Radiation Treatments for Clinically Localized Prostate Cancer

Tomas Dvorak, MD
Raveendhara R Bannuru, MD
Stanley Ip, MD
Tufts Medical Center, Boston
4-21-2010

Tomas Dvorak, MD
Speaker Disclosure Summary

- I or a member of my immediate family **have not** received anything of value related to the technology or topic being presented.
- Please indicate the financially interested company for any “Yes” response:
- **No** Research or institutional support from: none
- **No** Fees, honoraria or in-kind compensation other than cash (whether for consulting, speaking, legal testimony or advisory board service) from: none
- **No** Equity interest, stock or stock options from: none
- **No** Patent or other intellectual property rights from: none
- **No** Salary or royalty income from: none
- **No** Travel expenses or other financial benefit from: none

Comparative evaluation of radiation treatments for clinically localized prostate cancer: an update [draft]

S. Ip, T. Dvorak, W.W. Yu, K. Patel, N. Obadan, M. Chung, R. Bannuru, J. Lau

Tufts Medical Center Evidence-based Practice Center

Technology Assessment, 2010

Funded by the Technology Assessment Program at the Agency for Healthcare Research and Quality

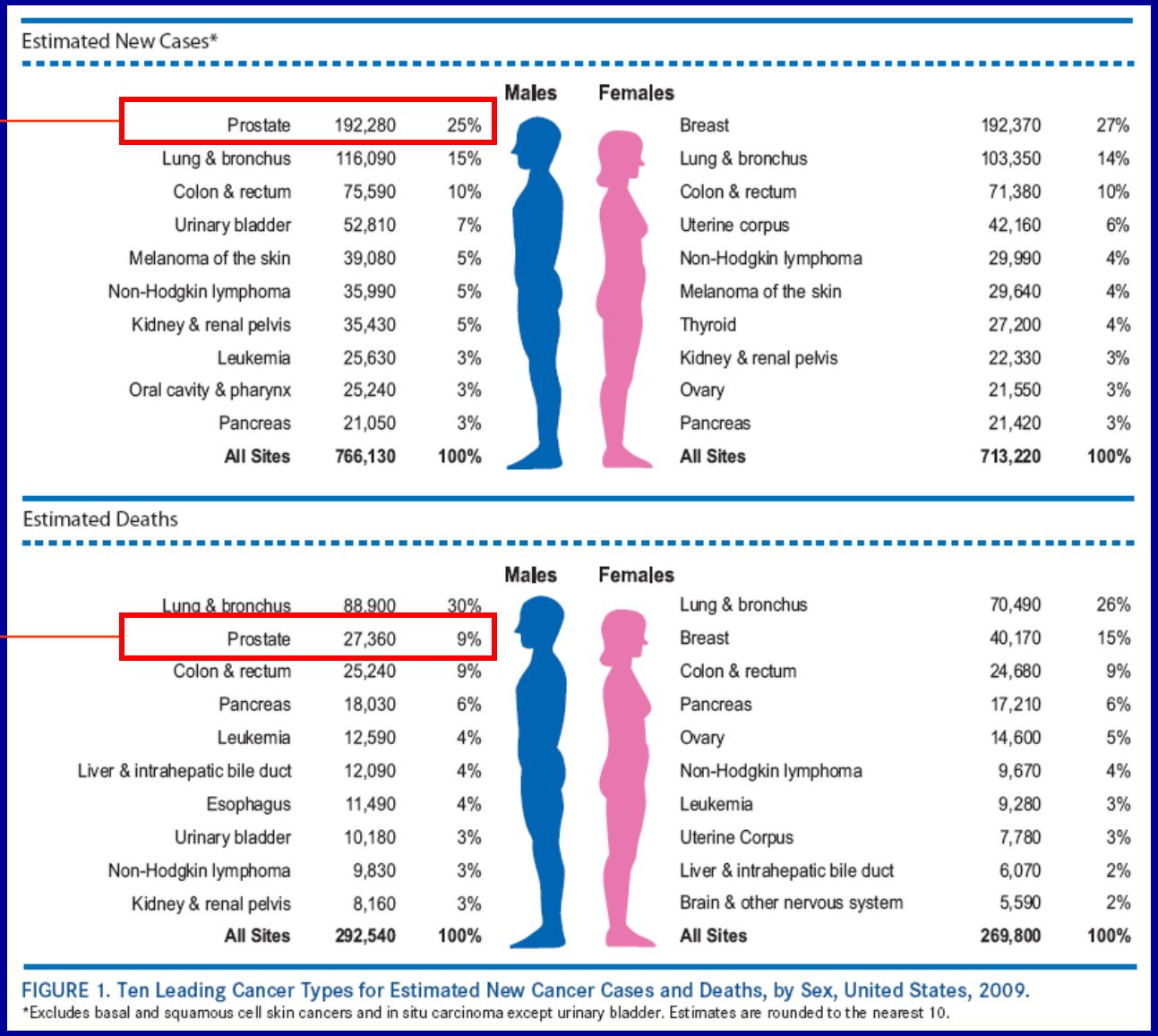
Potential conflict of interest: None

Topics

- disease burden
- management options
- different radiation treatment modalities
- review of Minnesota report
- comparative studies update
- conclusions
- limitations
- future research

Disease burden

14%



Estimated New Cases*

Males			Females		
Prostate	192,280	25%	Breast	192,370	27%
Lung & bronchus	116,090	15%	Lung & bronchus	103,350	14%
Colon & rectum	75,590	10%	Colon & rectum	71,380	10%
Urinary bladder	52,810	7%	Uterine corpus	42,160	6%
Melanoma of the skin	39,080	5%	Non-Hodgkin lymphoma	29,990	4%
Non-Hodgkin lymphoma	35,990	5%	Melanoma of the skin	29,640	4%
Kidney & renal pelvis	35,430	5%	Thyroid	27,200	4%
Leukemia	25,630	3%	Kidney & renal pelvis	22,330	3%
Oral cavity & pharynx	25,240	3%	Ovary	21,550	3%
Pancreas	21,050	3%	Pancreas	21,420	3%
All Sites	**766,130**	**100%**	**All Sites**	**713,220**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	88,900	30%	Lung & bronchus	70,490	26%
Prostate	27,360	9%	Breast	40,170	15%
Colon & rectum	25,240	9%	Colon & rectum	24,680	9%
Pancreas	18,030	6%	Pancreas	17,210	6%
Leukemia	12,590	4%	Ovary	14,600	5%
Liver & intrahepatic bile duct	12,090	4%	Non-Hodgkin lymphoma	9,670	4%
Esophagus	11,490	4%	Leukemia	9,280	3%
Urinary bladder	10,180	3%	Uterine Corpus	7,780	3%
Non-Hodgkin lymphoma	9,830	3%	Liver & intrahepatic bile duct	6,070	2%
Kidney & renal pelvis	8,160	3%	Brain & other nervous system	5,590	2%
All Sites	**292,540**	**100%**	**All Sites**	**269,800**	**100%**

FIGURE 1. Ten Leading Cancer Types for Estimated New Cancer Cases and Deaths, by Sex, United States, 2009.
*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates are rounded to the nearest 10.

Jemal 2009

Epidemiology

- median age at diagnosis = 68 years
- prevalence at autopsy
  - 40 year old: ~30%
  - 80 year old: 70-80%
- lifetime risk of carrying a diagnosis: 16%
- lifetime risk of prostate death: 3%

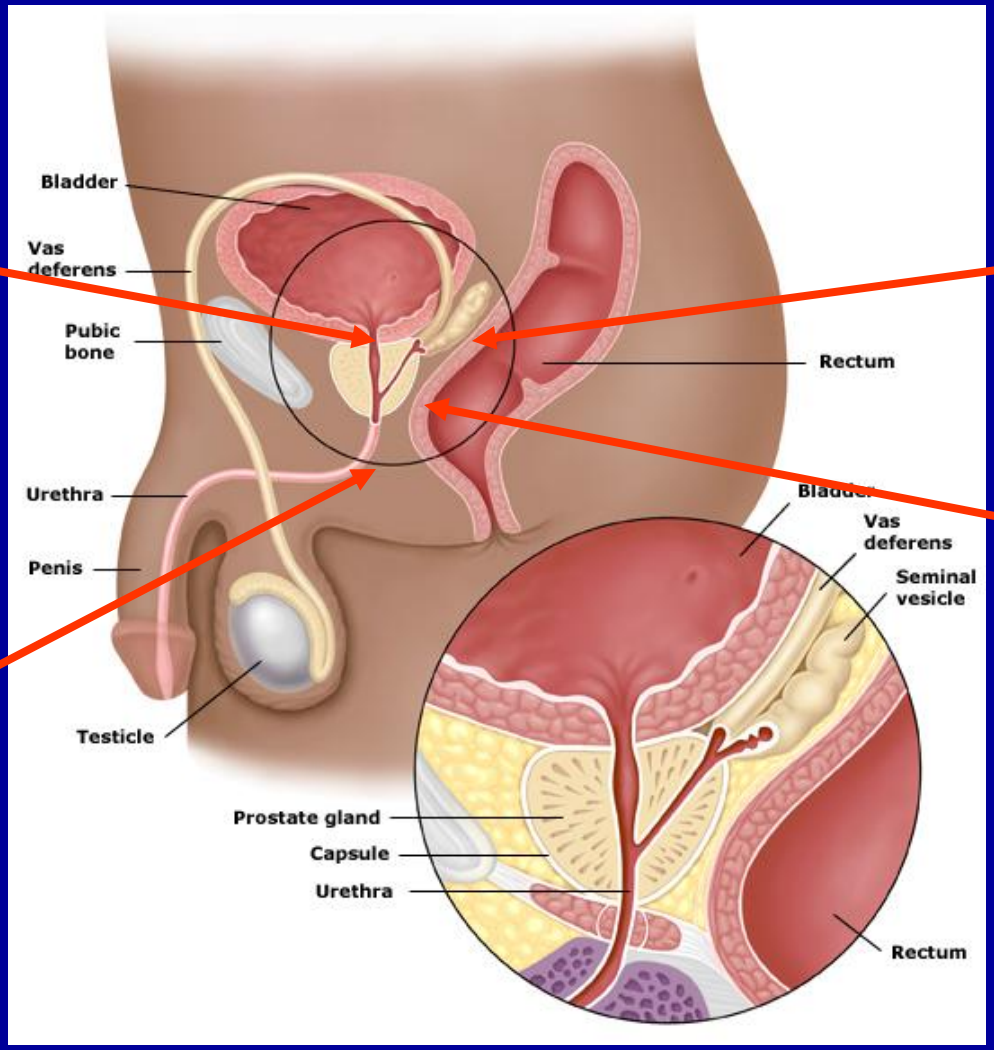
Diagnosis

- clinical symptoms (rare)
  - difficulty urinating, blood in urine
- routine digital-rectal examination
  - nodule on prostate gland
- PSA screening (most common)
  - estimated ~50% of men undergo screening
  - guidelines in flux
  - elevated PSA triggers biopsy

Prostate gland anatomy

GU Toxicity

Sexual dysfunction

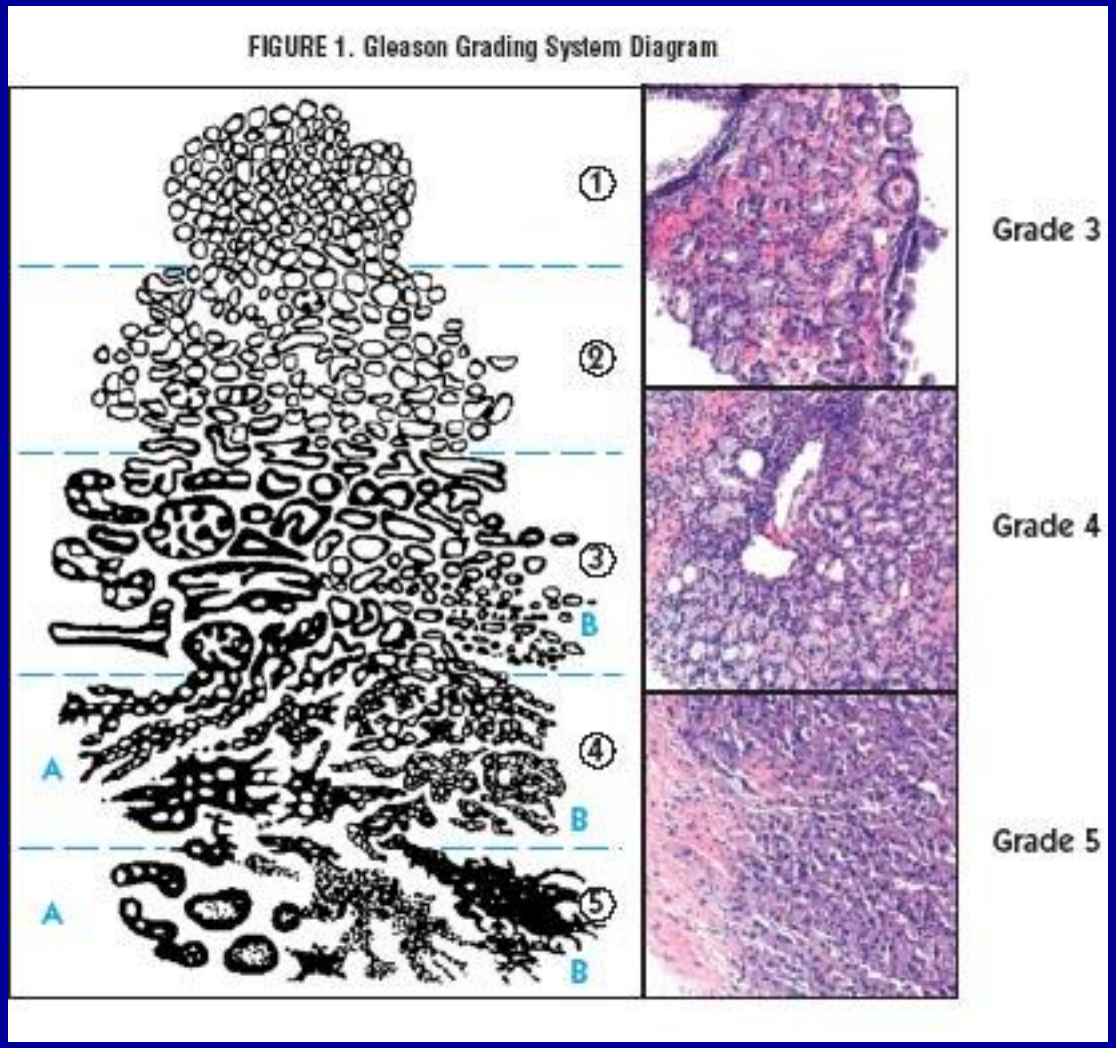


GI Toxicity

2nd Malignancy

www.uptodate.com

Gleason score = cancer grade

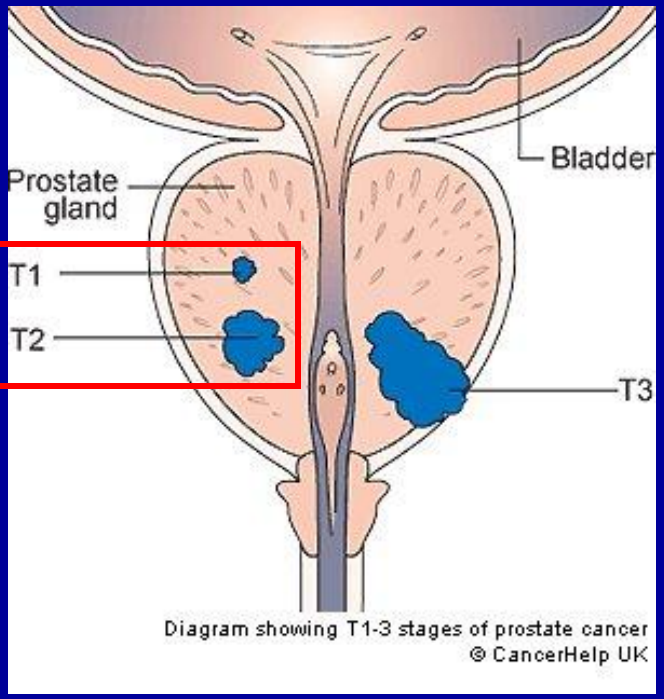


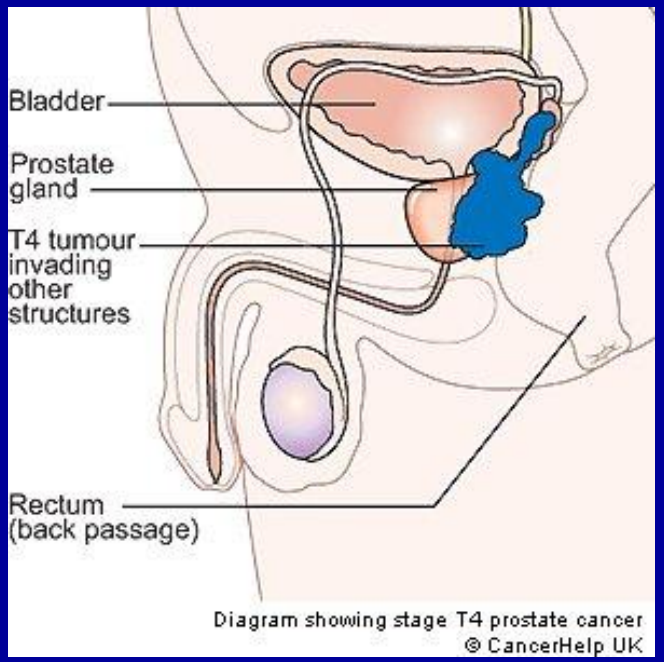
Gleason Score:

- Primary pattern (1-5)
- Secondary pattern (1-5)
- Sum = GS (2-10)
  - 3+3 = 6
  - 3+4 = 7
  - 4+3 = 7
  - 4+5 = 9
  - etc

- "Low" grade: 2-6
- "Intermediate" grade: 7
- "High" grade: 8-10

Prostate cancer staging





Tufts EPC TA Inclusion Criteria: Clinically localized prostate cancer (T1-T2)

- T1 - clinically inapparent tumor neither palpable nor visible by imaging
  - T1a - incidental histologic finding in 5% or less of tissue resected
  - T1b - incidental histologic finding in more than 5% of tissue resected
  - T1c - identified by needle biopsy (eg, because of elevated PSA)
- T2 - confined within prostate
  - T2a - involves one half of one lobe or less
  - T2b - involves more than one half of one lobe but not both lobes
  - T2c - involves both lobes

PLCO screening trial

N = 76,693

Clinical Stage	Screening	Control	
I	0.5%	0.5%	T1-T2
II	95.5%	93.8%	
III	1.4%	1.9%	
IV	2.1%	2.7%	
Unknown	0.4%	1.1%	

Andriole, 2009

Prostate cancer natural history

PSA Diagnosis (T1c)

Clinical Diagnosis (T2-T4)

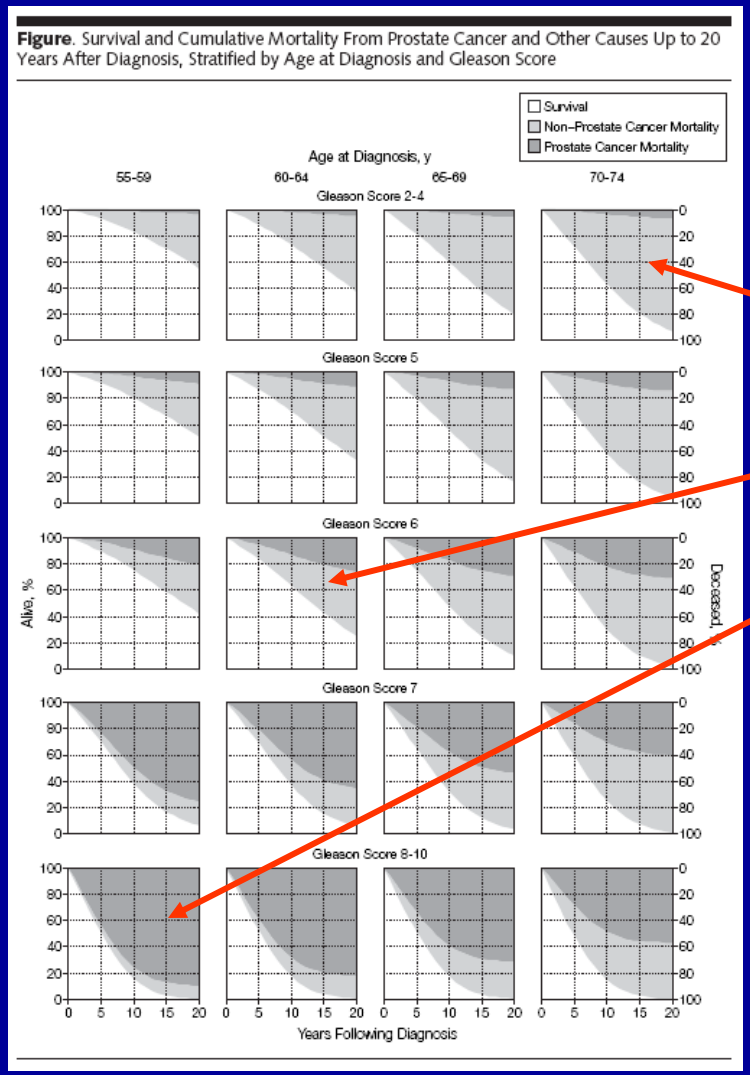
OS = 7% - 9%
CSS = 54% - 71%

11 years (estimate)

20 years (follow-up)

Draisma, 2003; Johansson 2004; Albertsen 2005

Variable prognosis



"Low"

"Intermediate"

"High"

No?

