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Review – Prostate Cancer – Editor's choice

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Risk Stratification of Patients with Recurrence After Primary Treatment for Prostate Cancer: A Systematic Review

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Abstract

Background and objective: Biochemical recurrence (BCR) after primary definitive treatment for prostate cancer (PCa) is a heterogeneous disease state. While BCR is associated with worse oncologic outcomes, risk factors that impact outcomes can vary significantly, necessitating avenues for risk stratification. We sought to identify prognostic risk factors at the time of recurrence after primary radical prostatectomy or radiotherapy, and prior to salvage treatment(s), associated with adverse oncologic outcomes.
Methods: We performed a systematic review of prospective studies in EMBASE, MEDLINE, and ClinicalTrials.gov (from January 1, 2000 to October 16, 2023) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (CRD42023466330). We reviewed the factors associated with oncologic outcomes among patients with BCR after primary definitive treatment.
Key findings and limitations: A total of 37 studies were included (total n = 10 632), 25 after prostatectomy (total n = 9010) and 12 after radiotherapy (total n = 1622). Following recurrence after prostatectomy, factors associated with adverse outcomes include higher pathologic T stage and grade group, negative surgical margins, shorter prostate-specific antigen doubling time (PSADT), higher prostate-specific antigen (PSA) prior to salvage treatment, shorter time to recurrence, the 22-gene tumor RNA signature, and recurrence location on molecular imaging. After recurrence following radiotherapy, factors associated with adverse outcomes include a shorter time to recurrence, and shorter PSADT or higher PSA velocity. Grade group, T stage, and prior short-term hormone

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therapy (4–6 mo) were not clearly associated with adverse outcomes, although sample size and follow-up were generally limited compared with postprostatectomy data.
Conclusions and clinical implications: This work highlights the recommendations and level of evidence for risk stratifying patients with PCa recurrence, and can be used as a benchmark for personalizing salvage treatment based on prognostics.

ADVANCING PRACTICE

What does this study add?
Several prior works have summarized retrospective data to help prognosticate patients with recurrence following primary treatment for prostate cancer. However, these data are often limited by selection bias which reduce external validity. This review synthesizes the most up-to-date prospective evidence and shows that prognostic risk factors after prostatectomy include grade, T-stage, surgical margin, PSA prior to salvage treatment, and shorter time to recurrence. After radiotherapy, prognostic risk factors include shorter time to recurrence and PSA kinetics.

Clinical Relevance
With an increasing availability of more sensitive restaging imaging options as well as novel loco-regional and systemic treatments, the arena of biochemical recurrence after local treatment with curative intent is getting more and more crowded. Though, patients with relapse after radical prostatectomy or radiation therapy represent a heterogeneous population with diverse prognosis, ranging from indolent phenotype to rapidly aggressive and lethal disease. This systematic review is unique in that it collates evidence from prospective studies/trials only, to identify risk factors able to stratify oncological outcomes. Some of the reported findings, albeit limited by moderate to low quality evidence, do not confirm what we have long known from retrospective studies of the past. It remains to be seen how these data will inform future trials of personalized salvage treatments right in the era of molecular imaging, hormonal treatment intensification and metastasis-directed therapies.
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Patient Summary
We summarize the data from previously reported clinical trials on the topic of which factors predict worse cancer outcomes for patients who recur with prostate cancer after their initial treatment.

1. Introduction

After radical therapy, recurrence in prostate cancer (PCa) is typically indicated by rising serum prostate-specific antigen (PSA), termed biochemical recurrence (BCR). While BCR predicts an increased risk of disease progression and death [1,2], recent research shows that it is not a direct surrogate for overall survival (OS) [3]. This discrepancy is due to the often slow progression of BCR, patient competing risks, and successful salvage therapies such as radiotherapy (RT) after radical prostatectomy (RP) as well as systemic therapies. However, some high-risk BCR patients may face elevated PCa-specific mortality, emphasizing the need for a risk assessment to guide potential treatments.

Extensive retrospective data identify prognostic factors at recurrence, vital for individualized management and targeted trials [2,4–6]. This systematic review consolidates prospective data on risk factors for adverse oncologic outcomes for recurrent PCa after primary definitive treatment (RP or RT) and offers recommendations for risk factor utilization in these patients.

2. Methods

2.1. Inclusion and exclusion criteria

We included English-language peer-reviewed studies published in manuscript form from January 1, 2000 to October 16, 2023. This included phase 2 or 3 trials (including post hoc analyses) and non-phase 1 prospective trials (observational and large single-arm trials). Patients had PCa treated with primary RP or RT with or without androgen deprivation therapy (ADT), exhibiting recurrence via a PSA rise or local recurrence only.

We decided a priori to exclude patients treated with any salvage treatments to more directly relate study findings to patients with their first BCR or local-regional recurrence. Importantly, this excluded the recent EMBARK and PRESTO trials, which comprised 50% and 89% of patients who received RP and RT, respectively [7,8]. We only assessed studies using standard salvage interventions including any androgen-receptor targeting therapies, RT, surgery, or any local procedures. We excluded studies lacking primary out-

come data on OS or the secondary outcomes: cancer-specific survival (CSS) or progression-free survival (PFS; metastatic and/or biochemical). We also excluded studies that did not assess risk factors before salvage treatments. This could have been based on subgroups analyses, multivariable analyses, or (for randomized controlled trials [RCTs]) clear inclusion criteria.

