Radical Prostatectomy or Radiotherapy in High-Risk Prostate Cancer: A Systematic Review and Metaanalysis

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Abstract

Background: Radical prostatectomy (RP) is one of the treatment options for localized, high-risk prostate cancer (PC), but it has never been compared with external beam radiotherapy (RT), which is an alternative approach, in a large randomized trial. To compare the outcomes of patients treated with surgery versus RT, we performed a metaanalysis of available studies on this topic. **Materials and Methods:** We performed a search of MEDLINE, EMBASE, Web of Science, SCOPUS, and The Cochrane Central Register of Controlled Trials (CENTRAL) for randomized or observational studies that investigated overall survival (OS) and PC-specific mortality (PCSM) risks in relation to use of surgery or RT in patients with high-risk PC. Fixed- and random-effect models were fitted to estimate the summary odds ratio (OR). Between-study heterogeneity was tested using χ^2 statistics and measured using the I^2 statistic. Publication bias was evaluated using a funnel plot and Egger regression asymmetry test. **Results:** Seventeen studies were included (1 randomized and 16 retrospective). RP was associated with improved OS (OR, 0.51; 95% confidence interval [CI], 0.38-0.68; $P < .00001$), PCSM (OR, 0.56; 95% CI, 0.37-0.85; $P = .007$), and non-PCSM (OR, 0.53; 95% CI, 0.35-0.8; $P = .002$) compared with RT. Biochemical relapse-free survival rates were similar to those of RT. **Conclusion:** Overall and cancer-specific mortality rates appear to be better with RP compared with RT in localized, high-risk PC. Surgery is also associated with a 50% decreased risk of non-PCSM compared with RT.

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Introduction

Radical retropubic prostatectomy (RP) is one treatment of choice in localized prostate cancer (PC) with low to intermediate risk features according to D'Amico classification.[1] Conversely, radiotherapy (RT) with androgen deprivation therapy (ADT) is considered the standard of care in high-risk/locally advanced or unresectable PC. In particular, for localized PC (≥ cT2c) (defined as high-risk cancer, based on a serum prostate-specific antigen [PSA] > 20 ng/mL or a Gleason score of 8-10), treatment options include RT (which is usually combined with ADT for 2-3 years) or, in selected patients, RP plus pelvic lymph node dissection.[2,3] In this case, RP is rarely the sole treatment modality, because poor-risk PC often requires additional adjuvant therapy to prevent local relapse or metastatic (biochemical or clinical) failure.

For example, among 7591 consecutive patients who underwent RP between 1987 and 2003, Boorjian et al found that the hazard ratio (HR) for death from PC after surgery in patients with high- or intermediate-risk disease was 11.5 (95% confidence interval [CI], 5.9-22.3; $P < .0001$) and 6.3 (95% CI, 3.3-12.3; $P < .0001$), respectively, compared with patients at low risk.[4] According to leading guidelines, surgery is not generally recommended in patients with life expectancies of < 10 years.[2,3] However, in patients with an estimated life expectancy ≥ 10 years at initial diagnosis, RP is apparently associated with improved survival compared with RT and observation, regardless of disease stage, according to a large Surveillance, Epidemiology, and End Results (SEER) database.[5]

In fit patients with reasonable life expectancy and no relevant competing cause of death, RP as a single treatment modality is associated with a good chance of survival. Yossepowitch et al showed

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that 10-year PC-specific mortality (PCSM) in high risk patients ranged from 3% to 11%.[6] In a series of 752 high risk patients, PCSM with external beam RT as a single treatment modality was 19% at 7 years. RT was administered (with no brachytherapy boost) either using 3-D RT or intensity modulated radiotherapy, with doses ranging from 66 to 86 Gy.[7] Dose, age, and neoadjuvant ADT were influential covariates associated with survival.

However, until now, no proper large, randomized, controlled trial has compared RP with RT directly in localized high-risk PC. In a small study, 95 patients with locally advanced PC were randomized to RP with ADT or RT with ADT.[8] At a median follow-up of 102 months, the 2 modalities showed similar results for survival and relapse. In a large cohort of 68,665 patients with localized PC, treated with RP or RT between 1992 and 2005, patients treated with surgery experienced a better outcome than those treated with RT.[9] In particular, those with high-risk PC benefitted the most from RP, even after adjusting for risk group, comorbidity, and age. Therefore, it is conceivable that fit and young, high-risk PC patients could be candidates for radical surgery, with satisfactory survival rates.

We performed a systematic review and metaanalysis of available studies to compare the survival rates of RP and RT in patients with high-risk PC.

Materials and Methods

This systematic review and metaanalysis was performed according to the recently published recommendations and checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the Preferred Reporting Items for Meta-Analysis of Observational Studies in Epidemiology recommendations for study reporting in the case of retrospective trials.[10]

Search Strategy and Study Selection

We carried out a search of the literature, using MEDLINE, EMBASE, SCOPUS, Web of Science, and The Cochrane Register of Controlled Trials (CENTRAL), to identify prospective or observational studies published from 1990 to August 2013 that investigated the outcomes of patients with high-risk PC treated with RP or RT. The following keywords and/or corresponding MeSH terms were used: (prostate cancer OR prostate carcinoma) AND (radiotherapy and prostatectomy) AND ((poor prognosis) or (high risk) or (poor risk) or (locally advanced)). The reference lists of reviews and metaanalyses published on this topic were also checked, to identify additional relevant publications. In addition, the Related Articles function was used to enrich the search.

