Original Article

P53 and survivin expression in renal cell carcinoma

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Abstract

Objective: Mutation of p53 is detected in more than 50% of human cancers, expression of p53 has a potential prognostic value in patients with renal cell carcinoma (RCC). Survivin is a member of the inhibitor of apoptosis protein family, its overexpression is observed in many malignancies, including RCC. The aim of the study was to estimate a correlation between survivin and p53 expression in tumor samples and the histologic type of a tumor, tumor stage, tumor grade, and survival of patients.

Materials and Methods: Tumor samples were collected from surgical specimens of 90 patients who underwent radical or partial nephrectomy for RCC between November 2017 and July 2020. Tumors were staged according to the UICC (The Union for International Cancer Control) TNM classification system and histopathologically graded according to Fuhrman nuclear grade system. Histopathological diagnosis was confirmed with standard light microscopic evaluation, using hematoxylin and eosin staining and standard p53 and survivin antibodies.

Results: Positive p53 staining was observed in 36.7% of tumor specimens and 24.4% were survivin positive. There was a statistically significant correlation between p53 or survivin expression and histologic subtype of clear cell RCC as well as Type I and II of papillary RCC. There was a statistically significant correlation between p53 expression and tumor size, stage, and grade. The p53 or survivin expression was related to lower overall survival.

Conclusion: The results of this study suggest that p53 overexpression and survivin positivity in RCC patients could be associated with poor prognosis. Thus, these proteins could be used as prognostic markers in RCC.

Keywords: Histopathology, p53, renal cell carcinoma, survivin

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INTRODUCTION

Renal cell carcinoma (RCC) accounts approximately for 3% of all cancers.[1] RCC is a highly aggressive tumor, with up to 17% of patients harboring distant metastases at the time of diagnosis.[2] The most effective method of treatment for localized RCC is surgery. However, the recurrence rate after radical or partial nephrectomy is between 20% and 40%.[3]

For years, conventional prognostic factors, such as histological subtype, stage, and grade were used for predicting the prognosis of the disease and setting up follow-up strategies. Complex and poorly understood

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biological behavior of RCC frequently makes these clinicopathological parameters insufficient for establishing an accurate prognosis of the disease. Therefore, novel molecular markers were evaluated in recent years as potentially valuable prognostic factors.[4]

The p53 protein is a tumor suppressor, which accumulation is induced by cellular or genotoxic stress. This protein is a transcription factor that promotes cell cycle arrest and DNA repair. When DNA repair is not possible, it induces apoptosis.[5] Mutation of p53 is associated with deregulation of the cell cycle, which is one of the cornerstones of carcinogenesis. Mutation of p53 is detected in more than 50% of human cancers, including RCC.[6] Therefore, the expression of p53 has a potential prognostic value in patients with this cancer.

Survivin is a member of the inhibitor of apoptosis protein family that regulates activation of caspases and apoptosis.[7] Survivin mutations reduce the susceptibility of tumor cells to proapoptotic stimuli and promote their proliferation. While this protein is almost nondetectable in terminally differentiated normal cells, its overexpression is observed in many malignancies, including RCC.[8] Survivin represents a promising predictor of disease outcomes in patients with RCC and is also a possible therapeutic target.[9]

The aim of the study was to estimate a correlation between survivin and p53 expression in tumor samples and the histologic type of a tumor, tumor stage, and tumor grade. The correlation between the expression of these proteins and the survival of patients was estimated too.

MATERIALS AND METHODS

Tumor samples were collected from surgical specimens of 90 patients who underwent radical or partial nephrectomy for RCC between November 2017 and July 2020. The study population consisted of 56 men (62%) and 34 women (38%). The median follow-up time was 43.6 months (a minimum of 11 months and a maximum of 67 months) after surgery. Preoperatively, all patients underwent physical examination, ultrasound of the urinary system, chest radiography, and multi-slice computed tomography (MSCT) examination. Postoperatively, patients underwent regular checkups with ultrasound every 3 months and MSCT examination every 6 months.

Tumors were staged according to the UICC TNM classification system and histopathologically graded according to Fuhrman nuclear grade system.[10,11] RCC type was classified according to 2016 WHO classification.[12] Clear cell RCC (ccRCC) specimens were subclassified into pure ccRCC, ccRCC with eosinophilic component, and ccRCC with sarcomatoid differentiation. Type I and Type II of the papillary RCC (pRCC) were also histologically evaluated and detected. Other clinicopathological parameters included in the study were tumor size, tumor necrosis, and blood vessel invasion.