To accommodate word count limits, further details of evidence acquisition as well as portions of the evidence synthesis are provided in the Supplementary material where mentioned.

3. Results

Thirty-five studies (total $n = 10\,632$) were included in the final systematic review, including 25 in the post-RP setting (total $n = 9010$) and 12 in the post-RT setting (total $n = 1622$; Table 1 and Fig. 1). A total of 16, two, and 19 studies were considered to have a low, moderate, and high risk of bias, respectively (Supplementary Table 1).

3.1. Recurrence after RP

Twenty-five studies in the postsurgery setting were included in the systematic review: 11 RCTs, seven post hoc analyses of RCTs, and seven single-arm prospective trials (Table 1).

3.1.1. Surgical pathology and staging

Twenty-one studies assessed surgical pathology and staging variables as risk factors [9–29].

3.1.1.1. Pathologic T stage. Fifteen studies assessed pathologic T stage (Supplementary Table 2) [10–16,18,20–22,24–26,29]. In the GETUG-AFU 16 trial, 743 patients were assigned randomly to receive salvage external beam radiation therapy (EBRT) ± 6 mo of ADT [11,29]. It was noted that seminal vesicle invasion (pT3b) was associated with a shorter time to progression in the multivariable analysis (hazard ratio [HR] 1.93, 95% confidence interval [CI] 1.4–2.7) [11]. Dess et al [13] and Feng et al [15] performed post hoc analyses of NRG/RTOG 9601, which randomized 760 patients to EBRT ± 24 mo of bicalutamide. In these analyses, pT3 versus pT2 was not associated with metastatic recurrence, death from PCa, or death [13,15]. In the study of Choo et al [12], among 75 patients with BCR managed with EBRT and 2 yr of ADT, pT3 versus pT2 was associated with a shorter time to progression in the multivariable analysis (HR 5.98, 95% CI 1.64–21.88). Bowden et al [10] treated 92 patients with salvage EBRT guided by inserted electromagnetic transponders following prostate-specific membrane antigen (PSMA) positron emission tomography (PET). Relative to pT2, pT3b was associated with a shorter time to BCR (HR 2.54, 95% CI 1.22–5.26) [10]. The SAKK 09/10 trial randomized patients with BCR to conventional-dose (64 Gy) or dose-intensified (70 Gy) salvage RT (SRT) [23], and a post hoc analysis assessed the outcomes in subgroups [22]. In that work, stage pT3b was not associated with shorter PFS (HR 1.12, 95% CI 0.59–2.10). In the SPPORT trial, 1716 patients with PSA levels 0.1–2 ng/ml, pT2–3, and pN0/Nx were randomized 1:1:1 to prostate bed-only SRT or with the addition of 4–6 mo ADT or with the addition of ADT and pelvic nodal RT [26]. SPPORT noted that pT3b disease was associated with shorter PFS (HR 2.19, 95% CI 1.42–2.36). In the study of Okubo et al [18], pT3–4 was not associated with the time to progression for patients managed with bicalutamide monotherapy in an unadjusted analysis (HR 1.05, 95% CI 0.62–1.75).

In the studies involving PET evaluations for patients with BCR, Emmet et al [14] found no association between T stage on surgical pathology and PFS, while the EMPIRE-1 trial, which randomized 165 patients to fluciclovine PET or conventional imaging before salvage EBRT, showed that extracapsular extension was associated with a longer time to progression (HR 0.45, 95% CI 0.21–0.95) [16].

While pathologic T stage has variable *prognostic* value across the studies mentioned, it does not clearly appear to be *predictive* of differential treatment benefit. In both GETUG-AFU 16 and SPPORT, patients with and without pT3b disease benefitted from the interventions in terms of MFS and PFS, respectively [26,29]. Similarly, data from three trials that randomized patients to adjuvant RT or SRT showed no interaction between pT3b disease and an interaction with the treatment arm and benefit in PFS (p for interaction = 0.30) [20,24,25,30]. The SALV-ENZA trial recruited 86 patients with high-risk BCR defined as BCR with pathologic grade group (GG) 4–5, or GG 2–3 if pT3 or R1 [21]. These patients were randomized to receive salvage EBRT ± 6 mo of enzalutamide. In this trial, patients with pT3 disease derived the most benefit from enzalutamide in addition to EBRT (HR 0.22, 95% CI 0.07–0.69) compared with those with pT2 (HR 1.54, 95% CI 0.43–5.47), although a statistical interaction was not significant (p for interaction = 0.19).