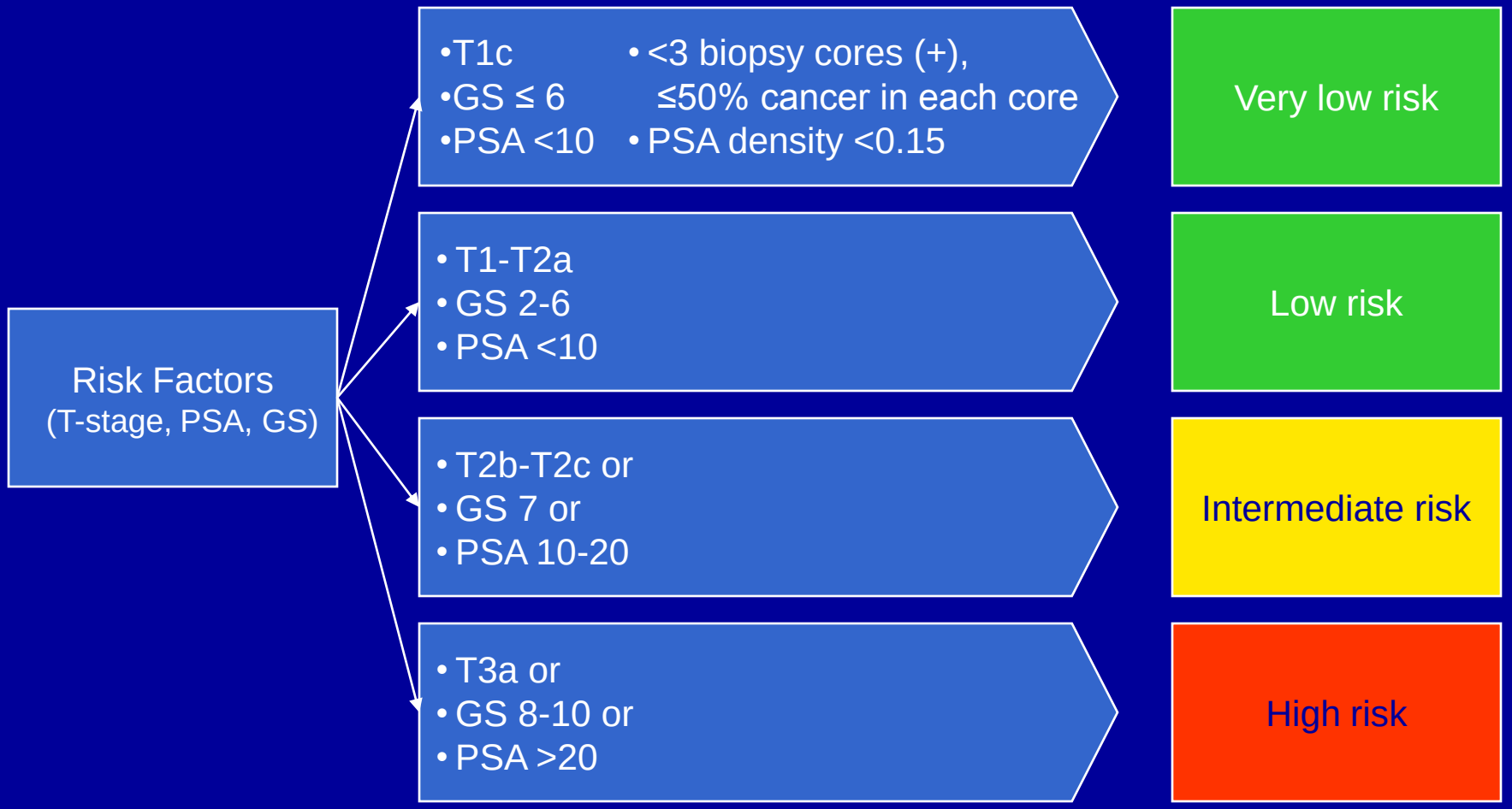
Yes?

Yes!

Who needs treatment?

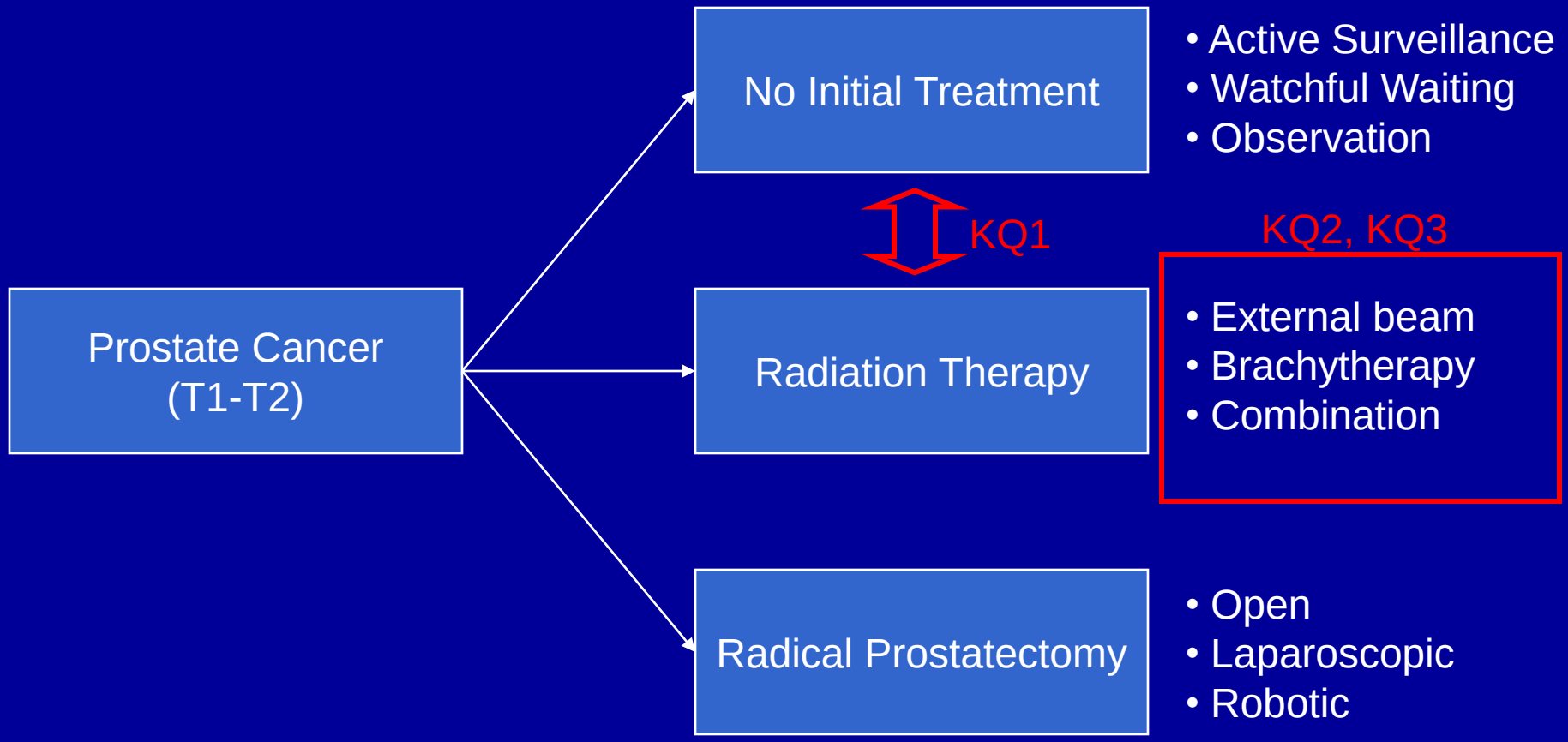
Albertsen 2005

Risk stratification



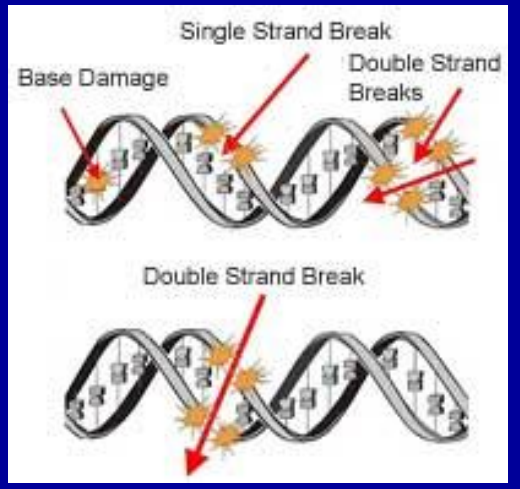
NCCN v1.2010

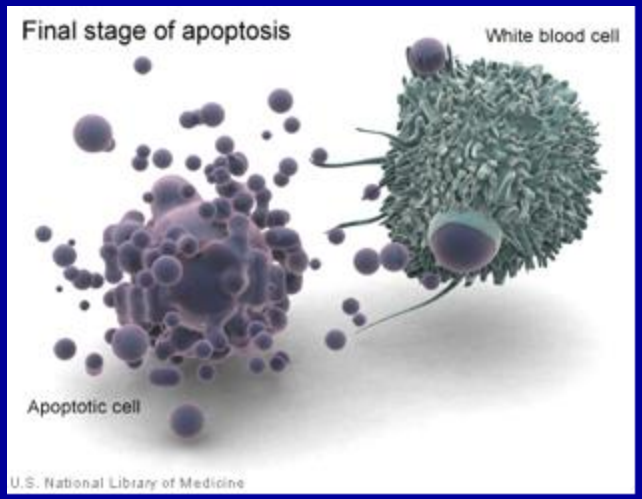
Management of prostate cancer



Radiation therapy

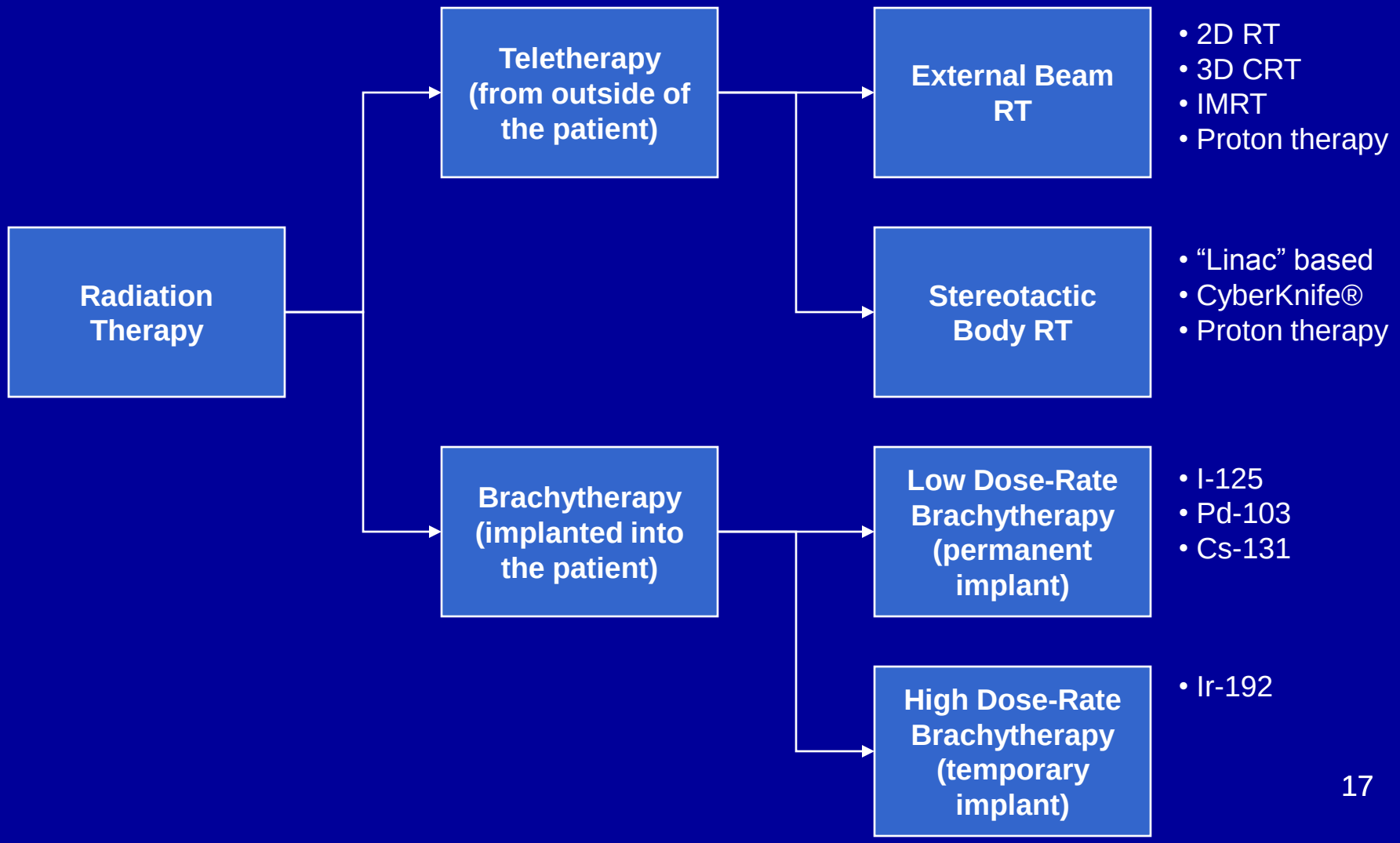
- rays that kill cells by DNA damage
  - photons (x-rays; electromagnetic radiation)
  - proton (particle)
  - other particles (electrons, alpha, etc)
- damage everything in their path
  - tumor
  - surrounding normal tissues
- different tumors and different normal tissues tolerate (repair) radiation differently
  - prostate tumor
  - bladder/urethra
  - rectal mucosa
  - penile bulb
  - blood vessels
  - nerves



