

## THE IMPACT OF ANGIOGENESIS ON THE PROGNOSIS OF ADVANCED RENAL CELL CARCINOMAS

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We studied the relationship between angiogenic factors and clinical responses in advanced renal cell carcinomas (RCCs) and evaluated the angiogenic factors to clarify the potential impact of these factors on the cancer-specific survival.

From January 1990 to December 2000, 148 patients underwent a nephrectomy for RCCs at our institution. Of the 32 patients who had distant metastasis, 17 met the histopathologic analysis requirements for an immuno-histochemical investigation. Fifteen of them were administered interferon- $\gamma$  and the remaining two patients were added to interferon- $\alpha$  and eight of seventeen patients also underwent radiation therapy. Both thymidine phosphorylase (TP) and Factor VIII immunostaining were performed.

The overall survival rates at 1, 5 and 10 years were 82.4%, 30% and 30%, respectively. Three of these patients were diagnosed with lung metastasis and a complete response was seen in two, while a partial response was observed in one. In addition another patient who was diagnosed with bone metastasis also showed a partial response (group A). The remaining 13 patients showed progressive disease (group B). Group A had a higher TP-positive ratio (TP-PR) than that of group B. A multivariate analysis of the clinicopathologic data showed that a positive mean vascular area (PMVA) could be an independent factor regarding the potential impact of these factors on a long survival in advanced RCCs.

PMVA was thus found to be an independent factor regarding the prognosis with advanced RCCs.

(Acta Urol. Jpn. 50: 157–163, 2004)

**Key words:** Renal cell carcinoma, Clinical response, Angiogenic factor

### INTRODUCTION

The annual death rate due to a malignancy in the kidney has increased from 1.7% to 5.0% per 100,000 population from 1975 to 1994<sup>1)</sup>. The incidence of metastatic disease among patients with newly diagnosed RCCs is approximately 18%, and the prognosis in most cases is poor<sup>2)</sup>. While reports on the spontaneous regression of metastases indicated the overall incidence of spontaneous regression to be about 0.7%, a spontaneous remission of advanced RCCs may also occur without surgery<sup>3)</sup>.

We previously described cases of liver involvement with RCCs in which surgical resection was performed following systemic therapy<sup>4)</sup>. The surgical management of metastasis could be hampered by the fact that metastatic lesions are usually multiple and invade more than one organ. Only a small number of advanced RCCs are solitary and surgery on such RCCs might be beneficial to these patients.

In the management of advanced RCCs as well as other cancers in humans, it is essential to identify

which advanced RCC shows a favorable response. Because previous investigators did not perform a histopathological analysis of angiogenic factors in advanced RCCs, such studies often failed to identify an association between favorable advanced RCCs cases and unfavorable cases.

To address this problem, we documented the clinical response in advanced RCCs, based on the factors of angiogenesis. Thymidine phosphorylase (TP) is known to play an important role in the development of new blood vessels in several types of human cancers<sup>5)</sup>. We previously investigated the relationship between TP and angiogenesis. In addition, TP might be a predictor of postoperative recurrence in patients with localized RCCs<sup>6)</sup>. The aim of the present study was to investigate the relationship between TP and Factor VIII in advanced RCCs with adjuvant therapy and to assess its relationship with a clinical response in advanced RCCs, then to clarify which clinicopathologic factors including clinical responses have a potential impact on the long term survival in patients with advanced

RCCs.

## METHOD

### Patients

From January 1990 to December 2000, 148 patients underwent a nephrectomy for RCCs at our institution. Thirteen out of 148 patients were diagnosed to have distant metastasis at the time they underwent a nephrectomy. RCCs recurred after a nephrectomy in 24 out of 135 patients.