All tumor specimens were fixated in 10% formalin and embedded in paraffin. Histopathological diagnosis was confirmed with standard light microscopic evaluation, using hematoxylin and eosin staining and standard p53 and survivin antibodies. The results of immunohistochemical staining were scored by semi-quantitative technique: the absence of staining in all tumor cells (negative staining); positive staining involving <20% of cells (focal expression); 20%–50% of cells (moderate expression); and more than 50% of cells (diffuse expression) in case of survivin. In the case of p53, positive staining involved <1% of cells (focal expression), 1%–20% of cells (moderate expression), and more than 20% of cells (diffuse expression).

Statistical analysis

Statistical analysis of data was performed using SPSS version 18.0 (IBM SPSS Inc., Chicago, IL, USA). The correlation between survivin and p53 expression and clinicopathological parameters was analyzed using the Chi-square test. Kaplan–Meier method was used for the calculation of survival curves. Log-rank test was used for the analysis of statistically significant differences in survival. $P < 0.05$ was considered statistically significant.

RESULTS

Results regarding p53 expression and clinicopathological parameters are presented in Table 1. Positive p53 staining was observed in 36.7% of tumor specimens. P53 expression was detected in 31% of ccRCC, 56% of pRCC, and 14.3% of chromophobe RCC (chRCC). There was a statistically significant correlation between p53 expression and histologic subtype ($P = 0.041$). P53 immunoreactivity was seen in 22.9% of pure ccRCC, 29.4% of ccRCC with eosinophilic component, and 83.3% of ccRCC with sarcomatoid component. The difference in p53 expression between subgroups of ccRCC was statistically significant ($P = 0.015$). Regarding pRCC, 100% of Type I were p53 positive and 26.7% of Type II. The difference between Type I and Type II pRCC in relation to the p53 expression was statistically significant ($P < 0.0001$). The statistically significant correlation between p53 expression and tumor size, stage, and grade was also observed ($P = 0.01$, $P < 0.0001$, $P = 0.04$).

Table 2 displays results regarding clinicopathological parameters and survivin expression. A total of 22 of 90 tumor specimens (24.4%) were survivin positive. Among different histological types, positive surviving expression was detected in 17.2% of ccRCC, 48.0 of pRCC, and 0.0% of chRCC. The difference in survivin immunoreactivity between these RCC subtypes was of statistical significance (P = 0.03). Statistical difference in survivin immunoreactivity was seen with Type I versus Type II pRCC (P = 0.006). A statistically significant correlation of survivin expression with other clinicopathological parameters was not shown.

There was no statistically significant association between survivin positivity and p53 overexpression (P = 0.325).

The follow-up period was between 11 and 67 months (mean: 43.6). Overall survival rate was 70.0% (75.0% for the male gender and 61.8% for the female gender). The mean survival time was 54.128 months (95% confidence interval [CI] 49.982–58.274).

Among patients with positive p53 expression, the overall survival rate was 45.5%. The mean survival time in these patients was 43.184 months (95% CI 35.560–50.808). In p53-negative patients, it was 60.481 months (95% CI 56.489–64.474). A significant relationship between p53 expression and overall survival was shown [P < 0.0001, Figure 1].

Overall survival in patients with survivin expression was 50.0%. The mean survival time in these patients was 46.409 months (95% CI 37.659–55.159), much lower than the mean survival rate in survivin-negative patients (56.639 months, 95% CI 52.098–61.181). There was a statistically significant correlation between survivin expression and overall survival [P = 0.023, Figure 2].

DISCUSSION

P53 is a key regulator of the cell cycle, providing genetic stability, and inducing cell cycle arrest or apoptosis in the presence of damaged DNA.[13] P53 mutations are responsible for uncontrolled tumor cell proliferation and progression to malignancy. Despite being one of the most studied molecules in science, the impact of p53 in RCC carcinogenesis and prognosis is still controversial.

Table 1: Clinicopathological parameters and p53 expression

Variable	Total	p53-positive (%)	p53-negative (%)	*P*
Total	90	33 (36.7)	57 (63.3)	
Gender				
Male	56	17 (30.4)	39 (69.6)	0.11
Female	34	16 (47.1)	18 (52.9)	
Stage				
pT1	33	4 (12.1)	29 (87.9)	<0.001
pT2	17	7 (41.2)	10 (58.8)	
pT3	37	19 (51.4)	18 (48.6)	
pT4	3	3 (100.0)	0	
Grade				
1	4	0	4 (100.0)	0.04
2	45	13 (28.9)	32 (71.1)	
3	37	16 (43.2)	21 (56.8)	
4	4	4 (100.0)	0	
Blood vessel invasion				
Yes	38	17 (44.7)	21 (55.3)	0.174
No	52	16 (30.8)	36 (69.2)	
Tumor necrosis				
Yes	57	24 (42.1)	33 (57.9)	0.159
No	33	9 (27.3)	24 (72.7)	
Histologic type				
Clear cell RCC	58	18 (31.0)	40 (69.0)	0.041
Papillary RCC	25	14 (56.0)	11 (44.0)	
Chromophobe RCC	7	1 (14.3)	6 (85.7)	

