Prostate cancer (PCa) risk stratification is based on tumour size, PSA level and Gleason Score, but it remains imprecise. Current research focuses on the discovery of novel biomarkers to improve the identification of patients at risk of tumour progression. The purpose of this study was to develop a gene expression signature for predicting tumour progression after radical prostatectomy.

Gene expression signature predicts biochemical and metastatic recurrence in men with clinically localized prostate cancer treated with radical prostatectomy.

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MP64-19

Background and objective

✓**Prostate cancer (PCa) risk stratification is based on tumour size, PSA level and Gleason Score, but it remains imprecise. Current research focuses on the discovery of novel biomarkers to improve the identification of patients at risk of tumour progression.**

✓**The purpose of this study was to identify gene expression profiles for predicting tumour progression after radical prostatectomy.**

Methods

✓**Retrospective study which includes 188 PCa patients who attended at our department between 2000 and 2007.**
✓**Formalin-fixed paraffin embedded PCa tissue samples were collected.**
✓**Biochemical recurrence (BCR) was defined as 2 consecutive PSA values ≥ 0.2ng/mL or any salvage treatment 6 months after radical prostatectomy.**

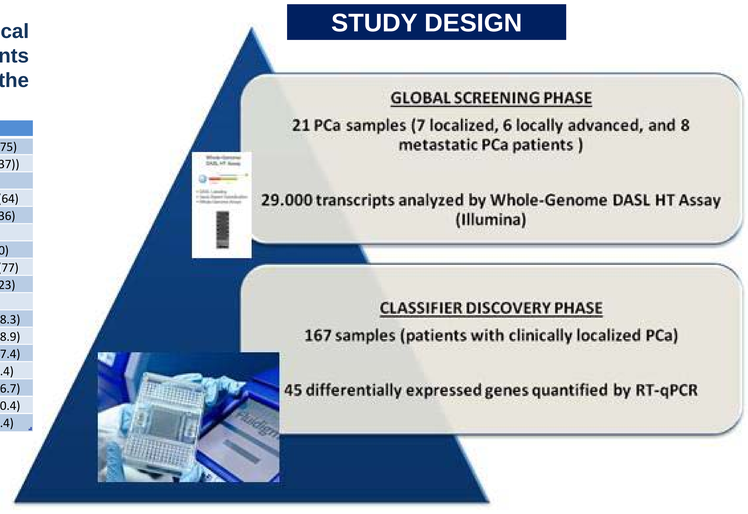
Table 1. Clinical characteristics of the 21 patients included in the global screening phase.

Clinical Stage	PSA (ng/ml)	T stage	Score Gleason	N stage	M stage	Treatment
Localized PCa	16	T1c	3+3	Nx	Mx	Surgery
	4.6	T1c	3+3	Nx	Mx	Surgery
	4.7	T1c	3+3	Nx	Mx	Surgery
	4.9	T1c	3+3	Nx	Mx	Surgery
	4.3	T2a	3+4	Nx	Mx	Surgery
	7.9	T1c	3+3	N0	M0	Surgery
	7	T2a	3+3	Nx	Mx	Surgery
Locally advanced PCa	19	T3	4+5	N0	M0	RDT*+HT**
	2.7	T3	4+5	N0	M0	RDT+HT
	10	T3	4+4	N0	M0	RDT+HT
	29	T3	4+3	N0	M0	RDT+HT
	20	T3	4+4	N0	M0	RDT+HT
	4.8	T3	3+4	N0	M0	Surgery
Metastatic PCa	19	T3	4+5	N1	M1	HT
	32	T4	5+4	N1	M1	HT
	2300	T2b	5+4	N1	M1	HT
	34	T3	5+4	N0	M1	HT
	93	T3	3+4	N0	M1	HT
	8659	T4	4+4	N1	M1	HT
	25	T3	3+3	N1	M1	RDT+HT
	99	T3	4+3	N0	M1	HT

Table 2. Demographic and clinical characteristics of the 167 patients with localized PCa from the discovery phase.

Clinicopathological and demographic characteristics	
Age (years), *median (range)*	64 (46-75)
PSA (ng/mL), *median (range)*	8 (1-37))
Clinical stage (T), *n (%)*	
T1	106 (64)
T2	61 (36)
Pathological stage (pT), *n (%)*	
pT1	0 (0)
pT2	129 (77)
pT3	38 (23)
Score Gleason (CAPRAS), *n (%)*	
Gleason ≤ 6	64 (38.3)
Gleason 3+4	65 (38.9)
Gleason 4+3	29 (17.4)
Gleason ≥ 10	9 (5.4)
Positive margin, *n (%)*	78 (46.7)
Extracapsular extension, *n (%)*	34 (20.4)
Seminal vesical invasion, *n (%)*	9 (5.4)

