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The importance of serum osteopontin and stanniocalcin-1 in renal cell carcinoma

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A total of 56 RCC patients with staging ≥ pT1b were enrolled in a prospective study to assess the prognostic importance of serum levels of osteopontin (OP), stanniocalcin-1 (SC), FGF-23, alpha Klotho and 25-OH-D at the time of diagnosis in renal cell carcinoma (RCC) patients. The relationship between the serum level of the analyzed parameters and recurrence-free survival (RFS), overall survival (OS) and cancer-specific survival (CSS) was examined, and our control group consisted of 20 patients without cancer. The levels of osteopontin, stanniocalcin-1, FGF-23 and alpha Klotho were determined by Enzyme-Linked Immunosorbent Assay (ELISA) and 25-OH-D by chemiluminiscence immunoanalysis (CLIA). The follow-up period median was 46 months. Renal cell carcinoma recurred in 9 patients and 20 patients died during follow-up; 12 of them from RCC. The level of osteopontin and stanniocalcin-1 varied between the control group and RCC patients (at p=0.02 and p=0.0003). Higher levels of stanniocalcin-1 were detected in the metastatic RCC group than in the localized RCC group (p=0.003). Only the stanniocalcin-1 level at the time of surgery was associated with RFS (p=0.0004). Both OS and CCS were associated with the osteopontin, stanniocalcin-1 and FGF preoperative level. Patients with stanniocalcin-1 level over 1,277 pg/ml and osteopontin level over 100 ng/ml had 17.8 times higher and 7.9 times higher risk of dying from RCC progression, respectively (p<0.001 and p=0.002). High levels of osteopontin, stanniocalcin-1 and FGF 23 at the time of surgery are important prognostic factors related to CSS and OS. Patients with high stanniocalcin-1 level were at risk of tumor recurrence.

Key words: Renal cell carcinoma, osteopontin, stanniocalcin-1, overall survival, cancer-specific survival, recurrence-free survival

Renal cell carcinoma (RCC) is the third most common urogenital malignancy in adults, with 235,000 new cases recorded globally in 2015 [1], and The Czech Republic has the highest RCC incidence in the world [1]. The disease is generalized in up to 20% of patients at the time of diagnosis. Up to one third of patients relapse in the follow-up period following radical surgery, and the mortality rate is approximately one third of the incidence rate (11 patients per 100,000 inhabitants) [2]. Laboratory markers for prediction of the biological behavior of renal lesions, the clinical stage of the disease and the success of surgical treatment relative to the disease-free, disease-specific and overall survival of RCC patients are currently lacking.

Possible factors contributing to RCC development are obesity and the deregulated production of adipokines which also affect angiogenesis and insulin resistance development [3, 4]. A similar relationship in RCC is observed between vascular endothelial growth factor (VEGF), hypoxia inducible factor 1 alpha (HIF-1 alpha) and calcium phosphate metabolism.

Higher plasma levels of 25-OH-D and vitamin D binding protein are believed to be associated with a lower risk of developing kidney cancer in both men and women [5]. Calcitriol has a proven anti-proliferative and pro-apoptotic and immunomodulatory effects in tumors [6], and some parameters of calcium phosphate metabolism are considered possible prognostic factors of renal cell carcinoma.

Stanniocalcin-1 is a glycoprotein hormone involved in calcium regulation. It also has a role in angiogenesis, oxidative stress regulation and apoptosis. This can therefore play a

significant role in carcinogenesis. Increased stanniocalcin-1 expression has also been observed in breast, hepatocellular and colorectal cancers and non-small-cell lung carcinoma [7]. The hypothesis of possible stanniocalcin-1 relationship to RCC is based on both its relationship to vascular endothelial growth factor (VEGF) upregulation and its ability to respond to hypoxia by stimulating the production of hypoxia inducible factor 1 alpha (HIF-1 alpha) which is related to von Hippel-Lindau gene and tumorigenesis in kidney cancer [8].