RCC: Renal cell carcinoma

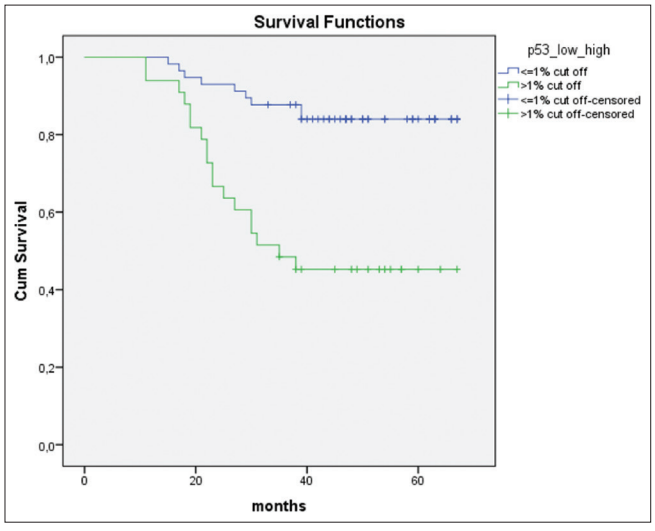

Figure 1: Kaplan–Meier curves for overall survival in p53-positive and p53-negative patients (P < 0.0001)

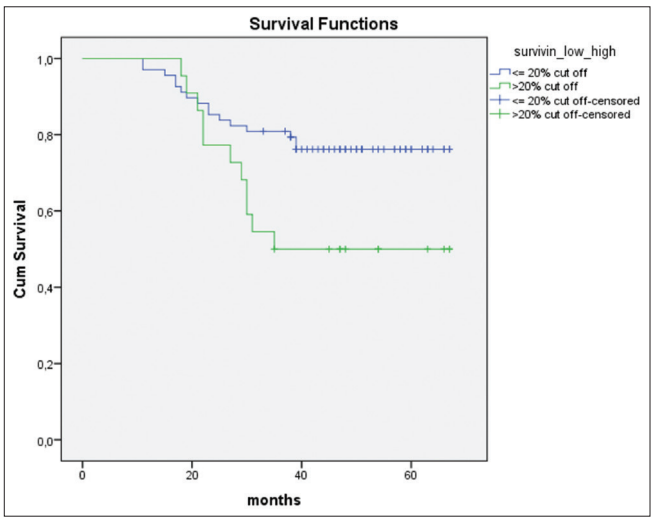

Figure 2: Kaplan–Meier curves for overall survival in survivin-positive and survivin-negative patients (P = 0.023)

Table 2: Clinicopathological parameters and survivin expression

Variable	Total	Survivin-positive (%)	Survivin-negative (%)	*P*
Total	90	22 (24.4)	68 (75.6)	
Gender				
Male	56	12 (21.4)	44 (78.6)	0.39
Female	34	16 (47.1)	18 (52.9)	
Stage				
pT1	33	6 (18.2)	27 (81.5)	0.172
pT2	17	3 (17.6)	14 (82.4)	
pT3	37	13 (35.1)	24 (64.9)	
pT4	3	0	3 (100.0)	
Grade				
1	4	1 (25.0)	3 (75.0)	0.79
2	45	9 (20.0)	36 (80.0)	
3	37	11 (29.7)	26 (70.1)	
4	4	1 (25.0)	3 (75.0)	
Blood vessel invasion				
Yes	38	17 (44.7)	21 (55.3)	0.174
No	52	16 (30.8)	36 (69.2)	
Tumor necrosis				
Yes	57	16 (28.1)	41 (71.9)	0.293
No	33	6 (18.2)	27 (81.8)	
Histologic type				
Clear cell RCC	58	10 (17.2)	48 (82.8)	0.03
Papillary RCC	25	12 (48.0)	13 (52.0)	
Chromophobe RCC	7	0	7 (100.0)	

RCC: Renal cell carcinoma

Immunohistochemical detection of p53 protein is believed to be associated with p53 mutation.[14]