Inclusion and Exclusion Criteria

Randomized or retrospective studies were included, provided that they (1) specifically mentioned that participants were affected by high-risk PC according to D'Amico classification; (2) investigated outcome after RP or external beam RT (with or without adjuvant treatment and without brachytherapy); (3) assessed either overall survival (OS) and/or PCSM (the primary end points) and/or the risk of biochemical relapse (b-RFS); and (4) reported crude or adjusted estimates of the association between treatment and outcome (that is, relative risk [RR], odds ratio [OR], HRs, and the corresponding 95% CI or P value), or sufficient raw data to perform the calculation. When multiple reports describing the same population were published, the most updated and complete report was used.

If the study did not separate the outcomes of high- and intermediate-risk patients, data were collected for the population overall. Studies were excluded if (1) they included patients treated with primary exclusive hormonal therapy; (2) they included patients treated with brachytherapy; (3) they included patients with metastatic disease; or (4) the publication was not in English. Two readers (FP and AC) independently determined the eligibility of each article for inclusion. Discrepancies between readers were resolved by the team.

Data Collection

For each included study, we extracted details on study design, publication year, median age, median follow-up, rate and characteristics of high-risk patients (PSA, Gleason score, clinical stage), oncological treatment types (eg, surgery, RT dose, adjuvant therapies), rate of deaths (due to PC or not), b-RFS rates, RRs (or other association measures if reported), and the corresponding 95% CI, and adjusted HRs per specific covariates, if available.

Statistical Methods

The summary ORs of patients who underwent RP or RT was the measure of interest, because of the retrospective nature of almost all of the studies. The primary end points were OS and PCSM, and the secondary end points were non-PCSM and b-RFS. Whenever possible, we pooled adjusted estimates from the original studies; otherwise, we used raw data and computed unadjusted ORs. We pooled the original estimates using the fixed-effects model and the random-effects model proposed by DerSimonian and Laird.[11] In the fixed-effects model, it is assumed that there is one true effect size that is shared by all of the included studies. It follows that the combined effect is the estimate of this common effect size. Conversely, in the random-effects model, the true effect could vary from study to study; thus, the study-specific estimates are assumed to be a random sample of the relevant distribution of effects, and the combined effect estimates the mean effect in this distribution. Heterogeneity between study-specific estimates was tested using the Q statistic, which is computed by summing the weighted squared deviations of each study estimate from the fixed-effects summary estimate.[12] When significant heterogeneity was found, the results from the random-effects model were presented. Moreover, the total variation across studies that is due to heterogeneity rather than chance was evaluated using the I^2 statistic.[13]

In the presence of a significant summary OR, an influence analysis was conducted by omitting 1 study at a time, to identify the extent to which the results were influenced by a single study (1-study-removed procedure). A meta-regression to explore whether a linear relationship exists between PCSM and specific covariates (as adjuvant ADT in RT arms, median age, rate of PSA $>$ 20 ng/mL, rate of $\geq$ cT2c tumors, and rate of Gleason scores 8-10 in surgery arms) was performed. Finally, publication bias was evaluated using funnel plot analysis and Begg and Egger tests.[14] For all hypothesis tests, evidence was based on $P < .05$, and the 95% CIs were therefore presented.

The corresponding calculations and graphical visualizations of Forest and funnel plots were respectively performed using Review Manager 5.1 (Review Manager version 5.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and Comprehensive Meta Analysis software (version 2.2.064).

