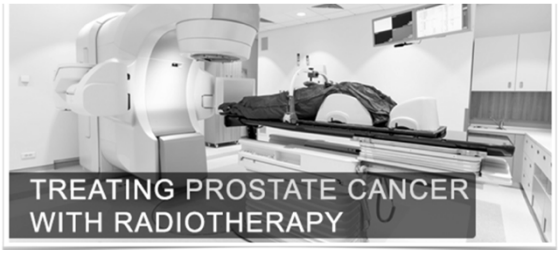


# Metaanalysis

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## Flow of presentation

- Prostate cancer overview
- Staging
- Stratification of risk
- NCCN guidelines of management

- Various metaanalysis
- Take home message

## Overview

**Prostate Cancer**

- **World wide :**
  - 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 and
    - 97.2 per 100,000 Northern America

## In India

- Previously – thought - prevalence of prostate cancer in India is far lower compared to western countries but …
  - – 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

**American Joint Committee on Cancer (AJCC)**
**TNM Staging System For Prostate Cancer (8th ed., 2017)**
***Table 1.* Definitions for T, N, M**
***Clinical T (cT)***

| T | Primary Tumor |
|---|---|
| **TX** | Primary tumor cannot be assessed |
| **T0** | No evidence of primary tumor |
| **T1** | Clinically inapparent tumor that is not palpable |
| T1a | Tumor incidental histologic finding in 5% or less of tissue resected |
| T1b | Tumor incidental histologic finding in more than 5% of tissue resected |
| T1c | Tumor identified by needle biopsy found in one or both sides, but not palpable |
| **T2** | Tumor is palpable and confined within prostate |
| T2a | Tumor involves one-half of one side or less |
| T2b | Tumor involves more than one-half of one side but not both sides |
| T2c | Tumor involves both sides |
| **T3** | Extraprostatic tumor that is not fixed or does not invade adjacent structures |
| T3a | Extraprostatic extension (unilateral or bilateral) |
| T3b | Tumor invades seminal vesicle(s) |
| **T4** | Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall. |

***Pathological T (pT)***

| T | Primary Tumor |
|---|---|
| **T2** | Organ confined |
| **T3** | Extraprostatic extension |
| T3a | Extraprostatic extension (unilateral or bilateral) or microscopic invasion of the bladder neck |
| T3b | Tumor invades seminal vesicle(s) |
| **T4** | Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall |

*Note: There is no pathologic T1 classification.
**Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

| N | Regional Lymph Nodes |
|---|---|
| **NX** | Regional lymph nodes cannot be assessed |
| **N0** | No positive regional nodes |
| **N1** | Metastases in regional node(s) |

| M | Distant Metastasis |
|---|---|
| **M0** | No distant metastasis |
| **M1** | Distant metastasis |
| M1a | Non-regional lymph node(s) |
| M1b | Bone(s) |
| M1c | Other site(s) with or without bone disease |

*Note: When more than one site of metastasis is present, the most advanced categor is used. M1c is most advanced.

**Table 2. AJCC Prognostic Groups***

| Group | T | N | M | PSA (ng/mL) | Grade Group |
|---|---|---|---|---|---|
| **Stage I** | cT1a-c | N0 | M0 | PSA <10 | 1 |
| | cT2a | N0 | M0 | PSA <10 | 1 |
| | pT2 | N0 | M0 | PSA <10 | 1 |
| **Stage IIA** | cT1a-c | N0 | M0 | PSA ≥10 <20 | 1 |
| | cT2a | N0 | M0 | PSA ≥10 <20 | 1 |
| | pT2 | N0 | M0 | PSA ≥10 <20 | 1 |
| | cT2b | N0 | M0 | PSA <20 | 1 |
| | cT2c | N0 | M0 | PSA <20 | 1 |
| **Stage IIB** | T1-2 | N0 | M0 | PSA <20 | 2 |
| **Stage IIC** | T1-2 | N0 | M0 | PSA <20 | 3 |
| | T1-2 | N0 | M0 | PSA <20 | 4 |
| **Stage IIIA** | T1-2 | N0 | M0 | PSA ≥20 | 1-4 |
| **Stage IIIB** | T3-4 | N0 | M0 | Any PSA | 1-4 |
| **Stage IIIC** | Any T | N0 | M0 | Any PSA | 5 |
| **Stage IVA** | Any T | N1 | M0 | Any PSA | Any |
| **Stage IVB** | Any T | Any N | M1 | Any PSA | Any |

Note: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

**Histopathologic Type**
This classification applies to adenocarcinomas and squamous carcinomas, but not to sarcoma or transitional cell (urothelial) carcinoma of the prostate. Adjectives used to describe histologic variants of adenocarcinomas of the prostate include mucinous, signet ring cell, ductal, and neuroendocrine, including small cell carcinoma. There should be histologic confirmation of the disease.

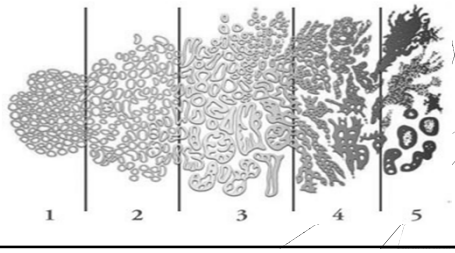
**Definition of Histologic Grade Group (G)**
Recently, the Gleason system has been compressed into so-called Grade Groups.

| Grade Group | Gleason Score | Gleason Pattern |
|---|---|---|
| 1 | ≤6 | ≤3+3 |
| 2 | 7 | 3+4 |
| 3 | 7 | 4+3 |
| 4 | 8 | 4+4, 3+5, 5+3 |
| 5 | 9 or 10 | 4+5, 5+4, 5+5 |

GLEASON GRADING SYSTEM

- Core biopsies are measured for histologic aggressiveness using the above system, correlates w/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

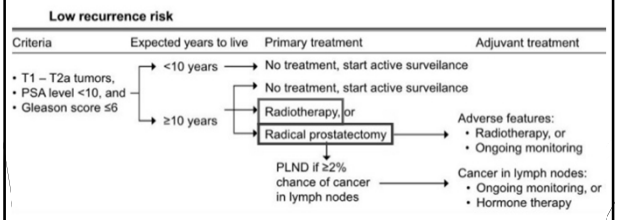


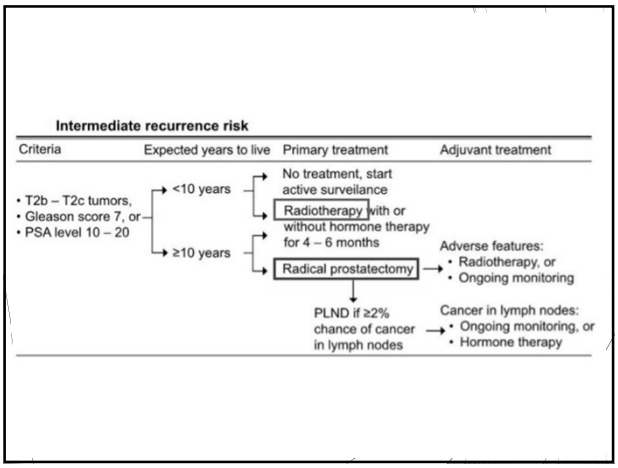

## Risk Stratification Systems

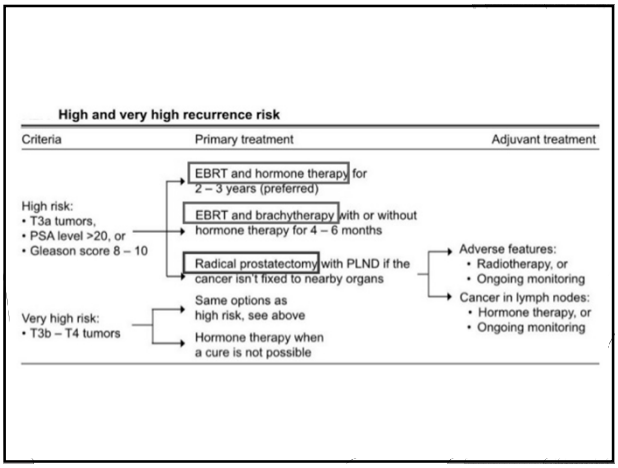
- Based on tumor stage, pretreatment PSA, and biopsy Gleason score- several risk stratification models have developed.

| Risk Group | Low | Intermediate | High |
|---|---|---|---|
| Seattle/MSKCC | PSA <10 ng/mL and GS 2-6 and stage T1-T2b | PSA >10 ng/mL or GS >=7 or stage >=T2c | Two or three of the intermediate risk factors |
| Mt. Sinai | PSA <10 ng/mL and GS 2-6 and stage T1-T2a | PSA 10.1-20 ng/mL or GS 7 or stage T2b | Two or three of the intermediate risks and/or PSA >20 ng/mL and/or GS 8-10 and/or stage >=T2c |
| D'Amico | PSA <10 ng/mL and GS 2-6 and stage T1-T2a | PSA 10.1-20.0 ng/mL and/or GS 7 and/or stage T2b | PSA >20 ng/mL and/or GS 8-10 and/or stage >=T2c |

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






## Radiation therapy

- **RADICAL RADIOTHERAPY** ( MONOTHERAPY)
- **SALVAGE RADIOTHERAPY**
  PSA recurrence after surgery
  No distant mets
  Few months to yeats after RP
- **ADUVANT 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
  - uresectable,
  - elderly , frail, comorbid condition
  - refusal for surgery
  - prohibitive morbidity due to surgery
- Post op radiotherapy
  - pT3/4
  - Close & positive margins
  - Extracapsular extension
  - Invasion to
    - Seminal vesicles
    - Extraprostatic extension
  - multiple nodes
  - R1 resection
  - Pre op PSA >10ng/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 systemic review and metaanalysis
- 2. Adjuvant RT following radical prostatectomy for pT3 or margin positive PCa.: A systemic review and metaanalysis
- 3. Higher then conventional radiation doses in localised Pca treatment : A metaanalysis of RCT
- 4. Does harmone treatment added to RT improve outcome in locally advanced PCa
- 5. SBRT for primary PCa : A systemic review
- 6. Comparison of treatment related toxicities in men: IMRT versus 3D CRT
- 7. Comparison of HRQOL among surgery & RT for localised PCa : A systemic review and metaanalysis

## RP-PLND vs RT for clinically localised prostate cancer

*Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis.*
*Christopher J.D.Wallis* doi.org/10.1016/j.eururo.2015.11.010

**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-localized prostate cancer.

Nineteen studies of low to moderate risk of bias were selected

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 therapies as the specific objective.
- Studies assessing nonstandard treatments (such as cryotherapy).

