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European Association of Urology

Review – Prostate Cancer

Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review

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Abstract

Context: In men with prostate cancer (PCa) treated with curative intent, controversy exists regarding the impact of biochemical recurrence (BCR) on oncological outcomes.
Objective: To perform a systematic review of the existing literature on BCR after treatment with curative intent for nonmetastatic PCa. Objective 1 is to investigate whether oncological outcomes differ between patients with or without BCR. Objective 2 is to study which clinical factors and tumor features in patients with BCR have an independent prognostic impact on oncological outcomes.
Evidence acquisition: Medline, Medline In-Process, Embase, and the Cochrane Central Register of Controlled Trials were searched. For objective 1, prospective and retrospec-

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tive studies comparing survival outcomes of patients with or without BCR following radical prostatectomy (RP) or radical radiotherapy (RT) were included. For objective 2, all studies with at least 100 participants and reporting on prognostic patient and tumor characteristics in patients with BCR were included. Risk-of-bias and confounding assessments were performed according to the Quality in Prognosis Studies tool. Both a narrative synthesis and a meta-analysis were undertaken.

Evidence synthesis: Overall, 77 studies were included for analysis, of which 14 addressed objective 1, recruiting 20 406 patients. Objective 2 was addressed by 71 studies with 29 057, 11 301, and 4272 patients undergoing RP, RT, and a mixed population (mix of patients undergoing RP or RT as primary treatment), respectively. There was a low risk of bias for study participation, confounders, and statistical analysis. For most studies, attrition bias, and prognostic and outcome measurements were not clearly reported. BCR was associated with worse survival rates, mainly in patients with short prostate-specific antigen doubling time (PSA-DT) and a high final Gleason score after RP, or a short interval to biochemical failure (IBF) after RT and a high biopsy Gleason score.

Conclusions: BCR has an impact on survival, but this effect appears to be limited to a subgroup of patients with specific clinical risk factors. Short PSA-DT and a high final Gleason score after RP, and a short IBF after RT and a high biopsy Gleason score are the main factors that have a negative impact on survival. These factors may form the basis of new BCR risk stratification (European Association of Urology BCR Risk Groups), which needs to be validated formally.

Patient summary: This review looks at the risk of death in men who shows rising prostate-specific antigen (PSA) in the blood test performed after curative surgery or radiotherapy. For many men, rising PSA does not mean that they are at a high risk of death from prostate cancer in the longer term. Men with PSA that rises shortly after they were treated with radiotherapy or rapidly rising PSA after surgery and a high tumor grade for both treatment modalities are at the highest risk of death. These factors may form the basis of new risk stratification (European Association of Urology biochemical recurrence Risk Groups), which needs to be validated formally.

1. Introduction

Patients with nonmetastatic prostate cancer (PCa) who are fit enough to receive curative treatment generally have a good prognosis. This was particularly true in historical series when many patients with low-risk cancer were included [1–3]. After treatment with curative intent, the most sensitive and the only validated biomarker for disease recurrence remains prostate-specific antigen (PSA) measurement [4,5]. Biochemical recurrence (BCR), defined as the return of measurable PSA, does not necessarily indicate that an individual will develop clinically relevant recurrence and/or die of his disease, with studies reporting that only approximately 30% of patients with BCR after primary surgery develop clinical recurrence [6], with only 16.4% dying from their disease [7]. Furthermore, for patients with BCR after radical prostatectomy (RP) or primary radiotherapy (RT), several authors have reported that only certain patient subgroups with poor tumor differentiation and PSA kinetics are at a high risk of progressive disease [8–10]. Understanding the true impact of BCR on oncological outcomes is crucial because, first of all, it occurs frequently, in about 35% of patients who have undergone treatment for localized PCa [11]. Furthermore, in case of BCR, clinicians need to counsel their patients as to who might benefit from potentially toxic salvage therapies.

The objectives of this systematic review are to determine whether BCR is associated with oncological outcomes (objective 1) and which clinical factors have independent prognostic impact for oncological outcomes after BCR has occurred (objective 2).

2. Evidence acquisition

This review was commissioned and undertaken by the European Association of Urology (EAU) Prostate Cancer Guideline Panel as part of its guideline update for 2019. The protocol for this review has been published (http://www.crd.york.ac.uk/PROSPERO; registration number CRD42015026807).

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [12] and Cochrane review principles [13] (Supplementary material, Search strategy 1). PICO development was performed by the EAU PCa panel, based on the expertise of urologists, oncologists, radiotherapists, radiologists, pathologists, and a patient representative. English-language articles published from January 2000 to July 2018 were included. The year 2000 was used as the cutoff due to the need for sufficiently long follow-up (at least 10 yr) after PSA was introduced (at the end of the 1980s). All abstracts and resulting full-text articles were independently screened in duplicate (T.V.D.B., R.V.D.B., N.A., T.G., and L.M.), and disagreement was resolved by discussion or reference to an independent third party (N.M. and T.L.).

To investigate the research objectives on the impact of BCR on oncological outcomes (objective 1) and prognostic clinical factors in patients experiencing BCR (objective 2), studies that investigated the clinical impact of BCR after RP or RT were included. Owing to the expected heterogeneity of BCR definitions used in different studies, all studies investigating the above objectives were included, irrespective of the BCR definition that was used (studies investigating patients with

PSA persistence were excluded). The study population was limited to men with histologically proven nonmetastatic PCa who underwent treatment with curative intent and a minimal median follow-up of 5 yr after BCR. The primary outcome was overall mortality (OM), and secondary outcomes were PCa-specific mortality (PCSM) and development of distant metastases (DM). Risk of bias (RoB) was assessed using the Quality In Prognosis Studies (QUIPS) tool [14], as recommended by the Cochrane Prognosis Methods Group. Double data extraction was performed independently in duplicate relating to the prespecified outcomes. Subgroup analysis was preplanned based on the following variables: T/N stage, primary treatment, disease risk classification, Gleason score (GS), characteristics of BCR (PSA doubling time [PSA-DT], interval to biochemical failure [IBF]), surgical margin status, salvage treatment, and extent of lymphadenectomy for RP.

A meta-analysis was performed regarding the risk effects associated with reported patient and tumor variables for three different endpoints: DM, PCSM, and OM. This was performed separately for patients treated with RP or RT. A meta-analysis of the observed risk effects was performed using the random-effect linear regression model to account for the expected clinical heterogeneity across studies. Since various studies included multiple codependent variables into one multivariable analysis (MVA; eg, GS 7 vs 6 and 8–10 vs 6), a study grouping variable was included as a random effect. Sensitivity analysis was performed by comparing the results of the primary analysis with the results of (1) a fixed-effect model, (2) a random-effect model without a random effect that accounts for between-study dependence, and (3) a conservative strategy to test the sensitivity of the primary analysis. Potential publication biases were investigated using visual inspection of funnel plots and calculated using the rank test and regression test (Egger's test). For full methodological information, consult the Supplementary material (Search strategy, selection of studies and data extraction).

3. Evidence synthesis

3.1. *Quantity of evidence identified*

The study selection process is outlined in the PRISMA flow diagram (Fig. 1). In total, 10 863 records were identified through database searching and 6759 were screened after removal of duplicates. Of these, 381 articles were eligible for full-text screening. Finally, 77 studies met the inclusion criteria (14 and 71 studies dealing with oncological outcomes [objective 1] and prognostic factors [objective 2], respectively) [7–9,11,15–87].

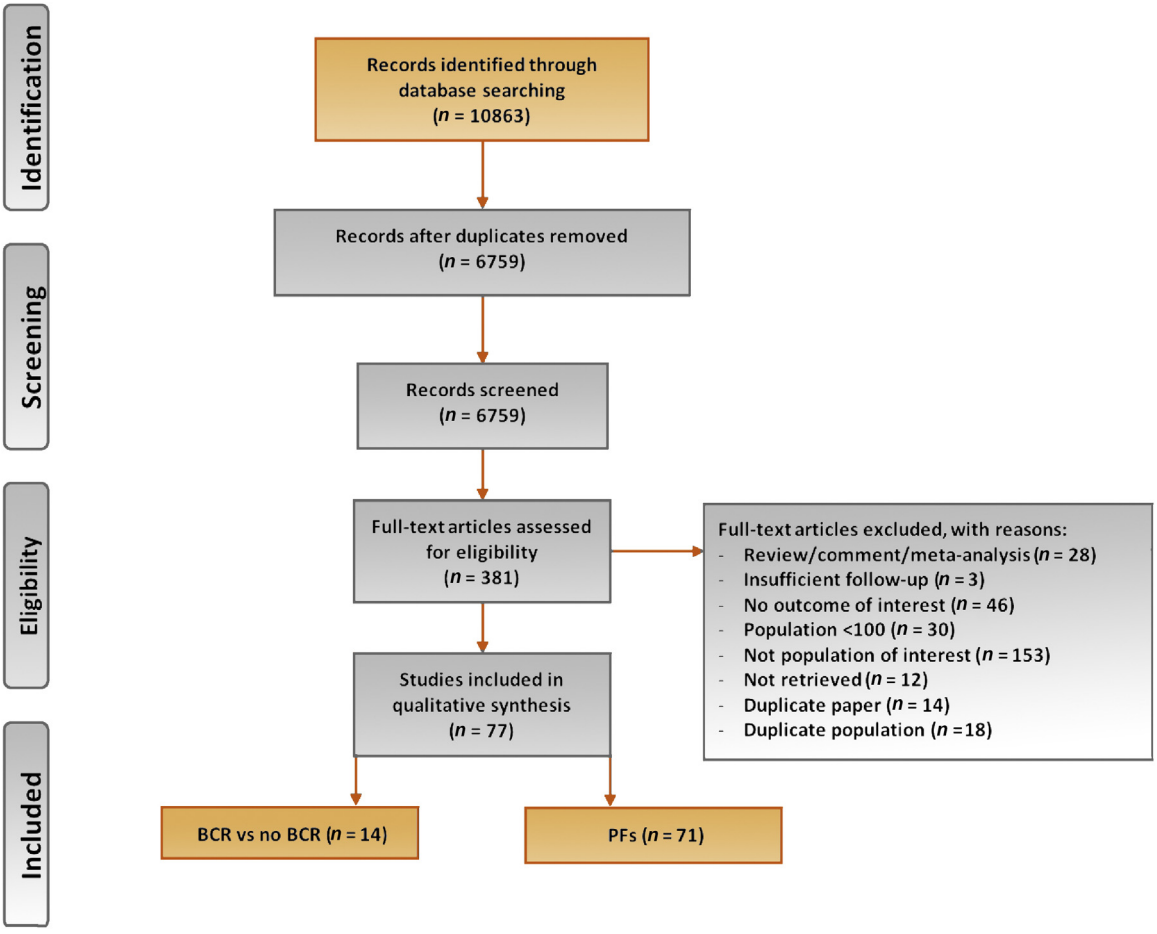

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis flow chart. BCR = biochemical recurrence; PFs = prognostic factors.