3.1.1.2. Grade group. Fifteen studies evaluated pathologic GG (Supplementary Table 3) [10,11,13–16,18,19,21,22,24–27,29]. GETUG-AFU 16 showed that GG $\geq$4 was associated with shorter PFS in the univariable analysis (HR 1.81, 95% CI 1.6–2.6) [11]. Similarly, in post hoc assessments of NRG/RTOG 9601 [27], GG $\geq$4 was associated with a shorter time to metastatic recurrence (HR 2.68, 95% CI 1.27–5.64) and death from any cause (HR 1.91, 95% CI 1.09–3.34) in Dess et al's [13] study as well as CSS in Feng et al's [15] study (HR 2.53, 95% CI 1.38–4.49). In the SPPORT trial, GG 4–5 was associated with shorter PFS compared with GG 3 (HR 2.05, 95% CI 1.66–2.53) [26]. In the study of Bowden et al [10], GG 3 and 4–5 diseases were associated with a shorter time to BCR after SRT (HR 5.44, 95% CI 1.66–17.80 and HR 7.90, 95% CI 2.27–27.49, respectively). However, a multivariable analysis from SAKK 09/10 showed that GG 4–5 was not associated with a shorter time to progression [22]. In summary, data are mixed regarding a higher GG as a marker of poor risk after post-RP BCR, but studies before SRT from GETUG-AFU 16, NRG/RTOG 9601, and SPPORT largely support its prognostic value.

In Rigatti et al's [19] study, 72 patients underwent choline PET before salvage lymphadenectomy, and GG 4–5 was not associated with PFS in univariable Cox regression compared with GG 1 (HR 1.06, 95% CI 0.24–4.59). In multivariable Cox regression for PFS in 260 patients who under-

Table 1 – Studies included in the review

First author	Year	Patients	Study design	Sample size	Risk factors assessed/ inclusion criteria	Outcomes
After surgery (n = 25)						
Autio [31]	2021	BCR	Phase 2 RCT: AAP vs AAP + ADT vs AAP	122	PSA metrics	BCRFS
Bitting [9]	2021	BCR	Phase 2 single arm: 6 mo ADT and Enza + 66 Gy EBRT to prostate bed	38	pN1	BCRFS
Bitting [33]	2023	BCR	Phase 2 single arm: 6 mo ADT and Enza + EBRT to prostate bed	31	RNA-based signature	BCRFS
Bowden [10]	2021	BCR	Phase 2 single arm: PSMA PET + EBRT to prostate bed if M0	92	Surgical pathology PSA metrics Time from surgery to PET	BCRFS
Carrie [11]	2016	BCR	Phase 3 RCT: EBRT vs EBRT + 6 mo ADT	743	Patient age Surgical pathology PSA metrics Time from surgery to BCR	PFS
Carrie [29]	2019	BCR	Post hoc analysis of phase 3 RCT: EBRT ± 6 mo ADT	743	Surgical pathology PSA metrics Risk groups	PFS, MFS
Choo [12]	2009	BCR	Phase 1/2 single arm: EBRT + 24 mo ADT	75	Surgical pathology Time from surgery to BCR BCR only vs BCR + local recurrence	PFS
Dal Pra [22]	2022	BCR	Post hoc analysis of phase 3 RCT: EBRT 64 vs 70 Gy	226	RNA-based signature PSA metrics Surgical pathology	PFS, MFS, MFS or OS
Dess [13]	2020	BCR	Post hoc analysis of phase 3 RCT: EBRT ± 24 mo bicalutamide	760	PSA metrics Patient age Surgical pathology	MFS, OS
Emmett [14]	2020	BCR	Prospective single arm: PSMA PET ± EBRT	260	Surgical pathology PSA metrics Time from surgery to PET	PFS
Feng [15]	2021	BCR	Post hoc analysis of phase 3 RCT: EBRT ± 24 mo bicalutamide	486	RNA-based signature Patient age and race PSA metrics Surgical pathology	MFS, CSS, OS
Ghadjar [23] [a]	2021	BCR	Phase 3 RCT: EBRT 64 vs 70 Gy	350	PSA >0.1 and ≤2 pT2a-3b, R0–1, pN0	PFS, OS
Jani [16]	2021	BCR	Phase 2/3 RCT: conventional imaging ± fluciclovine PET	165	Patient age and race PSA metrics Surgical pathology	PFS
Kneebone [24]	2020	BCR in the SRT group	Phase 3 RCT: ART vs SRT at PSA ≥0.2	167	PSA metrics [b] Surgical pathology CAPRA-S	BCRFS
Lawal [17]	2023	BCR receiving SRT	Post hoc analysis of phase 2/3 RCT: conventional imaging ± fluciclovine PET	157	PSA metrics Surgical pathology ADT intent	PFS
Lawal [55]	2023	BCR evaluated by fluciclovine PET	Post hoc analysis of phase 2/3 RCT: conventional imaging ± fluciclovine PET	79	PET findings	PFS
Okubo [18]	2018	BCR	Prospective single arm: 24 mo bicalutamide	91	Patient age PSA metrics Surgical pathology Time from surgery to BCR	PFS
Parker [25]	2020	BCR in the SRT group	Phase 3 RCT: ART vs SRT at PSA ≥0.1 or 3 rises	699	PSA metrics [b] Surgical pathology CAPRA-S	MFS
Pollack [26]	2022	BCR	Phase 3 RCT: prostate-bed RT vs +4–6 mo ADT vs +pelvic nodal RT	1716	PSA metrics Surgical pathology	PFS, MFS, CSS, OS
Rigatti [19]	2011	BCR	Prospective single arm: salvage lymphadenectomy based on choline PET	72	PSA metrics Surgical pathology Time from surgery to BCR PET findings	PFS
Sargos [20]	2020	BCR in the SRT group	Phase 3 RCT: ART vs SRT at PSA ≥0.2	212	PSA metrics [b] Surgical pathology	EFS, OS
Shipley [27]	2017	BCR	Phase 3 RCT: EBRT ± 24 mo bicalutamide	760	Surgical pathology PSA metrics	MFS, OS
Sood [32]	2022	BCR	Post hoc analysis of phase 3 RCT: EBRT ± 24 mo bicalutamide	670	PSA metrics	PFS, MFS, CSS, OS
Tran [21]	2023	BCR	Phase 2 RCT: EBRT ± Enza	86	PSA metrics Surgical pathology Patient age RNA-based signatures	BCRFS
Yokomizo [28]	2020	BCR	Phase 3 RCT: bicalutamide ± EBRT	210	pT0–3, pN0/Nx, and PSA 0.4–1	BCRFS
After radiotherapy (n = 12)						
Bruchovsky [56]	2008	BCR	Phase 2 single arm: intermittent ADT	109	Patient age Clinicopathologic variables Baseline testosterone	PFS

