP) and external beam radiation therapy (EBRT) for localized prostate cancer. A total of six studies containing 4423 patients were included. (2615 men underwent RP and 1808 with EBRT)

Studies included
1. men diagnosed with localized prostate cancer  
2. treatment group is RP and EBRT  
3. outcome data were presented or can be calculated as mean and standard deviation (SD)  
4. health-related QOL outcomes were presented as EPIC domain summary scores, specifically, urinary, sexual, and gastrointestinal scores  
5. the most recent or representative study of the same author or group was selected to include.

Studies excluded
1. no mean or SD values can be get  
2. not written in English  
3. not use EPIC score as QOL measurement tool.

Characteristics of studies included in this meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>QOL measures</th>
<th>Patient numbers</th>
<th>Treatment cohorts</th>
<th>QOL domains</th>
<th>NOS score</th>
<th>Follow-up time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanda 2009</td>
<td>Prospective study</td>
<td>EPIC</td>
<td>RP = 571, EBRT = 553</td>
<td>RP: Neoadjuvant hormonal therapy + RP, EBRT: Boosted dose EBRT</td>
<td>Sexual, hormonal, sexual, hormonal and social</td>
<td>7</td>
<td>3, 6, 12, 18 months</td>
</tr>
<tr>
<td>Kate 2012</td>
<td>Retrospective study</td>
<td>EPIC</td>
<td>RP = 127, EBRT = 114</td>
<td>RP: Neoadjuvant hormonal therapy + RP, EBRT: EBRT</td>
<td>Urinary, sexual, hormonal, social</td>
<td>5</td>
<td>1, 6, 12, 24, 36 months</td>
</tr>
<tr>
<td>Gore 2009</td>
<td>Prospective study</td>
<td>EPIC</td>
<td>RP = 522, EBRT = 456</td>
<td>RP: Neoadjuvant hormonal therapy + RP, EBRT: EBRT</td>
<td>Urinary, sexual, hormonal, social</td>
<td>6</td>
<td>3, 6, 12, 24 months</td>
</tr>
<tr>
<td>Zaman 2016</td>
<td>RCT</td>
<td>EPIC</td>
<td>RP = 331, EBRT = 321</td>
<td>RP: Open surgical, EBRT: EBRT</td>
<td>Urinary, sexual, hormonal, social</td>
<td>7</td>
<td>6, 12, 24, 48, 68, 120 months</td>
</tr>
<tr>
<td>Rassweiler 2013</td>
<td>Prospective study</td>
<td>EPIC</td>
<td>RP = 440, EBRT = 411</td>
<td>RP: LRP, EBRT: EBRT</td>
<td>Urinary, sexual, hormonal, social</td>
<td>7</td>
<td>6, 12, 24, 48, 100 months</td>
</tr>
<tr>
<td>Vincenzo 2014</td>
<td>Cross-over trial</td>
<td>EPIC</td>
<td>RP = 29, EBRT = 29</td>
<td>RP = RP, EBRT: EBRT</td>
<td>Urinary, sexual, hormonal, social</td>
<td>4</td>
<td>36 months</td>
</tr>
</tbody>
</table>

Abbreviations: RP: radical prostatectomy; EBRT: external beam radiation therapy; RCT, Randomized trial; EPIC, Expanded Prostate Cancer Index Composite; QOL, quality of life; NOS, Newcastle-Ottawa scale; NS, not stated or controlled trial.