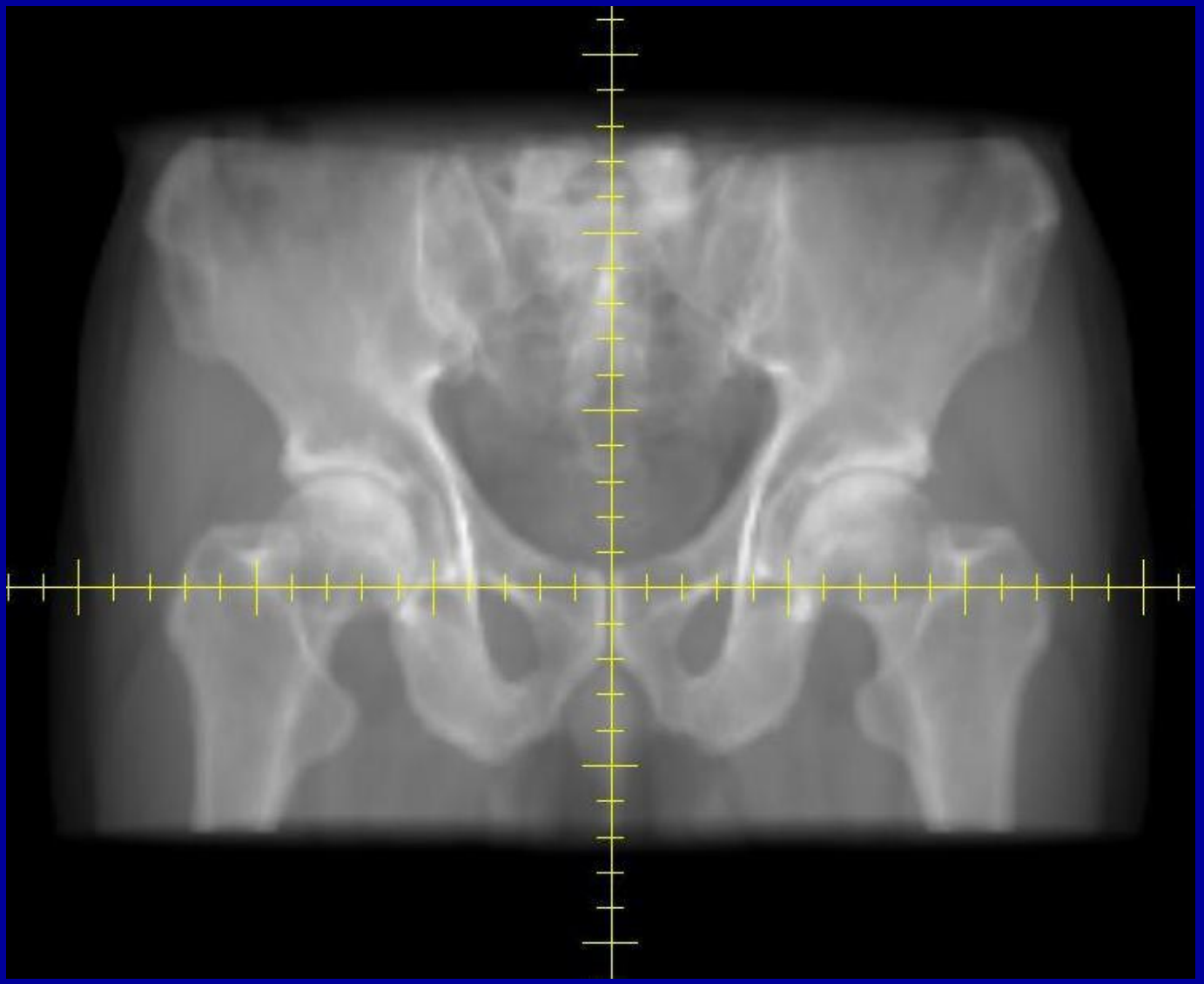


US NLM

Radiation therapy modalities



Prostate: Radiation view



Efficacy vs toxicity

Treat the target

Avoid surrounding tissues

Major focus of radiation oncology research efforts

2D RT

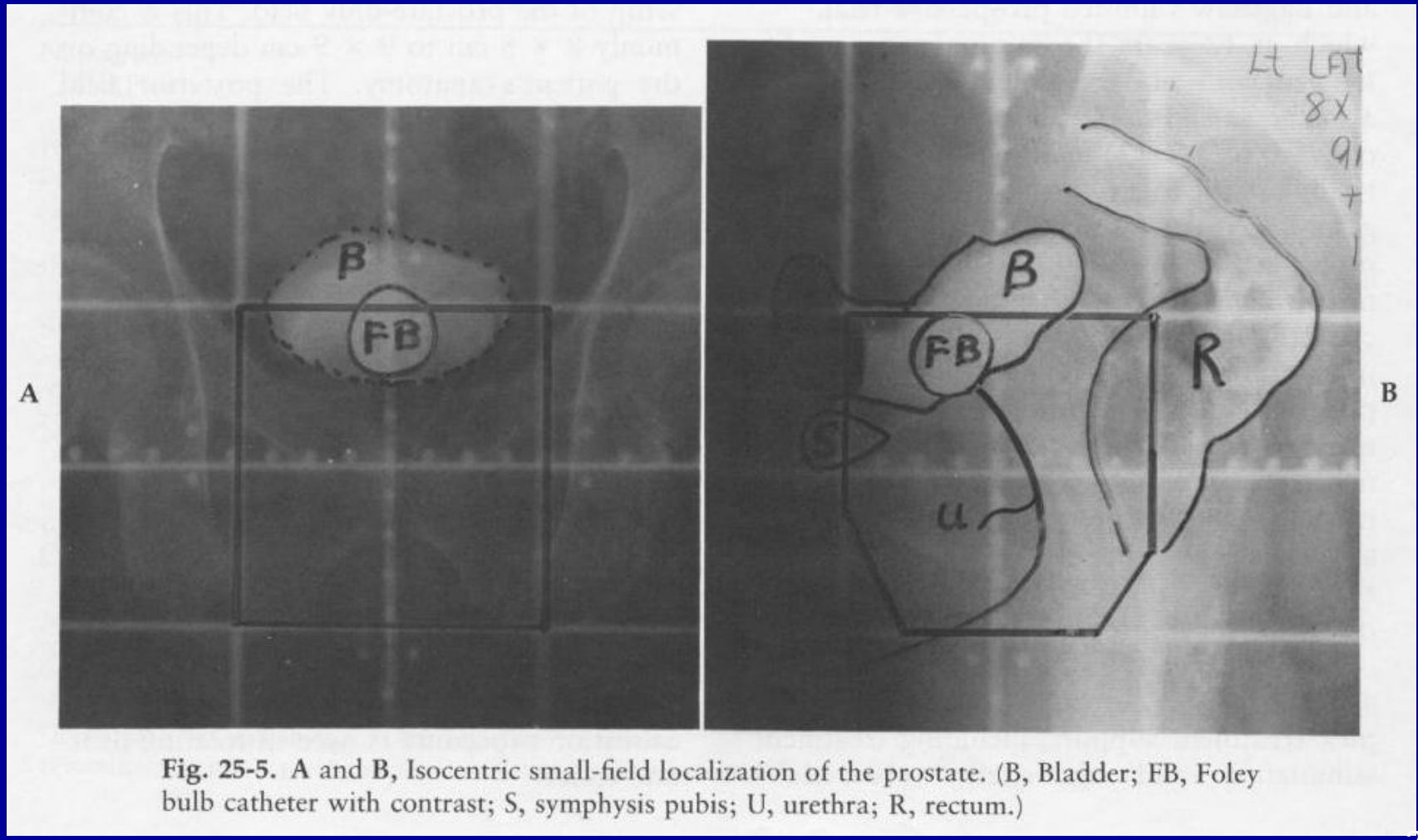
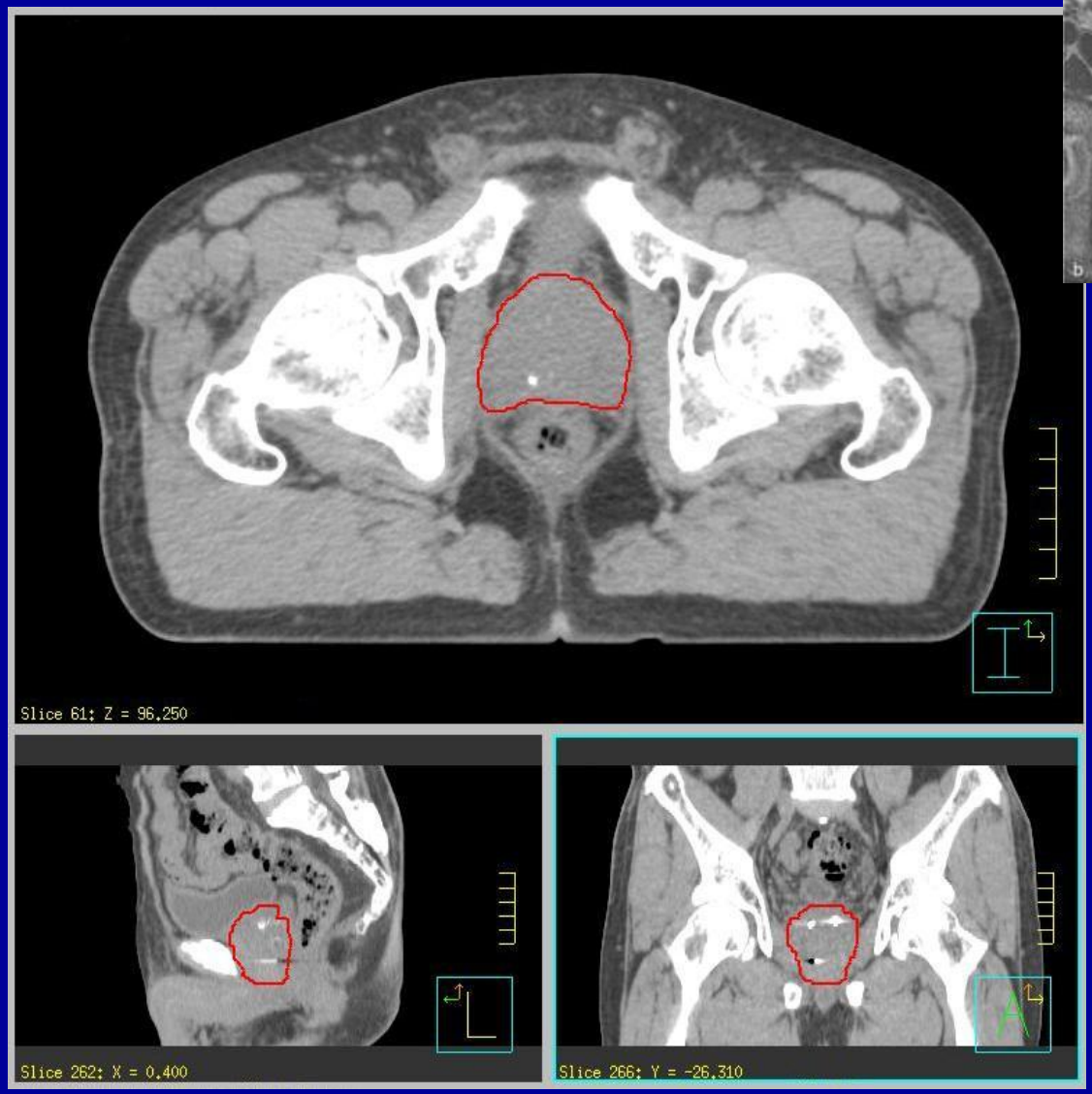
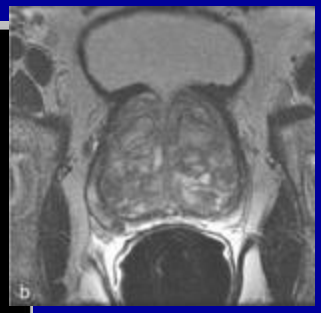


Fig. 25-5. **A** and **B**, Isocentric small-field localization of the prostate. (B, Bladder; FB, Foley bulb catheter with contrast; S, symphysis pubis; U, urethra; R, rectum.)

