Clinical Case Conference

Intermediate-risk prostate cancer
08/06/2014

Long Pham

Clinical Case

- 64 yo man was found to have elevated PSA of 8.65.
- TRUS-biopies were negative.
- Surveillance PSA was 7.2 in 3 years later.
- Repeat biopsy year 3 → small focus of atypical glands in right lobe and benign prostatic tissue in left lobe.
- Repeat biopsy year 4 → 1/5 cores in the right lobe positive for adenocarcinoma, GS 3+3, 10 % of core involved.
- He decided to go with active surveillance.
- PSA was noted to rise to 11.44 at year 5.
- Repeat biopsy in year 5 showed prostate adenocarcinoma, GS 3+4, 3/6 cores positive of the left lobe in up to 80% tissue involved, 0/6 cores positive on the right lobe.

Clinical Case

- Clinical sxs:
  - Sensation of weak stream
  - Incomplete emptying,
  - Post-void dribbling
  - Urinary frequency
  - Nocturia x 3 daily
  - IPSS of 20.
  - No erectile dysfunction nd his SHIM score was 24.

- Exam:
  - DRE: no nodularity or induration.

Clinical Case

- PMHx:
  - HLP, meningioma s/p cyberknife tx
  - PSHx:
    - None
- Allergy:
  - NKDA
- Medications:
  - Pravastatin, Aspirin
- FamHx:
  - No family Hx of cancer
- Social Hx:
  - Former smoker with remote 5 pack-year hx

Epidemiology – Prostate Cancer

- Estimated 233,000 new cases in 2014
  - 27% of new cancer cases in men
- Prostate-cancer death: 29,480 in 2014.
- PSA Screening – Stage Migration
  - Locally advanced/metastatic disease → clinically nonpalpable disease.
- 2 large prostate cancer registries:
  - CaPSURE: Cancer of the Prostate Strategic Urologic Research Endeavor
    - High risk disease:
      - 27.4% (1990-1994) → 13.7% (2004-2007)
    - Stage T1:
      - 16.9% (1990-1994) → 49.4% (2004-2007)
  - DoD CPDR: Center for Prostate Disease Research
    - T3-T4: 19.2% (1988) → 4.4% (1998)
    - T1c: 0% (1988) → 47.8% (1998)

Clinical Presentation – Prostate Cancer

- Asymptomatic
- Lower Urinary Tract Symptoms:
  - Nocturia
  - Urinary frequency and/or urgency
  - Decrease flow
  - Incomplete voiding
  - Intermittent flow
  - Urinary hesitancy
- Difficulty of passing stool
- Bloody stool

Risk Factors – Prostate Cancer

- Hormonal factors
- Dietary factors
- Familial factors
- Genetic and Molecular factors
- Chronic and recurrent inflammation of prostate/prostatitis

TNM Staging – Prostate Cancer

Stage	Description
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
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 (e.g., because of elevated PSA)
T2a/pT2a	Unilateral, one-half of one side or less
T2b/pT2b	Unilateral, involving more than one-half of side but not both sides
T2c/pT2c	Tumor involves both lobes (i.e., bilateral involvement)
T3a/pT3a	Extraprostatic extension or microscopic invasion of bladder neck
T3b/pT3b	Tumor invades seminal vesicle(s)
T4/pT4	Tumor is fixed or (pathologically) invades adjacent structures other than seminal vesicles (such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Stage	Description
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1a	Distant metastasis to non-regional lymph nodes
M1b	Distant metastasis to skeletal system
M1a	Distant metastasis to additional sites with or without skeletal metastasis

Risk Classification – Prostate Cancer

- D'Amico, et al. JAMA 1998
  - Low-risk
    - T1c-T2a, PSA<10, <u>AND</u> Gleason score ≤ 6
  - Intermediate-risk
    - T2b or T2c, PSA 10-20, OR Gleason score 7
  - High-risk
    - T3a, PSA > 20, OR Gleason score 8-10
  - Widely used and basis for NCCN guidelines
  - 2010 AJCC includes grouping system to include PSA and Gleason's score
- D'Amico, et al. IJROBP 2001; 49(3)
  - Independent prognostic capabilities of percentage of positive biopsy cores [PPC] (# of postive cores/# total cores biopsied) of PSA control.
  - Intermediate-risk disease:
    - PPC <34% : similar outcomes as low-risk pts
    - PPC >50% : similar outcomes as high-risk pts

Risk Classification – Partin Table

Clinical stage, PSA, GS → predicting

OC = Organ confined

EPE = Extraprostatic extension

SV+ = Seminal vesicle involvement

LN+ = Lymph node involvement

Table 2 Predicted probability (95% confidence interval) of pathological stage according to clinical stage (TNM), PSA level, and biopsy Gleason score (Johns Hopkins RP patients 2006–2011).

PSA	Pathological stage	Biopsy Gleason Score				
		6	3+4	4+3	8	9–10
Clinical stage T1c (n = 4380)						
0–2.5	OC (n = 289)	93 (91–95)	83 (78–87)	80 (74–85)	79 (72–85)	74 (61–83)
	EPE (n = 21)	7 (5–8)	15 (11–20)	17 (12–22)	18 (12–24)	20 (12–29)
	SV+ (n = 4)	0 (0–1)	2 (0–3)	3 (1–6)	3 (1–6)	5 (1–12)
	LN+ (n = 0)	0 (0–0)	0 (0–1)	0 (0–2)	0 (0–2)	2 (0–6)
2.6–4.0	OC (n = 751)	87 (85–89)	71 (67–75)	66 (60–71)	65 (57–72)	56 (44–67)
	EPE (n = 133)	12 (10–14)	25 (22–29)	27 (22–32)	28 (22–34)	29 (20–40)
	SV+ (n = 10)	0 (0–1)	2 (1–4)	4 (2–7)	4 (2–8)	7 (3–12)
	LN+ (n = 4)	0 (0–0)	1 (0–2)	3 (1–5)	3 (1–6)	8 (3–16)
4.1–6.0	OC (n = 1439)	84 (83–86)	66 (63–69)	60 (55–65)	59 (51–66)	50 (38–60)
	EPE (n = 371)	15 (13–16)	29 (26–33)	31 (26–36)	32 (25–38)	32 (23–42)
	SV+ (n = 37)	1 (0–1)	4 (2–5)	6 (4–9)	6 (4–10)	10 (5–16)
	LN+ (n = 11)	0 (0–0)	1 (0–2)	3 (2–5)	3 (1–6)	8 (4–15)
6.1–10.0	OC (n = 686)	80 (78–82)	59 (55–63)	53 (47–58)	52 (44–59)	42 (31–52)
	EPE (n = 226)	18 (16–20)	34 (30–38)	35 (30–40)	36 (29–43)	36 (26–46)
	SV+ (n = 36)	1 (1–2)	6 (4–8)	9 (6–13)	9 (5–14)	14 (8–21)
	LN+ (n = 8)	0 (0–0)	1 (0–2)	3 (1–5)	3 (1–6)	8 (4–14)
>10.0	OC (n = 191)	69 (64–74)	42 (36–48)	34 (28–40)	33 (26–40)	23 (15–32)
	EPE (n = 121)	27 (22–31)	42 (36–47)	28 (32–45)	39 (31–47)	33 (24–44)
	SV+ (n = 28)	3 (2–5)	13 (9–18)	20 (14–27)	20 (12–28)	25 (15–36)
	LN+ (n = 14)	0 (0–1)	3 (1–5)	8 (4–14)	8 (3–14)	18 (9–30)
Clinical stage T2a (n = 897)						
0–2.5	OC (n = 140)	90 (87–92)	76 (70–81)	72 (65–79)	71 (62–79)	65 (51–76)
	EPE (n = 23)	10 (7–13)	22 (17–28)	24 (17–30)	24 (18–33)	27 (18–39)
	SV+ (n = 1)	0 (0–1)	2 (0–4)	3 (1–7)	3 (1–7)	6 (1–13)
	LN+ (n = 1)	0 (0–0)	0 (0–1)	1 (0–4)	1 (0–3)	2 (0–9)
2.6–4.0	OC (n = 139)	82 (78–84)	61 (56–66)	56 (48–62)	54 (46–63)	45 (33–56)
	EPE (n = 52)	18 (15–21)	34 (29–39)	35 (29–42)	36 (29–44)	36 (26–49)
	SV+ (n = 5)	1 (0–1)	3 (1–5)	5 (2–8)	5 (2–9)	7 (3–14)
	LN+ (n = 5)	0 (0–0)	1 (0–3)	4 (1–8)	4 (1–10)	11 (4–23)
4.1–6.0	OC (n = 183)	78 (74–81)	56 (51–60)	49 (43–56)	48 (40–56)	39 (28–50)
	EPE (n = 91)	21 (18–24)	38 (34–43)	39 (33–46)	40 (32–48)	39 (28–50)
	SV+ (n = 8)	1 (1–1)	4 (3–6)	7 (4–10)	7 (4–11)	10 (5–16)
	LN+ (n = 3)	0 (0–0)	2 (1–3)	4 (2–7)	4 (2–8)	11 (4–21)
6.1–10.0	OC (n = 104)	73 (68–77)	48 (43–54)	42 (36–49)	41 (33–50)	32 (23–43)
	EPE (n = 72)	26 (22–30)	44 (39–49)	44 (37–50)	45 (36–52)	43 (31–54)
	SV+ (n = 10)	1 (1–2)	6 (4–9)	10 (6–15)	10 (5–16)	14 (7–22)
	LN+ (n = 4)	0 (0–0)	1 (1–3)	4 (2–7)	4 (1–8)	10 (4–20)
>10.0	OC (n = 22)	60 (53–66)	32 (26–39)	25 (20–31)	24 (18–32)	16 (10–24)
	EPE (n = 22)	36 (30–42)	50 (43–56)	44 (36–53)	45 (35–55)	37 (25–49)
	SV+ (n = 10)	4 (2–6)	14 (8–20)	20 (12–29)	20 (11–30)	24 (13–38)
	LN+ (n = 2)	1 (0–2)	4 (2–7)	10 (4–18)	10 (4–20)	22 (10–37)
Clinical stage T2b or T2c (n = 352)						
0–2.5	OC (n = 26)	82 (76–87)	61 (52–70)	55 (45–66)	54 (44–66)	45 (32–60)
	EPE (n = 13)	17 (12–23)	33 (25–42)	34 (25–44)	35 (24–46)	35 (23–48)
	SV+ (n = 0)	1 (0–2)	5 (1–10)	8 (2–16)	8 (2–16)	13 (3–24)
	LN+ (n = 0)	0 (0–0)	1 (0–3)	2 (0–9)	3 (0–9)	7 (0–21)
2.6–4.0	OC (n = 27)	70 (63–75)	44 (37–51)	36 (29–44)	35 (27–44)	24 (16–35)
	EPE (n = 30)	28 (22–35)	46 (39–53)	43 (35–51)	44 (34–53)	37 (26–51)
	SV+ (n = 3)	2 (1–3)	6 (3–10)	10 (5–16)	10 (5–17)	13 (6–23)
	LN+ (n = 2)	1 (0–2)	4 (2–8)	11 (5–20)	11 (4–21)	25 (12–42)
4.1–6.0	OC (n = 52)	64 (58–70)	38 (32–44)	30 (24–37)	30 (22–37)	20 (13–29)
	EPE (n = 45)	32 (27–39)	49 (42–56)	45 (38–52)	46 (37–55)	38 (26–51)
	SV+ (n = 14)	2 (1–4)	9 (6–13)	14 (9–20)	13 (8–21)	17 (9–28)
	LN+ (n = 12)	1 (0–2)	4 (2–8)	11 (5–17)	11 (5–19)	24 (12–40)
6.1–10.0	OC (n = 25)	58 (50–65)	31 (25–37)	24 (19–31)	24 (18–31)	16 (10–23)
	EPE (n = 36)	38 (32–45)	52 (46–59)	47 (40–55)	48 (39–57)	40 (28–52)
	SV+ (n = 7)	4 (2–6)	12 (8–18)	19 (12–25)	18 (10–26)	23 (12–34)
	LN+ (n = 5)	1 (0–2)	4 (2–7)	10 (5–16)	10 (5–18)	22 (10–35)
>10.0	OC (n = 8)	42 (34–50)	17 (13–23)	12 (8–16)	11 (8–16)	6 (4–11)
	EPE (n = 21)	47 (39–55)	50 (41–59)	39 (30–49)	40 (28–51)	27 (18–40)
	SV+ (n = 18)	9 (5–14)	23 (15–33)	30 (20–41)	29 (18–42)	30 (17–45)
	LN+ (n = 8)	2 (0–4)	9 (4–16)	20 (10–31)	20 (9–32)	36 (20–53)

