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Platinum Priority – Review – Prostate Cancer

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Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: To date, there is no Level 1 evidence comparing the efficacy of radical prostatectomy and radiotherapy for patients with clinically-localized prostate cancer.
Objective: To conduct a meta-analysis assessing the overall and prostate cancer-specific mortality among patients treated with radical prostatectomy or radiotherapy for clinically-localized prostate cancer.
Evidence acquisition: We searched Medline, EMBASE, and the Cochrane Library through June 2015 without year or language restriction, supplemented with hand search, using Preferred Reporting Items for Systematic Reviews and Meta-Analysis and Meta-analysis of Observational Studies in Epidemiology guidelines. We used multivariable adjusted hazard ratios (aHRs) to assess each endpoint. Risk of bias was assessed using the Newcastle-Ottawa scale.
Evidence synthesis: Nineteen studies of low to moderate risk of bias were selected and up to 118 830 patients were pooled. Inclusion criteria and follow-up length varied between studies. Most studies assessed patients treated with external beam radiotherapy, although some included those treated with brachytherapy separately or with the external beam radiation therapy group. The risk of overall (10 studies, aHR 1.63, 95% confidence interval 1.54–1.73, $p < 0.00001$; $I^2 = 0\%$) and prostate cancer-specific (15 studies, aHR 2.08, 95% confidence interval 1.76–2.47, $p < 0.00001$; $I^2 = 48\%$) mortality were higher for patients treated with radiotherapy compared with those treated with surgery. Subgroup analyses by risk group, radiation regimen, time period, and follow-up length did not alter the direction of results.
Conclusions: Radiotherapy for prostate cancer is associated with an increased risk of overall and prostate cancer-specific mortality compared with surgery based on observational data with low to moderate risk of bias. These data, combined with the forthcoming randomized data, may aid clinical decision making.
Patient summary: We reviewed available studies assessing mortality after prostate cancer treatment with surgery or radiotherapy. While the studies used have a potential for bias due to their observational design, we demonstrated consistently higher mortality for patients treated with radiotherapy rather than surgery.

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1. Introduction

Nonconservative treatment options for patients diagnosed with clinically-localized prostate cancer include radical prostatectomy and radiotherapy [1]. Currently, there are no published randomized controlled trials comparing their efficacy. For patients desiring nonconservative treatment, established clinical guidelines recommend either treatment option and patients must ultimately decide for themselves which treatment to undertake [2,3].

Few reviews and meta-analyses have been published on this subject. Recent reviews have focused on patients with high-risk prostate cancer [4,5]. These have reported a benefit of radical prostatectomy over radiotherapy for both overall and prostate cancer specific mortality [4,5]. The limited scope of previous reviews and recent publication of a number of studies assessing prostate cancer-specific and overall survival for patients treated with contemporary forms of radiotherapy [6–8] requires a new, comprehensive meta-analysis.

Our objective was to systematically review and 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.

2. Evidence acquisition

2.1. Research question

Do patients treated with radical prostatectomy for clinically-localized prostate cancer have improved overall or prostate cancer-specific mortality compared with those treated with radiotherapy?

2.2. Types of studies

We included randomized controlled trials, cohort, and case-control studies. Case series lacking comparator groups were excluded. Other publications including editorials, commentaries, and review articles were excluded. Publications not subject to peer-review (ie, reports of data from vital statistics and dissertations or theses) were also excluded. Where there was more than one publication resulting from the same patient cohort, to prevent the duplication of patients from one cohort, for each of our analyses we selected one study based on a hierarchical assessment of comparability of study groups, time period of study (preference for more recent), and number of patients (Supplementary data).

2.3. Types of participants and exposure

We reviewed studies reporting on 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. We excluded studies assessing adjuvant or salvage therapies as the specific objective. We included studies irrespective of dose and duration of radiotherapy. In order to be included, studies had to have a comparison group comprising patients treated with radical prostatectomy. Studies assessing nonstandard treatments (such as cryotherapy) were excluded.