(*continued on next page*)

Table 1 (*continued*)

First author	Year	Patients	Study design	Sample size	Risk factors assessed/ inclusion criteria	Outcomes
Crook [41]	2022	LF	Phase 2 single arm: LDR brachytherapy	92	Clinicopathologic variables Patient age Time from EBRT to salvage RT	PFS, CSS, OS
D'Amico [45]	2006	BCR	Post hoc analysis of phase 3 RCT: EBRT ± 6 mo ADT	81	Prior ADT Age at BCR PSA metrics	OS
Dason [57]	2018	BCR and LF	Prospective single arm: whole-gland HIFU	24	EBRT vs brachytherapy Prior ADT PSA metrics	PFS
Denham [42]	2008	BCR	Post hoc analysis of phase 3 RCT: EBRT ± 3–6 mo ADT	436	PSA metrics Time from primary treatment to BCR	CSS
Hostiou [58]	2019	LF	Phase 2 single arm: whole-gland HIFU	50	Patient age Clinicopathologic variables PSA metrics Prior ADT	PFS
Shipley [59]	2002	BCR	Post hoc analysis of phase 3 RCT: EBRT ± 4 mo ADT	247	Prior ADT	CSS, OS
Siddiqui [60]	2016	LF	Prospective single arm: whole-gland cryoablation	157	PSA metrics	BCRFS, MFS
Siddiqui [61]	2017	LF	Phase 2 single arm: whole-gland HIFU	81	Clinicopathologic variables	BCRFS
Spiess [62]	2013	BCR	Prospective single arm: whole-gland cryoablation	156	PSA metrics	BCRFS
van Son [44]	2020	BCR	Prospective single arm: focal HDR brachytherapy	50	Clinicopathologic variables Patient age PSA metrics	BCRFS
Wo [43]	2009	BCR	Post hoc analysis of phase 3 RCT: EBRT ± 6 mo ADT	89	Patient age Prior ADT Clinicopathologic variables Comorbidities PSA metrics Time from primary treatment to BCR	OS

AAP = abiraterone acetate and prednisone; ADT = androgen deprivation therapy; ART = adjuvant radiotherapy; BCR = biochemical recurrence; BCRFS = biochemical recurrence-free survival; CSS = cancer-specific survival; EBRT = external beam radiotherapy; EFS = event-free survival; Enza = enzalutamide; HDR = high dose rate; HIFU = high-intensity focused ultrasound; LDR = low dose rate; LF = local failure; OS = overall survival; MFS = metastasis-free survival; PET = positron emission tomography; PFS = progression-free survival; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RCT = randomized clinical trial; RT = radiotherapy; SRT = salvage radiotherapy.

[a] Risk factors assessed in a post hoc analysis by Dal Pra et al [22].

[b] Subgroup analyses were assessed in the three trials comparing adjuvant versus early salvage radiotherapy using a collaborative meta-analysis [30].

went PSMA PET to plan salvage EBRT, Emmet et al [14] showed that GG on surgical pathology was ultimately not associated with outcomes (continuous; HR 0.69, 95% CI 0.23–2.06). This was similarly noted in multivariable Cox regression for PFS in the EMPIRE-1 trial (GG 4–5 vs GG <4; HR 0.98, 95% CI 0.49–1.98) [16]. Although it is not possible to show directly, one can speculate that the ability of PET to risk stratify might mitigate the prognostic value of GG in this setting.

Similar to T stage, GG does not appear to serve as a predictive biomarker based on the treatment arm in GETUG-AFU 16 (SRT ± 6 mo of ADT), RAVES and RADICALS-RT (adjuvant vs SRT), Okubo et al's [18] study (SRT ± 24 mo of bicalutamide), or SALV-ENZA (SRT ± enzalutamide) [21,24,25,29,30].

3.1.2. *PSA metrics*

Nineteen studies evaluated various PSA metrics [10,11,13–22, 24–27,29,31,32].