PSA, prostate-specific antigen; RP, radical prostatectomy; OC, organ confined; EPE, extraprostatic extension; SV+, seminal vesicle involvement; LN+, lymph node involvement.

http://urology.jhu.edu/prostate/partintables.php

Risk Classification – Kattan Nomograms

- http://nomograms.mskcc.org/Prostate/index.aspx

- 4 nomograms
  - Pre-treatment nomogram
    - Progression free probability after radical prostatectomy or brachytherapy
  - Post-radical prostatectomy nomogram
    - Probability of recurrence after radical prostatectomy (rising PSA after prostatectomy)
  - Salvage Radiation Therapy
    - Probability that recurrence after radical prostatectomy can be successfully treated with salvage radiation therapy.
  - Hormone Refractory
    - Survival probability in one or two years for patients with hormonal refractory metastatic prostate cancer.

Risk Classification – Roach's Formula

- Extracapsular Extension

    ○ $\frac{3}{2} \times PSA + [(GS - 3) \times 10]$

- Seminal Vesicle Involvement

    ○ $PSA + [(GS - 6) \times 10]$

    ○ (<13% → actual risk 7%)

    ○ (≥ 13% → actual risk 37%)

- Lymph Node Involvement

    ○ $\frac{2}{3} \times PSA + [(GS - 6) \times 10]$

    ○ (<15% → actual risk 6%)

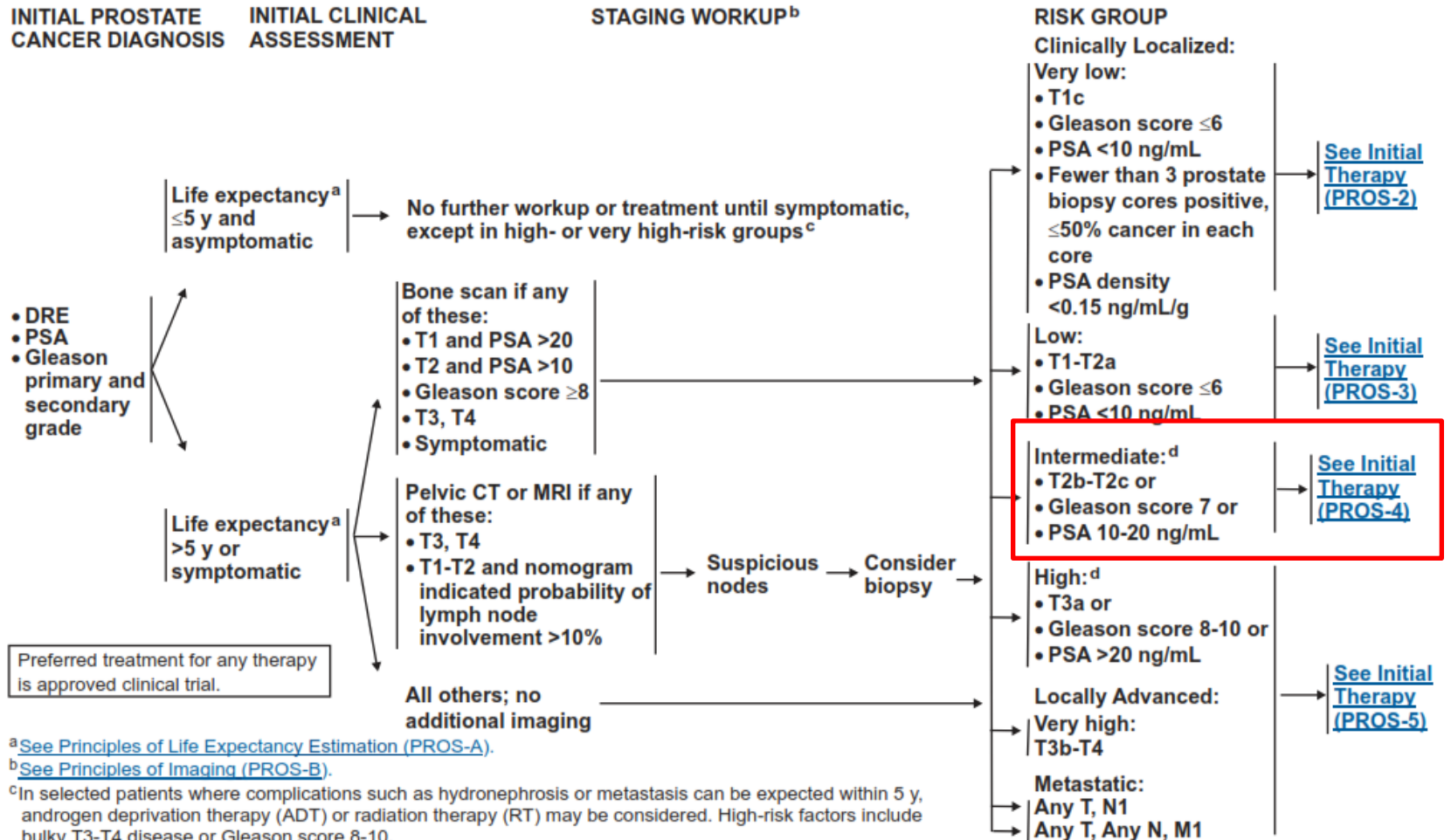   ○ (≥ 15% → actual risk 40%)

Risk Classification – CaPRA Score

- UCSF-CaPRA score: 0-10
  - Age at diagnosis
    - <50   = 0
    - ≥50   = 1
  - PSA at diagnosis
    - ≤6   = 0
    - 6.1-10   = 1
    - 10.1-20   = 2
    - 20.1-30   = 3
    - >30   = 4
  - Gleason score
    - no 4 or 5   = 0
    - secondary pattern 4 or 5   = 1
    - primary pattern 4 or 5   = 3
  - Clinical stage (T stage)
    - T1 or T2   = 0
    - T3a   = 1
  - Percent of biopsy cores positive
    - < 34%   = 0
    - ≥ 34%   = 1

