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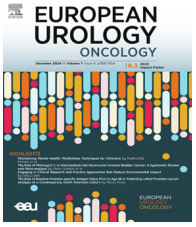

European Association of Urology

Review

Prognostic and Predictive Role of SPOP Mutations in Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: Mutations in the speckle-type POZ (*SPOP*) gene are frequently identified in prostate cancer (PC); yet, prognostic implications for affected patients remain unclear. Limited consensus exists regarding tailored treatments for SPOP-mutant (SPOPmut) PC.
Objective: To elucidate the prognostic and predictive significance of SPOP mutations across distinct PC stages and treatments.
Evidence acquisition: A systematic literature search of PubMed, Embase, and Scopus was conducted up to January 29, 2024. The meta-analysis included studies comparing survival outcomes between SPOPmut and SPOP wild-type (SPOPwt) PC.
Evidence synthesis: From 669 records, 26 studies (including five abstracts) were analyzed. A meta-analysis of metastasis-free survival in localized (hazard ratio [HR]: 0.72, 95% confidence interval [CI]: 0.59–0.88; $p < 0.01$) and overall survival (OS) in metastatic PC (HR: 0.64, 95% CI: 0.53–0.76; $p < 0.01$) showed a favorable prognosis for patients with SPOPmut PC. In metastatic settings, SPOP mutations correlated with improved progression-free survival (PFS) and OS in patients undergoing androgen deprivation therapy ± androgen receptor signaling inhibitor (HR: 0.51, 95% CI: 0.35–0.76, $p < 0.01$, and HR: 0.60, 95% CI:0.46–0.79, $p < 0.01$, respectively). In metastatic castration-resistant PC, only abiraterone provided improved PFS and OS to patients with SPOP mutations compared with patients with SPOPwt, but data were limited. SPOP mutations did not correlate with improved PFS ($p = 0.80$) or OS ($p = 0.27$) for docetaxel.
Conclusions: Patients with SPOPmut PC seem to exhibit superior oncological outcomes compared with patients with SPOPwt. Tailored risk stratification and treatment approaches should be explored in such patients.

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Patient summary: Speckle-type POZ (SPOP) mutations could be a favorable prognostic factor in patients with prostate cancer (PC) and may also predict better progression-free and overall survival than treatment with hormonal agents. Therefore, less intensified treatments omitting chemotherapy for patients with SPOP-mutant PC should be explored in clinical trials.

1. Introduction

Prostate cancer (PC) is the second most diagnosed solid tumor and the sixth leading cause of cancer death among men worldwide [1,2].

Beyond the well-established hereditary forms of PC accounting for over 15% of cases [3], multiple somatic recurrent genomic alterations, encompassing mutations, DNA copy-number changes, rearrangements, and gene fusions, have been identified in PC tissues and used for classification into distinct subtypes [4]. Fusions involving androgen-regulated promoters with members of the ETS transcription factors family (eg, TMPRSS2-ERG fusion) are among the most frequently observed alterations, within around 45% of PC cases [5]. Additionally, primary PC exhibits frequent single-gene mutations, with those involving speckle-type POZ (SPOP), TP53, FOXA1, and PTEN being the most prevalent [6].

SPOP is an E3 ubiquitin ligase adaptor protein integral to a larger ubiquitin ligase complex responsible for the degradation of multiple protein substrates, including androgen receptor (AR), TRIM24, SRC-3, BRD2/3/4, and C-MYC [7], among others. SPOP mutations disable protein ubiquitylation and degradation of these substrates, and thereby stabilize these oncogenes to promote cell proliferation and cancer development [8].

In the context of PC, SPOP mutations are detected among 4–14% of patients [9] and tend to co-occur with CHD1 deletions [4,10]. Conversely, SPOP mutations are strictly mutually exclusive with ERG fusions. The latter requires wild-type SPOP (SPOPwt) to dampen AR signaling for optimal support of the ERG's oncogenic function [10]. Multiple lines of evidence suggest that PC with an *SPOP* gene mutation (SPOP-mutant [SPOPmut] PC) is exquisitely driven and dependent on AR signaling, as SPOPmut directly stabilizes AR and its coactivators and enhances intratumoral testosterone synthesis [11]. In preclinical studies, SPOPmut models display enhanced sensitivity to the inhibition of the AR signaling pathway, supported by growing clinical evidence in SPOPmut PC [12].

While the clinicopathological features of SPOPmut PC have been reviewed systematically [13], the prognostic and predictive roles of SPOP mutations in PC remain underexplored.

To date, therapeutic options available for PC encompass a diverse array of systemic treatments in various settings [14–16].

Currently, there is no consensus and insufficient evidence supporting a distinct and specific treatment approach for most PC genetic subtypes, including SPOPmut PC.

To our knowledge, this is the first systematic review and meta-analysis conducted to assess whether the detection of *SPOP* gene mutations holds significant prognostic and predictive value within localized PC and metastatic PC (mPC).

2. Evidence acquisition

This systematic review with meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The study protocol was registered on PROSPERO (CRD42024497724).

2.1. Search strategy

We undertook a systematic search of the literature up to January 29, 2024. The search was conducted across two bibliographic databases (PubMed and Embase) and one citational database (Scopus). The search string can be found in the Supplementary material.

2.2. Study selection

We conducted a systematic review including retrospective studies or post hoc analyses of prospective trials describing treatment-related outcomes such as patterns of response and survival outcomes (outcome) in SPOPmut PC (population), in both localized and metastatic settings. The analysis of SPOP mutations was conducted using samples obtained from either tissue specimens or liquid biopsies. For the meta-analysis, only studies that compared SPOPmut with SPOPwt patients (comparison) were eligible for inclusion. In the localized setting (setting A), patients had to undergo prostatectomy to be included in the meta-analysis (intervention A). In metastatic settings (setting B), patients had to be exposed to systemic treatments such as androgen deprivation therapy (ADT), androgen receptor signaling inhibitors (ARSIs), docetaxel, or combinations thereof (intervention B). The selected studies were required to report survival outcomes, such as overall survival (OS), event-free survival (EFS), disease-free survival (DFS), metastasis-free survival (MFS), and progression-free survival (PFS) encompassing radiological, clinical, and biochemical progression, or time to castration resistance (TTCR; outcome). In order to be included in the meta-analysis, studies had to provide sufficient data to calculate hazard ratios (HRs) and relative 95% confidence intervals (95% CIs). Two investigators (M.P. and G.S.) performed initial screening of all published manuscripts independently. Exclusion criteria are provided in the Supplementary material.

