

CADHERIN-6: A NEW PROGNOSTIC MARKER FOR RENAL CELL CARCINOMA

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ABSTRACT

Purpose: Cadherin-6, a new cell adhesion molecule of the cadherin family, is expressed in normal kidney and renal cell carcinoma. First results demonstrated that the expression of cadherin-6 in renal cell carcinoma may have prognostic value. We prospectively evaluated the importance of cadherin-6 in renal tumors in a large cohort of patients.

Materials and Methods: A total of 216 patients with renal cell carcinoma who underwent tumor nephrectomy were evaluated for cadherin-6 expression by immunohistochemistry and immunoblotting. The expression pattern was correlated with known prognostic factors of renal cell carcinoma. Statistical analysis was performed by the Mann-Whitney U and Pearson chi-square tests. Multivariate analysis was performed by the proportional hazard Cox model.

Results: Cadherin-6 expression in renal cell cancer correlated with known prognostic factors, such as pT stage ($p = 0.03$), pN stage ($p = 0.001$), histological growth pattern ($p = 0.001$), M stage ($p = 0.06$) and renal venous involvement ($p = 0.019$). There was no correlation with tumor grading ($p = 0.74$) or tumor size ($p = 0.84$). We developed a relative risk factor for renal cell cancer for our patients using the multivariate proportional hazard Cox model, which showed a statistically significant correlation with cadherin-6 expression ($p = 0.028$).

Conclusions: Cadherin-6, a new cell adhesion molecule of the cadherin family, is specifically expressed in the proximal tubule of normal kidneys and in renal cell cancer. In our prospective analysis the pattern of cadherin-6 expression correlated with known prognostic factors of renal cell cancer on univariate and multivariate analysis. Our data suggest that cadherin-6 is a new prognostic factor for renal cancer.

KEY WORDS: kidney; carcinoma, renal cell; cadherins; cell adhesion molecules; tumor markers, biological

Renal cell cancer accounts for approximately 3% of all adult malignancies. Renal carcinoma can be cured in the early stage only. Advanced tumor stages are associated with poor prognosis, especially due to observed chemoresistance and radio-resistance. Immunotherapy protocols result in partial and complete remission in a subset of patients.¹ Prognostic markers are needed to identify patients at risk for the recurrence and metastasis of renal cell carcinoma and, thus, would benefit from additional therapeutic modalities. Current prognostic factors, such as tumor grade, renal vein involvement and extension to regional lymph nodes, have limited value in this respect.²

Cadherins, a family of cell-cell adhesion molecules, have demonstrated their ability as prognostic markers for various neoplasms. Dysfunction of cadherins has a major impact in the progression of epithelial tumors.³ Loss or abnormal expression of cadherins in tumors can lead to tumor invasion and disease progression, as demonstrated for E-cadherin expression in the prostate.⁴ Studies of the role of abnormal cadherin expression are less conclusive in regard to its use as a marker for renal cell carcinoma progression.

We have previously reported a new cell adhesion molecule, cadherin-6, which was first described by Shimoyama et al.⁵ We noted that cadherin-6 is expressed in the proximal renal tubules and in renal cell cancer.⁶ In this study we investi-

gated the role of cadherin-6 as a prognostic factor for renal tumors in a large cohort of patients.

MATERIALS AND METHODS

Surgical specimens. Fresh renal tissue was obtained at surgery. Normal renal tissue and tumor material were harvested, immediately frozen in liquid nitrogen and stored at -70°C .

Antibodies. A polyclonal anticadherin-6 antibody was generated by immunization of a rabbit, as previously described.⁶ The antibody was highly specific for cadherin-6 and K-cadherin.

Immunohistochemistry. Frozen sections were cut at $6\text{ }\mu\text{m}$, mounted, air-dried for 30 minutes and used immediately. Immunohistochemistry was performed as described previously.⁶ Specimens were considered positive if more than 90% of cells demonstrated immunoreactivity for anticadherin-6. Heterogeneous expression was noted if 10% to 90% of cells showed immunoreactivity and negative if less than 10% stained positive for anticadherin-6. Abnormal staining was noted if expression of cadherin-6 was negative or heterogeneous and normal if staining was positive.