Low Risk: 0-2

Intermediate Risk: 3-5

High risk: 6-10

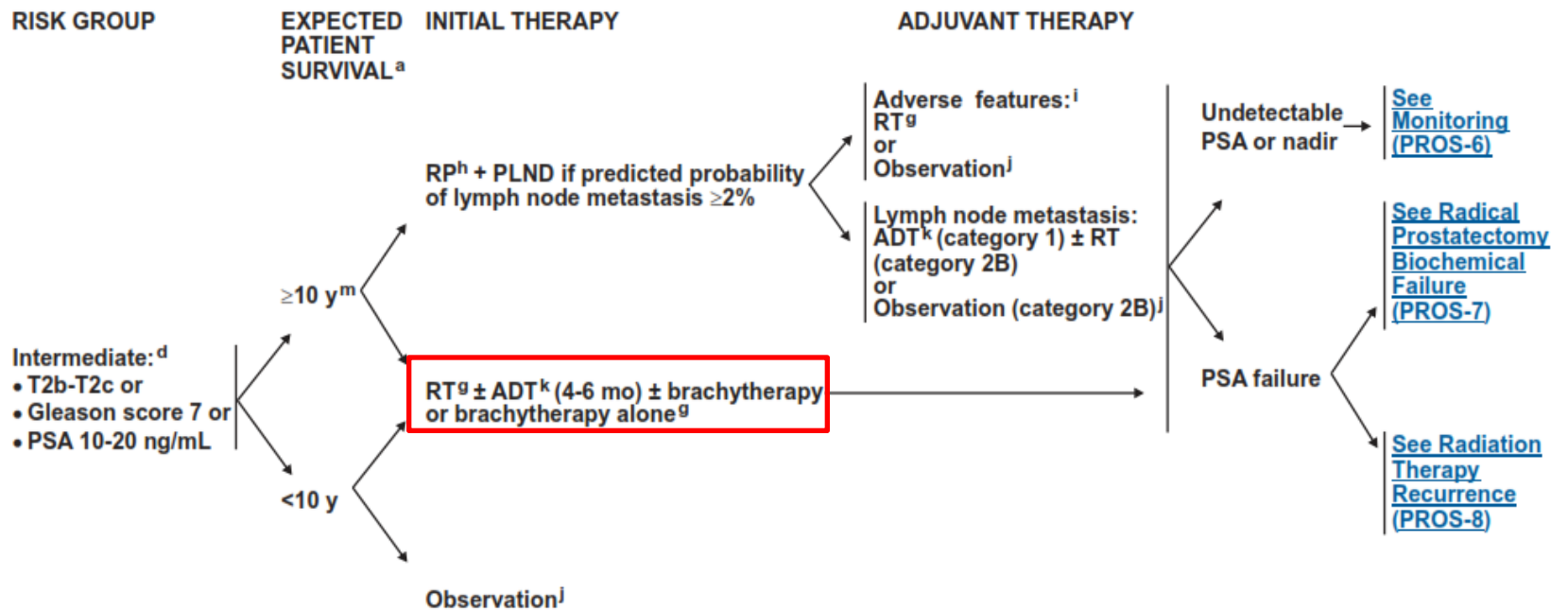# Treatment Guidelines – Prostate Cancer

NCCN Guidelines - 2014

Treatment Guidelines – Prostate Cancer

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Prostate Cancer

NCCN Guidelines Index
Prostate Table of Contents
Discussion

RISK GROUP	EXPECTED PATIENT SURVIVAL[a]	INITIAL THERAPY	ADJUVANT THERAPY		

Intermediate:[d]
- T2b-T2c or
- Gleason score 7 or
- PSA 10-20 ng/mL

≥10 y[m]

RP[h] + PLND if predicted probability of lymph node metastasis ≥2%

Adverse features:[i]
RT[g]
or
Observation[j]

Lymph node metastasis:
ADT[k] (category 1) ± RT (category 2B)
or
Observation (category 2B)[j]

Undetectable PSA or nadir → See Monitoring (PROS-6)

RT[g] ± ADT[k] (4-6 mo) ± brachytherapy or brachytherapy alone[g]

PSA failure

See Radical Prostatectomy Biochemical Failure (PROS-7)

See Radiation Therapy Recurrence (PROS-8)

<10 y

Observation[j]
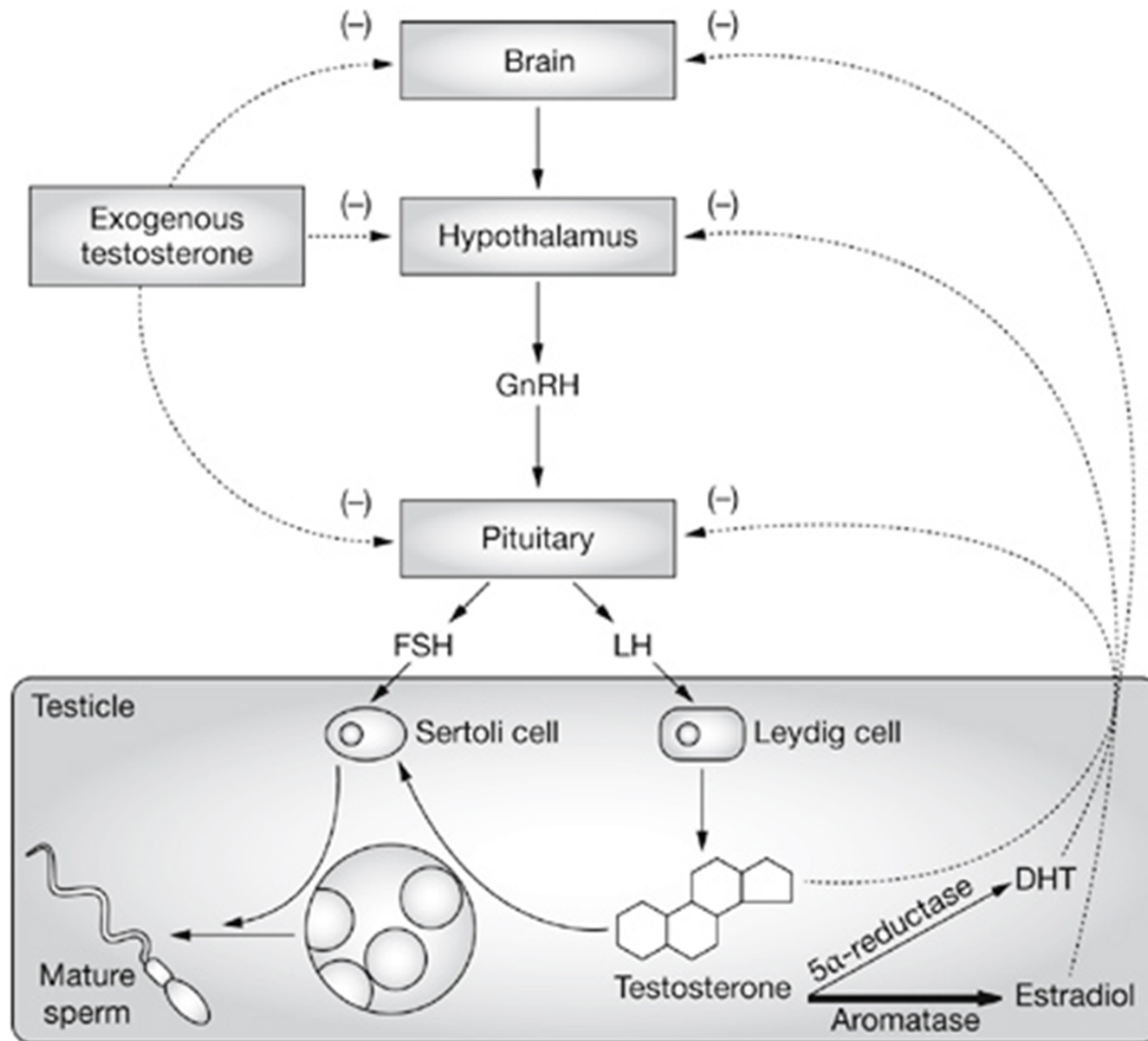
NCCN Guidelines - 2014

Intermediate-risk Prostate Cancer – Treatment Decision

◦ ADT ?

◦ Pelvic Radiotherapy ?

The role of ADT in intermediate-risk prostate cancer

The role of ADT in intermediate-risk prostate cancer

- ## Most common forms of ADT
- ## Surgical castration
  - Orchiectomy
- ## Chemical castration
  - LHRH agonists/GnRH agonists
    - Goserelin (Zoladex)
    - Leuprolide (Lupron, Eligard)
    - Triptorelin (Trelstar)
  - LHRH antagonists/GnRH antagonists
    - Degarelix (Firmagon)

- ## Anti-androgen therapy – Androgen receptor blocker
  - Bicalutamide (Casodex)
  - Flutamide (Eulexin, Flutamin, Cytomid)
  - Nilutamide (Nilandron)
  - Enzalutamide (Xtandi)

The role of ADT in intermediate-risk prostate cancer

- D'Amico et al., JAMA 2004 and D'Amico et al., JAMA 2008.
- 1995-2001: Prospective randomized control trial
- 206 pts
  - TNM: T1b-T2b Nx M0
  - PSA: 10-40
  - GS: at least 7
  - Endorectal coil MRI evidence of ECE or SV invasion for low-risk pts.
  - Negative bone scan & negative pelvic node by MRI or CT within 6 mos.
- Arm 1: EBRT alone (70 Gy 3D-CRT) [104 pts]
- Arm 2: EBRT + 6-month AST
- RT: (1.8 Gy x 25)+(2 Gy x 11) → 67 Gy normalized to 95% → 70.35 Gy (4-field 3D-CRT) → Prostate and SV in initial radiation field.
- AST: Leuprolide or Goserelin + Flutamide
- Median F/U: 4.52 yrs and 7.6 yrs

D'Amico et al. JAMA. 2004 Aug 18;292(7):821-7   D'Amico et al., JAMA. 2008 Jan 23;299(3):289-95.

The role of ADT in intermediate-risk prostate cancer

- Study designed to detect a difference in freedom from biochemical progression between 2 treatment groups with 80% power.

Figure 1. Flow of Study Patients
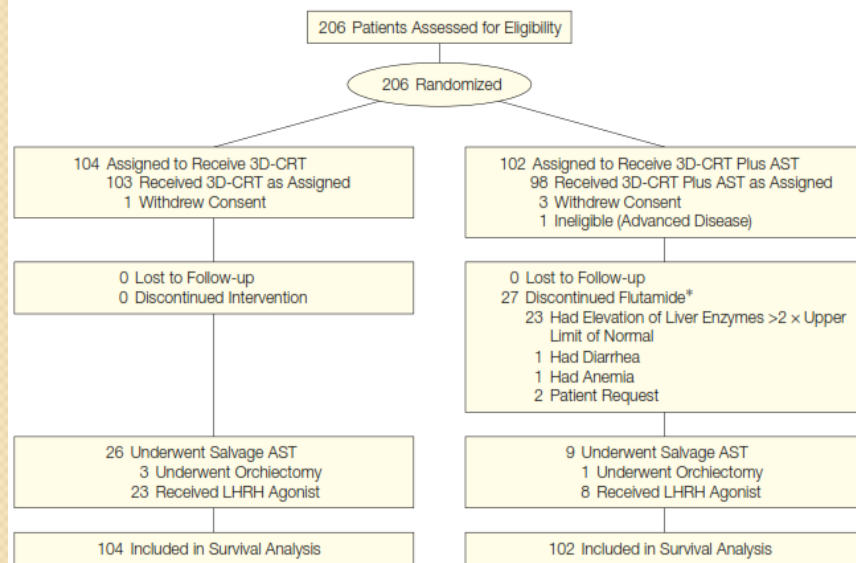
AST indicates androgen suppression therapy; 3D-CRT, 3-dimensional conformal radiation therapy; LHRH, luteinizing hormone–releasing hormone.
*Flutamide is the minor component of AST.