Of 37 patients, five who underwent surgical resection of the metastatic lesion were excluded. Of the remaining 32 patients only 17 met the histopathologic analysis requirements for immunohistochemical staining. Fifteen of them were administered interferon- $\gamma$  alone and the remaining two patients received interferon- $\alpha$  in addition. Eight of the 17 patients also underwent radiation therapy. The mean age of the patients was 61.8 years (range, 48–75). The clinicopathologic factors were examined based on the criteria of the Japanese Urological Association<sup>7)</sup>.

### Histology

All histochemical analyses were performed on hematoxylin and eosin stained sections of tissue from surgery. TP, which recognized PD-ECGF/dThdPase, was supplied by Nippon Roche, Tokyo, Japan. A mouse monoclonal antibody that recognized factor VIII related antigen was purchased from DAKO, Copenhagen, Denmark.

### Immunohistochemical analysis

Samples were fixed with 10% formaldehyde in phosphate-buffered saline (PBS) embedded in paraffin and then were cut into 3- $\mu$ m thick sections. The sections were deparaffinized with xylene and dehydrated with 98% ethanol. Endogenous peroxide was blocked by 0.3% hydrogen peroxidase in absolute methanol for 20 min at 21°C. The primary antibody, TP and Factor VIII related antigens were applied to the sections, which were then incubated overnight at 4°C and then were incubated for 30 min with biotinylated antimouse immunoglobulin G at 21°C. After washing three times in PBS for 15 min, the immune complex was then visualized by incubating the sections with 0.5 mg/ml diaminobenzidine and 0.03% H<sub>2</sub>O<sub>2</sub> in PBS for 5 min.

Both the Factor VIII-related antigens were analyzed by a computer-assisted digital image analysis to identify a positive ratio (VIII-TR, TP-PR). Regarding Factor VIII-related antigen, the microvasculature of each tumor was assessed by two additional methods. The number of microvessels in each tumor (NM) was defined by counting each vessel. The positive mean vascular area (PMVA) in each section was also detected when the VIII was divided by the NM<sup>6)</sup>

### Statistics

The relationship between TP-PR and categorical variety was evaluated using the  $\chi^2$  analysis. Statistical differences between the two groups were computed using the Mann-Whitney U test. Survival, defined as the interval from study entry to death, was calculated by the method of Kaplan and Meier, and statistical significance was analyzed by the log rank test. Significant factors were analyzed by computer, using Cox's multivariate proportional hazard model analysis to determine the prognostic value. All analyses were performed using STATVIEW Ver. 5 (Abacus Concepts, CA, USA) and JMP Ver. 3 (SAS institute INC, NC, USA).

Differences between the groups were considered to be statistically significant when P was less than 0.05.

## RESULT

### Clinical response

The median follow-up of the 17 patients was 38 months. The overall survival rates at 1, 5 and 10 years were 82.4, 30% and 30%, respectively. Table 1 shows the characteristics of the 17 patients enrolled in this study. RCCs recurred after a nephrectomy in 8 patients (47%), while the remaining 9 patients (53%) had already been diagnosed with distant metastasis at the time they underwent a nephrectomy. The average disease-free interval was 11.5 months. Four of the 8 patients who had recurrence after a nephrectomy had been administered IFN- $\gamma$  until recurrence occurred. Compared to the patients with metastasis at the time of undergoing a nephrectomy, the group with postoperative recurrence was more likely to have a clinical response, but the difference was not statistically significant.

Regarding the metastasis site, Table 1 shows the clinical response. The mean duration of the clinical response in 4 cases was 26 months. Three of these patients were diagnosed with lung metastasis and two showed a complete response<sup>8,9)</sup>, one a partial response, while another one who was diagnosed with bone metastasis showed a partial response<sup>10)</sup> (group A). The remaining 13 patients did not show a clinical response (group B). All twelve deaths were related to RCCs, and eight of them underwent an autopsy. There was no statistical significance regarding gender, growth type, maximum tumor diameter, histological grade and the degree of micro vessel invasion between groups A and B (Table 2). Survival and progression