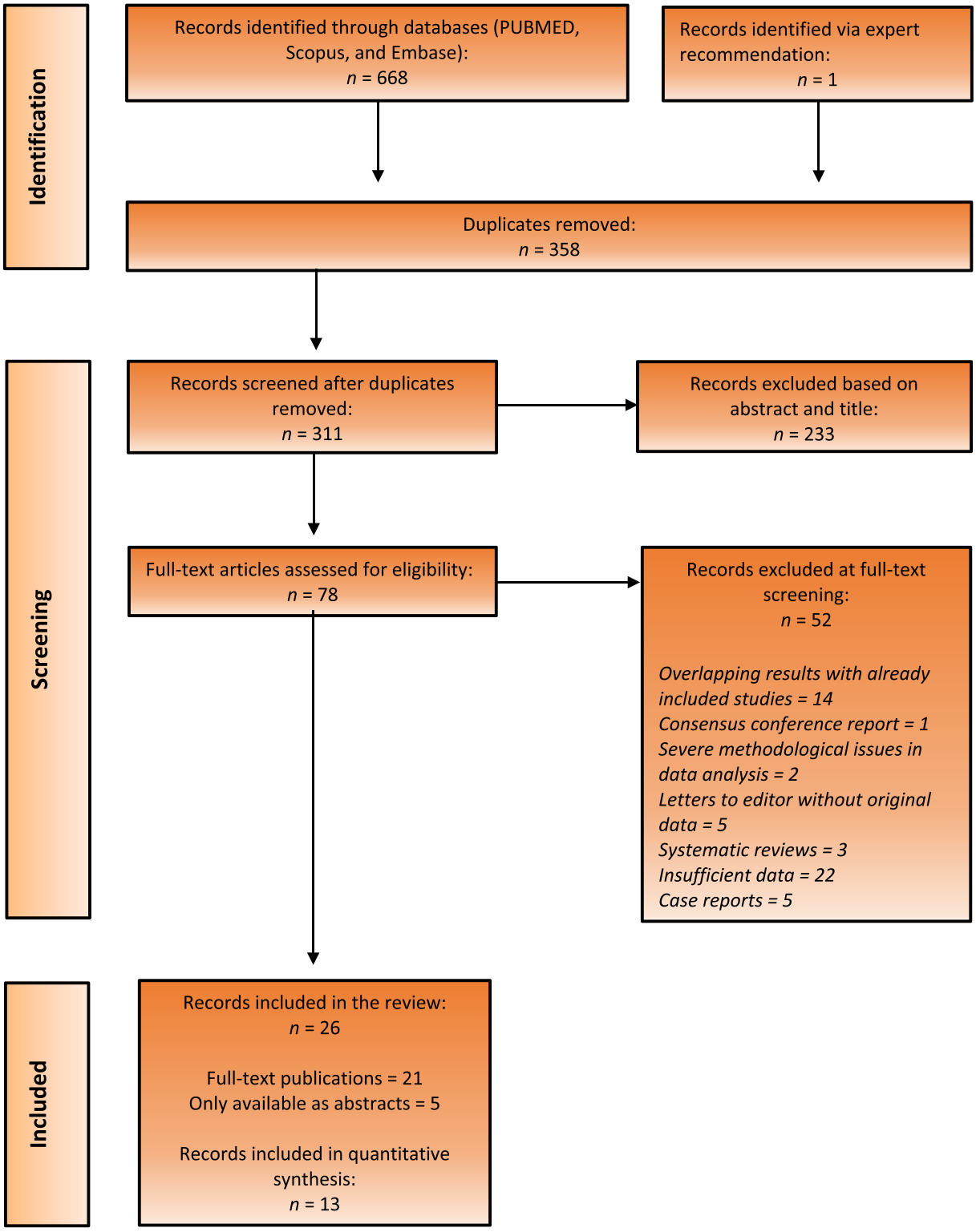

Fig. 1 – PRISMA flowchart. Flow diagram outlining the search strategy and the final included and excluded studies. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

2.3. Data extraction

Two authors (M.P. and G.S.) performed data extraction independently. Any disagreements were discussed with a third author (R.P.M.) and resolved by consensus. Study characteristics including author, year, recruitment period, country, primary and secondary endpoints evaluated, patient demographics, type of treatment (ADT, ARSIs, docetaxel, or combination thereof), PC stage, and SPOP mutation prevalence

Table 1 – Characteristics of included studies

Ref. no.	Authors (year)	Type of study	Type of treatment (%)	Study population (stage, SPOPmut *n*/total *n*, % SPOPmut)	Median follow-up, median age at diagnosis (years old)	Methods	Outcomes	Main findings Notes
Localized prostate cancer								
[32]	García-Flores et al (2014)	Retrospective analysis of RNAseq database	Radical prostatectomy (100%)	Localized PC, 9/90, 10% SPOP low expressor (below the first quartile): 66/256, 25.8%	96 mo (2–189 mo), NA	PCR for expression studies NGS for gene mutations	BPFS, PFS	SPOPmut had worse BPFS at both UV ($p = 0.009$) and MV (HR: 3.4, 95% CI: 1.5–7.6, $p = 0.004$). SPOP expression was associated with both BPFS ($p = 0.003$) and PFS ($p = 0.023$) with low level of expression of SPOP having the worst prognosis MV analysis in very low expressor patients resulted in the same findings in both BPFS (HR: 0.5, 95% CI: 0.4–0.9, $p = 0.011$) and PFS (HR: 0.6, 95% CI: 0.4–1, $p = 0.046$) SPOP expression was lost in all cases with mutations, but no association between SPOP mutations and expression level was found Notes: all patients were TMPRSS2-ERG (T2E) negative.
[29]	Liu et al (2018)	Retrospective	Radical prostatectomy (100%)	Localized PC, 146/1626, 9%	NA	Novel gene expression signature classifier based on transcriptional data	MFS, PCSM-free survival, and BCR (in SPOPmut vs SPOPwt vs other molecular subgroups)	At UV Cox analysis, SPOPmut subclass had the highest BCR and MFS, and the lowest PCSM compared with ERG- and ETS-positive subclasses. Higher MFS at UV analysis for SPOPmut versus SPOPwt ($p = 0.002$, HR not shown), and a positive trend was also seen for PCSM-free survival ($p = 0.064$, HR not shown) Based on PSA level at diagnosis and SPOP mutational status, when comparing same PSA-level groups, SPOPmut subgroups had better MFS ($p < 0.001$) than their SPOPwt counterparts. Four groups were identified (PSA <10/SPOPwt, PSA >20/SPOPwt, PSA <10/SPOPmut, and PSA >20/SPOPmut with 807, 79, 215, and 39 patients, respectively). PCSM-free survival showed a similar trend ($p = 0.102$) PSA >20/SPOPmut patients compared with all patients with PSA <10 had no differences in terms of both MFS ($p = 0.828$) and PCSM ($p = 0.68$)
[46]	Wankowicz et al (2018)	Retrospective (abstract)	Neoadjuvant ADT plus abiraterone/enzalutamide	Localized PC, 4/14, 28.6%	NA	whole exome and whole transcriptome sequencing	Response	SPOP mutations were observed only in exceptional responders (4/8 vs 0/6), and TP53 and PTEN mutations were observed only in nonresponders (4/6 vs 0/8) Definitions: exceptional responders ($n = 8$; MRD: $\leq$0.5 mm of tumor at RP); nonresponders ($n = 6$; pT3 or lymph node positive at RP)

Table 1 (**continued**)

Ref. no.	Authors (year)	Type of study	Type of treatment (%)	Study population (stage, SPOPmut *n*/total *n*, % SPOPmut)	Median follow-up, median age at diagnosis (years old)	Methods	Outcomes	Main findings Notes
[47]	McBride et al (2019)	Ad interim results of phase 2 AASUR trial (abstract)	Ultrahypofractionated RT with 6 mo of abiraterone, apalutamide, and leuprolide	38 very high risk (VHR) localized PC NGS performed on 20 patients: 15% SPOPmut (3/20), 20% FOXA1mut (4/20)	NA	NGS assay (MSK IMPACT) performed on CTCs isolated using EPIC Sciences platform	PSA response	A trend towards an association with SPOP/FOXA1 mutations and undetectable (<0.05 ng/ml) PSA was found among patients with normalized testosterone after protocol treatment ($n = 16$). Of SPOP/FOXA1 mutated patients, 83.3% (5/6) had undetectable PSA versus 30% without (3/10) ($p = 0.12$) Notes: VHR was defined as Gleason 9–10 or two high-risk features (radiographic T3/T4 or >4 cores of Gleason 8).
[25]	Faisal et al (2020)	Retrospective monocentric	Radical prostatectomy (100%)	African American localized PC, 23/205, 11.2%	5 yr (IQR 2–10), 58 (IQR 53–63)	NGS analysis using custom-designed Pan-GU panel (35 genes)	MFS, BFS	SPOPmut PC was not associated with MFS or BFS at UV and MV analysis MFS UV HR 1.05 (95% CI: 0.30–3.62, $p = 0.942$); MV HR 1.34 (95% CI: 0.34–5.32, $p = 0.678$) BFS UV HR 0.61 (95% CI: 0.28–1.33, $p = 0.210$); MV HR 0.75 (95% CI: 0.33–1.71, $p = 0.497$)
[26]	Hernández-Llodrà et al (2021)	Retrospective	Radical prostatectomy (100%)	Localized PC, 6/102 SPOP mutated, 5.9%; 85/198 IHC SPOP loss, 42.9%	NA; approximately 65	IHC and PCR analyses; data from the MARBiobanc	Time to PSA recurrence (rPSA)	rPSA Cox univariate analysis performed for: SPOP protein expression loss versus wt levels ($p = 0.53$), different combinations of SPOP and/or PTEN protein loss ($p = 0.31$), SPOPmut versus SPOPwt ($p = 0.77$)
[27]	Shoag et al (2020)	Retrospective	Radical prostatectomy (100%)	Intermediate- to high-risk localized PC, 127/1421, 8.93%	9 yr (IQR: 6–12), 60 (56–64)	DNA sequencing or transcriptional signature	PCSM, MFS, biochemical recurrence	SPOPmut patients had numerically lower rates of biochemical recurrence (HR: 0.90, 95% CI: 0.69−1.16), metastases (HR: 0.72, 95% CI: 0.51−1.02), and PCSM (HR: 0.71, 95% CI: 0.44−1.15) on MV Cox regression model (adjusted for prostatectomy pathological features) Notes: survival analysis performed in Decipher retrospective cohort
[28]	Liu et al (2021)	Retrospective	Radical prostatectomy (100%)	Localized PC. Decipher retrospective (8% SPOPmut) and prospective cohort (4% SPOPmut)	NA	Application of transcriptional classifiers (microarray-based gene expression data—Decipher prostate cancer test)	MFS, BFS, and PCSM in SPOPmut versus CHD1del patients	Significant differences in MET-free survival rates ($p = 0.001$) Differences in prognostic outcome were described also between late events of PTEN and CHD1 deletions, and early events of ERG fusion and SPOP mutation for BCR- and PCSM-free survival rates Notes: survival analysis population: 238 localized PC (128 SPOPmut, 110 CHD1del)
[30]	Sumiyoshi et al (2024)	Retrospective analysis of the phase 3 CALGB 90203 trial	Arm A (91 patients): ADT+ docetaxel + radical prostatectomy Arm B (81 patients): radical prostatectomy	High-risk localized PC, 20/173, 11.56%	6.1 yr (0.1–12.1), 62 (58–66)	Targeted DNA sequencing performed using a panel of prostate cancer genes at the Vancouver Prostate Centre	EFS, PSA PFS, OS	No association between TP53 or SPOP alterations and pathological treatment effect in either arm UV EFS: arm A HR 0.9 (95% CI: 0.4–2.2, $p = 0.86$); arm B HR 1 (95% CI 0.4–2.2, $p = 0.98$) UV OS: arm A HR 2.1 (95% CI: 0.2–17.4, $p = 0.51$); arm B HR 0.7 (95% CI: 0.1–5.2, $p = 0.7$) UV PSA PFS: arm A HR 1 (95% CI: 0.2–4.4, $p = 1.00$); arm B HR 3 (95% CI: 0.9–10, $p = 0.07$) Notes: MV Cox regression analysis was adjusted for tumor fraction, pathological tumor cellularity, ISUP grade, pathological treatment effect, and intraductal carcinoma.