Results:

Health-related quality of life (QOL) outcome comparison between RP and EBRT for localized prostate cancer

Urinary quality of life:

- Patients undergoing RP had lower urinary domain scores than men undergoing EBRT (SMD = -0.38, 95% CI = -0.53 to -0.23)  
- In sub-group analysis, compared to EBRT group, RP group had the lowest urinary domain scores in the first months (SMD = -0.41, 95% CI = -0.50 to -0.32) and experienced a sharp increase in the following two months (SMD = -0.61, 95% CI = -0.74 to -0.48).
- The gap between RP and EBRT was narrowing over the years and only minimal difference existed in the 15th year (SMD = -0.31, 95% CI = -0.45 to -0.17).
Health-related quality of life (QOL) outcome comparison between RP and EBRT for localized prostate cancer

**Sexual quality of life:**
- Patients undergoing RP had lower sexual domain scores than men undergoing EBRT (SMD = −0.58; 95% CI = –0.72 to –0.44). In sub-group analysis, compared to EBRT group, RP group had the lowest sexual domain scores in the first month (SMD = −2.05; 95% CI = −2.35 to −1.75) and experienced a sharp decrease in the second month (SMD = −0.76; 95% CI = –0.93 to –0.59).
- The gap between RP and EBRT was diminished afterwards and got to the minimum difference in the 15th year (SMD = –0.31; 95% CI = –0.35 to 0.14).
- In the 15th year, sexual quality of life was slightly better for RP than EBRT group (SMD = 0.22; 95% CI = 0.03 to 0.41).

**Bowel quality of life:**
- Patients undergoing RP had higher bowel domain scores than men undergoing EBRT (SMD = 0.42, 95% CI = 0.33 to 0.52).
- In sub-group analysis, compared to EBRT group, RP group had the highest bowel domain scores in the first month (SMD = 1.69; 95% CI = 1.37 to 2.01) and experienced a sharp decrease in the second month (SMD = 0.50; 95% CI = 0.33 to 0.64).
- The difference between RP and EBRT was shortening over the time and got to the minimum in the 15th year (SMD = 0.17; 95% CI = –0.04 to 0.34).
- Remarkably, bowel problems happened in the sixth month (SMD = 0.23; 95% CI = 0.07 to 0.39) and reached to a new peak in the 15th year (SMD = 0.76; 95% CI = 0.64 to 0.88), indicating EBRT may have long-term bowel side effects.

**Discussion:**

- Urinary problems in patients undergoing RP developed most severely in the first month, dropped fast in the next two months and resolved in the long term. Both RP and EBRT group reached a comparable outcome regarding urinary QOL in the long term.
- RP experienced impaired sexual QOL immediately after surgery, which returned fast in the second month and improved over time. In the 15th year, sexual QOL was slightly better for RP than EBRT group (SMD = 0.22; 95% CI = 0.03 to 0.41).
- EBRT group had the highest incidence of bowel side effects in the first month and resolve quickly within two months, which can be controlled well in the subsequent five years. Bowel symptoms exacerbated 5 years later especially in the 15th year, indicating EBRT may have long-term bowel side effects which cannot be ignored.

**Conclusion:**

Men treated with RP experienced an acute worsen with respect to urinary and sexual QOL in the first two months post-operation, which subsided rapidly after two months. Both RP and EBRT group reached a comparable outcome regarding urinary QOL in the long term.

The two treatment groups continue to have similar health-related prognosis in the long-term follow-up.

- RP group had the highest incidence of bowel side effects in the first month and resolve quickly within two months, which can be controlled well in the subsequent five years.
- Bowel symptoms exacerbated 5 years later especially in the 15th year, indicating EBRT may have long-term bowel side effects which cannot be ignored.

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**Meta-Analysis in treatment of Carcinoma Prostate Dr. Preety Jain**
Key Takeaway Messages

- Lower the PSA better the outcome
- Start RT at the earliest after PSA > 0.2 ng/ml
- Higher dose/PG (70 Gy) clearly better
- Adjacent and salvage-RT after RPE both improve recurrence free survival and offer a second chance of cure
- Adjacent RT should be considered in patients with positive margins
- SBRT/extremely hypofractionated image-guided IMRT regimens (6.5 Gy per fraction or greater) can be considered as an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.
- HT along with RT
- Improves outcome
  
Duration uncertain
Balance toxicities

Thank you

A lot is known and a lot is yet to be explored