Table 1 – Baseline characteristics of studies evaluating the impact of BCR on oncological endpoints

Study ID; design; country; recruitment period	Primary treatment	Definition of BCR	*N* BCR/no BCR	FU	Age (yr)	iPSA (ng/ml)	GS	T stage N stage	SM status	Adjuvant treatment	Salvage treatment	Comment
Primary treatment: radical prostatectomy												
Jackson [25] Retrospective 2017 USA 1986–2013	RP	Rise above the post-sRT PSA nadir ≥0.2 ng/ml followed by second PSA of equal or higher value	BCR: 285 (50%) No BCR: 277 (49%) Missing data: 4 (1%)	From sRT: 8.2 yr (NR)	63 (IQR: 58–69)	NR	7 (IQR: 7–8)	T3a (IQR: T2b–T3a)	NR	NR	Salvage RT: 566 (100%)	Second BCR.
Fryczkowski [46] Retrospective 2011 Poland 1995–2009	RP	2 consecutive PSA rises ≥0.2 ng/ml	102 145	From RP: 64.3 mo (NR)	63 (R: 49–75)	15.5 (NR) 10.4 (NR)	6.06 (NR) 5.1 (NR)	NR	NR	0%	Salvage RT: 39 (15.8%) Salvage ADT: 63 (25.6%)	–
Choueiri [56] retrospective 2009 USA 1988–2008	RP	>0.2 ng/ml at 2 consecutive postoperative visits starting 30 d after the completion of RP	BCR: 546 (18%) No BCR: 2525 (82%)	From RP: 7.4 yr (IQR: 3.1–12.0)	65.5 (IQR: 60.0–69.8) 62.2 (IQR: 56.8–67.3)	11.4 (IQR: 6.7–21.6) 5.7 (IQR: 4.2–8.1)	pGS ≤6: 123 (23%) 7: 261 (48%) 8–10: 162 (30%) pGS ≤6: 1343 (53%) 7: 1038 (41%) 8–10: 144 (6%)	pT T2: 163 (30%) T3a: 198 (36%) ≥T3b: 185 (34%) pT T2: 1842 (73%) T3a: 568 (23%) ≥T3b: 115 (5%)	SM positive 329 (60%) SM positive 658 (26%)	0 (0%)	347 (63%) NA	–
Stephenson [67] Retrospective 2006 USA 1985–2006	RP	Different cutoffs used	Total cohort: 3125 (number of BCR patients dependent on BCR definition)	49 mo (R: 1–227)	NR	6.13 (IQR: 4.49–9.00)	bGS 2–6: 60% (*n* = 1863) 3 + 4: 18% (*n* = 560) 4 + 3: 7% (*n* = 221) 8–10: 5% (*n* = 167) NA: 10% (*n* = 314)	cT T1AB: 2% (*n* = 52) T1 C: 48% (*n* = 1501) T2A: 20% (*n* = 624) T2B: 18% (*n* = 548) T2 C: 8% (*n* = 234) T3: 2% (*n* = 46) NA: 3% (*n* = 263)	R1: 25% (*n* = 770)	NR	NR	–
Primary treatment: radiotherapy/brachytherapy												
Freiberger [78] Retrospective 2017 Germany 2000–2003	RT	Phoenix def: PSA nadir + 2 ng/ml	NR	From RT: 108 mo (R: 7–157)	71 (R: 49–83)	9 (R: 1–300)	GS >6: 13% (*n* = 38)	>T2a: 21% (*n* = 62)	NA	NR	NR	–
Royce [86] Retrospective 2017 USA 1995–2001	RT	NR	BCR: 54% (*n* = 85) No BCR: 46% (*n* = 72)	16 yr (NR)	72.1 (R: 67.4–75) 73.1 (R: 70–76.3)	12.2 (R: 8.4–17.8) 10 (R: 6–13.5)	≤6: 22% (*n* = 19) 7: 64% (*n* = 54) 8–10: 14% (*n* = 12) ≤6: 40% (*n* = 29) 7: 51% (*n* = 37) 8–10: 8% (*n* = 6)	T1: 40% (*n* = 34) T2: 60% (*n* = 51) T1: 65% (*n* = 47) T2: 35% (*n* = 25)	NA	RT + ADT: 29% (*n* = 25) RT: 71% (*n* = 60) RT + ADT: 74% (*n* = 53) RT: 26% (*n* = 19)	NR	–

Table 1 (*Continued*)

Study ID; design; country; recruitment period	Primary treatment	Definition of BCR	*N* BCR/no BCR	FU	Age (yr)	iPSA (ng/ml)	GS	T stage N stage	SM status	Adjuvant treatment	Salvage treatment	Comment
Herbert [87] Retrospective 2011 Canada 1994–2000	RT	Phoenix def: PSA nadir + 2 ng/ml	1060 (BCR and no BCR)	125 mo (R: 51–176; from RT)	71 (R: 46–86)	9.4 (R: 0.3–238)	bGS ≤6: 646 (61.1%) 7: 291 (27.5%) 8–10: 120 (11.4%)	cT 1a: 2 (0.2%) 1b: 29 (2.8%) 1c: 137 (13.1%) 2a: 171 (16.3%) 2b: 234 (22.4%) 2c: 132 (12.6%) 3a: 185 (17.7%) 3b: 51 (4.9%) 3c: 86 (8.2%) 4: 19 (1.8%)	NA	ADT: 442 (41.7%)	NA	–
Kapadia [15] Retrospective 2012 USA 1998–2008	RT	Phoenix def: PSA nadir + 2 ng/ml	BCR: 147 (21%) No BCR: 563 (79%)	64 mo (IQR: 36–89; from RT)	69 (IQR: 63–74)	7.8 (IQR: 5.3–12.1) Short IBF: 26.1 (IQR: 12.4–48) Long IBF: 11.3 (6.0–24)	bGS GS 2–6: 248 (35%) GS 7: 322(45%) GS 8: 79(11%) GS 9–10: 61 (9%)	cT T1–T2a: 507 (71%) T2b–2c: 125 (18%) T3–4: 78(11%)	NA NA	ADT: 75 (51%) ADT: 208 (37%)	Salvage ADT: 91 (62%) –	
Abramowitz [16] Retrospective 2008 USA 1987–2001 BCR = Phoenix definition MVA2: BCR = ASTRO definition	RT	Phoenix and ASTRO definitions	Phoenix: 389 (21%) ASTRO: 460 (25%)	From RT: 71 mo (R: 1–204)	69 (R: 43–89)	7.1 (R: 0–371)	bGS 2–6: 1244 (67.9%) 7: 442 (24.1%) 8–10: 145 (7.9%)	cT T1: 716 (41.1%) T2: 857 (49.1%) T3/4: 171 (9.8%)	NA	ADT: 291 (16%)	ADT: 195 (10.7%)	MVA1:
Williams [17] retrospective 2004 Australia 1990–1997	RT	3× PSA rises (ASTRO). Before ASTRO: BCR at date of clin. failure	BCR: 1069 No BCR: 502	From RT: 88.1 mo (NR)	68.9 (R: 42.3–87.0)	15.2 (R: 0.5–340)	bGS 2–4: 29.6% 5–7: 63.8% 8–10: 6.6%	cT T1: 19.7% T2: 71% T3–T4: 9.2%	NA	NR	Salvage ADT: 613 (39%)	–
Pollack [18] retrospective 2003 USA 1989–1995	RT	3× PSA rises (ASTRO)	BCR: 316 No BCR: 626	From RT: 73 mo (R: 3–164)	69 (R: 46–89)	9.9 (R: 0.2–191)	bGS 2–4: 19% 5–6: 54% 7: 21% 8–10: 6%	cT T1: 34% T2: 54% T3: 12%	NA	Neoadjuvant ADT: 13% for a median of 3 mo (range 1–6)	ADT (before DM): 189 (59.8%) NA	–
Kupelian [19] retrospective 2002 USA 1987–1993	RT	3× PSA rises (ASTRO)	BCR: 316 (34%) No BCR: 620 (66%)	From RT: 77 mo (NR) From RT: 49 mo (NR)	69 (NR)	<4: 6 (2%) 4–10: 85 (27%) 10–20: 107 (34%) >20: 118 (37%) <4: 61 (10%) 4–10: 342 (55%) 10–20: 147 (24%) >20: 70 (11%)	bGS ≤6: 163 (52%) 7: 93 (29%) ≥8: 60 (19%) bGS ≤6: 393 (63%) 7: 171 (28%) ≥8: 56 (9%)	cT T1–T2a: 151 (48%) T2b–T2c: 114 (36%) T3: 51 (16%) cT T1–T2a: 441 (71%) T2b–T2c: 141 (23%) T3: 38 (6%)	NA	ADT: 26 (8%) ADT: 155 (25%)	Salvage ADT: 182 (58%) –	–

Table 1 (*Continued*)

Study ID; design; country; recruitment period	Primary treatment	Definition of BCR	*N* BCR/no BCR	FU	Age (yr)	iPSA (ng/ml)	GS	T stage N stage	SM status	Adjuvant treatment	Salvage treatment	Comment
Primary treatment: mixed (RT/RP)												
Uchio [20] retrospective 2010 USA 1991–1995	RP: 225 (36%) RT: 398 (64%)	For RP: PSA ≥0.4 ng/ml For RT: Phoenix def: PSA nadir + 2 ng/ml	RP: BCR: 81 (36%) No BCR: 144 (64%) RT: BCR: 161 (40%) No BCR: 237 (60%)	NR (R:11–16 yr)	50–59: 19 (8.4%) 60–69: 143 (63.6%) 70–79: 63 (28%) ≥80: 0 (0%) 50–59: 8 (2%) 60–69: 134 (33.7%) 70–79: 242 (60.8%) ≥80: 14 (3.5%)	0–<4.0: 39 (17.3%) 4.0–<10.0: 105 (46.7%) 10.0–<20.0: 49 (21.8%) ≥20.0: 29 (12.9%) Unknown: 3 (1.3%) 0–<4.0: 38 (9.5%) 4.0–<10.0: 157 (39.5%) 10.0–<20.0: 118 (29.6%) ≥20.0: 84 (21.1%) Unknown: 1 (0.3%)	bGS 2–4: 57 (25.3%) 5–7: 147 (65.3%) 8–10: 21 (9.4%) 2–4: 81 (20.4%) 5–7: 254 (63.8%) 8–10: 63 (15.8%)	cT T1/T2: 221 (98.2%) ≥T3: 4 (1.8%) T1/T2: 374 (94%) ≥T3: 24 (6%)	NR NA	NA NA	ADT: 32 (14.2%) RT: 10 (4.4%) NR	–
Agarwal [21] Retrospective 2007 USA 1989–2004	RP: 4342 RT: 935	PSA >0.2 ng/ml or introduction of salvage treatment ASTRO definition or introduction of salvage treatment	1003 (23%) 587 (63%)	NR	<55: 690 (16%) 55–64: 1976 (46%) 65–74: 1608 (37%) <75: 68 (2%) <55: 30 (3%) 55–64: 156 (17%) 56–74: 495 (53%) <75: 254 (27%)	<4: 602 (15%) 4.1–10: 2579 (64%) 10.1–20: 615 (15%) >20: 240 (6%) Missing data: 306 <4: 57 (7%) 4.1–10: 341 (43%) 10.1–20: 204 (26%) >20: 193 (24%) Missing data: 140	bGS 2–4: 315 (8%) 5–6: 2641 (64%) 7: 928 (23%) 8–10: 236 (6%) Missing data: 222 bGS: 2–4: 86 (11%) 5–6: 344 (44%) 7: 222 (28%) 8–10: 130 (17%) Missing data: 153	cT T1: 1818 (44%) T2: 2263 (54%) T3: 84 (2%) T4: 2 (<1%) Missing data: 175 cT T1: 266 (30%) T2: 514 (58%) T3: 92 (10%) T4: 8 (1%) Missing data: 55	R1: 29.1% NA	RT: 30 (3%) (Neo)adjuvant ADT: 188 (18.7%) (Neo)adjuvant ADT: 231 (39%)	RT: 248 (40%) ADT: 367 (59.2%) ADT: 402 (93.5%)	–

ADT = androgen deprivation therapy; ASTRO = American Society for Radiation Oncology; BCR = biochemical recurrence; bGS = biopsy Gleason score; clin. = clinical; cT = clinical T stage; DM = distant metastasis; FU = follow up; GS = Gleason score; IBF = interval to biochemical failure; iPSA = initial (pretreatment) prostate-specific antigen; IQR = interquartile range; MVA = multivariable; *N* = number of patients; NA = not assessed; NR = not reported; NR = not reported; pGS = pathological Gleason score; PSA = prostate–specific antigen; pT = pathological T stage; RP = radical prostatectomy; RT = radiotherapy; SM = surgical margin; sRT = salvage RT.