Table 1. Baseline Clinical Characteristics of the Study Patients (N = 206)*

Characteristic	3D-CRT (n = 104)	3D-CRT Plus AST (n = 102)
Clinical characteristics, median (range)		
Age, y	73 (51-81)	72 (49-82)
Baseline PSA level, ng/mL	11 (0.9-40)	11 (1.3-36)
Positive prostate biopsies, %	50 (17-100)	50 (17-100)
Gleason score†	7 (5-9)	7 (5-10)
5 or 6	27 (26)	30 (29)
3 + 4	37 (36)	35 (34)
4 + 3	24 (23)	23 (23)
8-10	16 (15)	14 (14)
Prostate gland volume, mL	41 (15-110)	37 (15-117)
Treatment stratification		
PSA of 20-40 ng/mL	13 (13)	12 (12)
Gleason score ≥7	64 (62)	64 (63)
PSA of 10-20 ng/mL and Gleason score ≤6	24 (23)	24 (24)
Low risk and endorectal MRI category T3	3 (3)	2 (2)
1992 AJCC clinical tumor category‡		
T1b	3 (3)	1 (1)
T1c	41 (40)	54 (53)
T2a	26 (25)	20 (20)
T2b	34 (33)	27 (27)
ECOG performance status§		
0	101 (97)	95 (93)
1	3 (3)	7 (7)
Potent at randomization	42 (40)	38 (37)

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; AJCC, American Joint Commission on Cancer; AST, androgen suppression therapy; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.
*Data are No. (%) unless otherwise specified. Percentages may not sum to 100 due to rounding.
†Gleason score range is from 5 to 10. One patient among the 27 patients with a score of 5 or 6 in the 3D-CRT group who had a Gleason score of 3 + 3 disease was noted to have a tertiary grade of 4.
‡One patient in the combined therapy group had category T2c disease.
§ECOG performance status of 0 indicates asymptomatic and fully active; 1, restricted only in physically strenuous activity.

D'Amico et al. JAMA. 2004 Aug 18;292(7):821-7   D'Amico et al., JAMA. 2008 Jan 23;299(3):289-95.

The role of ADT in intermediate-risk prostate cancer

Figure 2. Overall Survival for 3D-CRT vs 3D-CRT Plus AST
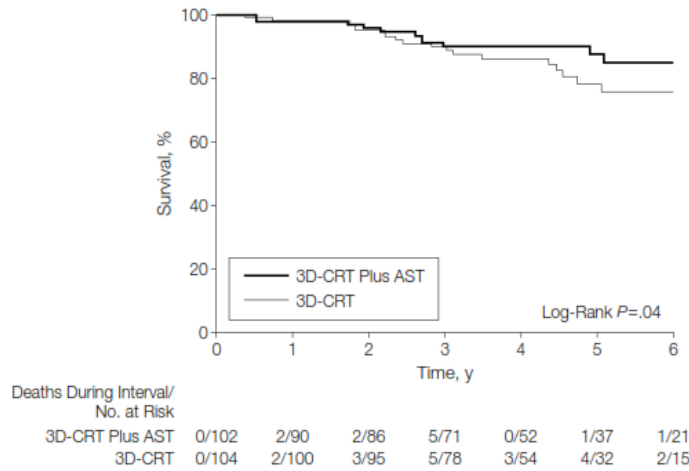
AST indicates androgen suppression therapy; 3D-CRT, 3-dimensional conformal radiation therapy.


Figure 3. Cumulative Incidence of Prostate Cancer and Non-Prostate Cancer–Specific Mortality for 3D-CRT vs 3D-CRT Plus AST
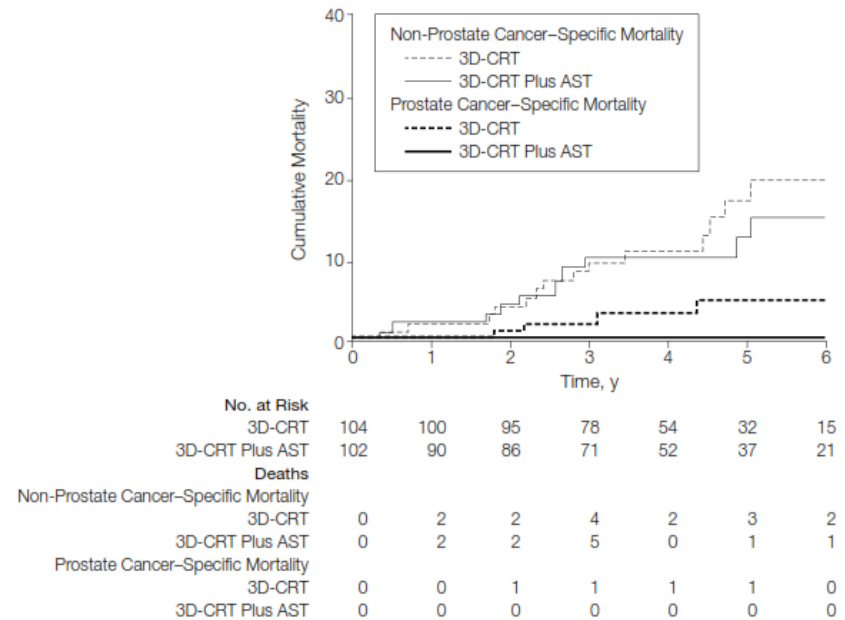
AST indicates androgen suppression therapy; 3D-CRT, 3-dimensional conformal radiation therapy. Log-rank P=.02 for prostate cancer–specific mortality; log-rank P=.31 for non-prostate cancer–specific mortality.

D'Amico et al. JAMA. 2004 Aug 18;292(7):821-7   D'Amico et al., JAMA. 2008 Jan 23;299(3):289-95.

The role of ADT in intermediate-risk prostate cancer

Figure 1. Kaplan-Meier Estimates of Overall Survival and Cumulative Incidence Estimates of Prostate Cancer–Specific Mortality for the 206 Men Stratified by Treatment
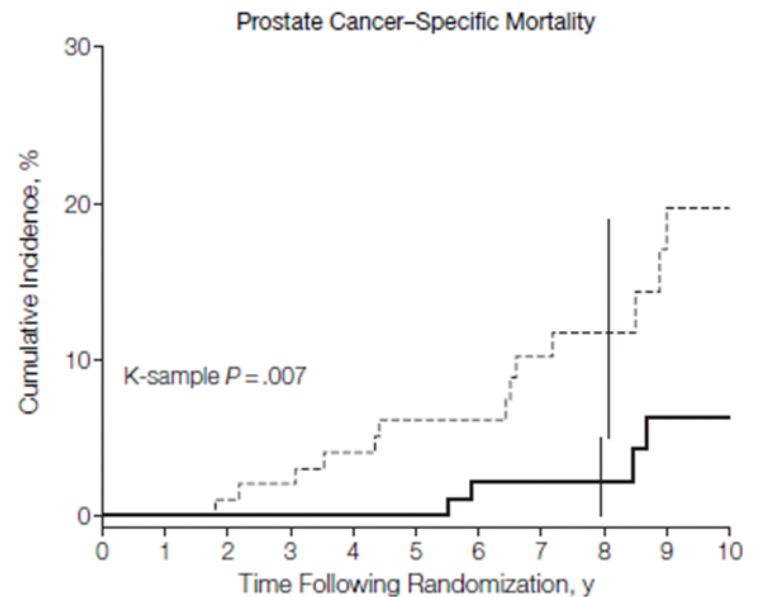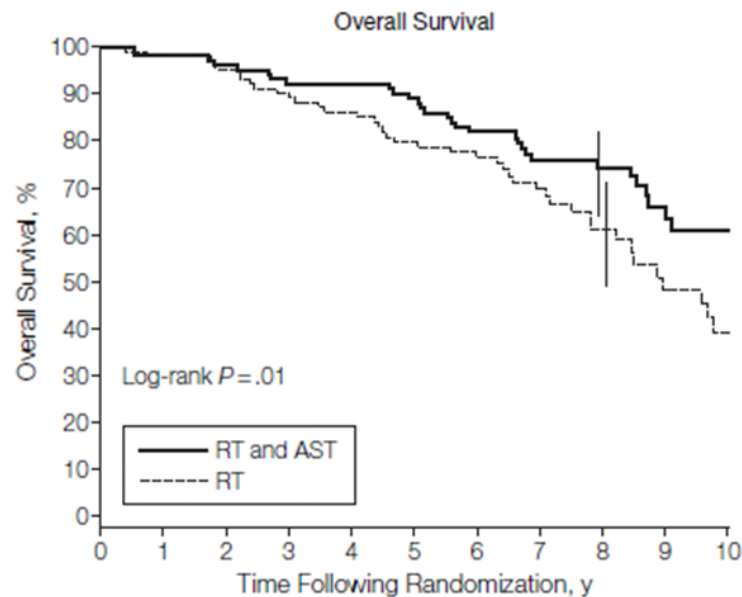
-OS at 8yrs was 74% with RT + AST vs. 61% with RT alone

-RT + AST also had less prostate cancer specific mortality than RT alone (HR 4.1)

Conclusions:

- RT + AST (6 mos) → increase OS in men (without moderate or severe co-morbidity) with localized but unfavorable-risk prostate cancer.

D'Amico et al. JAMA. 2004 Aug 18;292(7):821-7   D'Amico et al., JAMA. 2008 Jan 23;299(3):289-95.