Osteopontin is an integrin glycophosphoprotein involved in angiogenesis and tumor invasiveness. The expression of osteopontin is induced by a number of stimulating factors (vitamin D, interleukin 1, endothelin, interferon γ, transforming growth factor and fibroblast growth factor). Its primary roles are remodeling mineralized bone, regulation of immune processes, neovascularization and cell migration [9]. There are often necroses in kidney carcinoma caused by intra-tumorous hypoxia which then leads to up-regulation of osteopontin expression via Ras activators. Some studies have shown that osteopontin may be expressed in some types of more advanced and aggressive renal tumors, and it can therefore be a potential prognostic factor [10].

Fibroblast growth factor 23 (FGF23) is a bone hormone that protects against the potentially dangerous effect of hyperphosphatasemia by reducing phosphate reabsorption in the proximal tubules and further activates vitamin D synthesis in the kidney [11]. Within the framework of carcinogenesis, it is part of an alternative signaling VEGF pathway targeted by some modern drugs, including dovitinib, nintedanib and lenvatinib) [12]. Alpha Klotho acts as a co-receptor in the FGF 23 signaling pathway, and is known to weaken cell migration and invasiveness and can therefore have a protective effect in tumor suppression [13].

The primary objective of this study is to evaluate the relationship of pre-operative osteopontin, stanniocalcin-1, FGF-23, alpha Klotho and 25-OH-D levels with recurrence-free survival (RFS), overall survival (OS) and cancer-specific survival (CSS) in RCC patients. Our secondary objective is to evaluate the relationship of their pre-operative levels to RCC clinical and pathological prognostic factors.

Patients and methods

Patient selection and study procedures. A total of 56 patients with histologically proven RCC staged ≥pT1b were enrolled in the study from September 2011 to November 2012. Abdominal CT and chest X-ray or CT were performed in all patients, and some underwent bone scintigraphy. Radical nephrectomy was carried out in 30 (55.6%) patients and kidney resection in 24 (42.9%) patients, and tumor biopsy was performed in two cases before biological treatment. The exclusion criteria were: benign kidney tumor, renal cancer classified as pT1a, history of another tumor (except non-melanoma skin tumors), creatinine >200 μmol/l, ALT and/or AST ≥5 times the upper limit of normal, fasting blood sugar >15 mmol/l and hemoglobin <70 g/l. Blood was taken from all the patients on the morning of their surgery. The tumor size, grade and stage were determined by histological examination. The patients then underwent a prospective follow-up as recommended by the European Association of Urology [5]. The control group consisted of 20 patients without cancer.

This research project was designed as a prospective observational cohort study approved by the Ethics Committee in accordance with the Declaration of Helsinki. All study participants signed their respective informed consent forms.

Laboratory analyses. Blood for special biochemical analyses was drawn into anticoagulant-free tubes, centrifuged at 1,450 g for 10 minutes and the serum was frozen at –80 °C.

Enzyme-Linked ImmunoSorbent Assay (ELISA) determined OSTEOPONTIN (RD Systems, Minneapolis, MN, USA), SC (Biovendor – Laboratorní medicína a.s., Brno, CZ), FGF-23 C-term (Immutopics Inc., San Clemente, California, USA) and alpha Klotho (IBL International GmbH, Hamburg, Germany). 25-OH-D was determined by chemiluminiscence immunoanalysis (CLIA) on LIAISON® XL analyzer, Diasorin, Italy.

Statistical analysis. The statistical analysis was performed using SAS 9.4 software (Cary, NC, USA) and graphs were performed by Statistica software (StatSoft, Inc., Tulsa, OK, USA).