Immunoblotting. Frozen renal tissue was lysed in 2% sodium dodecyl sulfate, 100 mM NaCl, 1 mM ethylenediaminetetraacetic acid and 62.5 mM tris-HCl, pH 6.8. Immunoblotting was performed as described previously.⁶ Specimens were only included in analysis if there was a single band for cadherin-6 in corresponding normal renal tissue at 130 kDa (fig. 1).

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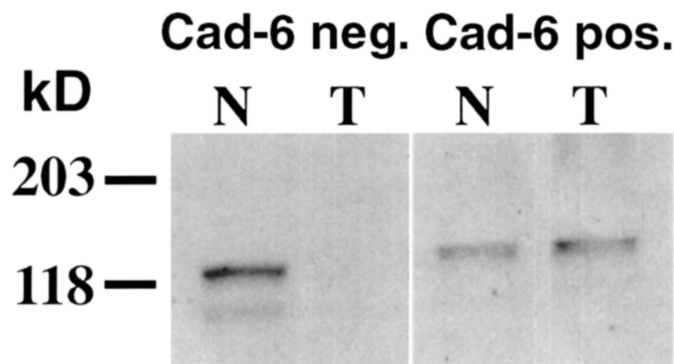


FIG. 1. Immunoblotting of renal carcinoma with anticadherin-6 antibody demonstrates complete loss of cadherin-6 (*Cad-6*) expression in left tumor and homogeneous positive (*pos.*) immunoreactivity in right tumor (*T*) compared with normal kidney (*N*). *neg.*, negative. *kD*, kDa.

DNA flow cytometry. Tumor specimens were homogenized and re-suspended in trypsin, sodium citrate, 0.1% Tween-80, 1.5 mM spermine tetrahydrochloride and tris buffer, pH 7.6. After 30 minutes of incubation at room temperature trypsin inhibitor and ribonuclease A were added and incubated for 10 minutes. Suspension was filtered (50 μ m pores) and 250 μ l were stained with propidium iodide, 0.1% Tween 80, 1.5 mM spermine tetrahydrochloride and tris buffer, pH 7.6. Analysis was performed using a FACS-Calibur system and CellQuest (Becton Dickinson, Sunnyvale, California) software.

Patients. To evaluate prognostic factors in renal cell cancer all 1,262 patients with renal cell cancer who underwent radical nephrectomy from 1983 to 2000 at the department of urology at Technische Universitaet Munich were evaluated. Altogether 216 patients at our 2 institutions were included for immunohistochemistry and immunoblotting of cadherin-6 expression in renal cell cancer.

Statistical analysis. Statistical analysis was performed using SPSS, version 10 (SPSS, Chicago, Illinois) software. Descriptive and comparative statistics were done using the Mann-Whitney U and Kruskal-Wallis tests for continuous variables, and the Pearson chi-square or Fisher exact test for nominal variables. Survival analysis was done by the Kaplan-Meier method and differences were evaluated by the log rank test. For multivariate analysis we used a proportional hazard Cox model with stepwise forward selection of variables. Statistical significance was considered at 5% ($p < 0.05$). Highly statistically significance was assumed at $p < 0.01$ and a statistical trend for missing significance of up to 20%.

RESULTS

Cadherin-6 expression in renal cell cancer. A total of 216 patients were included in the analysis. In all cases immuno-

blotting of corresponding normal renal tissue demonstrated a single band at 130 kDa of cadherin-6 as proof of the quality of the frozen tissue (fig. 2). Scoring was considered positive, heterogeneous or negative for cadherin-6 (fig. 1).