The role of ADT in intermediate-risk prostate cancer

- RTOG 94-08
- 1994-2001
- Prospective RCT of 1979 men with Prostate CA $\leq$T2b AND PSA <20
- Arm 1: EBRT alone
- Arm 2: EBRT + 4 months ADT (2 mos before RT + 2 mos after RT)
- RT was 46.8 Gy to the whole pelvis with cone-down to the prostate up to 66.6 Gy.
  - Omission of pelvic LN treatment in pts with negative LN dissections or PSA < 10 AND GS <6.
- ADT was goserelin or leuprolide (GnRH agonists) + Flutamide (ARB) initially.
- Median F/U was 9.1 yrs
- Primary end point: OS
- Secondary end points: Disease-specific mortality, distant metastasis, biochemical failure, rate of (+) findings on repeat bx

Jones et al. NEJM 2011; 365: 107-18

The role of ADT in intermediate-risk prostate cancer

- Trial design to provide 90% power to detect a 7% absolute difference in the 8-yr survival rate.
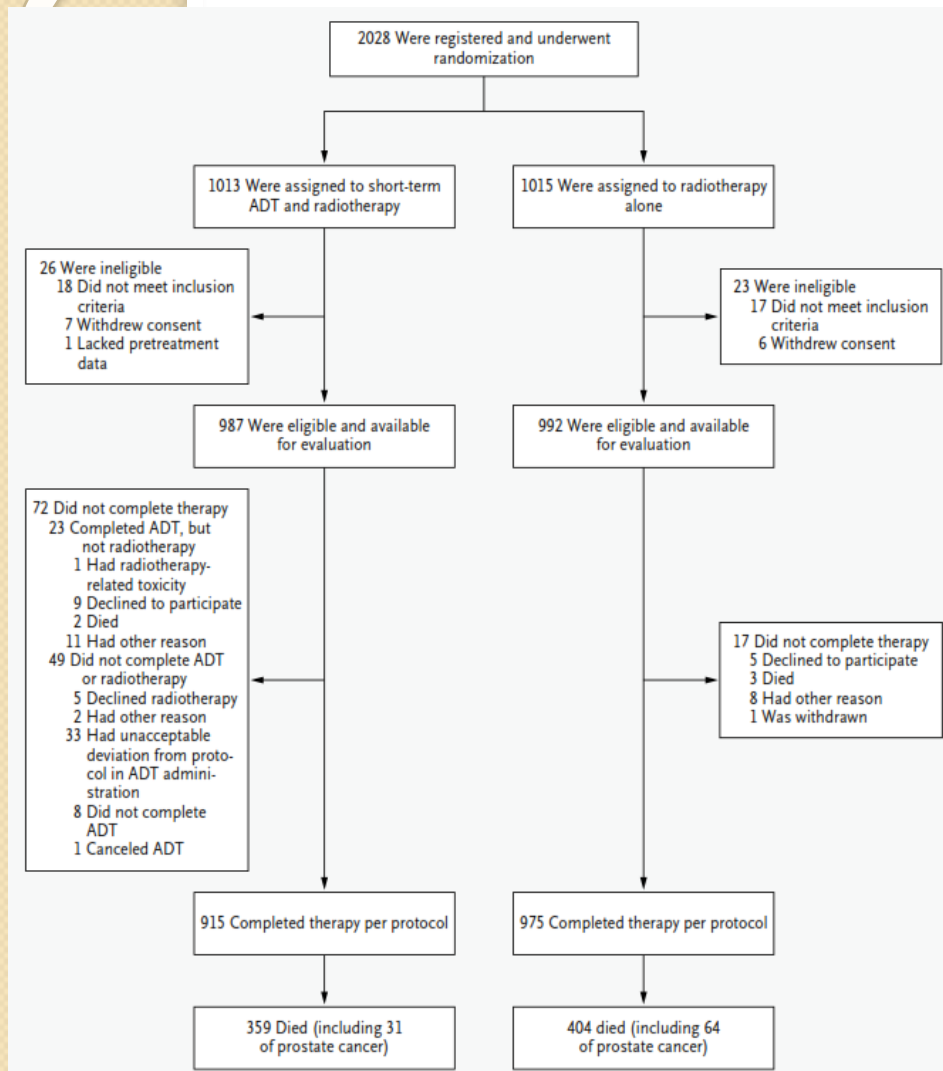

2028 Were registered and underwent randomization

1013 Were assigned to short-term ADT and radiotherapy

1015 Were assigned to radiotherapy alone

26 Were ineligible
  18 Did not meet inclusion criteria
  7 Withdrew consent
  1 Lacked pretreatment data

23 Were ineligible
  17 Did not meet inclusion criteria
  6 Withdrew consent

987 Were eligible and available for evaluation

992 Were eligible and available for evaluation

72 Did not complete therapy
  23 Completed ADT, but not radiotherapy
    1 Had radiotherapy-related toxicity
    9 Declined to participate
    2 Died
    11 Had other reason
  49 Did not complete ADT or radiotherapy
    5 Declined radiotherapy
    2 Had other reason
    33 Had unacceptable deviation from protocol in ADT administration
    8 Did not complete ADT
    1 Canceled ADT

17 Did not complete therapy
  5 Declined to participate
  3 Died
  8 Had other reason
  1 Was withdrawn

915 Completed therapy per protocol

975 Completed therapy per protocol

359 Died (including 31 of prostate cancer)

404 died (including 64 of prostate cancer)

Jones et al. NEJM 2011; 365: 107-18

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Short-Term ADT plus Radiotherapy (N=987)	Radiotherapy Alone (N=992)
Age — yr		
Median	70	71
Range	47–91	47–88
Karnofsky performance score — no. (%)		
90–100	905 (92)	920 (93)
70–80	82 (8)	72 (7)
Intercurrent disease — no. (%)		
Present	742 (75)	712 (72)
Absent	245 (25)	275 (28)
Unknown	0	5 (<1)
Tumor stage — no. (%)		
T1	488 (49)	476 (48)
T2	499 (51)	516 (52)
Nodal stage — no. (%)		
NX	944 (96)	954 (96)
N0	43 (4)	38 (4)
Differentiation — no. (%)		
Well differentiated	135 (14)	150 (15)
Moderately differentiated	625 (63)	620 (62)
Poorly differentiated or undifferentiated	227 (23)	222 (22)
Gleason score — no. (%)†		
2–6	623 (63)	592 (60)
7	252 (26)	286 (29)
8–10	93 (9)	87 (9)
Unknown	19 (2)	27 (3)
PSA — no. (%)		
<4 ng/ml	109 (11)	100 (10)
4–20 ng/ml	878 (89)	892 (90)
Race or ethnic group — no. (%)		
White	745 (75)	756 (76)
Black	198 (20)	197 (20)
Hispanic	27 (3)	26 (3)
Other or unknown	17 (2)	13 (1)
Risk subgroup — no. (%)‡		
Low risk	351 (36)	334 (34)
Intermediate risk	524 (53)	544 (55)
High risk	112 (11)	114 (11)

* Percentages may not sum to 100 because of rounding. ADT denotes androgen-deprivation therapy, and PSA prostate-specific antigen.

The role of ADT in intermediate-risk prostate cancer

Overall Survival

RT+ADT   RT

10-yr OS: 62%   vs 57%

Figure 2. Kaplan–Meier Estimates of Overall Survival.
ADT denotes androgen-deprivation therapy. Panels B, C, and D show post hoc analyses.

Jones et al. NEJM 2011; 365: 107-18
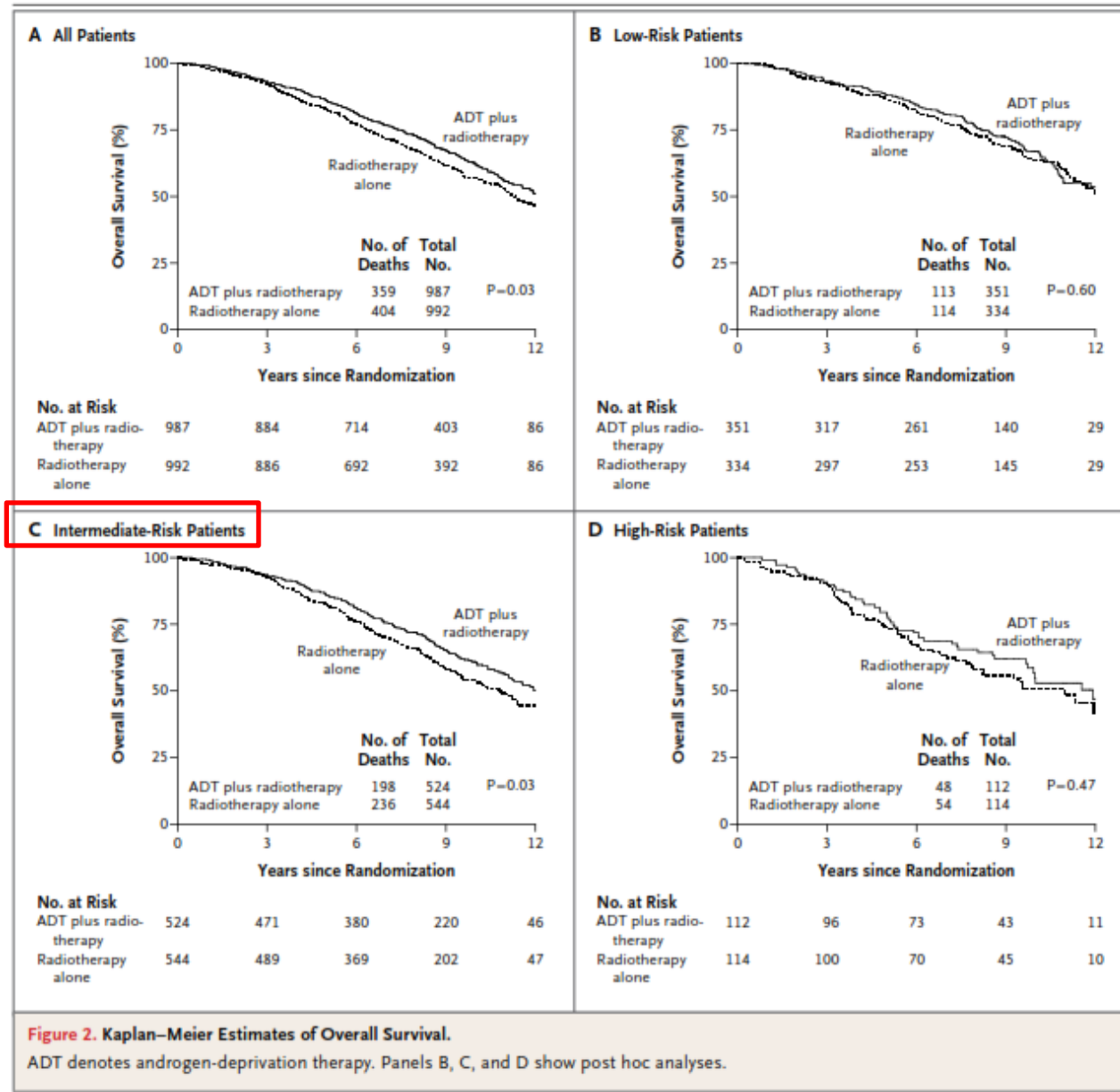
The role of ADT in intermediate-risk prostate cancer