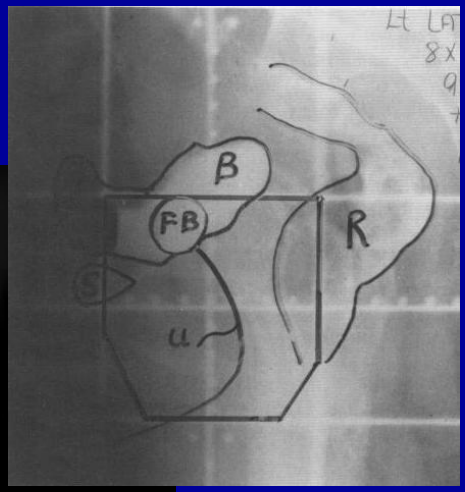
Hanks, 1989

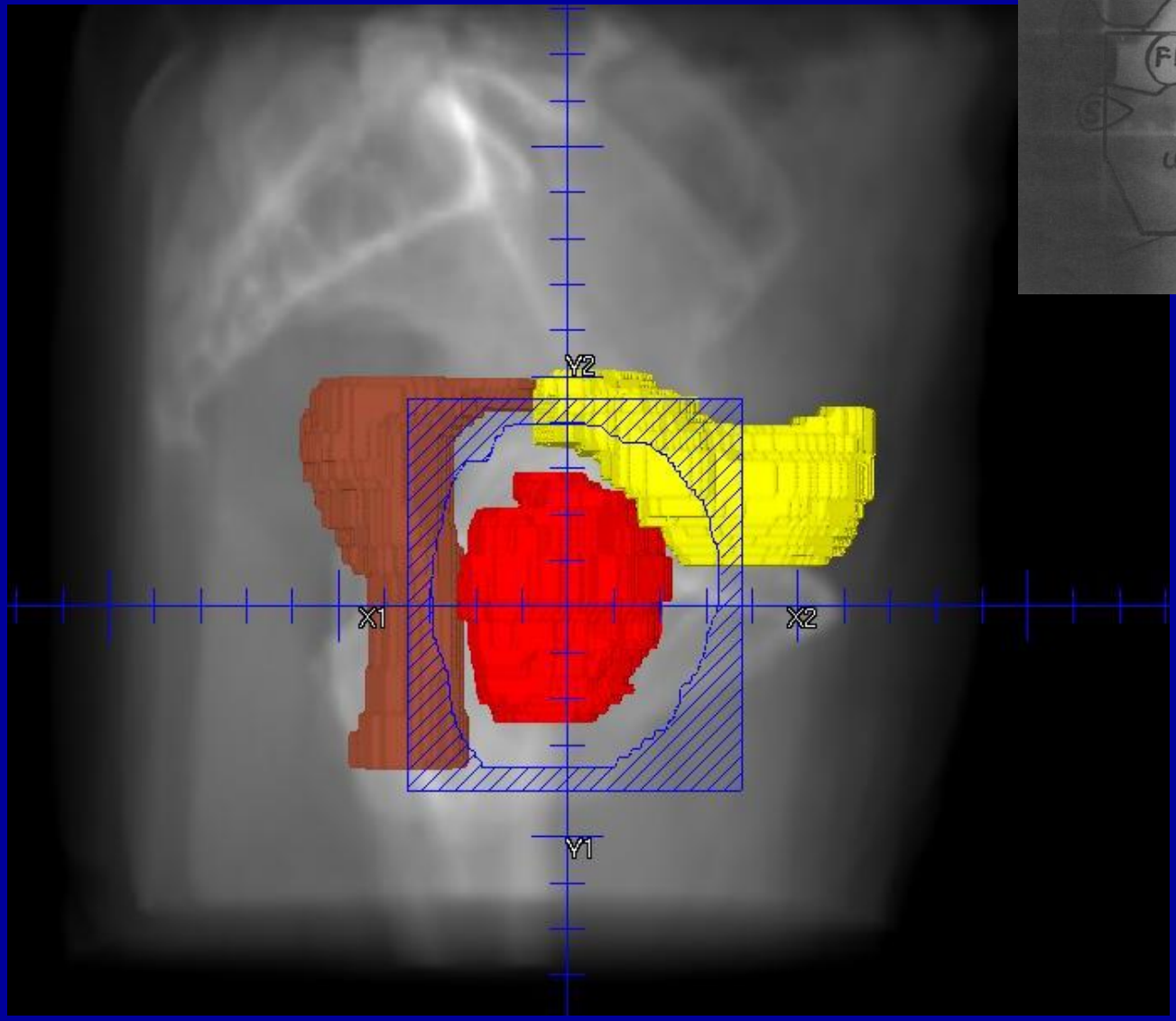
Prostate: Planning CT scan





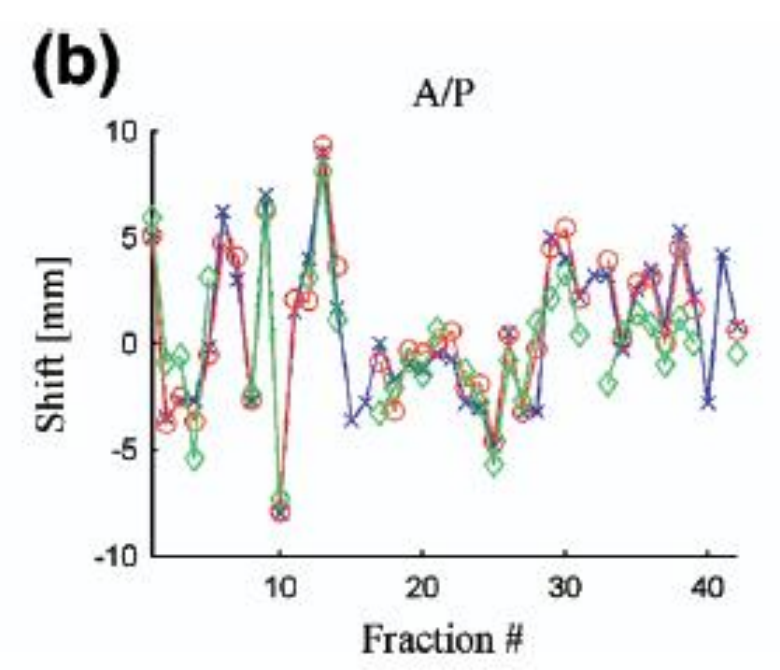
3D Conformal RT



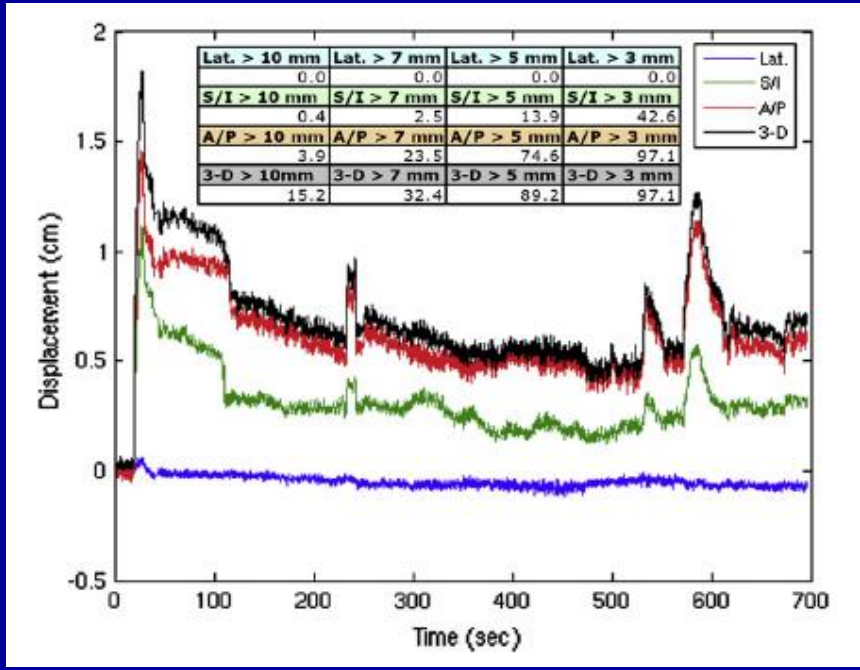


Prostate motion

Inter-fraction

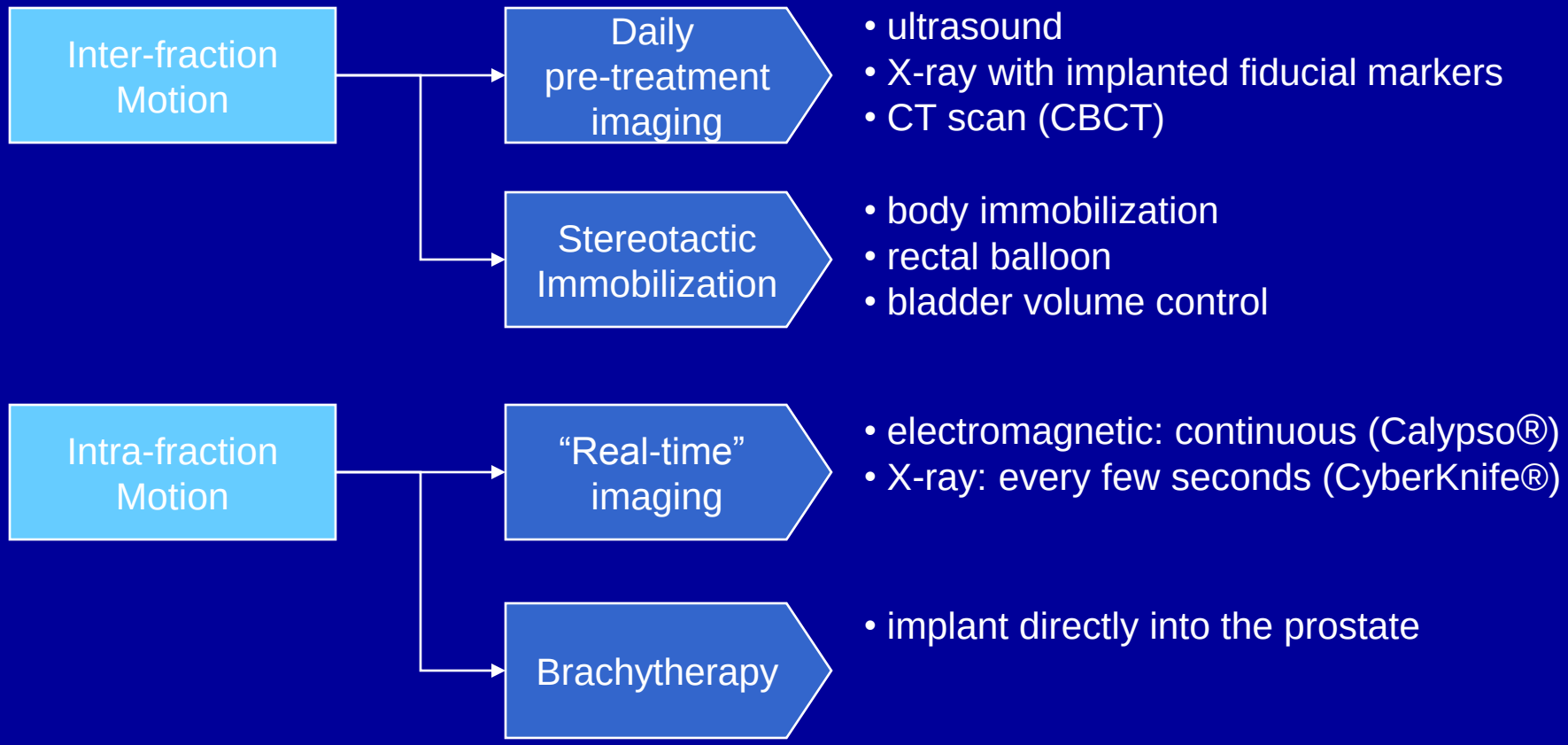


Intra-fraction

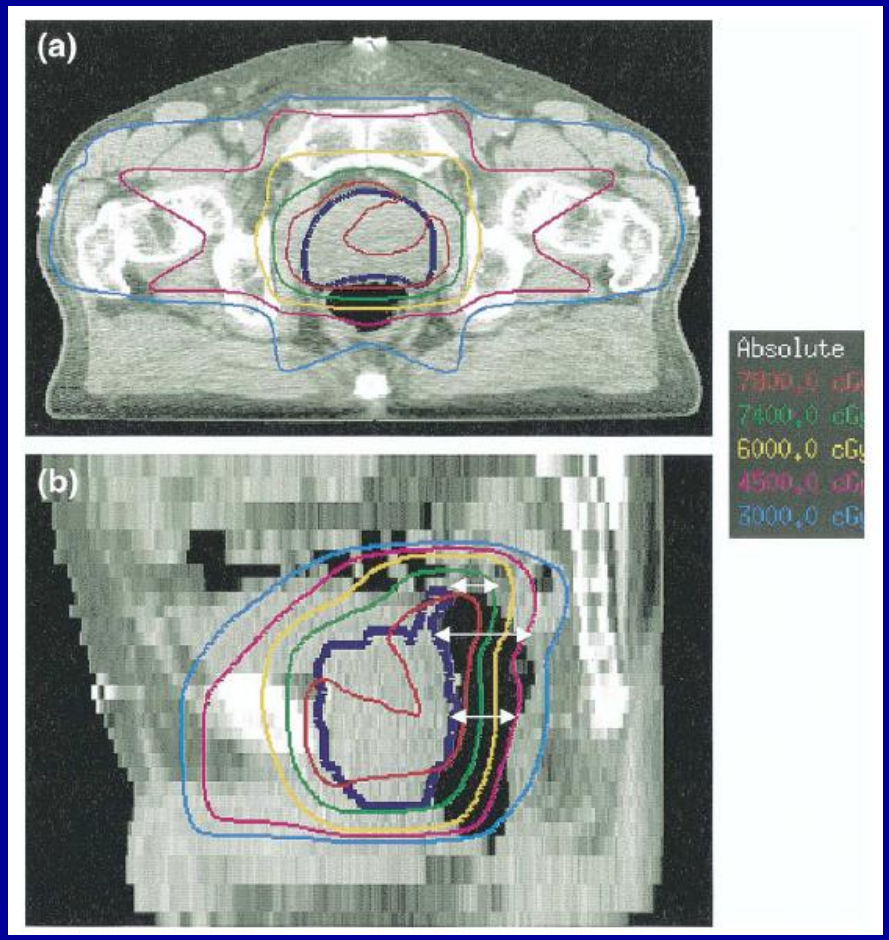


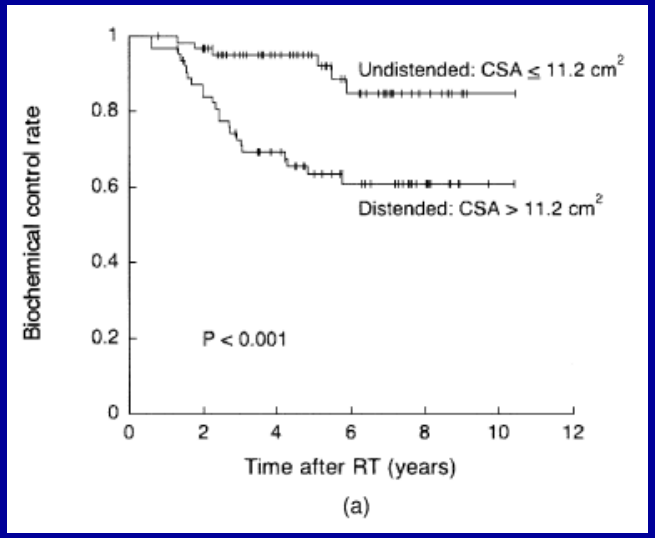
Moseley, 2007; Langen, 2008

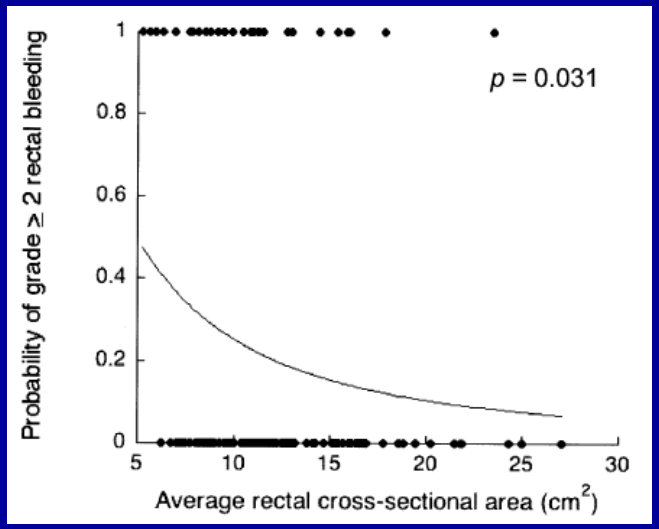
Motion management



Clinical impact of motion

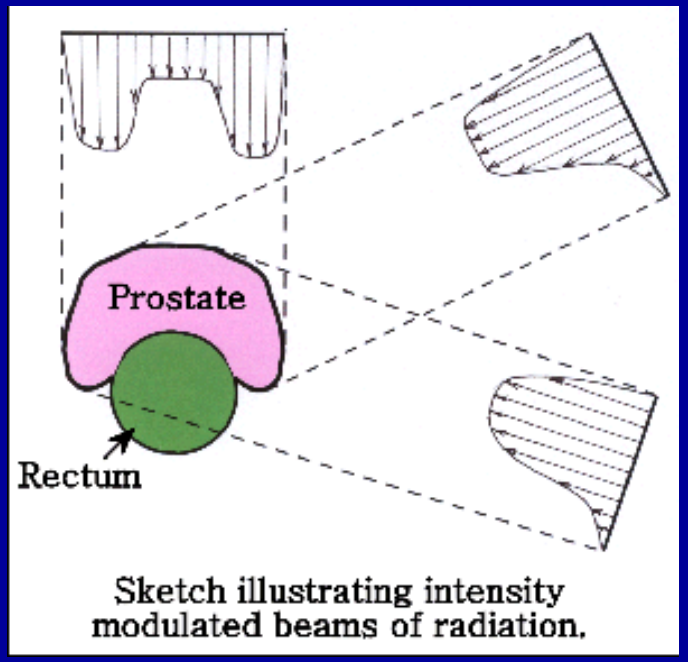




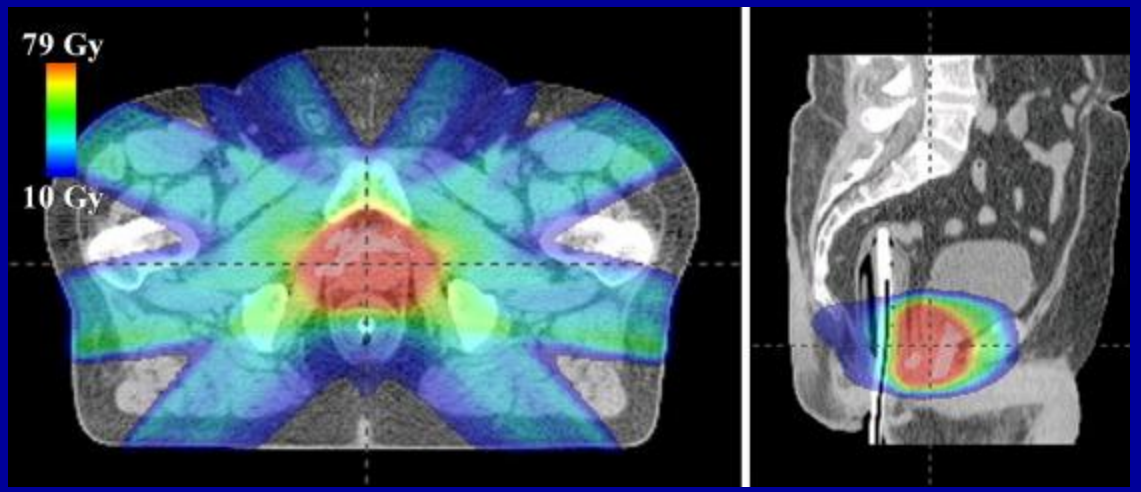


de Crevoisier, 2005

Intensity modulation (IMRT)

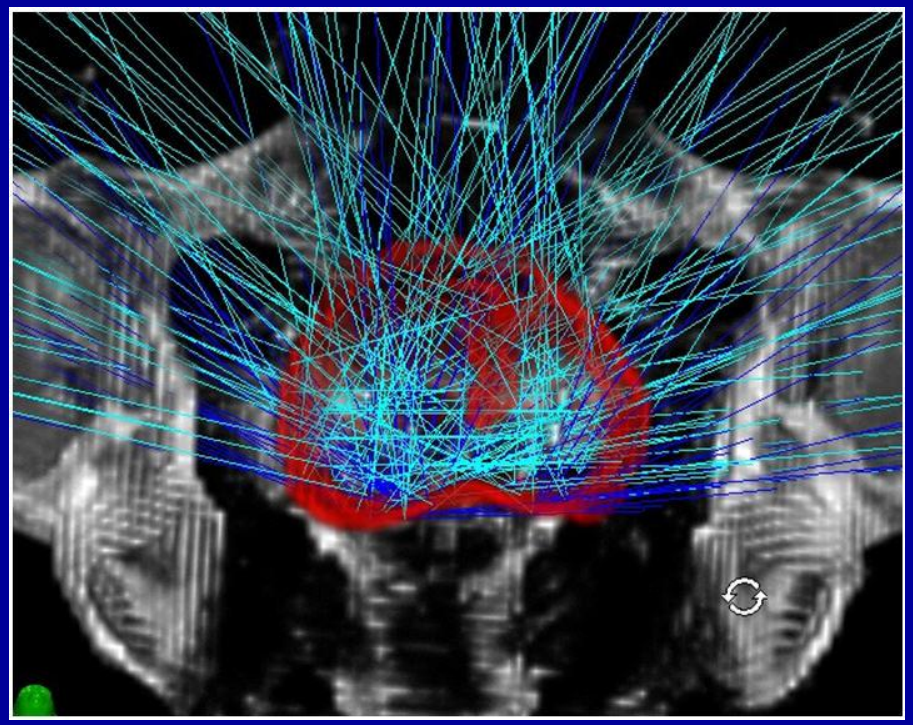


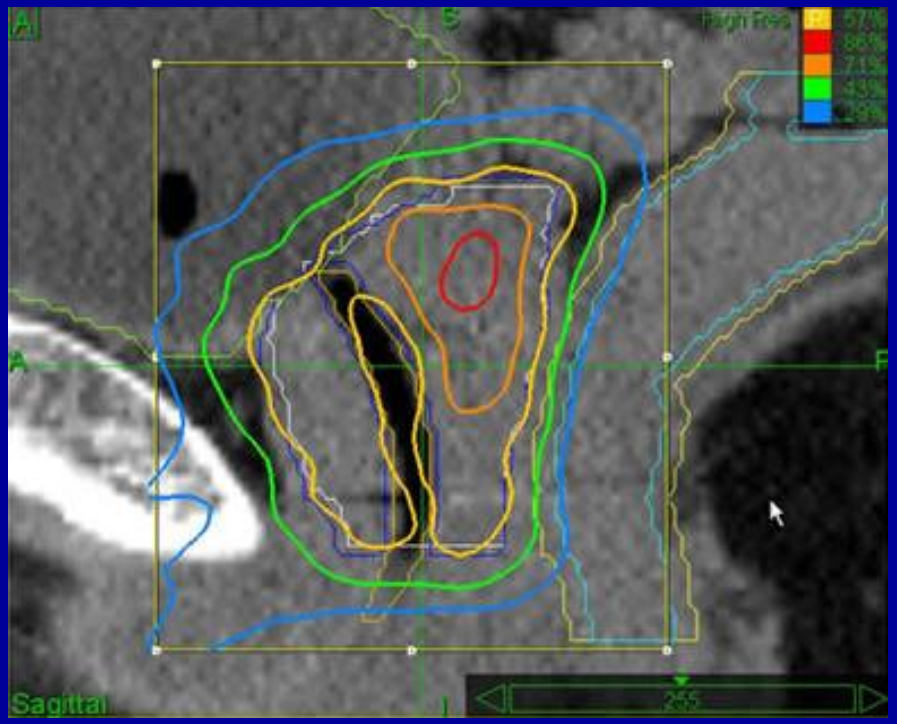
Sketch illustrating intensity modulated beams of radiation.



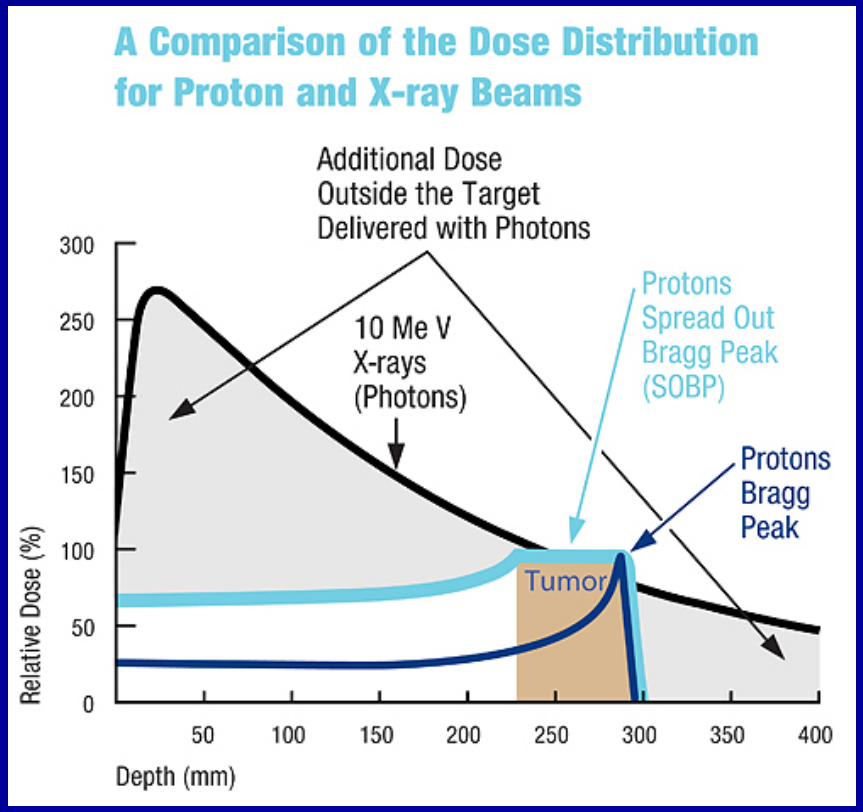
Fontenot 2009

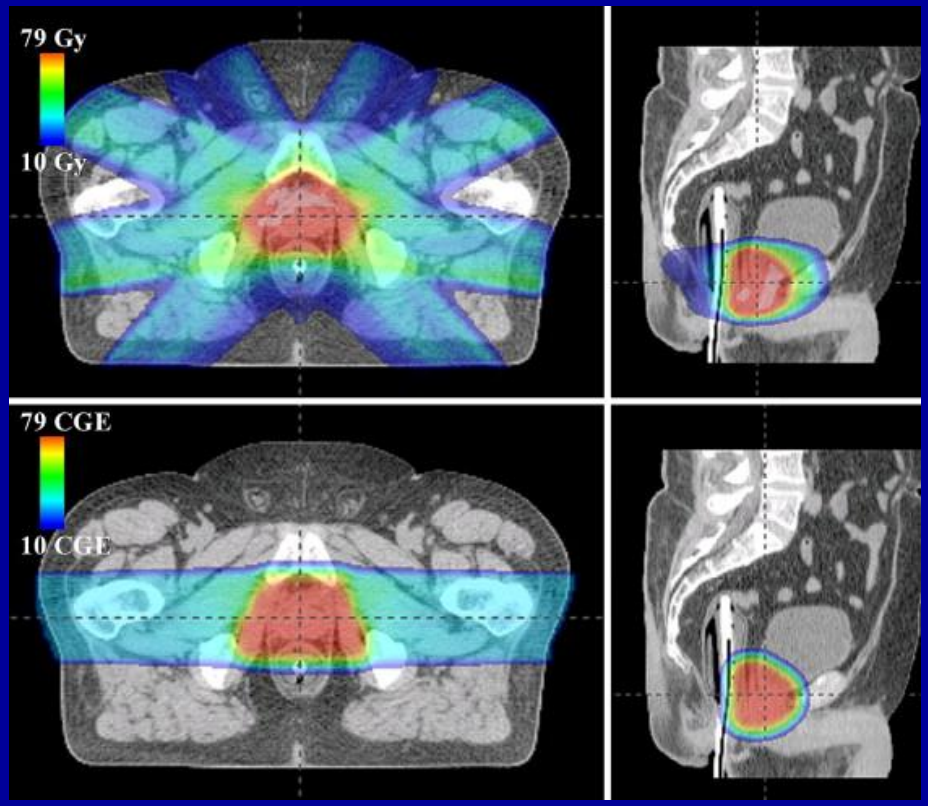
CyberKnife®





Proton therapy





www.procure.com; Fontenot 2009

Radiation dose

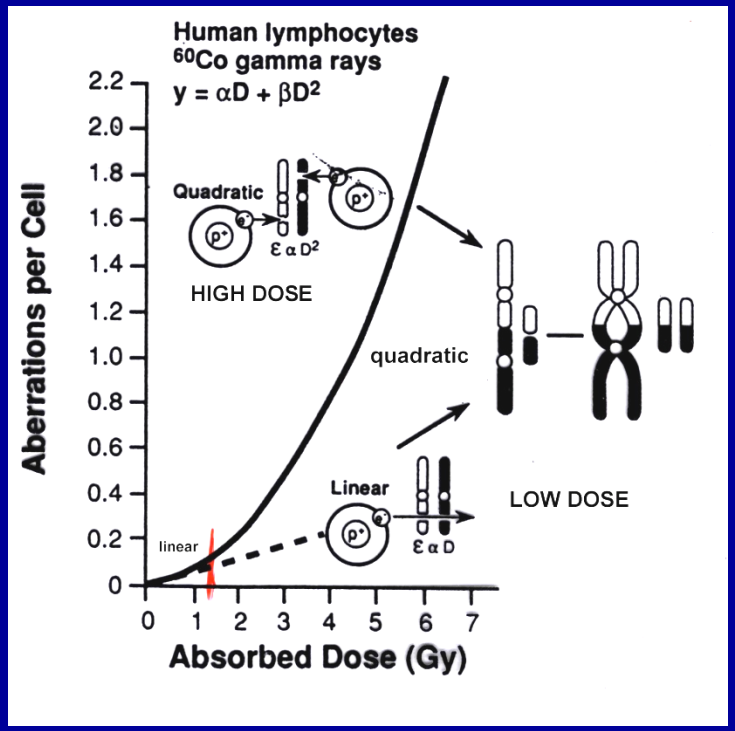
- conventional dose = 1.8 – 2 Gy per day
- max tolerated 2D dose = 70 Gy
  - unacceptable GI toxicity
- max tolerated 3D CRT dose = 79.2 Gy?
- max tolerated IMRT dose = 86.4 Gy?
- proton therapy dose = similar to IMRT?

- What dose is necessary for prostate cancer?

Dose per fraction

- 80 Gy ≠ 80 Gy
  - 2 Gy x 40 fraction
  - 10 Gy x 8 fractions
- Biologic Effective Dose (BED)
  - Total Dose * “conversion factor”
  - Depends on radiobiology of irradiated tissue
  - Tumor (eg, α/β 15)
  - Acute toxicity (eg, α/β 10)
  - Late toxicity (eg, α/β 2)
- BED (prostate cancer α/β 2?)
  - 80Gy: 2 Gy x 40 == 133 Gy
  - 80Gy: 10 Gy x 8 == 347 Gy

Exponential damage



Published dose comparisons

Dose/fx	No. Fractions	Total Dose	Tumor BED*	Acute Rectal BED$	Late Rectal BED#
1.8 Gy/fx	44	79.2 Gy	150 Gy	93 Gy	108 Gy
2.0 Gy/fx	38	76 Gy	152 Gy	91 Gy	106 Gy
2.5 Gy/fx	28	70 Gy	158 Gy	88 Gy	105 Gy
3.0 Gy/fx	20	60 Gy	150 Gy	78 Gy	96 Gy
4.3 Gy/fx	12	51.6 Gy	163 Gy	74 Gy	96 Gy
7.25 Gy/fx	5	36.25 Gy	168 Gy	63 Gy	89 Gy

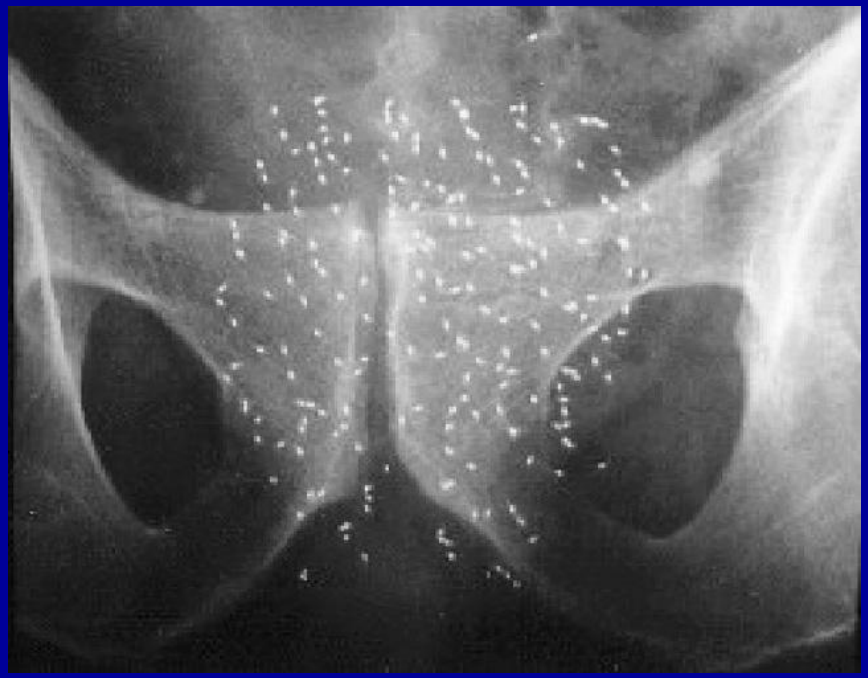
*Assumes α/β 2
$Assumes α/β 10
#Assume α/β 5

Teletherapy/EBRT summary

	CT Planning	Intensity Modulation	Daily Imaging	Stereotactic Immobilization	1-5 “Large” Fractions
2D RT					
3D CRT	X				
IMRT	X	X			
SBRT	X	X	X	X	X
Protons	X	+/-	X	X	+/-