Standard descriptive statistics such as mean, SD, median, minimum, maximum and interquartile range were used to describe quantitative continuous variables and categorical data was described by frequency tables. Survival data for 56 patients with renal cancer were censored at the last date the patient was known to be alive or at the analysis cut-off date, whichever came first. Surviving patients without proven metastases were censored for recurrence-free survival (RPS) analysis. All deaths (irrespective of the primary cause) and proven relapses were defined as a study event. For each study group, the time to the study event of overall survival (OS), disease-specific survival (DSS) and recurrence-free survival (RFS) were expressed by Kaplan-Meier survival curves and study event risk (Hazard Ratio + 95% confidence interval). The difference in OS, DSS and RFS among given groups was tested using the Log-rank test. The optimum cut off value of the study parameter was sought by maximizing the test criterion for the Cox regression model, and then always for several different cut-off points. Given the distribution of examined variables, non-parametric tests (Wilcoxon Two Sample test and Kruskal-Wallis test) were used to assess the difference of the study parameters for the stage, grade of differentiation, metastatic disease, histology and tumor size in the set of all patients. The difference in category variables in the study groups was tested by Chi-square and statistical significance was determined at alpha = 5%.

Results

The mean age of the patients was 66 years (39–82) and almost three-quarters were male. Most patients were overweight with mean body mass index of 29.1 (18.9–37.1). Approximately one quarter of the patients were active smokers with an average consumption of 34 pack years; 31% of the patients were former smokers and more than 42% of the patients were non-smokers. Eleven percent of patients had a positive family history. Less than three-quarters of the tumors were found incidentally (71.2%) and the leading symptom was hematuria (17.8%); predominantly microscopic hematuria. Patients with benign renal tumors and renal cancer histologically classified as pT1a were excluded from the evaluated group. The study group comprised malign kidney tumors with staging ≥pT1b and metastatic RCC was found in nearly 10% of patients. Table 1 shows the clinical and pathological characteristics. Three-quarters of patients underwent open surgery, and almost half had kidney resection.

Table 1. Study group characteristics.

	N	%
All patients	56	100
Histology	56	
Papillary renal cell cancer	9	16.1
Chromophobe renal cell cancer	3	5.4
Clear renal cell cancer	44	78.5
Stage group at time of RCC diagnosis	56	
localized	44	78.6
metastatic	12	21.4
Stage	56	
Stage I	10	17.9
Stage II	10	17.9
Stage III	23	41.1
Stage IV	13	23.2
Grade	53	
Grade 1	5	9.4
Grade 2	22	41.5
Grade 3	17	32.1
Grade 4	9	17.0
Type of operation	56	
Nephrectomy	30	55.6
- open	19	63.3
- laparoscopic	11	36.7
Nephron sparing surgery (partial nephrectomy)	24	42.9
- open	15	62.5
- laparoscopic	9	37.5
Percutaneous biopsy	2	5.48

Abbreviations: RCC – renal cell cancer

Table 2. Study group characteristics.

Group characteristics	Number of cases (%)
localized RCC at time of diagnosis	44 (78.6%)
metastatic RCC at time of diagnosis	12 (21.4%)
recurrent RCC at follow-up	9
patients alive	34
patients with non-cancer cause death	8
patients with cancer cause death	12
control group (patients without cancer)	20

Follow-up data was available for 54 patients with RCC. One patient died peri-operatively and a second patient died of embolism in the early post-operative period; both were excluded from analysis. The data from 54 patients was used for survival analyses. Five patients were lost to follow-up; all of these patients had a localized RCC at the time of surgery and did not show any relapse of the disease before being lost to follow-up. During the study with a median of 46 months (9–76 months), nine patients had disease relapse, of which loco-regional relapse occurred in two cases (inoperable in one patient, the other patient refused re-operation). Metastatic disease developed in seven patients and 20 patients died; 12 as a result of RCC progression. This is summarized in Table 2.