We included 140 male (64.8%) and 76 female (35.2%) patients. Mean age was 60.3 years (range 18 to 82). We noted 194 renal cell cancers, 5 oncocytomas, 4 transitional cell cancers, 7 angiomyolipomas, 2 collecting duct carcinomas, 1 benign nephroma, 1 ganglioneuroma, 1 Wilms tumor and 1 leiomyosarcoma (table 1). Mean tumor size was 6.2 cm, that is 6.0 cm in those with normal and 6.3 cm in those with abnormal cadherin-6 expression (table 1). For stratification we used the 1997 TNM classification (table 2).⁷ Of pT1 and pT2 tumors we noted homogeneous expression of cadherin-6 in 34.8% and 55.5%, respectively. The pT3 tumors showed positive cadherin-6 expression in only 25.8% and all 3 included pT4 tumors demonstrated abnormal immunoreactivity. Almost half of all pN0 renal cell cancers had homogeneous cadherin-6 expression, while in cases of lymph node metastases (pN1 and pN2) none of the tumors showed normal expression. Of nonmetastasized tumors 45.1% were positive for cadherin-6 but only 21.4% were positive with metastases (table 2). We also analyzed cadherin-6 expression according to the 1969 Robson classification.⁸ We noted a decrease in cadherin-6 positive results in Robson stage IV tumors but for stages I to III the rate of homogeneous expression of cadherin-6 was similar at between 45.2% and 49.4% (table 2).

For highly differentiated renal cell cancers (G1) the rate of normal cadherin-6 expression was 50.0%, for G2 tumors the rate decreased to 42.6% and for undifferentiated tumors (G3-4) only 37.1% showed homogeneous cadherin-6 expression (table 2). We also evaluated differences in the histological growth pattern in 194 renal cell cancers only. Overall 156 tumors could be classified. The majority of investigated renal tumors were clear cell carcinoma (117). This variant demonstrated homogeneous, positive cadherin-6 expression in 47.0% of cases. Papillary renal cell carcinomas demonstrated normal cadherin-6 expression in 66.7% (table 3). Renal cell carcinomas with a sarcomatoid-like growth pattern showed a lack of positive cadherin-6 expression (table 3). We noted positive cadherin-6 expression in 38.9% in cases of no venous involvement and only 10.5% in tumors with thrombus (table 1). In a subset of 65 tumors ploidy status was evaluated. There was no difference between euploid (21.7%) and aneuploid (23.8%) tumors regarding homogeneous cadherin-6 expression (table 1).

Prognostic parameters of renal cell cancer. Immunohistochemistry and immunoblotting of cadherin-6 is effective only in fresh frozen material. For this reason patient followup was too short to analyze cadherin-6 expression by Kaplan-Meier analysis. Therefore, evaluation of the prognostic power of cadherin-6 was analyzed by correlating cadherin-6 with prognostic factors, which we established for our patient popula-

TABLE 1. Characteristics of cadherin-6 expression in patients with renal tumors

Parameter	Overall	Normal Cadherin-6	Abnormal Cadherin-6
Mean age (range)	60.3 (18–82)	59.8 (19–79)	60.7 (18–82)
No. sex (%):			
Male	140	(55) (39.3)	85 (60.7)
Female	76	(30) (39.5)	46 (60.5)
No. side (%):			
Lt	52	(16) (30.8)	36 (69.2)
Rt	45	(14) (31.1)	31 (68.9)
Mean cm tumor size (range)	6.2 (1.7–22)	6.0 (2.5–11)	6.3 (1.7–22)
No. venous involvement (%):			
None	72	(28) (38.9)	44 (61.1)
Thrombus	19	(2) (10.5)	17 (89.5)
Ploidy:			
Euploid	23	(5) (21.7)	18 (78.3)
Aneuploid	42	(10) (23.8)	32 (76.2)

Expression was considered normal (positive) and abnormal (heterogeneous or negative).