2.4. Outcome measures

The primary outcome was overall mortality and the secondary outcome was 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 [8,9], we considered studies only reporting multivariable adjusted hazard ratios (aHR). We excluded crude or unadjusted outcome measures since these would provide biased estimates given the known differences in age and comorbidity between patients treated with radiotherapy and surgery.

2.5. Methods of review

We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analysis of Observational studies in Epidemiology guidelines for reporting of this systematic review and meta-analysis [10,11].

2.6. Search strategy

Medline, EMBASE, and EBM Reviews Cochrane Central Register of Controlled Trials databases were searched using the OvidSP search platform for studies indexed from database inception to June 1, 2015 with the assistance of a professional librarian. We used both subject headings and text-word terms for "radical prostatectomy", "prostate cancer surgery", "radiotherapy", "outcome", "survival/mortality", and related and exploded terms including medical subject headings terms in combination with keyword searching. A full search strategy is presented in the Supplementary data. No limitations were placed with respect to publication language or publication year. Following the literature search, all duplicates were excluded. References from review articles, commentaries, editorials, included studies, and conference publications of relevant medical societies were reviewed and cross-referenced to ensure completeness. Conference abstracts were excluded.

2.7. Review methods

Two authors performed the study selection independently (C.J.D.W. and R.S.). Disagreements were resolved by consensus with the senior author (R.K.N.). Titles and abstracts were used to screen for initial study inclusion. Full-text review was used where abstracts were insufficient to determine if the study met inclusion or exclusion criteria. The final list of selected studies was agreed upon by urologists (C.J.D.W. and R.K.N.), radiation oncologists (R.C. and C.D.), and an epidemiologist (R.S.). One author (C.J.D.W.) performed all data abstraction including evaluation of study

characteristics, risk of bias, and outcome measures with independent verification performed by other authors.

2.8. Risk of bias assessment

We used the Newcastle-Ottawa Scale for risk of bias assessment. This scale assesses risk of bias in three domains [12]: (1) selection of the study groups; (2) comparability of groups; and (3) ascertainment of exposure and outcome [13]. Studies with scores ≥ 7 were considered as having a low risk of bias, scores of 4–6 as having a moderate risk of bias, and scores < 4 as having a high risk of bias. We assessed that follow-up was adequate if the median or mean follow-up was in excess of 5 yr.

2.9. Measures of treatment effect

We assessed the aHR for mortality for patients treated with radiotherapy and surgery.

2.10. Assessment of heterogeneity

We identified heterogeneity using the Q test, estimated it using the DerSimonian-Laird method, and quantified it using I^2 values [14]. Furthermore, we employed random-effects models for each of our analyses given the identified clinical heterogeneity.

2.11. Assessment of reporting bias

We assessed publication bias for outcomes with more than 10 included studies using funnel plots.

2.12. Data synthesis

Meta-analysis was performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) software. We used the inverse variance technique for meta-analysis of hazard ratios. Due to the clinical heterogeneity inherent in our data, random-effects models were used for all meta-analyses.

2.13. Subgroup analysis

We performed a number of a priori subgroup analyses. We planned subgroup analyses restricted to EBRT, IMRT, brachytherapy, and brachytherapy with EBRT boost. However, data were only available for subgroup analyses of EBRT, IMRT, and brachytherapy. We also performed subgroup analysis assessing the impact of: (1) prostate cancer risk stage (low, intermediate, and high); (2) duration of follow-up (<5 yr, 5–8 yr, >8 yr); (3) study era ("old" if the accrual started prior to 1990 or ended prior to 2005 and "newer" otherwise); and (4) study location (USA and rest of the world).

We did not encounter any issues with repeated measures, unit of analyses, or missing data.

