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*Source / Izvornik:* **Virchows Archiv, 2006, 448, 24 - 28**

**Journal article, Accepted version**

**Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)**

<https://doi.org/10.1007/s00428-005-0090-4>

*Permanent link / Trajna poveznica:* <https://urn.nsk.hr/urn:nbn:hr:105:066945>

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*Download date / Datum preuzimanja:* **2024-08-19**



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### **Središnja medicinska knjižnica**

Tomić, K., Tomas, D., Tomašković, I., Kos, M., Belicza, M., Krušlin, M. (2006) *Renal artery changes in patients with primary renal cell carcinoma*. *Virchows Archiv*, 448 (1). pp. 24-28.

<http://www.springerlink.com/content/u7384712077q0464/>  
The original publication is available at [www.springerlink.com](http://www.springerlink.com)

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## RENAL ARTERY CHANGES IN PATIENTS WITH PRIMARY RENAL CELL CARCINOMA

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Pages: 13

Words in abstract: 198

Tables: 2

Figures: 1

Acknowledgement: Presented in part at the XXV International Academy of Pathology Congress,  
Brisbane, Australia, October 10-15, 2004

## ABSTRACT

Arterial fibromuscular dysplasia (FMD) is a non-inflammatory, non-atherosclerotic, occlusive condition of the systemic arteries, most frequently affecting renal arteries. Renal cell carcinoma (RCC) might be associated with arterial hypertension, however, there are no data in the literature regarding the relationship between RCC and associated renal artery changes.

We analyzed a consecutive series of 57 (35 male and 22 female) patients aging from 35 to 79 years (mean 58.9 years) who underwent nephrectomy due to RCC in the year 2003. The patients had RCC measuring from 2-16 cm (mean 7.1 cm). Specimens were routinely fixed, embedded in paraffin, cut and stained with hematoxylin and eosin, Mallory trichrome method and orcein.

Renal arteries of 26 patients (20 male, 6 female) showed no changes. In these patients RCC measured 2.5-11 cm in largest diameter (mean 6.6 cm). In 24 patients (10 male, 14 female) renal arteries showed FMD. RCCs in these patients measured between 2-16 cm (mean 8.0 cm). Seven patients had atherosclerotic changes in renal arteries.

In this series FMD was found in a significant proportion of patients with RCC, mainly in women. The cause of such changes and their relationship with RCC and systemic hypertension should be further analyzed.

Key words: fibromuscular dysplasia, renal cell carcinoma, renal arteries

## INTRODUCTION

The renal arteries arise from the abdominal aorta at the level of L2 and the right renal artery is longer than the left one. Different lesions may involve main renal artery including atherosclerosis, fibromuscular dysplasia and some other conditions, such as Takayasu arteritis, radiation injury and congenital malformations [11].

Arterial fibromuscular dysplasia (FMD) is a non-inflammatory, non-atherosclerotic, occlusive condition of systemic arteries, the renal arteries being most frequently affected. Major clinical conditions associated with FMD are hypertension, stroke, claudication and intestinal ischemia [7]. FMD of renal arteries is bilateral in nearly half of patients, more commonly on the right side (3:1); is usually diagnosed in the fourth decade, with female predominance and most frequently involving the distal two thirds of the renal artery and its branches [11, 12]. Incidence of the FMD found at autopsy study is about 1% [4, 8].

There are three principal pathologic types of FMD: intimal, medial and adventitial fibromuscular dysplasia. Primary intimal fibroplasia (type I) is a rare condition that occurs in children and young adults, comprising about 2% to 5% of all FMD lesions [3, 9, 14, 15] and sometimes it can be difficult to distinguish this type of FMD from non-specific fibrosis as seen in atherosclerosis [9]. This type can be connected with progressive renal artery obstruction and ischemic atrophy of the kidney [3]. Medial fibromuscular dysplasia (type II) can be further subdivided into three subtypes: medial “muscular” hyperplasia (type IIa), medial fibroplasia with aneurysms (type IIb) and perimedial fibroplasias (type IIc) of which medial fibroplasia is the most common type of FMD (about 70%). The lesion usually affects women aging 25 to 50 years, with bilateral involvement in about 60% [3, 9]. Adventitial fibroplasia (type III) is very rare and represents less

than 1% of all FMDs [3].

