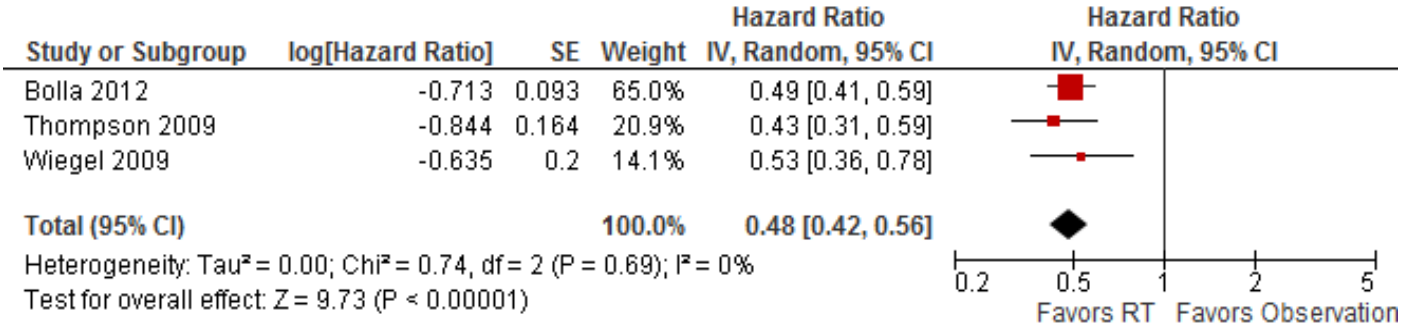
Appendix A. Meta-analysis of biochemical recurrence data from SWOG 879427, EORTC 2291125, and ARO 96-0226



Appendix B. Outcomes from Randomized Controlled Trials

(yellow highlighting = statistically significant comparison at p<0.05; green highlighting = borderline significant comparison at p<0.06)						
	SWOG 8794		**EORTC 22911**		**ARO 96-02**	
	RP + RT	**RP only**	**RP + RT**	**RP only**	**RP + RT**	**RP only**
Biochemical recurrence and **Biochemical recurrence-free survival**	60/172 (34.9%) recurrence 5 y bRFS: 71.0% 10 y bRFS: 53.0%	112/175 (64%) recurrence 5 y bRFS: 44.0% 10 y bRFS: 26.0%	198/502 (39.4%) recurrence 5 y bRFS: 74.0% 10 y bRFS: 60.6%	311/503 (61.8%) recurrence 5 y bRFS: 54.0% 10 y bRFS: 41.1%	38/148 (25.7%) recurrence 5 year bRFS: 72%	67/159 (42.1%) recurrence 5 year bRFS: 54%
	Comparison: HR = 0.43 (95% CI: 0.31-0.58; p<0.001)		Comparison: HR = 0.49 (95% CI: 0.41-0.59; p<0.001)		Comparison: HR = 0.53 (95% CI: 0.37 – 0.79; p=0.0015)	
Local recurrence, local recurrence-free survival, cumulative local relapse	15/190 (8%) local recurrence at median 10.6 y	40/184 (22%) local recurrence at median 10.6 y	42/502 (8.4%) w/ locoregional failure 10 y cumulative local relapse rate: 7.3% (95% CI: 4.9-9.8%)	87/503 (17.3%) locoregional failure 10 y cumulative local relapse rate: 16.6% (95% CI: 13.1-20.1%)	NR	NR
	Comparison: no HR reported; p<0.01		Comparison: HR = 0.45 (95% CI: 0.32 – 0.68; p<0.0001)		NR	
Hormonal therapy-free survival (hTFS)	5 y hTFS: 90.0% 10 y hTFS: 84.0%	5 y hTFS: 79.0% 10 y hTFS: 66.0%	NR	NR	NR	NR
	Comparison: HR = 0.45 (95% CI: 0.29 – 0.68; p<0.001)		NR		NR	
Metastases, **Metastases-free survival (mRFS), cumulative**	93/214 (43.5%) had metastases or died of any cause	114/211 (54%) had metastases or died of any cause	55/502 (11.0%) had distant metastases 10 y cumulative metastatic rate:	57/503 (11.3%) had distant metastases 10 y cumulative metastatic rate:	4/148 (2.7%) had distant metastases at median 4.5 y	5/159 (3.1%) had distant metastases at median 4.5 y