Relationship between OP, SC, FGF-23 C-term, alpha Klotho and 25-OH-D levels and clinical-pathological parameters. Table 3 shows the study parameter values for each tumor progression stage, differentiation and size. The osteopontin and stanniocalcin-1 levels varied between the control group and clear RCC (cRCC) patients (p=0.02 and p=0.003, respectively). The osteopontin level in the control group was approximately 33% lower than in cRCC; for stanniocalcin-1 it was almost 50% lower in the control group. Only the osteopontin level was significantly higher in the group of papillary and chromophobic RCC versus the control group (p=0.03). Higher levels of SC were detected in the mRCC group than in the localized RCC group (p=0.003), and stanniocalcin-1 also correlated positively with RCC size (p=0.004). Significant difference in serum 25-OH-D was observed between the histological grade (p=0.037), whereas levels of osteopontin and stanniocalcin-1 varied in the localized RCC between the pT groups (p=0.016 and p=0.008, respectively).

Survival analyses. As part of univariate analysis, significant predictive factors of OS were identified; osteopontin, stanniocalcin-1, FGF-23 and 25-OH-D. Table 4 shows the cut-off values for the tested parameters with statistical significance, HR and 95% CI for the OS, DSS and RFS groups.

The CSS was associated with the osteopontin, stanniocalcin-1 and FGF 23. Patients with osteopontin levels more than 100ng/ml and stanniocalcin-1 levels more than 1,277 pg/ml had 7.9 times higher and 17.8 times higher risk of cancer specific mortality, respectively (p=0.002 and p=0.0001). FGF-23 levels higher than 116 RU/ml increased the risk of death associated with RCC 4.1 times (p=0.01).

From the study parameters, only the level of stanniocalcin-1 at the time of surgery was associated with RFS (cut off ≤744 pg/ml, p=0.0004, HR 5.561, CI 1.903–16.249).

Multivariate analysis identified combined stage and osteopontin level with a cut off value of 100 ng/ml as a significant prognostic factor for cancer-specific survival (Figure 1). None of the patients with disease stage 1 to 3 who had initial pre-operative OP level below 100 ng/ml died due to the progression of RCC; and in contrast, all patients in stage 4 who had osteopontin entry value above 100 ng/ml died of RCC. Similarly, in the multivariate analysis we found tumor size and stanniocalcin-1 with a cut off value of 744 pg/ml significant in improving RFS estimation. Patients with an initial tumor size above 100mm and stanniocalcin-1 above 744 pg/ml had the highest probability of relapse (Figure 2).

Discussion

Levels of osteopontin and stanniocalcin-1 were higher in clear cell RCC (ccRCC) patients than in the control group. Higher levels of stanniocalcin-1 were detected in the mRCC group than in the localized RCC group. Stanniocalcin-1 also correlated positively with RCC size. In addition, we found that osteopontin and stanniocalcin-1 levels varied in the localized RCC for each disease stage category. Strong connection between the preoperative serum osteopontin, stanniocalcin-1 and FGF 23 levels and the CSS and OS in RCC patients was found in this study. High pre-operative osteopontin, stanniocalcin-1 and FGF-23 levels had a negative effect on CSS. Finally, the level of stanniocalcin-1 at the time of surgery was associated with RFS.

In this era of modern imaging techniques, there are still patients diagnosed with advanced and metastatic RCC who have poor prognosis. This is caused by its asymptomatic nature and the absence of diagnostic markers able to discover the disease both early and non-invasively. Not all factors contributing to the disease development have been identified, and there are no reliable prognostic markers that can enable individualized treatment.

Some mediators of calcium phosphate metabolism are related to alternative cancer pathways. Resistance to VEGF inhibition appears to result largely from activation of compensatory angiogenesis pathways (including the fibroblast growth factor pathway) and some medications used in new targeted treatments (regorafenib, dovitinib, nintedanib, lenvatinib) are already effectively blocking this route [12]. However, the relationship between FGF-23 and RCC has not been subjected to enough study. In our study, we demonstrated the relationship of pre-operatively elevated serum

Table 3. Associations among osteopontin, stanniocalcin-1, FGF-23, alpha Klotho and 25-OH-D and clinical and pathological characteristics.