## Characteristics of included studies

| Author (yr) | Data source (study interval) | Follow-up (median) | Inclusion criteria | Radiation modality | Radiation dose | Study size | Adjuvant therapies | Age | | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | RP | XRT | |
| Abdollah (2012) | SEER (1992–2005) | 52 mo | Clinically localized, age 65–79 | Unspecified | NA | 68 665 | ADT: RP: 0% XRT: 9% | 65–69: 53% 70–74: 39% 75–79: 9% | 65–69: 24% 70–74: 41% 75–79: 35% | PCM |
| Albertsen (2007) | Connecticut Tumor Registry (1992–2005) | Mean 13.3 yr | Clinically localized, age < 75 | EBRT | NA | 1618 | Excluded | median 65 | median 71 | PCM |
| Arvold (2011) | 21st Century Oncology, Chicago Prostate Center, Duke University (1988–2008) | 6.1 yr (RP) and 3.6 yr (XRT) | Low risk or intermediate risk* | Brachy | min 115 Gy | 8839 | Included but proportion not specified | median low risk: 61.4; int risk: 62.9 | median low risk: 68.8; int risk: 71.2 | PCM |
| Boorjian (2011) | Mayo Clinic, Fox Chase (1988–2004) | 10.2 yr (RP) and 6.0–7.3 yr (XRT) | High risk* | EBRT (conformal, 3DCRT, IMRT) | median 72 Gy (range, 50–79) | 1847 | ADT: RP: not specified XRT: 56% | median 66.0 | median with ADT: 68.8; no ADT: 69.3 | OM, PCM |
| Cooperberg (2010) | CaPSURE (1997–2007) | 3.9 yr (RP) and 4.5 yr (XRT) | Clinically localized | EBRT | NA | 6209† | ADT RP: 6.7% XRT: 49.7% Postop XRT: 3% | median 62 | median 72 | OM, PCM |
| DeGroot (2013) | Ontario Cancer Registry (1990–1998) | NR | "Candidate for therapy": low and intermediate risk* | EBRT | median 66 Gy (range, 40–70) | 1090 | ADT RP: 29% XRT: 22% | mean 63 | mean 69 | PCM |
| Hoffman (2013) | PCOS (1994–2010) | 15 yr | Clinically localized, age 55–74 | EBRT | NA | 1655 | ADT: RP: 0% XRT: 11% | 55–64: 52% 65–74: 48% | 55–64: 23% 65–74: 77% | OM, PCM |
| Jeldres (2008) | Quebec Health Plan (1989–2006) | 7.4 yr | Age > 70 | EBRT | NA | 6183 | Included but proportion not specified | median 71 | median 74 | OM |
| Kibel (2012) | Barnes-Jewish Hospital (BJ), Cleveland Clinic (CC) (1995–2005) | 67 mo | Clinically localized | EBRT (3DCRT, IMRT), brachy | median 74 Gy (BJ) and 78 Gy (CC) | 10 429 | ADT: RP: not specified XRT: 34% | median BJ: 61; CC: 60 | median BJ-EBRT: 70; BJ-brachy: 69; CC-EBRT: 69; CC-brachy: 68 | OM, PCM |
| Ladjevardi (2010) | Swedish National Prostate Cancer Registry (1996–2006) | 4.4 yr | T1–3, N0–X, M0–X, PSA < 20, age < 75 | EBRT, brachy | NA | 19 258‡ | Not specified | <55: 10% 55–59: 23% 60–64: 33% 65–69: 27% 70–75: 8% | <55: 4% 55–59: 13% 60–64: 25% 65–69: 33% 70–75: 25% | OM |
| Lee (2014) | Severance Hospital, Seoul Korea (1990–2008) | 76 mo | Clinically localized high risk* | EBRT | 74–79 Gy | 376 | ADT RP: 0% XRT: 100% Postop XRT: 10% | mean 67.5 | mean 68.6 | PCM |
| Merglen (2007) | Geneva Cancer Registry (1989–1998) | 6.8 yr | Clinically localized | EBRT | NA | 363 | ADT RP: not specified XRT: 26% | <60: 23% 60–69: 52% 70–79: 18% ≥80: 7% | <60: 9% 60–69: 52% 70–79: 38% ≥80: 1% | OM, PCM |

## RP-PLND vs RT for clinically localised prostate cancer

**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

| Author | Inclusion criteria | Overall mortality | | Prostate cancer mortality | |
|---|---|---|---|---|---|
| | | RP | XRT | RP | XRT |
| Abdollah (2012) | Clinically localized, age 65–79 | NA | NA | 10 yr low/int: 1.4%<br>10 yr high: 6.8% | 10 yr low/int: 3.9%<br>10 yr high: 11.5% |
| Abersten (2007) | Clinically localized, age < 75 | 10 yr: 17%* | 10 yr: 22%* | 10 yr low: 3%<br>10 yr int: 6%<br>10 yr high: 10% | 10 yr low: 7%<br>10 yr int: 12%<br>10 yr high: 20% |
| Arvold (2011) | Low risk or intermediate risk | NA | NA | 10 yr low: 0.4%*<br>10 yr int: 0%* | 10 yr low: 0.8%*<br>10 yr int: 3.5%* |
| Boorjian (2011) | High risk | 10 yr: 23% | 10 yr RT + ADT: 33%<br>10 yr RT: 48% | 10 yr: 8% | 10 yr RT + ADT: 8%<br>10 yr RT: 12% |
| Cooperberg (2010) | Clinically localized | NA | NA | 10 yr: 5%* | 10 yr: 12%* |
| DeGroot (2013) | "Candidate for therapy": low and intermediate risk | NA | NA | NA | NA |
| Hoffman (2013) | Clinically localized, age 55–74 | 15 yr: 35%* | 15 yr: 58%* | NA | NA |
| Jeldres (2008) | Age > 70 | 10 yr: 40.7%<br>15 yr: 72.7% | 10 yr: 60.7%<br>15 yr: 86.7% | NA | NA |
| Kibel (2012) | Clinically localized | 10 yr: 11.1% | 10 yr EBRT: 17.4%<br>10 yr brachy: 18.3% | 10 yr: 1.8% | 10 yr EBRT: 2.9%<br>10 yr brachy: 2.3% |
| Ladjevardi (2010) | T1–3, N0–X, M0–X, PSA<20, age < 75 | Relative survival is given resulting in survival estimates > 100% and therefore mortality < 0. | | | |
| Lee (2014) | Clinically localized high risk | NA | NA | 10 yr: 10%* | 10y r: 20%* |
| Mergfen (2007) | Clinically localized | NA | NA | 10 yr: 17% | 10 yr: 25% |
| Merino (2013) | Clinically localized | 5 yr: 3.8%<br>7 yr: 6.3% | 5 yr: 11.6%<br>7 yr: 16.9% | 7 yr: 1.9% | 7 yr: 7.9% |
| Rice (2013) | Low risk, age > 70 | 10 yr: 18%* | 10 yr: 30%* | | |
| Sooriakumaran (2014) | All | 10 yr low: 10%*<br>10 yr int: 15%*<br>10 yr high: 20%* | 10 yr low: 16%*<br>10 yr int: 22%*<br>10 yr high: 30%* | 10 yr low: 1%*<br>10 yr int: 3%*<br>10 yr high: 8%* | 10 yr low: 1%*<br>10 yr int:8%*<br>10 yr high: 15%* |
| Sun (2013) | Clinically localized, age 65–80 | 10 yr: 20% | 10 yr: 37% | NA | NA |
| Tewari (2007) | Clinically localized, high risk, age < 75 | 10 yr: 54% | 10 yr: 75% | 10 yr: 25% | 10 yr: 43% |
| Westover (2012) | Clinically localized, Gleason score 8–10, age < 75 | NA | NA | 5 yr: 0% | 5 yr: 1.5% |
| Zelefsky (2010) | T1c–T3b | NA | NA | 8 yr: 1.4% | 8 yr: 4.7% |

ADT = androgen deprivation therapy; brachy = brachytherapy; EBRT = external beam radiotherapy; NA = not applicable or assessed in the manuscript; PSA = prostate specific antigen; RP = radical prostatectomy; RT = radiotherapy; XRT = radiotherapy.
* Denotes that estimate is imputed from a graph or figure in the original manuscript.