TABLE 2. *Cadherin-6 expression in patients with renal cell carcinoma by tumor stage and grade*

Stage	No. Pts	No. Cadherin-6 (%)		
		Pos	Heterogeneous	Neg
pT1	46	16 (34.8)	13 (28.3)	17 (36.9)
pT2	18	10 (55.5)	3 (16.7)	5 (27.8)
pT3	58	21 (25.8)	21 (33.8)	16 (40.4)
pT4	3	0	0	3 (100)
pN0	143	64 (44.8)	41 (28.7)	38 (26.5)
pN1/pN2	8	0	1 (12.5)	7 (87.5)
M0	162	73 (45.1)	44 (27.2)	45 (27.8)
M1	14	3 (21.4)	3 (21.4)	8 (57.1)
G1	16	8 (50.0)	4 (25.0)	4 (25.0)
G2	94	40 (42.6)	25 (26.6)	29 (30.8)
G3-4	62	23 (37.1)	22 (35.5)	17 (27.4)

TNM classification⁷ and Robson staging system.⁸TABLE 3. *Cadherin-6 expression by different histological growth patterns of renal cell cancers only*

Histological Growth Pattern	No. Pts	No. Cadherin-6 (%)		
		Pos	Heterogeneous	Neg
Clear cell type	117	55 (47.0)	33 (28.2)	29 (24.8)
Granular cell type	14	9 (64.3)	4 (28.6)	1 (7.1)
Papillary tumors	18	12 (66.7)	4 (22.2)	2 (11.1)
Sarcomatoid type	5	0	3 (60.0)	2 (40.0)
Collecting duct type	2	2 (100)	0	0

Total of 156 patients.

tion. At the department of urology at Technische Universität Munich 1,262 patients underwent radical nephrectomy between 1983 and 2000. We did not find a significant difference between overall and tumor specific survival in patients with renal cell carcinoma. Therefore, we only present data regarding overall survival.

By Kaplan-Meier analysis and the log rank test we noted that the TNM staging system⁷ as well as the Robson classification system⁸ had equal prognostic power on univariate analysis ($p < 0.0001$, table 4). Grading and venous involvement were also statistically highly significant ($p < 0.0001$). Ploidy status failed to show statistical significance in our population ($p = 0.24$). We noted a trend toward a worse prognosis in male than in female patients ($p = 0.06$). Tumor size was a significant prognostic factor as well as residual disease (R1 and R2). We could not find a difference in tumor side, tumor location within the kidney or patient age (table 4).

We used a proportional hazard Cox model with stepwise forward selection of variables for multivariate analysis (table 5). There were 3 independent prognostic factors in our analysis, namely the TNM staging system, venous involvement

TABLE 5. *Cox proportional hazard model of prognostic factors in patients with renal cell cancer to predict overall survival after radical nephrectomy*

Parameter	Cox Model		95% CI
	p Value	Relative Risk	
TNM classification:			
pT1 + 2, pN0, M0	<0.001	—	—
pT3 or greater, pN0, M0	0.879	1.0	0.49–2.32
pTx, pN+, M0	<0.001	7.5	3.57–15.88
pTx, pNx, M1	<0.001	4.4	2.21–8.88
Venous involvement	<0.001	2.4	1.47–4.01
Tumor size greater than 8 cm	0.001	2.4	1.47–4.01

Total of 1,262 patients.

and tumor size with a cutoff of 8 cm. We developed a relative risk factor by simple multiplication of the relative risk for each of the 3 prognostic factors (table 5).

Correlation of cadherin-6 expression with prognostic markers for renal cell cancer. We correlated the expression pattern of cadherin-6 with our established prognostic factors (table 4). We observed that cadherin-6 expression correlated with T stage ($p = 0.03$), N stage ($p = 0.0001$), Robson stage ($p = 0.041$), venous involvement ($p = 0.019$) and histological growth pattern ($p = 0.0001$). We noted a trend with M stage ($p = 0.06$), which failed to show statistical significance because of the low number of patients with metastasis. We did not find a correlation with grading ($p = 0.74$), tumor size ($p = 0.84$), ploidy status, gender, tumor side or location, or patient age with the expression pattern of cadherin-6.

We also correlated cadherin expression with our proportional hazard Cox model. In our model we included only renal cell cancers for analysis. In this multivariate analysis only pT stage, venous involvement and tumor size were predictive of outcome in our cohort of 1,262 patients with long followup. We found a statistically significant correlation with our established relative risk factor (1-sided Mann-Whitney U test $p = 0.028$, fig. 2). It demonstrated an elevated risk factor for tumor progression and, therefore, decreased survival in patients with abnormal cadherin-6 expression compared with the group with normal cadherin-6 expression.