Modern SBRT

LDR Brachytherapy

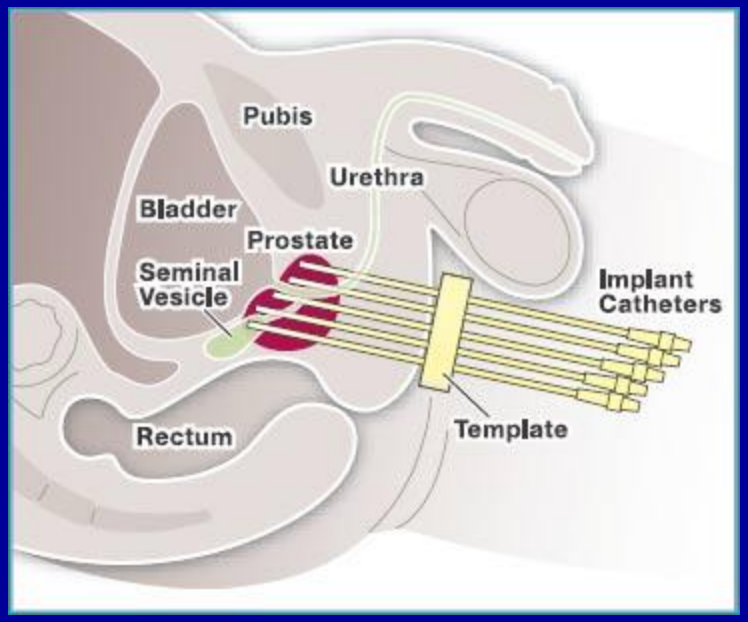


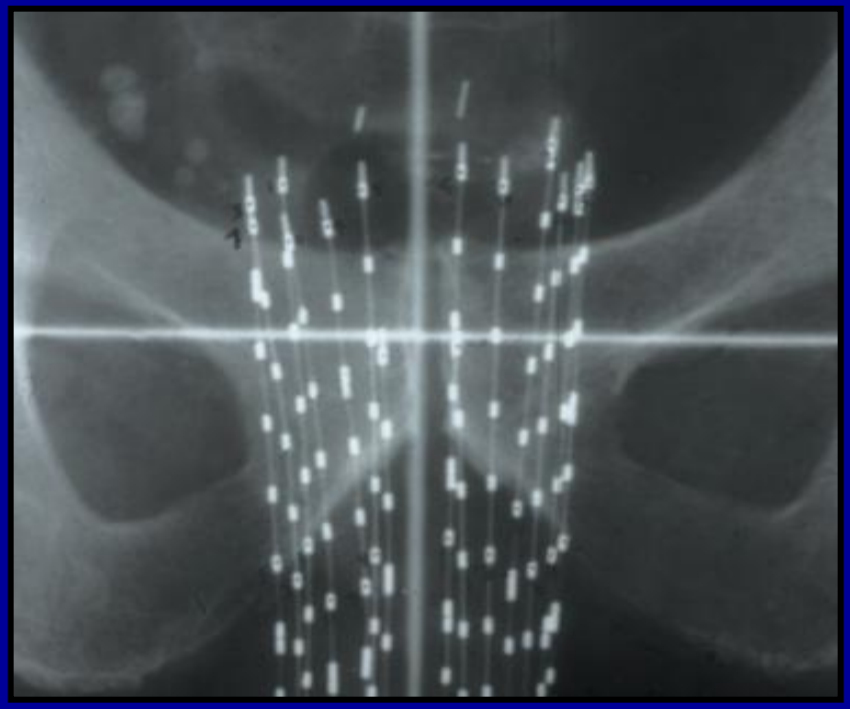
Img.medscape.com

LDRBT Technique

- Which radionuclide?
  - different energy: how far penetrate
  - different half-life: how quickly deposit dose (BED implication)
- Available
  - Iodine (I-125)
  - Palladium (Pd-103)
  - Cesium (Cs-131)
- What cumulative dose?

HDR Brachytherapy



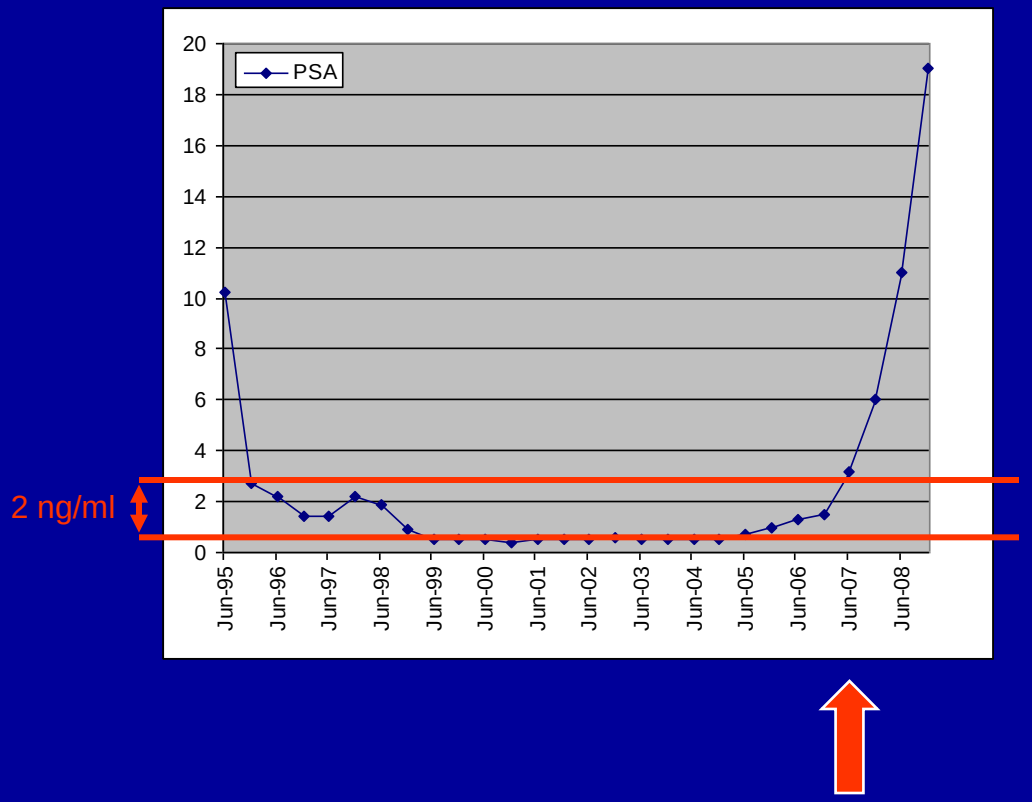


HDRBT Technique

- One radionuclide
  - Iridium (Ir-192)
- What dose schedule?
  - Implant may require hospitalization
  - Typically only one or two implants performed due to patient comfort
  - Fractions typically twice a day
  - Dose schedule not well established (SBRT?)

Treatment efficacy

- clinical outcomes
  - overall survival
  - disease-specific survival
  - clinical progression
- biochemical outcomes
  - PSA
  - failure: nadir + 2 ng/ml
- toxicity/quality of life
  - gastrointestinal (GI)
  - genitourinary (GU)
  - sexual dysfunction
  - second malignancy



Treatment toxicity

	[0]	[1]	[2]	[3]	[4]
LOWER G.I. INCLUDING PELVIS	No change	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/ mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pads /abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
GENITOURINARY	No change	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/ without clot passage	Hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration or necrosis

Comparative effectiveness of therapies for clinically localized prostate cancer

(Minnesota EPC; AHRQ CER No. 13, Wilt et al., 2/2008; available at effectivehealthcare.gov/reports/final.cfm)

- radical prostatectomy (RP), radiation therapy (EBRT), androgen deprivation (ADT), watchful waiting (WW)
- search date: through 9/2007
- 18 RCTs and 473 observational studies

Findings from Minnesota report (I)

- no one therapy can be considered the preferred treatment (limitations in the body of evidence and tradeoffs between effectiveness and adverse effects)
- all treatment options result in adverse effects (urinary, bowel, and sexual)
- no trial enrolled pts with PSA-detected disease
- no RCTs compared EBRT with WW

Findings from Minnesota report (II)

- no EBRT regimen (conventional, high-dose CRT, standard or hypofractionation) was superior in reducing mortality
- no RCTs on BT, cryotherapy, robotic assisted RP, primary ADT, proton beam, or IMRT
- 1 trial (N=106); ▼disease recurrence in RP vs EBRT (14% vs 39%, P = 0.04)
- ▼ disease-specific mortality in RP vs WW (5% vs 10%; P = 0.01) in 1 trial; not sig in an older trial

Stanley Ip, MD
Speaker Disclosure Summary

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- **No** Equity interest, stock or stock options from: none
- **No** Patent or other intellectual property rights from: none
- **No** Salary or royalty income from: none
- **No** Travel expenses or other financial benefit from: none

Key questions in Tufts report

1. What are the benefits and harms of radiation therapy for clinically localized prostate cancer compared to no treatment or no initial treatment in terms of clinical outcomes?

2. What are the benefits and harms of different forms of radiation therapy for clinically localized prostate cancer in terms of clinical outcomes?

3. How do specific patient characteristics (eg, age, race/ethnicity, presence or absence of comorbidities) affect the outcomes of these different forms of radiation therapy?

Population

- men with clinically localized prostate cancer (T1-T2, N0-X, M0-X)
- regardless of age, histologic grade, or PSA concentration

Interventions and comparators of interest

- primary radiation treatment
  - EBRT (CRT, IMRT, proton)
  - SBRT (including CyberKnife®)
  - LDRBT (permanent implant)
  - HDRBT (temporary implant)
  - combinations of above
- no treatment or no initial treatment (watchful waiting, active surveillance, or observation)

- excluded studies specifically evaluating androgen deprivation therapy (ADT) + RT

Outcomes of interest

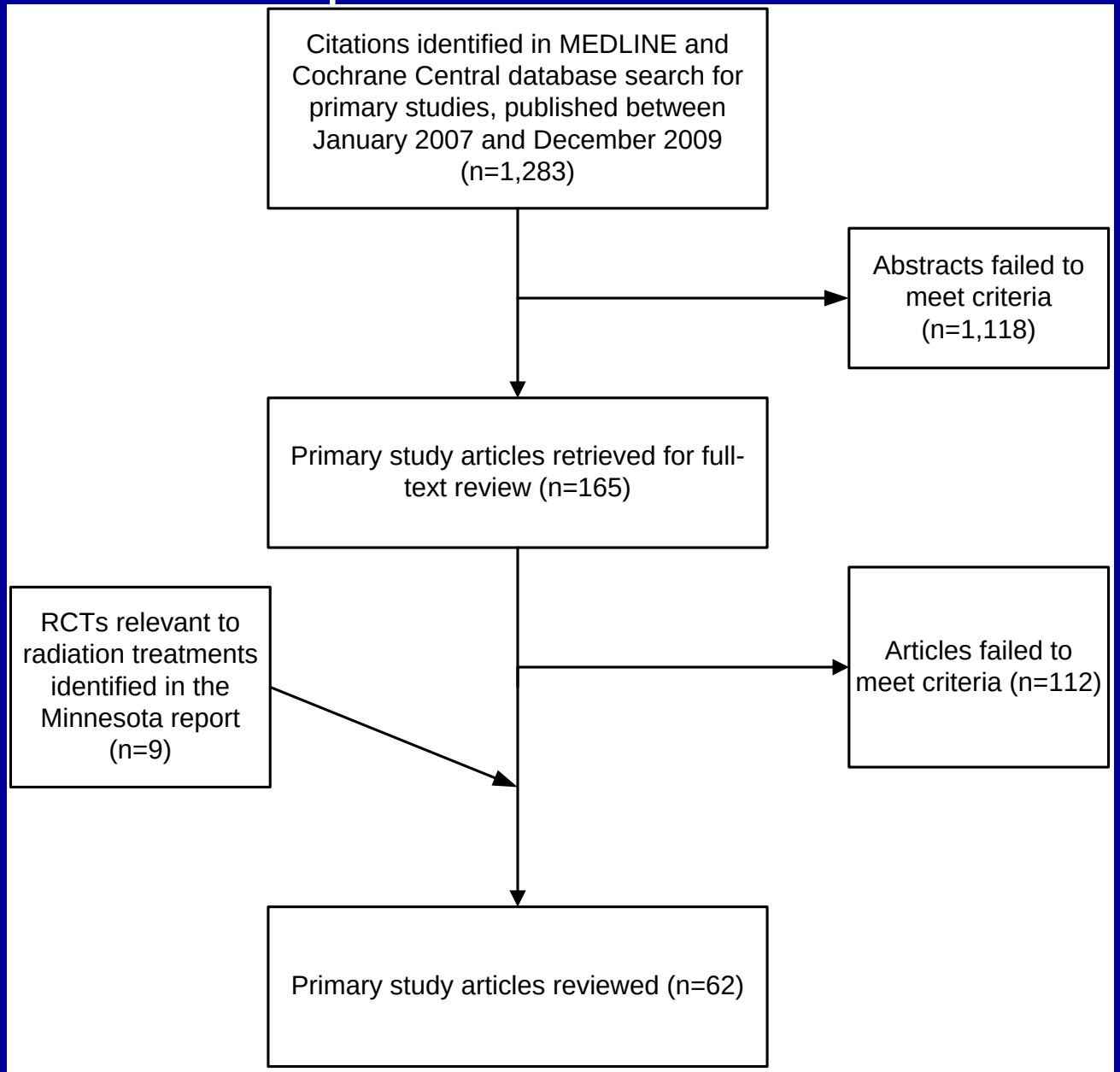
- overall and disease-specific survival
- clinical and/or biochemical progression free survival
- quality of life including bowel, bladder, and sexual dysfunction
- other adverse events (eg, second primary cancer)

Study design

- comparative studies
  - RCTs
  - non-randomized comparative studies

- excluded before-after single cohort studies

Study selection in radiation treatments of localized prostate cancer



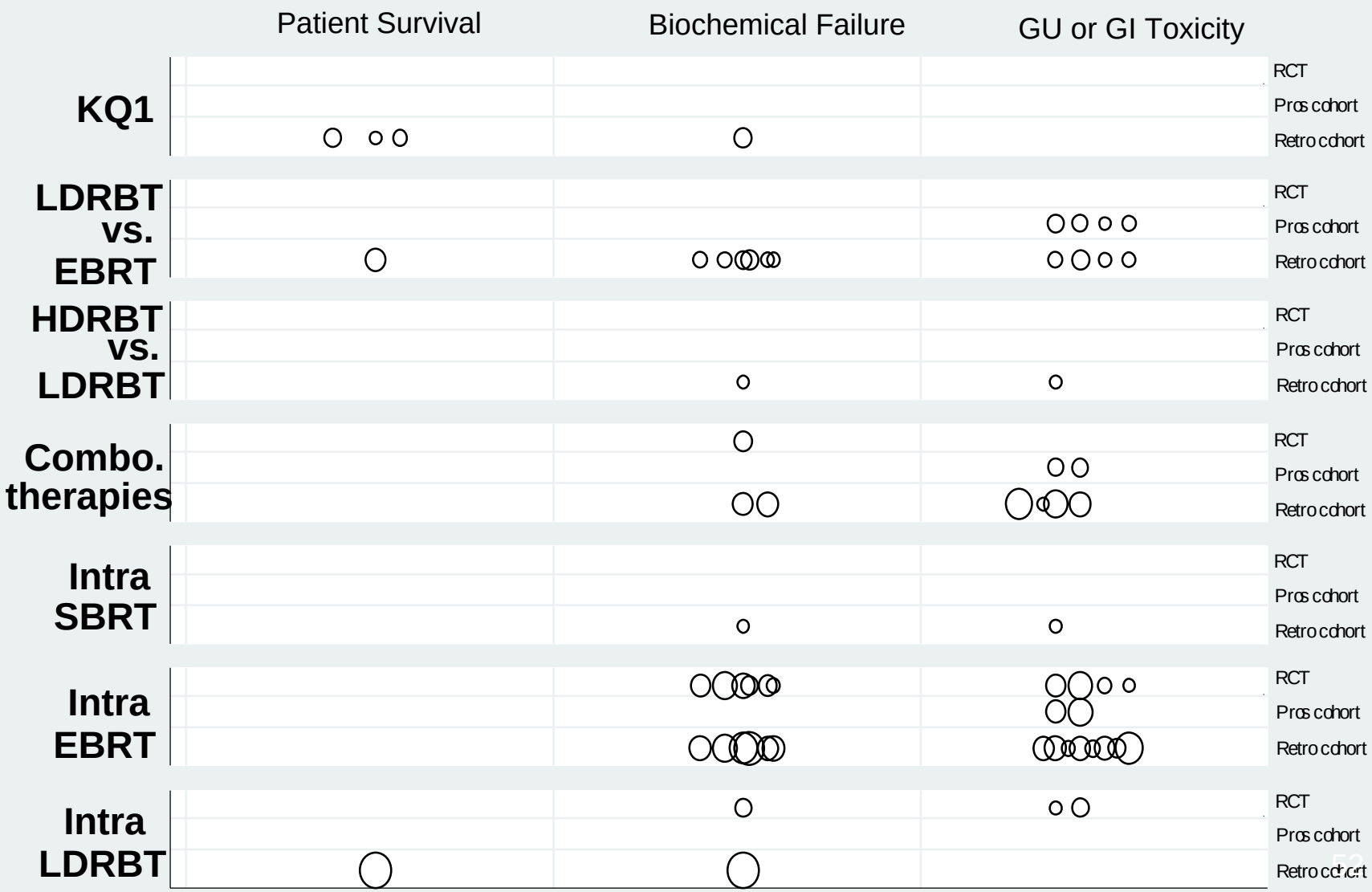
Rating the quality of the individual studies

- AHRQ CER Methods Guide 1.0 (effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf)
- 3 grades
  - A (low risk of bias)
  - B
  - C (high risk of bias)

Rating the strength of evidence for each key question

- number and quality of primary studies; study design; duration of follow-up; consistency of results across studies
- rating
  - HIGH confidence that the evidence reflects the true effect
  - MODERATE confidence that the evidence reflects the true effect
  - INSUFFICIENT – evidence is unavailable, limited, inconsistent, “C” quality, or does not permit an estimation of the true effect

Number of studies in RT for localized prostate cancer



Raveendhara R Bannuru, MD Speaker Disclosure Summary

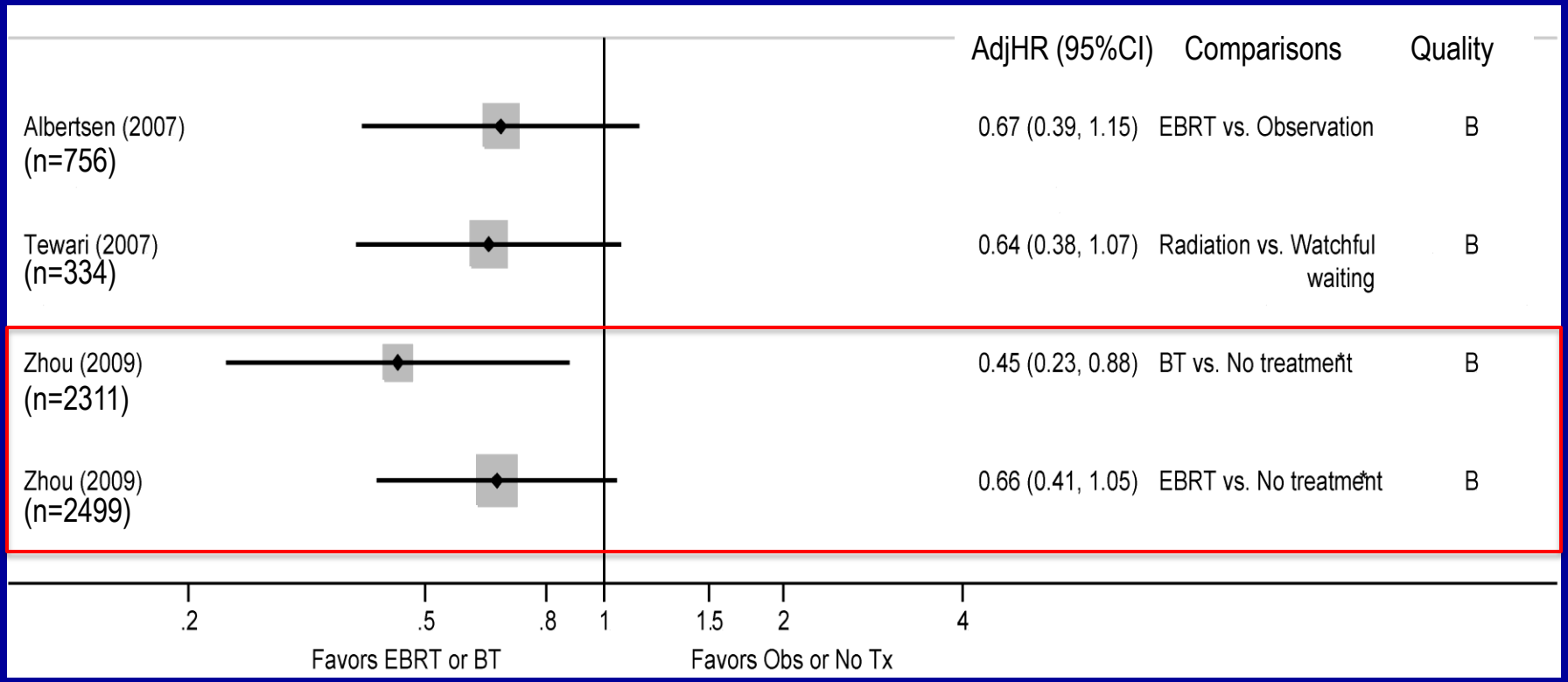
- I or a member of my immediate family **have not** received anything of value related to the technology or topic being presented.
- Please indicate the financially interested company for any “Yes” response:
- **No** Research or institutional support from: none
- **No** Fees, honoraria or in-kind compensation other than cash (whether for consulting, speaking, legal testimony or advisory board service) from: none
- **No** Equity interest, stock or stock options from: none
- **No** Patent or other intellectual property rights from: none
- **No** Salary or royalty income from: none
- **No** Travel expenses or other financial benefit from: none

Key question 1

What are the benefits and harms of radiation therapy (RT) for clinically localized prostate cancer compared to no treatment or no initial treatment (NT) in terms of clinical outcomes?