Atherosclerosis is a generalized progressive arterial disease associated with localized arterial occlusions and aneurysms [11]. It accounts for 90 % of the cases of renal-artery stenosis and usually involves the ostium and proximal third of the main renal artery and perirenal aorta [12].

Renal cell carcinoma (RCC) represents 2% of all human malignancies and over 90% of all malignancies of the kidney. It is two to three times more common in men than in women and the average age at diagnosis is 55 to 60 years [2, 11]. History of blood hypertension, obesity and tobacco smoking increases the risk of RCC [1, 11].

The aim of this study was to analyze renal artery changes in patients with renal cell carcinoma.

## MATERIALS AND METHODS

A consecutive series of 74 patients aging from 35-79 years with RCC who underwent nephrectomy in the year 2003 (44 male and 30 female) was analyzed. Seventeen patients (9 male and 8 female) were excluded from the study because 5 of them had only partial nephrectomy, 2 were sent for consultation from other hospitals (without renal arteries), in 4 cases renal arteries were tangentially cut and in 6 specimens renal arteries were not sampled. Finally, the study group consisted of 57 patients. All relevant patients' data including age, sex, tumor grade and size, the extent of tumor necrosis, blood pressure and vena cava status were analyzed. There were 35 male and 22 female patients with RCC ranging in age from 35-79 years (mean 58.9 years). The size of RCC was from 2-16 cm (mean 7.1 cm). Renal artery, and vein as well as ureter margin were routinely analyzed. Specimens were routinely fixed in 10% buffered formaldehyde, embedded in paraffin, cut and stained with hematoxylin and eosin, Mallory trichrome method and orcein, and examined by light microscopy. Immunohistochemistry was performed by Microwave

Streptavidine Immunoperoxidase protocol (MSIP) in DAKO TechMate™ Horizon automated immunostainer. We used primary antibodies to smooth muscle actin (SMA) that were purchased from DAKO, Copenhagen, Denmark. Dilution of the antibody was "ready to use". Nuclear grade of RCC was determined according to Fuhrmann et al [4].

Statistical analysis used in this study included F-test, T-test/Cochran-Cox method, and  $\chi^2$ -test. Level of significance was set at  $p < 0.05$ .

The classification of FMD included pathologic processes of intimal, medial and adventitial fibroplasia [3, 9, 15].

## RESULTS

Renal arteries of 26 patients (20 male and 6 female) ranging in age from 38-74 years (mean 58.6 years) showed no changes. RCC in these patients measured 2.5-11 cm in largest diameter (mean 6.6 cm). In 24 patients (M: F=10:14) aging from 35-79 years (mean 60.0 years) renal arteries showed FMD (Figure 1), and RCC in these patients were between 2-16 cm (mean 8 cm), while 7 patients (5 male and 2 female) aging 60-69 years (mean 62.0 years) had atherosclerotic changes in renal arteries. Tumor size in this group was 2.5-14 cm (mean 6.4 cm). In the first group (cases without renal artery changes) there were 3 patients with tumorous infiltration of the renal vein. The same number of cases with renal vein infiltration was found in the second group (fibromuscular changes of renal arteries) while only one patient from the third group who had atherosclerotic changes of renal arteries had tumorous infiltration of renal vein. Blood pressure in patients from the first group was from 100/70 to 160/100 mmHg (mean 125/84.5 mmHg), in the second group 110/80 to 200/100 mmHg (mean 138.5/86 mmHg) and in the third group 115/70 to 145/85 mmHg (mean 134/79 mmHg). There were no data about the blood pressure for 14