	Osteopontin (ng/ml)		Stanniocalcin 1 (pg/ml)		FGF 23 (RU/ml)		alpha Klotho (pg/ml)		25-OH-D (ng/ml)	
	mean ± SD	p-value	mean ± SD	p-value	mean ± SD	p-value	mean ± SD	p-value	mean ± SD	p-value
Control group (n=20)	**67.71±27.35**		504.3±291.4		85.76±40.43		379.1±119.7		20.02±8.47	
Localized ccRCC (n=34)	**95.56±42.61**	**0.017 * vs. controls**	**939.9±647.6**	**<0.001 * vs. controls**	92.61±56.39	0.929 vs. controls	522.6±345.8	0.076 vs. controls	17.98±7.07	0.466 vs. controls
Localized non clear cell RCC (n=10)	**229.92±176.64**	**0.030 * vs. controls**	**725.2±349.8**	**0.009 * vs. controls**	95.88±81.12	0.844 vs. controls	622.4±593.6	0.253 vs. controls	16.15±6.19	0.320 vs. controls
Diameter of tumor 1–39 mm (n=2)	**58.45±1.06**		**486.7±112.4**		44.85±10.68		363.4±29.3		24.35±3.18	
Diameter of tumor 40–69 mm (n=16)	**76.29±38.70**	**0.005 ***	**603.6±207.8**	**0.004 ***	85.02±29.65	0.217	463.6±154.2	0.595	18.48±7.25	0.241
Diameter of tumor above 70 mm (n=26)	**161.94±122.59**		**1105.5±689.7**		102.22±75.65		609.6±512.1		16.48±6.59	
Localized RCC (n=44)	126.1±105.7	0.084	**890.0±595.1**	**0.003 ***	93.36±61.80	0.835	545.3±499.0	0.866	17.57±6.85	0.684
Metastatic RCC (n=12)	178.1±126.7		**1743.4±854.8**		100.84±61.24		471.8±204.5		18.05±11.7	
Grade 1 (n=5)	123.7±77.7		923.7±748.8		88.66±60.90		477.3±188.5		**7.89±3.45**	
Grade 2 (n=22)	131.9±98.9	0.890	995.1±611.0	0.681	91.58±41.61	0.941	515.4±276.4	0.937	**19.02±7.45**	**0.037 ***
Grade 3 (n=17)	150.6±130.3		1168.1±854.7		100.89±74.50		573.9±481.1		**19.55±5.74**	
Grade 4 (n=9)	159.7±137.6		1346.4±898.1		105.33±87.32		563.0±512.9		**14.38±5.40**	
localized RCC pT1+pT2 (n=21)	113.5±105.6	0.143	811.2±564.1	0.225	91.0±60.08	0.837	**412.6±169.1**	**0.028 ***	11.34±6.48	0.962
localized RCC pT3 (n=22)	141.3±107.7		989.3±631.9		96.93±65.77		**680.8±526.0**		17.92±7.45	
localized RCC pT1 (n=10)	**71.43±47.82**		**529.5±150.2**		76.92±26.55		441.9±186.8		19.76±5.91	
localized RCC pT2 (n=11)	**151.78±129.92**	**0.016 ***	**1067.2±681.9**	**0.008 ***	103.76±78.79	0.841	386.0±155.5	0.054	15.15±6.44	0.331
localized RCC pT3 (n=22)	**141.34±107.68**		**989.3±632.0**		96.93±65.77		680.8±526.0		17.92±7.45	

Abbreviations: RCC – renal cell cancer, SD – standard deviation, * statistically significant difference

Table 4. Cut-off levels of osteopontin, stanniocalcin-1, FGF-23, alpha Klotho and 25-OH-D and their relationship to survival parameters.