DISCUSSION

To understand the initiation and progression of neoplasms it is important to investigate normal architecture. An impor-

relative risk factor

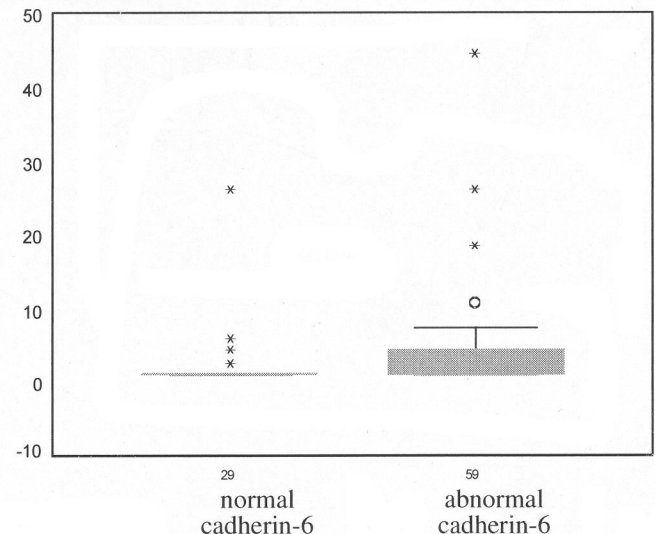


FIG. 2. Statistically significant difference in distribution of relative risk factor by proportional Hazard-Cox model for overall survival in patients with renal cell cancer with normal and abnormal cadherin-6 expression (1-sided Mann-Whitney U test $p = 0.028$).

TABLE 4. *Univariate analysis of prognostic factors in patients with renal cell carcinoma who underwent radical nephrectomy from 1983 to 2000*

Parameter	Log Rank Test	Correlation With Cadherin-6 Expression
T classification	0.0001	0.03
N classification	0.0001	0.001
M classification	0.0001	0.06
Robson classification	0.0001	0.041
Tumor grading	0.0001	0.74
Venous involvement	0.0001	0.019
Tumor size (cutoff 8 cm)	0.0001	0.84
Histological growth pattern	0.0001	0.001
Ploidy	0.24	0.65
Sex	0.06	0.99
Tumor side	0.95	0.96
Tumor location	0.31	0.31
Age (cutoff 70 yrs)	0.65	0.84

Kaplan-Meier analysis, log rank test and correlation with cadherin-6 expression in 216 of 1,262 patients (Mann-Whitney U and Pearson chi-square tests).

tant aspect of tissue architecture is cell adhesion. Cell adhesion molecules are necessary for cell-cell and cell-substrate contact, and they are involved in cell signaling, cell growth and differentiation. Cadherins are a family of cell adhesion molecules involved in cell-cell contact. There are more than 30 cadherins identified, including the well-known classic cadherins epithelial (E), neural (N) and placental cadherin, which can be found in various tissues. On the other hand, there are tissue specific cadherins, such as cadherin-6.

The loss of cell adhesion is an important factor in tumor invasion and progression, and probably also for circulating tumor cells and the initiation of metastases. In various tumors loss or dysfunction of cadherins has been reported.⁹ For example, in prostate cancer the loss of E-cadherin correlates with tumor progression.⁴ Up to now such a correlation had not been shown in renal tumors.¹⁰ Normal kidney expresses E-cadherin in the distal renal tubules and collecting duct system, and N-cadherin in the proximal tubule.¹¹

E-cadherin expression is found in about 30% of renal tumors.¹² Jin et al reported that E-cadherin can be found more often in papillary and chromophobe renal cancer but it is decreased in the clear cell variant.¹³ There are some reports that E-cadherin expression in renal cell cancer may be associated with a better prognosis.¹⁴ However, most groups agree that E-cadherin may not be the major cell adhesion molecule in renal cell cancer. N-cadherin, which is expressed in normal kidney, was retained in all investigated renal cell cancer cell lines.¹² Also, Tani et al noted retained N-cadherin expression in more than 90% of primary renal tumors, suggesting that N-cadherin is not involved in tumor progression in renal tumors.¹⁰