3.2. Characteristics of the included studies

Table 1 presents the baseline study characteristics of included studies dealing with objective 1, recruiting a total of 20 406 patients (one study did not report the number of included patients). Supplementary Tables 1–3 present the baseline characteristics of included studies dealing with objective 2. Supplementary Table 1 refers to studies reporting on patients who underwent RP (29 057 patients), Supplementary Table 2 refers to studies reporting on patients who underwent RT (11 301 patients; two studies did not report the number of included patients), and Supplementary Table 3 refers to a mixed population (4272 patients). For objective 1, four, seven, and 10 studies investigated DM, PCSM, and OM, respectively. For objective 2, 35, 47, and 28 studies correlated prognostic factors with DM, PCSM, and OM, respectively. Owing to the need of long-term follow-up for the reported outcomes, most RT studies reported on a population with different RT doses. Of all included RT studies, only five reported on a patient population with a median RT dose of ≥74 Gy [15,61,64,69,76].

3.3. RoB and confounding assessment of the included studies

Figure 2 summarizes the QUIPS-based RoB assessment of all included studies. Overall, there was a low RoB for the domains of study participation, study confounders, and statistical analysis. Most studies also had a low RoB on reporting on patient characteristics and corrected for confounding factors, although these confounders were not prespecified in any a priori protocol. Attrition bias was unclear in most studies due to the lack of reporting of patient dropouts. Prognostic factor and outcome measurements were unclear in a significant proportion of included studies mainly due to the lack of reporting on the methods of data collection.

3.4. Results of evidence synthesis

3.4.1. Impact of BCR on oncological outcomes (objective 1)

Fourteen studies directly compared patients with BCR versus no BCR. All studies found BCR to be an independent risk factor for the development of DM, PCSM, and to a lesser extent OM (Table 2).

Three studies directly compared OM of patients with or without BCR after RP. Choueiri et al. [56] investigated 3071 patients (of whom 454 died) with a median follow-up of 7 (interquartile [IQR]: 3.1–12.0) yr after primary treatment and concluded that the impact of BCR on OM rates was significant, but with a small effect size (hazard ratio [HR] 1.03; 95% confidence interval [CI] 1.004–1.06). The second study by Jackson et al. [35] found BCR to have a larger effect size on OM (HR 2.32; 95% CI 1.45–3.71) with a median follow-up of 8 yr. Finally, the study by Fryczkowski et al. [46] remained inconclusive as well due to the limited number of events, with only 11 and 20 reported cancer-specific and overall deaths out of 247 patients.

Studies reporting on patients who were treated with primary RT overall stated that BCR is an independent risk factor for the development of DM, PCSM, and to a lesser extent OM [15–19,21,78,86,87]. For cancer-related outcomes, all four studies investigating DM or PCSM as an outcome showed a significant negative impact of BCR with varying impact. In contrast, the impact of BCR on OM is less clear, but still five out of eight studies report an impact of BCR on OM rates [16,17,78,86,87], while the other three studies do not show this effect [15,18,19].

The impact of BCR on (cancer-related) survival outcomes remains controversial, with a part of the disparity between studies being related to the definition of BCR that has been used. Stephenson et al. [67] investigated different definitions of BCR after RP as primary treatment to determine which PSA cutoff and kinetics would best define which patients would eventually develop clinical progression. They suggested that progressively rising PSA of at least 0.4 ng/ml is most strongly associated with metastatic progression compared with definitions based on one PSA measurement (eg, one PSA of at least 0.2, 0.4, or 0.6) or PSA measurements based solely on their kinetics (eg, two or three consecutive rises). For RT, Abramowitz et al. [16] compared the impact of BCR based on which definition was used (American Society for Radiation Oncology [ASTRO] or Phoenix definition), and showed that the Phoenix definition was much more predictive for DM, PCSM, and OM compared with the ASTRO definition, with an HR of 173 (95% CI 74–

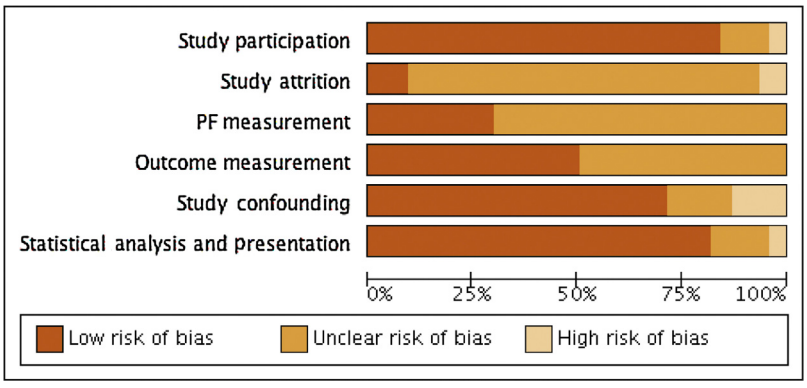

Fig. 2 – Risk of bias summary graph. PF = prognostic factor; RoB = risk of bias.

Table 2 – Impact of BCR on oncological outcomes

Study ID; design; country; recruitment period	Outcome	Incidence (%)	Subgroups	Value of variable (if applicable)	Statistical analysis	*p* value	Comment
Primary treatment: radical prostatectomy							
Jackson [25] Retrospective 2017 USA 1986–2013	OS PCSM	NR	NA	BCR vs no BCR	MVA: HR 2.32 (95% CI 1.45–3.71) MVA: HR 37.8 (95% CI 5.09–280.5)	<0.001 <0.001	Each model is corrected for GS, pT stage, log(PSA + 1), ADT, age at port, year of port
Fryczkowski [46] Retrospective 2011 Poland 1995–2009	OS CSS	20 (8.1%) deaths 11 (4.5%) metastatic events	NA	No BCR vs BCR + salvage RT (±ADT) vs BCR + salvage ADT No BCR vs BCR + salvage RT (±ADT) vs BCR + salvage ADT	5-yr OS: 98.7% vs 74.2% vs 88.3% 5-yr CSS: 76.9% vs 90.5% vs 100%	NR 0.001	
Choueiri [56] retrospective 2009 USA 1988–2008	OM	454 (14.8%) deaths	NA	BCR vs no BCR	MVA: HR 1.03 (95% CI 1.004–1.06)	0.025	
Stephenson [67] Retrospective 2006 USA 1985–2006	DM		NA	Single PSA ≥0.6 Single PSA ≥0.4 Single PSA ≥0.2 PSA ≥0.4 and rising PSA ≥0.2 and rising PSA ≥0.1 and rising 2 successive rises, final ≥0.2 3 successive rises 3 successive rises of ≥0.1 3 consecutive rises	MVA: 35 (95% CI 16–76) MVA: 30 (95% CI 14–65) MVA: 21 (95% CI 10–45) MVA: 31 (95% CI 19–50) MVA: 22 (95% CI 13–37) MVA: 14 (95% CI 7–25) MVA: 16 (95% CI 8–30) MVA: 8 (95% CI 5–13) MVA: 9 (95% CI 5–14) MVA: 11 (95% CI 7–17)	NR	Each model is corrected for iPSA, pGS, PSM, pT, secondary RT, and ADT
Primary treatment: radiotherapy/brachytherapy							
Freiberger [78] Retrospective 2017 Germany 2000–2003	OS	66% (*n* = 195)	NR	BCR vs no BCR	10-yr OS: BCR vs no BCR: 54% (NR) vs 74% (NR)	<0.01	
Royce [86] Retrospective 2017 USA 1995–2001	OM	70% (*n* = 110)	Men with no/minimal comorbidity	BCR vs no BCR	8-yr OM: BCR vs no BCR: 32.5% (95% CI 21.30–47.52%) vs 11.83% (7.23%–19.02%)	0.008	–
Herbert [87] Retrospective 2011 Canada 1994–2000	OS	NA	All patients NCCN high risk and estimated OS 10 yr >90% group NCCN intermediate risk and estimated OS 10 yr >90% group	No BCR vs BCR No BCR vs BCR No BCR vs BCR	10-yr OS BCR vs no BCR: 70.2% (66.3–74.1%) vs 77.4% (73.7–81.1%) 10-yr OS BCR vs no BCR: 62.1% (52.9–71.3%) vs 86.3% (78.5–94.1%) 10-yr OS BCR vs no BCR: 79.8% (68.0–91.6%) vs 95.3% (89.0–100%)	0.001 0.002 0.033	

Table 2 (*Continued*)