	OS				CSS				RFS			
	N	N of death (%)	p value (log-rank)	HR (95% CI)	N	N of death (%)	p value (log-rank)	HR (95% CI)	N	N of recurr. (%)	p value (log-rank)	HR (95% CI)
Osteopontin <100 ng/ml	28	**4**	**<0.001**	**5.983**	**28**	**2**	**0.002**	**7.876**			NS	
Osteopontin >100 ng/ml	26	16		**(1.981–18.063)**	26	10		**(1.701–36.478)**				
Stanniocalcin <1,277 pg/ml			NS		**37**	**2**	**<0.001**	**17.795**			NS	
Stanniocalcin >1277 pg/ml					16	10		**(3.846–82.328)**				
Stanniocalcin <744 pg/ml	**27**	**3**	**<0.001**	**8.594**			NS		**25**	**5**	**<0.001**	5.561
Stanniocalcin >744 pg/ml	26	16		**(2.490–29.661)**					16	11		(1.903–16.249)
FGF 23 <116 (RU/ml)			NS		**44**	**7**	**0.010**	**4.066**			NS	
FGF 23 >116 RU/ml					10	5		**(1.281–12.908)**				
FGF 23 <150 RU/ml	**48**	**15**	**0.002**	**4.356**			NS				NS	
FGF 23 >150 RU/ml	6	5		**(1.547–12.268**								
25-OH-D <14.3 ng/ml	**15**	**9**	**0.012**	**2.982**			NS				NS	
25-OH-D >14.3 ng/ml	39	11		**(1.223–7.271**								

Abbreviations: OS – overall survival, CSS – cancer specific survival, RFS – recurrence free survival, HR – hazard ratio, CI –Confidence Intervals, NS – not statistically significant

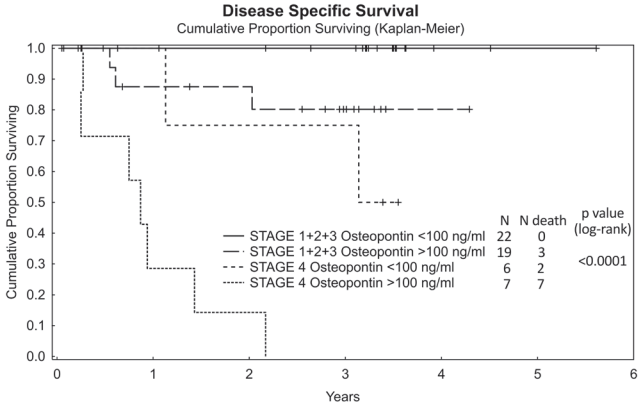

Figure 1. Multivariant analysis: Cancer specific survival.

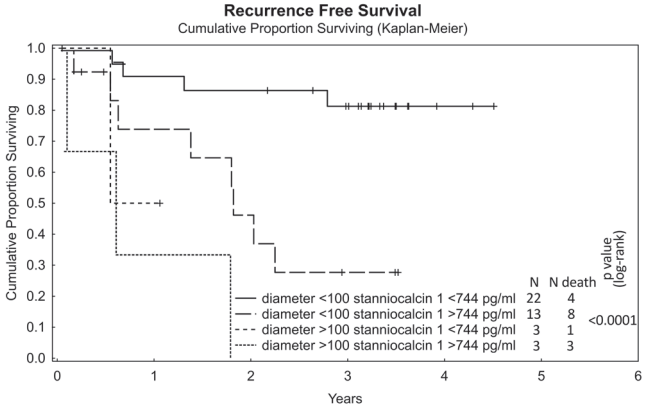

Figure 2. Multivariant analysis: Recurrence free survival.

levels of FGF 23 to both OS and CSS. We determined that patients with an initial level above 116 RU/ml had 4 times higher risk of death from RCC.

The renoprotective antiaging gene, alpha Klotho, has recently been found effective as a tumor suppressor in different human cancers. Alpha Klotho as a tumor suppressor factor is predominantly expressed in renal tubular cells, the origin of ccRCC, and altered expression or function of growth factor receptor has also been implicated in ccRCC development. Alpha Klotho suppresses tumor progression and acts as an upstream modulator of insulin-like growth factor-1 receptor signaling [13]. Its protein levels were significantly decreased in RCC tissues compared to normal tissues.