Four of the 17 cases showed a clinical response (group A), of these patients with a clinical response 3 demonstrated a local recurrence and metastasis after obtaining a clinical response. For these 3 cases, the disease free interval was 7.6 months, while they died an average of 22.5 months later from cancer. The overall cancer specific survival rates at 1, 5 and 10 years were 82.4, 30% and 30% respectively. There

Table 1. Clinical characteristics of the 17 patients with advanced RCC

Case	Gender (age)	Stage	Cell type	Grade	$\phi$ (mm)	Metastasis	Recurrence (DFI)	Adjuvant	Response
1	F (52)	IV	Granular	2	160	Lung		IFN- $\alpha$ + $\gamma$	CR (83 m alive)
2	M (66)	IV	Clear	1	50	Bone		IFN- $\gamma$ +rad	PR (38 m death)
3	M (50)	III	Clear	2	100		Lung (6 m)	IFN- $\gamma$	CR (5 m DFI), (26 m death)
4	M (67)	III	Granular	3	70		Lung (13 m)	IFN- $\alpha$ + $\gamma$ +rad	PR (22 m alive)
5	M (66)	I	Clear	1	45		Bone (23 m)	IFN- $\gamma$ +rad	PD (16 m death)
6	M (66)	II	Clear	2	50		Lung (49 m)	IFN- $\gamma$ +rad	PD (3 m death)
7	M (58)	IV	Clear	2	50	Lung		IFN- $\gamma$	PD (29 m death)
8	F (64)	I	Clear	2	50		Bone (6 m)	IFN- $\gamma$ +rad	PD (88 m death)
9	M (56)	I	Clear	2	50		Lung (2 m)	IFN- $\gamma$	PD (7 m death)
10	M (58)	IV	Clear	2	50	Bone		IFN- $\gamma$ +rad	PD (29 m death)
11	M (74)	IV	Clear	1	45	Bone		IFN- $\gamma$ +rad	PD (20 m death)
12	F (66)	IV	Clear	1	45	Bone		IFN- $\gamma$ +rad	PD (22 m death)
13	M (69)	IV	Clear	1	80	Lung		IFN- $\gamma$	PD (22 m death)
14	F (75)	IV	Granular	2	70	Muscle		IFN- $\gamma$ +rad	PD (16 m death)
15	M (70)	II	Clear	2	70		Kidney (32 m)	IFN- $\gamma$	PD (66 m alive)
16	F (59)	IV	Granular	2	70	Lung		IFN- $\gamma$	PD (9 m death)
17	F (48)	II	Clear	1	130		Kidney (24 m)	IFN- $\gamma$	PD (30 m alive)

From case No. 1 to No. 4 were observed clinical responses (group A), while none of No. 5 to No. 17 had evidence of clinical response (group B). Abbreviations: M; male, F; female, rad; radiation, PR; partial response, CR; complete response, m; months, DFI; disease-free interval.

Table 2. Clinicopathological analysis of 17 patients

	Response (n=4)	Pro-gressive (n=13)	Total	P value
Gender				0.62
Male	3	8	11	
Female	1	5	6	
Growing type				0.62
Slow	1	7	8	
Rapid	3	6	9	
Grade				0.93
1	1	3	4	
2	3	10	13	
Vessel invasion				0.2
Negative	1	8	9	
Positive	3	5	8	
Cell type				0.15
Clear	2	11	13	
Granular	2	2	4	
Tumor diameter	85 (50-160)	50 (30-130)	17	0.12
Median (range) mm				

There was no statistical significance between response group and progressive group using chi-square test.

was no statistically significant difference between group A and B (33.3% vs. 26.4% at 5 years, respectively, Fig. 1).