Study ID; design; country; recruitment period	Outcome	Incidence (%)	Subgroups	Value of variable (if applicable)	Statistical analysis	*p* value	Comment
Kapadia [15] Retrospective 2012 USA 1998–2008	OS, CSS	NA	All patients Low NCCN risk Intermediate NCCN risk High NCCN risk	No BCR vs BCR No BCR vs BCR No BCR vs BCR No BCR vs BCR	CSS OS CSS OS CSS OS CSS OS	<0.0001 0.36 0.017 0.91 <0.0001 0.55 <0.0001 0.90	
Abramowitz [16] Retrospective 2008 USA 1987–2001	DM CSM OM	NR	Phoenix definition ASTRO definition	BCR vs no BCR	DM: HR: 173 (95% CI 74–404) CSM: HR: 308 (95% CI 38–2483) OM: HR: 2.0 (95% CI 1.6–2.6) DM: HR: 62.7 (95% CI 27–143) CSM: HR: 26.0 (95% CI 8.5–79) OM: HR: 1.0 (95% CI 0.8–1.3)	<0.0001 <0.0001 <0.0001 <0.0001 <0.0001 0.98	MVA1: BCR = Phoenix definition MVA2: BCR = ASTRO definition
Williams [17] retrospective 2004 Australia 1990–1997	OM CSM	5 and 10-yr OS: 85.0% (95% CI 83.2–86.8%) and 61.1% (95% CI 57.7–64.5%)	All patients	BCR vs no BCR	CSM: RR: 19.10 (95% CI 7.6–47.7) OM: RR: 1.27 (95% CI 1.02–1.58) OM: BCR: 323 (30.2%) vs no BCR: 152 (30.3%) CSM: BCR: 179 (16%) vs no BCR: 5 (1%)	<0.001 0.035 NR NR	–
Pollack [18] retrospective 2003 USA 1989–1995	DM CSM OM	DM: 66 (7%) CSM: 32 (3%) OM: 230 (24%)	All patients	BCR vs no BCR	DM: RR: 95.0 (NR) CSM: RR: 18.91 (NR) OM: RR: NR	<0.0001 <0.0001 >0.05	–
Kupelian [19] retrospective 2002 USA 1987–1993	OM	5-yr OS: 89% (95% CI 86–91) 10-yr OS: 68% (95% CI 61–75%)	All patients	BCR vs no BCR	5-yr OS: BCR: 89% (95% CI 86–93%) vs no BCR: 89% (95% CI 86–92%) 10-yr OS: BCR: 65% (95% CI 56–74%) vs no BCR: 77% (95% CI 69–84%) MVA: HR NR	NA 0.68 0.052	–
Primary treatment: mixed (RT/RP)							
Uchio [20] retrospective 2010 USA 1991–1995	RP: CSM RP: OM RT: CSM RT: OM	CSM: 48 (12%) OM: 387(62%)	NA	No BCR vs BCR No BCR vs BCR No BCR vs BCR No BCR vs BCR	No BCR: 15-yr CSM: 0%; BCR: 5-, 10-, and 15-yr CSM: 3%, 11%, and 21% and MVA MVA: NA No BCR: 15-yr CSM: 1%; BCR: 5-, 10-, and 15-yr CSM: 11%, 20%, and 42% and MVA MVA: NA	<0.001 0.40 <0.001 0.33	CSM: remains significant after adjusting for age, comorbidity, GS, T stage
Agarwal [21] Retrospective 2007 USA 1989–2004	DM CSM OM	NR	All patients	No BCR vs BCR	DM: BCR: 15% vs no BCR: 1% CSM: BCR: 45% vs no BCR: 0% OM: BCR: 19% vs no BCR: 3%	<0.01 <0.01 <0.01	–

ADT = androgen deprivation therapy; ASTRO = American Society for Radiation Oncology; BCR = biochemical recurrence; CI = confidence interval; CSM = cancer-specific mortality; CSS = cancer-specific survival; DM = distant metastasis; GS = Gleason score; HR = hazard ratio; iPSA = initial (pretreatment) prostate-specific antigen; MVA = multivariable; NA = not assessed; NCCN = National Comprehensive Cancer Network; NR = not reported; OM = overall mortality; OS = overall survival; PCSM = prostate cancer–specific mortality; pGS = pathological Gleason score; PSA = prostate-specific antigen; PSM = positive surgical margin; pT = pathological T stage; RP = radical prostatectomy; RR = relative risk; RT = radiotherapy.

404) versus 62.7 (95% CI 27–143) for DM, 308 (95% CI 38–2483) versus 26.0 (95% CI 8.5–79) for PCSM, and 2.0 (95% CI 1.6–2.6) versus 1.0 (95% CI 0.8–1.3) for OM.

3.4.2. *Prognostic factors for oncological outcomes in patients who develop BCR (objective 2)*

All investigated prognostic factors reported in each individual study are summarized in Supplementary Tables 4 (after primary RP), 5 (after primary RT), and 6 (in mixed populations). Below we summarize prognostic factors that are reported most frequently in the included studies.

3.4.2.1. Age. For PCa-specific outcomes (DM and PCSM) and irrespective of the primary PCa treatment (RP or RT), age is not an unfavorable factor with HRs ranging from 0.98 (95% CI 0.95–1.01) to 1.02 (95% CI 0.99–1.04) for the development of DM and 0.96 (95% CI 0.91–1.00) to 1.05 (95% CI 1.01–1.08) for PCSM, with only two studies showing a small, but statistically significant unfavorable effect of increasing age [7,31]. Obviously, age is a significant risk factor for OM, in both patients undergoing RP and those undergoing RT. In the former group, HRs range from 1.04 (95% CI 1.02–1.07) to 1.79 (95% CI 1.48–2.17), and in the latter group, HRs range from 1.05 (95% CI 1.03–1.07) to 2.4 (95% CI 1.6–3.5) [11,15–17,22,42,44,56,63,64,69–71].

3.4.2.2. Initial PSA. Initial serum PSA (iPSA) levels prior to primary treatment were not uniformly found as a prognostic factor for any of the investigated outcomes. For patients undergoing RP, two out of six reported studies show a significant correlation with DM [8,26–28,43,53]. For RT, three out of five [16,17,60,61,71] and two out of five [16,17,60,61,63] studies showed a significant correlation with PCSM and OM, respectively.

3.4.2.3. Gleason score. For patients undergoing primary RP, a higher GS identified on prostatectomy histology report (pGS) is a strong prognostic factor for oncological outcomes in most studies. For DM and PCSM, 12 out of 14 [7,8,22,23,26–28,38,39,41,43,51,52,55] and 10 out of 13 [7,11,22,25,31,33,36,38–40,48,49,51] studies showed a positive association with HR ranging from 1.2 (95% CI 1–1.5) to 14.4 (95% CI 4.3–48.8) and from 1.35 (95% CI 1.07–1.71) to 10.8 (95% CI 3.1–37.9), respectively. Similarly, for patients with RT as primary treatment, eight out of eight [16,61,64,69,70,72,74,76], five out of eight [15–17,58,60,61,64,71], and seven out of nine [15–17,57,58,60,61,63,70] studies showed a positive association between a higher GS identified on prostate biopsies (bGS) and DM, PCSM, and OM, respectively, with HRs ranging from 1.7 (95% CI 1.1–2.7) to 3.7 (95% CI 1.4–10.3), 2.11 (95% CI 1.03–4.34) to 14.8 (95% CI 2–110), and 1.8 (95% CI 1.3–2.4) to 17.9 (95% CI 9.6–33), respectively. Only a limited number of studies used the recently introduced International Society of Urological Pathology (ISUP) grading in their MVA, allowing for a comparison between ISUP grades 2 and 3. For RP and RT, three studies investigated the impact of the different ISUP grades on DM, PCSM, or OM. One RT study compared the impact of bGS 3 + 4 and bGS 4 + 3 with that of bGS $\leq$6, reporting HRs of 0.99 (95% CI 0.60–1.68) and 1.55 (95% CI 0.98–2.47) for DM, 1.69 (95% CI 0.85–3.40) and 2.11 (95% CI 1.03–4.34) for PCSM, and 1.31 (95% CI 0.81–2.10) and 1.30 (95% CI 0.79–2.13) for OM, respectively [61]. Two RP studies compared pGS 3 + 4 and pGS 4 + 3 with pGS $\leq$6, reporting HRs of 5.55 (95% CI 1.30–23.78) and 10.82 (95% CI 2.56–45.76) for DM [26], 1.73 (95% CI 0.59–5.07) to 4.66 (95% CI 0.59–36.73) for pGS 3 + 4, and 2.5 (95% 0.83–7.56) to 8.04 (95% CI 1.04–61.96) for pGS 4 + 3 in relation to PCSM [26,40].

3.4.2.4. T category. Increasing T category at prostatectomy histology report (pT category) is not clearly associated with any of the oncological outcomes for patients undergoing RP, with only seven out of 13 [7,8,22,23,26–28,38,39,41,43,51,52], four out of 12 [7,22,26,31,33,36,38–40,48,49,51], and two out of six [22,33,38,42,44,56] studies showing a significant correlation for DM, PCSM, and OM, respectively. For RT, four out of six [16,61,64,69,70,76], three out of seven [16,17,58,60,61,64,71], and two out of six [16,57,58,60,61,63] studies showing a significant correlation between cT category and DM, PCSM, and OM, respectively.

3.4.2.5. Positive surgical margin. For patients who underwent RP, two out of eight studies showed an inverse relationship with DM (ie, "a protective effect") [23,26,27,38,39,41,43] and none of the eight studies investigating PCSM as an outcome showed a significant correlation [26,31,33,38–40,48,49].

3.4.2.6. Interval to biochemical failure. For patients undergoing RP as primary treatment, IBF was associated with DM in two out of six [7,8,22,26,28,38,42], PCSM in eight out of 11 [7,11,22,26,28,31,33,34,38,40,48], and OM in one out of four [11,33,38,42] studies, respectively. For patients undergoing RT as primary treatment, IBF had a clear association with oncological outcomes, with five out of five studies [61,62,64,72,74], five out of seven studies [15,60–62,64,71,74], and five out of six [15,59–63] studies showing a strong association with DM, PCSM, and OM, respectively. Although studies repeatedly reported this association, the effect size was less interpretable due to the use of different thresholds. However, it is clear that the shorter the IBF, the higher the risk of developing DM, PCSM, and OM after both RP and RT.

3.4.2.7. PSA-DT after radical treatment. There was a clear association between PSA-DT after primary therapy and oncological outcomes, being most pronounced in patients who underwent RP as primary treatment. All reported studies showed a significant correlation between shorter PSA-DT and DM [7,8,29,41,42,45,52,55], PCSM [11,29,31,33,45,48], and OM [11,29,33,42,56]. The shorter the PSA-DT, the higher the risk of developing worse oncological outcomes. Similarly, for patients who underwent RT, the limited number of studies consistently showed that PSA-DT was a risk factor for DM [61,69,72,76].