Disease-Specific Mortality
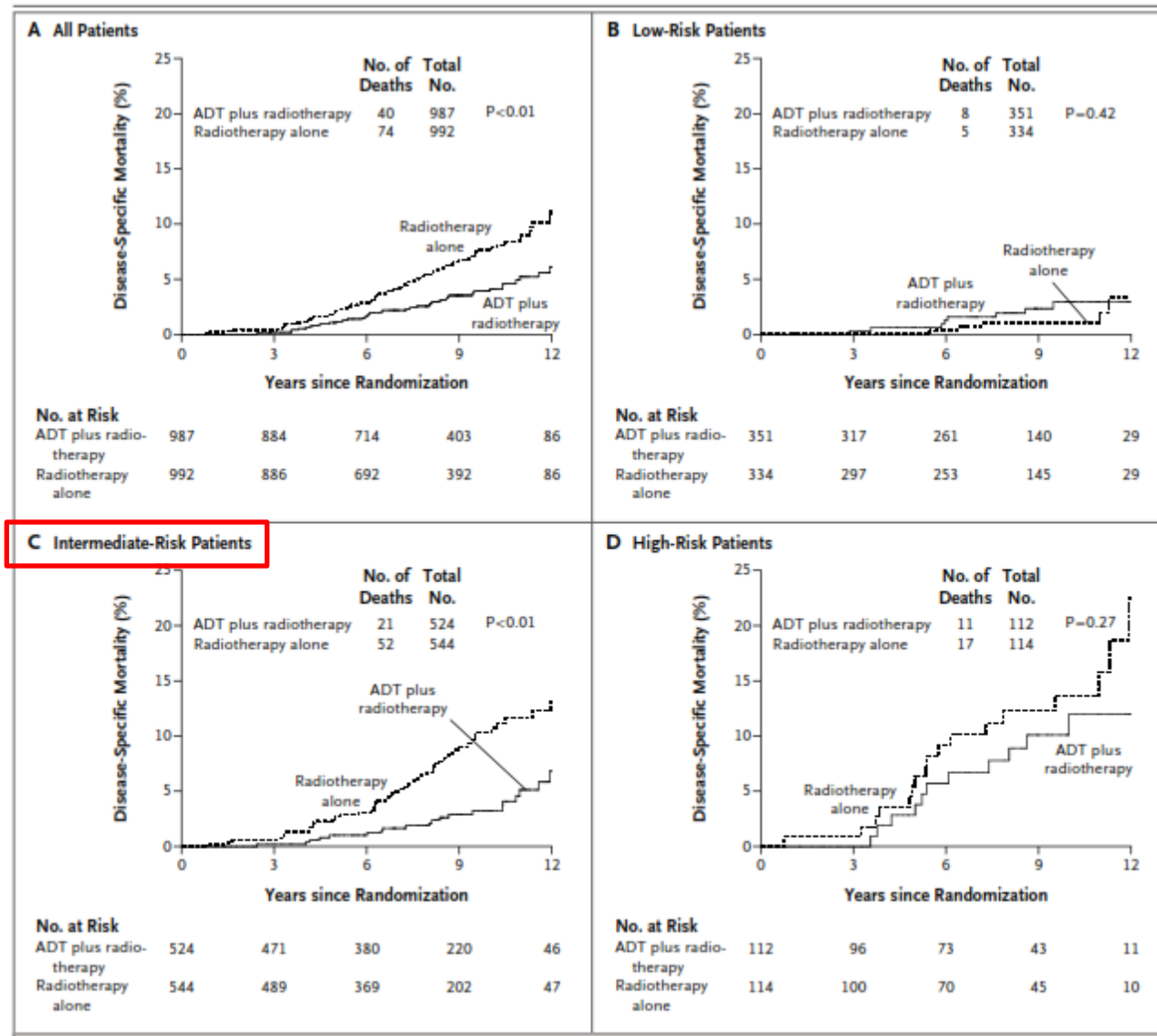
Disease-Specific Mortality

	RT+ADT	RT
10 yr rate:	4%	vs 8%

Figure 3. Cumulative-Incidence Estimate of Disease-Specific Mortality.
ADT denotes androgen-deprivation therapy. Panels B, C, and D show post hoc analyses.

Jones et al. NEJM 2011; 365: 107-18

The role of ADT in intermediate-risk prostate cancer

RTOG 0815

A Phase III Prospective Randomized Trial of Dose-Escalated Radiotherapy With or Without Short-Term Androgen Deprivation Therapy for Patients With Intermediate-Risk Prostate Cancer

SCHEMA

S T R A T I F Y	Number of Risk Factors*	R A N D O M I Z E	Arm 1
	1. One risk factor		Dose-escalated RT alone
	2. Two or 3 risk factors		
	Comorbidity Status		
	1. ACE-27** grade ≥ 2		
	2. ACE-27 grade < 2		
	RT Modality		**Arm 2**
	1. Dose-escalated EBRT		Dose-escalated RT combined with short-
	2. EBRT + LDR brachytherapy boost		term (6 months) androgen blockade (LHRH
	3. EBRT + HDR brachytherapy boost		agonist + antiandrogen)

*Intermediate risk factors: Gleason Score 7***; PSA >10 but ≤20; T-Stage T2b-T2c. Patients with all three intermediate risk factors and ≥ 50% of their sampled biopsy cores involved will <u>not</u> be eligible for this study. Note: The percentage of biopsy cores involved will only be considered with respect to eligibility for those patients with all 3 of the above risk factors (i.e., patients with one or two of the above risk factors are eligible irrespective of the percentage of biopsy cores involved).*

**The "untreated malignancy" section of the ACE-27 form is to be disregarded with respect to the patient's newly diagnosed, untreated prostate cancer.*

08/2014
Target Accrual: 1520   Current Accrual: 1222
Status: Open to Accrual

The role of pelvic RT in intermediate-risk prostate cancer

- GETUG-01 (French)(1998-2004)
- Randomized, multicenter, open phase III design
- 444 pts; T1b-T3, N0 pNx, M0
- Stratification of nodal involvement risk
  - Low risk: T1-2 and GS ≤ 6 and PSA < 3X the upper normal limit (4 ng/ml) [21%]
  - High risk: T3 and/or GS ≥ 7 and/or PSA ≥ 3X the upper normal limit (4 ng/ml) [79%]
  - Short-term ADT (6 mos) allowed for high-risk group.
- Arm 1 – Prostate + Pelvic RT
- Arm 2 – Prostate RT only
- RT dose
  - Pelvis: 46 Gy
  - Prostate: 66-70 Gy
- Median F/U: 3.5 years
- 5-year outcome: PFS 66% vs. 65% (NS); high risk PFS 63% vs. 60% (NS); low risk PFS 75% vs. 84% (NS)
- Toxicity: Pelvic arm small but nonsignificant late GI toxicity
- Conclusion: no benefit to pelvic radiotherapy

Pommier P et al. J Clin Oncol. 2007 Dec 1;25(34):5366-5373

The role of pelvic RT in intermediate-risk prostate cancer

- Trial design to detect an absolute difference in PFS of 15% at 5 years with a power of 80% and a unilateral significance level of 5% (60→75% increase in PFS in favor of pelvic RT).
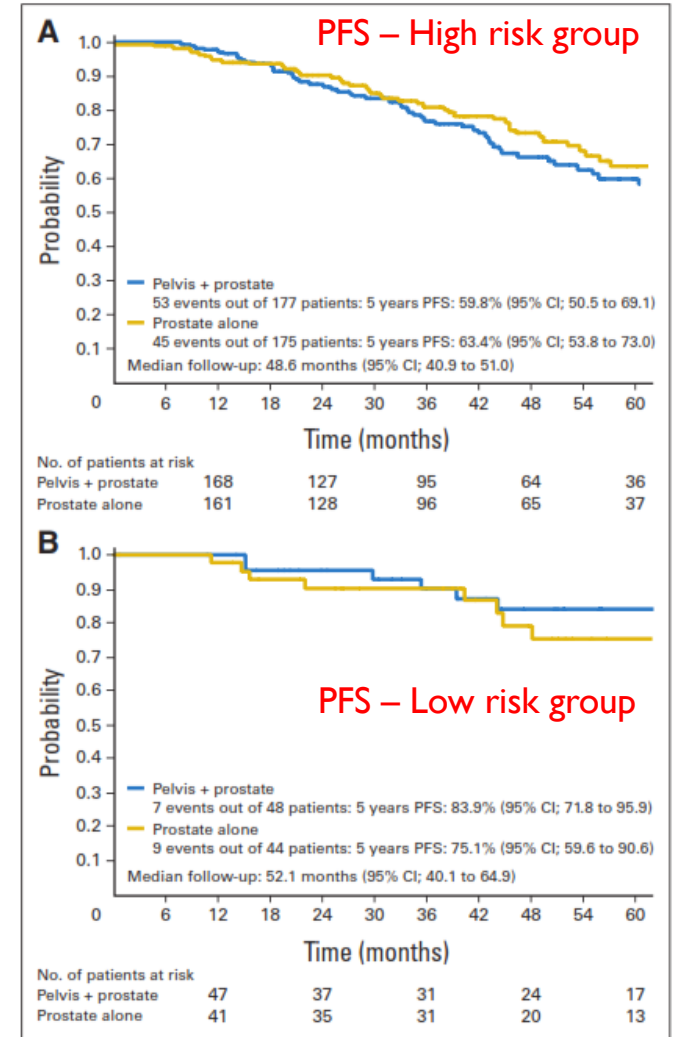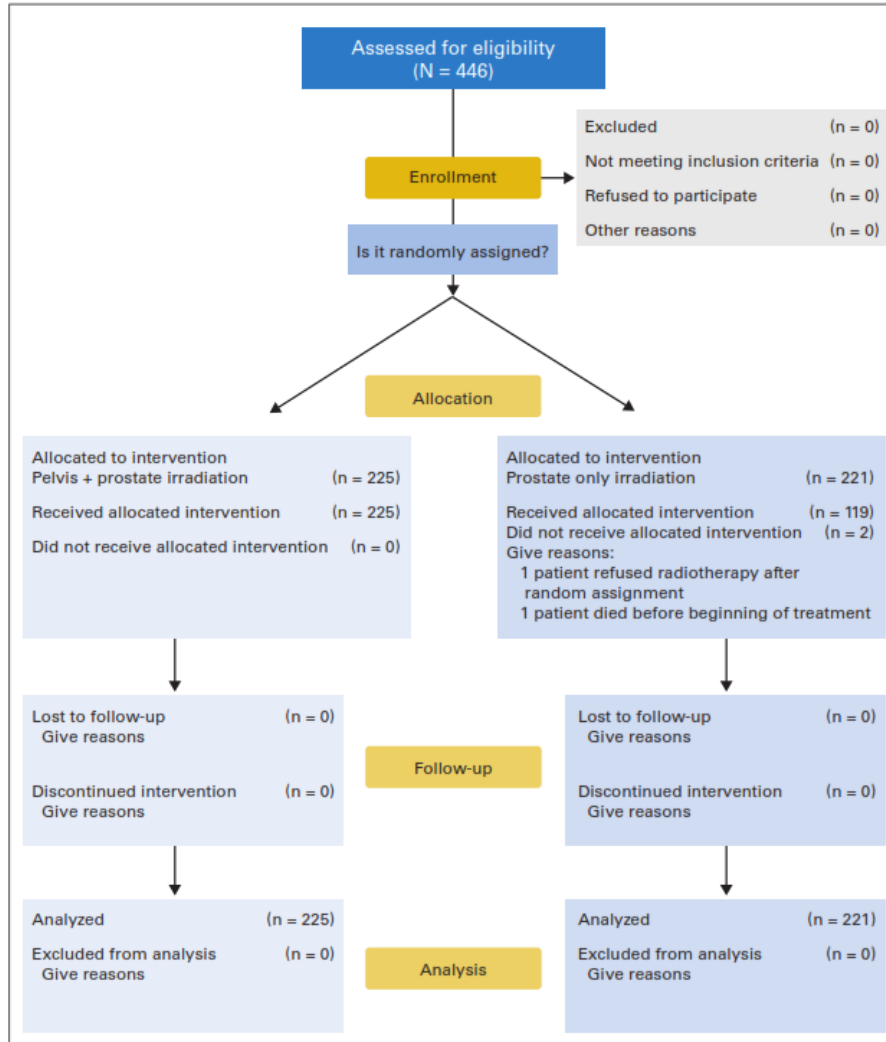