## 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% confidence interval [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 (aHR1.50, 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 (aHR1.80, 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 prost cancer-specific mortality following treatment with surgery or radiotherapy

| | Overall mortality | | Prostate cancer-specific mortality | |
|---|---|---|---|---|
| | Adjusted HR (95% CI, *p* value) | $I^2$ | Adjusted HR (95% CI, *p* value) | $I^2$ |
| Risk category | | | | |
| Low risk | 1.47 (1.19–1.83, p = 0.0004) | 59% | 1.70 (1.36–2.13, p < 0.00001) | 0% |
| Intermediate risk | 1.50 (1.24–1.82, p < 0.0001) | NA | 1.80 (1.45–2.25, p < 0.0001) | 0% |
| High risk | 1.88 (1.64–2.16, p < 0.00001) | 0% | 1.83 (1.51–2.22, p = 0.0001) | 42% |
| Radiotherapy modality | | | | |
| EBRT (CRT and IMRT) | 1.69 (1.55–1.85, p < 0.00001) | 8% | 2.26 (1.94–2.63, p < 0.00001) | 0% |
| IMRT | No studies available | | 2.26 (1.21–4.21, p = 0.01) | 0% |
| Brachytherapy | 1.70 (1.40–2.10, p < 0.001) | NA | 1.58 (1.01–2.49, p = 0.05) | 0% |
| Duration of follow-up | | | | |
| <5 yr | 1.54 (1.38–1.71, p < 0.00001) | 0% | 1.51 (0.25–9.19, p = 0.66) | 89% |
| 5–8 yr | 1.73 (1.49–2.02, p < 0.00001) | 18% | 1.80 (1.57–2.05, p < 0.00001) | 0% |
| >8 yr | 1.74 (1.55–1.95, p < 0.00001) | 0% | 2.26 (1.60–3.20, p < 0.00001) | 65% |
| Era of accrual | | | | |
| Early | 1.75 (1.57–1.97, p < 0.00001) | 5% | 2.04 (1.54–2.72, p < 0.00001) | 44% |
| Later | 1.59 (1.48–1.70, p < 0.00001) | 0% | 2.12 (1.69–2.66, p < 0.00001) | 58% |
| Geographic region | | | | |
| United States | 1.63 (1.54–1.73, p < 0.00001) | 0% | 2.11 (1.65–2.69, p < 0.00001) | 59% |
| Rest of the world | 1.65 (1.55–1.76, p < 0.0001) | 42% | 1.85 (1.59–2.15, p < 0.00001) | 0% |

CI = confidence interval; CRT = conformal radiation therapy; EBRT = external beam radiotherapy; HR = hazard ratio; IMRT = intensity modulated radiotherapy; NA = not applicable.

## RP-PLND vs RT for clinically localised prostate cancer

**Conclusion :**

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**

Three RCTs representing 1743 patients were included.

Eligibility Criteria :

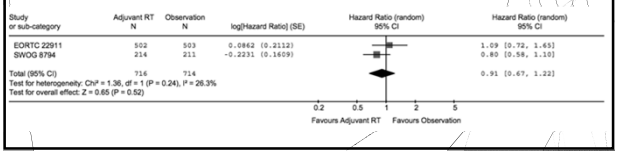
- Patients with prostate cancer treated initially with RP of any approach, and found to have either tumour extension beyond the prostatic capsule (pT3a), seminal vesicle invasion (pT3b), positive resection margins (R1) or more than one of these features.
- They randomized patients to receive either adjuvant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

Characteristics of eligible trials

| Trial descriptors | EORTC 22911 | SWOG 8794 | German Cancer Society ARO 96-02 and AUO AP 09/95 |
|---|---|---|---|
| Eligibility criteria | At least one of: extraprostatic extension, seminal vesicle invasion, or positive surgical margins (pT2 N0 M0 R1 or pT3 N0 M0 R0-1)<br>WHO PS 0-1<br>Age ⩽75 yrs | At least one of: extraprostatic extension, seminal vesicle invasion, or positive surgical margins (pT2 N0 M0 R1 or pT3 N0 M0 R0-1)<br>SWOG PS 0-2<br>Negative pelvic lymphadenectomy[a] | Extraprostatic extension or seminal vesicle invasion with or without positive surgical margins (pT3 N0 R0-1)<br>Undetectable PSA following RP |
| Median age | 65 yrs | 64.9 yrs | NR |
| Stratification variables | Institution; pT3a (present vs. absent); R0 vs. R1; pT3b (present vs. absent) | Tumour extent (pT3a or R1 vs. pT3b vs. R1 and pT3b); NADT (present vs. absent) | Gleason score (2–6 vs. 7–10); R0 vs. R1; pT3a vs. pT3b; NADT (present vs. absent) |
| NADT use (% of patients) | 10% | 8.5% | NR |
| Number randomized | 1005 | 431 | 307 |
| Number eligible | 968 | 425 | 300 |
| Time from RP until start of adjuvant RT | <16 weeks | <18 weeks | 8–12 weeks |
| Adjuvant RT dose–fractionation | 60 Gy in 30 fractions | 60–64 Gy in 30–32 fractions | 60 Gy in 30 fractions |
| Adjuvant RT volume | • Initial phase: 50 Gy to ''volume including surgical limits from seminal vesicles to apex with security margin to encompass subclinical disease in peri-prostatic area''<br>• 10 Gy boost to ''reduced volume circumscribing the previous landmarks of the prostate with a reduced security margin'' | Single phase: RT delivered to ''prostatic fossa and paraprostatic tissues'' | Prostatic fossa and region of seminal vesicles with 1 cm margin |
| Treatments received by observation arm (*n*) | Pelvic radiotherapy (113); hormonal treatment (45); surgical castration (1); other (4) | Pelvic radiotherapy (70); other therapies NR | NR |
| Median follow-up | 5 years | 10.6 years | 4.5 years |
| Primary endpoint | Biochemical progression-free | Metastasis-free survival | Biochemical progression-free |

## 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 metaanalysis (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%.

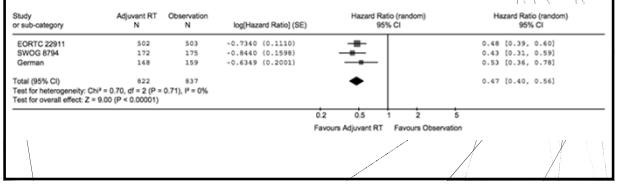



## Biochemical progression-free survival

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

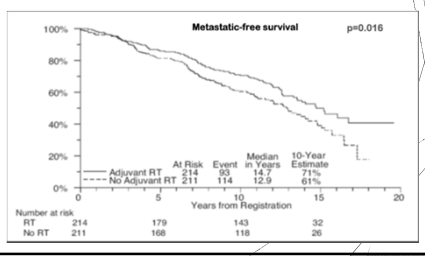
All three trials detected longer biochemical progression-free survival with adjuvant RT compared with observation that was statistically significant.

Pooling the results of the three trials in a meta-analysis (Fig.) produced an HR of 0.47 (95% CI 0.40–0.56; p < 0.00001), which represents a 53% decrease in biochemical progression with adjuvant RT compared to observation.



## Metastasis-free survival

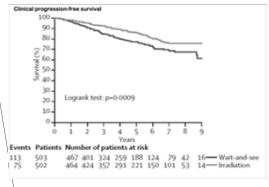
- Only the SWOG trial reported on this outcome.
- The improvement in metastasis-free survival observed with adjuvant RT did not quite reach statistical significanc (HR = 0.75; 95% CI 0.55–1.02; p = 0.06).
- The EORTC study reported 19 distant failures in the adjuvant RT treatment arm and 18 in the observation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



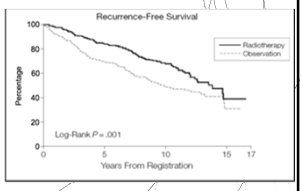

## Clinical progression-free survival

- 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; 98% 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."

**EORTC trial 22911 (n=1005)**
**clinical progression free survival**
**Bolla et al.**




**randomised study SWOG 8794 (n=425)**
**Thompson et al.**




## Conclusions

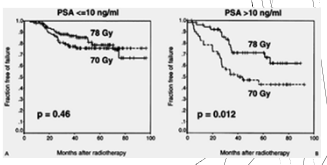
- Adjuvant RT following RP in patients with pathologic T3 or margin-positive prostate cancer reduces the risk of biochemical and locoregional failure compared to observation, and prolongs the time to initiation of ADT.
- Adjuvant RT is associated with a low rate of acute and late major toxicity.
- To 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

Prostate cancer radiation dose response: results of the M.D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 2002;53:1097-105.

The study enrolled 301 patients with T1 to T3 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

**Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate**: a randomized controlled trial. Zietman et al. JAMA 2005;294:1233-9.

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

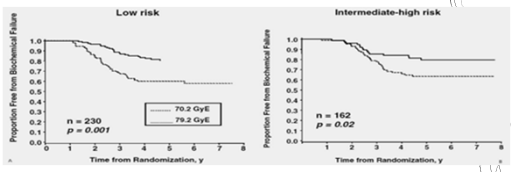
↓

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.

Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. Zietman et al. JAMA 2005;294:1233-9.

The median follow-up in this study was 5.5 years.




- The proportions of men free from biochemical failure at 5 years were 78.8% [corrected] (95% confidence interval, 73.1%-84.6%) [corrected] for conventional-dose and 91.3% [corrected] (95% confidence interval, 87.2%-95.4%) [corrected] 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]) [corrected]
- There has been no significant difference in overall survival rates between the treatment groups.

# The Role of Dose Escalation

Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. Zietman et al.JAMA 2005;294:1233-9.