3. Evidence synthesis

Our literature search identified 1624 unique references (Fig. 1). After full text review of 73 manuscripts, 19 were selected for inclusion. The reasons for exclusion are provided in Figure 1 and the Supplementary data. In particular, there were multiple publications arising from

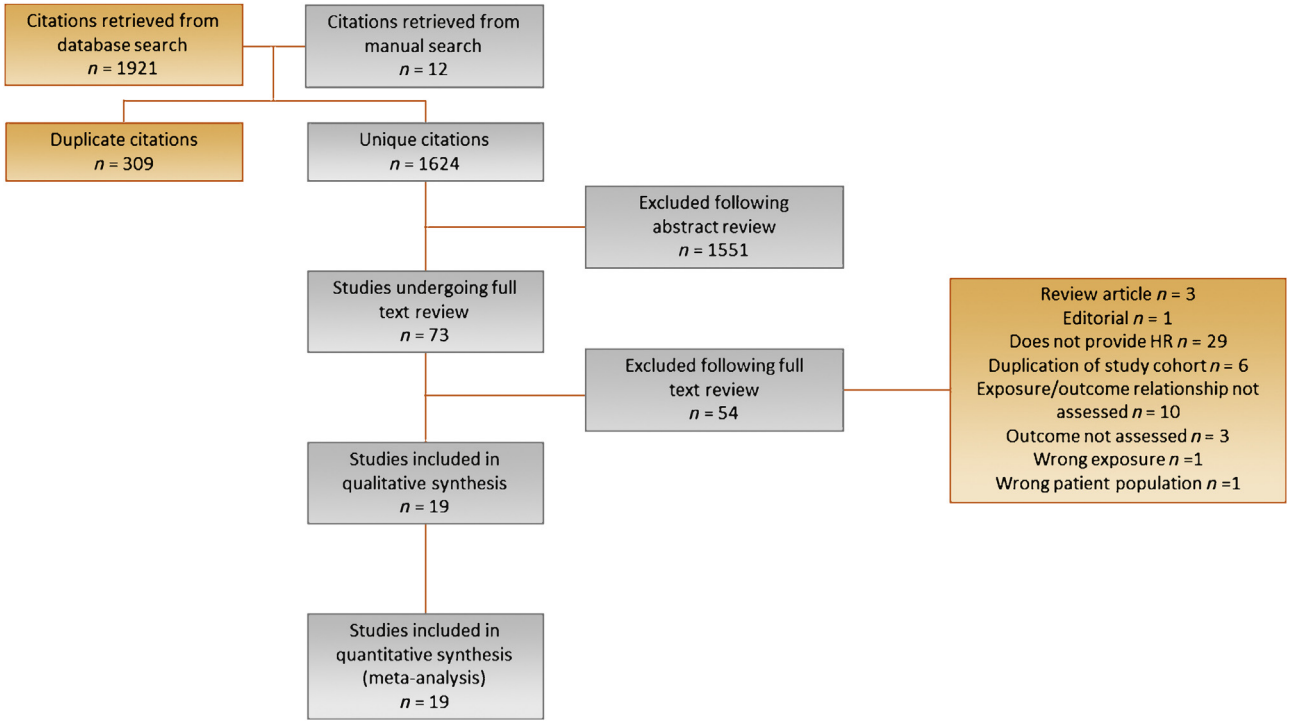

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram outlining search strategy and final included and excluded studies.

Table 1 – 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
Albersten (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 Centre, Duke University (1988–2008)	6.1 yr (RP) and 3.6 yr (XRT)	Low risk or intermediate risk[a]	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[a]	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 (1987–2007)	3.9 yr (RP) and 4.5 yr (XRT)	Clinically localized	EBRT	NA	6209[b]	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[a]	EBRT	median 64 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 (1989–2000)	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[c]	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 (1990–2009)	76 mo	Clinically localized high risk[a]	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