Fig 2. Progression-free survival (PFS) according to the stratified groups. (A) High-risk group. (B) Low-risk group.

Pommier P et al. J Clin Oncol. 2007 Dec 1;25(34):5366-5373

The role of pelvic RT in intermediate-risk prostate cancer

- RTOG 94-13 (1995-1999) – Multicenter, prospective, randomized phase III trial.
- 2x2 factorial design

RTOG 94-13

A Phase III Trial Comparing Definitive Whole Pelvic Irradiation Followed by a Conedown Boost to Boost Irradiation Only and Comparing Neoadjuvant to Adjuvant Total Androgen Suppression (TAS)

Stage
1. T1c, T2a
2. T1b, T2b
3. T2c-T4

S A R A I F

PSA
1. ≤ 30
2. > 30

Gleason Score
1. < 7
2. 7-10

R A N D O M I Z E

Arm 1: Neoadjuvant TAS 2 months before and during RT to the whole pelvis followed by a prostate boost. **T**

Arm 2: Neoadjuvant TAS 2 months before and during RT. RT to prostate only. **T**

Arm 3: RT to include whole pelvis followed by a boost to the prostate and then by 4 months of TAS. **Y**

Arm 4: RT to the prostate only followed by 4 months of TAS.

Radiation :

Patients on Arms 1 and 3 will receive whole pelvic irradiation to 50.4 Gy *(1.8 Gy/day five times a week x 28 fractions)* followed by a 19.8 Gy boost *(1.8 Gy/day,five times a week x 11 fractions)* to a total dose of 70.2 Gy to the prostate.
Total: 39 fractions in 8 weeks

Patients on Arms 2 and 4 will receive RT to prostate only *(1.8 Gy/day five days a week x 39 fractions)* to a total dose of 70.2 Gy.
Total: 39 fractions in 8 weeks

Total Androgen Suppression (TAS):

Patients on Arms 1 and 2 will receive Flutamide *(two 125 mg capsules t.i.d., p.o.)* and Zoladex *(3.6 mg s.c. monthly x four months)* or Lupron, beginning 2 months before RT and continuing until RT is completed.

Patients on Arms 3 and 4 will receive Flutamide and Zoladex *(or Lupron)* for four months beginning at completion of RT.

Roach et al. J Clin Oncol. 2003 May 15;21(10):1904-1911

The role of pelvic RT in intermediate-risk prostate cancer

- Study design to detect a 10% difference in 5-year PFS rates with a significance level of 0.025 and a statistical power of 0.80.

Table 2. 4-Year Outcomes: All Patients Radiation Field

End Point	WP RT + N & CHT (n = 641)* 4-Year Rate %	95% CI	Failures	PO RT + N & CHT (n = 638) 4-Year Rate %	95% CI	Failures	P†
PFS	54.2	50 to 59	260	47.0	42 to 52	294	.022
OS	84.7	81 to 88	87	84.3	81 to 88	88	.94
Local progression	9.1	6 to 12	49	8.0	6 to 10	46	.78
Regional nodal failure	1.3	0.3 to 2	7	2.5	1 to 4	14	.12
Distant metastasis	8.2	6 to 11	47	6.6	5 to 9	41	.54
Biochemical failure	33.5	29 to 38	188	39.7	35 to 44	215	.065

Abbreviations: WP RT + N & CHT, whole-pelvic radiotherapy and neoadjuvant hormonal therapy; PO RT + N & CHT, prostate-only radiotherapy and neoadjuvant hormonal therapy; PFS, progression-free survival; OS, overall survival; CI, confidence interval.

*One patient is excluded from the progression-free survival analysis because disease status is unknown (N = 640).

†P-value is from either the log-rank test (progression-free and overall survival) or Gray's test (local progression, regional nodal failure, distant metastasis, and biochemical failure) for comparing the survival curves.

4-yr PFS: 54.2% (WPRT) vs 47% (Prostate only RT)
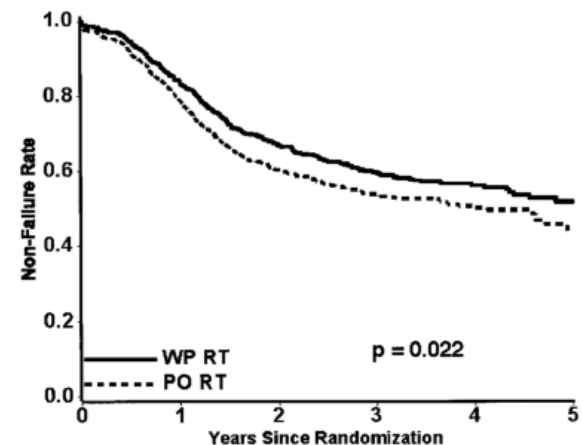P=0.022

Fig 1. Patients treated with whole-pelvic (WP) radiotherapy (RT) followed by a boost to the prostate experienced a 4-year progression-free survival (PFS) of 54.2% compared with 47% in patients treated with prostate only (PO) RT (P = .022).

Roach et al. J Clin Oncol. 2003 May 15;21(10):1904-1911

The role of pelvic RT in intermediate-risk prostate cancer

Table 5. 4-Year Outcomes: All Patients Radiation Field and Hormone Timing

	4-Year Rate								
	WP RT + N & CHT (n = 319)		PO RT + N & CHT (n = 316)		WP RT + AHT (n = 322)†		PO RT + AHT (n = 322)		
End Point	%	95% CI	%	95% CI	%	95% CI	%	95% CI	P
Progression-free survival	59.6	53 to 66	44.3	38 to 51	48.9	42 to 55	49.8	43 to 56	.008
Biochemical failure	30.3	24 to 36	42.8	36 to 49	36.7	30 to 43	36.5	30 to 43	.048

Abbreviations: WP RT + N & CHT, whole-pelvic radiotherapy and neoadjuvant hormonal therapy; PO RT + N & CHT, prostate-only radiotherapy and neoadjuvant hormonal therapy; WP RT + AHT, whole-pelvic radiotherapy and adjuvant hormonal therapy; PO RT + AHT, prostate-only radiotherapy and adjuvant hormonal therapy; CI, confidence interval.

*P value is from either the log-rank test (progression free) or Gray's test (biochemical failure) for comparing the four survival curves.

†One patient is excluded from the progression-free survival analysis because disease status is unknown (n = 321).
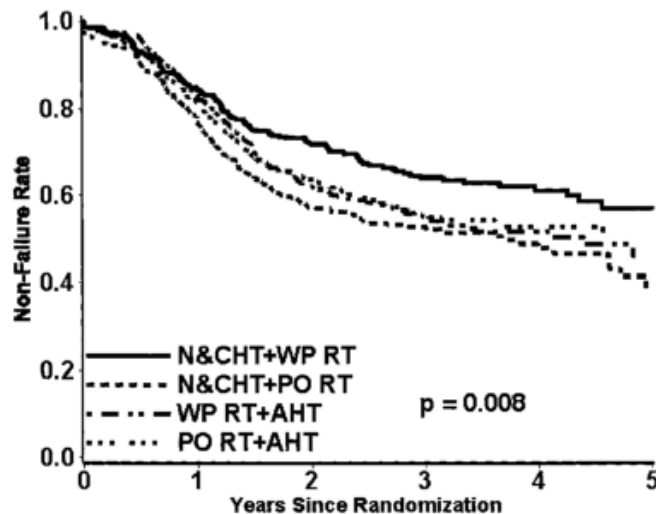

Fig 3. Four-year progression-free advantage for whole pelvic (WP) radiotherapy (RT) and neoadjuvant and concurrent hormonal therapy (NCHT) compared with prostate only (PO) RT and NCHT, and WP RT or PO RT and adjuvant hormonal therapy (AHT; 60 v 44, 49% and 50% respectively, P = .008).
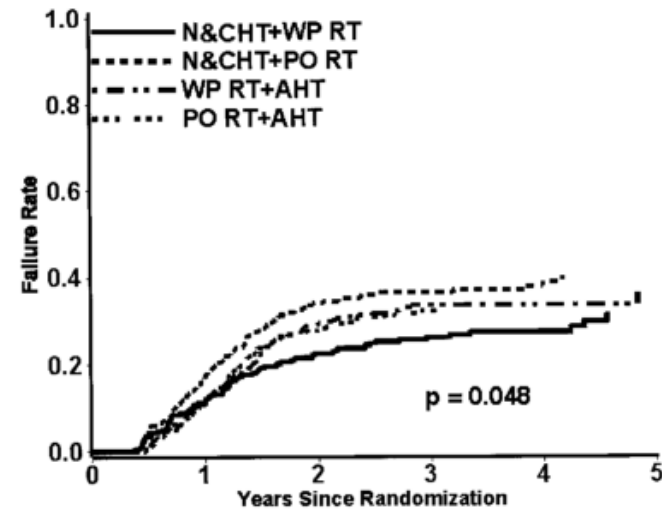
Fig 4. Prostate-specific antigen (PSA) control favors whole-pelvic (WP) radiotherapy (RT) and neoadjuvant and concurrent hormonal therapy (NCHT) compared with prostate only (PO) RT and NCHT, and WP RT or PO RT adjuvant hormonal therapy (AHT; P = .048).

