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Prognostic value of serum levels of soluble MICA (sMICA) in patients with prostate cancer

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Prostate cancer is a leading cause of cancer-related death of men globally. Since its introduction, there has been intense debate as to the effectiveness of the prostate-specific antigen (PSA) test as a screening tool [1]. However, the use of PSA has resulted in a significant prostate cancer over-diagnosis since elevated PSA levels are often found in patients with nonmalignant conditions such as benign prostatic hyperplasia [2]. It is now evident that the PSA test produces unacceptably high rates of false positive results and is not prognostic. Therefore, characterization of additional biomarkers that can indicate whether a histologically proven tumour will give rise to a clinical significant disease is strongly needed.

MHC class I–related chain A (MICA) is a ligand for the NKG2D activating immunoreceptor that mediates activation of natural killer (NK) cells [3]. Under physiologic conditions, MICA is only expressed in epithelial cells of the gastrointestinal tract and is only present at very low levels in most normal cells and tissues. However, many malignant carcinoma cells express high levels of MICA on their surface, making them susceptible to targeting and killing by NK cells [4]. Recent studies suggest that in addition to expressing membrane-bound MICA, carcinoma cells also have a mechanism to shed MICA from the cell surface into the extracellular domain, generating a soluble form (sMICA) [5,6]. This process leads to a decrease of membrane-bound MICA and an increase of sMICA. Experimental evidence confirms that upon binding to NKG2D, sMICA not only fails to activate NK cells but also further inhibits NK cell function via down-regulating the expression of NKG2D on the NK cell surface [7,8]. Therefore, a possible mechanism by which carcinoma cells escape immune surveillance is the expression and shedding of MICA as sMICA.

Previous studies have demonstrated that elevation of sMICA was shown to be associated with poor prognosis in various cancer patients, including osterosarcoma and multiple myeloma [9–11]. However, there is no data on sMICA and its prognostic value in prostate cancer. Accordingly, we hypothesized increase levels of sMICA in prostate cancer that were linked to disease stage. We also aimed to evaluate the long-term prognostic significance of sMICA, and determine potential links with relevant clinical and histological criteria.

This retrospective pilot study was approved by the affiliated hospital of Qingdao University, Shandong, China. Informed consent was obtained from 136 patients with prostate cancer, ages 51–84 years (65.4 ± 0.8 years). No patients had evidence of active infection or inflammatory disease, and none were under any treatment for prostate cancer at the time of examination. The diagnosis of prostate cancer was confirmed by needle biopsy or by transurethral resection of the prostate: 37 patients had well differentiated adenocarcinoma, 73 had moderately differentiated adenocarcinoma and 26 had poorly differentiated adenocarcinoma. The staging procedures included clinical examination, pyelography, bone scanning and computed tomography and/or ultrasonography and/or endorectal magnetic resonance imaging and/or magnetic resonance imaging of the abdomen and pelvic cavity. Bone metastases were detected by bone scintigraphy with 25 mCi Tc-99 m methylene diphosphonate. Bone lesions were graded based on the number of metastases identified on the bone scan according to the Extent of Disease (EOD) method [12]. The grades were: EOD 0, normal or abnormal due to benign bone disease; EOD1, <6 metastases; EOD 2, 6–20 metastases; EOD 3,>20 metastases but not a superscan; and EOD 4, superscan. The tumour was stage B in 36 patients, stage C in 20 patients and stage D in 80 patients. Ten of 36 patients with stage B disease were initially treated with radiation therapy or radical prostatectomy, and the remaining 26 patients were treated with endocrine therapy (medical castration using a

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luteinizing hormone-releasing hormone analogue or surgical castration) with or without antiandrogens. All patients with stage C and stage D disease were treated using immediate endocrine therapy. No local treatment was performed for stage C patients. The median (range) time of follow-up was 40 (9–87) months.

Samples were collected before patients undergoing prostate biopsy into serum separator gel vacuette tubes, allowed to clot for ~30 min at room temperature and centrifuged at room temperature for 10 min at 2500*g*. Serum was aliquoted, snap frozen in liquid nitrogen and stored at −80 °C. sMICA was quantified by commercial sandwich ELISA kits according to manufacturer's instructions (R & D Systems, Abingdon, UK). PSA was determined by E-Test Tosoh II PA (Shanghai Ailex Capital Iinvestment Co, Ltd, Shanghai, China). Each sample was tested twice in triplicates. All summary data in the tables are presented as the mean (with standard deviation). The patients were divided into groups according to tumour histology (well and moderately differentiated adenocarcinoma versus poorly differentiated adenocarcinoma), performance status (PS), (PS = 0 vs. PS ≥ 1), bone scan findings (EOD 0 vs. EOD ≥ ≤ 1 vs. EOD ≥ 2), pretreatment PSA levels (<100 vs. ≥ 100 ng/ml) and pretreatment sMICA levels (<283 vs. ≥ 283 pg/ml). Variables of two different groups were compared using Student's *t* test. Pearson's correlation coefficient (*r*) was used to describe the correlation between sMICA levels and PSA levels. Disease-free survival (DFS) was estimated using the Kaplan–Meier method and analysed using the log-rank test. Hazard ratios (HRs) with 95% CIs were calculated using Cox's proportional hazards models in univariate and multivariate analyses. To obtain a multivariate model with the maximum precision of the important variables, a stepwise selection procedure was used. In all analyses, $P < 0.05$ was considered statistically significant.