Merino (2013)	Pontificia Universidad Catolica de Chile (1999–2010)	92 mo (RP) and 76 mo (XRT)	Clinically localized	IMRT	76 Gy	1200	ADT: RP: 0% XRT: 42% Postop XRT: 5%	mean 63	mean 70	PCM
Rice (2013)	CPDR (1989–2009)	6.4 yr	Low risk[a], age > 70	EBRT	NA	446[d]	Not specified	mean 72.2	mean 74.1	OM
Sooriakumaran (2014)	PcBaSe Sweden (1996–2010)	5.4 yr	All	Unspecified	NA	32 846[e]	Not specified	median 62	median 66	PCM
Sun (2013)	SEER (1998–2005)	NR	Clinically localized, age 65–80	EBRT, brachy	NA	49 145[f]	Not specified	median 69	median 73	OM, PCM
Tewari (2007)	Henry Ford Health System (1980–1997)	68 mo (RP) and 54 mo (XRT)	Clinically localized, high risk[a], age < 75	Unspecified	NA	256[g]	ADT. RP: 18.5% XRT: 19%	mean 62.9	mean 68.0	OM, PCM
Westover (2012)	21st Century Oncology, Chicago Prostate Centre, Duke University (1988–2008)	4.6 yr	Clinically localized, Gleason score 8–10, age < 75	Combination EBRT+brachy	45 Gy EBRT + min 90–108 Gy brachy	657	ADT RP: 6% XRT: 100% Postop XRT: 6%	median 65	median 70	PCM
Zelefsky (2010)	Baylor College, Memorial Sloan Kettering (1993–2002)	5.1 yr (RP) and 5.0 yr (XRT)	T1c–T3b	IMRT	81 Gy (79%) or 86.4 Gy (21%)	2380	ADT RP: 1% XRT: 56% Postop XRT: 6%	median 60	median 69	PCM

3DCRT = 3-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; brachy = brachytherapy; CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor; CPDR = Center for Prostate Disease Research; EBRT = external beam radiotherapy; IMRT = intensity modulated radiotherapy; NA = not applicable; NR = not reported; OM = overall mortality; PCOS = Prostate Cancer Outcomes Study; PCM = prostate cancer mortality; RP = radical prostatectomy; SEER = Surveillance, Epidemiology and End Results; XRT = radiotherapy.

[a] Low risk prostate cancer = prostate specific antigen (PSA) < 10, Stage T1c–2a, Gleason score ≤ 6; intermediate risk prostate cancer = PSA 10–20, Stage T2b–c, Gleason score 7; high risk prostate cancer = PSA > 20, Stage >T3, Gleason score ≥ 8.

[b] Total study size is 7538, 6209 patients treated with either surgery or radiotherapy were included.

[c] Total study size is 31 903, 19 258 patients treated with either surgery or radiotherapy were included.

[d] Total study size is 770, 446 patients treated with either surgery or radiotherapy were included.

[e] Total study size is 34 502, 32 846 patients with nonmetastatic prostate cancer treated with either surgery or radiotherapy were included.

[f] Total study size is 67 087, 49 145 patients treated with either surgery or radiotherapy were included.

[g] Total study size is 453, 256 patients treated with either surgery or radiotherapy were included.

the same clinical cohorts over the same time period. To prevent the duplication of patients, a single study was chosen to represent each cohort for each comparison as outlined in the Supplementary data.

3.1. Study description

Three studies were from single centers, five were from multiple institutions, and the remaining 11 were from administrative databases (Table 1). The inclusion criteria and length of follow-up varied significantly between included studies (Table 1). Some studies imposed minimum age requirements while others imposed maximum age requirements which resulted in significant differences in age distribution between studies. Patients treated with radiotherapy were generally older in all of the included studies.

Most studies assessed the efficacy of EBRT with some including patients treated with brachytherapy. Two studies provided data restricted to patients treated with IMRT. The dosage of radiation was only available for eight of 19 (42%) studies. Brachytherapy dosage was in keeping with standard recommended doses, while only two studies provided "dose-escalated" EBRT treatments to all patients [7,15]. There was considerable variability in the use of adjuvant or salvage therapies. In some studies, patients receiving these treatments were excluded while in others all patients received adjuvant therapies.

Study inclusion criteria, including patient age and disease characteristics, significantly affected mortality rates for both all-cause and prostate cancer-specific mortality (Table 2). Overall mortality rates significantly exceeded prostate cancer-specific mortality, particular in patients with low-risk disease. Covariates included in the adjusted models varied significantly between studies though typically included age, clinical stage, Gleason score, and Charlson comorbidity (Supplementary Table 1).