**Table 2.** Acute and Late Genitourinary and Gastrointestinal (Rectal) Morbidity, by Assigned Radiation Therapy Dose and Toxicity Grade

| | No. (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 70.2 GyE (n = 196*) | | | | 79.2 GyE (n = 195) | | | |
| Morbidity | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Acute | | | | | | | | |
| GU | 79 (40) | 82 (42) | 2 (1) | 0 | 69 (35) | 95 (49) | 2 (1) | 1 (1) |
| GI | 62 (31) | 81 (41)† | 2 (1) | 0 | 48 (25) | 112 (57)† | 0 | 0 |
| Late | | | | | | | | |
| GU | 85 (43) | 35 (18) | 3 (2) | 0 | 84 (43) | 39 (20) | 1 (1) | 0 |
| GI | 71 (36) | 15 (8)‡ | 1 (1) | 0 | 84 (43) | 33 (17)‡ | 1 (1) | 0 |

Abbreviations: GI, gastrointestinal; GU, genitourinary.
*One patient underwent radical prostatectomy rather than radiation therapy because the bowel was too close to the prostate for safe administration of radiation. This patient was excluded from analysis of morbidity.
†$P = .004$ by $\chi^2$ test.
‡$P = .005$ by $\chi^2$ test.

Only 1% of patients receiving conventional-dose and 2% receiving high-dose radiation experienced acute urinary or rectal morbidity of Radiation Therapy Oncology Group (RTOG) grade 3 or greater. So far, only 2% and 1%, respectively, have experienced late morbidity of RTOG grade 3 or greater.

CONCLUSIONS:

Men with clinically localized prostate cancer have a lower risk of biochemical failure if they receive high-dose rather than conventional-dose conformal radiation. This advantage was achieved without any associated increase in RTOG grade 3 acute or late urinary or rectal morbidity.

# The Role of Dose Escalation

**HIGHER-THAN-CONVENTIONAL RADIATION DOSES IN LOCALIZED PROSTATE CANCER TREATMENT: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS. doi:10.1016/j.ijrobp.2008.10.091**

**Purpose:**

To determine in a meta-analysis whether the outcomes in men with localized prostate cancer treated with high-dose radiotherapy (HDRT) 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.

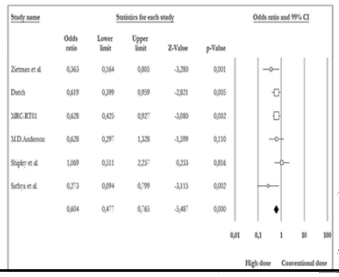
**Characteristics of studies of high-dose radiotherapy for localized prostate cancer**

| Study (reference), patient number, and risk groups | Treatment modality | PTV, CTV, and setup | Risk group definition | Biochemical failure definition |
|---|---|---|---|---|
| Zietman *et al.* (23) | Conformal radiotherapy was given with photons and phase 2 with protons | CTV = prostate, with 5-mm margin. | Low risk: Stage <T2a and Gleason score ≤6 and PSA ≤10 ng/mL. | Defined using the American Society for Therapeutic Radiology and Oncology criteria of three successive increases in PSA level. |
| N = 393 | | PTV = CTV + 7–10 mm. | High risk: Stage T3 or Gleason score ≥8 or PSA >20 ng/mL. Intermediate risk: all others. | |
| HDRT: 197 | | Setup: error was minimized by obtaining daily portal images throughout the first phase; portal images were obtained weekly during the second phase. | | |
| Low: 116<br>Intermediate: 61<br>High: 15<br>CDRT: 196<br>Low: 111<br>Intermediate: 68<br>High: 18 | | | | |
| Dutch (25) | Conformal radiotherapy with photons | CTV = prostate ± SV + 10 mm ± 5 mm (except toward the rectum, 0 mm) for the last 10 Gy in the high-dose arm. | Low risk: Stage <T2a and Gleason score ≤6 and PSA ≤10 ng/mL. | Biochemical failure was defined according to the definition of the American Society of Therapeutic Radiation Oncology and was considered three consecutive increases in PSA level after a nadir. |
| N = 664 | | Setup: not reported. | High risk: Stage T3 or Gleason score ≥8 or PSA >20 ng/mL. Intermediate risk: all others. | |
| HDRT: 333<br>Low: 64<br>Intermediate: 92<br>High: 177<br>CDRT: 331<br>Low: 56<br>Intermediate: 90<br>High: 185 | | | | |

| | | | | |
|---|---|---|---|---|
| MRC RT01 (27)<br><br>N = 843<br><br>HDRT: 422<br>Low: 99<br>Intermediate: 127<br>High: 184<br>CDRT: 421<br>Low: 95 | Conformal radiotherapy with photons | CTV = GTV plus a 0–5-cm margin. PTV = 0.5–1.0 cm.<br><br>Setup: not reported. | Low risk: Stage <T2a and Gleason score ≤6 and PSA ≤10 ng/mL.<br><br>High risk: Stage T3 or Gleason score ≥8 or PSA >20 ng/mL.<br>Intermediate risk: all others. | PSA failure was defined as an increase in PSA concentration to greater than the nadir by at least 50% and greater than 2 ng/mL 6 mo or more after the start of radiotherapy. |
| M. D. Anderson (22)<br><br>N = 301<br><br>HDRT: 151<br>Low: 30<br>Intermediate: 68<br>High: 53<br>CDRT: 150<br>Low: 31<br>Intermediate: 71<br>High: 48 | Conventional four boxes and conformal radiation in the phase 2 after the first 46 Gy. | Phase 1= field sizes 11 × 11 cm for the anterior and posterior fields and 11 × 9 cm for the lateral fields.<br><br>Phase 2 CTV = prostate and SV. PTV = CTV + 1.25–1.5 cm in the anterior and inferior dimensions and 0.75–1.0 cm in the posterior.<br>Setup: not reported. | Low risk: Stage <T2a and Gleason score ≤6 and PSA ≤10 ng/mL.<br><br>High risk: Stage T3 or Gleason score ≥8 or PSA >20 ng/mL.<br><br>Intermediate risk: all others. | The nadir + 2 ng/mL failure definition was used to define PSA failure. |
| Shipley *et al.* (26)<br><br>N = 202<br><br>HDRT: 103<br>Low<br>Intermediate<br>High<br>CDRT: 99<br>Low<br>Intermediate<br>High | Conventional four box with photons and protons in Phase 2 after the first 50.4 Gy in the high-dose arm. | Anteroposterior fields 15 cm high × 16 cm wide; lateral 15 cm high× 11.5 cm deep.<br><br>Setup: Biplane diagnostic radiographs were taken before each proton treatment session to assure correct positioning of the target in the beam. | Not reported | PSA value of 4 ng/mL or more, or if the serum PSA level increased by more than 10% compared with a previous value obtained less than 2 y after treatment. |

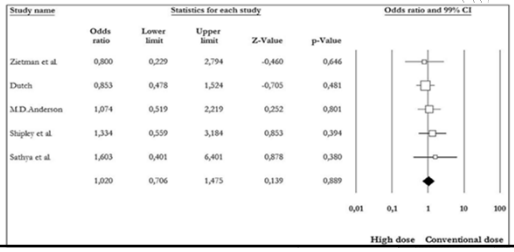
## Biochemical failure

- 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.



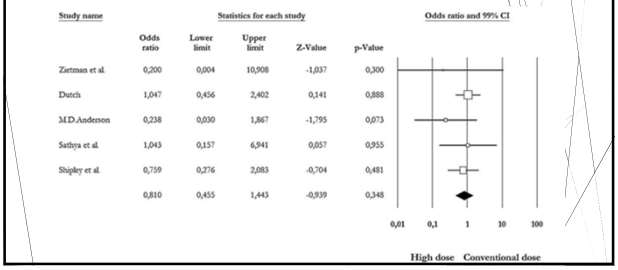

## Mortality rate

- 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 examined 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 1.24–2; p < 0.0001), 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 0.93–1.54; p = 0.054), as shown in Figs.

| | GI * | | GU* | |
|---|---|---|---|---|
| Study (reference)/toxicity criteria | High dose | Conventional | High dose | Conventional |
| Zietman *et al.* (23)/RTOG scale | 43% G1 | 36% G1 | 43% G1 | 43% G1 |
| | 17% G2 | 8% G2 | 20% G2 | 18% G2 |
| | 1% G3 | 1% G3 | 1% G3 | 2% G3 |
| Dutch (25)/RTOG/EORTC | 32% G≥2 | 27% G≥2 | 39% G≥2 | 41% G≥2 |
| | 5% G≥3 | 4% G≥3 | 13% G≥3 | 12% G≥3 |
| MRC RT01 (27)/RTOG scale | 60% G≥1 | 58% G≥1 | 26% G≥1 | 22% G≥1 |
| | 33% G≥2 | 24% G≥2 | 11% G≥2 | 8% G≥2 |
| | 10% G≥3 | 6% G≥3 | 4% G≥3 | 2% G≥3 |
| M. D. Anderson (22)/RTOG/EORTC | 42% G1 | 66% G1 | 35% G1 | 21% G1 |
| | 28% G2 | 42% G2 | 7% G2 | 11% G2 |
| | 10% G3 | 3% G3 | 7% G3 | 5% G3 |
| GETUG (28)/RTOG modified | 57% G1 | 42% G1 | 65% G1 | 67% G1 |
| | 43% G2 | 28% G2 | 46% G2 | 48% G2 |
| | 3% G3 | 10% G3 | 11% G3 | 8% G3 |
| Sathya *et al.* (24)/CTC scale | 3.9% G3 or G4 | 1.9% G3 or G4 | 13.7% G3 or G4 | 3.8% G3 or G4 |
| Shipley *et al.* (26)/RTOG scale | 27% G≥2 | 9% G≥2 | 14% G≥2 | 6% G≥2 |

**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 increase)
2. clinical PFS (clinical progression-free survival, time between randomization and clinical appearance 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 (GU),
7) gastrointestinal grade 3-4 toxicities (GI), and
8) cardiac deaths.