The mean (SD) sMICA in all 136 patients with prostate cancer was (283 ± 10) pg/ml. The sMICA level in patients with stages B, C and D prostate cancer was 198 ± 7, 230 ± 8 pg/ml, and 578 ± 12 pg/ml, respectively. The serum PSA level in these respective groups was 63 ± 14, 78 ± 15 and 704 ± 158 ng/ml, respectively. sMICA failed to correlate significantly with PSA ($r = 0.23$, $P = 0.086$). sMICA levels in patients with well, moderately and poorly differentiated adenocarcinoma were 204 ± 6 pg/ml, 243 ± 7 pg/ml and 512 ± 13 pg/ml, respectively. The patients were divided into two groups according to sMICA level (283 vs. ≥ 283 pg/ml). The former group was 70 ± 2 years old, the latter was 71 ± 1 years old ($P = 0.68$). The serum PSA levels in the patients with sMICA levels ≥283 pg/ml were 1130 ± 493 ng/ml, which was significantly higher than those in patients with sMICA levels < 283 pg/ml (278 ± 78 ng/ml, $P < 0.05$).

To identify the variables of potential prognostic significance, univariate analysis of each variable was performed in relation to the survival time. The difference in prognosis was assessed by hazard ratio each variable, which showed that patients with EOD ≥ 1, sMICA ≥ 283 pg/ml, PS ≥ 1 and PSA > 100 ng/ml had a significantly lower survival rate than their respective counterparts ($P < 0.05$; Table 1). Tumour histology was not significantly linked with the prognosis in this univariate analysis. The relative importance of each variable was then determined by multivariate Cox's proportional hazards model analysis. Stepwise inclusion of variables in the model showed that the significant prognostic factors were EOD and sMICA (Table 1). In the 100 patients with stage C and stage D prostate cancer, univariate analysis showed that EOD ≥ 1, sMICA ≥ 283 pg/ml, PS ≥ 1 and PSA > 100 ng/ml were significantly related to survival (Table 2). Cox's proportional hazards analysis using a stepwise inclusion of variables demonstrated that EOD ≥ 1 and sMICA ≥ 283 pg/ml were significant prognostic factors (Table 2). In the 80 patients with stage D prostate cancer, univariate analysis showed that EOD ≥ 2 (Hazard ratio (HR) 6.27, $P = 0.005$), sMICA ≥ 284 pg/ml (HR 4.37, $P = 0.012$) and PSA > 10 ng/ml (HR 6.03, $P = 0.014$) were significantly related to survival. Cox's proportional hazards analysis using a stepwise inclusion of variables demonstrated that EOD ≥ 2 [HR 6.14 (95% CI, 2.16–19.4), $P = 0.0038$] and sMICA ≥ 283 pg/ml [HR 4.38 (95% CI, 1.27–20.4), $P = 0.018$] were significant prognostic factors.

Prostate cancer is the most commonly diagnosed neoplasm and the third most common cause of cancer-related death amongst men in the Western world. It is a clinically highly heterogeneous disease, and distinction between aggressive and indolent disease is a major challenge for management [13]. Currently, no biomarkers or prognostic tools can accurately predict tumour progression at the time of diagnosis. Thus, improved biomarkers for prognosis are urgently needed. The PSA test is currently the gold-standard for prostate cancer detection, but is limited for specificity and has limited capacity for prognostic prediction; consequently, it cannot readily

Table 1. Hazard ratios of survival in univariate and multivariate analyses in all 136 patients.

	Univariate		Multivariate		
	Hazard ratio	*P*	Hazard ratio	95% confidence interval	*P*
Performance status (PS) ≥ 1	2.96	0.015			
Extent of disease ≥ 1	8.76	<0.001	8.36	5.14–28.7	<0.00103
Poorly differentiated vs. well differentiated tumour	1.98	0.149			
sMICA ≥ 283 pg/ml	4.20	0.0006	2.94	1.04–7.98	0.041
PSA ≥ 100 ng/ml	5.14	<0.0001			

Table 2. Hazard ratio of survival in univariate and multivariate analyses in patients with stages C and D prostate cancer.

	Univariate		Multivariate		
	Hazard ratio	*P*	Hazard ratio	95% confidence interval	*P*
Performance status (PS) ≥ 1	2.76	0.038			
Extent of disease ≥ 1	8.56	0.003	8.36	3.83–36.4	0.0025
Poorly differentiated vs. well differentiated tumour	2.28	0.098			
sMICA ≥ 283 pg/ml	4.76	0.001	3.16	1.15–11.4	0.027
PSA ≥ 100 ng/ml	6.18	0.0042			

discriminate patients at higher risk of progressive disease or mortality from those who have a more favourable prognosis.

Increased sMICA is present in many malignant tumours, such as lung, colorectal and breast cancer and neuroblastoma. Patients with metastatic pancreatic cancer [14] and advanced hepatocellular carcinoma [15] have higher sMICA levels than those without disseminated disease. Multiple myelomas patients with sMICA levels >305 pg/mL have poor progression-free survival rates than those with levels <305 pg/mL [11]. We add to the literature, reporting, sMICA levels to be significantly higher in patients with stage D prostate cancer than in patients with stage B and stage C prostate cancer, suggesting that patients with metastatic prostate cancer had significantly elevated sMICA levels compared with other prostate cancer patients.

Univariate analysis demonstrated that EOD, PSA and sMICA were associated with a poor prognosis in stage D prostate cancer patients. Multivariate analyses showed that PS, PSA and sMICA were all non-significant as prognostic variables. This may be partly because these variables probably reflect the metastatic burden and interact with EOD and partly because most patients with prostate cancer now begin therapy before a decrease in PS. We also found the variables with a significant influence on survival in patients with advanced prostate cancer according to multivariate analysis were EOD and sMICA.

These results indicate that the sMICA level may be associated with the prognosis of patients with prostate cancer. This work represents an advance in biomedical science because it shows that sMICA and EOD are both prognostic factors that can be used to identify patients with a poor prognosis who may benefit from more aggressive management.

Disclosure statement

No potential conflict of interest was reported by the authors.

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