#### Pathological analysis

As shown in Fig. 2, only the TP-PR level was found to show a significant difference among them ( $p=0.020$ ). Regarding VIII-PR, NM and PMVA, no significant difference was observed between group A

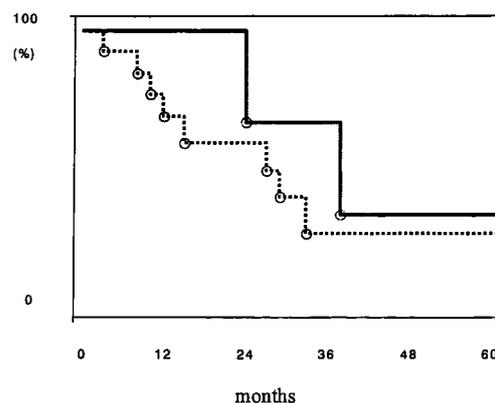


Fig. 1. Survival curves for advanced RCC (n=17).  $p=0.41$ . — Clinical response group (group A) n=4, 5-year survival 33.3%. ... Progressive group (group B) n=13, 5-year survival 26.4%. There is no statistical difference between group A and group B.

and B. To clarify the potential impact of these factors on survival, the patients were divided into two groups according to the median of those expressed. Excluding PMVA, none of these factors (TP-PR, Factor VIII and NM) have a potential impact on the cancer-specific survival rates (Table 3). No significant association was observed in Factor VIII, NM, PMVA and TP-PR. The information obtained from these calculations was compared with that obtained from a multivariate analysis (Table 4). These analyses showed that PMVA was thus found to be an independent factor regarding the prognosis with advanced RCCs.

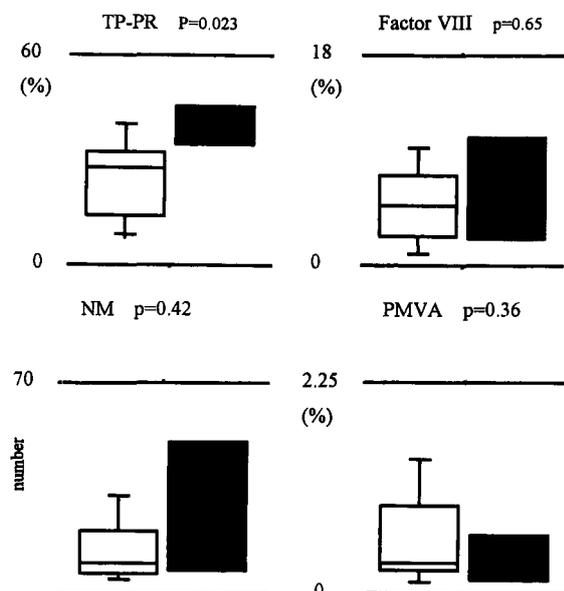


Fig. 2. Comparison of histopathological analysis. □ Progressive group (group B) n=13. ■ clinical response group (group A) n=4. TR-PR showed a significant association between group A and group B ( $p=0.023$ ). Abbreviations: TP-PR; thymidine phosphorylase positive ratio, NM; number of microvessels, PMVA; positive mean vascular area.

Table 3. Comparison of the 5-year survivals

	Category	5-year survivals	p value
TP-PR	28.4 > (n=10)	42.0%	0.87
	28.4 ≤ (n= 7)	17.1%	
Factor VIII (%)	5.1 > (n= 9)	38.1%	0.14
	5.1 ≤ (n= 8)	15.6%	
NM	10 > (n= 8)	23.3%	0.35
	10 ≤ (n= 9)	27.8%	
PMVA (%)	0.29 > (n= 9)	55.6%	0.004
	0.29 ≤ (n= 8)	0 %	

TP-PR, Factor VIII, Tumor diameter, NM and PMVA were divided into two categories by median of 17 cases. PMVA showed significant difference using log-rank test. Abbreviations: TP-PR; thymidine phosphorylase positive ratio, NM; number of micro vessels, PMVA; positive mean vascular area.