metastatic rate	20/214 (9.3%) had metastases 5 y mRFS: 88% 10 y mRFS: 71%	37/211 (17.5%) had metastases 5 y mRFS: 84% 10 y mRFS: 61%	10.1% (95% CI: 7.2-13.0%)	11% (95% CI: 8.0-14.0%)		
	Comparison: HR = 0.71 (95% CI: 0.54 – 0.94; p=0.016)		Comparison: HR = 0.99 (95% CI: 0.67 – 1.44; p=0.94)		NR	
Clinical progression and clinical progression-free survival (cPFS); does not include bRFS	84/214 (39.3%) clinical progression or death at median 10.6 y 10 y cPFS: 70%	111/211 (52.6%) clinical progression or death at median 10.6 y 10 y cPFS: 49%	157/502 (31.3%) clinical progression or death at median 10.6 y 10 y cPFS: 70.3%	181/503 (36.0%) clinical progression or death at median 10.6 y 10 y cPFS: 64.8%	NR	NR
	Comparison: HR = 0.62 (95% CI: 0.46 – 0.82; p=0.001)		Comparison: HR = 0.81 (95% CI: 0.65 – 1.01; p=0.054)		NR	
Deaths from cancer and cancer-specific survival	NR	NR	25/502 (5.0%) deaths from prostate cancer 10 y cumulative prostate cancer mortality rate: 3.9% (95% CI: 2.0-5.7%)	34/503 (6.8%) deaths from prostate cancer 10 y cumulative prostate cancer mortality rate: 5.4% (95% CI: 3.2-7.5%)	NR	NR
	NR		Comparison: HR = 0.78 (95% CI: 0.46 – 1.33; p=0.34)		NR	
Overall survival (OS)	88/214 (41.1%) deaths at median 12.7 y 10 y OS estimate: 74.0%	110/211 (52.1%) deaths at median 12.5 y 10 y OS estimate: 66.0%	130/502 (25.9%) deaths at median 10.6 y 10 y OS estimate: 76.9%	115/503 (22.9%) deaths at median 10.6 y 10 y OS estimate: 80.7%	5/148 (3.4%) deaths at median 4.5 y	8/159 (5.0%) deaths at median 4.5 y
	Comparison: HR = 0.72 (95% CI: 0.55 – 0.96; p=0.023)		Comparison: HR = 1.18 (95% CI: 0.91 – 1.53; p=0.20)		NR	

Appendix C: Risk Factor Subgroup Findings from RCTs

(all comparisons statistically significant at p<0.05 unless otherwise noted)			
	SWOG 8794	**EORTC 22911**	**ARO 96-02**
Gleason 2-6	**Met RFS:** Obs. = RT[**] (HR approx. 0.90, CI 0.55-1.50)	**Biochem RFS:** Obs < RT[****] (HR approx. 0.44; CI 0.26-0.82)	**Biochem RFS:** Obs < RT[†] (HR 0.42, CI 0.20-0.89)
Gleason 7-10	**Met RFS:** Obs. < RT[**] (HR approx. 0.58, CI 0.35-0.92)	**Biochem RFS:** -Gleason 7: Obs < RT[****] but dif n.s. (HR approx. 0.63; CI 0.38-1.00) -Gleason 8-10: Obs < RT[****] but dif n.s. (HR approx. 0.52; CI 0.26-1.20)	**Biochem RFS:** Obs < RT[†] (HR 0.59, CI 0.37-0.95)
No SVI	*Not reported*	**Biochem RFS:** Obs. < RT[***] (HR 0.43, CI 0.35-0.54) **Clin RFS:** Obs. = RT[***] (HR 0.8; CI 0.61-1.04) **Overall survival:** Obs. = RT[***] (HR 1.30, CI 0.95-1.77)	*Not reported*
SVI	**Biochem RFS:** Obs < RT[*] (HR 0.23, CI 0.06 to 0.84) **Met RFS:** Obs. < RT[**] but dif ns (HR approx. 0.68, CI 0.42-1.07) **Clin RFS:** Obs = RT[*] (HR 0.76, CI 0.33 to 1.74)	**Biochem RFS:** Obs. < RT[***] (HR 0.60, CI 0.44-0.82) **Clin RFS:** Obs. = RT[***] (HR 0.82; CI 0.58-1.16) **Overall survival:** Obs. = RT[***] (HR 1.00, CI 0.66-1.52)	**Biochem RFS:** Obs = RT[†] but dif n.s. (pT3c: HR 0.77, CI 0.42-1.40)
Negative margins	*Not reported*	**Biochem RFS:** Obs. < RT[***] (HR 0.61, CI 0.45-0.81) **Clin RFS:** Obs. = RT[***] (HR 1.08; CI 0.78-1.55) **Overall survival:** Obs. >	**Biochem RFS:** Obs = RT[†] (HR 0.95, CI 0.47-1.93)