Results

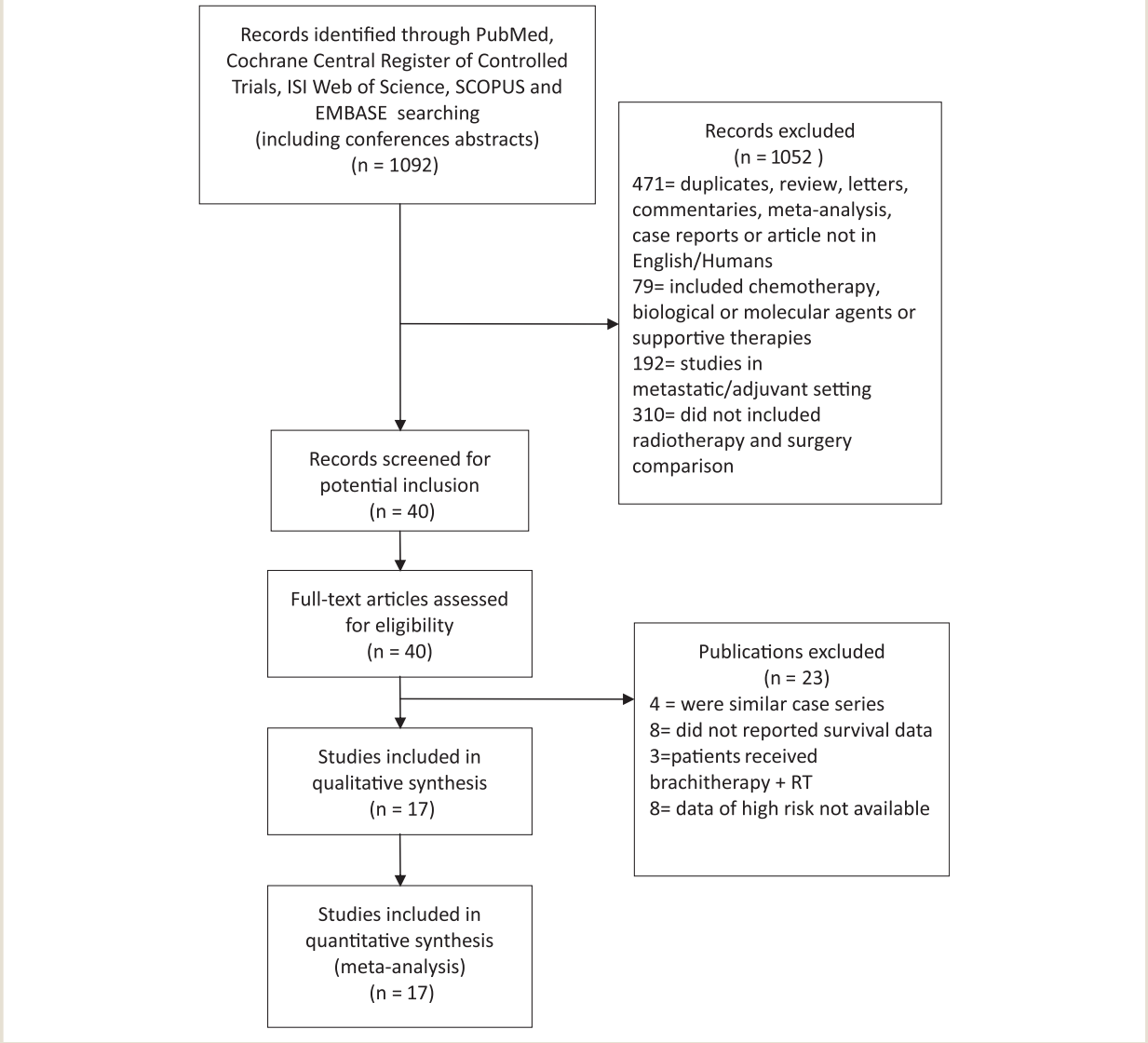
Figure 1 shows the flow diagram for study inclusion. On the basis of the search criteria, we identified 1092 papers. We excluded 1052 because they were not related to the study objective. The remaining 40 articles were considered of interest, and their full text was retrieved for detailed evaluation. Of these, 23 articles were further excluded because they did not satisfy the inclusion criteria. The remaining 17 studies[5,8,15-29] met the inclusion criteria and were considered for metaanalysis. The main characteristics of the studies that were included are reported in Table 1.[5,8,15-29] Overall, there were 16 retrospective series and 1 prospective, randomized trial. A total of 13,704 PC patients, treated with RP or RT, were included.

Primary End Points: OS and PCSM

Seven studies (1 prospective and 6 retrospective cohort studies, n = 8516 patients) reported OS data. The summary OR for RP versus RT was 0.51 (95% CI, 0.38-0.68; $P < .00001$; Fig. 2). There was high and significant heterogeneity among the studies, so a random-effects model was used ($P = .0009$; $I^2 = 74\%$).

Ten studies presented data for PCSM (1 prospective and 9 retrospective cohort studies, n = 11,297 patients). The summary OR

Figure 1 Selection of Publications Included in the Pooled Analysis



Abbreviation: RT = radiotherapy.