3.2. Risk of bias assessment

The majority of included studies were felt to have low to moderate risk of bias (Table 3). Some studies used

Table 2 – 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% 10 yr high: 6.8%	10 yr low/int: 3.9% 10 yr high: 11.5%
Albersten (2007)	Clinically localized, age < 75	10 yr: 17%[a]	10 yr: 22%[a]	10 yr low: 3% 10 yr int: 6% 10 yr high: 10%	10 yr low: 7% 10 yr int: 12% 10 yr high: 20%
Arvold (2011)	Low risk or intermediate risk	NA	NA	10 yr low: 0.4%[a] 10 yr int: 0%[a]	10 yr low: 0.8%[a] 10 yr int: 3.5%[a]
Boorjian (2011)	High risk	10 yr: 23%	10 yr RT + ADT: 33% 10 yr RT: 48%	10 yr: 8%	10 yr RT + ADT: 8% 10 yr RT: 12%
Cooperberg (2010)	Clinically localized	NA	NA	10 yr: 5%[a]	10 yr: 12%[a]
DeGroot (2013)	"Candidate for therapy": low and intermediate risk	NA	NA	NA	NA
Hoffman (2013)	Clinically localized, age 55–74	15 yr: 35%[a]	15 yr: 58%[a]	NA	NA
Jeldres (2008)	Age > 70	10 yr: 40.7% 15 yr: 72.7%	10 yr: 69.7% 15 yr: 86.7%	NA	NA
Kibel (2012)	Clinically localized	10 yr: 11.1%	10 yr EBRT: 17.4% 10 yr brachy: 18.3%	10 yr: 1.8%	10 yr EBRT: 2.9% 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%[a]	10y r: 20%[a]
Merglen (2007)	Clinically localized	NA	NA	10 yr: 17%	10 yr: 25%
Merino (2013)	Clinically localized	5 yr: 3.8% 7 yr: 6.3%	5 yr: 11.6% 7 yr: 16.9%	7 yr: 1.9%	7 yr: 7.9%
Rice (2013)	Low risk, age > 70	10 yr: 18%[a]	10 yr: 30%[a]		
Sooriakumaran (2014)	All	10 yr low: 10%[a] 10 yr int: 15%[a] 10 yr high: 20%[a]	10 yr low: 16%[a] 10 yr int: 22%[a] 10 yr high: 30%[a]	10 yr low: 1%[a] 10 yr int: 3%[a] 10 yr high: 8%[a]	10 yr low: 1%[a] 10 yr int:8%[a] 10 yr high: 15%[a]
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.

[a] Denotes that estimate is imputed from a graph or figure in the original manuscript.

Table 3 – Newcastle-Ottawa Scale for risk of bias assessment of studies included in the meta-analysis

Study	Selection				Comparability	Outcome			Overall
	Representativeness of exposed cohort	Selection of nonexposed	Ascertainment of exposure	Outcome not present at start		Assessment of outcome	Adequate follow-up length	Adequacy of follow-up	
Abdollah (2012)	☆	☆	☆	☆	☆☆	☆			7
Albertsen (2007)	☆	☆	☆	☆	☆☆	☆	☆		8
Arvold (2011)	☆		☆	☆	☆☆				5
Boorjian (2011)	☆		☆	☆	☆☆	☆	☆		7
Cooperberg (2010)	☆	☆	☆	☆	☆☆	☆			7
DeGroot (2013)	☆	☆	☆	☆	☆☆	☆	☆		8
Hoffman (2013)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Jeldres (2008)	☆	☆	☆	☆	☆☆	☆	☆		8
Kibel (2012)	☆	☆	☆	☆	☆☆	☆	☆		8
Ladjevardi (2010)	☆	☆	☆	☆	☆☆	☆		☆	8
Lee (2014)	☆	☆	☆	☆	☆☆	☆	☆		8
Merglen (2007)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Merino (2013)	☆	☆	☆	☆	☆☆		☆		7
Rice (2013)	☆	☆	☆	☆	☆☆	☆	☆		8
Sooriakumaran (2014)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Sun (2013)	☆	☆	☆	☆	☆☆	☆		☆	7
Tewari (2007)	☆	☆	☆	☆	☆☆	☆			7
Westover (2012)	☆		☆	☆	☆☆	☆			6
Zelefsky (2010)	☆		☆	☆	☆☆	☆		☆	7

radiotherapy and surgery patients from different clinical centers, thus introducing the risk of a selection bias. The adequacy of follow-up was often not described in the included studies which raise concern for attrition bias.