3.4.2.8. Salvage RT. Four studies included salvage RT (sRT) as a covariable in their MVAs, of which three studies showed a

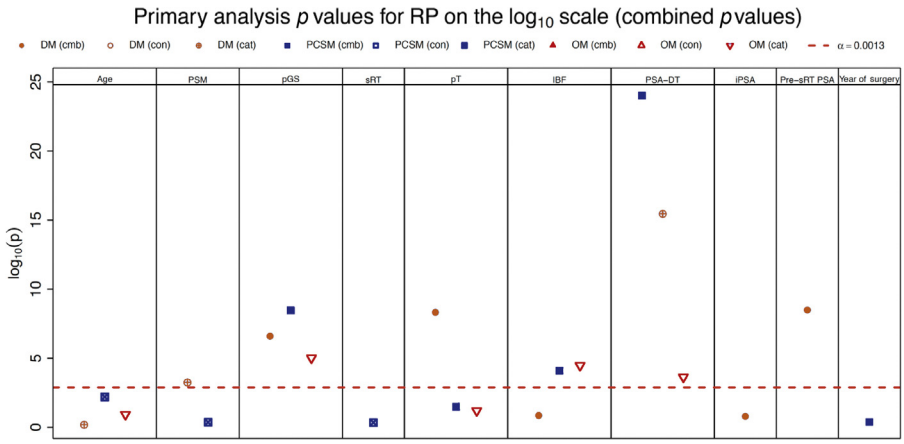

Fig. 3 – Plot of primary analysis combined *p* values (combination of continuous and categorical variables using Fisher combination method within each variable/endpoint combination) for RP for various variables, with up to three endpoints (DM, PCSM, and OM) for each variable (on a logarithmic scale). This figure also includes *p* values for the variable/endpoint combinations that had only one type of response (continuous or categorical). cat = categorical; cmb = combination; con = continuous; DM = distant metastasis; IBF = interval to biochemical failure; iPSA = initial (pretreatment) prostate-specific antigen; PCSM = prostate cancer–specific mortality; PSA = prostate-specific antigen; PSA-DT = PSA doubling time; PSM = positive surgical margin; OM = overall mortality; pGS = pathological Gleason score; RP = radical prostatectomy; sRT = salvage radical prostatectomy.

significant impact on survival outcomes. Two studies showed a protective effect of sRT on OM, with HRs ranging from 0.19 (95% CI 0.09–0.38) to 0.55 (95% CI 0.38–0.78) [44,56]. Furthermore, Cotter et al. [44] compared the prognostic role of sRT on OM in relation to PSA-DT. Compared with patients with PSA-DT <6 mo who received no sRT, patients with PSA-DT <6 mo who received sRT had an HR of 0.35 (95% CI 0.17–0.72). Patients with PSA-DT ≥6 mo with or without sRT had HRs of 0.19 (95% CI 0.09–0.38) and 0.31 (95% CI 0.17–0.56), respectively. Importantly though, all patients were compared with the group with PSA-DT <6 mo, so the impact of sRT in patients with PSA-DT >6 mo is hard to interpret in this study. Similarly, Trock et al. [48] investigated the impact of sRT on PCSM in relation to PSA-DT. They concluded that for patients with PSA-DT <6 mo, sRT resulted in a reduction of PCSM with HRs of 0.24 (95% CI 0.07–0.77) and 0.14 (95% CI 0.05–0.39) with or without concomitant androgen deprivation therapy (ADT). In patients with PSA-DT >6 mo, they reported no effect of sRT with HRs of 0.66 (95% CI 0.28–1.58) and 0.85 (95% CI 0.45–1.59) with or without ADT. Furthermore, they concluded that in patients with PSA-DT <6 mo, only when started within 2 yr of BCR, sRT had an impact on PCSM with an HR of 0.14 (95% CI 0.06–0.034) compared with 0.80 (95% CI 0.11–5.93) when started with a delay of at least 2 yr. For patients with PSA-DT ≥6 mo, the delay in sRT initiation did not have any effect on outcomes [48]. In contrast, Boorjian et al. [7] failed to show an impact of sRT on DM and PCSM. However, the median PSA-DT values of patients with early and late BCR were 0.7 (IQR 0.4–2.8) and 1.3 (IQR 0.7–3.5) yr, respectively. Based on the findings by Trock et al. [48] as described above, it could be expected that due to the relatively long PSA-DT, the authors failed to show a protective effect of sRT on PCSM.

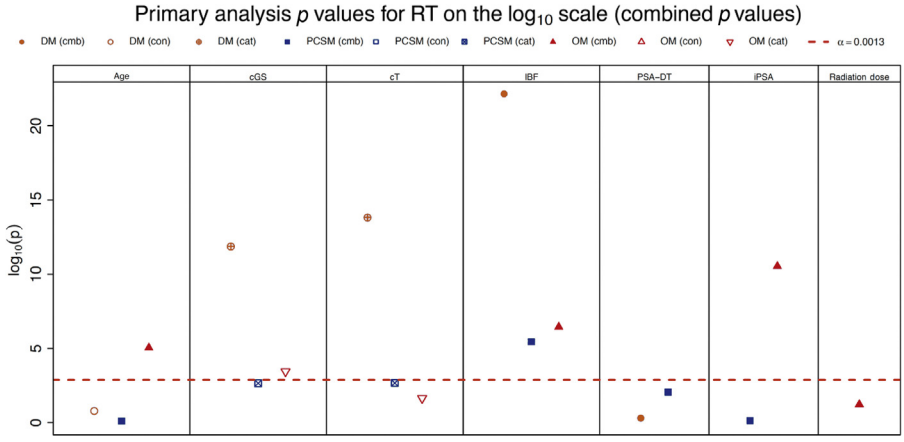

Fig. 4 – Plot of primary analysis combined *p* values (combination of continuous and categorical variables using Fisher combination method within each variable/endpoint combination) for RT for various variables, with up to three endpoints (DM, PCSM, and OM) for each variable (on a logarithmic scale). This figure also includes *p* values for the variable/endpoint combinations that had only one type of response (continuous or categorical). cGS = clinical Gleason score; DM = distant metastasis; IBF = interval to biochemical failure; iPSA = initial (pretreatment) prostate-specific antigen; PCSM = prostate cancer–specific mortality; PSA-DT = prostate-specific antigen doubling time; OM = overall mortality.

Eleven studies investigated only patients who received sRT [22–24,26–28,30,33,38,39,52]. For these patients, pGS remained a strong predictor for DM and to a lesser extent for PCSM. In two out of four and four out of five studies investigating IBF in their MVA for DM and PCSM as outcomes, respectively, this was significant. PSA-DT was only investigated by one study and showed a significant effect [33]. Closely related were the PSA levels before initiation of sRT, which showed to be a significant predictor for DM and PCSM, with seven out of nine and three out of four studies showing a significant impact on DM and PCSM, respectively. With increasing PSA levels, the risk of having worse oncological outcomes increased. Abugharib et al. [26] showed that patients with a pre-sRT PSA level of >0.5 versus 0.01–0.2 had an increased risk of developing DM and PCSM with HRs of 4.45 (95% CI 2.45–8.06) and 4.07 (95% CI 1.69–9.81), respectively. In contrast, patients with a PSA level ranging between 0.2 and 0.5 μg/l (vs 0.01–0.2) did not seem to have an increased risk. Two other studies compared a pre-sRT PSA level of >0.5 versus ≤0.5 μg/l, with one showing a clear effect and the other study showing only a trend [27,28]. Again, this could be due to PSA being a continuous biomarker and its associated risks increasing gradually as well, which is confirmed by the studies by Jackson et al. [39], Johnson et al. [38], and Stish et al. [22]. These data suggest that a PSA cutoff of 0.4 μg/l that keeps increasing is probably indeed a good definition for BCR and that initiating sRT based on this definition is probably desirable.

3.4.2.9. Salvage ADT. A limited number of studies report on the prognostic effect of salvage ADT (sADT) after RP [7,40,44,56] or RT [18,60,69,77,79]. After RP as primary therapy, HRs range from 0.83 (95% CI 0.45–1.55) to 1.09 (95% CI 0.5–2.36) for PCSM [7,40,56] and H from 0.54 (95% CI 0.31–0.94) to 0.55 (95% CI 0.38–0.78) for OM [44,56]. After RT, four studies report on the prognostic effect of sADT on DM based on an MVA and state it to have a protective effect [18,69,77,79], but only one study reports the actual HR of 0.43 (95% CI 0.28–0.69) [69]. For PCSM, two studies report contradictory findings [60,77].

3.5. Meta-analysis

With multiple variables for each of the two therapy types, three different endpoints, and two different study types (continuous/categorical), the meta-analysis yielded a total 58 models (ie, 58 *p* values). After combining the *p* values for each variable/endpoint combination (combining *p* value for categorical and continuous study types using the Fisher combination method) and correcting for multiple testing using the Bonferroni method, there were 38 *p* values of which 19 were significant (11 for RP and eight for RT; Figs. 3 and 4). The combined *p* values for each variable/endpoint combination are shown in Table 3, and significant prognostic factors were extracted from this table and are summarized below.

For patients with BCR after RP, the following outcomes are associated with significant prognostic factors:

1. Distant metastatic recurrence: positive surgical margin, high pGS, high pT category, short PSA-DT, and high pre-sRT PSA (Fig. 5)
2. PCSM: high pGS, short IBF, and short PSA-DT (Fig. 6)
3. OM: high pGS, short IBF, and short PSA-DT (Fig. 7)

For patients with BCR after RT, the corresponding outcomes are:

1. Distant metastatic recurrence: high bGS, high cT category, and short IBF (Fig. 8)
2. PCSM: short IBF (Fig. 9)
3. OM: high age, high bGS, short IBF, and high iPSA (Fig. 10)

Table 3 – Results of meta-analyses after combination of *p* values using the residual maximum likelihood method with accounting for study dependence (random-effect model)

Variable	End.point	Type	Nstud	Nind	*p* value	Sgnf
RP age	DM	Categ	3	3	6.6^{e}–01	
RP age	PCSM	Categ	5	5	6.4^{e}–03	
RP age	OM	Categ	5	5	1.2^{e}–01	
RP PSM	DM	Categ	8	8	5.6^{e}–04	*
RP PSM	PCSM	Categ	7	7	4.4^{e}–01	
RP pGS	DM	Conti + categ	24	14	2.5^{e}–07	*
RP pGS	PCSM	Conti + categ	26	13	3.4^{e}–09	*
RP pGS	OM	Categ	11	7	9.7^{e}–06	*
RP sRT	PCSM	Categ	3	3	4.6^{e}–01	
RP pT	DM	Conti + categ	18	12	4.8^{e}–09	*
RP pT	PCSM	Conti + categ	19	11	3.3^{e}–02	
RP pT	OM	Categ	10	6	6.4^{e}–02	
RP IBF	DM	Conti + categ	9	7	1.4^{e}–01	
RP IBF	PCSM	Conti + categ	13	11	8.0^{e}–05	*
RP IBF	OM	Categ	4	4	3.4^{e}–05	*
RP PSA-DT	DM	Categ	16	7	3.5^{e}–16	*
RP PSA-DT	PCSM	Conti + categ	12	6	9.8^{e}–25	*
RP PSA-DT	OM	Categ	10	5	2.3^{e}–04	*
RP iPSA	DM	Conti + categ	5	4	1.6^{e}–01	
RP pre-sRT PSA	DM	Conti + categ	8	7	3.2^{e}–09	*
RP year of surgery	PCSM	Conti + categ	4	3	4.2^{e}–01	
RT age	DM	Conti	3	3	1.6^{e}–01	
RT age	PCSM	Conti + categ	5	5	7.9^{e}–01	
RT age	OM	Conti + categ	8	7	9.0^{e}–06	*
RT bGS	DM	Categ	15	8	1.4^{e}–12	*
RT bGS	PCSM	Categ	15	7	2.2^{e}–03	
RT bGS	OM	Categ	15	8	3.6^{e}–04	*
RT cT	DM	Categ	9	6	1.5^{e}–14	*
RT cT	PCSM	Categ	10	6	2.1^{e}–03	
RT cT	OM	Categ	8	6	2.2^{e}–02	
RT IBF	DM	Conti + categ	7	5	7.1^{e}–23	*
RT IBF	PCSM	Conti + categ	14	7	3.6^{e}–06	*
RT IBF	OM	Conti + categ	8	6	3.6^{e}–07	*
RT PSA-DT	DM	Conti + categ	4	4	4.9^{e}–01	
RT PSA-DT	PCSM	Conti + categ	6	3	8.7^{e}–03	
RT iPSA	PCSM	Conti + categ	7	5	7.4^{e}–01	
RT iPSA	OM	Conti + categ	6	6	2.9^{e}–11	*
RT radiation dose	OM	Conti + categ	3	3	6.0^{e}–02	

bGS = biopsy Gleason score; categ = categorical; conti = continuous; cT = clinical T stage; DM = distant metastasis; End.point = type of endpoint; IBF = interval to biochemical failure; iPSA = initial (pretreatment) prostate-specific antigen; Nstud = number of meta-analyzed studies; Nind = number of independent studies; OM = overall mortality; PCSM = prostate cancer-specific mortality; pGS = pathological Gleason score; PSA = DT = prostate-specific antigen doubling time; PSM = positive surgical margin; pT = pathological T stage; Sgnf = indicator of significance; RP = radical prostatectomy; RT = radiotherapy; sRT = salvage RT.