## ADT with RT vs RT alone in locally advanced prostate cancer

TRIAL CHARACTERSTICS

| Authors | Pts | HT Duration | Experimental Arm | Median FU, y | Primary Endpoint | Secondary Endpoint | % Node Positive | % Gleason Score 7-10 | % T3-T4 |
|---|---|---|---|---|---|---|---|---|---|
| Bolla 2002[9],2006[14] | 415 | LT | Goserelin 3 y+EBRT (70 Gy) | 9.1 | DFS | OS | 3.4 | 34.1 | 91.0 |
| Pilepich 2005[10] | 977 | LT | Goserelin until progression+EBRT (65-70 Gy) | 7.6 | LR, DM, DFS | CSS | 26.9 | 62.2 | 69.8 |
| See & Tyrrell 2006[12] | 1,370 | LT | Bicalutamide 150 mg (median 1.8 y)+EBRT (64 Gy) | 7.2 | PFS | OS | 1 | 24.6 | 22.0 |
| D'Amico 2008[13] | 206 | ST | AST 6 mo prior and concurrent with 3D-EBCRT (70 Gy) | 7.6 | BF | CSS, OS | 0 | 72.3 | 0 |
| Denham 2005[7] | 802 | ST | STAD 3 or 6 mo prior and concurrent with EBRT (66 Gy) | 5.9 | Time to LR, CSS | Time to LR, time to DM | 0 | 38.0 | 40.1 |
| Laverdiere 2004[8] | 161 | ST | 3 mo AS (Group 2) or 10 mo AS (Group 3)+EBRT (64 Gy) | 5.0 | BNED | NR | 0 | 26.0 | 30.0 |
| Roach 2006[11] | 456 | ST | ADT 4 mo prior and concurrent with EBRT (65-70 Gy) | 12.6 | LR | DFS, OS | 8.1 | 65.9 | 70.0 |

Pts indicates patients; HT, hormone treatment; FU, follow-up; LT, long term; EBRT, external beam radiotherapy; Gy, gray; DFS, disease-free survival; OS, overall survival; LR, local relapse; DM, distant metastases; CSS, cancer-specific survival; PFS, progression-free survival; ST, short term; AST, androgen suppression therapy; 3D, 3-dimensional; BF, biochemical failure; STAD, short-term androgen deprivation; AS, androgen suppression; BNED, no biochemical evidence of disease; NR, not reported; ADT, androgen deprivation therapy.

## ADT with RT vs RT alone in locally advanced prostate cancer

**Primary Outcomes**

- HT significantly decreased biochemical and clinical failure over exclusive RT by 24% and 19%, respectively.
- The absolute benefit was 10% 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 18 NNT.
- In the sensitivity analysis, the absolute benefit in cancer-specific survival ranges from 5.3% 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 relapse (LR) and DM were significantly decreased (36% and 28%, respectively) by the addition of HT to RT, with a 9.8% and 9.5% absolute benefit, corresponding to 11 NNT.

## ADT with RT vs RT alone in locally advanced prostate cancer

| Outcomes | Pts (RCTs) | RR (95% CI) | *P* | Heterogeneity *P* | % AD | NNT |
|---|---|---|---|---|---|---|
| **BF** | 3956 (7) | 0.76 (0.70-0.82) | <.0001 | .08 | 10.0 | 10 |
| LT | 2656 (3) | 0.79 (0.75-0.83) | <.0001 | .50 | 8.6 | 12 |
| ST | 1300 (4) | 0.67 (0.55-0.82) | <.0001 | .006 | 14.2 | 7 |
| **CPFS** | 4020 (5) | 0.81 (0.71-0.93) | .002 | <.0001 | 7.7 | 13 |
| LT | 2762 (3) | 0.81 (0.61-0.95) | .011 | .005 | 7.4 | 14 |
| ST | 1258 (2) | 0.83 (0.67-1.02) | .088 | <.0001 | — | — |
| **CSS** | 4266 (6) | 0.76 (0.69-0.83) | <.0001 | .56 | 5.5 | 18 |
| LT | 2762 (3) | 0.77 (0.60-0.84) | <.001 | .89 | 5.3 | 19 |
| ST | 1464 (3) | 0.67 (0.49-0.91) | .022 | .25 | 7.2 | 14 |
| **OS** | 4266 (6) | 0.86 (0.80-0.93) | <.0001 | .36 | 4.9 | 20 |
| LT | 2762 (3) | 0.84 (0.75-0.94) | .003 | .21 | 5.6 | 18 |
| ST | 1464 (3) | 0.87 (0.79-0.97) | .013 | .34 | 4.1 | 21 |
| **LR** | 2650 (4) | 0.64 (0.54-0.75) | <.0001 | .27 | 9.8 | 11 |
| LT | 1392 (2) | 0.65 (0.53-0.78) | <.0001 | .36 | 8.7 | 12 |
| ST | 1258 (2) | 0.61 (0.44-0.84) | .002 | .09 | 11.8 | 8 |
| **DM** | 2650 (4) | 0.72 (0.65-0.81) | <.0001 | .43 | 9.5 | 11 |
| LT | 1392 (2) | 0.70 (0.61-0.79) | <.0001 | .99 | 11.1 | 9 |
| ST | 1258 (2) | 0.80 (0.65-0.99) | .04 | .24 | 5.7 | 17 |

Pts indicates patients; RCT, randomized clinical trial; RR, relative risk; CI, confidence interval; AD, absolute difference; NNT, number needed to treat; BF, biochemical failure; LT, long-term hormone treatment; ST, short-term hormone treatment; CPFS, clinical progression-free survival; CSS, cancer-specific survival; OS, overall survival, LR, local relapse; DM, distant metastases.

## 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 metaregression analysis, none of the considered predictors significantly affected outcome, with the exception of lymph node positivity and Gleason score, which significantly influenced clinical progressionfree survival.

***Combined Toxicity and Cardiac Deaths Results***

| Outcomes | Pts (RCTs) | RR (95% CI) | *P* | Heterogeneity *P* |
|---|---|---|---|---|
| Overall toxicity | 2050 (4) | 0.92 (0.87-1.11) | .41 | .55 |
| GU toxicity | 2050 (4) | 0.66 (0.36-1.22) | .19 | .05 |
| GI toxicity | 2050 (4) | 0.69 (0.46-1.03) | .07 | .71 |
| Cardiac deaths | 4266 (6) | 0.87 (0.70-1.09) | .24 | .69 |

Pts indicates patients; RCT, randomized clinical trial; RR, relative risk; CI, confidence interval; GU, genitourinary; GI, gastrointestinal.

***Meta-regression Analysis Model P Values According to Selected Predictors (ie, Regression of the Selected Predictor on the Log Risk Ratio of the Corresponding Outcome)***

| Outcome | Node Positive | Gleason 7-10 | T3-T4 |
|---|---|---|---|
| BF | .22 | .65 | .62 |
| CPFS | .026 | .00003 | .24 |
| CSS | .67 | .23 | .39 |
| OS | .51 | .44 | .99 |
| LR | .28 | .06 | .17 |
| DM | .50 | .85 | .16 |

BF, biochemical failure; CPFS, clinical progression-free survival; CSS, cancer-specific survival; OS, overall survival; LR, local relapse; DM, distant metastases.

## ADT with RT vs RT alone in locally advanced prostate cancer

**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 of GU 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 trial 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

***The effectiveness of intensity modulated radiation therapy versus three-dimensional radiation therapy in prostate cancer: A meta-analysis of the literatures.Yu T, Zhang Q, Zheng T, Shi H, Liu Y, Feng S, et al. doi.org/10.1371/journal.pone.0154499***

**PURPOSE :**

To assess whether IMRT can provide better clinical outcomes in comparison with 3DCRT 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 GI and late GU toxicity were scored according to the Fox Chase (FC) modification of the Radiation Therapy Oncology Group (RTOG) and Late Effects Normal Tissue Task Force (LENT) toxicity criteria (RTOG/FC-LENT late toxicity criteria)/Common Terminology Criteria (CTC) (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)

# IMRT vs 3D-CRT for Prostate cancer

**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 study design was more often a retrospective (n = 16) than a prospective cohort study (n = 5).
- The prescribed doses to the primary tumor were 70–85.3 Gy in IMRT group and 55.8–84.8 Gy in 3DCRT group.
- Stage I/II comprised 77.3% of the patients, and the remaining 22.7% were in stage III/IV.
- The median follow-up time ranged from 5.3 months to 120 months.