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Table 1 (**continued**)

Ref. no.	Authors (year)	Type of study	Type of treatment (%)	Study population (stage, SPOPmut *n*/total *n*, % SPOPmut)	Median follow-up, median age at diagnosis (years old)	Methods	Outcomes	Main findings Notes
[31]	Bidot et al (2024)	Retrospective	Radical prostatectomy and lymph node dissection (100%)	African American locally advanced PC all pN+, 4/17, 23.5%	23.0 mo (IQR 21.7–24.3), NA	WES and WTS of DNA and RNA	DFS	No difference in DFS between SPOPmut and SPOPwt at UV analysis ($p = 0.75$); overall median DFS was 4.1 mo
Prostate cancer, any stage								
[48]	Ma et al (2017)	Retrospective (abstract)	Multiple treatment types (not specified)	Both localized and metastatic patients, 16/198, 8.1%	27 mo, NA	Pyrosequencing	Risk of PSA failure	SPOPmut had 1.27× higher risk of metastasis ($p = 0.003$) and of PSA failure (35.49 times, $p < 0.003$) versus SPOPwt; associations remain significant at MV analyses Notes: SPOP mutation prevalence was completely unbalanced between metastatic and localized study populations, possibly driving to wrong conclusions (56.3% of SPOPmut patients were metastatic, while only 11.5% SPOPwt patients were metastatic).
[33]	Lehrer and Rheinstein (2020)	Retrospective	NA	PC at any stage, 57/492, 11.59%	NA, 61 ± 6.8	RNAseq data from the GDC-TCGA PRAD data set	OS	Increased expression of SPOP in 492 PC cases at any stage was associated with reduced survival ($p = 0.00275$, log rank test 8.966) Notes: SPOPlow expressors: 241/492, 48.98%.
[34]	Cavalcante et al (2023)	Retrospective large-scale multiomic analysis	Multiple treatment types: ADT, ARTA, docetaxel, platinum salts, PARPi, RT	Mixed PC stages, 601/6546, 9.18% SPOPmut. Localized, 386/3738, 10.33%. Metastatic, 215/2808, 7.66%.	NA	NGS on genomic DNA using a 592-gene panel or whole-exome sequencing (700 genes at high coverage and read depth)	OS (subgroup analysis by type of treatment start and type of SPOP hotspot mutation)	SPOPmut was associated with better UV OS in the total population (both localized and metastatic): HR 0.644 (95% CI: 0.549–0.756, $p < 0.00001$) Different outcomes were found when considering OS from type of treatment start (taxanes, ADT, antiandrogen, RT, platinum compounds, CIIs, or PARP inhibitors) with respective HR (and 95% CI) on UV OS analysis: 0.723 (0.521–1.003, $p = .051$); 0.718 (0.563–0.916, $p = 0.007$); 0.697 (0.572–0.849, $p < 0.001$); 0.638 (0.462–0.881; $p = 0.006$); 0.526 (0.195–1.421, $p = 0.198$); 1.669 (0.516–5.396, $p = 0.384$); 1.064 (0.517–2.191, $p = 0.869$), respectively HR (and 95% CI) on UV OS analysis of different SPOPmut showed that hotspot location affected outcomes: in particular, Y87 mutation was not significantly associated with OS from diagnosis (HR: 0.658, 95% CI: 0.424–1.022, $p = 0.061$) or ADT start ($p = 0.733$) and antiandrogen start ($p = 0.946$), in contrast with F102 mutation ($p = 0.002$, $p = 0.023$, $p < 0.001$)
Metastatic hormone-sensitive prostate cancer (mHSPC)								
[49]	Chi et al (2019)	Retrospective (abstract)	Randomized to ADT+ abiraterone/prednisone versus placebo	De novo high-risk mHSPC patients	NA	DNA ($n = 43$) and RNA ($n = 48$) extracted from archived tumor samples	rPFS, OS	LATITUDE study subgroup analysis: associations with clinical outcomes were not meaningful; results were limited by fewer samples and events

Table 1 (**continued**)

Ref. no.	Authors (year)	Type of study	Type of treatment (%)	Study population (stage, SPOPmut *n*/total *n*, % SPOPmut)	Median follow-up, median age at diagnosis (years old)	Methods	Outcomes	Main findings Notes
[35]	Swami et al (2020)	Retrospective multicenter	Standard ADT	De novo mHSPC patients, 25/121, 21%	33.9 mo, 66 (NA-NA)	NGS of tumor tissue biopsy	OS from ADT start, PFS from ADT start	SPOPmut had significantly improved PFS and OS on MV analysis (35 vs 13 mo, HR: 0.47, 95% CI: 0.25–0.87; $p = 0.016$; 97 vs 69 mo, HR: 0.32, 95% CI: 0.12–0.88; $p = 0.027$) compared with those with SPOPwt Notes: MV Cox regression analysis was adjusted for age, PSA, and Gleason. PFS was defined as biochemical, radiological, or clinical progression as per the PCWG2 criteria.
[38]	Stopsack et al (2020)	Retrospective monocentric	22% on continuous ADT, 78% NA	mHSPC, 55/424, 13% De novo, 275, 65% Metachronous, 149, 35%	TTCR: 27.2 mo OS: 30.5 mo; 66 (59–72)	DNA sequencing from FFPE samples	Time to CRPC, OS	SPOPmut mHSPC had longer time to CRPC (HR: 0.59, 95% CI: 0.39–0.89; HR:0.63, 95% CI: 0.39–1.00) and OS (HR: 0.28, 95% CI: 0.11–0.79; HR: 0.33, 95% CI: 0.13–0.34) on both UV and MV analyses Notes: MV Cox regression analysis was adjusted for genomic pathways mutually, disease volume, timing of metastases, age, PSA, type of sample (prostate vs metastasis), and fraction of genome altered.
[37]	Nizialek et al (2021)	Retrospective monocentric	ADT monotherapy (74.4%) ADT + ARSI (8.81%) ADT + docetaxel (15.86%)	mHSPC patients (53.3% de novo, 46.7% metachronous), 28/227, 22.04% De novo, 14/121, 11.6% Metachronous, 14/106, 13.2%	32.92 mo, NA	NGS on somatic tumor DNA data, 69% primary prostatic tumor biopsies or prostatectomies, 22% metastatic biopsies, and 8% ctDNA analysis	PFS (radiological or biochemical progression), OS	In UV analysis on the entire population, SPOPmut was not predictive of PFS (HR: 0.74, CI: 0.42–1.31) or OS (HR: 0.77, CI: 0.35–1.78), while in MV analysis, a positive trend was seen for PFS (HR: 0.53, CI: 0.28–1.04) and OS became significant (HR: 0.34, CI: 0.13–0.89) In UV analysis among either de novo or metachronous mHSPC patients, SPOPmut was not predictive of either PFS (HR: 0.82, CI: 0.38–1.80, $p = 0.61$; HR: 0.73, CI: 0.32–1.70, $p = 0.47$) or OS (HR: 0.87, CI: 0.30–2.49, $p = 0.79$; HR: 0.79, CI: 0.24–2.58, $p = 0.69$) Notes: MV Cox regression analysis was adjusted for age, Gleason, PSA type of treatment, and disease volume.
[36]	Swami et al (2022)	Retrospective multicenter	First-line ARSI (52.1%) First-line docetaxel (47.9%)	De novo mHSPC, 38/447, 8.5% First-line ARSI, 20/233, 8.6% First-line docetaxel, 18/214, 8.4%	21.2 mo (12.8–34.4); 67.0 (60.0–74.0)	NGS on tumor biopsies	Time to CRPC, OS SPOPmut vs SPOPwt	In the ARSI cohort, SPOPmut had better time to CRPC(HR: 0.20, 95% CI: 0.06–0.63, $p = 0.006$) and OS (HR: 0.19, 95% CI: 0.05–0.79; $p = 0.022$) than SPOPwt In the docetaxel cohort, time to CRPC not OS was better (HR: 0.86, 95% CI: 0.46–1.58, $p = 0.62$; HR: 1.18, 95% CI: 0.57–2.44; $p = 0.66$; respectively) Notes: first-line ARSI (SPOPwt: 61.4% abiraterone, 8.2% apalutamide, 30.5% enzalutamide; SPOPmut: 75% abiraterone, 5% apalutamide, 20% enzalutamide); first-line docetaxel (one SPOPwt patient received cabazitaxel).