Q1. RT vs NT patient survival

Studies	3 retro cohorts (n = 334 to 3094)
Strength of evidence	insufficient (few studies)



Q1. RT vs NT genitourinary toxicity

Study	1 retro cohort (n = 2053)*
Findings	BT vs NT adjHR 1.68 (P = NS) EBRT vs NT adjHR 1.77 (P = NS) BT+EBRT vs NT adjHR 4.56 (P = 0.02)
Strength of evidence	insufficient

*Elliott et al. J Urology.178(2):529-534, 2007

Q1. RT vs NT
second primary cancer (SPC)

Studies	1 retro cohort*
Findings	BT vs NT (n = 50956) overall: adjHR 0.96 (P = NS) late (≥ 5 yr): adjHR 1.20 (P = NS) EBRT vs NT (n = 89133) overall: adjHR 1.14 (P < 0.0001) late (≥ 5 yr): adjHR 1.26 (P < 0.0001)
Strength of evidence	insufficient

*Abdel-Wahab et al. Int J Radiation Oncology Biol Phy 72(1):58-68, 2008

Key questions 2

What are the benefits and harms of different forms of radiation therapy for clinically localized prostate cancer in terms of clinical outcomes?

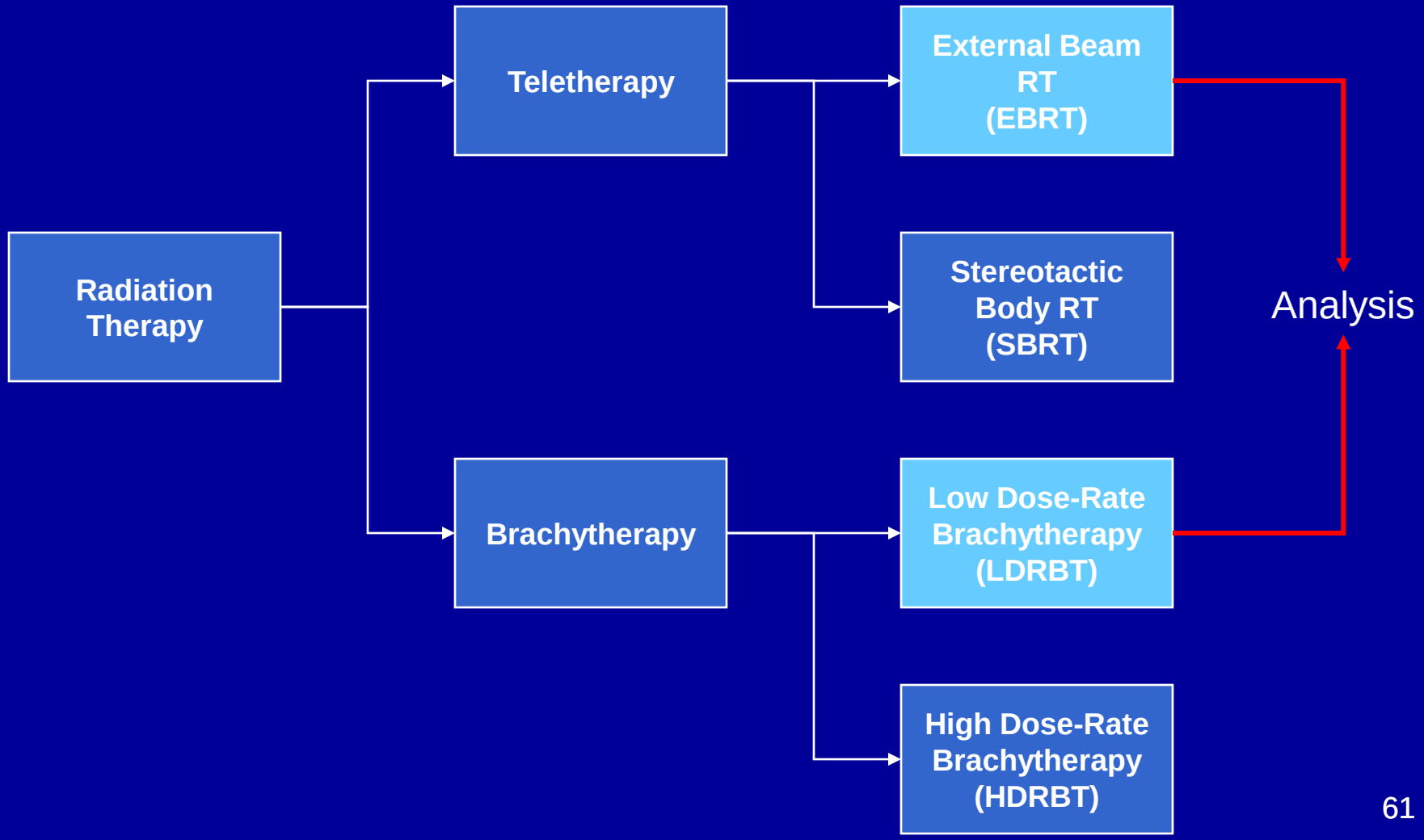
Q2. Comparing different RTs

- SBRT vs other modalities
- LDRBT vs EBRT
- LDRBT vs HDRBT
- combination therapies
- intra-SBRT comparisons
- intra-EBRT comparisons
- intra-LDRBT comparisons

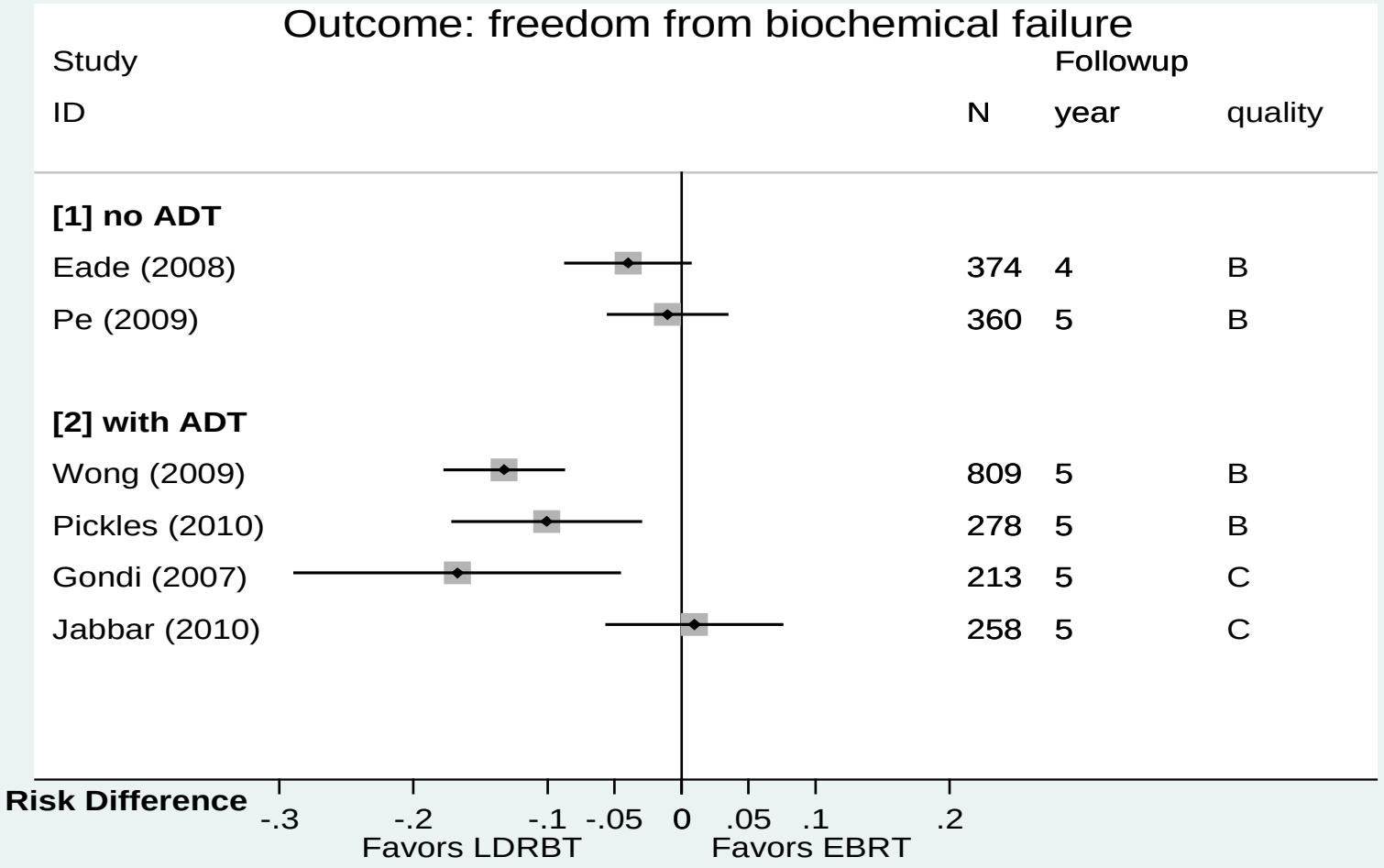
Stereotactic Body Radiation Therapy (including CyberKnife®) vs other radiation modalities

Findings	no studies
Strength of evidence	insufficient

LDRBT vs EBRT



LDRBT vs EBRT
freedom from biochemical failure



LDRBT vs EBRT
freedom from biochemical failure

Studies	6 retro cohorts (n = 278 to 853)
Findings	no diff (no ADT, 2 studies) ▲ freedom from biochemical failure with LDRBT (ADT included)
Strength of evidence	insufficient (only 2 “no ADT” studies)

LDRBT vs EBRT
disease-specific mortality

Study	1 retro cohort (n = 1520)*
Findings	7 yr disease-specific mortality adjRR 0.68 (95% CI 0.30,1.5)
Strength of evidence	insufficient

*Zhou et al. Int J Radiation Oncology Biol Phys 73 (1):15 -23, 2009

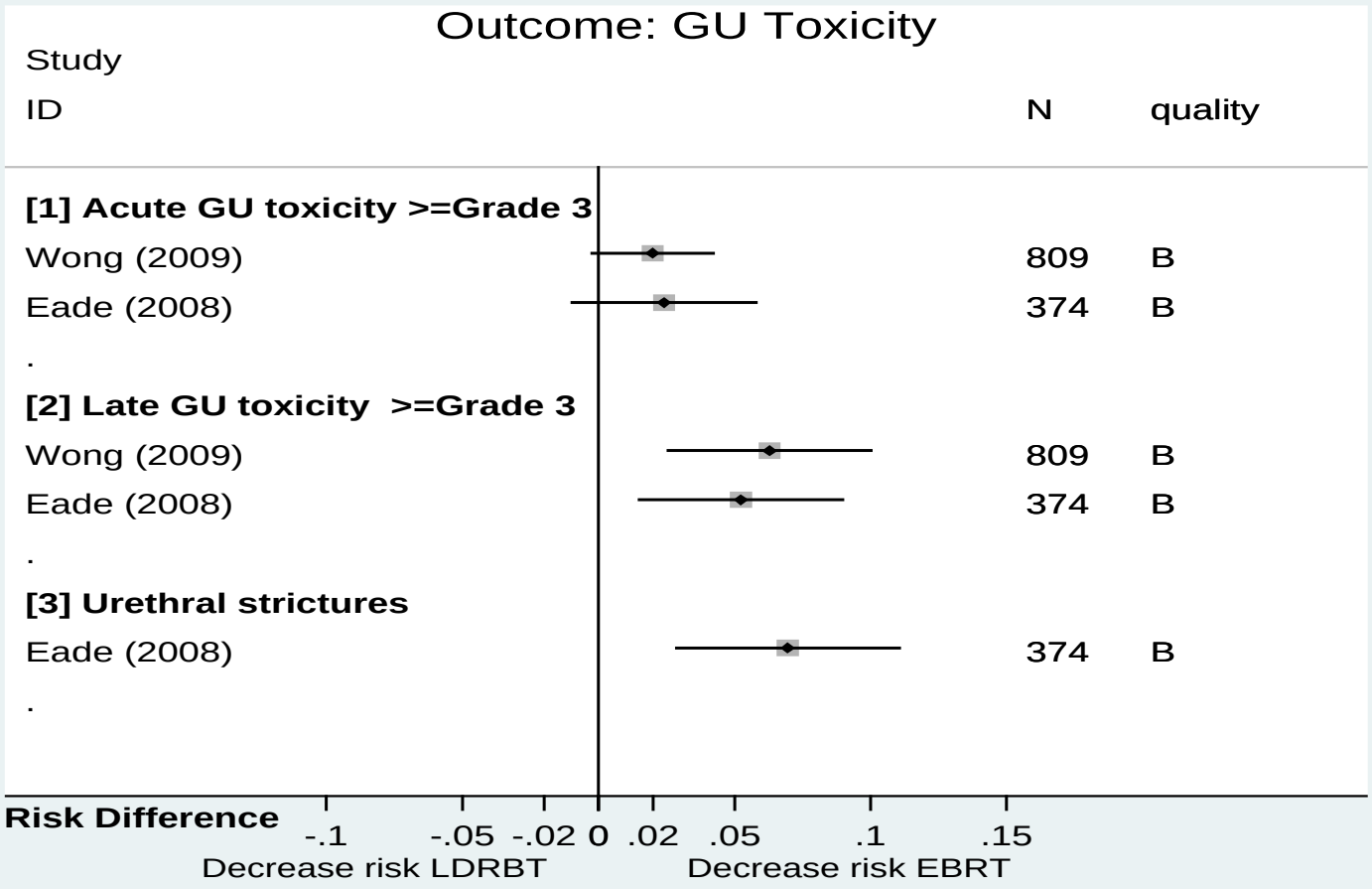
LDRBT vs EBRT genitourinary toxicity/QoL

Studies	4 pro cohorts (n = 168 to 598) 2 retro cohorts (n = 374 and 853)

Outcome	Quality of life instrument	Study	findings	P Value	Quality
Prospective studies LDRBT vs. EBRT					
Disease-specific QoL: urinary scores	EPIC 26 score	Sanda (2008)	more	NR	B
	EPIC 50 score	Ferrer (2008)	No diff	NS	B
	UCLA PCI/AUA symptom index	Litwin (2007) or Gore (2009)	**more**	<0.05	C
	PCSI score	Chen (2009):	No diff	NR	C

NS: Not Significant NR: Not Reported

LDRBT vs EBRT genitourinary toxicity (RTOG)



LDRBT vs EBRT genitourinary outcomes

Studies	4 pro cohorts (n = 168 to 598) 2 retro cohorts (n = 374 and 853)
Findings	GU: ▲ with LDRBT or no difference
Strength of evidence	insufficient (few high quality studies)

LDRBT vs EBRT
bladder cancer incidence

Study	1 retro (n=115,948)*
Findings	▼ bladder cancer incidence 10 yrs after Tx in LDRBT RR 0.72 (95% CI 0.59, 0.87)
Strength of evidence	insufficient

*Nieder et al. J Urology 180 (5):2005-2009, 2008

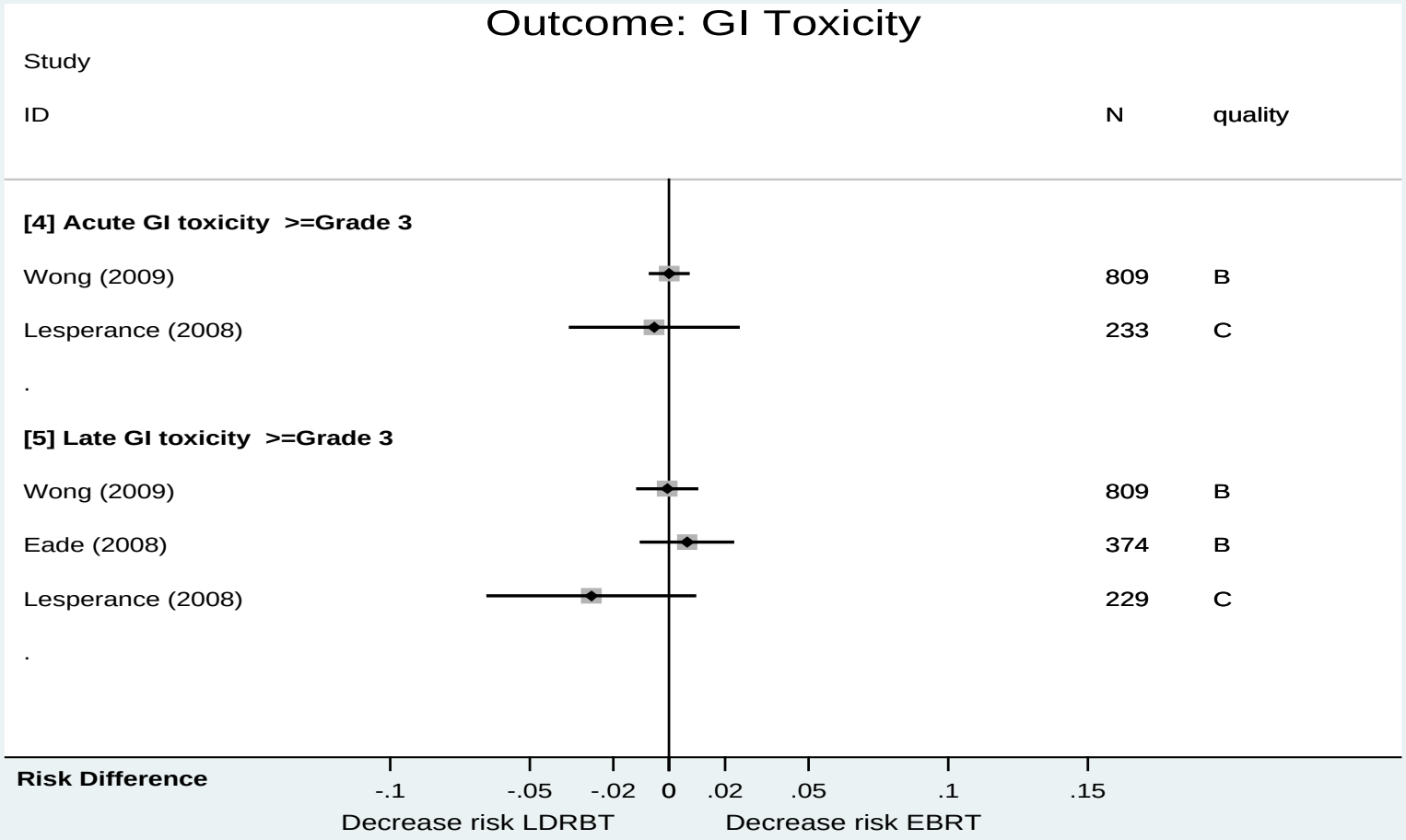
LDRBT vs EBRT gastrointestinal toxicity/QoL

Studies	4 pro (n = 168 to 598) 3 retro (n = 233 to 853)

Outcome	Quality of life instrument		Findings	P value	Quality
Prospective Studies LDRBT vs. EBRT					
Disease-specific QoL: bowel scores	EPIC 26 score	Sanda (2008)	No diff	NR	B
	EPIC 50 score	Ferrer (2008)	**less**	<0.05	B
	UCLA PCI/AUA symptom index	Litwin (2007) or Gore (2009)	No diff	NS	C
	PCSI score	Chen (2009)	less	NR	C

NS: Not Significant NR: Not Reported

LDRBT vs EBRT gastrointestinal toxicity (RTOG)



LDRBT vs EBRT
gastrointestinal outcomes

Studies	4 pro (n = 168 to 598) 3 retro (n = 233 to 853)
Findings	GI: ▼ with LDRBT or no diff
Strength of evidence	insufficient (few high quality studies)