The role of pelvic RT in intermediate-risk prostate cancer

Table 6. 4-Year Progression-Free Survival: Intermediate-Risk Patients (PSA < 30 & GS = 7-10 or PSA ≥ 30 & GS = 2-6)

Treatment Arm	Failures	n	4-Year Rate %	95% CI	P
WP RT + N & CHT	64	198	63.9	56 to 72	.014
PO RT + N & CHT	91	196	46.4	38 to 55	—
WP RT + AHT	88	197	48.9	41 to 57	—
PO RT + AHT	88	196	49.3	41 to 58	—

Abbreviations: PSA, prostate-specific antigen; CI, confidence interval; WP RT + N & CHT, whole-pelvic radiotherapy and neoadjuvant hormonal therapy; PO RT + N & CHT, prostate-only radiotherapy and neoadjuvant hormonal therapy; WP RT + AHT, whole-pelvic radiotherapy and adjuvant hormonal therapy; PO RT + AHT, prostate-only radiotherapy and adjuvant hormonal therapy.

*P value from log-rank test for comparing the four survival curves.

Conclusion:
1. WP RT + NCHT improves the freedom from progression compared with PO RT + NCHT, PO RT + AHT and WP RT + AHT in pts with a risk of LN involvement of more than 15% (Roach's formula)

The role of pelvic RT in intermediate-risk prostate cancer

- RTOG 94-13 - Update
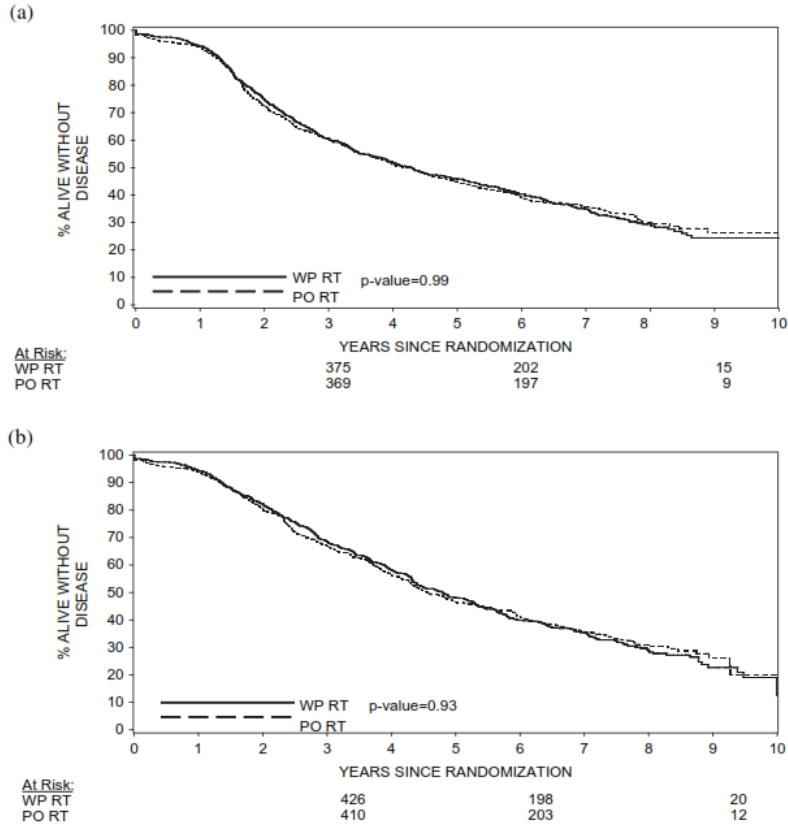
WP RT vs PO RT

N-CHT vs AHT

Fig. 2. Progression-free survival for whole pelvis radiotherapy (WPRT) vs. prostate only radiotherapy (PORT) (a) protocol definition of biochemical failure and (b) Phoenix definition of biochemical failure.
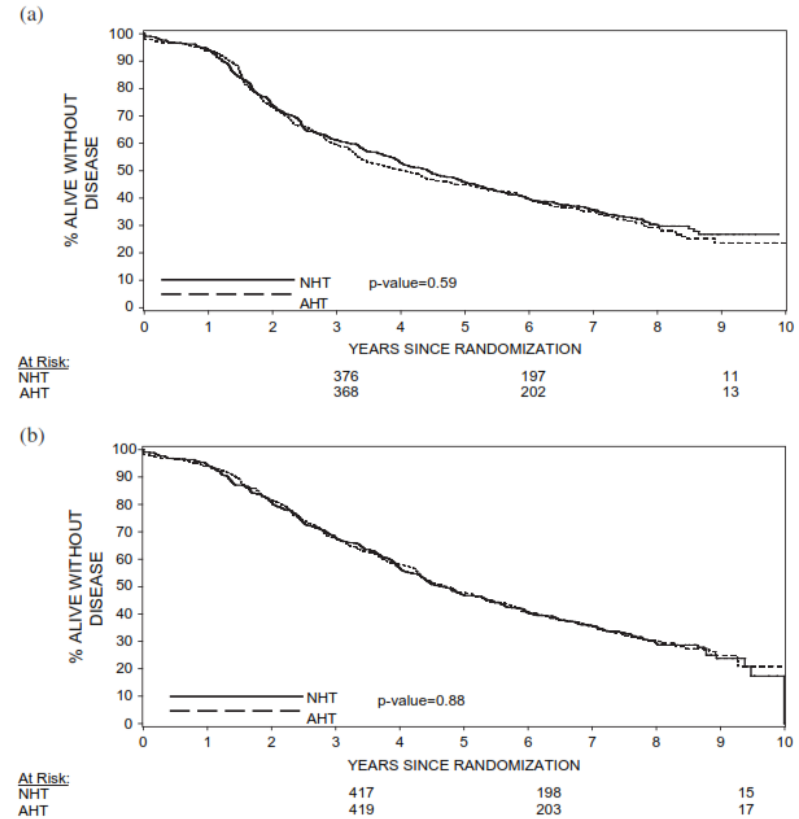
Fig. 1. Progression-free survival for neoadjuvant hormonal therapy (NHT) vs. adjuvant hormonal therapy (AHT) using (a) protocol definition of biochemical failure and (b) Phoenix definition of biochemical failure.

The role of pelvic RT in intermediate-risk prostate cancer

- RTOG 94-13 - Update

Table 2. Progression-free survival*

Treatment arm	n	p*
WPRT + NHT	198/320	0.065
PORT + NHT	210/316	
WPRT + AHT	220/319	
PORT + AHT	199/320	
Pairwise comparison		
WPRT + NHT vs.		
PORT + NHT		0.066
WPRT + AHT		0.022
PORT + AHT		0.75
PORT + NHT vs.		
WPRT + AHT		0.69
PORT + AHT		0.15
WPRT + AHT vs.		
PORT + AHT		0.057

Abbreviations as in Table 1.
* p value is from the Log–rank for comparing progression-free survival curves.

Table 3. Overall survival

Treatment arm	n	p
WPRT + NHT	104/320	0.027*
PORT + NHT	99/316	
WPRT + AHT	130/319	
PORT + AHT	101/320	
Pairwise comparison		p value†
WPRT + NHT vs.		
PORT + NHT		0.9629
WPRT + AHT		0.019
PORT + AHT		0.80
PORT + NHT vs.		
WPRT + AHT		0.019
PORT + AHT		0.86
WPRT + AHT vs.		
PORT + AHT		0.01

Abbreviations as in Table 1.
* Log–rank test for comparing overall survival curves.
† p value is from the log rank for comparing overall survival curves.

Study is not powered to compare the four arms separately.

Lawton et al. IJROBP, Vol. 69, No. 3, 2007:646-655

The role of pelvic RT in intermediate-risk prostate cancer

RTOG 0924

Androgen Deprivation Therapy and High Dose Radiotherapy With or Without Whole-Pelvic Radiotherapy in Unfavorable Intermediate or Favorable High Risk Prostate Cancer: A Phase III Randomized Trial

SCHEMA

S T R A T I F Y	**Risk Group** 1. GS 7-10 + T1c-T2b + PSA < 50 ng/ml 2. GS 6 + T2c-T4 or > 50% biopsies + PSA < 50 ng/ml 3. GS 6 + T1c-T2b + PSA > 20 ng/ml	R A N D O M I Z E	**Arm 1:** Neoadjuvant androgen deprivation therapy + prostate & seminal vesicle RT + boost to prostate & proximal seminal vesicles
	Type of RT Boost 1. IMRT 2. Brachytherapy (LDR using PPI or HDR) **Duration of Androgen Deprivation Therapy** 1. Short Term (6 months) 2. Long Term (32 months)*		**Arm 2:** Neoadjuvant Androgen Deprivation Therapy + whole-pelvic RT + boost to prostate & proximal seminal vesicles

* 32 months chosen because RTOG 9202 used 28 months and EORTC used 36 months = avg 32 months

Clinical Case

- ## Definitive EBRT
  - 180 cGy x 45 to 8100 cGy to prostate and proximal vesicle.

Thank you