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Table 1 (**continued**)

Ref. no.	Authors (year)	Type of study	Type of treatment (%)	Study population (stage, SPOPmut *n*/total *n*, % SPOPmut)	Median follow-up, median age at diagnosis (years old)	Methods	Outcomes	Main findings Notes
Metastatic castration-resistant prostate cancer (mCRPC)								
[39]	Abida et al (2019)	Retrospective multicenter	ARSI (abiraterone, enzalutamide, or apalutamide)	mCRPC, 9/128, 7.03%	NA, 61 (38–89)	WES and RNAseq (of the 444 biopsies, 37% were lymph node, 36% were bone, and 14% were liver)	OS from ARSI start, time on treatment with first-line ARSI	SPOPmut was not correlated with longer OS from start of first-line ARSI in mCRPC (HR: 0.77, 95% CI: 0.31–1.90, $p = 0.565$), while was associated with longer time on treatment with a first-line ARSI (median 13.7 mo in SPOPmut vs 8.3 mo in SPOPwt, $p = 0.04$)
[40]	Stangl et al (2023)	Retrospective monocentric	ARSI as first line in 97 patients (65% enzalutamide, 35% abiraterone) Docetaxel in 49 patients (first-line in 6 patients, 100% SPOPwt)	103 mCRPC patients, 13/103, 12.6% First-line ARSI, 13/94, 13.83% First-line enzalutamide, 10/63, 15.87% First-line abiraterone, 3/34, 8.82% Any line docetaxel, 4/49, 8.16%	NA SPOPwt 62 (55.2–68.0) SPOPmut 66.0 (63.0–71.0)	Tumor DNA sequencing	OS from the start of ARSI or docetaxel, PSA PFS from the start of ARSI or docetaxel, PSA response on treatment, time on treatment	UV and MV OS analyses from ARSI start (HR: 0.47 95% CI: 0.11–1.97, $p = 0.30$; HR: 0.38, 95% CI: 0.09–1.62, $p = 0.19$) and docetaxel start (HR: 0.39, 95% CI: 0.05–2.91, $p = 0.36$; HR: 0.42, 95% CI: 0.05–3.26, $p = 0.403$) showed no association with SPOPmut SPOPmut was associated with PSA PFS from ARSI start with a trend toward longer median PSA PFS on UV analysis (1.79 vs 0.84 yr, log-rank $p = 0.06$), reaching statistical significance on MV (HR: 0.37; 95% CI: 0.17–0.84; $p = 0.02$), while no significant difference was found from docetaxel start (median PSA PFS 0.4 vs 0.5 yr) at both UV and MV analyses (HR: 1.29, 95% CI: 0.39–4.28, $p = 0.678$; HR: 1.29, 95% CI: 0.35–4.72, $p = 0.699$) Median PSA decline from ARSI start was higher in SPOPmut than in SPOPwt (median decline 100% vs 92%, $p = 0.02$), while no association was found with PSA response (defined as percentage change on PSA nadir) to docetaxel (median decline 37% vs 37%) SPOP mutation was not associated with the median duration of ARSI treatment (12.7 vs 13.7 mo, $p = 0.98$) Notes: MV Cox regression analysis was adjusted for age, race, metastasis, Gleason, and PSA. PSA progression was defined as an increase in PSA of >25% and >2 ng/ml above nadir.
[44]	Orme et al (2023)	Retrospective multicenter	100% PARP inhibitors (93.9% olaparib, 2.29% rucaparib, 2.29% talazoparib, 1.52% veliparib)	mCRPC BRCA2mut, 14/131, 10.69%	NA	NGS	Response rate (50% PSA), PARP inhibitor treatment duration, PFS, OS	Among BRCA2-mutated patients treated with PARP inhibitors, co-occurring SPOPmut predicted better response rate (85.7% vs 53.8%, likelihood ratio: 4.07, $p = 0.044$), PARP inhibitor treatment duration (HR: 0.51, 95% CI: 0.26–1.0, $p = 0.05$), biochemical PFS (HR: 0.33, 95% CI: 0.15–0.72, $p = 0.005$; multivariable HR: 0.16, 95% CI: 0.05–0.47, adjusted $p = 0.001$), rPFS (HR: 0.4, 95% CI: 0.18–0.86, $p = 0.02$; multivariable HR: 0.28, 95% CI: 0.1–0.81, adjusted $p = 0.019$), and OS (HR: 0.41, 95% CI: 0.15–1.12, $p = 0.08$; multivariable HR: 0.19, 95% CI: 0.05–0.69, adjusted $p = 0.012$)

Table 1 (**continued**)

Ref. no.	Authors (year)	Type of study	Type of treatment (%)	Study population (stage, SPOPmut *n*/total *n*, % SPOPmut)	Median follow-up, median age at diagnosis (years old)	Methods	Outcomes	Main findings Notes
[45]	Powles et al (2022)	Randomized controlled trial	172 (12 SPOPmut, 7.0%) treated with enzalutamide; 153 (6 SPOPmut, 3.9%) treated with atezolizumab + enzalutamide	325/759 mCRPC patients with available SPOP status data;. 5.54% (18/325) SPOPmut	In the general study population: 15.2 mo atezo + enza vs 16.6 enza; 70.0 (40–92)	NGS	PFS (PCWG3 criteria)	SPOPmut did not predict a PFS benefit from the addition of atezolizumab to enzalutamide treatment (HR: 1.29, CI: 0.4–4.14)
Metastatic prostate cancer, both mHSPC and mCRPC								
[41]	Boysen et al (2018)	Retrospective monocentric	mHSPC: 100% ADT mCRPC: 100% first-line docetaxel Abiraterone as second line in 61 patients	mHSPC docetaxel first-line, 23/71, 32.39% mCRPC abiraterone second-line, 17/61, 27.8%	NA	NGS on DNA isolated from tumor tissue biopsies	Time to CRPC, OS, time on treatment, abiraterone response	SPOPmut did not predict longer time to CRPC or OS from PC diagnosis, nor OS from CRPC diagnosis (HR: 1.13, CI: 0.68–1.87, $p = 0.64$; HR: 0.80, CI: 0.46–1.38, $p = 0.43$; and $p = 0.31$, respectively) SPOPmut predicted better OS from abiraterone start ($p < 0.001$) with SPOPmut mOS of 35.0 (3.3–55.0) versus 14.3 (8.4–26.1) mo for SPOPwt SPOPmut response to abiraterone was higher in SPOPmut (OR: 14.50, $p = 0.001$; $p = 0.03$ if only considering 50% PSA fall) SPOPmut was associated with longer duration of abiraterone treatment (HR: 0.37, 95% CI: 0.20–0.69, $p = 0.002$) Notes: response to abiraterone was defined as RECIST v1.1 and/or PSA falls ≥50%.
[42]	Nakazawa et al (2022)	Retrospective monocentric	mHSPC: notes mCRPC: notes	mHSPC (31.9% de novo; 68.1% metachronous), 72/72, 100% Progressed to CRPC, 31/72, 43.1%	NA; 64 (46–85)	NGS of primary tumors ($n = 57$), metastatic lesions ($n = 13$), or liquid biopsies ($n = 2$)	Time to CRPC, PSA PFS on abiraterone or enzalutamide (in mCRPC)	In HSPC context (mixed localized and metastatic), SPOPmut cancers treated with ADT had a median time to castration resistance of 42.0 (95% CI: 25.7–60.8) mo In CRPC context, mPFS was 8.9 (95% CI: 6.7–NR) mo on abiraterone and 7.3 (95% CI: 3.2–NR) mo on enzalutamide Notes: mHSPC: 80.6% ADT (52.8% ADT alone, 8.3% + abiraterone, 4.2% + enzalutamide, 15.2% + docetaxel). PARPi in three patients mCRPC (any line): 67.7% abiraterone, 51.6% enzalutamide, 19.4% docetaxel, 19.4% cabazitaxel, and 12.9% PARPi.
[43]	Zhou et al (2022)	Retrospective	NA	Metastatic PC, 216/1799, 12%	22.56 mo (0–77.7), NA	RNAseq and NGS on tumor samples (data from cbioPortal)	OS, risk of death	SPOPmut mOS was significantly longer ($p < 0.0001$) than SPOPwt mOS with 60.68 (95% CI: 49.58–72.15) and 72.35 mo (95% CI: 65.35–NA), respectively In both UV and MV OS analyses, SPOP mutations were independent prognostic factors for better prognosis (HR: 0.592, 95% CI: 0.427–0.819, $p < 0.001$). Notes: MV Cox regression analysis was adjusted for age, metastatic count, metastatic site count, and genetic mutational status.