## DISCUSSION

Our results showed that 2 of the 13 patients who had no evidence of a clinical response survived more than 60 months with disease, while 2 of the four patients who had a clinical response did not survive more than 60 months. Interferon therapy represents one of the first breakthroughs in immunotherapy for this disease. It is currently believed that interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes responsible for the inhibition of virus replication in infected cells, the suppression of cell proliferation, and

Table 4. A multivariate analysis of the angiogenesis for 17 patients with RCC

	Category	Risk ratio CI	p value
TP-PR	28.4 > (n=10)	1.52	0.29
	28.4 ≤ (n= 7)	(0.69 -3.72)	
Factor VIII (%)	5.1 > (n= 9)	0.63	0.22
	5.1 ≤ (n= 8)	(0.27 -1.32)	
NM	10 > (n= 8)	1.0	0.85
	10 ≤ (n= 9)	(0.53 -2.28)	
PMVA (%)	0.29 > (n= 9)	0.30	0.0094
	0.29 ≤ (n= 8)	(0.096-0.75)	

TP-PR, Factor VIII, Tumor diameter, NM and PMVA were divided into two category by median of 17 cases. These results showed that PMVA could be an independent factor of cancer-specific survival of advanced RCC. Abbreviations: CI; Confidence interval, TP-PR; thymidine phosphorylase positive ratio, NM; number of microvessels, PMVA; positive mean vascular area.

immunomodulatory activities such as the enhancement of cytotoxicity of lymphocytes for target cell. IFN- $\gamma$  is known to be produced by T-lymphocytes after their activation by a variety of antigens or cytokines and appears to act on cell surface receptors other than those shared by IFN- $\alpha$  IFN- $\beta$ <sup>11</sup>. Aulitzky et al., reported that 6 of 22 RCCs patients with disease progression showed a response with 2 a CR and 4 a PR. The authors thus suggested the clinical efficacy of low dose IFN- $\gamma$  for the treatment of advanced RCCs<sup>12</sup>. The results of Phase II trials utilizing low dose intermittent subcutaneous injection IFN- $\gamma$  have recently been reported in 121 patients: These was a 15% overall response rate and a 13-month median survival, the patients with disease limited to a single site had a 23% response rate, and thus low dose IFN- $\gamma$  was found to be effective in a small proportion of patients with limited disease<sup>13</sup>. We previously described that postoperative IFN- $\gamma$  adjuvant therapy was effective in RCCs<sup>14</sup>. There remains some question, however, as to why IFN- $\gamma$  appears to be effective on a limited number of cases with advanced RCCs. The relationship between the angiogenesis and both the clinical and pathological factors needs to be elucidated to answer these questions.

Slaton et al., reported that microvessel density (using CD34) did not correlate with metastasis<sup>15</sup>. By contrast, the expression levels of basic fibroblast growth factor (bFGF), matrix metalloproteinase (MMP), vascular endothelial growth factor (VEGF) and IL-8 did not correlate with the development of metastasis<sup>15</sup>. The ratio of MMP to E-cadherin was considered the most significant independent prognostic variable for an advanced pathological stage, followed by bFGF and the pathological grade. The up-regulation of proteolytic enzymes MMP-2 in combination with a down-regulation of the homotypic coherence E-cadherin indicated higher rates of

both metastasis and postoperative recurrence<sup>15)</sup> Nativ et al. suggested a close association to exist between MVD and the prognostic results in RCCs<sup>16)</sup> Suzuki et al.<sup>17)</sup> showed that even though no correlation existed between TP, MVD and arteriography, TP might be an independent prognostic factor. Interestingly, Delahunt et al.<sup>18)</sup> confirmed that tumor microvascular density was inversely correlated with the tumor grade and patient survival in a series of conventional clear cell RCC. The discrepancy of these results may be attributed to the development of large vessels within advanced RCCs<sup>18)</sup> We previously reported that no correlation was seen between the TP expression and either VIII, NM, or PMVA in localized RCCs cases<sup>6)</sup> Although, our results showed no significant relationship to exist among the angiogenic factors concerning advanced RCCs, these results did provide evidence that PMVA is an independent prognostic factor with advanced RCCs. This might be due to the fact that T cells produce VEGF which thus induces MMP. As mentioned above, this enzyme can play a role in degrading the extracellular matrix. In addition, an increase in TP might also be an unfavorable predictive factor for postoperative recurrence.