3.1.2.1. PSA value prior to salvage treatment. Thirteen studies evaluated the outcomes associated with PSA values before salvage treatment (Supplementary Table 4) [11,13, 15,18–22,24–27,32]. In the three studies comparing SRT versus adjuvant RT, salvage treatment was triggered at a cutoff of 0.2 ng/ml for RAVES, 0.2 ng/ml and rising for GETUG-AFU 17, and two rises with the second ≥0.1 ng/ml or three consecutive rises for RADICALS-RT [20,24,25]. A collaborative meta-analysis of these trials showed no difference in PFS between the salvage and adjuvant arms (HR 0.95, 95% CI 0.75–1.21) [30]. In a post hoc assessment of SAKK 09/10, PSA >0.5 ng/ml was associated with a shorter time to progression in a multivariable analysis (HR 2.64, 95% CI 1.66–4.08) [22].

Six studies examined interventions involving adding hormonal therapy to EBRT [11,13,15,21,27,32]. Data from GETUG-AFU 16 [11], RTOG 9601 [15,27,32], and SPPORT [26] all showed an association between higher PSA and worse outcomes (Supplementary Table 4). While Okubo et al [18] showed that PSA >0.4 ng/ml at the start of bicalutamide was not a significant predictor of second BCR (HR 1.63, 95% CI 0.97–2.75), Rigatti et al [19] showed that PSA >4 ng/ml was associated with shorter PFS than PSA >4 ng/ml prior to salvage lymph node dissection (HR 2.13, 95% CI 1.05–2.41).

While PSA was generally highly prognostic, it was also the variable most consistently shown to be predictive. In RTOG-9601, there was a significant interaction with PSA and treatment arms, suggesting that patients with higher PSA prior to SRT benefited most from the addition of bicalutamide [13,32]. In SALV-ENZA, a baseline PSA cutoff of 0.5 ng/ml did not inter-

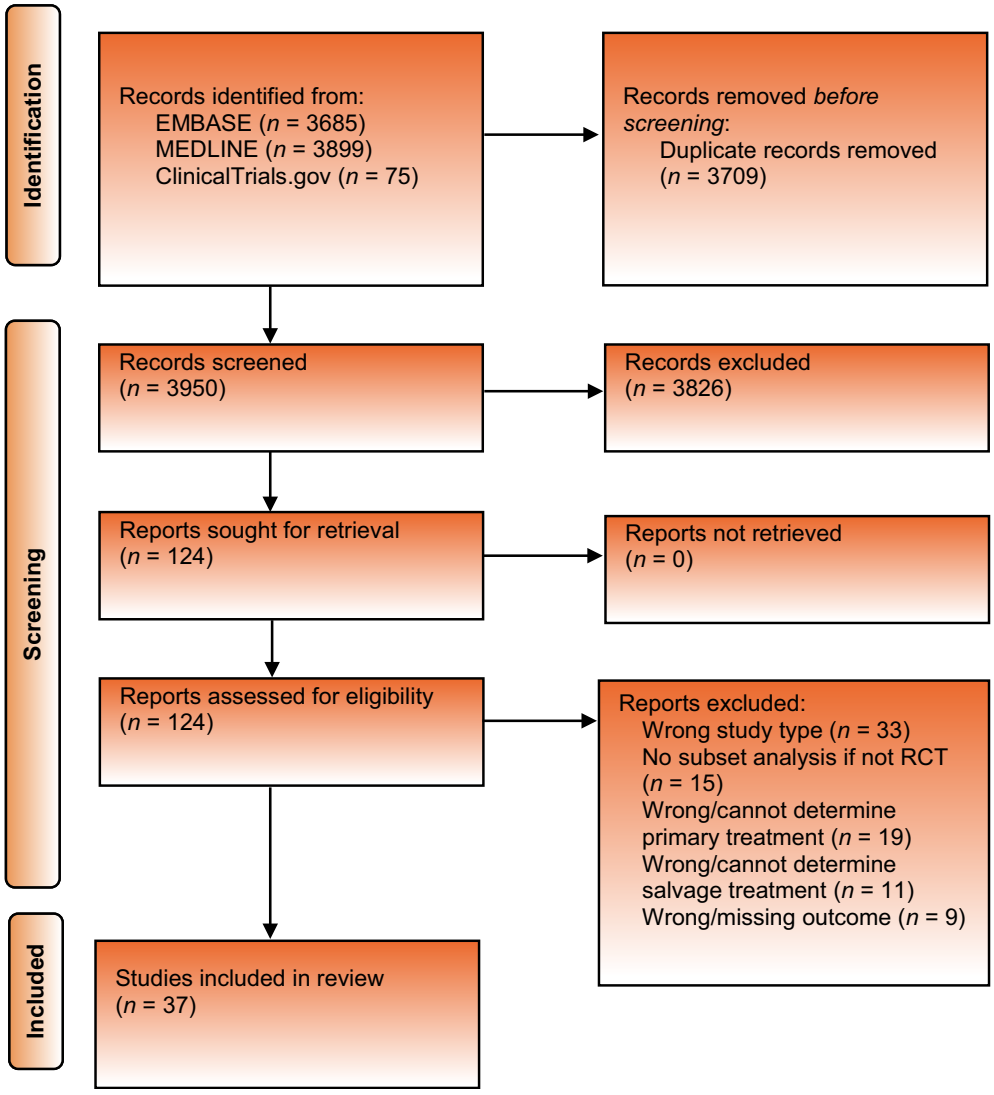

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram. RCT = randomized controlled trial.