Table 1 Characteristics of the Included Studies

First Author/Year	Type of Study (Year of Diagnosis)	High-Risk Patients	Median or Mean Age, Years	S Arm	RT Arm	Median or Mean PSA, ng/mL	Adjuvant ADT, %	Adjuvant RT, %	Median Follow-Up, Months	Available Outcome Data				Adjusted HR for OS/PCSM (S vs. RT)
		S/RT	S/RT	cT/GS (%)	cT/GS, %, Dose, Gy	S/RT	S/RT	S/RT		OS	PCSM	Not PCSM	b-RFS	
Sun/2013[5]	Retrospective cohort SEER database (1992-2005)	3432/2158	70/73 (in overall population)[a]	100 cT2c/<8	100 cT2c/<8-NA	NA/NA	NA	0/NA	NA	X	X	X	—	0.54 and 0.63/0.14 ($P = .01$) and NA[b]
Hoffman/2013[15]	Observational cohort study (PCOS: 1994-1995)	381/56	48% versus 77%, age 65-74[c]	100 (PSA >10 ng/mL or GS ≥8)	100 (PSA >10 ng/mL or GS ≥8)-NA	NA	0/100	0/NA	15 years	X	X	X	—	0.65/0.36
Boorjian/2011[16]	Retrospective databases (1988-2004)	1238/609 (RT with ADT/RT)	66/68.8-69.3 (RT with ADT/RT)	33.2 cT3-4/37.5, GS 8-10	CT3-4 (42.7-31)/8-10 (47.7-20)-72 Gy	20.5/17.4-22 (RT with ADT/RT)	33.5/56	20.4/NA	10.2 (S)/6-7.3 (RT with ADT/RT) years	X	X	X	—	RT with ADT versus RP = 1.6; RT versus RP = 2.04; RT with ADT versus RP = 1.14; RT versus RP = 2.14
Takizawa/2009[19]	Retrospective cohort study (1998-2004)	24/37 ($P < .001$)	64.9/71.1	100 (cT3 or GS ≥8 or PSA >20 ng/mL)	100 (cT3 or GS ≥8 or PSA >20 ng/mL) to 70-71 Gy	NA	83.3/91.9	NA/NA	41	—	—	—	X	NA
Aizer/2009[17]	Retrospective cohort study (1997-2005)	42/117	12% versus 72%, >75 years	100 (>cT2b or PSA >10 ng/mL or GS ≥7)	100 (>cT2b or PSA >10 ng/mL or GS ≥7 to ≥72 Gy	4 versus 13 > 20 ng/mL in all cohorts	3 (all S cohort)/97.4	NA/NA	46 (S)/40 (RT)	—	—	—	X	HR b-RFS RT versus RP: 0.36
Arcangeli/2009[18]	Retrospective cohort study (2003-2007)	122/162	65.5/75	7 >cT2c/9 GS ≥8	9 >cT2c/25 GS ≥8; 80 Gy	47%/39% >20 ng/mL	NA/100	68/NA	33.8 (S)/38.6 (RT)	—	—	—	X	HR b-RFS RP versus RT = 2.47
Tsai/2006[22]	Retrospective databases (1981-2002)	2690/550	64/71	73 cT2/9 GS 8-10	60 cT2/24 GS 8 to 10-NA	14%/23% >20 ng/nL	0/100 (6 months)	0/NA	4.2 (S)/4.6 (RT)	—	X	—	—	NA
Tewari/2007[21]	Retrospective cohort study (1980-1997)	119/137	62.9/68.1	NA/100 GS ≥8	NA/100 GS ≥8-NA	NA	18.5/19	0/NA	68 (S)/54 (RT)	X	X	X	—	RR: 0.46/0.51

Table 1 Continued

First Author/ Year	Type of Study (Year of Diagnosis)	High-Risk Patients	Median or Mean Age, Years	S Arm	RT Arm	Median or Mean PSA, ng/mL	Adjuvant ADT, %	Adjuvant RT, %	Median Follow-Up, Months	Available Outcome Data				Adjusted HR for OS/PCSM (S vs. RT)
		S/RT	S/RT	cT/GS (%)	cT/GS, %, Dose, Gy	S/RT	S/RT	S/RT		OS	PCSM	Not PCSM	b-RFS	
Saito/2006[23]	Retrospective cohort study (1992-2003)	30/78	64/69.3	100 cT3/16 GS 8-10	100 cT3/28 GS 8-10, 69 Gy	80%/89% ≥10 ng/mL	100/100	0/NA	55	X	X	X	—	RR 1.186 (no vs. RP)
Nguyen/ 2009[20]	Retrospective cohort databases (1965-2002)	659/404 (RT with ADT/RT)	29% versus 65% >70 years	2.5 ≥cT2c/11 GS 8-10	14.6 ≥cT2c/17 GS 8-10, 70.2 Gy	7%/16.5% >20 ng/mL	0/29	0/NA	5.6 years	—	X	—	—	0.46/NA (RP vs. RT)
Akakura/ 2006[8]	Randomized controlled trial (1989-1993)	46/49	68.1/68.7	63 stage C/26 high grade	73 stage C/32 high grade, 60-70 Gy	19.9/21.6	100/100 (until PD or death)	NA/NA	102	X	X	X	—	NA
D'Amico/ 2003[24]	Retrospective cohort databases (1988-2002)	753/695	13 versus 54% >70 years in all cohorts	100 cT2c or GS 8-10 or PSA >20 ng/mL	100 cT2c or GS 8-10 or PSA >20-NA	7%/15% >20 ng/mL	100 (3 months)/0	0/NA	4.1 (S)/4.4 (RT) years	—	X	—	—	NA
Kupelian/ 2002[25]	Retrospective cohort study (1987-2000)	115/182	42 versus 75% ≥65 years	50 ≥cT2b/100 GS 8-10	58 ≥cT2b/100 GS 8-10, 74 Gy	27%/35% >20 ng/mL	16/23 (83% ≤6 months)	NA/NA	42	—	—	—	X	OR b-RFS RP versus RT = 1.39
D'Amico/ 2002[26]	Retrospective cohort study (1988-2000)	429/118	NA/NA	100 cT1c-T2/35 GS 8-10	100 cT1c-T2/35 GS 8-10, 70.4 Gy	40%/50% >20 ng/mL	0/0	0/NA	3 (S)/3.2 (RT) years	—	—	—	X	NA
Barry/2001[27]	Retrospective cohort study (1971-1984)	106/77	NA/NA	NA/100 GS 8-10	NA/100 GS 8 to 10-NA	NA	NA/10	NA/NA	NA	X	X	X	—	NA
Stokes/2000[28]	Retrospective cohort study (1988-1994)	134/95	NA	100 cTc-T3 or GS 7-10 or PSA >20 ng/mL	100 cTc-T3 or GS 7-10 or PSA >20 ng/mL, 65-70 Gy	NA	0/0	0/NA	73 (S)/75.5 (RT)	—	—	—	X	NA
Ciezki/2008[29]	Retrospective (1996-2007)	100/100	NA	36<cT3/NA[d]	53 <cT3/NA[d]	NA/NA[d]	18/90	NA/100	43	—	—	—	X	RT versus S ($P < .0001$ for b-RFS)