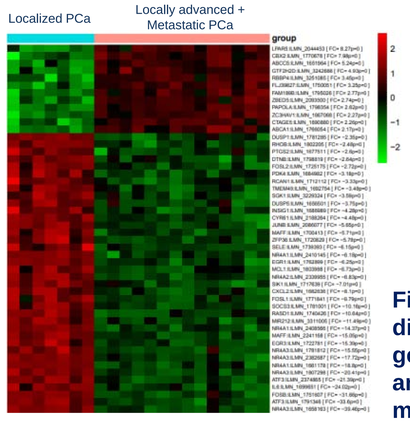
*RDT: radiotherapy;
**HT: Hormonal treatment



✓**RT-qPCR was normalized with 3 endogenous controls: *CLTC, RPL13A* and *GAPDH.***
✓**Univariate and multivariate logistic regression analysis was used to identify individual predictors of BCR and metastatic recurrence.**
✓**Kaplan Meier curves were used to discriminate two groups of localized PCa patients with a different probability of tumour progression.**

Results

1. GLOBAL SCREENING PHASE



15800 genes differentially expressed (FDR<0.1)

Fig 1. Top 50 differentially expressed genes between localized and locally advanced+ metastatic Pca.

2. CLASSIFIER DISCOVERY PHASE

✓Median follow-up of the series was 131.8 months (range 120-194).
✓During the surveillance period, 55 patients developed BCR (33%) and 6 metastatic recurrence (3.6%).
✓Overall, three patients died of PCa (1.8%), and 22 due to other causes (13%).

Gene	Fold Change	False Discovery Rate	*Gene*	Fold Change	False Discovery Rate
ADAMTS4	-7.60	0.00	*KRT16*	-5.83	0.00
AOF2	6.38	0.00	*KRT17*	-6.96	0.00
ARC	-7.25	0.00	*LPAR5*	8.27	0.00
*ASF1B**	2.75	0.64	*MCL1*	-6.73	0.00
ATF3	-33.60	0.00	*MED25*	5.33	0.29
CBX2	7.98	0.00	*MSMB*	-5.34	0.36
CCNO	8.84	0.00	*MYBPC1**	-2.07	1.29
*CDC20**	2.60	1.63	*NEK11*	6.93	0.00
CDCA5	6.63	0.00	*NR4A1*	-14.37	0.00
*CENPF**	4.15	0.36	*NR4A3*	-17.72	0.00
CSF3	-11.72	0.00	*OLFM4*	-6.00	2.00
CSF3	-5.54	0.19	*PSRC1*	6.47	0.00
CXCL2	-8.10	0.00	*RABGAP1**	1.95	0.47
*EDG7**	-4.64	0.64	*SELE*	-6.15	0.00
EGR3	-15.39	0.00	*SERPINE1*	-6.33	0.00
FOS	-8.94	0.00	*SIK1*	-7.01	0.00
FOSB	-31.66	0.00	*SLC44A1**	1.96	0.12
FOSL1	-9.79	0.00	*SOCS3*	-10.16	0.00
GDF15	-6.92	0.00	*TPM2**	-1.96	2.50
*IGFBP3**	3.02	0.47	*TPX2**	2.25	3.04
IL6	-24.02	0.00	*VEGFA*	-6.41	0.00
IL8	-8.79	0.00	*ZFP36*	-5.78	0.00
JUNB	-5.65	0.00			

Table 3. List of selected genes to be analyzed by RT-qPCR (* the 10 genes selected from literature).

Fig 2. Prognostic factors of biochemical recurrence

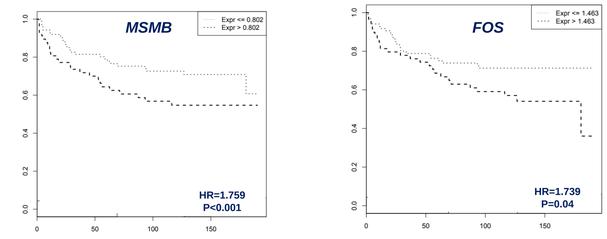
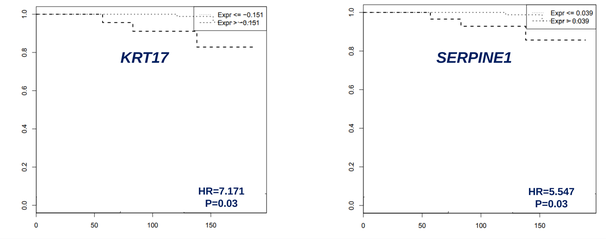


Fig 3. Prognostic factors of metastatic recurrence



Conclusions

✓**Gene expression levels in PCa tissue can be useful for distinguishing patients with clinically localized disease who will develop BCR or metastatic recurrence after radical prostatectomy.**

✓**These gene expression biomarkers could have potential clinical utility for identifying the subset of patients that would benefit from closer surveillance and adjuvant therapy.**