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The Prolaris Test on Diagnostic Biopsy for Localized Prostate Cancer Prognosis Across Risk Groups and Management: An Individual Participant Data Meta-analysis

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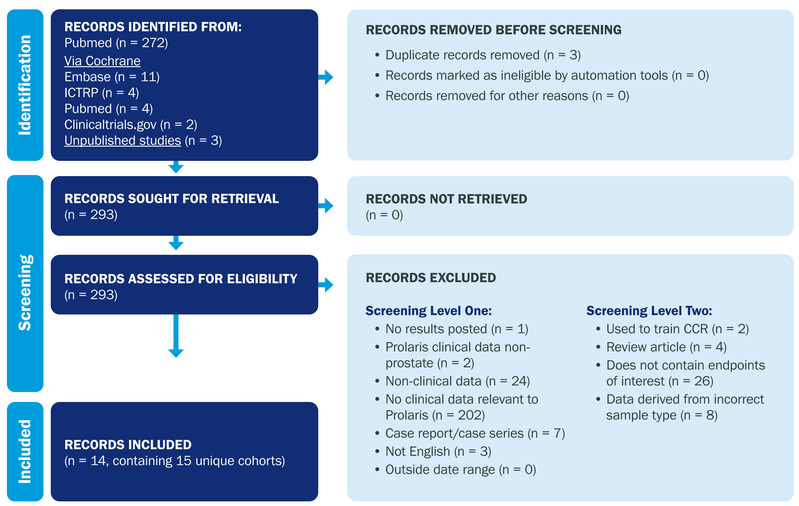
Background

- While patients with localized prostate cancer have relatively favorable outcomes, prostate cancer remains the second-most lethal cancer in men in the United States.
- Advanced tools beyond clinicopathologic features can improve risk stratification and aid disease management decisions.
- A model that incorporates both clinicopathologic features with the expression of 31 mRNA cell cycle biomarkers creates the Combined Clinical Risk (CCR) score, which is offered commercially via a test called Prolaris.
- Prolaris categorizes individual patient risk of distant metastasis (DM) and prostate cancer-specific mortality (PCSM) based on validated active surveillance (AS) and multi-modal therapy thresholds.

Materials and Methods

- A systematic literature search was performed, and individual participant data (IPD) were collected where possible to perform a two-step IPD analysis (**Figure 1**).
- The primary endpoint was a composite of DM and PCSM, also analyzed individually.
- Within each cohort, Cox proportional hazards models were fit adjusting for initial management (non-interventional, single-modal, multi-modal).
- Random-effects meta-analyses with Knapp-Hartung adjustment were used to create combined hazard ratio (HR) estimates across studies.

Figure 1. PRISMA Diagram



Results

- Fourteen eligible studies included 8,480 total patients, of which 7,926 had IPD available for analysis.
- The breakdown of NCCN Risk Groups and initial management is shown in **Figure 2**.
- CCR was prognostic for composite DM-PCSM after accounting for initial management received (HR 2.28 (95% CI 1.92, 2.62), p=9.14x10^{-9}; **Figure 3**) with insignificant heterogeneity (I^2=14%, p=0.3) and was also individually prognostic for DM (p=1.87x10^{-6}; **Table 1**) and PCSM (p=3.14x10^{-4}; **Table 1**).
- Influence analyses demonstrated that results were not materially influenced by any one study (results not shown).
- Additional meta-analyses demonstrated that CCR adds independent prognostic information to Gleason, CAPRA, and NCCN (all p<10^{-5}; **Table 2**).
- Prolaris management recommendations are prognostic for composite DM-PCSM and individual endpoints (all p<0.05; results not shown).
- Risk of composite DM-PCSM is significantly lower in patients recommended to active surveillance than patients recommended to definitive therapy, and in patients recommended to single-modal therapy than in patients recommended to multi-modal therapy (**Figure 4A/B**).

Figure 2. Distribution of **(A)** NCCN Risk Groups and **(B)** initial managements in the individual patient-level data

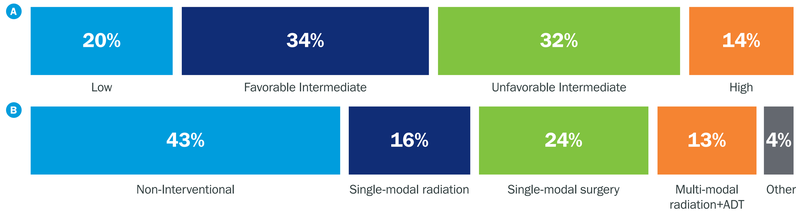


Table 1. Results of meta-analyses of CCR prognosticating DM and PCSM separately, accounting for initial management