Abbreviations: ADT = androgen deprivation therapy; b-RFS = biochemical relapse; GS = Gleason score; HR = hazard ratio; OS = overall survival; PCOS = Prostate Cancer Outcomes Study; PCSM = prostate cancer-specific mortality; PD = progression of disease; PSA = prostate-specific antigen; RFS = relapse-free survival; RP = radical prostatectomy; RR = relative risk; RT = radiotherapy; S = surgery; SEER = Surveillance, Epidemiology, and End Results.

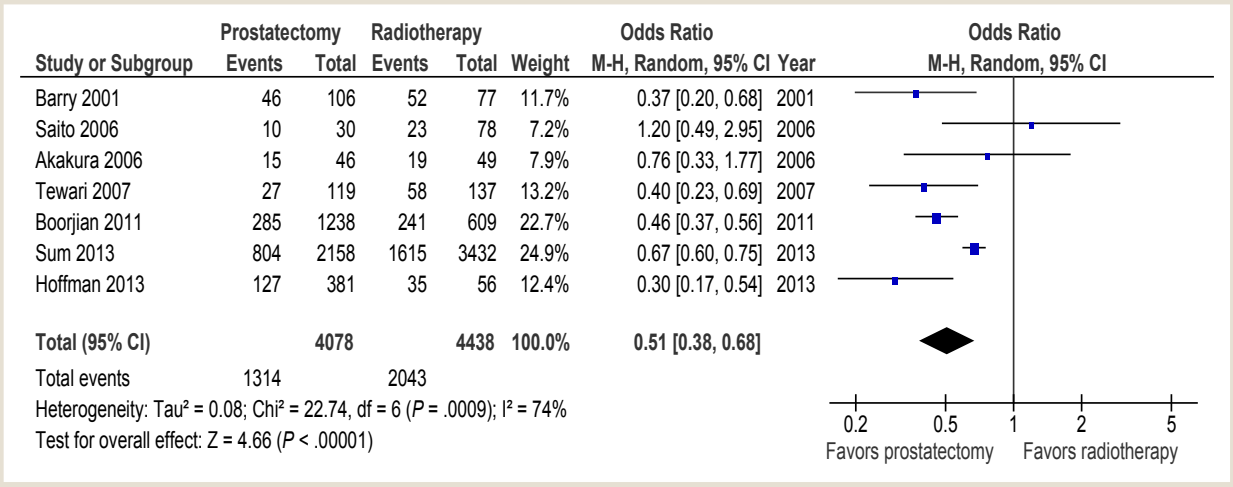
[a]Statistically significant.

[b]In patients with more or less than 10 years of life expectance.

[c]In all cohorts.

[d]All patients have a GS ≥ 8 and PSA ≥ 20 ng/mL or at least 2 of the following: cT2b/c, GS 7, or PSA 10-20 ng/mL.

Figure 2 Metaanalysis of Overall Survival



Abbreviation: M-H = Mantzel-Haenzel.

for RP versus RT was 0.56 (95% CI, 0.37-0.85; $P = .007$; Fig. 3). There was high and significant heterogeneity among the studies, so a random-effects model was used ($P < .00001$; $I^2 = 83\%$).

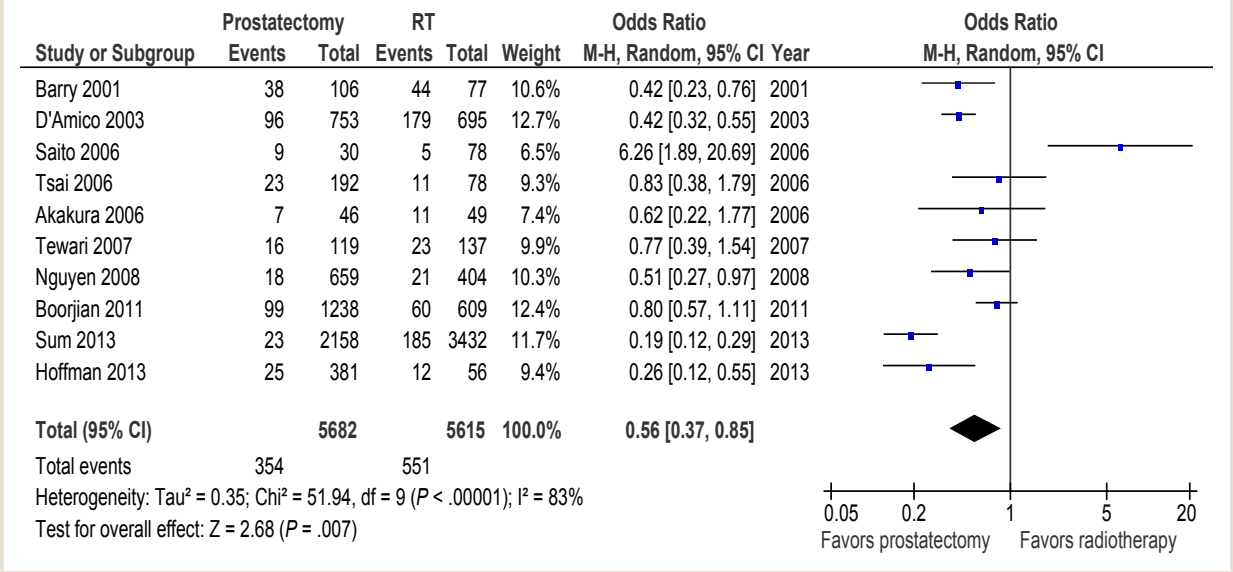
Three and 2 studies provided HRs for OS and PCSM, respectively, adjusted for covariates. The pooled HRs were 0.62 (95% CI, 0.48-0.8; $P < .0001$) and 0.31 (95% CI, 0.18-0.54; $P < .0001$), respectively.