(*continued on next page*)

Table 1 (continued)

Ref. no.	Authors (year)	Type of study	Type of treatment (%)	Study population (stage, SPOPmut *n*/total *n*, % SPOPmut)	Median follow-up, median age at diagnosis (years old)	Methods	Outcomes	Main findings Notes
[50]	Thomas et al (2023)	Retrospective (abstract)	mHSPC: 39% ADT alone, 59% combinations mCRPC: 83% ADT + abiraterone or enzalutamide, 17% NA	mHSPC, 70/70, 100% mCRPC, 29/29, 100%	NA, 75 (50–91)	NGS on tumor samples	Treatment comparison in SPOPmut population, PFS, OS	mHSPC-PFS: 28.1 mo for ADT alone versus 35 mo for ADT + ADE ($p = 0.08$) Median CRPC second-line PFS was 15 mo; median CRPC second-line ARSI (abiraterone or enzalutamide) PFS was 15.3 mo; median OS for the entire group was 173 mo (95% CI:135–NR) Notes: PFS was defined as time to next line of therapy. PSA progression by PCWG2 criteria, or clinical progression. mHSPC: 39% ADT alone, 59% ADT + abiraterone, docetaxel, or enzalutamide: 2% (2 patients) only observation.

ADT = androgen deprivation therapy; ARSI = androgen receptor signaling inhibitors; atezo = atezolizumab; BCR = biochemical recurrence–free survival; BFS = biochemical recurrence–free survival; BPFS = biochemical progression-free survival; CI = confidence interval; CRPC = castration-resistant prostate cancer; CTC = circulating tumor cell; ctDNA = circulating tumor DNA; DFS = disease-free survival; EFS = event-free survival; enza = enzalutamide; FFPE = formalin-fixed paraffin embedded; GU = genitourinary; HR = hazard ratio; HSPC = hormone-sensitive prostate cancer; IHC = immunohistochemistry; IQR = interquartile range; ISUP = International Society of Urological Pathology; MET = metastasis; MFS = metastasis-free survival; mOS = median OS; mPFS = median PFS; MRD = minimal residual disease; MV = multivariate analysis; NA = not applicable; NGS = next-generation sequencing; NR = not reached; OR = odds ratio; OS = overall survival; PARP = poly ADP-ribose polymerase; PARPi = PARP inhibitor; PC = prostate cancer; PCR = polymerase chain reaction; PCSM = prostate cancer–specific mortality; PCWG = Prostate Cancer Working Group; PFS = progression-free survival; PSA = prostate-specific antigen; RNAseq = RNA sequencing; RP = radical prostatectomy; rPFS = radiographic PFS; RT = radiotherapy; SPOP = speckle-type BTB/POZ protein; SPOPmut = SPOP mutant; SPOPwt = SPOP wild type; TTCR = time to castration resistance; UV = univariate analysis; WES = whole exome sequencing; WTS = whole transcriptome sequencing.

were collected. Treatment-related outcomes including OS, PFS, EFS, DFS, MFS, and TTCR, and their respective HRs and 95% CI values were extracted from each study including the supplementary data.

2.4. Statistical analysis

The methods described by Tierney et al [17] were adopted for the prognostic meta-analysis and for the collection of time-to-event data. HRs of individual trials were taken directly from the articles or calculated using validated methods [18]. Forest plots were used to visually assess pooled HRs for the association between SPOP mutations and survival outcomes. The primary objectives encompassed a pooled analysis of MFS, PFS (encompassing radiological, clinical, and biochemical progression, or TTCR), and OS. To examine the influence of each study on the pooled estimates, we planned subgroup and sensitivity analyses based on castration status, type and line of treatment, survival endpoint definitions, and risk of bias (RoB) of included trials. Heterogeneity among the results of studies analyzed in the meta-analysis was assessed using the Cochrane Q test [19,20]. The I^2 statistics were used to describe the proportion of interstudy variation caused by heterogeneity.

Given a limited study pool and expected heterogeneity, we employed an REML random-effect model [21] for the estimation of robust pooled estimates and predictive intervals. To bolster our examination of heterogeneity, alternative models (those of DerSimonian and Laird [22], Sidik and Jonkman [23], and Hartung and Knapp) were included in a sensitivity analysis. Furthermore, we conducted metaregression analyses focused on the percentages of patients undergoing docetaxel or ADT ± ARSI treatments. Rigorous exploration for a publication bias involved visual inspection through funnel plots [24] and statistical evaluation with the Egger test, implemented when the number of included studies exceeded 10. All statistical analyses were performed using R v4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.5. RoB assessment

Two authors (M.P. and G.S.) evaluated each study independently using the Newcastle-Ottawa Scale for quality assessment of retrospective studies analyzing survival outcomes. The RoB graphic was created using the package "robvis" in R v4.3.2.

3. Evidence synthesis

3.1. Study selection and characteristics

The PRISMA flowchart is presented in Figure 1. After applying the selection criteria, we included 21 original articles [25–45]. Additionally, five abstracts from international congresses [46–50] were incorporated into the systematic review, although excluded from the meta-analysis. The selected studies focused on localized PC ($n = 10$), mPC ($n = 13$), or both settings ($n = 3$; Table 1).