# Summary of the studies included in the meta-analysis.

| Author | Year | Study design | Number (3DCRT/ IMTR) | PTV | total dose/ fraction dose (Gy) (3DCRT VS IMRT) | Margin (mm) | Method for dose prescript-ion | Image guidance | ADT%(3DCRT/ IMRT) & p value | Tumor stage III (III/IV) | Median follow-up (m) (3DCRT/ IMRT) | score criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Post-operative RT (n = 2)** | | | | | | | | | | | | |
| Mongi F[36] | 2009 | Retro. | 172(81/91) | Prostatic bed, Pelvic nodes | 72.1/1.8 **VS** 72.5/1.8 | 8 | Isodose level | NO | 61/56n.s. | NR/NR | 3/3 | RTOG toxicity scale |
| Goenka A [37] | 2011 | Retro. | 285 (109/ 176) | NR | 66-72/NR VS 66-72/NR | NR | NR | NO | 100/100n.s. | NR/NR | 97/53 | RTOG toxicity scale, CTCAE version 3.0 |
| **Primary RT (n = 21)** | | | | | | | | | | | | |
| Dehnan JB [38] | 2005 | Retro. | 27 (14/13) | Prostatic bed, Pelvic nodes, seminal vesicles | 75.6/1.8 **VS**81/ 1.8 | 10 | Isocenter | NO | 100/100n.s. | 12/15 | 30/30 | RTOG toxicity scale |
| Cho JH[39] | 2008 | Retro. | 50 (35/15) | Prostatic bed | 70.2/1.8 **VS**70/ 2.5 | NR | Isocenter | NO | 44/44n.s. | 26/24 | 3/3 | RTOG toxicity scale |
| Zelezel M [40]* | 2010 | Pro. | 232 (94/ 138) | Prostatic bed, Pelvic nodes, seminal vesicles | 74/2 **VS**78/2 | 10 | Isocenter | NO | 94.7/55 | 76/156 | 68.4/37.2 | RTOG toxicity scale |
| Zelezel M [41]* | 2015 | Pro. | 533 (320/ 233) | Prostatic bed, seminal vesicles | 70–74/2 **VS**78–82/2 | 10 | Isocenter | NO | 40.3/62.3 | 332/221 | 104/60 | RTOG toxicity scale, ASTROPhoenix definition |
| Forsythe K [42] | 2011 | Retro. | 812 (521/ 291) | Prostatic bed, seminal vesicles | NR | 10–12 | Isocenter | Partly | 87.9/75.9p <0.01 | NR/NR | 74.4/33.6 | RTOG toxicity scale |
| Jani AB[43] | 2007 | Pro. | 481(373/ 108) | Prostatic bed, seminal vesicles | 68.5/1.8–2 **VS**75/1.8–2 | 10 | NR | NO | 53/51 | 413/68 | NR/NR | RTOG toxicity scale |
| Kim H[44] | 2014 | Retro. | 86 (56/30) | Prostatic bed, Pelvic nodes, seminal vesicles | 70/1.8 **VS**70/2.5 | 5 | Isocenter | NO | 56.7/53.6n.s. | 43/43 | 78.6/73.4 | RTOG toxicity scale |
| Kupelian PA [45]* | 2002 | Retro. | 282 (116/ 166) | Prostatic bed, Pelvic nodes, seminal | 78/2 **VS**70/2.5 | 8–15 | Isodose level | NO | 72/60p = 0.049 | 263/19 | 25/25 | RTOG toxicity scale, ASTROPhoenix definition |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kidrazka K [45]* | 2010 | Retro. | 340(228/112) | Prostatic bed, seminal vesicles | 70/2 VS78/2 | 10–15 | Isocenter | NO | 19.7/54.5 | NR/NR | 70.8/36 | RTOG toxicity scale |
| Pathayake N[47] | 2013 | Pro. | 103 (52/51) | Prostatic bed, Pelvic nodes, seminal vesicles | 74 or 78/2 VS78/2 | 7–10 | Isodose level | YES | 31/59p = 0.06 | 83/19 | 48/38 | RTOG toxicity scale |
| Sharma NK [48] | 2007 | Retro. | 293(170/123) | Prostatic bed, Pelvic nodes, seminal vesicles | 76/2 VS76/1.8 | 10 VS 3–5 | Isodose level | NO | 100/100n.s | 223/70 | 86/40 | RTOG toxicity scale |
| Someya M [49] | 2015 | Retro. | 129 (55/74) | Prostatic bed, seminal vesicles | 70/2 VS 78/2 | 10 VS 8 | Isocenter | NO | 83.6/70.3 | 104/25 | 85/38 | RTOG toxicity scale |
| Sveistrup J [50] | 2014 | Retro. | 503(115/388) | Prostatic bed, seminal vesicles | 76/2 VS 78/2 | 10 VS 5–7 | NR | IG-IMRT | 88/95p = 0.019 | 128/373 | 98.4/42 | CTCAE version 4.0, ASTROPhoenix definition |
| Roeller A [51]* | 2015 | Pro. | 1115(457/658) | Prostatic bed, seminal vesicles | 75.6/1.8 VS 75.6/1.8 | 10 | Isodose level | YES | 23.2/19.9 p = 0.21 | NR/NR | 106.8/55.2 | CTCAE version 3.0 |
| Vora SA[52] | 2007 | Retro. | 416(271/145) | Prostatic bed, seminal vesicles | 68.4/NR VS75.6/NR | 10–20 VS 6–10 | NR | NO | 17.6/30.3 | 386/30 | 60/48 | RTOG toxicity scale, ASTROPhoenix definition |
| Wong WW [53] | 2009 | Retro. | 584(270/314) | Prostatic bed, seminal vesicles | 68.4/1.8–2 VS 75.6/NR | 10–20 VS 6–10 | NR | NO | 17/36 | 543/41 | 120/120 | RTOG toxicity scale, ASTROPhoenix definition |
| Zelefsky MJ [53] | 2000 | Retro. | 232(61/171) | Prostatic bed, seminal vesicles | 81/1.8VS 81/1.8 | 10 | Isocenter | NO | 34/53 | 194/38 | 39/12 | RTOG toxicity scale |
| Zelefsky MJ [54] | 2007 | Retro. | 1571(830/741) | NR | 66-81/1.8 VS 81/NR | NR | Isocenter | NO | 43 | NR/NR | 120/78 | CTCAE version 3.0 |
| Zhu HK[55] | 2001 | Retro. | 44 (26/18) | Prostatic bed, seminal vesicles | NR | 7.5–10 | Isodose level | NO | 79.5 | 33/11 | 30.1/18.7 | RTOG toxicity scale |
| Wortel RC [56]* | 2015 | RCT | 475(215/260) | Prostatic bed, seminal vesicles | 78/2 VS 78/2 | 10 VS 5–8 | NR | IG-IMRT | 19.5/66.9 | 262/213 | 3/3 | RTOG toxicity scale |
| Matzinger O [57] | 2009 | RCT | 791(652/139) | NR | 70-78/2VS 74-78/2 | NR | Isodose | NO | 50 | 791/0 | NR/NR | CTCAE version 2.0 |

Abbreviations: PTV = Planning target volume;retro = Retrospective study; pro = prospective study; RCT = Randomized controlled trial; ADT = Androgen deprivation therapy; NR = Not reported.

## 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 IMRTgroup to that of 3DCRT group, including late GI toxicity (n = 13), late GU toxicity (n = 12) and late rectal bleeding (n = 5).
- 6 studies compared the biochemical controlbetween IMRT group and 3DCRT group, and
- 3 studies compared the OS between IMRT group and 3DCRT group

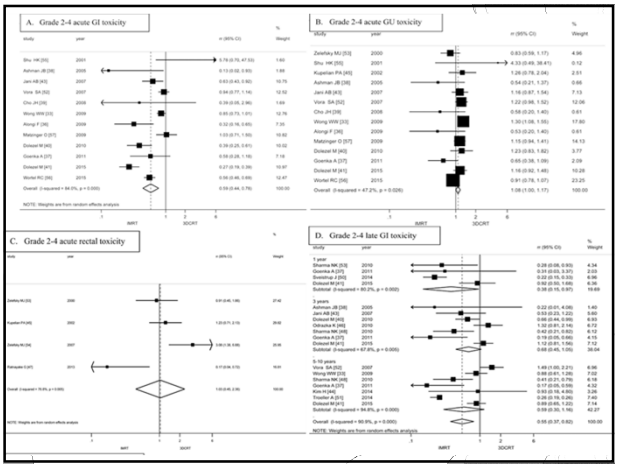
## IMRT vs 3D-CRT for Prostate cancer

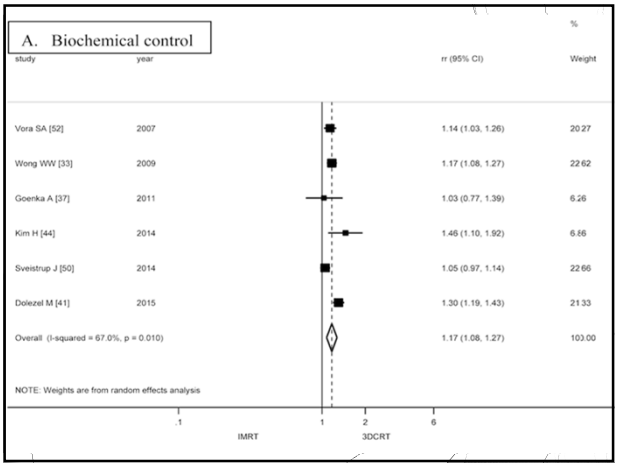
| Group | No. of studies | No. of total patients | RR (95% CI) (IMRT VS 3DCRT) | P for heterogeneity | $I^2$ |
|---|---|---|---|---|---|
| Acute GI toxicity (grade 2–4) | 12 | 4142 | 0.59 (0.44, 0.78) | 0.000 | 84.0% |
| Acute GU toxicity (grade 2–4) | 14 | 4603 | 1.08 (1.00, 1.17) | 0.026 | 47.2% |
| Acute rectal toxicity (grade 2–4) | 4 | 2188 | 1.03 (0.45, 2.36) | 0.005 | 76.8% |
| Late GI toxicity (grade 2–4) | | | | | |
| 1 year | 4 | 1634 | 0.38 (0.15, 0.97) | 0.002 | 80.2% |
| 3 years | 7 | 2243 | 0.70 (0.44, 1.13) | 0.004 | 71.3% |
| 5–10 years | 8 | 4900 | 0.55 (0.31, 0.98) | 0.000 | 93.9% |
| Total | 13 | 6519 | 0.54 (0.38, 0.78) | 0.000 | 90.4% |
| Late GU toxicity (grade 2–4) | | | | | |
| 1 year | 3 | 1341 | 0.83 (0.64, 1.06) | 0.415 | 0.0% |
| 3 years | 5 | 1815 | 1.00 (0.79, 1.28) | 0.905 | 0.0% |
| 5–10 years | 8 | 4128 | 1.03 (0.69, 1.51) | 0.000 | 83.7% |
| Total | 12 | 5608 | 1.03 (0.82, 1.30) | 0.000 | 72.3% |
| Late rectal bleeding (grade 2–4) | 5 | 1972 | 0.48 (0.27, 0.85) | 0.05 | 58% |
| Biochemical control | 6 | 2416 | 1.17 (1.08, 1.27) | 0.010 | 67.0% |
| OS | 3 | 924 | 1.07 (0.96, 1.19) | 0.009 | 79.0% |