A metaregression to explore if the PCSM was better as a function of patients not exposed to adjuvant ADT in RT arms was performed, but was not significant. Similarly, median age, median PSA, rate of Gleason score from 8 to 10, and rate of cT2c tumors, were not associated linearly with better PCSM.

Secondary End Points: Non-PCSM and b—RFS-Free Survival

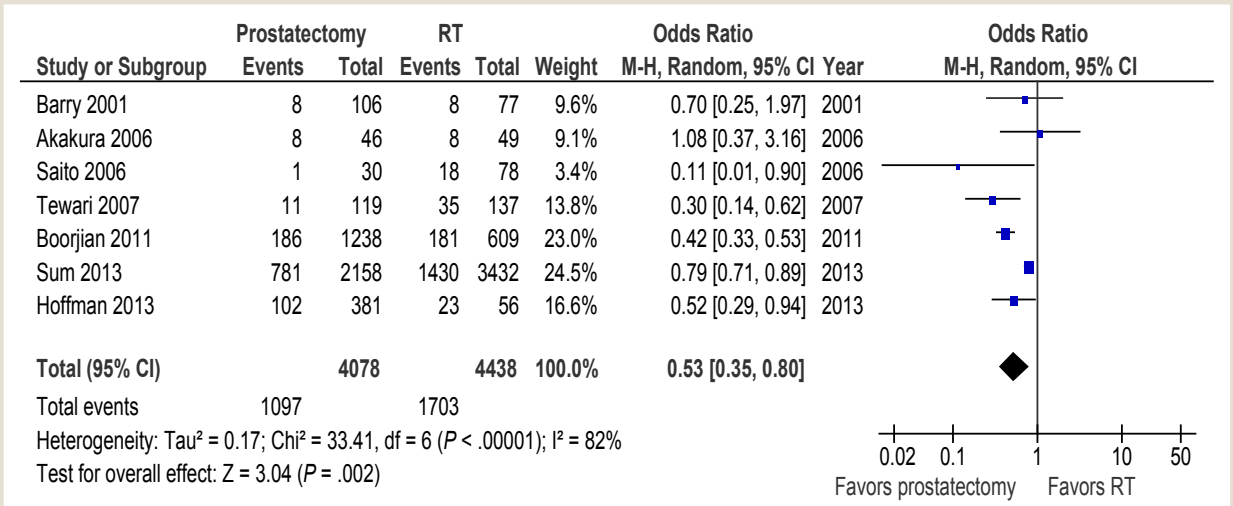
Seven studies permitted the calculation of non-PCSM (n = 8516 patients). Overall, the OR of non-PCSM was 0.53 (95% CI, 0.35-0.8; $P = .002$; Fig. 4). There was high and significant heterogeneity among the studies, so a random-effects model was used ($P < .00001$; $I^2 = 82\%$).

Figure 3 Metaanalysis of Prostate Cancer-Specific Mortality



Abbreviation: M-H = Mantzel-Haenzel.

Figure 4 Metaanalysis of Non-Prostate Cancer-Specific Mortality



Abbreviations: M-H = Mantzel-Haenzel; RT = radiotherapy.

Data for b-RFS were available in 8 studies (1 prospective and 7 retrospective, n = 2505). Overall, the risk of b-RFS was worse, but not significantly, with RP than with RT (OR, 1.44; 95% CI, 0.81-2.56; $P = .21$).

The results remained unaltered for OS and PCSM after the 1-study-removed procedure. No visible publication bias of OS analysis was found using funnel plot visualisation (Fig. 5A) and Begg ($P = .54$) and Egger ($P = .33$) tests. Similarly, Begg and Egger tests were not significant ($P = .15$ and $P = .39$, respectively) for PCSM (Fig. 5B).