act with the treatment arm and PFS ($p = 0.85$) [21]. In the SPPORT trial, patients with PSA ≤0.35 ng/ml did not derive a significant benefit (log-rank one-sided $p = 0.44$) from nodal RT (arm 3) when compared with without nodal RT (arm 2), but patients with PSA >0.35 ng/ml derived a significant benefit (log-rank one-sided $p = 0.038$). Across all pre-salvage PSA strata, patients benefitted from the addition of pelvic lymph node irradiation with or without short-term ADT in the SPPORT trial [26].

3.1.2.2. PSA doubling time. In GETUG-AFU 16, PSA doubling time (PSADT) of <6 mo was associated with shorter PFS in the multivariable analysis (HR 1.44, 95% CI 1.1–1.9; Supplementary Table 5) [11]. However, PSADT below and above the 6-mo cutoff did not identify differential benefit from the addition of ADT to SRT [29]. Autio et al [31] investigated abiraterone and prednisone, ADT, or the combination in patients who had PSA ≥1 ng/ml and PSADT ≤9 mo, and found that the combination led to similar rates of undetectable PSA at 18 mo with recovered testosterone, suggesting that the combination is not superior to ADT alone using those inclusion criteria. Thus, PSADT data, while limited, may be prognostic, but are not clearly predictive of response to treatment.

3.1.3. *Timing of BCR*

Five studies assessed the timing of recurrence after surgery (Supplementary Table 6) [10–12,18,19]. In Bowden et al's [10] study, increasing months between surgery and PET imaging at the time of recurrence was slightly associated with a longer time to progression (HR 0.99, 95% CI 0.97–1.00). Similarly, in the study of Choo et al [12], a gap of ≥2 yr between surgery and BCR was associated with longer PFS (HR 0.20, 95% CI 0.05–0.93). In Okubo et al's [18] study, a gap of <6 mo between surgery and BCR was associated with shorter PFS (HR 2.10, 95% CI 1.22–3.61). GETUG-AFU 16 showed that a gap of ≤30 mo between surgery and recurrence was not associated with PFS in a univariable analysis (HR 1.32, 95% CI 1.0–1.7) [11]. Finally, in the study of Rigatti et al [19], among patients undergoing salvage lymphadenectomy, time from surgery to BCR <24 mo was not significantly associated with PFS (HR 0.88, 95% CI 0.44–1.74).

3.1.4. Tumor RNA-based signatures

Four studies assessed RNA-based signatures (Supplementary Table 7) [15,21,22,33]. In a post hoc analysis of the STREAM trial, 31 tumors from prostatectomy underwent RNA profiling [33]. The study associated several signatures with an increased risk of progression on a univariable analysis, including a PCa risk score [34], a PTEN loss signature (shorter PFS) [35], a subtyping score based on luminal cell RNA expression patterns (longer PFS) [36], a model predictive of homologous recombination deficiency (shorter PFS) [37], and a signature predictive of response to ADT [38]. Similarly, 44 tumors from prostatectomy in the SALV-ENZA trial were profiled to assess a variety of RNA-based signatures in subgroup analyses [21]. Of interest, patients with tumors positive for a signature predictive of alterations in *ERG* benefited more from the addition of enzalutamide to SRT (HR 0.11, 95% CI 0.01–0.90) [39]. Post hoc assessments of SALV-ENZA, SAKK 09/10, and RTOG 9601 showed that each assessed an RNA-based genomic classifier originally developed to predict metastatic recurrence after RP (22-gene Decipher classifier) [15,21,22,40]. The score is based on the weighted expression of 22 genes, ranging from 0 to 1, and is commonly split into a low-risk (0–0.45), intermediate-risk (0.45–0.60), or high-risk group (0.60–1). In SALV-ENZA, patients with high scores had a greater magnitude of benefit from enzalutamide than those with low or intermediate scores (HR 0.35, 95% CI 0.06–1.97 vs HR 0.70, 95% CI 0.20–2.39) [21]. In both RTOG 9601 and SAKK 09/10, higher scores were associated with all outcomes (OS, CSS, MFS, and PFS) [15,22]. Thus, it appears that select RNA-based signatures are useful to determine prognostic risk and personalize salvage treatments after prostatectomy. These signatures hold promise as tools in prospective trials to identify patients most likely to benefit from intensified salvage treatments.

Assessments of surgical margin, nodal status, PSA prior to molecular imaging, PSA nadir, PSA prior to RP, other patient factors, and risk groups are provided in the Supplementary material and Supplementary Tables 8–15.

3.2. Recurrence after primary radiotherapy

Twelve studies assessing patients following primary RT were included (Table 1): zero primary assessments of RCTs, four post hoc analyses of RCTs, and eight single-arm prospective trials. Overall quantity and quality of studies were generally lower with shorter follow-up than those of studies that assessed recurrence after RP.