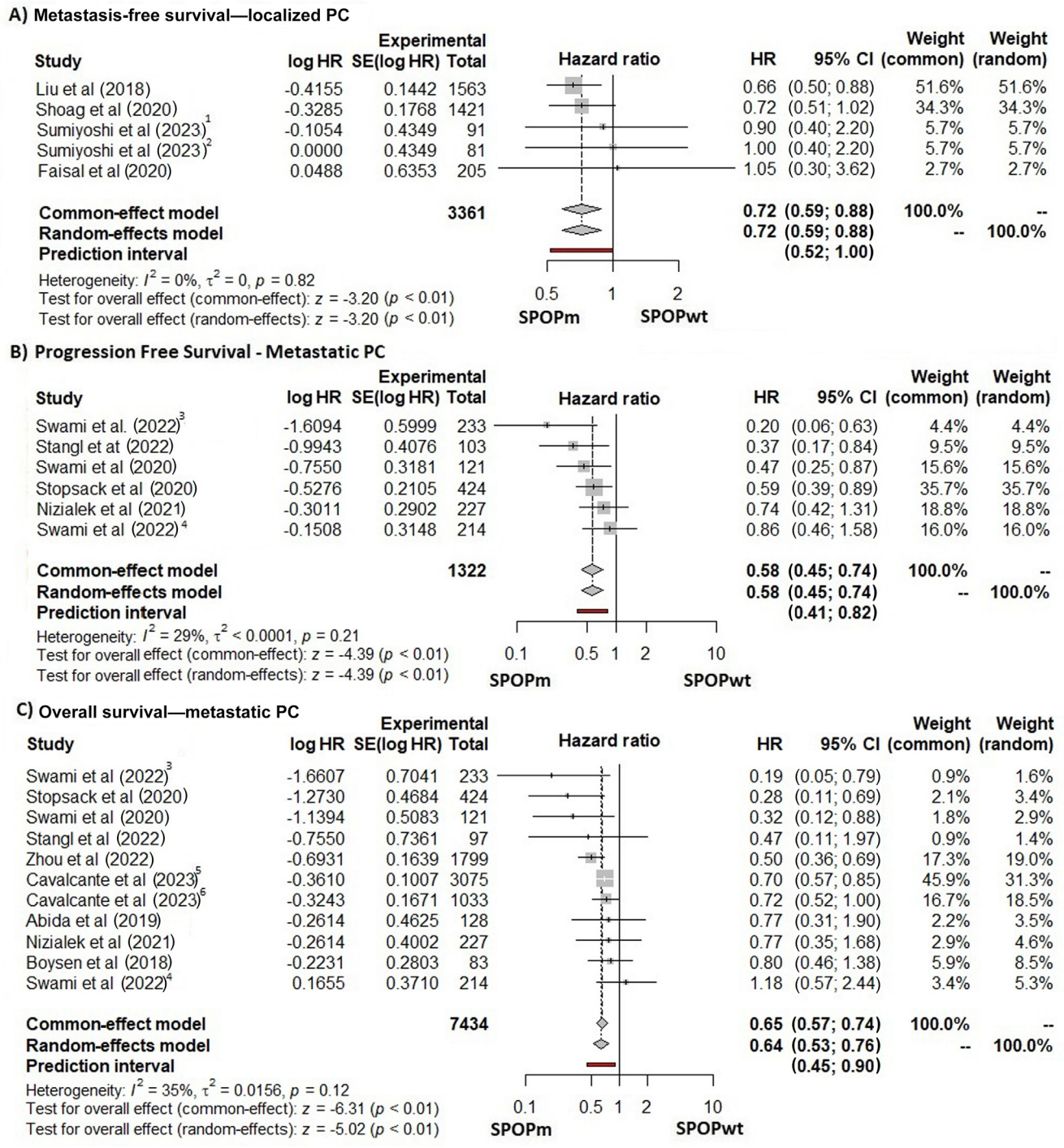

Fig. 2 – Meta-analysis forest plot of primary endpoint. Forest plot assessing (A) metastasis-free survival in localized PC following prostatectomy, (B) progression-free survival, and (C) overall survival in metastatic PC. In (A), Sumiyoshi et al [30] was included twice in the meta-analysis, denoted as 1 and 2, representing two distinct populations (1 corresponds to patients treated with radical prostatectomy and 2 pertains to the neoadjuvant docetaxel plus radical prostatectomy arm). In (B) and (C), Swami et al [36] and Cavalcante et al [34] were included twice in the meta-analysis, denoted as 3, 4, 5, and 6 representing distinct populations (3 and 5 correspond to the first-line hormonal treatments population, and 4 and 6 pertains to the first-line docetaxel population). CI = confidence interval; HR = hazard ratio; PC = prostate cancer; SE = standard error; SPOPm = speckle-type POZ (SPOP) gene mutated patients; SPOPwt = SPOP nonmutated (wild-type) patients; Total = total number of patients.

In the localized setting, four studies [25,27,29,30] were included in the MFS meta-analysis. For mPC, a meta-analysis of OS comprised nine studies [34–41,43], while five [35–38,40] studies were included for the PFS meta-analysis.

3.2. *Prognostic role of SPOP mutations*

3.2.1. *Localized PC*

Study populations differed between studies based on PC risk category [27,31,47], ethnicity [25,31], and treatment modalities [30,33,34,46–48].

Among localized PC patients, conflicting results emerged regarding the association between SPOP mutational status and various survival outcomes, including prostate-specific antigen (PSA) PFS [25–27,30,32,48], DFS [31], EFS [30], MFS [27], OS [29,30,34], and PC-specific mortality (PCSM) [27].

Five studies reported no associations between SPOP mutational status and PSA PFS ($p > 0.05$) [25–27,30,31]. Bidot et al [31] found no differences in DFS for patients after radical prostatectomy, but the median follow-up was short (23.0 mo). Sumiyoshi et al [30] drew the same conclusion in terms of EFS.

One study [27] found lower rates of biochemical recurrence (HR: 0.90, 95% CI: 0.69–1.16), metastases (HR: 0.72, 95% CI: 0.51–1.02), and PCSM (HR: 0.71, 95% CI: 0.44–1.15) in patients with SPOP mutations, although not statistically significant.

Two studies reported a higher risk of biochemical progression in SPOPmut patients ($p < 0.05$) [32,48].

Conversely, two studies found a statistically significant positive impact of SPOP mutations on OS [34], MFS [29], and PCSM [29].

In the study published by Liu et al [29], patients with localized SPOPmut PC were also stratified based on PSA levels (ng/ml), creating four distinct groups: PSA <10/SPOPwt, PSA >20/SPOPwt, PSA <10/SPOPmut, and PSA >20/SPOPmut. Both groups harboring SPOP mutations exhibited superior MFS to their respective SPOPwt counterparts ($p < 0.001$) in both high- and low-PSA groups. PCSM-free survival showed a similar trend ($p = 0.102$). Interestingly, when PSA >20/SPOPmut patients were compared with all patients with PSA <10, there were no differences in terms of both MFS ($p = 0.828$) and PCSM ($p = 0.68$). Moreover, two studies [28,29] compared SPOPmut PC versus other genetic subtypes, as described in the Supplementary material.

Given the conflicting results on survival outcomes in the published literature, we conducted a meta-analysis [25,27,29,30] including a total of 3361 patients with localized PC who underwent radical prostatectomy. The forest plot showed that patients with SPOPmut PC derive a statistically significant MFS benefit (pooled HR: 0.72, 95% CI: 0.59–0.88; $p < 0.01$, $I^2 = 0\%$; Fig. 2A). The funnel plot did not show any publication bias.

3.2.2. Metastatic PC

Eight studies reported data from patients with metastatic hormone-sensitive PC (mHSPC) [35–38,41,42,49,50]. Four studies [35,37,38,41] investigated PFS yielding conflicting results. Four studies demonstrated longer OS for patients with mHSPC and SPOP alterations ($p < 0.05$) [35,37,38,43].

Six studies provided clinical outcome data for metastatic castration-resistant PC (mCRPC) patients considering their SPOP mutational status [39–42,45,50].

Three studies demonstrated no association with OS from mCRPC diagnosis ($p > 0.05$) [39–41].

In order to consolidate the data from the literature, we performed a meta-analysis of PFS [35–38,40] and OS [34–41,43] in mPC, which consistently highlighted the positive prognostic impact of SPOP mutations. Clinically relevant effect sizes were observed (for PFS—pooled HR: 0.58, 95% CI:0.45–0.74, $p < 0.01$, $I^2 = 29\%$; for OS—pooled HR: 0.64, 95% CI: 0.53–0.76, $p < 0.01$, $I^2 = 35\%$), as illustrated in Figures 2B and 2C, respectively. The Cochrane Q test revealed negligible heterogeneity between both the endpoints analyzed ($p = 0.21$ and $p = 0.12$, respectively). The funnel plot did not show any publication bias.

When we restricted our meta-analysis of OS to mHSPC patients, incorporating data from five studies [35–38,41] for a total of 1302 patients, SPOP mutations correlated with longer OS (pooled HR: 0.55, 95% CI: 0.32–0.94, $p = 0.03$, $I^2 = 57\%$; Supplementary Fig. 3A). The Cochrane Q test revealed moderate heterogeneity ($p = 0.04$) related to the different treatment strategies adopted (Table 1), as shown by the sensitivity analysis (Supplementary Table 3).

Our subgroup OS meta-analysis limited to mCRPC patients incorporating data from three studies [39–41] did not find a significant OS advantage (pooled HR: 0.73, 95% CI: 0.45–1.16; $p = 0.82$, $I^2 = 0\%$; Supplementary Fig. 3B).

3.3. *Predictive role of SPOP mutations*

Cavalcante et al [34] demonstrated that the predictive role of SPOP mutations for a response to hormonal treatment varies depending on the specific mutated protein residue of the gene. In their report, hotspot F102 and W131 mutations correlated with improved OS from the initiation of treatment with ADT and an ARSI (abiraterone, bicalutamide, or enzalutamide; HR: 0.47, 95% CI: 0.311–0.71, $p < 0.001$, and HR: 0.598, 95% CI: 0.37–0.964, $p = 0.033$, respectively), while Y87 and F133 mutations did not confer any significant OS advantage.

3.3.1. *ADT ± ARSI*

In the localized setting, three studies showed favorable survival outcomes for SPOPmut PC patients treated with radical intent and ADT alone or in association with an ARSI [34,46,47].

In the metastatic setting, among studies where mHSPC patients were treated predominantly with ADT as a single-agent therapy, patients with SPOP alterations experienced a median time to mCRPC of 42.0 mo (95% CI: 25.7–60.8) [42] and were associated with improved OS from treatment initiation (HR: 0.34, 95% CI: 0.13–0.89) [37].

In a multicenter cohort of de novo metastatic HSPC patients treated with a combination of either ADT and docetaxel or ADT and an ARSI (abiraterone, enzalutamide, or apalutamide) as first-line treatment, only in the latter group SPOPmut PC patients exhibited longer time to mCRPC and longer OS (HR: 0.20, 95% CI: 0.06–0.63, $p = 0.006$, and HR: 0.19, 95% CI: 0.05–0.79, $p = 0.022$, respectively) [36].