Discussion

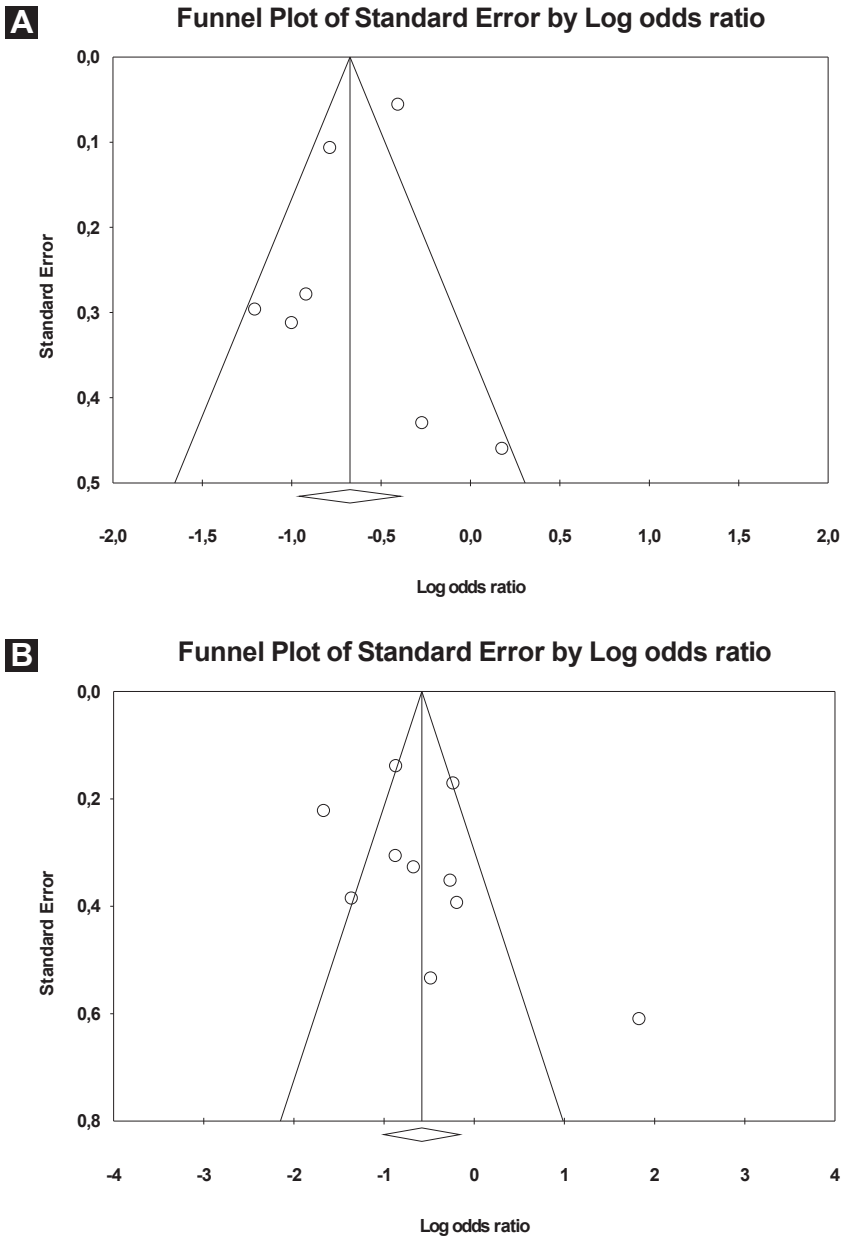
According to the leading international guidelines, radical RT plus ADT is 1 of the preferred treatment options for high-risk PC. However, RP is reserved for young and healthy patients with localized disease and high-risk features, if the tumor is not fixed to the adjacent structures. In the randomized PIVOT (Prostate Cancer Intervention versus Observation) trial, surgery was shown to be superior to observation alone in patients with localized PC. In particular, RP was associated with reduced overall mortality among men with a PSA value > 10 ng/mL and among those with intermediate-risk or high-risk tumors.[30] The choice of surgery or radiation for patients with high-risk PC and a long life expectancy has to be discussed with each subject with some retrospective data in mind. However, there are currently no randomized comparisons of RT (with or without ADT) and RP.

Our metaanalysis, which included all retrospective and prospective published trials that compared the outcomes of PC patients treated with RT or RP shows that surgery is associated with better OS, PCSM, and death not related to cancer than RT. Conversely, RT is associated with a slightly better b-RFS than RP alone. In particular, the OS and PCSM rates are 49% and 44% better, respectively, and non-cancer mortality is 50% lower with RP compared with RT. Comparing the 2 treatment modalities in a retrospective process is difficult, because of evident selection bias. In fact, most of the patients treated with RT were aged, with more comorbidities and adverse clinical PC features (eg, higher rate of Gleason score ≥ 8 PC and higher median PSA values) than surgically treated patients. As such, competing causes of death could have adversely biased the OS results of this metaanalysis. Briganti and colleagues have well demonstrated the link about older age and cause of death other than PC in patients with high-risk PC.[31] However, our analysis shows that metaanalysis of published HRs, adjusted for covariates such as age and comorbidities, results in a pooled risk reduction of approximately 40% for death and 70% for PC mortality, consistent with primary unadjusted ORs. These results are in line with a recent large observational Swedish/Dutch study of more than 35,000 patients treated with surgery or RT. Despite the limitation of a retrospective and biased analysis (RT patients were older and with higher Gleason score and PSA values), PCSM favored surgery for localized PC patients. Conversely, survival with RP and RT was similar only for patients with locally advanced/metastatic disease.[32]

