Serum thymidine kinase 1 level predicts prostate cancer-specific survival

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Background

- Thymidine kinase 1 (TK1) phosphorylates thymidine as part of the DNA synthetic pathway.
- TK1 expression is a marker of active cellular proliferation; intracellular concentrations are low during the G0/G1 phases of the cell cycle, increasing during the S/G2 phases
- Previous studies have suggested that serum TK1 levels could be used as marker for presence of prostate cancer (PCa).
- No studies have evaluated TK1 as predictor of prostate cancer prognosis

-Here, we evaluated the risk of prostate cancer death in relation to serum TK1 levels and compared the levels between metastatic and localized PCa cases

Materials and methods

- Study population included 40 men with clinically defined T1/T2NxM0 PCa and 43 men with *de novo* metastatic cancer (M1) at diagnosis as confirmed by bone scan imaging. Patients were diagnosed and treated at the Tampere University Hospital, Tampere, Finland during 2000-2010
- A serum sample for TK1 measurement obtained for all participants at the time of PCa diagnosis, assayed with Arocell TK 210 ELISA kit (www.arocell.com).

-Information on deaths and causes of deaths was obtained from the national Death Certificate Registry of Statistics Finland

- Cox regression and Kaplan-Meier Curves with adjustment for established prognostic factors (biopsy Gleason grade, TNM stage, and PSA level at diagnosis) were used to evaluate risk of PCa death in relation to TK1 level as a categorical variable (median or below vs. above median)
- Risk trends were evaluated by analyzing TK1 concentration as a continuous variable
- Mann-Whitney U test was used to compare TK1 concentrations between M0 and M1 cases
- Random forest classification was used to evaluate additional predictive value of TK1 in combination with established prognostic factors as a predictor of PCa death

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Table 1. Distribution of participant clinical characteristics

	Prostate cancer M-stage	
Participant characteristics:	M0; 40 men	M1; 43 men
Serum TK1 concentration at diagnosis (µg/L); median (IQR)	0.228 (0.152-0.412)	0.611 (0.332-0.821)
	p for difference < 0.001	
Age at diagnosis (yrs); median (IQR)	62 (57-65)	72 (66-76)
Prostate volume (mL); median (IQR)	35 (28.7-40)	39 (28-46)
PCa clinical characteristics:		
PSA at diagnosis (ng/mL); median (IQR)	6.7 (4.7-8.8)	50 (18-240)
Clinical T-stage at diagnosis; n (%):		
T1	23 (57.5%)	1 (2.3%)
T2	17 (42.5%)	7 (16.3%)
T3	0	18 (41.9%)
T4	0	17 (39.5%)
Gleason score, ISUP grade; n (%):		
1	16 (40%)	6 (14%)
2	12 (30%)	5 (11.6%)
3	8 (20%)	10 (23.3%)
4	1 (2.5%)	6 (14%)
5	3 (7.5%)	16 (37.2%)

Table 2. Prostate cancer treatment and survival

	Prostate cancer M-stage	
Primary treatment; n (%):	M0; 40 men	M1; 43 men
Radical prostatectomy	35 (87.5%)	0
External beam radiation therapy	3 (7.5%)	2 (4.7%)
Androgen deprivation / anti-androgen monotherapy	1 (2.5%)	39 (90.7%)
Other	1 (2.5%)	1 (2.3%)
Unknown	0	1 (2.3%)
Survival after prostate cancer diagnosis:		
Follow-up (months); median (IQR)	120 (114-128)	67 (22-110)
Deaths; n (%)	2 (5.0%)	36 (83.7%)
Prostate cancer deaths; n (%)	1 (2.5%)	24 (55.8%)

Results

-Stratification by tertiles of TK1 concentration defined three distinct groups with differing risks for PCa death (Figure 1 and Figure 2)

- TK1 concentration in the highest tertile defined a distinct group with a poor prognosis, especially, among men with *de novo* metastatic disease at diagnosis (Figure 2)

-Compared to men with localized PCa, those with metastatic disease were older and had more often received androgen deprivation as primary management. Localized cases were most commonly managed with radical prostatectomy (Table 1 and 2)

- Within a median follow-up of 113 months post PCa diagnosis, 55.8% of the M1 cases and 2.5% of the M0 cases had died of PCa (Table 2)
- Median serum TK1 levels were significantly higher among M1 cases compared to M0 cases (p for difference 0.001) (Table 1).

- A TK1 concentration above the median was an independent predictor of prostate cancer-specific and overall death, both overall and in subgroup of M1 cases(Table 3)

-In random forest classification, the classification error estimate for PCa death was lowest in the model including PSA, age, TK1, and Gleason grade (Figure 3)

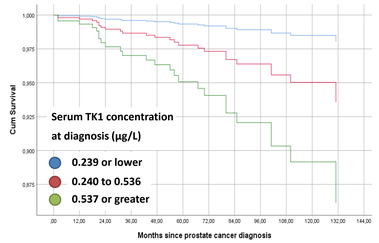

Figure 1. Prostate cancer-specific survival after diagnosis stratified by TK1 concentration (tertiles), all cases combined. Analysis adjusted for age and tumor clinical characteristics

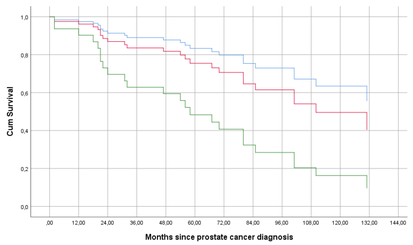

Figure 2. Prostate cancer-specific survival after diagnosis stratified by TK1 concentration (tertiles), men with *de novo* metastatic disease. Analysis adjusted for age and tumor clinical characteristics

Table 3. Risk of death due to prostate cancer or any cause stratified by median TK1 concentration

	Prostate cancer death		Death due to any cause	
Serum TK1 concentration at diagnosis (µg/L)	HR (95% CI) age-adjusted	HR (95% CI) multivariable-adjusted	HR (95% CI) age-adjusted	HR (95% CI) multivariable-adjusted
All cases combined				
0.347 (Median) or below	Reference	Reference	Reference	Reference
0.348 or higher	8.24 (2.76-24.63)	8.33 (2.05-33.88)	5.27 (2.41-11.52)	5.53 (1.93-15.85)
p for trend	0.001	0.249	<0.001	0.004
M1 cases				
0.611 (Median) or below	Reference	Reference	Reference	Reference
0.612 or higher	2.47 (1.05-5.82)	2.08 (0.80-5.43)	3.08 (1.49-6.36)	3.27 (1.41-7.57)
p for trend	0.043	0.241	<0.001	0.005

Conclusions

•The proliferation biomarker TK1 in serum predicts survival after PCa diagnosis, with an independent predictive value over established clinical risk factors.

•If confirmed in further prospective studies, this biomarker could be incorporated in prostate cancer risk stratification when selecting optimal treatment and surveillance schedules.

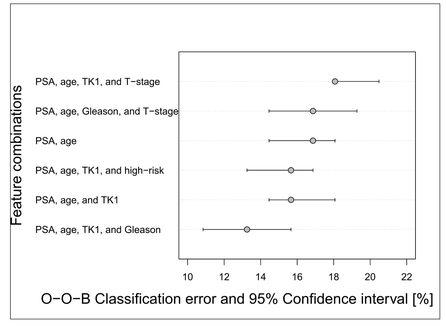

Figure 3. Random forest classification for prostate cancer death using different sets of predictors.