(24.6%) patients. Four patients with no renal artery changes and 5 patients from the second group (FMD) were receiving antihypertensive therapy. Necrosis was observed in 45 of 57 tumors (78.9%). There was no statistically significant correlation between the presence ( $p=0.750$ ) and type ( $p=0.052$ ) of FMD and the extent of the necrosis in RCCs. Tumors with type I of FMD 3/7 (42.9%) showed more than 50% necrosis, while only 1/15 (6.7%) tumors with FMD type IIb had the same extent of necrosis. One of two cases with FMD type IIa showed necrosis in more than 50% of tumor mass.

Clinicopathologic features of patients with renal cell carcinoma are shown in Table 1 and 2.

Statistical analysis showed no significant difference in the age ( $p=0.486$ ), tumor size ( $p=0.112$ ) and mean systolic ( $p=0.918$ ) and diastolic ( $p=0.448$ ) blood pressure between the first and the second group of patients. However, FMD was found significantly more often in female patients ( $p=0.009$ ). Furthermore, there was no statistically significant difference in the age, tumor size and blood pressure between the first and third group and second and third group of patients. In the group of patients with atherosclerosis and without significant pathomorphologic changes of renal arteries men were more frequent ( $p=0.028$ ).

## DISCUSSION

The incidence of RCC is significantly higher in people with a history of blood hypertension that is not dependent on obesity and tobacco smoking. One of the causes of hypertension is renal-artery stenosis due to atherosclerosis in 90 percent of cases [12].

Fibromuscular dysplasia accounts for less than 10 percent of cases of renal artery stenosis, the medial type representing about 90 percent of cases [8, 14].

Atherosclerotic renal artery stenosis is a common and progressive disease, however it is probable that many atherosclerotic stenoses are never detected because refractory hypertension or



renal failure does not develop [12]. In the hypertensive population, high blood pressure may be attributed to renovascular FMD in less than 2% of patients [15]. In patients with renovascular hypertension, FMD is the underlying cause in 20-50% of cases [8]. The etiology of FMD is unknown, although many theories have been advanced, including those involving a genetic predisposition, smoking, hormonal factors and disorders of vasa vasorum as risk factors [8, 14]. The patients with FMD may be asymptomatic and the natural history of the disease is relatively benign with progression occurring in only the minority of patients [8].

In our previous study fibromuscular dysplasia of renal arteries was found in a significant proportion of patients with RCC, mainly in females [7]. These changes might be primary, but also could be the result of some other factor or the effect of the tumor itself.

Hypertension has been implicated as a risk factor for the development of RCC, but quantitative data concerning the levels of blood pressure are limited [1]. A small case-control study based on medical records found that the risk of RCC was higher with higher blood pressure within 5 to 10 years before the diagnosis of RCC. In the study with long-term follow-up, Chow et al [1] showed that blood pressure was positively related to the risk of RCC. The risk of RCC in men with diastolic pressure of 90 mmHg or more was more than double the risk in men with diastolic pressure below 70 mmHg. Similar data were reported on the relationship and risk for systolic pressure [1, 13].

In our study, renal artery changes were observed in 31 out of 57 patients with RCC. There was no correlation between blood pressure and the presence of FMD.

There are few studies on the relation between RCC and blood pressure that were based on relatively small number of subjects except for the study of Chow et al [1] on 363.992 Swedish men in whom 759 RCC developed during the 25 years period of follow-up.

Grossly, RCC usually shows large areas of necrosis. Such changes are usually attributed

to some abnormalities in tumor vascularization. The data in the literature pointed out to the relationship between the presence and extent of tumor necrosis in RCC and different features including tumor size, cell type, nuclear grade as well as microvessel density and the expression of different markers [6]. However, there are no data about the relationship between fibromuscular dysplasia like changes and renal cell carcinoma. Onishi et al reported histological features of hypovascular and avascular RCC, however, the cause of vascular changes was not furtherly analyzed [10]. We observed tumor necrosis in 78.9% of tumors, but there was no statistically significant correlation between the presence and type of FMD and the extent of the necrosis of RCC. However, it seems that a larger study is needed to confirm the relationship between FMD type and tumor necrosis.