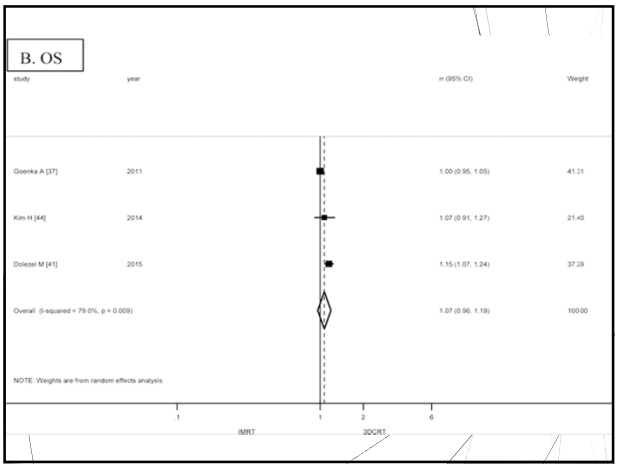
# IMRT vs 3D-CRT for Prostate cancer

**OUTCOME :**

- IMRT significantly decreased grade 2–4 ***acute GI toxicity*** compared with 3DCRT [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 3DCRT, which showed modest effect [RR = 1.08, 95% CI (1.00, 1.17)]
- There was no significant difference between IMRT and 3DCRT 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, 0.78)].
- IMRT was with comparable grade 2–4 ***late GU toxicity*** with 3DCRT [RR = 1.03, 95% CI (0.82, 1.30)] The results clearly favor IMRT over 3DCRT 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 in comparison with 3DCRT.
- A non-significant increase in **overall survival** favoring IMRT was found [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 3DCRT.
- IMRT and 3DCRT 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 responsible for most of the toxicity reported with radiation, appropriately designed radiation treatment fields and schedules using extremely hypofractionated 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 35–36.25 Gy in five fractions, used in nine out of 14 studies.
- Ten of 14 studies used CyberKnife.

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

| Study, year | Institution | Analysis | Dose | Delivery | Median follow-up (months) | *n* | Received hormone therapy (%) | Risk group | bPFS |
|---|---|---|---|---|---|---|---|---|---|
| King *et al.* 2013[17] | Pooled analysis‡ | Retrospective | 36.25 Gy in 5# (54%)<br>35 Gy in 5# (35%)<br>38–40 Gy in 5# (11%)<br>(daily for 95% of patients) | CK | 36 | 1100 | L (8), I (15), H (38) | L, I, H | L = 95%, I = 84<br>H = 81% at 4<br>months |
| Madsen *et al.* 2007[14] | Virginia Mason, Seattle, USA | Phase I/II trial | 33.5 Gy in 5# | Conformal RT | 41 | 40 | Nil | L | 90% at 48 mon |
| Loblaw *et al.* 2013[25] | Sunnybrook, Canada | Phase I/II | 35 Gy in 5# | IMRT | 55 | 84 | 1 (1) | L | 98% at 60 mon |
| Cooke *et al.* 2011[26] | Dallas, USA | Phase I | 45 Gy in 5#<br>47.5 Gy in 5#<br>50 Gy in 5# | Tomotherapy; some patients received a Calypso transponder | 30<br>18<br>12 | 15<br>15<br>15 | 10 (22) | L, I | 100% |
| Jabbari *et al.* 2012[27] † | UCSF, San Francisco, USA | Retrospective | 38 Gy in 4# | CK | 18.3 | 20 | Nil | L, I, H | 100% |
| Alongi *et al.* 2013[28] | Rozzano, Milan, Italy | Phase I/II | 35 Gy in 5# | VMAT | 11 | 40 | 10 (25) | L, I | N/A |
| Jang *et al.* 2011[29] | Korea Cancer Centre Hospital, Seoul, Korea | Retrospective | 32 Gy in 4#<br>34 Gy in 4#<br>36 Gy in 4# | CK | 40 | 44 | 38 (87) | L, I, H | 93.6% |
| Lee *et al.* 2012[30] | Seoul St. Mary's Hospital, Korea | Retrospective | Median 36 Gy in 5#<br>(range 35–37.5 in 5#) | CK | 41 | 29 | 6 (20) | L, I, H | 86% |
| Xia *et al.* 2013[31] | Drexel University College, Philadelphia, USA | Retrospective | 35 Gy in 5#<br>37.5 Gy in 5#<br>36.25 Gy in 5# | CK | 31 | 70 | 23 (33) | L, I, H | 94.5% at 36 m |

Jabbari *et al.*[27] also analysed SBRT as a boost post-EBRT as part of their study, statistics shown SBRT as monotherapy only. ‡Patients incorporated in the CK pooled analysis were from New York; Na
L; Beth Israel; Boston, MA; Radiosurgery Medical Group, San Diego, CA; San Bortolo, Vicenza, Italy; Stanford, CA; Georgetown University, Washington, DC; and the Swedish Medical Center, Seattle
C.R. King et al. pers. comm., 2014). To avoid overlap in calculating bPFS, data from Friedland *et al.*,[20] Katz *et al.*,[21] King *et al.*,[22] McBride *et al.*[24] and Chen *et al.*[32] have not been repeated in this table
CyberKnife; EBRT, external beam radiotherapy; H, high-risk group; I, intermediate-risk group; IMRT, intensity-modulated radiation therapy; L, low-risk group; N/A, not available from publication
adiotherapy; SBRT, stereotactic body radiotherapy; UCSF, University California San Francisco; VMAT, volumetric modulated arc therapy.

## Stereotactic body radiotherapy for primary prostate cancer:

**Outcome**:

- 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 (35–40 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.
- Langen 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 >5mm approximately 14% and 3% of the time, respectively.
- Lifetime costs and QALY for hypothetical cohorts of SBRT-treated patients were simulated on parameters including assumed mortality, bPFS and toxicity and compared with similar parameters from IMRT-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.

## 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 0–29% 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.

## Stereotactic body radiotherapy for primary prostate cancer:

**Conclusion:**

- SBRT for prostate cancer remains a promising new treatment for the future, with high local control rates and toxicity rates comparable with fractionated radiotherapy.
- The duration of treatment is significantly shorter and significantly cheaper when compared with conventional fractionation IMRT.
- SBRT studies suggest that there is an excellent early biochemical control and equivalent early and late urinary and rectal toxicity rates when compared with historical data of patients treated with conventional fractionation.
- QOL post-treatment with regard to urinary and sexual symptoms appears to favour SBRT over radical prostatectomy at 36 months follow-up.
- Rectal QOL symptoms were temporarily worse with SBRT over radical prostatectomy but improved after 12 months.
- Ultimately, further studies are required for formal evaluation of SBRT regimes to assess differences in toxicity and biochemical control, especially when comparing modern technologies, such as VMAT, tomotherapy and CK, and more widely available technology such as IMRT, to deliver treatment.

## 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

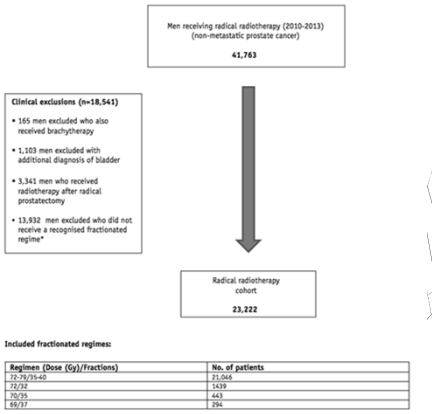
**Purpose :**

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 database of care episodes in National Health Service hospitals.

## Inclusion and exclusion criteria




**Included fractionated regimes:**

| Regimen (Dose (Gy)/Fractions) | No. of patients |
|---|---|
| 72-78/35-40 | 21,046 |
| 72/32 | 1439 |
| 70/35 | 443 |
| 66/37 | 294 |

## IMRT vs 3D-CRT for Prostate cancer

**Patient population :**

- Among the 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 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 nodes compared with the IMRT group.
- Median (interquartile range) follow-up was 3.6 (1.9) years for all men in the study; 2.7 (1.0) years for the IMRT group and 4.1 (1.6) years for the 3D-CRT group.

| Characteristic | 3D-CRT (n = 16,289) | IMRT (n = 6933) | *P* |
|---|---|---|---|
| Year of radiation therapy | | | <.01 |
| 2010 | 4248 (26.1) | 216 (3.1) | |
| 2011 | 5159 (31.7) | 624 (9.0) | |
| 2012 | 4678 (28.7) | 1605 (23.1) | |
| 2013 | 2204 (13.5) | 4488 (64.7) | |
| Age (y) | | | <.01 |
| <60 | 1069 (6.5) | 532 (7.7) | |
| 60-64 | 2409 (14.8) | 1096 (15.8) | |
| 65-74 | 9311 (57.2) | 3879 (56.0) | |
| >75 | 3500 (21.5) | 1426 (20.6) | |
| RCS Charlson comorbidity score | | | <.01 |
| 0 | 12,407 (76.2) | 5463 (78.8) | |
| ≥1 | 3882 (23.8) | 1470 (21.2) | |
| Socioeconomic deprivation status (national quintiles) | | | .19 |
| 1 (least deprived) | 3683 (22.6) | 1649 (24.0) | |
| 2 | 4063 (25.0) | 1735 (25.2) | |
| 3 | 3552 (21.8) | 1471 (21.4) | |
| 4 | 2707 (16.6) | 1112 (16.2) | |
| 5 (most deprived) | 2270 (14.0) | 919 (13.4) | |
| Missing | 14 | 47 | |
| Prostate cancer risk group | | | <.01 |
| Locally advanced | 6433 (56.4) | 3603 (59.4) | |
| Intermediate risk localized | 4433 (38.9) | 2211 (36.4) | |
| Low risk localized | 534 (4.7) | 384 (5.3) | |
| Missing | 4889 | 864 | |
| Radiation therapy treatment region | | | <.01 |
| Prostate | 11,782 (72.3) | 5786 (86.4) | |
| Prostate and regional | 950 (5.8) | 911 (13.6) | |
| Missing | 3557 | 236 | |

*Abbreviations:* 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; RCS = Royal College of Surgeons.
Values are number (percentage).