3.3. *Overall mortality*

Ten studies reporting on 95 791 patients were aggregated to assess the effect of treatment modality on overall mortality.

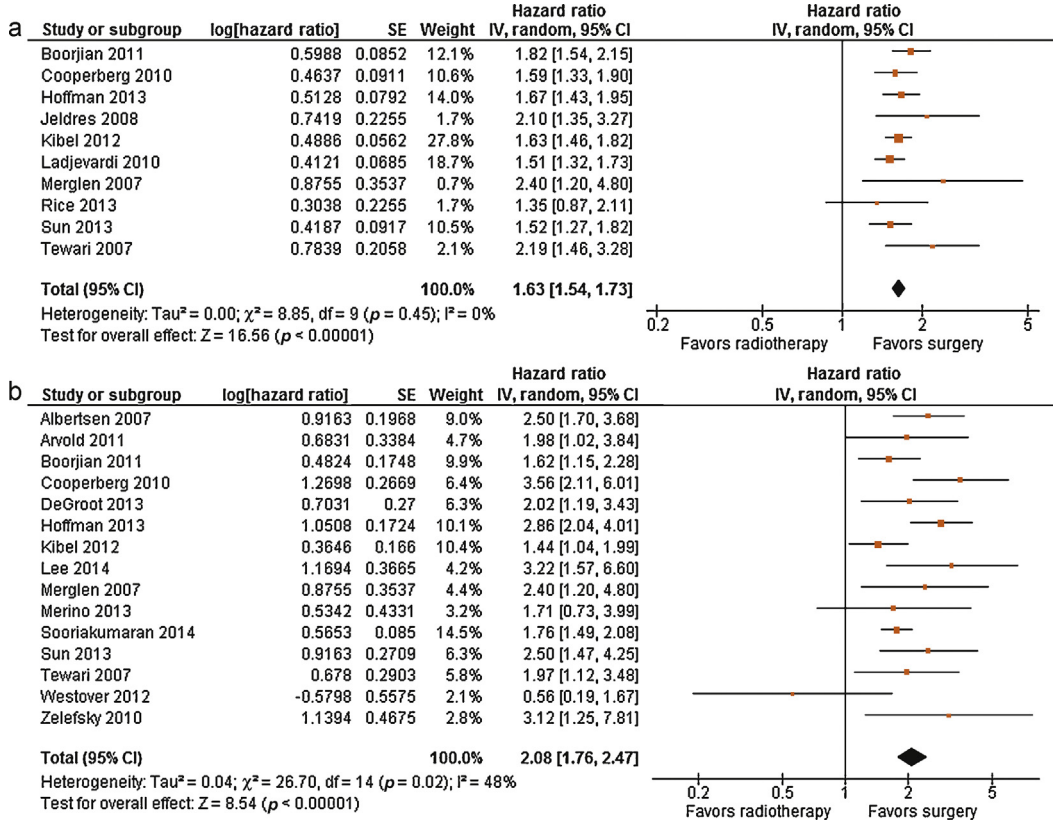

Fig. 2 – Forrest plot assessing the risk of (a) overall mortality and (b) prostate cancer-specific mortality following radiotherapy and surgery for prostate cancer.
CI = confidence interval; IV = inverse variance; SE = standard error.

Table 4 – Subgroup analysis assessing risk of overall mortality and prostate 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.

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, $p < 0.00001$; $I^2 = 0\%$; Fig. 2a). Where authors provided outcome data for patients treated with radiotherapy alone and radiotherapy with androgen deprivation therapy (ADT), we used the aggregate results for both groups.