Endpoint	Overall hazard ratio for CCR with 95% confidence interval	P-value
Distant metastasis	**2.80** (2.22, 3.53)	**1.9 x 10^{-6}**
Prostate-cancer specific mortality	**2.18** (1.70, 2.80)	**9.7 x 10^{-4}**

Table 2. Results of meta-analyses of CCR prognosticating DM-PCSM after accounting for initial management and clinical features

Clinical variable adjustment	Overall hazard ratio for CCR with 95% confidence interval	P-value
After accounting for Gleason Score	**2.29** (1.97, 2.67)	**1.2 x 10^{-7}**
After accounting for CAPRA Score	**3.19** (2.38, 4.29)	**1.1 x 10^{-6}**
After accounting for NCCN risk group	**2.23** (1.95, 2.56)	**2.1 x 10^{-8}**

Figure 3. Meta-analysis of CCR score prognosticating composite DM-PCSM after accounting for initial management.

Cohort	N(events)	Endpoint	HR (95% CI)	P-value	Weight
URO-008	217 (1)	Metastasis	0.01 (7.05x10^{-10}, 10.10)	0.21	0.01%
TURP1B	292 (87)	PCSM	2.05 (1.76, 2.40)	8.0x10^{-20}	30.2%
TAPG-1	175 (40)	PCSM	2.09 (1.57, 2.83)	1.8x10^{-7}	13.4%
TAPG-2	583 (98)	PCSM	2.14 (1.81, 2.54)	4.3x10^{-20}	27.4%
URO-004	693 (47)	Metastasis	2.31 (1.64, 3.27)	1.1x10^{-6}	10.5%
Hutten	554 (31)	Metastasis	2.32 (1.17, 4.59)	0.02	3.1%
URO-005	932 (7)	Metastasis	2.64 (1.00, 6.82)	0.050	1.6%
PR-04	3286 (22)	Metastasis	2.79 (1.49, 5.26)	0.0014	3.6%
Ochsner	683 (23)	Metastasis	3.38 (2.32, 4.97)	3.2x10^{-10}	8.9%
Henriquez-Lopez 2017	28 (6)	Metastasis	3.93 (0.87, 19.84)	0.075	0.6%
Martini Clinic	154 (1)	Metastasis	5.30 (0.62, 88.45)	0.12	0.2%
URO-009	639 (5)	Metastasis	23.84 (1.84, 776.54)	0.013	0.2%
University of Utah	114 (3)	Metastasis	28.51 (3.90, 924.10)	2.5x10^{-4}	0.2%
Durham VA	128 (2)	Metastasis	84.21 (2.94, 2.91x10^{7})	0.0012	0.02%
Overall effect			**2.28 (2.01, 2.58)**	**3.6x10^{-39}**	
Overall effect, HK adj.			**2.28 (1.98, 2.62)**	**9.1x10^{-9}**	

Heterogeneity: I^2 = 13.78%, τ^2 = 0.01, p = 0.30

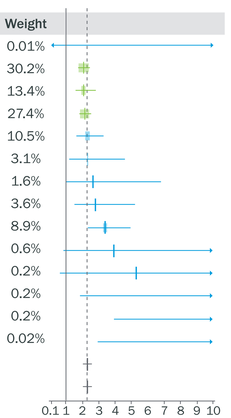
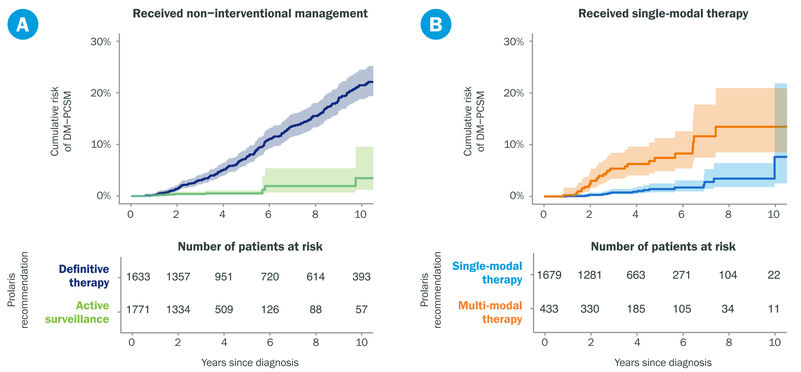


Figure 4. Kaplan-Meier figures showing **(A)** patients recommended by Prolaris to active surveillance have lower rates of DM-PCSM than patients recommended to definitive therapy when receiving non-interventional management, and **(B)** patients recommended to single-modal therapy have lower rates of DM-PCSM than patients recommended to multi-modal therapy when receiving single-modal therapy.



Conclusions

- Prolaris improves prognostication across NCCN Risk Groups and management strategies in localized prostate cancer.
- Prognostic value persists after adjusting for initial management and established clinical factors, highlighting utility in supplementing conventional risk models.

Email questions or comments to matt.schiewer@myriad.com.