Statistically significant differences are found between serum alpha Klotho levels and tumor size, Fuhrman grade and clinical stage, and CSS and progression free survival were significantly shorter in patients with lower levels of alpha Klotho [14]. In our study, we only identified the different alpha Klotho level between stages of RCC; surprisingly this level was higher in more advanced RCC than in the less differentiated RCC. However, we did not confirm any effect of alpha Klotho on metastatic disease and survival or on any other reported parameters.

Stanniocalcin-1 mRNA and protein expression were significantly up-regulated in RCC tumors compared with non-tumor tissues; with the greatest expression observed in metastatic tissues. Stanniocalcin-1 expression was associated with Fuhrman tumor grade and tumor stage, and stanniocalcin-1 expression was also elevated in small T1 stage metastatic tumors compared to localized larger tumors, and it positively correlated with average tumor diameter [15]. Also strong cytoplasmic stanniocalcin 2 expression was

significantly associated with shorter patient survival [16]. In our study, stanniocalcin-1 is the most important diagnostic and prognostic marker and patients with RCC had higher serum stanniocalcin-1 than the control group. Higher preoperative stanniocalcin-1 levels were found in patients with higher staging and grading, and also in patients with primarily metastatic or bulky RCC. Serum pre-operative stanniocalcin-1 levels above 1,277pg/ml increased risk of death from RCC up to 17 times and stanniocalcin-1 also has a significant effect on OS. It is also the only tested parameter which affects the time of disease recurrence.

In normal renal parenchyma, the expression of osteopontin was seen in distal tubular epithelial cells, calcifications and some stromal cells. Osteopontin over-expression correlates with tumor size, Fuhrman nuclear grade and pathological stage. Moreover, patients with strongly osteopontin-expressed tumors had significantly worse prognosis than patients with tumors lacking osteopontin protein expression [10].

Osteopontin is a univariate prognostic factor for OS, CSS and disease-free survival; where it outperformed Karakiewitz nomogram and the post-operative SSIGN score for OS but not for CSS. Osteopontin and carbonic anhydrase 9 identified several subsets of poor prognostic patients; including T1 patients who may benefit from adjuvant therapy and increased surveillance [17]. The osteopontin serum levels in RCC patients with distant metastases were also significantly elevated compared to those without metastases and controls, but they did not differ between patients with bone and non-bone metastases.

High osteopontin values are associated with poor survival [18]. In our study, osteopontin clearly distinguished RCC patients from controls, and its serum level increased with the size and stage of RCC. We also demonstrated that osteopontin is an important prognostic factor for OS and CSS; patients with pre-operative serum osteopontin above 100ng/ml are approximately 7.8 times more likely to die from RCC.

To the best of our knowledge, this is the first study evaluating the relationship between the pre-operative serum level of stanniocalcin-1 and recurrence free survival. We have also confirmed certain clinical and pathological relationships between RCC and osteopontin and stanniocalcin-1. While we have proven the importance of osteopontin, stanniocalcin-1 and FGF-23 as independent predictive factors related to OS and CSS, our study did not determine that alpha Klotho is an important survival prognostic factor. The study also has limitations, because it involved a small, heterogeneous study population on which we only performed one pre-operative blood sampling, and pT1a RCC patients were not included. While the long-term developmental trends arising from the study parameter levels are not established, we have confirmed that stanniocalcin-1 and osteopontin pre-operative serum levels are most significant prognostic factors for RCC.

In conclusion, Osteopontin and stanniocalcin-1 achieved significantly different levels in the RCC and control groups. The stanniocalcin-1 level clearly correlates with RCC stage; with higher stanniocalcin-1 levels detected in the mRCC group than in the localized RCC group. High osteopontin, stanniocalcin-1, FGF-23 and 25-OH-D levels at the time of RCC surgery impose adverse effect on overall survival. Finally, it is apparent from our results that high levels of osteopontin, stanniocalcin-1 and FGF 23 at the time of surgery are important prognostic factors for cancer specific survival of renal cell carcinoma. Most importantly, patients with high stanniocalcin-1 level are at great risk of tumor recurrence.

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