3.2.1. Timing of recurrence

Three prospective studies assessed the timing of recurrence (Supplementary Table 16) [41–43]. Denham et al [42] performed a post hoc assessment of patients with recurrence after primary treatment with EBRT with or without 3 or 6 mo of ADT (TROG 96.01; $n = 436$). In their work, they assess both time to BCR and PSADT as surrogates for CSS. Through their rigorous assessment of surrogacy, they found that BCR timings of 1.5–2.5 yr were predictive of CSS. Neither Crook et al [41] nor Wo et al [43] showed an association between time to BCR and outcomes in their smaller studies. Thus, based on an assessment of prospective data from Denham et al's [42] study TROG 96.01 alone, it appears that a shorter time to BCR is associated with worse outcomes.

3.2.2. PSA velocity

Four studies assessed PSADT or velocity using prospective data (Supplementary Table 17) [42–45]. D'Amico et al [45] found that PSADT of <6 mo was associated with shorter OS than that of >12 mo (HR 4.9, 95% CI 1.1–23). Based on the data from TROG 96.01, PSADT cutoffs of <12 and <15 mo fulfilled the Prentice criteria for surrogacy for CSS [42]. The time to CSS was much shorter for patients with BCR and PSADT of <12 mo than for those with BCR and PSADT ≥12 mo (HR 23.49, 95% CI 12.94–42.63). In the study of Wo et al [43], increasing PSA velocity (continuous, log-transformed increase per ng/ml, per year) was associated with shorter OS (HR 1.60, 95% CI 1.23–2.09). Finally, van Son et al [44] reported on 50 patients who received salvage focal high-intensity focused ultrasound and showed that PSADT was not associated with PFS (continuous; HR 0.98, 95% CI 0.95–1). Thus, the highest level of evidence suggests that measures of PSA rises such as PSADT and velocity can help risk stratify patients with recurrence after EBRT.

Assessments of clinicopathologic variables, PSA cutoffs, prior ADT, and other patient factors are provided in the Supplementary material and Supplementary Tables 18–21.

4. Discussion

This systematic review provides insights into prospective data evaluating risk factors for adverse oncologic outcomes among patients with recurrence following primary RP or RT for PCa (Tables 2 and 3). Notably, all identified risk factors were supported by moderate or lower evidence strength

Table 2 – Summary of findings and recommendations for risk stratifying patients with recurrence after primary radical prostatectomy[a]

Risk factor	Findings and recommendation	Strength of evidence
Surgical pathology	≥pT3, GG ≥4, and R0 are risk factors for adverse oncologic outcomes	●●●○ Moderate
PSA prior to salvage treatment	PSA >0.5 or >1 ng/ml is associated with worse oncologic outcomes	●●●○ Moderate
PSA doubling time	PSA doubling time <6 mo might be associated with worse oncologic outcomes	●●○○ Low
Other PSA metrics	PSA nadir after surgery and PSA before surgery are not associated with worse oncologic outcomes	●●○○ Low
Patient factors and timing of recurrence	Shorter time between surgery and recurrence (<2 yr) is associated with shorter time to progression. Neither race nor patient age is prognostic	●●○○ Low
Tumor RNA signatures	A 22-gene genomic classifier is a useful risk factor for patients receiving salvage treatments	●●●○ Moderate
Molecular imaging	No recurrent disease or disease confined to the prostate fossa is a favorable risk factor	●●○○ Low
Risk groups and other risk factors	No risk groups have been shown to be predictive in prospective studies	●○○○ Very low

GG = grade group; PSA = prostate-specific antigen.
[a] Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) was used to define the strength of evidence.

Table 3 – Summary of findings and recommendations for risk stratifying patients with recurrence after primary radiotherapy

Risk factor	Findings and recommendation	Strength of evidence
Clinicopathologic variables	Value of these variables such as biopsy GG or clinical T stage are limited	●●●○ Moderate
Timing of recurrence	Shorter time to BCR (<1.5 to <2.5 yr) is a risk factor for poor oncologic outcomes	●●●○ Moderate
Prior ADT	Short-term prior ADT (4–6 mo) is not associated with adverse oncologic outcomes. There were no data on prior longer-term ADT	●●●○ Moderate
PSA metrics	Measures of PSA kinetics (shorter PSADT and higher PSA velocity) are associated with worse oncologic outcomes, in particular, PSADT <12 mo	●●●○ Moderate
Patient factors	No other patient factors are associated with oncologic outcomes	●○○○ Very low

ADT = androgen deprivation therapy; BCR = biochemical recurrence; GG = grade group; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time.
Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) was used to define the strength of evidence.

owing largely to heterogeneity in salvage treatments and reliance mainly on PFS based on PSA rises as opposed to CSS or MFS. The only risk factors with moderate evidence supporting their use following RP were clinicopathologic variables (GG, T stage, and margin status), PSA prior to salvage treatment, and shorter time to BCR (Table 2). Following RT, these factors are shorter time to BCR and PSA kinetics (Table 3). These findings highlight the critical needs for future research to risk stratify patients who might benefit most from treatment intensification.