		RT*** (HR 1.68, CI 1.10-2.56)	
Positive margins	**Biochem RFS:** Obs. < RT* (HR 0.44, CI 0.3 to 0.65)) **Clin RFS:** Obs < RT* (HR 0.64, CI 0.45 to 0.93)	**Biochem RFS:** Obs. < RT*** (HR 0.44, CI 0.35-0.75) **Clin RFS:** Obs. < RT*** (HR 0.69; CI 0.53-0.91) **Overall survival:** Obs. = RT*** (HR 0.98, CI 0.72-1.34)	**Biochem RFS:** Obs < RT† (HR 0.41, CI 0.25-0.66)
No EPE	*Not reported*	**Biochem RFS:** Obs. < RT*** (HR 0.51, CI 0.35-0.75) **Clin RFS:** Obs. = RT*** (HR 0.78; CI 0.49-1.24) **Overall survival:** Obs. = RT*** (HR 1.21, CI 0.70-2.08)	*Not reported*
EPE	*Not reported*	**Biochem RFS:** Obs. < RT*** (HR 0.49, CI 0.40-0.60) **Clin RFS:** Obs. = RT*** (HR 0.83; CI 0.65-1.05) **Overall survival:** Obs. = RT*** (HR 1.16, CI 0.88-1.54)	**Biochem RFS:** Obs < RT† (pT3a/b: HR 0.34, CI 0.19-0.64)
EPE or Positive margins	**Met RFS:** Obs. < RT** but dif n.s. (HR approx. 0.73, CI 0.52-1.08)	*Not reported*	*Not reported*
SVI and Positive margins	**Biochem RFS:** Obs < RT* (HR 0.40, CI 0.20-0.77) **Clin RFS:** Obs < RT* (HR 0.47, CI 0.27-0.81)	*Not reported*	*Not reported*
Age	*Not reported*	**Biochem RFS:** -<65 y: Obs. < RT*** (HR 0.43, CI 0.33-0.56)	*Not reported*

		-65-69 y: Obs. < RT*** (HR 0.46, CI 0.34-0.61) -≥70 y: Obs. < RT*** but dif n.s. (HR 0.75, CI 0.52-1.08) **Clin RFS:** -<65 y: Obs. < RT*** (HR 0.57, CI 0.40-0.79) -65-69 y: Obs. = RT*** (HR 0.81, CI 0.57-1.15) -≥70 y: Obs. > RT*** (HR 1.78, CI 1.14-2.78) **Overall survival:** -<65 y: Obs. = RT*** (HR 0.91, CI 0.60-1.39) -65-69 y: Obs. = RT*** (HR 0.97, CI 0.65-1.44) -≥70 y: Obs. < RT*** (HR 2.94, CI 1.75-4.93)	

* Thompson[23]; median 10.6 years follow-up; all bRFS analyses conducted in patient subset of 348 who had post-RP PSA </= 0.4 ng/ml

** Thompson[26]; median 12.7 years follow-up for RT group; median 12.5 years follow-up for Observ group; all bRFS analyses conducted in patient subset of 348 who had post-RP PSA </= 0.4 ng/ml

*** Bolla[24]; median 10.6 years follow-up

**** Van der Kwast[310]; patient subset (n=552) of total eligible sample (n=972) who had central pathology review; included here are data from Fig. 2 which consists of only patient with post-RP PSA ≤ 0.2 ng/ml

† Wiegel[25]; median 4.5 years follow-up; 1992 AJCC – pT3a/b – EPE; pT3c – SVI

Appendix D: RTOG Acute and RTOG/EORTC Late Radiation Morbidity Scoring Criteria

	Acute		Late	
	Gastrointestinal	**Genitourinary**	**Gastrointestinal**	**Genitourinary**
Grade 0	No change	No change	None	None
Grade 1	Anorexia with ≤5% weight loss; nausea, abdominal discomfort, increased frequency or change in bowel habits, rectal discomfort; no need for medications	urinary frequency or nocturia that is twice pre-treatment levels, dysuria, urgency; no need for medications	mild diarrhea, mild cramping, bowel movement 5/day, slight rectal discharge or bleeding	slight bladder epithelial atrophy, minor telangiectasia (microscopic hematuria)
Grade 2	anorexia with ≤15% weight loss, nausea and/or vomiting or abdominal pain requiring medication, diarrhea requiring parasympatholytics, mucus discharge not requiring sanitary pads, rectal/abdominal pain requiring analgesics	urinary frequency or nocturia that is <1/hour, dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	moderate diarrhea and colic, bowel movement >5/day, excessive mucus or intermittent bleeding	moderate frequency, generalized telangiectasia, intermittent macroscopic hematuria
Grade 3	anorexia with >15% weight loss or nausea/vomiting or diarrhea requiring nasogastric (NG) tube or parenteral support; abdominal pain that is severe despite medications, hematemesis or melena, abdominal distension; severe mucus/blood discharge requiring sanitary pads	urinary frequency with urgency and nocturia hourly or more frequently with dysuria, pelvis pain or bladder spasm requiring regular frequent narcotics or gross hematuria with/without clot passage	Obstruction or bleeding requiring surgery	Severe frequency and dysuria, severe generalized telangiectasia (often with petechiae), frequent hematuria, reduction in bladder capacity (<150 cc)
Grade 4	ileus, subacute or acute obstruction, fistula, perforation, GI bleeding requiring transfusion, abdominal pain requiring tube decompression or bowel diversion	hematuria requiring transfusion, acute bladder obstruction not secondary to clot passage; ulceration or necrosis	Necrosis, perforation, fistula	Necrosis, contracted bladder (capacity <100 cc), severe hemorrhage, cystitis