Transitioning to mCRPC patients treated with ARSIs, Abida et al [39] found SPOP mutations to be associated with longer time to treatment failure at a univariate analysis. Stangl et al [40] found patients with SPOPmut PC to have longer PSA PFS in the multivariate analysis when accounting for age, race, metastasis, Gleason sum, PSA at diagnosis, or pretreatment (HR: 0.37, 95% CI: 0.17–0.84, $p = 0.02$), and no significant association between SPOP mutation presence and OS from the start of ARSI treatment (HR: 0.77, 95% CI: 0.31–1.90, $p = 0.565$, and HR: 0.47, 95% CI: 0.11–1.97,

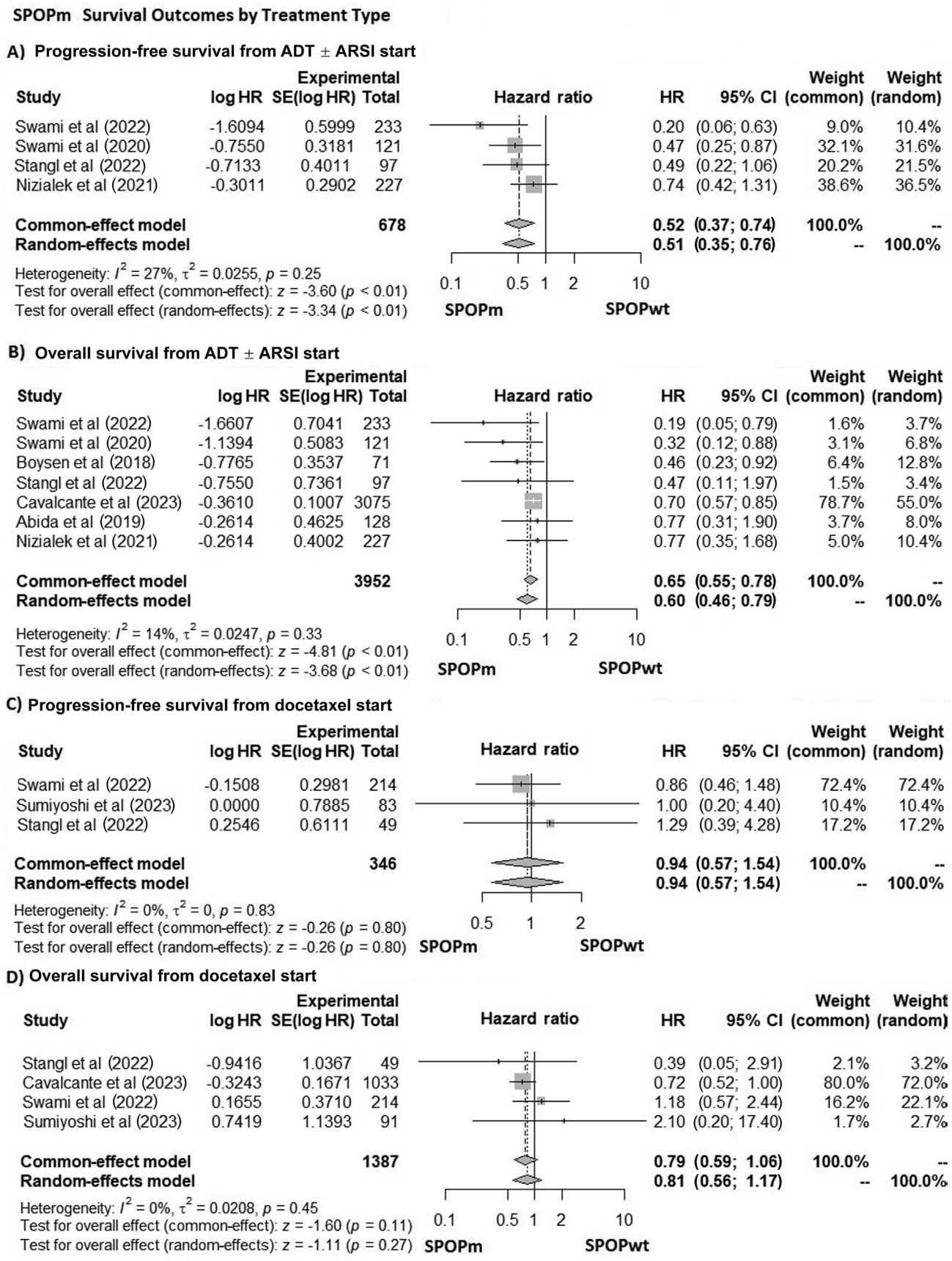

Fig. 3 – Meta-analysis forest plot of secondary endpoint. Forest plot assessing (A) progression-free survival in mPC from ADT ± ARSI start, (B) overall survival in mPC from ADT ± ARSI start, (C) progression-free survival in mPC from docetaxel start, and (D) overall survival in mPC from docetaxel start. ADT = androgen deprivation therapy; ARSI = androgen receptor signaling inhibitor; CI = confidence interval; HR = hazard ratio; mPC = metastatic prostate cancer; SE = standard error; SPOPm = speckle-type POZ (*SPOP*) gene mutated patients; SPOPwt = SPOP nonmutated (wild-type) patients; Total = total number of patients.

$p = 0.30$, respectively) in contrast to the studies conducted in the mHSPC setting.

To evaluate mPC survival outcomes from the initiation of ADT ± ARSI treatment, we performed a meta-analysis of PFS (Fig. 3A) [35–37,40] and OS (Fig. 3B) [34–37,39–41] including a total of 678 and 3952 patients, respectively. We found SPOP mutations to correlate with longer PFS and OS with clinically relevant effect sizes (HR: 0.51, 95% CI: 0.35–0.76, $p < 0.01$, $I^2 = 27\%$, and HR: 0.60, 95% CI: 0.46–0.79, $p < 0.01$, $I^2 = 14\%$, respectively). The Cochrane Q test revealed low to moderate heterogeneity ($p = 0.25$ and $p = 0.33$).

3.3.2. ADT + abiraterone acetate/prednisone

Boysen et al [41] examined a cohort of 71 mCRPC patients treated with abiraterone acetate upon recurrence after first-line docetaxel treatment and observed significantly longer OS from the initiation of abiraterone treatment ($p < 0.001$) in SPOPmut PC than in SPOPwt PC patients, while OS from the start of first-line treatment with docetaxel did not differ ($p = 0.31$). Furthermore, SPOP mutations were predictive of a better response to abiraterone ($p = 0.001$) and SPOPmut patients experienced a longer median duration of abiraterone treatment ($p = 0.002$).

One retrospective study conducted exclusively among SPOPmut mCRPC patients revealed that this subgroup seemed to exhibit longer median PSA PFS when treated with abiraterone than when treated with enzalutamide (median PSA PFS of 8.9 and 7.3 mo, respectively) [42].

3.3.3. Taxanes

In the localized setting, no association was reported between SPOP mutations and treatment effect on pathological response (defined by the percentage of tumor regression on prostatectomy) in patients treated with neoadjuvant ADT plus docetaxel [30].

In the metastatic settings, only one study showed a trend to an improved OS from the initiation of taxane treatment (docetaxel, cabazitaxel, or paclitaxel), but statistical significance was not reached (HR: 0.723, 95% CI: 0.521–1.003, $p = 0.051$) [34]. Moreover, Swami et al [36] found no benefit in either OS (HR: 1.18, 95% CI: 0.57–2.44, $p = 0.66$) or TTCR (HR: 0.86, 95% CI: 0.46–1.58, $p = 0.62$) from first-line docetaxel in SPOPmut de novo mHSPC patients. Similarly, two studies reported no OS benefit from first-line docetaxel in mCRPC patients ($p = 0.31$ and 0.678, respectively) [40,41].

To evaluate mPC survival outcomes from the initiation of taxane treatment, we performed a meta-analysis of PFS [35–37,40] and OS [30,34,36,40] including a total of 346 and 1387 patients, respectively. SPOP mutations did not correlate with either PFS (Fig. 3C) or OS (pooled HR: 0.94, 95% CI: 0.57–1.54, $p = 0.80$, $I^2 = 0\%$; pooled HR: 0.81, 95% CI: 0.56–1.17, $I^2 = 0\%$; Fig. 3D). The Cochrane Q test revealed low heterogeneity ($p = 0.83$ and $p = 0.45$, respectively).

3.3.4. Other treatments

Investigators from the IMbassador250 trial observed that patients with SPOPmut mCRPC did not experience significant improvements in PFS from the addition of atezolizumab to enzalutamide in their treatment. Conversely, a PFS advantage from the combination therapy was shown in patients with SPOPwt PC [45].

Similarly, Cavalcante et al [34] reported an association of SPOP mutations with shorter median OS (5.9 vs 9.9 mo) from the start of either pembrolizumab or nivolumab in 96 treated PC patients (but only five were SPOPmut). Furthermore, authors reported no OS difference from the initiation of platinum-based treatment (HR: 0.526, 95% CI: 0.195–1.421, $p = 0.198$) or poly ADP-ribose polymerase (PARP) inhibitors olaparib or rucaparib (HR: 1.064, 95% CI: 0.517–2.191, $p = 0.87$) between patients with SPOPmut and SPOPwt PC [34].