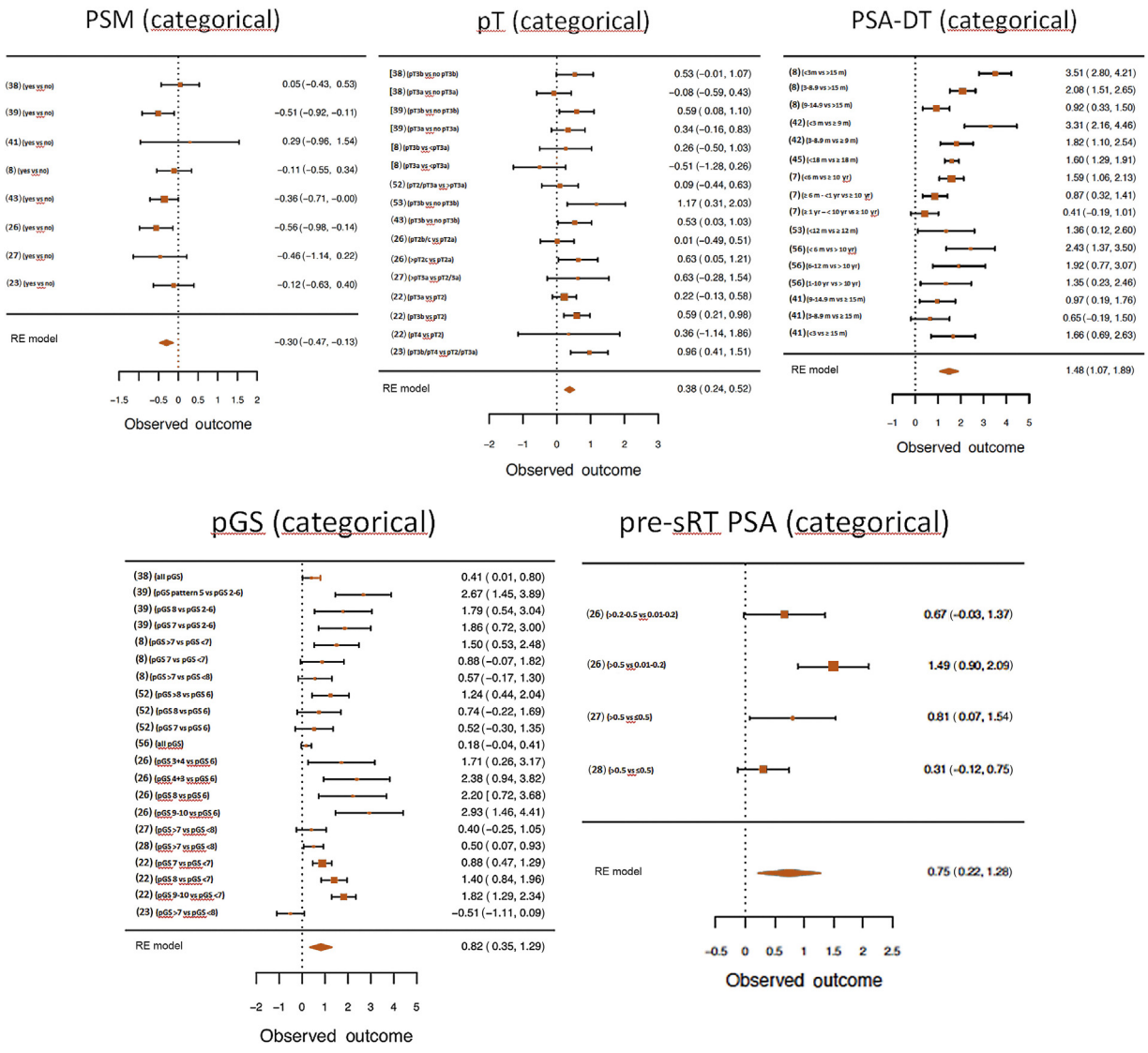

Fig. 5 – Forest plot showing the clinical factors that are significantly associated with the development of distant metastases (DM) in patients with BCR after primary radical prostatectomy. BCR = biochemical recurrence; pGS = pathologic Gleason score; pre-sRT = presalvage radiotherapy; PSA = prostate-specific antigen; PSA-DT = prostate-specific antigen doubling time; PSM = positive surgical margin; pT = pathological T stage; RE = random effect; sRT = salvage radiotherapy.

Results of the sensitivity analysis are shown in Supplementary Tables 7 (fixed-effect model), 8 (random-effect model without accounting for dependence), and 9 (conservative strategy). The first two models yielded 35 (21 for RP and 14 for RT) and 26 (14 for RP and 12 for RT) significant results, respectively. Last, the conservative analysis yielded 17 significant results (10 for RP and seven for RT). Potential publication biases in this meta-analysis were investigated using visual inspection of funnel plots, and the rank and regression tests (Egger's test) for symmetry of observed effects. For RP (Supplementary Fig. 1–3), funnel plots of pGS for outcomes DM and PCSM (especially categorical) show noticeable asymmetry with both tests of symmetry (rank and regression tests) producing significant *p* values. This is likely due to a disparity between included studies for RP pGS. For DM, studies by both Jackson et al. [39] and Abugharib et al. [26] reported substantially higher effects and standard deviations. Similarly, for PCSM, the effects reported by Jackson et al. [39], Abugharib et al. [26], and Nini et al. [51] are much larger (and less certain) than the other studies. None of the other funnel plots for RP show clear signs of asymmetry. For RT (Supplementary Fig. 4–6) the situation is similar. Perhaps with a possible exception of clinical GS for the endpoint OM, the funnel plots do not show clear signs of asymmetry.

3.6. *Discussion*

3.6.1. *Principal findings*

The available data demonstrated that patients experiencing BCR have an increased risk of developing DM and dying of PCa, and to a lesser extent higher OM rates. However, the

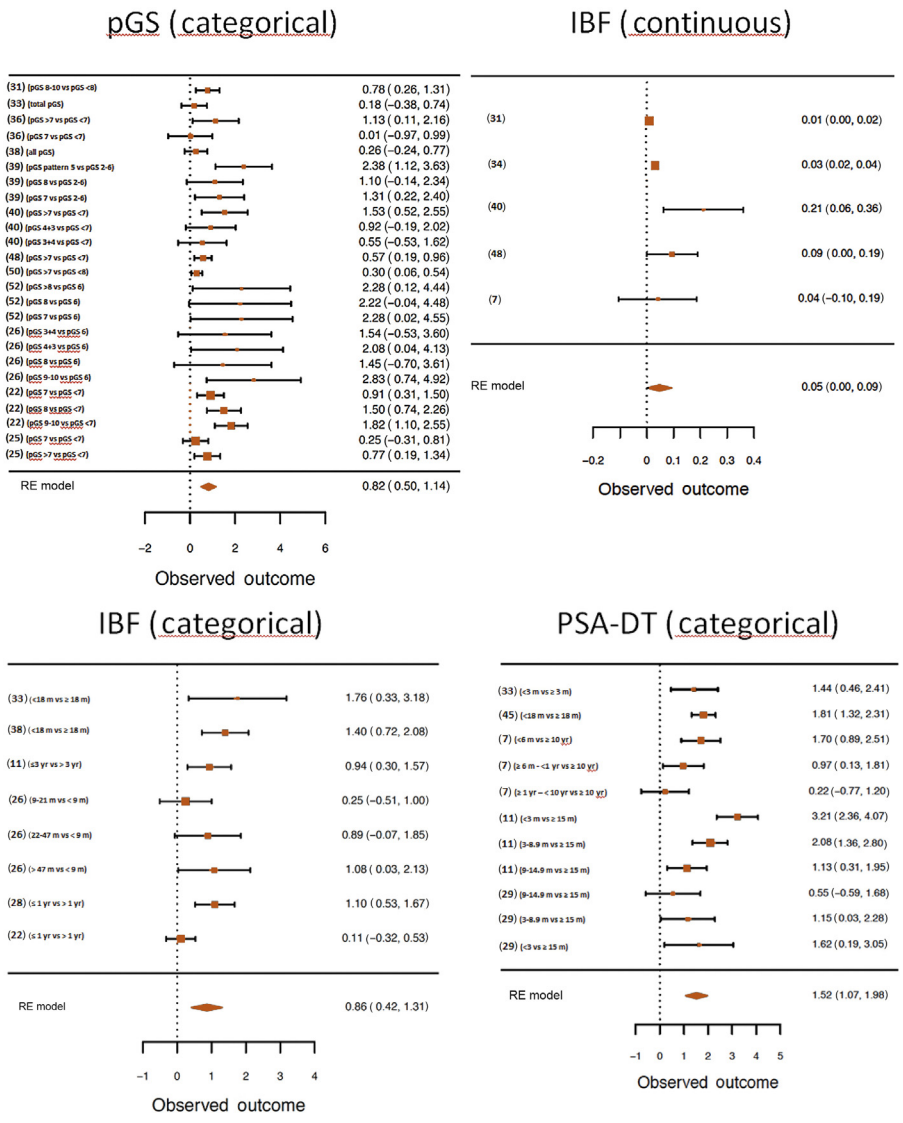

Fig. 6 – Forest plot showing the clinical factors that are significantly associated with prostate cancer–specific mortality in patients with BCR after primary radical prostatectomy. BCR = biochemical recurrence; IBF = interval to biochemical failure; pGS = pathological Gleason score; PSA-DT = prostate-specific antigen doubling time; RE = random effect.

effect size of BCR as a risk factor for mortality was highly variable, with HRs ranging from 1.03 (95% CI 1.004–1.06) to 2.32 (95% CI 1.45–3.71) after primary RP [35,56]. Similarly, for patients who underwent primary RT, there is a clear correlation between BCR and mortality. Owing to differences in statistical reporting, it is hard to define a precise effect size of BCR on OM. However, as an example, two recently published studies reported absolute survival data and showed approximately 20% lower survival rates at 8–10 yr of follow-up, even in men with minimal comorbidity [78,86]. Nevertheless, the variability in reported effect sizes of BCR remains high and suggests that only certain patient subgroups with BCR might be at an increased risk of mortality. It is for this reason that we further investigated which patient and tumor characteristics in patients experiencing BCR were prognostic for oncological endpoints.