In our previous series we noted that another cadherin, cadherin-6, which was first described by Shimoyama et al,⁵ is specifically expressed in the proximal renal tubules of the normal kidney.⁶ Today cadherin-6 has been detected in other tissues¹⁵ than the kidney, especially in neurons.¹⁶ First results were tempting that cadherin-6 is the major cadherin molecule in normal renal tissue and renal cell cancer. Especially the fact that most renal cell cancers are thought to arise from the proximal renal tubule¹⁷ with our first observation that cadherin-6 expression is retained in only a subset of renal tumors⁶ suggested that cadherin-6 might be associated with tumor progression in renal cancer. Our hypothesis was that the loss of cadherin-6 expression in renal cell cancer is associated with a poor prognosis. We investigated this hypothesis in the current study in a large cohort of patients.

Immunohistochemistry and immunoblotting of cadherin-6 are not effective in paraffin embedded tissue. Thus, we were not able to use archival material for our analysis. Although frozen sections are of poor quality regarding the histoarchitecture of renal cell cancer, frozen sections provide adequate information regarding cadherin-6 expression. To confirm the immunohistochemistry data we performed immunoblotting of cadherin-6 in our tissue specimen. Because we did not have long-term followup on our patients, we sought a correlation of cadherin-6 expression with known prognostic parameters in renal cell cancer. Followup was not long enough in our cohort to analyze tumor progression and survival by Kaplan-Maier analysis. To rule out the influence of poor frozen section quality in renal cell cancer we confirmed the results of immunohistochemistry data by immunoblotting in all cases.

In our large series of renal tumors we investigated 216 patients. We observed that the pattern of cadherin-6 expression correlated with established prognostic parameters, such as TNM classification, Robson staging system, venous involvement and others. Cadherin-6 expression correlated not only on univariate analysis, but also on multivariate analysis. We established a relative risk factor for our patient population and noted that patients with abnormal cadherin-6 expression had a statistically significantly higher relative risk factor than those with normal cadherin-6 expression. It

means that patients with abnormal cadherin-6 expression have a statistically significant poorer prognosis regarding overall survival than those with renal cancer and retained cadherin-6 expression.

From these results we conclude that cadherin-6 serves as a new prognostic parameter in renal tumors. To date there has been only 1 other report on the prognostic power of cadherin-6. Shimazui et al investigated 43 renal cancers.¹⁸ Interestingly they could not find a statistical significant correlation of cadherin-6 expression with T stage or N stage but there was one for M stage and venous involvement. If we compare these results with our data, the most striking difference may be the different patient populations. In the investigation of Shimazui et al 32.6% of patients had metastases compared with only 8.6% of our population. The same observation is true for lymph node metastases. We included 5.6% of patients with lymph node metastases but Shimazui et al included 18.6%. In regard to tumor grading we found more well differentiated tumors in the investigation of Shimazui et al. On the other hand, in our analysis we included more poorly differentiated tumors.¹⁸ When Shimazui et al assessed the subpopulation of E-cadherin negative renal cell cancers, they found a statistically highly significant difference on Kaplan-Meier analysis for patients with normal vs abnormal cadherin-6 expression. Patients who lacked E-cadherin and cadherin-6 had a poor prognosis. Unfortunately this subgroup of E-cadherin negative renal tumors is too small to prove this hypothesis.

CONCLUSIONS

We can state that cadherin-6 expression in renal cell cancers correlates with the most important prognostic parameters but not all of them. We cannot yet answer the question of whether the expression pattern of cadherin-6 correlates with tumor progression and survival in renal carcinoma. However, the results of our analysis are tempting. Cadherin-6 may be a new prognostic marker for renal tumors. If we can prove this fact, we think that we have also identified a tissue specific protein that may be a possible target for further therapies for renal cell cancer.

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