Appendix E: Acute Toxicity Effects of Radiotherapy After Prostatectomy

(Ranges based on RTOG or CTCAE Grading Systems)				
	Genitourinary		Gastrointestinal	
Study Arm Type	**Grade 1-2**	**Grade 3-4**	**Grade 1-2**	**Grade 3-4**
Adjuvant	10.5 - 26%	2.0 - 8.0%	22.0 – 25.0%	0.0 – 2.0%
Salvage	3.0 - 82.0%	0.0 – 6.0%	2.9 – 96.0%	0.0 – 2.2%
Mixed	5.0 – 92.0%	0.0 – 3.0%	4.3 – 87.0%	0.0 – 1.3%

Appendix F: Late Toxicity Effects of Radiotherapy After Prostatectomy

(Ranges based on RTOG/EORTC or CTCAE Grading Systems)				
	Genitourinary		**Gastrointestinal**	
Study Arm Type	**Grade 1-2**	**Grade 3-4**	**Grade 1-2**	**Grade 3-4**
Adjuvant	2.0 – 22.0%	0.0 - 10.6%	1.0 – 12.7%	0.0 – 6.7%
Salvage	1.0 – 49.0%	0.0 – 6.0%	0.0 – 66.0%	0.0 – 18.0%
Mixed	1.3 – 79.0%	0.0 – 17.0%	2.0 – 59.0%	0.0 – 4.3%

Appendix G: 15-Year Biochemical Recurrence-Free Survival (%) in Men Treated with Radical Prostatectomy in the PSA era (adapted from Mullins[218])

Pathology Finding	Pathological Gleason Score		
	3 + 3	**3 + 4**	**≥ 4 + 3**
Organ-confined	99	86	79
No EPE; Margin +	94	75	67
EPE; Margin -	89	72	41
EPE; Margin +	75	45	27 (at 14 years)
SVI	39	39	15

Appendix H: 15-Year Metastatic Recurrence-Free Survival (%) in Men Treated with Radical Prostatectomy in the PSA era (adapted from Mullins[218])

Pathology Finding	**Pathological Gleason Score**		
	3 + 3	**3 + 4**	**≥ 4 + 3**
Organ-confined	100	98	92
No EPE; Margin +	100	100	50
EPE; Margin -	100	97	75
EPE; Margin +	100	88	73
SVI	86	93	38
EPE – extraprostatic extension; SVI – seminal vesicle invasion			

Appendix I: Abbreviations

3D-CRT	three-dimensional conformal radiotherapy
ADT	androgen deprivation therapy
ARO	Arbeitsgemeinschaft Radiologische Onkologie
ART	adjuvant radiotherapy
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
bRFS	biochemical recurrence-free survival
CCT	controlled clinical trial
CI	confidence interval
cPFS	clinical progression-free survival
CSS	cancer-specific survival
CT	computed tomography
CTCAE	Common Toxicity Criteria Adverse Event
DWE	diffusion weighted
EBRT	external beam radiotherapy
ED	erectile dysfunction
EORTC	European Organisation for Research and Treatment of Cancer

EPE[1]	extraprostatic extension
GC	Guidelines Committee
GI	gastrointestinal
GU	genitourinary
Gy	Gray
HR	hazard ratio
hRTS	hormonal therapy-free survival
IMRT	intensity-modulated radiotherapy
ml	milliliter
MR	magnetic resonance
mRFS	metastatic recurrence-free survival
MRI	magnetic resonance imaging
ng	nanogram
NNT	number needed to treat
OS	overall survival
PET	positron emission tomography
PGC	Practice Guidelines Committee
PIVOT	Prostate Cancer vs. Observation Trial

[1] The Panel selected the term "EPE" (meaning extraprostatic extension) instead of "ECE" (meaning extracapsular extension) based on reports that the prostate lacks a true capsule and the term "extraprostatic extension" is more accurate[310-12].

PSA	prostatic specific antigen
QoL	quality of life
QUADAS	quality assessment tool for diagnostic studies
RCT	randomized controlled trial
RFS	recurrence-free survival
RP	radical prostatectomy
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
SRT	salvage radiotherapy
STIR	short T1 inversion recovery
SVI	seminal vesicle invasion
SWOG	Southwest Oncology Group
y	years