A meta-analysis was undertaken to explore which factors were most strongly associated with oncological outcomes in nonmetastatic patients who underwent RP or RT. Owing to the heterogeneity of the studied populations and measurement of prognostic factors, we did not report on a pooled HR for the different prognostic factors. Rather, the meta-analysis is an exploratory analysis to attempt more complete insight into the most strongly associated prognostic factors. Based on these analyses, in patients who underwent RP as primary treatment, the main prognostic factor for DM, PCSM, and OM was *short PSA-DT*. Owing to the heterogeneity in the PSA-DT cutoffs that were investigated, no cutoff can be identified as being the most significant one for disease recurrence. However, most studies associate a PSA-DT cutoff of <12 mo with an increased risk of clinical disease recurrence. This risk increases further with decreasing PSA-DT (more rapidly rising PSA). The shortest

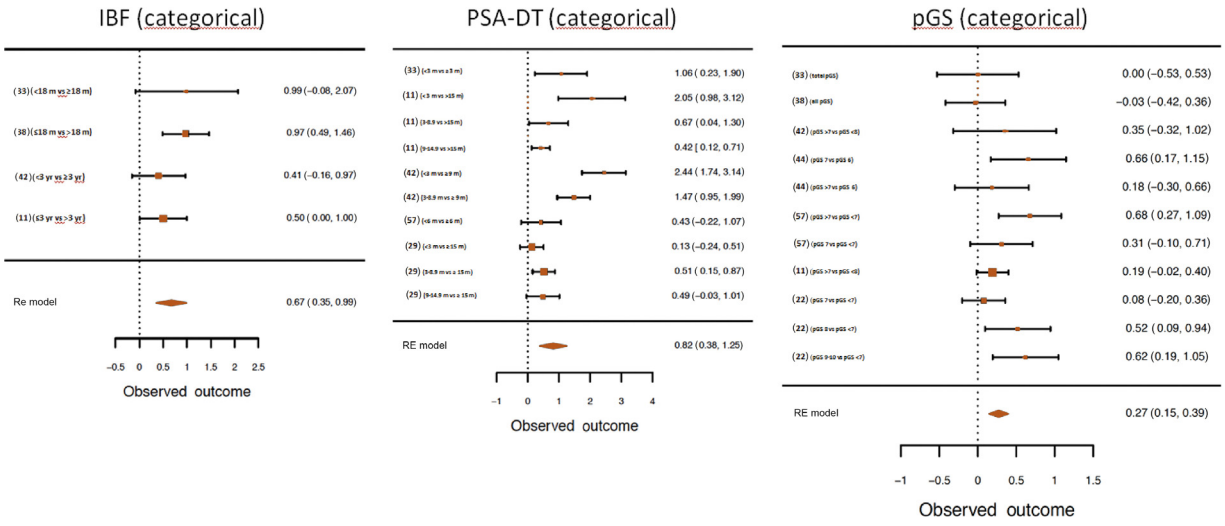

Fig. 7 – Forest plot showing the clinical factors that are significantly associated with overall mortality in patients with BCR after primary radical prostatectomy. BCR = biochemical recurrence; IBF = interval to biochemical failure; pGS = pathological Gleason score; PSA-DT = prostate-specific antigen doubling time RE = random effect.

cutoff investigated is PSA-DT <3 mo, which has the strongest association with clinical disease recurrence. To a lesser extent, a shorter IBF and an increasing pGS is associated with PCSM and OM, respectively. Again, the higher the pGS, the higher the reported risk of clinical disease recurrence, with pGS 8–10 being most associated with a poor prognosis. Similar to PSA-DT, different studies investigated different cutoffs, but most studies associated an IBF of <18 mo with an increased risk of disease recurrence. For patients who underwent primary RT, clearly the strongest prognostic factor for DM, PCSM, and OM was *a short IBF*. The cutoffs used between studies were heterogeneous; however, most studies use IBF <18 mo as a conservative cutoff that is associated with an increased risk of clinical disease recurrence. Compared with RP patients, IBF is probably more prognostic for patients who underwent RT because it unifies two prognostic PSA kinetic factors after RT: PSA nadir and PSA-DT. A short IBF could, therefore, be caused by reaching the PSA nadir early (with higher PSA nadir levels reached early as a sign of poor response to RT) and/or short PSA-DT after the PSA nadir has been reached (as a sign of cancer progression). Increasing bGS is also associated with DM and OM. Although only five studies reported on a population that received a median radiation dose of >74 Gy, data reported in these studies are highly similar to those reported in the meta-analysis (which was performed on all studies). However, we believe that the reported data remain generalizable to today's treatment regimens. Although the radiation dose affects treatment effectiveness, the investigated population is a patient group that has already failed their treatment. Furthermore, treatment biology and therefore cancer cell response

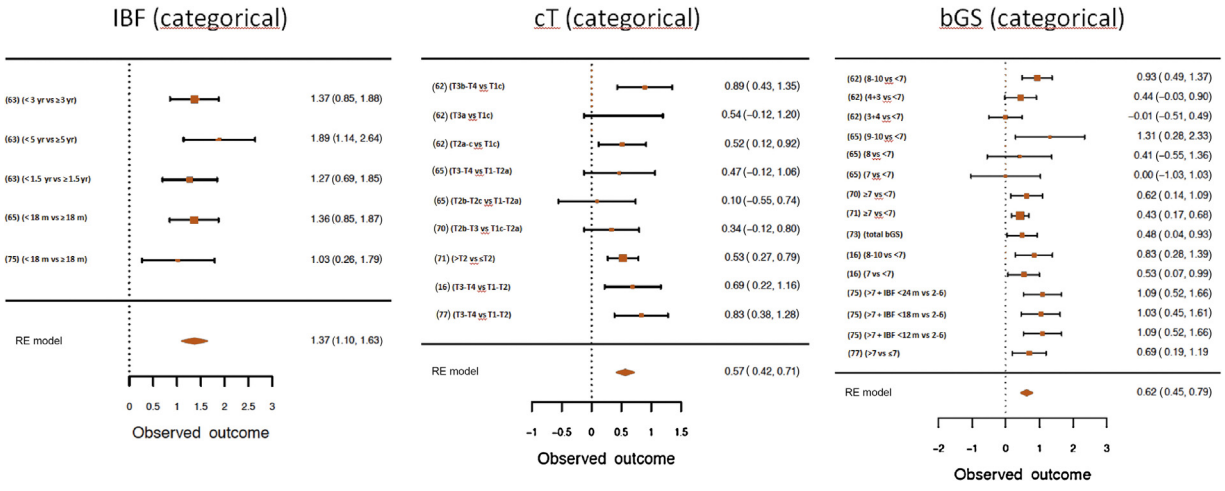

Fig. 8 – Forest plot showing the clinical factors that are significantly associated with the development of distant metastases in patients with BCR after primary radiotherapy. BCR = biochemical recurrence; bGS = biopsy Gleason score; cT = clinical T stage; IBF = interval to biochemical failure; RE = random effect.

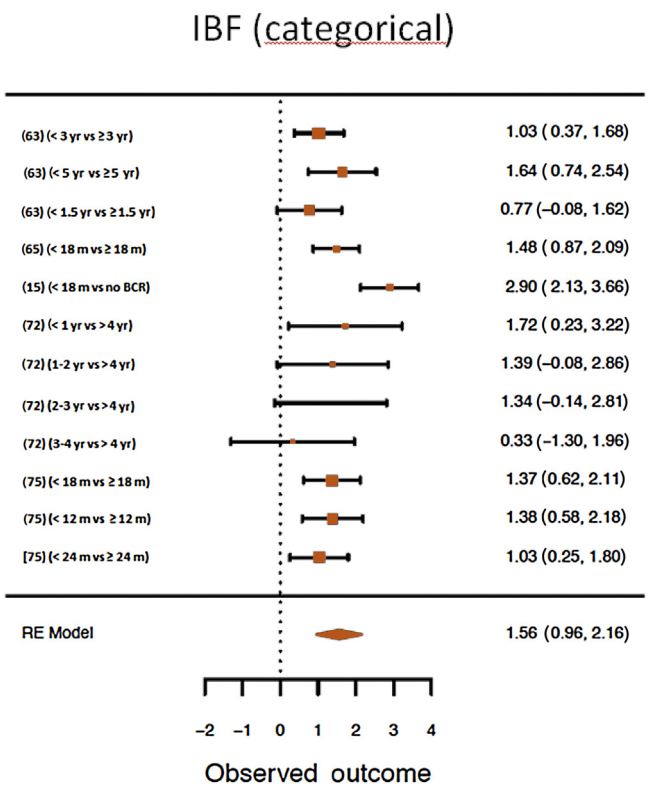

Fig. 9 – Forest plot showing the clinical factors that are significantly associated with prostate cancer–specific mortality in patients with BCR after primary radiotherapy. BCR = biochemical recurrence; IBF = interval to biochemical failure; RE = random effect.

probably remain similar irrespective of the dose. Age determines OM as expected, for both patients receiving RP and those receiving RT.

As a primary meta-analysis a random-effect model was used, which assumes that the investigated studies were drawn from populations that differ in ways that could impact the outcome, for example, the age of the participants or disease stage. Owing to the introduction of multiple covariables in the same meta-analysis (eg, pGS 7 vs pGS 6 and pGS 8–10 vs pGS 6 of the same study), these covariables were treated as being dependent on each other. Therefore, under the random-effect model, the goal is not to estimate one true effect (one HR summarizing all data), but to estimate the mean of a distribution of effects. In contrast to the random-effect model, the fixed-effect model assumes that all studies are more or less homogeneous and share a common true effect size. For sensitivity analysis of the meta-analysis, we therefore compared the results of the fixed-effect model with the primary random-effect model. The former has a lot more significant results, suggesting that the assumption of homogeneity between the studies would be inappropriate and the results obtained via the random-effect model are likely more reliable compared with the fixed-effect model. If we apply the random-effect model without accounting for study dependence, we observe a slightly larger number of identified associations (three or more for RT). However, not accounting for dependence is clearly methodologically ill advised. In addition, given that the primary analysis model was able to identify almost as many associations while properly accounting for the dependence of certain studies, our confidence about its suitability seems justified. Last, comparing our primary analysis with a conservative analysis strategy (an analysis designed to avoid the detection of false positives) yielded almost the same set of significant results. The high degree of agreement between these two types of analyses provides further evidence of robustness (insensitivity) of the outcome of the primary analysis. To exclude the potential publication bias of the meta-analysis results, funnel plots were developed for each covariable. The only clearly asymmetrical funnel plots were for the covariable pGS for the outcomes DM and PCSM. This effect is due to a small number of studies with a high observed effect and a large standard error (Supplementary Fig. 1 and 2). Although this could be attributed to a potential publication bias, we are convinced that this does not compromise the validity of the results, since overall most studies clearly show a prognostic role for pGS (12/14 studies for DM and 10/13 studies for PCSM; see above), and excluding these studies would not change the impact of pGS. Furthermore, a priori we decided not to report on a pooled effect size for the reported meta-analysis because we expected study heterogeneity. Therefore, the inclusion of a limited number of studies with a very high effect size does not affect our study outcomes.