In the study by Nakazawa et al [42], seven SPOPmut mPC patients were treated with PARP inhibitors, and none of them demonstrated radiographic or PSA responses. However, none of them presented co-occurring BRCA1/2 mutations, which have been shown to predict a benefit from PARP inhibitor treatment in mCRPC patients [44].

3.4. Risk of bias

The RoB was evaluated for all included studies. A single study [31] exhibited a high RoB and was excluded from the meta-analysis. The RoB summary table can be found in the Supplementary material, and Supplementary Figures 1 and 2.

3.5. Limitations

Our study is subject to several limitations that warrant acknowledgment. The first limitation is the absence of randomized trials focused exclusively on SPOPmut patients. Second, substantial heterogeneity is evident across retrospective trials concerning study populations, drug regimens, treatment modalities, and treatment lines, with detailed information provided inconsistently. Third, SPOPmut patient distribution among risk categories was not available consistently. Notably, data regarding SPOPmut PC patients treated with recently introduced therapeutic options, such as Lu-PSMA and triplet combinations, were unavailable. Finally, our meta-analysis could not include certain studies due to incomplete data.

4. Discussion

We report the first systematic review and meta-analysis of survival outcomes comparing SPOPmut and SPOPwt PC patients confirming improved survival for patients with alterations in SPOP in the localized and metastatic hormone-sensitive settings. While acknowledging and addressing potential heterogeneity as a primary limitation, the consistently low interstudy variation estimate of I^2 observed in our meta-analyses, coupled with the results of preplanned sensitivity and subgroup analyses, contributes to the coherence of our findings unveiling distinct roles of SPOP mutations across different scenarios.

Our meta-analysis of MFS affirms the positive prognostic role (lower metastatic risk and prolonged survival) of the presence of SPOP mutations in PC patients who underwent radical prostatectomy. This evidence, taken together with the findings from Liu et al [29] underscores the potential

utility to integrate SPOP mutational testing into clinical practice for a more granular risk stratification of patients with localized PC. Specifically, in patients identified as having a "high risk" solely based on their PSA levels, SPOP alterations may be a helpful factor to reclassify these patients if our findings are validated prospectively in a large cohort [51]. Whether this factor adds to other commercially available genomic classifiers (eg, Decipher) is not clear.

The positive prognostic role of SPOP mutations remains consistent in mPC, as evidenced by our comprehensive meta-analysis on OS in a substantial patient cohort (n = 7434).

Within the metastatic hormone-sensitive setting, our meta-analysis supports the substantial and favorable prognostic impact associated with the presence of SPOP mutations.

In the castration-resistant setting, conversely, the substantial discrepancy in outcomes between SPOPmut and SPOPwt PC patients diminishes. Here, SPOP mutations no longer appear to predict longer OS. Notably, studies indicating this lack of prognostication often aggregate statistical calculations across all patients without distinguishing between different therapies.

The question of whether SPOP alterations could also serve as predictive factors is more complex and of relevant clinical interest. The sensitivity of SPOPmut PC to ADT and ARSIs is supported strongly by preclinical studies, as SPOPmut PC exhibits heightened AR protein expression and relies heavily on AR signaling for cancer growth [8,10,52,53]. In addition, Shi et al [54] showed that SPOP mutations could induce resistance to docetaxel by enhancing the assembly of stress granules in PC cell and xenograft models.

Fitting with this preclinical hypothesis, patients with localized PC harboring SPOP mutations emerge as exceptional responders to neoadjuvant ADT plus ARSI in one study [46], while SPOPmut patients treated with neoadjuvant ADT + docetaxel exhibited no additional benefit in terms of pathological response compared with SPOPwt patients [30].

In the metastatic setting (both mHSPC and mCRPC), our meta-analysis shows that SPOPmut PC patients derive larger PFS and OS benefits from hormonal treatments, with either ADT alone or ADT in combination with an ARSI, compared with SPOPwt PC patients. Nevertheless, these benefits are not seen for taxane-based treatments, as shown by our meta-analysis of OS and PFS from taxane treatment initiation.

These findings necessitate a thorough examination, as the survival benefit seen in SPOPmut mPC patients (irrespective of their castration status) seems to be specific for the addition of an ARSI to ADT. However, they may have a limited immediate impact on treatment decisions, as mPC patients respond to ADT and also to the ARSI irrespective of the SPOP mutational status. In contrast, it may potentially help decide in which patients to add docetaxel as a third systemic treatment, a topic that is discussed widely and on which strong data are missing. It would be very helpful to have additional factors apart from the timing and burden of disease to help guide treatment decisions in this respect. A predictive marker in this case helping to define which patients are not profiting from the addition of docetaxel would be of utmost interest to avoid unnecessary toxicity. However, this hypothesis has to be validated in a prospective clinical trial [55–57]. Nevertheless, in light of the current absence of data specifically addressing SPOPmut PC patients treated with "triplet systemic therapy," we cannot draw conclusions about this specific treatment strategy.

In the metastatic castration-resistant setting, SPOP mutations are detected in a lower percentage of PC cases, and the lack of a correlation between their presence and longer OS observed in our meta-analysis might be affected by the substantially smaller sample size, leading to reduced statistical power. Usually, mCRPC is less dependent on AR signaling [58,59], potentially undermining the prognostic role of SPOP mutations in this context. On the contrary, a study employing abiraterone exclusively as the second-line treatment for patients with mCRPC revealed that the presence of SPOP mutations correlated with a better treatment response, longer treatment duration, and improved OS from the initiation of abiraterone treatment [41]. Additionally, Nakazawa et al [42] reported longer median PSA PFS among SPOPmut mCRPC patients when treated with abiraterone than when treated with enzalutamide.

Such findings are hypothesis generating and may suggest the use of abiraterone as the preferred ARSI option in SPOPmut mCRPC patients. There are preclinical studies supporting this hypothesis, as SPOPmut PC metabolism relies on higher intratumoral testosterone synthesis [11,12], effectively inhibited by abiraterone. The absence of this inhibitory mechanism may oversaturate AR-binding sites with androgens, rendering AR-inhibiting agents less effective, as suggested in the literature [59]. While the evidence is not conclusive, it holds promise and warrants further evaluation through prospective randomized trials. A potential additional impact of prednisone, administered with abiraterone, on patients with SPOPmut PC has never been investigated and thus cannot be ruled out definitively.

Interestingly, further data from Wankowicz et al [46] and McBride et al [47] suggest a benefit from the combination of enzalutamide or apalutamide added to ADT and abiraterone as a treatment for localized SPOPmut PC compared with SPOPwt , therefore generating the hypothesis that selected patients may profit from the association of ADT, abiraterone, and an AR antagonist.

Preclinical studies have linked SPOP mutations with higher PDL-1 expression and genomic instability [60,61]. However, two studies, including the IMbassador250 trial, suggested that patients with SPOPmut PC might not derive significant PFS or OS benefits from treatment with immune checkpoint inhibitors (ICIs) [34,45]. Data are limited by the small number of SPOPmut PC patients included in the studies and have small clinical relevance as ICIs are not considered a standard of care in PC treatment.

On a final note, the prognostic and predictive role of SPOP mutations varies by muted gene locus, with mutations involving hotspot F102 and W131, but not F133 and Y87, correlating with improved OS from the initiation of ADT and/or ARSI treatment [34]. Furthermore, the co-

occurrence of *SPOP* and other gene mutations, such as *CHD1* and *BRCA2*, confers PC enhanced sensitivity to specific treatments [41,44]. This underscores the importance for clinicians to recognize potential variations in treatment sensitivity based on the specific gene locus affected by SPOP mutations and co-occurring mutations.

5. Conclusions

In conclusion, our systematic review with meta-analysis highlights a strong and clinically significant positive prognostic role for SPOP mutations in hormone-sensitive disease (both localized and metastatic). In localized PC, the correlation with a reduced risk for metastases and extended survival supports the inclusion of SPOP mutational status in the risk stratification of patients with localized PC, when validated prospectively. However, this positive effect seems to decrease in patients exposed to docetaxel and in the mCRPC setting, where abiraterone, as supported by preclinical evidence and clinical data, emerges as the potentially preferred ARSI option. However, this finding also needs to be validated first in a prospective study since there is a relevant risk of confounding factors in the studies on which we based our analysis. In personalized treatment decisions, considering SPOP mutation loci and co-occurring mutations is crucial. Future prospective and randomized trials would allow validating the role of SPOP mutations as a predictive factor.

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Appendix A. Supplementary data

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