We found a similar direction of effect when we examined patients with low risk prostate cancer (aHR 1.47, 95% CI 1.19–1.83, $p = 0.0004$, $I^2 = 59\%$), intermediate risk prostate cancer (aHR1.50, 95% CI 1.24–1.82, $p < 0.0001$; $I^2 = N/A$), or high risk prostate cancer (aHR 1.88, 95% CI 1.64–2.16, $p < 0.00001$; $I^2 = 0\%$).

Further subgroup analyses did not differ in direction from the primary results (Table 4). Patients treated with radiotherapy who were treated in the earlier era (study accrual period prior to 2005) had similar outcomes to those treated in the newer era ($p = 0.14$; Table 4). While assessing by radiotherapy modality, we found a similar risk for patients treated with EBRT (conformal radiation therapy [CRT] or IMRT) and with brachytherapy (Table 4). No studies were identified that reported on the risk of overall survival while comparing IMRT to surgery. There were no "between group" differences observed with respect to duration of follow-up ($p = 0.24$; $I^2 = 30\%$; Table 4). One study did not report follow-up duration. Similarly, there were no differences between the treatment eras ($p = 0.14$; $I^2 = 53\%$). Finally, there was no difference observed whether the study cohort was from the USA or the rest of the world ($p = 0.52$; $I^2 = 0\%$; Table 4).

3.4. 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, $p < 0.00001$; $I^2 = 48\%$; Fig. 2b) compared with those treated with surgery.

We found similar results when we examined only patients with low risk prostate cancer (aHR 1.70, 95% CI 1.36–2.13, $p < 0.00001$; $I^2 = 0\%$), intermediate risk prostate cancer (aHR1.80, 95% CI 1.45–2.25, $p < 0.0001$; $I^2 = 0\%$), or high risk prostate cancer (aHR 1.83, 95% CI 1.51–2.22, $p = 0.0001$; $I^2 = 42\%$).

Subanalyses for this endpoint also had similar direction of results to the primary analysis. We observed no between-subgroup differences when examining the effect of study era ($p = 0.85$; $I^2 = 0\%$; Table 4). Assessing the effect of specific radiotherapy modalities, we found an increased risk for those treated with EBRT (CRT or IMRT), IMRT alone, and brachytherapy alone (Table 4). There were no "between-group" differences observed with respect to duration of follow-up ($p = 0.47$; $I^2 = 0\%$), although the magnitude of effect increased with increasing length of follow-up (Table 4). Two studies did not report follow-up duration. Similarly, results were consistent regardless of geographic location of publication ($p = 0.26$; $I^2 = 22\%$; Table 4).

3.5. Publication bias

We assessed publication bias using funnel plots comparing effect size and measure of precision of the effect size for the main analysis of our primary and secondary analyses (Supplementary Fig. 1). We did not identify any evidence of publication bias.

4. Discussion

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

clinically localized prostate cancer. These findings were supported with subgroup analyses which assessed the impact of prostate cancer risk category, radiotherapy modality, duration of follow-up, era of study accrual, and geographic region.

To our knowledge, this represents the most comprehensive and up-to-date review on this topic. Petrelli et al [5] conducted a meta-analysis examining the survival outcomes among patients with only high risk prostate cancer treated with surgery or radiotherapy [5]. They found better overall and prostate cancer-specific survival for patients treated with surgery compared with radiotherapy. A key limitation of this study was that they used adjusted and unadjusted odds ratios which do not take into account the time-to-event outcome measures as our study has done [16]. Other recent reviews have been restricted to randomized controlled trials [17], to high-risk patients [4], or did not provide aggregate risk estimates [18].

Two small randomized controlled trials have compared survival outcomes for patients treated with surgery or radiotherapy for prostate cancer [19,20]. These were largely underpowered and have not been used to guide treatment decision making. Other trials have closed prematurely due to poor accrual [21] because of patients' unwillingness to leave their treatment to chance [22].

We performed a number of prespecified subgroup analyses to explore potential areas of bias, but analyses stratified by prostate cancer risk category, radiotherapy modality, duration of follow-up, era of study accrual, and geographic region did not differ from the overall analysis. Recently, radiation dose escalation was associated with improved overall survival in patients with intermediate- and high-risk prostate cancer compared with standard dosing [23]. While we were not able to ascertain specific radiation doses from many studies, the majority of included patients were treated with standard-dose regimens. Zelefsky et al [15] used dose-escalated IMRT (>81 Gy) and found results similar to the other included studies.