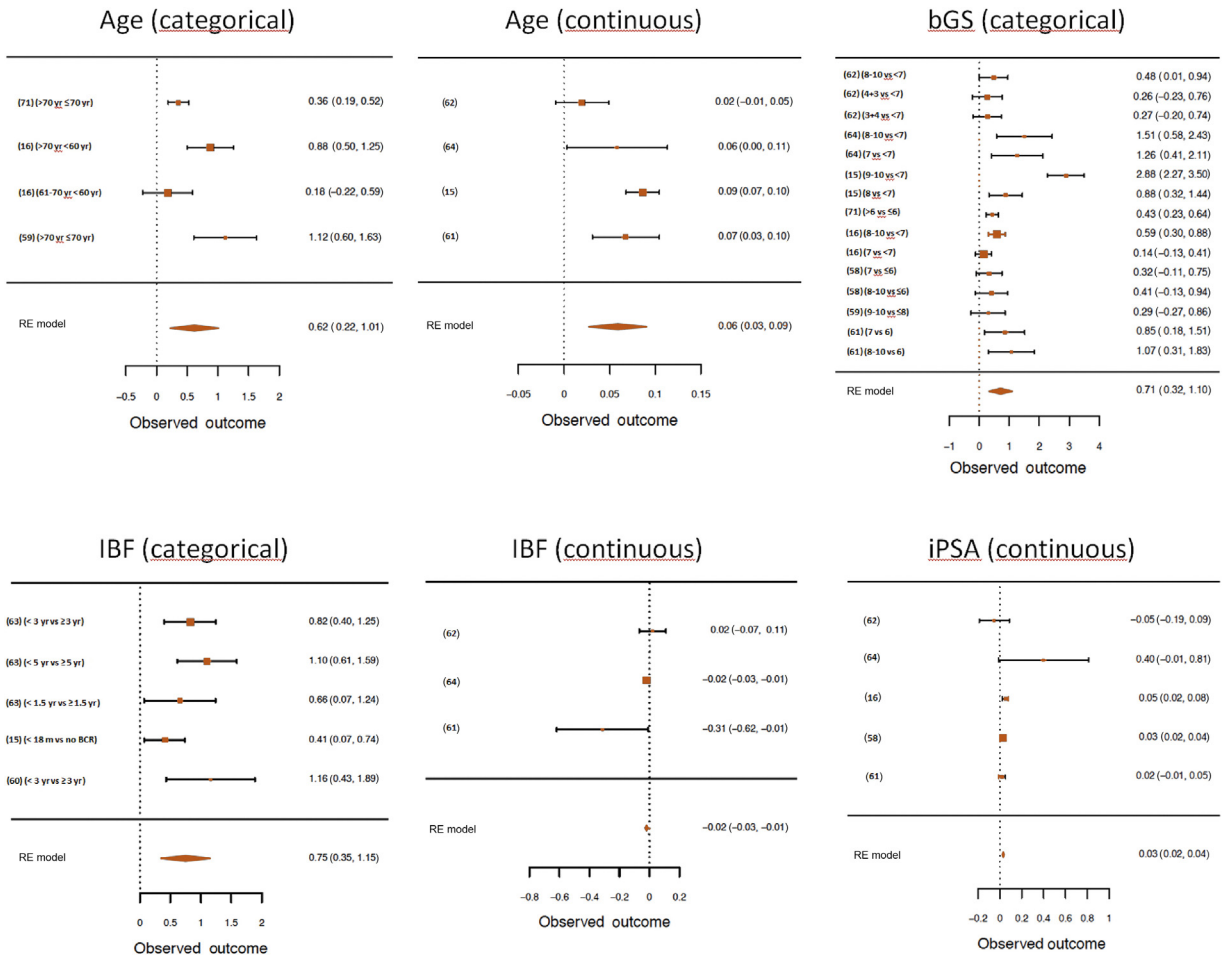

Fig. 10 – Forest plot showing the clinical factors that are significantly associated with overall mortality in patients with BCR after primary radiotherapy. BCR = biochemical recurrence; bGS = biopsy Gleason score; IBF = interval to biochemical failure; iPSA = initial (pretreatment) prostate-specific antigen; RE = random effect.

3.6.2. Implications for clinical practice and further research

Currently, the EAU PCa guidelines present a list of risk factors associated with oncological outcomes based on a limited number of large studies. Based on these extensive analyses, we can refine this list to a limited number of risk factors, which should be taken into consideration when following up patients who develop BCR. Therefore, we propose the introduction and further investigation of a novel BCR risk stratification. Patients experiencing BCR with PSA-DT >1 yr and a pGS of <8 for RP, or an IBF of >18 mo and a bGS of <8 for RT have a significantly lower risk of clinical progression and could be classified as having "*EAU low-risk BCR*." In contrast, patients with shorter PSA-DT of ≤1 yr or a pGS of 8–10 for RP, or an IBF of ≤18 m or a bGS of 8–10 for RT have a higher risk of clinical progression and could be classified as having "*EAU high-risk BCR*." Therefore, both its prognostic value and the potential benefit/toxicities of initiating salvage treatment(s) should be discussed with the patient. Although data are limited, the most robust analysis regarding the impact of sRT based on the currently available patient risk profiles has been performed by Trock et al. [48]. In this study, in patients with PSA-DT <6 mo, sRT ± ADT resulted in a reduction of PCSM with HRs of 0.14 (95% CI 0.05–0.39) to 0.24 (95% CI 0.07–0.77). In contrast, in patients with PSA-DT ≥6 mo, sRT ± ADT had no prognostic value with HRs of 0.66 (95% CI 0.28–1.58) to 0.85 (95% CI 0.45–1.59). For sADT, the level of evidence is too low to suggest any recommendations. Although we acknowledge that a prognostic study design is not the appropriate study design to investigate the therapeutic effect of a certain treatment, it shows that not all patients with BCR are equal in outcome and therefore should not receive the same treatment. As an example, if a PSA rise of >0.2 ng/ml is confirmed in a patient after primary RP, the pGS is ≤7, and if PSA kinetics are favorable (PSA-DT >12 mo, IBF >18 mo), patients should be informed that they have *low-risk BCR* and the potential toxicities of additional treatments should be discussed to allow the patient to make a well-informed decision. The included study designs do not allow us to make any further recommendations if or when to start salvage therapies when BCR occurs, as this was not the goal of this review. Furthermore, the introduced risk stratifica-

tion is proposed only to make clinicians aware that not all patients with BCR have equally poor outcomes. Its predictive and prognostic power needs to be formally validated in either retrospective or prospective cohorts of patients, incorporating individual patient data. Owing to clinical heterogeneity and a heterogeneous study design, a more in-depth interpretation of the available data (such as reporting on a pooled HR for the investigated risk factors) would be inappropriate. In an ideal situation, access to individual patient data from each study would allow us to perform a robust meta-analysis, with standardization of patient criteria, outcomes, and subgroup analyses to explore interactions between variables. To this end, the EAU Guidelines Office has established the *PIONEER consortium* with the purpose of combining data from large organizations across different countries, allowing us to work with big data, answering critical questions in PCa care. Finally, with the introduction of novel, more sensitive imaging techniques such as prostate-specific membrane antigen positron emission tomography and computed tomography scan, more patients with BCR will be diagnosed with metastatic disease at lower PSA levels. Although the diagnostic landscape will change (and in many countries has changed already) due to these imaging techniques, currently it still remains unclear what the therapeutic implications of these metastatic lesions are. Only future research will be able to answer these questions.

3.6.3. Limitations and strengths

The current study represents the first systematic review addressing the impact of BCR on clinically important endpoints (ie, development of DM, PCSM, and OM). The review elements were developed in conjunction with a multidisciplinary panel of experts (EAU Prostate Cancer Guidelines Panel) including a patient representative, and the review was performed robustly in accordance with recognized standards. Important prognostic factors for cancer-related outcomes in patients with BCR were identified, and the review highlighted further areas of research that could help define which patients are at the highest and lowest risks of clinical progression. Another strength of the review is the robustness of the analysis, with additional sensitivity and publication bias analysis being performed to test the integrity of the results. Limitations include the retrospective nature of the majority of studies, reliability of PSA-DT measurements in low-ranged PSA levels, heterogeneity in PSA-DT measurement (number of data points, interval between PSA data points to calculate PSA-DT), and the overall significant clinical and methodological heterogeneity across studies, which limited the quality of the data and precluded further strong recommendations.

4. Conclusions

BCR is an independent risk factor for the development of DM, cancer-specific mortality, and to a lesser extent OM. In patients who underwent RP as primary treatment and who subsequently developed BCR, the main prognostic factor for DM, PCSM, and OM is short PSA-DT (ie, <1 yr) and a high pGS, and to a lesser extent a short IBF. The main prognostic factors for patients developing BCR following primary RT are a short IBF (<18 mo) and a high bGS. After primary RP, sRT protects patients from experiencing disease progression, but this effect is limited to a subpopulation of patients at the highest risk of progression with PSA-DT <6 mo. Therefore, based on this systematic review, we recommend that patients experiencing BCR should not all be treated equally. Rather, we propose patients to be stratified into having EAU low-risk BCR (PSA-DT >1 yr and pGS <8 for RP, IBF >18 mo and bGS <8 for RT) or EAU high-risk BCR (PSA-DT ≤ 1 yr or pGS 8–10 for RP, IBF ≤ 18 mo or bGS 8–10 for RT), raising awareness that not all patients with BCR have similar outcomes. The potential benefit of initiating salvage treatment(s) should be discussed with each individual patient. In contrast, in the absence of risk factors, the nonaggressive course of the disease and the toxicities of salvage treatments should be discussed to allow patients to make a well-informed decision. The predictive and prognostic performance of this risk classification and its clinical value should be assessed and validated in future studies.

This systematic review was performed under the auspices of the European Association of Urology Guidelines Office Board and the European Association of Urology Prostate Cancer Guideline Panel.

Author contributions: Thomas Van den Broeck 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: Van den Broeck, van den Bergh, Mottet.
Acquisition of data: Van den Broeck, van den Bergh, Moris, Arfi.
Analysis and interpretation of data: Van den Broeck, van den Bergh, Arfi, Gross, Moris, Briers, Cumberbatch, De Santis, Tilki, Fanti, Fossati, Gillessen, Grummet, Henry, Lardas, Liew, Rouvière, Pecanka, Mason, Schoots, van Der Kwast, van Der Poel, Wiegel, Willemse, Yuan, Lam, Cornford, Mottet.
Drafting of the manuscript: Van den Broeck, van den Bergh, Gross, Moris.
Critical revision of the manuscript for important intellectual content: Arfi, Gross, Moris, Briers, Cumberbatch, De Santis, Tilki, Fanti, Fossati, Gillessen, Grummet, Henry, Lardas, Mason, Liew, Rouvière, Schoots, van Der Kwast, van Der Poel, Wiegel, Willemse, Yuan, Lam, Cornford, Mottet.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.10.011.

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