LDRBT vs EBRT
rectal cancer incidence

Study	1 retro (n=115,948)*
Findings	▼ rectal cancer incidence 10 yrs after Tx in LDRBT RR 0.64; 95% CI (0.45,0.91)
Strength of evidence	insufficient

*Nieder et al. J Urology 180 (5):2005-2009, 2008

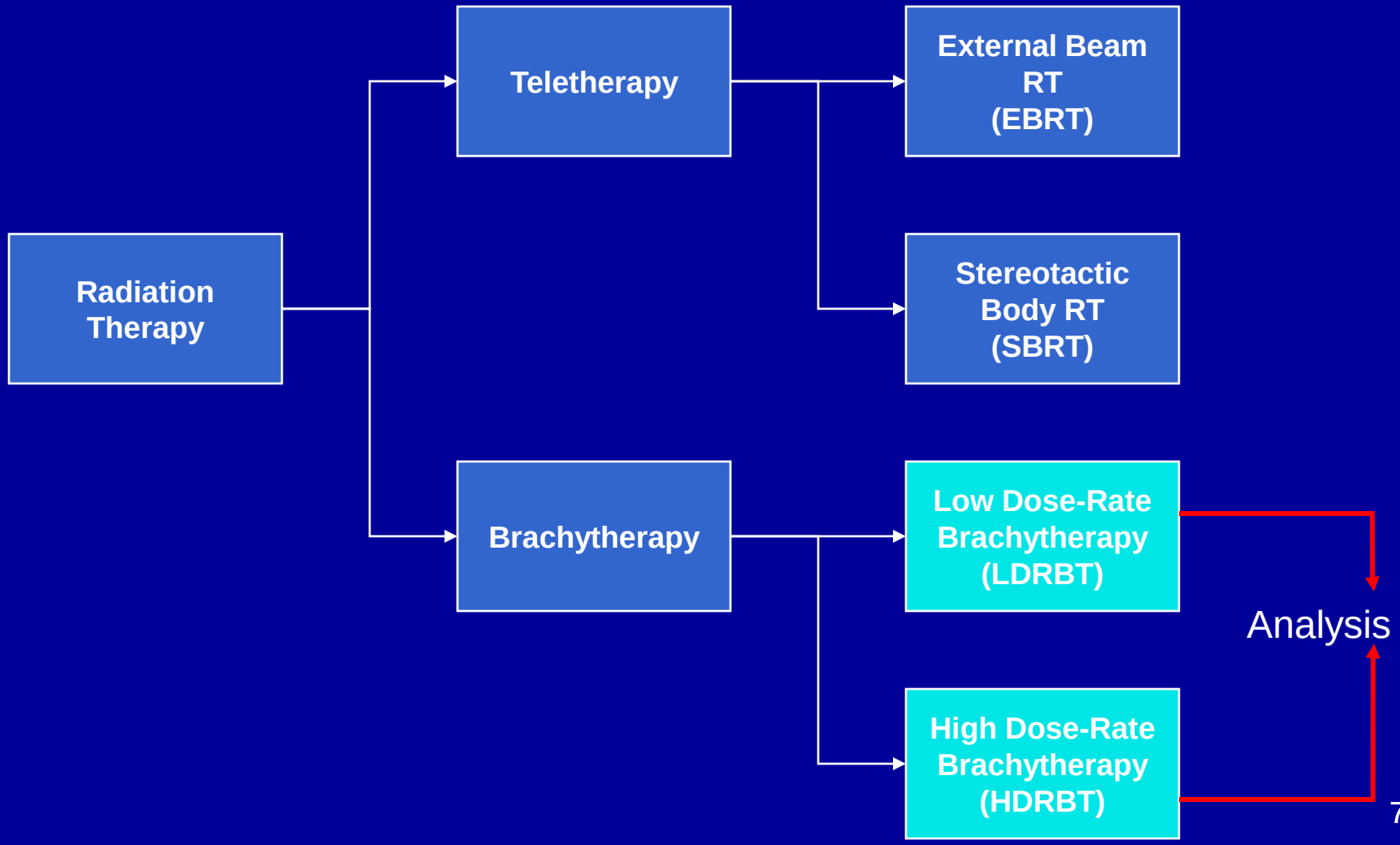
LDRBT vs EBRT sexual dysfunction

Author Year [UI] Country	Outcome	Intervention	Follow -up, yr	No. Analyzed	Findings	Quality
Sanda 2008 [18354103] USA	EPIC-26 sexual score	LDRBT	1	272	less	B
		EBRT	1	258		
Ferrer 2008 [18325680] Spain	EPIC-50 sexual score	LDRBT	2	275	**less**	B
		EBRT	2	205		
Litwin 2007 [17455209]	UCLA PCI sexual score	LDRBT (25.6% received EBRT)	2	90	**more**	C
Gore 2009 [19509365] USA		EBRT	2	78		
Chen 2009 [19620493] USA	PCSI sexual dysfunction score	BT	3	26 29 20	less less less	C
		EBRT	3	31 39 80		

LDRBT vs EBRT
sexual dysfunction

Studies	4 pro cohorts (n = 168 to 598)
Findings	1 less,1 more with LDRBT
Strength of evidence	insufficient (inconsistent results)

HDRBT vs LDRBT



HDRBT vs LDRBT biochemical control

Study	1 retro cohort, (n = 454)* Ir-192 vs Pd-103
Findings	88% vs 89% (P = NS)
Strength of evidence	insufficient

*Martinez et al. Am J Clin Oncol. Nov 2009

HDRBT vs LDRBT genitourinary and gastrointestinal toxicity

Study	1 retro cohort, (n=454)* Ir-192 vs Pd-103
Findings	GU toxicity acute: 4.5% vs 14.5% (P = NR) late: 9% vs 8.5% (P = NR) GI toxicity acute: 0% vs 0.5% (P = NR) late: 0.5% vs 2% (P = NR)
Strength of evidence	insufficient

*Martinez et al. Am J Clin Oncol. Nov 2009

HDRBT vs LDRBT sexual dysfunction

Study	1 retro cohort, (n = 454)* Ir-192 vs Pd-103
Findings	20% vs 30% (P = NS)
Strength of evidence	insufficient

*Martinez et al. Am J Clin Oncol. Nov 2009

Combination therapies

- LDRBT plus different EBRT doses
- EBRT vs (EBRT + bHDRBT)
- (EBRT + LDRBT) vs (EBRT + HDRBT)
- LDRBT vs (LDRBT + EBRT)
- EBRT vs BT vs (EBRT + BT)
- EBRT vs LDRBT vs (EBRT + LDRBT)

BT + EBRT vs EBRT genitourinary outcomes

Studies	2 retro cohorts (n = 358; 876)
Findings	LDRBT + EBRT vs EBRT* GU toxicity: 18% vs 5% (P = 0.009) BT + EBRT vs EBRT** urethral strictures: 5.2% vs 1.7% (P = 0.013)
Strength of evidence	insufficient (few studies)

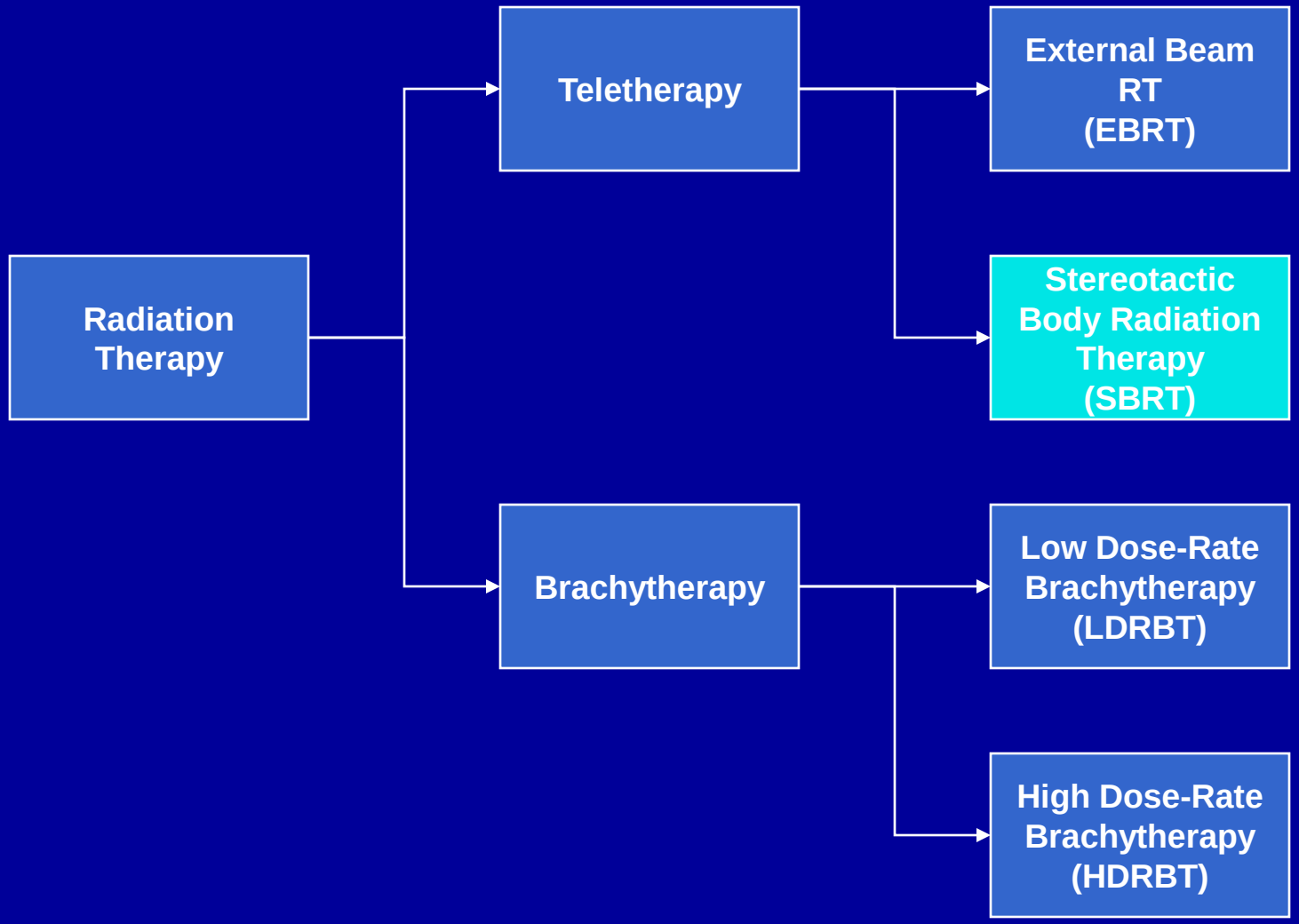
*Wong et al. Cancer 115 (23):5596 -606, 2009; **Elliot et al. J Urology 178 (2):529 -34, 2007

BT + EBRT vs EBRT
second primary cancer

Studies	1 retro cohort (n = 57,496)*
Findings	▲ second primary cancers in combo 10.3% vs 5.7% (P < 0.0001) ▲ late (≥ 5 yrs) second primary cancers in combo 4.2% vs 1.4% (P < 0.0001)
Strength of evidence	insufficient

*Abdel-Wahab et al. Int J Radiation Oncology Biol Phy 72(1):58-68, 2008

Intra-SBRT

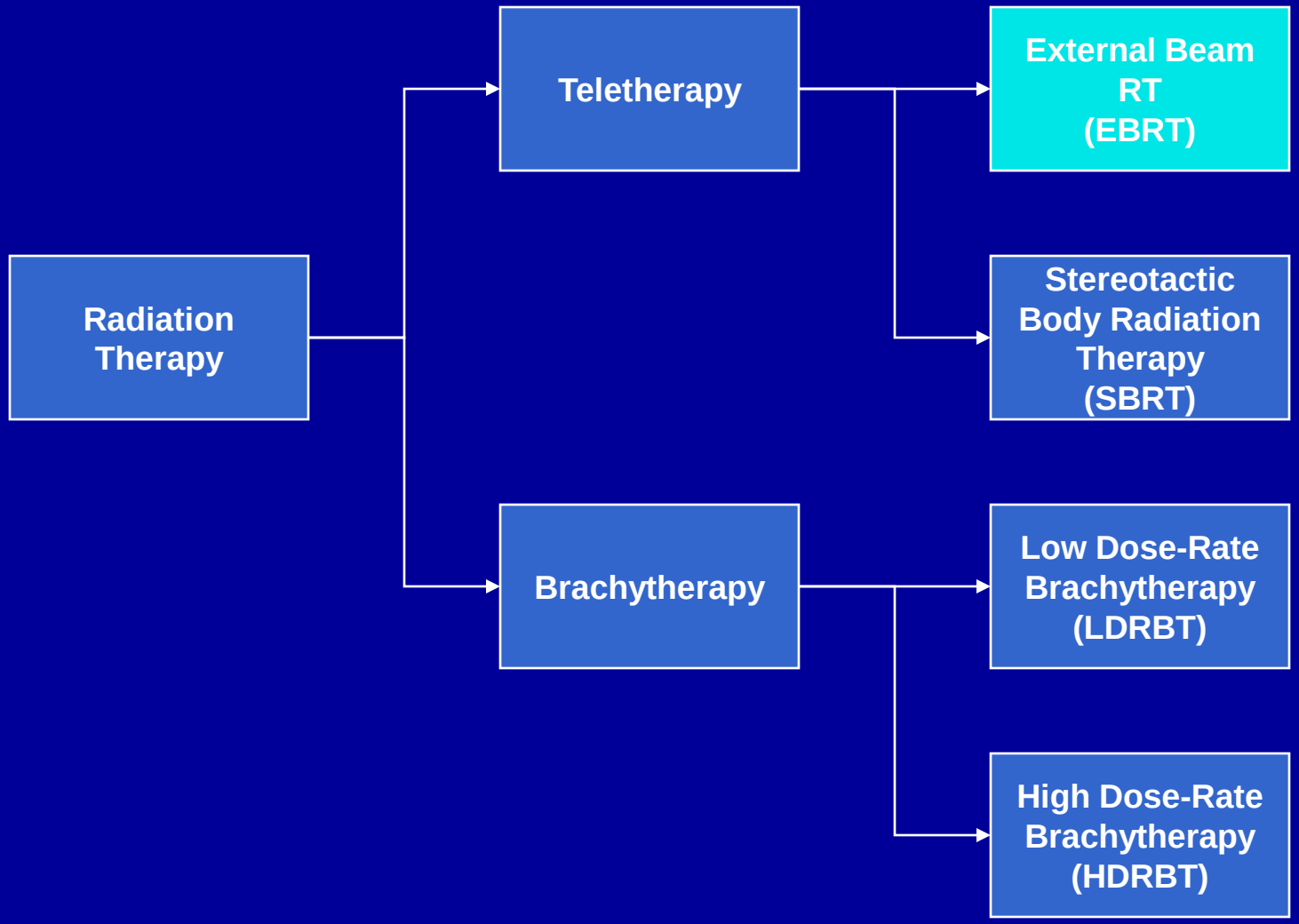

Radiation Therapy
Teletherapy
Brachytherapy
External Beam RT (EBRT)
Stereotactic Body Radiation Therapy (SBRT)
Low Dose-Rate Brachytherapy (LDRBT)
High Dose-Rate Brachytherapy (HDRBT)

Intra-SBRT genitourinary and gastrointestinal toxicity

Study	1 retro cohort (n = 304)*
Findings	35 Gy vs 36.25 Gy in 5 fractions Late GU: 0% vs 0.5% (P = NS) Late GI: 0% vs 0%
Strength of evidence	insufficient

*Katz et al. BMC Urol. 1;10(1):1, 2010

Intra-EBRT

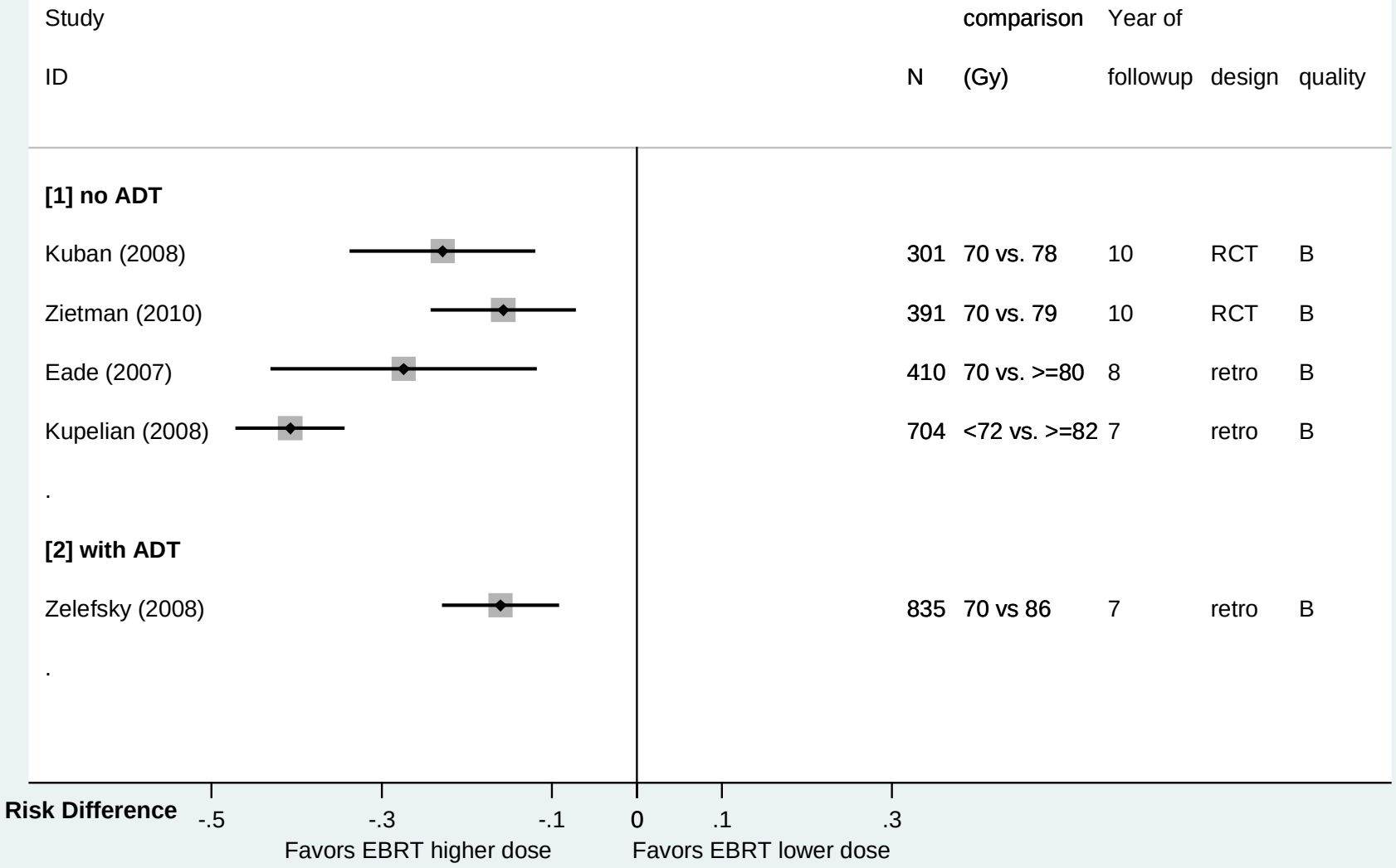


- Dose
- Fraction size

EBRT dose comparisons freedom from biochemical failure

Studies	3 RCTs (n= 301 to 664) 5 retro cohorts (n=398 to 2047)
Findings	increased dose ▲ freedom from biochemical failure at 5 to 10 years
Strength of evidence	moderate (consistent results)