Rates of p53 overexpression in RCC patients are highly variable in the literature, going between 5.98% and 42%.[15-18] Molecular and cancer genome researchers reported p53 mutations in <10% of ccRCC and pRCC and >30% of chRCC.[19] Li *et al*. reported p53 overexpression in 11.9% of ccRCC, 70% of pRCC, and 27.3% of chRCC, which was statistically significant.[18] On the other hand, in the study of Baytekin *et al*., no statistically significant difference was noted between p53 expression and histologic type of RCC.[17] In our study, positive p53 staining was observed in 36.7% of tumor specimens. P53 expression was detected in 31% of ccRCC, 56% of pRCC, and 14.3% of chRCC, with statistical significance ($P = 0.041$). Alternative pathways of carcinogenesis could explain this difference in p53 expression among different RCC subtypes. We found a positive correlation between p53 overexpression and sarcomatoid dedifferentiation of ccRCC, which is consistent with data from Debien *et al*., who implied that p53 overexpression is critical for sarcomatoid transformation of RCC.[20]

We found that p53 overexpression is correlated with poor clinicopathological parameters, as tumor size >7 cm, high stage, high grade, and overall survival. This finding is consistent with the results of multiple authors, who have reported that p53 overexpression had a significant impact on overall, cancer-specific, and recurrence-free survival.[18,21] Moreover, in a meta-analysis from 2017, which included a total of 2013 patients from 22 studies, p53-positive expression was associated with poor overall survival, cancer-specific survival, higher TNM stage, and Fuhrman grade.[6] On the other hand, multiple investigators did not find a significant correlation between p53 immunoreactivity and clinicopathological parameters.[15,17,22]

Survivin plays an important role in the inhibition of apoptosis and the regulation of cell division. Inhibition of apoptosis has been implicated in carcinogenesis, tumor progression, and resistance of tumor cells to chemotherapy.[23] Normally, survivin is expressed only during embryonic development. Positive survivin expression in adult tissues is observed in various malignancies, such as lung, colon, bladder, and prostate cancer.[24]

The rate of survivin expression in RCC patients varies between 24% and 79% in the literature.[9,17,25,26] In the present study, it was 24.4%. Previous studies have not shown a correlation between survivin expression and histologic RCC subtypes.[17] On the other hand, our results indicate a statistically significant difference in survivin immunoreactivity between RCC subtypes, with predominant expression in pRCC. Although we found a significant difference in survivin expression between papillary Type I versus Type II RCC tumors, these results have limited statistical power due to small number of specimens. Multiple studies have shown an association between survivin expression and higher tumor stage and grade.[9,25,26] We found that survivin expression was higher in high grade (Grade 3 and 4) and stage (Stage 3 and 4) versus low grade and stage tumors, but this association did not reach statistical significance.

In the present study, Kaplan–Meier analysis showed that the overall survival of survivin-positive patients was significantly shorter than in survivin-negative patients, which is in accordance with current literature.[9,25,26]

It is hypothesized that p53 dysregulation can be associated with survivin expression in various malignancies, such as hepatocellular and lung cancer.[27] Studies suggested that the functional loss of wild-type p53 is often associated with upregulation of survivin. Mutant p53 does not suppress the anti-apoptotic function of survivin, thus promoting dysregulation of cell cycle and possible tumor cell proliferation. In our study, there was no positive correlation between p53 accumulation and survivin expression in RRC tumor specimens.

Due to the often insufficient prognostic value of conventional clinical and histological variables in RRC patients, a variety of studies investigated p53 and survivin as potential molecular predictors of disease outcome. Immunohistochemical assessment of these proteins at primary RCC diagnosis could help in establishing of molecularly-based postoperative follow-up and identifying patients with poor prognosis. In our study, we found that p53 overexpression was statistically significantly correlated with a high stage of disease, high nuclear grade, sarcomatoid dedifferentiation, and poor overall survival. Survivin expression was also associated with poor overall survival. These findings suggested that p53 and survivin-positive expression were unfavorable predictors for prognosis in RCC. Still, the prognostic role of these proteins in RCC remains controversial, due to inconsistent and contradictory results in the literature. Lack of standardized techniques in immunohistochemical assessment, reflected in the use of the various monoclonal antibodies and cutoff values for staining, as also a small number of patients in the studies, are probable factors influencing those inconsistencies.

The results of this study suggest that p53 overexpression and survivin positivity in RCC patients could be associated with poor prognosis. Thus, these proteins could be used as prognostic markers in RCC.

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Conflicts of interest

There are no conflicts of interest.

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