We found statistically significant between-study heterogeneity for our pooled analysis of prostate cancer-specific mortality, but not overall mortality. This is likely due to increased uncertainty and methodologic differences in assigning cause of death. Some studies used administrative death records. Other studies used outcome determination at the discretion of the treating physician [15,24], and yet others used a combination of death certificates and physician correspondence [25,9].

Major strengths of this review include a comprehensive search strategy, careful selection of studies, critical and thorough quality appraisal of included studies, a priori subgroup analyses, and the use an outcome measure which incorporates the time-to-event nature of the data and adjusts for known confounders. A meta-analysis depends on the validity of the included studies to draw accurate conclusions. Therefore, a key limitation of our study is the effect of residual confounding as this analysis is based on observational data. It is well established that patients treated with radiotherapy tend to be older and have a higher level of comorbidity. As the vast majority of the included studies measured comorbidity using the Charlson comorbidity index, there remains the potential for heterogeneity within the categories resulting in residual confounding. Giordano et al [26] postulate that this may be driven by unmeasured differences in functional status and self-reported health. While current statistical methodologies such as regression and matching are unable to fully adjust for selection bias and unmeasured confounders [26], we only used multivariable aHRs in our study in an attempt to provide more accurate risk estimates. Also, the use of salvage therapies may explain some of the survival differences between the groups. Patients initially treated with surgery may undergo salvage radiotherapy while patients who fail after radiotherapy are less often offered salvage surgery. In contrast, patients with recurrence following radiotherapy are typically managed with ADT. In the included studies, the use of adjuvant or salvage radiotherapy varied—many did not specify the use of this therapy, some excluded these patients, and usage ranged from 3–10% in the remainder. Additionally, the use of ADT, either as adjuvant or salvage therapy, varied widely as expected given the heterogeneity of prostate cancer disease characteristics included. ADT usage was higher in patients treated with radiotherapy in the vast majority of studies. This is in keeping with expectations as the use of neoadjuvant, concurrent, or adjuvant ADT is often part of standard care in the radiotherapy setting, as its benefit has been shown in several large randomized radiotherapy studies. Also, for overall survival, there were insufficient data to assess the efficacy of IMRT, which has largely supplanted three-dimensional CRT in many jurisdictions [27]. Finally, a pathological review is rarely undertaken in large databases. As a result, heterogeneity may exist within pathological grading in these data sources due to interobserver variability.

Implications for future research assessing the comparative efficacy of surgery and radiotherapy in prostate cancer will largely depend on the results of the upcoming randomized ProtecT trial [28]. Clinical implications will likely depend on the congruence of the observational and randomized data. Prospective data derived from randomized controlled trials will allow for better management of confounding in addition to allowing for longitudinal quality-of-life assessment which is unavailable from large administrative datasets. As is emphasized in current clinical guidelines, both treatment modalities should be discussed with eligible patients prior to initiation of either therapy [1]. Given that current clinical guidelines do not discriminate patients by age and comorbidity level, the results of this study would be an important consideration for patients and physicians.

5. Conclusions

We identified an increased risk of overall and prostate cancer-specific mortality for patients treated with radiotherapy compared with surgery after adjustment for common patient and tumor prognostic factors. Methodologic limitations of the observational studies included should be considered while interpreting these results.

Author contributions: Christopher J.D. Wallis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: CJDW, RC, CD, RKN.
Acquisition of data: CJDW, RS.
Analysis and interpretation of data: CJDW, PSS.
Drafting of the manuscript: CJDW, PSS, RKN.
Critical revision of the manuscript for important intellectual content: RS, RC, SH, RTK, RS, CD.
Statistical analysis: CJDW, PSS.
Obtaining funding: RKN.
Administrative, technical, or material support: PSS, RKN.
Supervision: RTK.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2015.11.010.

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