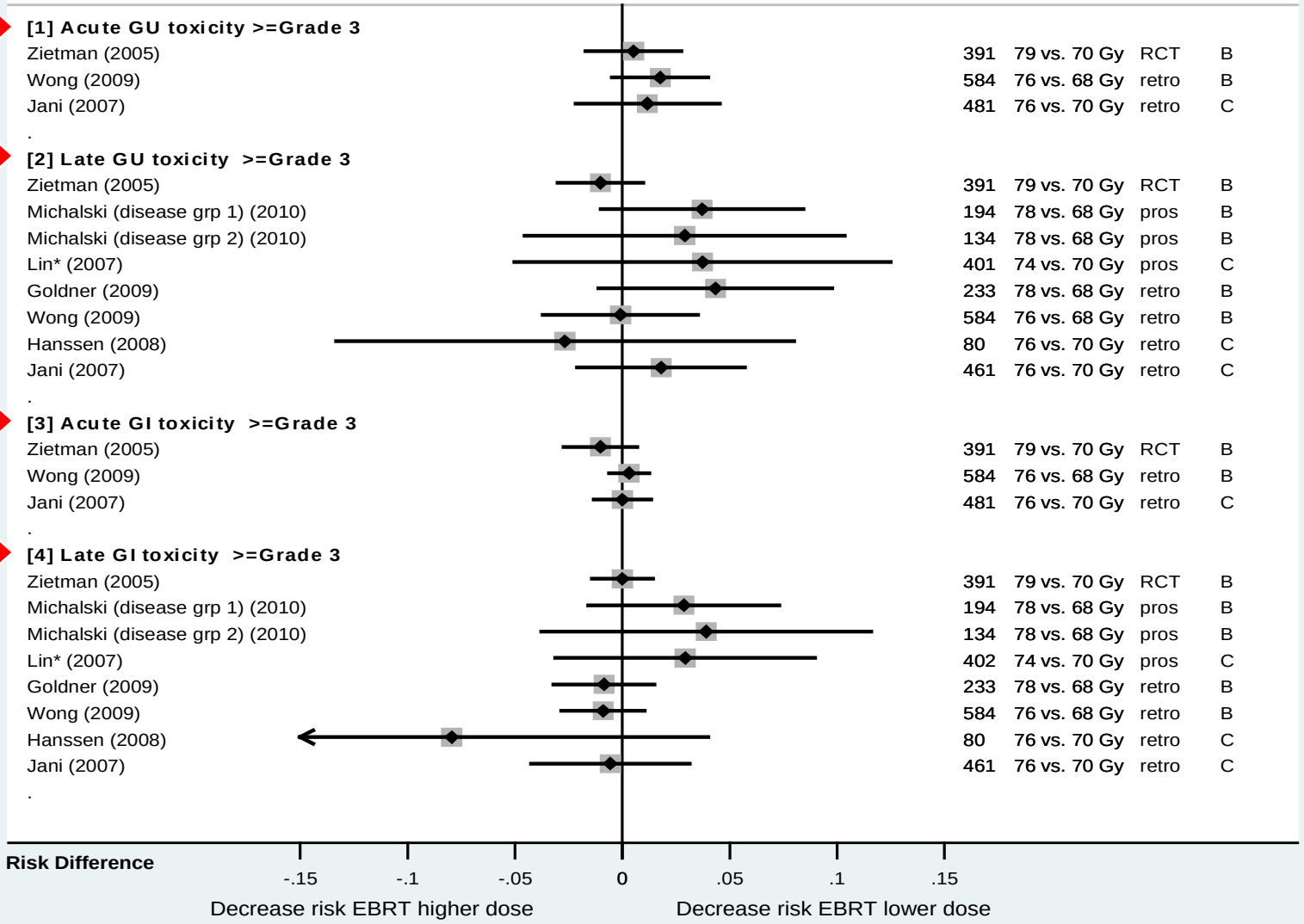
Outcome: Freedom from biochemical failure (>5 years of followup)



EBRT dose comparisons toxicity

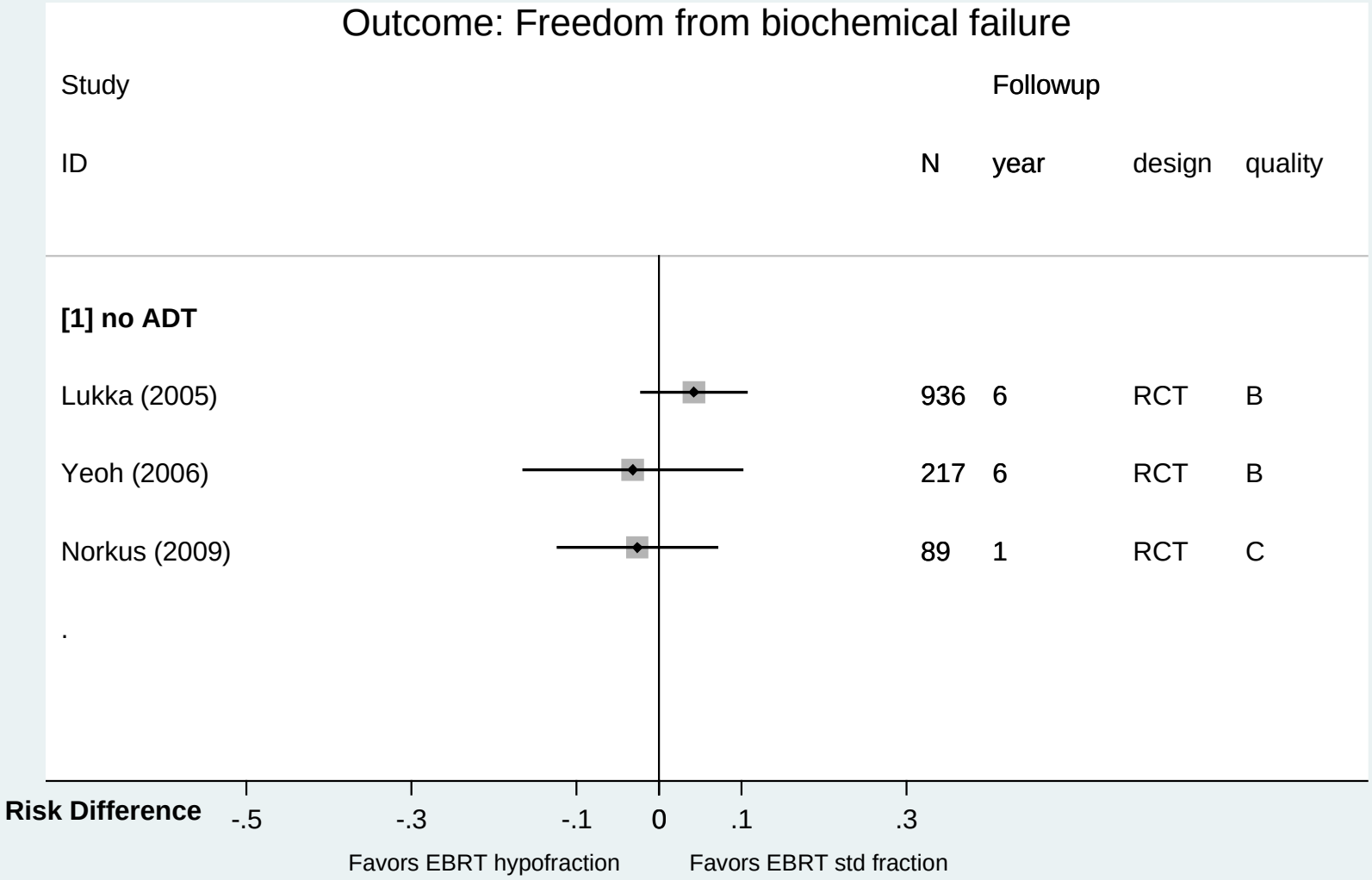
Studies	1 RCT (n=392) 2 pro cohorts (n=402, 956) 6 retro cohorts (n=80 to 1571)
Findings	no diff in acute and late GU or GI toxicities
Strength of evidence	moderate (consistent results)

Outcome: Toxicity or Adverse Outcomes



EBRT fraction size comparisons freedom from biochemical failure

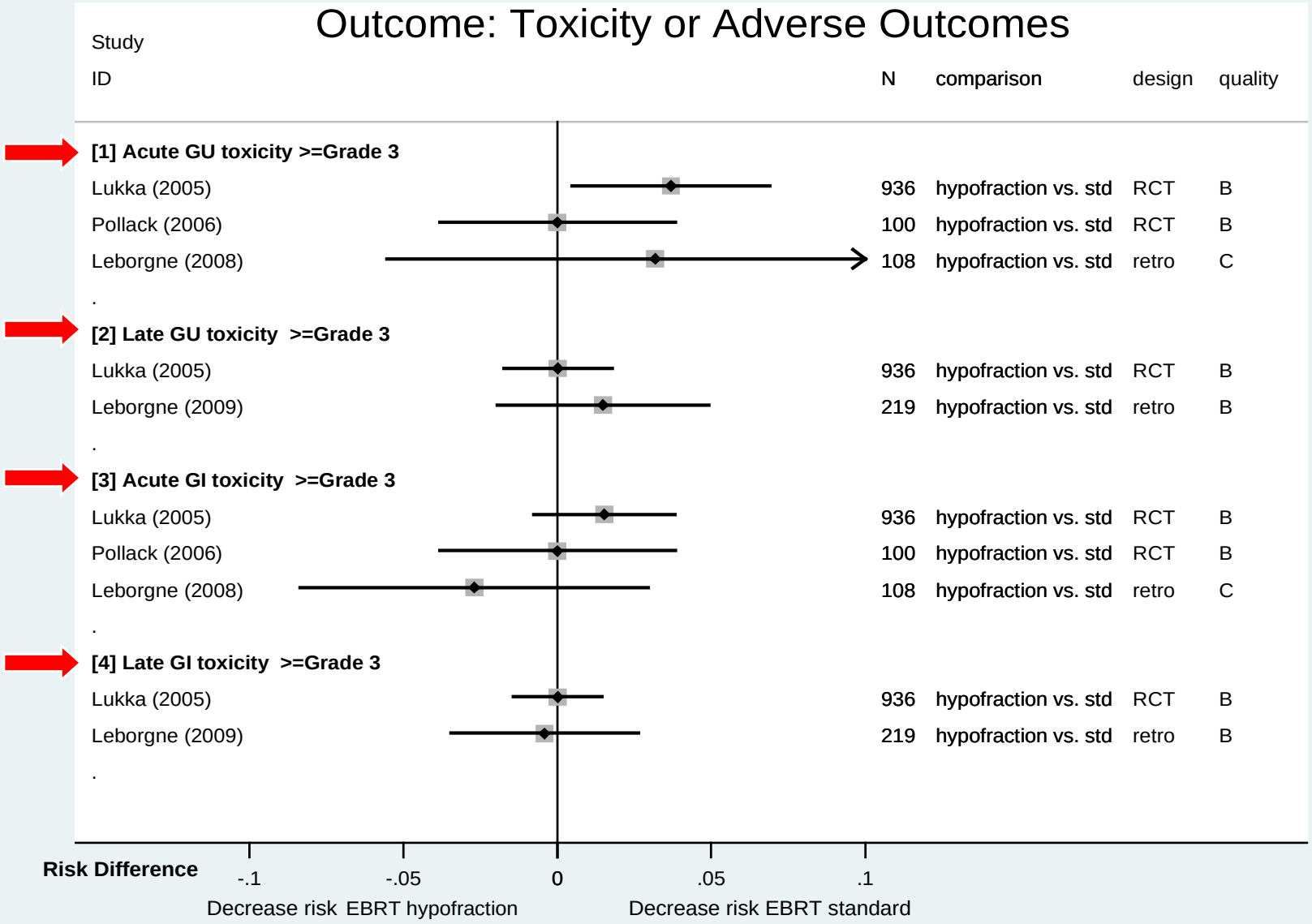
Studies	3 RCTs (n = 89 to 936)
Findings	no diff between standard and hypofractionation
Strength of evidence	moderate (consistent results)


Outcome: Freedom from biochemical failure
Study
ID
Followup
N
year
design
quality
[1] no ADT
Lukka (2005)
936
6
RCT
B
Yeoh (2006)
217
6
RCT
B
Norkus (2009)
89
1
RCT
C
.
Risk Difference
-.5
-.3
-.1
0
.1
.3
Favors EBRT hypofraction
Favors EBRT std fraction

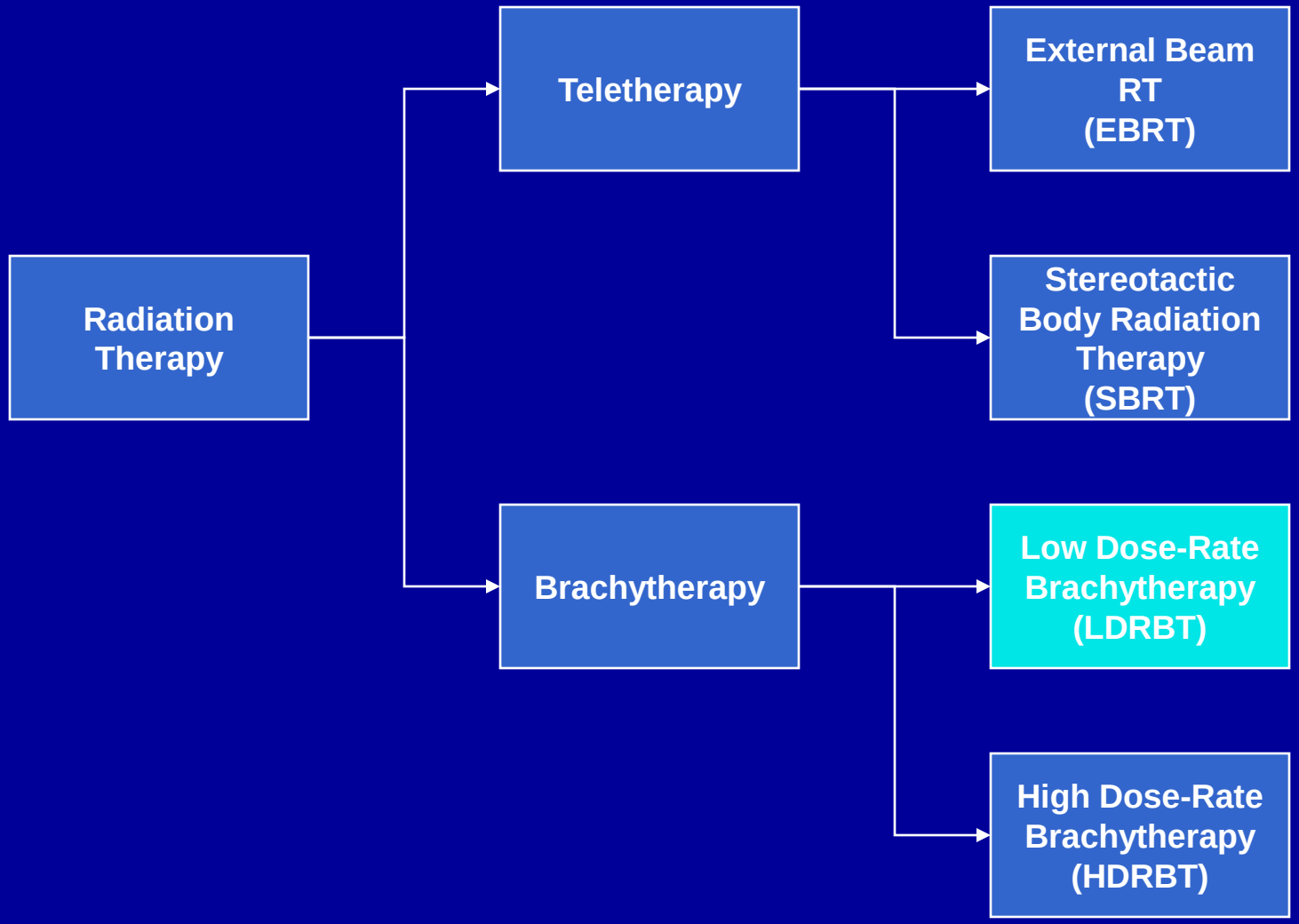
EBRT fraction size comparisons genitourinary and gastrointestinal toxicity

Studies	2 RCTs (n =100, 936) 2 retro cohorts (n =130, 219)
Findings	little or no diff in acute and late GU or GI toxicities
Strength of evidence	moderate (consistent results)

Outcome: Toxicity or Adverse Outcomes



Intra-LDRBT


Radiation Therapy
Teletherapy
External Beam RT (EBRT)
Stereotactic Body Radiation Therapy (SBRT)
Brachytherapy
Low Dose-Rate Brachytherapy (LDRBT)
High Dose-Rate Brachytherapy (HDRBT)

Intra-LDRBT comparisons overall survival

Study	1 retro cohort (n = 3928)*
Findings	(BED < 200 Gy, 200-220 Gy, > 220 Gy): ▲ survival with ▲ dose 87% vs 89% vs 95% (P = 0.048)
Strength of evidence	insufficient

*Stone et al. Int J Radiation Oncology Biol Phys 73(2):341-346, 2009

Intra-LDRBT freedom from biochemical failure

Studies	1 RCT (n=314), 1 retro cohort (n=3928)
Findings	RCT (I-125 vs Pd-103)* 97% vs 99% (P = NS) retro cohort** (BED <140 Gy, 140-200 Gy, >200 Gy) ▲ freedom from failure with ▲ dose 41% vs 78% vs 83% (P <0.0001)
Strength of evidence	insufficient (few studies)

*Wallner et al. Int J Radiation Oncology Biol Phys 57(5):1297-1303, 2003; Merrick et al. Am J Clin Oncology 30(3):228-233,2007; **Stone et al. Int J Radiation Oncology Biol Phys 69(5):1472-1477, 2007

Intra-LDRBT comparisons genitourinary & gastrointestinal toxicity

Studies	2 RCT (n = 314; n = 69)
Findings	RCT (I-125 vs Pd-103)* GU toxicity: no diff (AUA score) GI toxicity: no diff (rectal bleed) RCT (LDRBT ± hyaluronic acid)** ▼ GI toxicity with hyaluronic acid 12% vs 0% (P = 0.047)
Strength of evidence	insufficient

*Herstein et al. Cancer J 11(5):385-389, 2005; **Prada et al. Brachytherapy 8(2):210-217, 2009

Key question 3

How do specific patient characteristics (eg, age, race/ethnicity, presence or absence of comorbidities) affect the outcomes of these different forms of radiation therapy?

Baseline risk as outcome modifiers

	Low	Intermediate	High
EBRT vs Obs	↑survival EBRT	↑survival EBRT	↑survival EBRT
Intra-EBRT (78 vs 70 Gy)	▲ bFFF ▲ dose	no diff	▲ bFFF ▲ dose
Intra-LDRBT (140, 140-200, >200 Gy)	▲ bFFF ▲ dose	▲ bFFF ▲ dose	▲ bFFF ▲ dose
EBRT or BT or EBRT + BT	no diff	bFFF: 3D<BT<hi-IMRT< EBRT+BT	no diff
Intra-EBRT (70.2, 75.6, 81, 86.4)	no diff	▲ bFFF ▲ dose	▲ bFFF ▲ dose
Strength of evidence	insufficient (only 1 study per comparison)		

Baseline PSA as outcome modifiers

Study	1 RCT, 78 Gy vs 70 Gy (n = 301)*
Findings	PSA ≤10 ng/ml: no diff PSA >10 ng/ml: ▲ bFFF with ▲ EBRT dose (P <0.001)
Strength of evidence	insufficient

*Kuban et al. Int J Radiation.Oncology, Biol Phys 70(1):67-74,2008

Baseline Gleason score as outcome modifiers

Study	1 retro cohort (n = 3928)*
Findings	Score 7: no diff in bFFF with ▲ BT dose Score 8-10: ▲ bFFF with ▲ BT dose (P <0.001)
Strength of evidence	insufficient

*Stone et al. Int J Radiation Oncology Biol Phys 69(5):1472-1477, 2007

Strength of evidence for RT for clinically localized prostate cancer

Comparisons	Disease specific survival	Freedom from biochemical failure	GU/GI toxicity
RT vs NT	insuff	insuff	insuff
SBRT vs EBRT	insuff	insuff	insuff
SBRT vs HDRBT	insuff	insuff	insuff
SBRT vs LDRBT	insuff	insuff	insuff
EBRT vs HDRBT	insuff	insuff	insuff
EBRT vs LDRBT	insuff	insuff	insuff
HDRBT vs LDRBT	insuff	insuff	insuff
Combined mod.	insuff	insuff	insuff
Intra SBRT	insuff	insuff	insuff
Intra EBRT	insuff	moderate	moderate
Intra LDRBT	insuff	insuff	insuff

Conclusions

- insufficient data to determine if RT is superior to no Tx or no initial Tx
- could not determine if one form of RT is superior to another form in terms of overall or disease-specific survival
- ▲ EBRT dose is associated with long-term biochemical control
- BT is associated with ▲ GU and ▼ GI toxicity compared with EBRT

Limitations

- paucity of high quality adequately powered RCTs
- variability in outcome measures (eg, definitions of biochemical failure)
- differences in baseline disease risk between comparison groups

Future research

- standardize outcome measures
- RCT
  - RT vs NT (2 ongoing – UK; Canada)
  - extreme hypofractionation (1-5) vs standard fractionation
  - BT vs EBRT
  - proton vs others
- safety data related to RT delivery

Acknowledgement

Mei Chung, MPH

Joseph Lau, MD

Ndidiamaka Obadan, MD, MSc

Kamal Patel, MPH, MBA

Winifred W. Yu, MS, RD