On the basis of our results we may conclude that fibromuscular dysplasia of renal artery occurs in a significant proportion of female patients with renal cell carcinoma, while male patients more frequently had atherosclerosis or no pathomorphologic renal artery changes. However further studies are needed to elucidate these changes and to determine whether are primary or represent a consequence of the tumor.

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Table 1. Clinicopathologic features of 57 patients with renal cell carcinoma with regard to renal artery status (Group I - without artery changes, Group II - FMD, Group III - atherosclerosis)

	Group I	Group II	Group III
Male	20	10	5
Female	6	14	2
Age	38-74 years (mean 58.6)	35-79 years (mean 60.0)	60-69 years (mean 62.0)
Tumor size	2.5-11 cm (mean 6.6)	2-16 cm (mean 8)	2.5-14 cm (mean 6.4)
Tumor necrosis	Less than 50% - 21 More than 50% - 5	Less than 50% - 19 More than 50% - 5	Less than 50% - 6 More than 50% - 1
Blood pressure	110/70-160/100 mmHg (mean 125/84.5)	110/80-200/100 mmHg (mean 138.5/86)	115/70-145/85 mmHg (mean 134/79)
Cell type of RCC	Clear cell-10 Chromophilic eosinophilic-5, Mixed (Clear and eosinophilic)-7 Mixed with sarcomatoid component-3 Chromophobe-1	Clear cell-8 Chromophilic eosinophilic-3 Mixed (Clear and eosinophilic)-8 Mixed with sarcomatoid component-5	Clear cell-5 Chromophilic eosinophilic-1 Mixed with sarcomatoid component-1
Nuclear grade	G1 - 3 G2 - 7 G3 - 10 G4 - 6	G1 - 0 G2 - 8 G3 - 9 G4 - 7	G1 - 1 G2 - 6 G3 - 0 G4 - 0

Table 2. Clinicopathologic features of 57 patients with RCC regarding three different types of FMD (Type I - intimal, Type IIa - medial muscular, Type IIb - medial fibromuscular)

	Type I	Type IIa	Type IIb
Male	3	0	7
Female	4	2	8
Age	52-74 years (mean 62)	35-66 years (mean 50)	36-79 years (mean 60.5)
Tumor size	2-14 cm (mean 7.4)	6-12 cm (mean 9.0)	3-16 cm (mean 8.0)
Blood pressure	120/70-200/100 mmHg (mean 150/90)	120/80-140/95 mmHg (mean 130/87.5)	110/80-175/95 mmHg (mean 136.3/84.2)
Nuclear grade	Predominantly G3	Predominantly G2	Equally G2,3 i 4
Cell type of RCC	Clear cell-2 Chromophilic eosinophilic-1 Mixed (Clear and eosinophilic)-3 Mixed with sarcomatoid component-1	Chromophilic eosinophilic-2	Clear cell-6 Chromophilic eosinophilic-1 Mixed (Clear and eosinophilic)-3 Mixed with sarcomatoid component-5
Tumor necrosis	Less than 50% - 4 More than 50% - 3	Less than 50% - 1 More than 50% - 1	Less than 50% - 14 More than 50% - 1

Figure 1. Renal artery dysplasia of medial fibromuscular type IIb in a patient with renal cell carcinoma, A – Hematoxylin and eosin stained section showing protrusion of fibromuscular ridge into the arterial lumen, B – Mallory stained section showing proliferation of smooth muscle and connective tissue, C – Orcein stained section showing the internal lamina D – Smooth muscle actin (SMA) immunostaining showing architectural disarray of the smooth muscle cells. (All microphotographs were made under low magnification, 40X.)