## 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 followup, compared with 2.4 in the 3D-CRT group.
- Men treated with IMRT were less likely to experience GI toxicity (HR 0.66; 95% CI 0.61-0.72; P< 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; PZ.31)

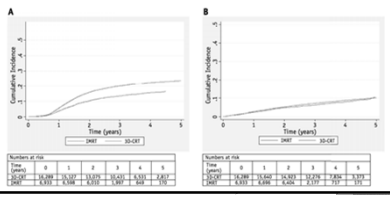
| | GI toxicity | | | | GU toxicity | | | |
|---|---|---|---|---|---|---|---|---|
| Therapy | 5-y cumulative incidence (%) (95% CI) | Rate (total events/100 person years) | HR* (CI) | *P* | 5-y cumulative incidence (%) (95% CI) | Rate (total events/100 person-years) | HR* (CI) | *P* |
| 3D-CRT | 24.5 (23.8-25.3) | 6.5 | 1.00 | - | 11.1 (9.2-13.3) | 2.4 | 1.00 | - |
| IMRT | 17.0 (15.6-18.5) | 4.9 | 0.66 (0.61-0.72) | <.01 | 10.7 (10.1-11.3) | 2.3 | 0.94 (0.84-1.06) | .31 |

*Abbreviations:* CI = confidence interval; HR = hazard ratio. Other abbreviations as in Table 1.
* Adjusted for year of radiation therapy treatment, age, RCS Charlson comorbidity score, socioeconomic deprivation status, prostate cancer risk group, and radiation therapy treatment region.

## IMRT vs 3D-CRT for Prostate cancer

**Timing and frequency of occurrence of toxicity**

- Cumulative incidence curves showed GI toxicity was low in the first 9 months (approximately 2%) and similar in the IMRT and 3D-CRT groups.
- However, beyond 9 months after RT, patients in the 3D-CRT group more frequently had complications than the IMRT group.
- Conversely, GU toxicity steadily increased in both IMRT and 3D-CRT groups after radical RT




## IMRT vs 3D-CRT for Prostate cancer

**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 3DCRT.

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

Comparisons of health-related quality of life among surgery and radiotherapy for localized prostate cancer: a systematic review and meta-analysis Cheng Chen Oncotarget, 2017, Vol. 8, (No. 58), pp: 99057-99065

**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** met the criteria:

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 deviations (SD);
4. health-related QOL outcomes were presented as EPIC domain summary scores, specifically, urinary sum score, sexual sum score and bowel sum score.
5. the most recent or representative study of the same author or group was selected to include.

Studies were **excluded** based on criteria:

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

## Characteristics of studies included in this meta-analysis

| Study | Design | QOL measure | Patient numbers | Treatment cohorts | QOL domain | NOS score | Follow-up time |
|---|---|---|---|---|---|---|---|
| Sanda 2008 | Prospective study | EPIC | RP:603 EBRT:292 | RP: Retropubic, laparoscopic or robot-assisted techniques with nerve-sparing at the surgeon's discretion EBRT: Intensity-modulated radiotherapy or highly conformal techniques with ADT | Sexual, Bowel QOL | 7 | 2, 6, 12, 24 months |
| Katz 2012 | Retrospective study | EPIC | RP:123 EBRT:216 | RP: Retropubic prostatectomy with nerve-sparing at the surgeon's discretion EBRT: 35 Gy in the first 38 patients and 36.25 Gy in the remaining without ADT | Urinary, Sexual, Bowel QOL | 5 | 1, 6, 12, 24, 36 months |
| Ferrer 2008 | Prospective study | EPIC | RP:134 EBRT:205 | RP: Retropubic prostatectomy with nerve-sparing at the surgeon's discretion EBRT: 3D conformal technique | Urinary, Sexual, Bowel QOL | 6 | 3, 6, 12, 24 months |
| Donovan 2016 | RCT | EPIC | RP:553 EBRT:545 | RP: Open retropubic, nerve-sparing approach EBRT: 3D conformal radiotherapy at a total dose of 74 Gy with ADT | Urinary, Sexual, Bowel QOL | 7 | 6, 12, 24, 36, 48, 60, 72 months |
| Resnick 2013 | Prospective study | EPIC | RP:1164 EBRT:491 | RP, EBRT | Urinary, Sexual, Bowel QOL | 7 | 6, 12, 24, 60, 180 months |
| Nicolaisen 2014 | Cross-sectional survey | EPIC | RP:38 EBRT:59 | RP, EBRT | Urinary, Sexual, Bowel QOL | 4 | 36 months |

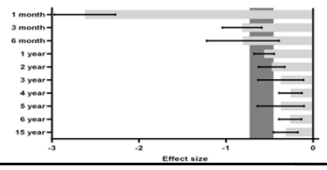
Abbreviations: RP, radical prostatectomy; EBRT, external beam radiation therapy; BT, brachytherapy; EPIC, Expanded Prostate Cancer Index Composite; QOL, quality of life; ADT, androgen deprivation therapy; NOS, Newcastle–Ottawa scale; RCT, randomized controlled trial.

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

**Results :**

**Urinary quality of life :**

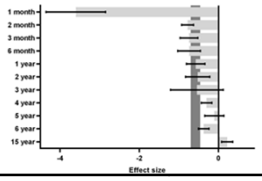
- Patients undergoing RP had lower urinary domain scores than men undergoing EBRT (SMD = –0.59; 95% CI = –0.73 to –0.45).
- In sub-group analysis, compare to EBRT group, RP group had the lowest urinary domain scores in the first month (SMD = –2.62; 95% CI = –2.97 to –2.27) and experienced a sharp increase in the following two months (SMD = –0.81; 95% CI = –1.04 to –0.59).
- 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 :**

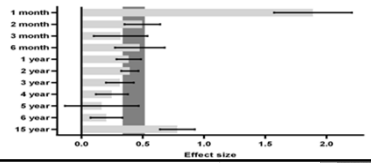
- Patients undergoing RP had lower sexual domain scores than men undergoing EBRT (SMD = −0.58; 95% CI = −0.72 to −0.44).
- In sub-group analysis, compare to EBRT group, RP group had the lowest sexual domain scores in the first month (SMD = −3.60; 95% CI = −4.35 to −2.85) and experienced a sharp increase in the second month (SMD = −0.78; 95% CI = −0.93 to −0.63).
- The gap between RP and EBRT was diminished afterwards and got to the minimum difference in the fifth year (SMD = −0.11; 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 = 0.08 to 0.36).




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

**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, compare to EBRT group, RP group had the highest bowel domain scores in the first month (SMD = 1.89; 95% CI = 1.57 to 2.21) and experienced a sharp decrease in the second month (SMD = 0.50; 95% CI = 0.35 to 0.64).
- The difference between RP and EBRT was shortening over the time and got to the minimum in the fifth year (SMD = 0.17; 95% CI = −0.14 to 0.47).
- Afterwards, rebound happened in the sixth year (SMD = 0.20; 95% CI = 0.07 to 0.33) and reached to a new peak in the 15th year (SMD = 0.78; 95% CI = 0.64 to 0.92), indicating EBRT may have long-term bowel side effect.




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

**Discussion :**

**Conclusion**

Men treated with RP experienced an acute worsen with respect to urinary and sexual QOL in the first two months post operation, which also happened in EBRT with bowel function.

The two treatment groups continued to relieve in all functional outcomes to have similar health-related prognosis in the long-term followup.

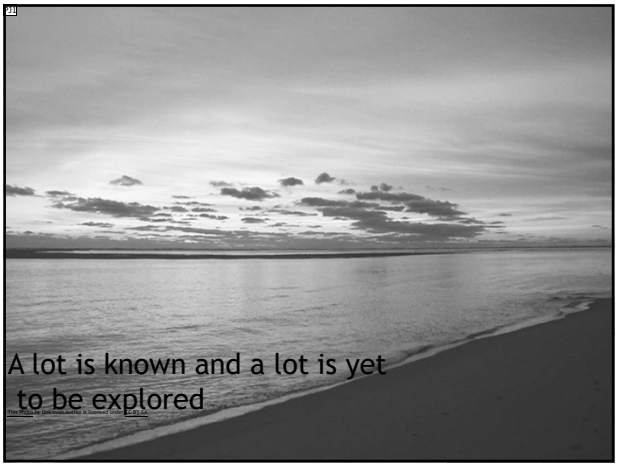
androgen-deprivation therapy

- EBRT group had the highest incidence of **Bowel side effects** in the first month and resolve quickly within two month which can be controlled well in the subsequent five years.

Bowel symptoms deteriorated 5 years later especially in the 15th year, indicating EBRT may have long-term bowel side effect which cannot be ignored.

## Key Takeaway Messages

- **Lower the PSA better the outcome**
  - **Start RT at the earliest after PSA > 0.2 ng/ml**
- **Higher dose(upto 70 Gy) clearly better**
- **Adjuvant and salvage-RT after RPE both improve recurrence free survival and offer a second chance of cure**
- **Adjuvant 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**

## Slide 81

**PJ1** Preety Jain, 13-08-2018