Overall, the risk of PCSM is 14 times higher in surgery and RT cohorts of high-risk subjects compared with low-risk patients, as demonstrated by D'Amico et al.[24]

In a cohort of 11,000 patients in Sweden, after adjusting for age, comorbidity, Gleason score, T category and PSA level at the time of diagnosis, any curative treatment appears to be of benefit in high-risk patients (PSA 20-100 ng/mL and no distant metastasis) compared with any palliative therapy, with a dramatic reduction in cause-specific death.[33] There is no doubt that localized, high-risk PC is associated with satisfying survival with surgery alone, as shown in the PIVOT trial, in which PC mortality was 9% (compared with 17.5% with observation).[30] In a randomized phase III trial of a population with very high-risk PC (mainly cT3-4 or cT2 with elevated PSA levels), RT with ADT was associated with a 10-year survival rate of 55%, compared with 49% with ADT

Figure 5 Funnel Plot of Standard Error According to Log Odds Ratio. (A) Funnel Plot for Publication Bias for Overall Survival. (B) Funnel Plot for Publication Bias for Prostate Cancer-Specific Mortality



alone.[34] In the large SEER analysis of Abdollah et al, retrospectively comparing RT with RP, patients who underwent surgery fared better in all categories, but the largest benefit was in high-risk patients (absolute PCSM gain 2.5% vs. 4.7% in low-intermediate vs. high-risk).[9] In this last subgroup, the focus of our metaanalysis, the absolute non-PCSM was 21% versus 32.9% in the RP and RT groups, respectively; however, the patients in the RT cohort were older and had more comorbidities.

There is no formal confirmation in the literature that RT with ADT is comparable with RP in terms of outcome in young patients without comorbidity. A retrospective analysis of 6692 patients in 2 US centers showed that RT was associated with increased mortality compared with surgery, even if PCSM was the same.[35] If equivalence cannot be demonstrated, the absolute benefit of RP over RT should be observed properly in a high-risk population, as demonstrated by Cooperberg et al.[36]

Toxicity was not an end point of this metaanalyses because data were not reported, and only 1 randomized trial was included. In the Japanese study, incontinence (requiring more than 1 pad per day) was observed more frequently in the surgery group than in the radiation group. The other toxicities were similar, with comparable rates of erectile dysfunction likely due to hormonal therapy. In a

large series by Resnick et al from the Prostate Cancer Outcomes Study (PCOS), no significant differences in toxicity emerged, at 15 years, among RP and RT populations.[37] Concerns were raised for late risk of secondary (radiation-related) cancers in PC patients, too. In our series no detailed information was provided about reason for non-PC deaths, but relatively old RT techniques were used. A prospective series of 91 patients treated with modern intensity modulated radiotherapy techniques and followed for 12 months did report reduced bowel, sexual, and urinary functions that only slightly improved at 1 year.[38] A metaanalysis of dose escalation trials with intensity modulated radiotherapy (or protons) compared with classical 3-D RT, showed lower late gastrointestinal toxicity rates with modern (dose-escalated) RT than those associated with 3-D RT. Follow-up is too short, however, to explore the incidence of secondary cancers with actual treatments.[39]

As with other metaanalyses of observational studies, our results have some limitations. First, they are biased by physician choice of treatment in every cohort. We captured estimated OS according to adjustment for confounders, and available HRs confirmed the benefit of RP versus RT. In general, the clinical characteristics of patients treated with external beam RT are different from those of patients treated surgically; in particular, comorbidities could have influenced physician and patient preference. Thus, even correcting for different covariates, it is not possible to completely eliminate the potential of residual confounding, due to physician indication and patient choice. Second, in the included studies, the RT group consisted of PC patients who were likely older than the RP patients, treated with old RT techniques, and possibly, with suboptimal doses. Higher doses, in fact, have been proven to be associated with reduced biochemical recurrence, but similar mortality.[40] Third, the use of adjuvant therapies resulted in an imbalance between the 2 groups, with a larger number of patients treated with RT who received ADT as neo/adjuvant therapy (approximately 30% of the RT population). In the RP arms, only a minority of the patients received adjuvant RT, a treatment that improved survival at 10 years according to the 2011 Cochrane metaanalysis.[41] If ADT in the RT arms could have prevented some b-RFS, as metaanalysis shows for b-RFS, the lack of postoperative RT in RP patients could have amplified the results of the surgery.

However, this metaanalysis, which includes more than 13,000 patients, is the largest comprehensive review that analyses the outcomes of high-risk PC patients treated with RP or external beam RT. No evidence of significant publication bias was observed, and the studies included a relatively homogeneous population of high-risk patients, which is common in clinical practice. In absolute terms, overall mortality and PCSM were significantly reduced, by 15% and 5%, respectively.

Conclusion

In a disease in which competing causes of death are relevant and cancer-related mortality is relatively low, the judicious use of all available resources has to be implemented for every patient. RT combined with ADT still remains the treatment modality of choice for high-risk PC, particularly for aged patients with limited life expectancy and comorbidities.

We believe that surgery, provided it is adequate and radical, could be considered a possible treatment modality in selected high-risk PC patients, with no or minimal comorbidities and an average life expectancy.

Disclosure

The authors have stated that they have no conflicts of interest.

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