There remains a discrepancy because TP might be one of the predictive factors for postoperative recurrence, while our present study suggested that TP might also be a predictor of an objective clinical response. This discrepancy might be related to the functional activity of TP.

TP is known to play an important role as a metabolic enzyme for fluoropyrimidine, mainly 5-fluorouracil (5FU), doxi fluridine (5'-DFUR) and capecitabine<sup>17)</sup>. Hofmockel et al.<sup>19)</sup> reported that combined chemotherapy with 5-FU, interferon and IL-2 to be effective for the treatment of RCCs. Joffe et al.<sup>20)</sup> evaluated the combination of interferon- $\alpha$  and IL-2 with 5-FU in patients with advanced and recurrent RCCs. Morita et al.<sup>21)</sup> also reported that an IFN- $\alpha$ -enhanced TP expression results in an increased sensitivity to 5-FU. In contrast, regarding the relationship between IFN- $\gamma$  and TP, Keane et al.<sup>22)</sup> reported a relationship between IFN- $\gamma$  and the angiogenic environment. IFN- $\gamma$  induces (IFN- $\gamma$  inducible protein-10) IP 10 which regulates the angiogenesis. IP-10 was initially characterized as a chemoattractant for T lymphocytes, and it has angiogenic activities that appear to be mediated by its direct effect on endothelial cells<sup>23)</sup>. Chemokine receptors have also been found on epithelial cells, although their functional significance remains unclear. These receptors may be involved in the pattern of metastatic spread. IFN- $\gamma$  is a potent growth inhibitor of a number of normal and transformed cell types including endothelial cells<sup>23)</sup> Leek et al.<sup>24)</sup> reported that IFN- $\gamma$  can inhibit

angiogenesis induced by TP, while IFN- $\gamma$  also potentially activates tumor infiltrating macrophages, which thus results in the increased production of angiogenic factor. Therefore, regarding the selection of the optimal treatment for advanced RCCs, the characteristics of IFN- $\gamma$  may play a role in boosting the production of angiogenic factors<sup>24)</sup> In addition, our results suggest that postoperative adjuvant therapy with IFN- $\gamma$  might therefore be an appropriate treatment modality for advanced cases of RCCs.

### CONCLUSION

We investigated the relationship between the clinical responses in advanced RCCs and the findings of a histopathologic analysis of angiogenesis. Four of our seventeen patients, who showed a clinical response, had a higher TP-PR level than that observed in the progressive cases. Therefore, PMVA might be a useful predictor of the prognosis in advanced RCCs cases.

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(Received on December 16, 2002)  
(Accepted on November 23, 2003)

## 和文抄録

## 血管新生が進行性腎細胞癌の遠隔成績におよぼす影響

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進行性腎細胞癌における血管新生因子について、治療に奏功した症例と進行した症例の相違について検討し、また遠隔成績に与える影響について検討した。

1990年から2000年12月までに当施設で腎細胞癌の診断で腎摘除を行った148例のうち32例に遠隔転移を認めた。17例が免疫組織学的に評価可能であった。15例は interferon- $\gamma$ 、2例は interferon- $\alpha$  を追加投与した。8例は放射線照射を行った。Thymidine phosphorylase (TP) と factor VIII について免疫組織学的に検討した。

1年、5年そして10年生存率は各々82.4%、30%、30%であった。奏功症例 (group A) は計4例で肺転移は3例に認められ、2例に著効そして1例が有効であった。骨転移1例は有効であった。13例には奏功所見は認められなかった (group B)。TP は group A が group B より陽性率が高く、また多変量解析の結果、positive mean vascular area (PMVA) が進行腎細胞癌における遠隔成績に影響をおよぼす独立した因子であることが示された。

(泌尿紀要 50 : 157-163, 2004)