This review also demonstrated moderate evidence that GG, clinical T stage, and prior short-term ADT were not associated with adverse outcomes following BCR after primary RT. These factors should not be considered when counseling patients with BCR following RT or designing clinical trial entry. Overall, prospective evidence in the setting of BCR following RT was limited compared with that following RP, highlighting important avenues for future research.

Large retrospective cohort studies have attempted to identify risk factors associated with adverse oncologic outcomes following BCR [4–6]. These works have hugely been important in initial considerations for risk stratifying patients with BCR. However, these retrospective data have common forms of potential bias and confounding such as a selection bias limiting external validity. For instance, the European Association of Urology BCR risk groups were based on a systematic review of almost exclusively retrospective studies and were assessed in retrospective cohorts to help validate the value of these groupings [1,46,47]. Recent work showed that patients with high-risk BCR after RP benefitted from SRT, while those with low-risk BCR did not [48]. However, in another work, the risk of death from PCa within 10 yr in the low-risk group following RT was as high as 24% [1]. To avoid the risk of selection bias in retrospective studies, this review was limited to prospective studies as a novel approach to the question of risk stratifying these patients. As a result, this review provides the highest level of evidence on this subject. It is important to note that this review was purposely limited to the context of first recurrence before any adjuvant or salvage treatment. Thus, findings here cannot be extrapolated directly to, for instance, patients with BCR following RP and SRT.

Ultimately, how trials define patients with low- or high-risk recurrence will determine treatment paradigms. In the recently published EMBARK trial, 1068 patients with high-risk BCR were randomized 1:1:1 to ADT, ADT plus enzalutamide, or enzalutamide alone [8]. Enrolled patients had PSA >1 ng/ml after surgery or >2 ng/ml above a post-RT nadir and PSADT ≤9 mo. Compared with ADT alone (71.4%), ADT plus enzalutamide and enzalutamide alone improved 5-yr MFS (87.3% and 80%, respectively; HR 0.42, 95% CI 0.30–0.61 and HR 0.63, 95% CI 0.46–0.87, respectively). Similarly, the PRESTO trial enrolled 503 patients with high-risk BCR defined as PSADT ≤9 mo [7]. Both ADT plus apalutamide and ADT plus apalutamide and abiraterone prolonged PFS compared with ADT alone (HR 0.52, 95% CI 0.35–0.77 and HR 0.48, 95% CI 0.32–0.71, respectively). Thus, a single PSADT cutoff could define high-risk BCR, but further work is needed to define patients with low-risk BCR. Neither EMBARK nor PRESTO provided subgroup assessments of patients based on only prior RT or RP, so further work is needed to individualize salvage hormone therapy based on prior local therapy.

The ongoing STARTAR phase 2 trial defines high-risk BCR with surgical pathology (GG 4–5 or 2–3, and pT3, R1, or N1 disease) [49]. In that cohort, the addition of docetaxel to SRT, ADT, and apalutamide resulted in 3-yr PFS of 72%, which was superior to that seen with just SRT, ADT, and enzalutamide in the STREAM trial (53%) [9]. Thus, the value of risk factors in the context of various potential salvage treatments remains an ongoing question.

Tumor bulk RNA biomarkers seem to be a valuable factor for continued prospective assessment [15,22]. NRG-GU006 is a completed randomized trial for patients with BCR after RP, which stratified patients by luminal versus basal transcriptomic biology and randomized patients to SRT with or without 6 mo of apalutamide (NCT03371719) [50]. The 22-gene classifier has also been used to stratify patients in NRG-GU002 (SRT + ADT ± docetaxel; NCT03070886) and was utilized in the FORMULA-509 randomized trial (SRT + ADT ± apalutamide and abiraterone) [51]. Similar evaluations should be considered in patients with recurrence following primary RT.

Finally, most reviewed studies did not use PET. PET can detect more metastases at BCR than conventional imaging [52] and potentially improve oncologic outcomes [16]. Additionally, with trials continuing to evaluate treatment paradigms for oligometastatic PCa, molecular imaging could continue to refine the natural history of recurrent disease. In the ORIOLE trial assessing metastasis-directed therapy, patients with any untreated lesions on PSMA PET were at a higher risk of progression at 6 mo (63% vs 16%; $p = 0.006$) [53]. It is also estimated that as many as 40% of patients who could qualify for EMBARK would have metastatic disease on PSMA PET [54]. The ongoing phase 3 INNOVATE trial (NCT04134260) will randomize patients with recurrence after RP to SRT and ADT without or with apalutamide. Metastatic disease will be ruled out by and radia-

tion planning will be based on PET. Large trials such as INNOVATE will serve as rich sources of risk factor assessment.

5. Conclusions

This review systematically assembled prospective evidence on risk factors for patients with BCR after primary RP or RT. All risk factors assessed were of moderate or lower quality evidence. Thus, this review benchmarks a significant gap in knowledge on how to identify patients who would benefit from treatment intensification or novel trials. Ongoing clinical trials stratifying patients by these risk factors will be paramount to an overall effort to advance precision care following PCa recurrence.

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Acquisition of data: Weiner, Kakani, Kanabur.
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Supplementary data

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