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## The use of Doppler vascular resistance in the early diagnosis of chronic kidney disease progression in patients with renal cell carcinoma

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### Abstract

Development and progression of chronic kidney disease (CKD) in patients with renal cell carcinoma (RCC) after radical nephrectomy remains an extremely pressing contemporary issue.

Postoperative changes of the ultrasound resistance index (RI) in the contralateral kidney not affected by the tumor after surgical treatment of RCC, as well as correlations between changes in IR and in glomerular filtration rate (GFR) remain far from being comprehensively investigated.

The RI changes in the parenchyma of the intact (unaffected by the tumor) kidney before and after surgical treatment for RCC, and establishing correlations between RI changes and creatinine-dependent GFR remain unexplored issues.

**Objective.** To assess the correlation between RI and GFR in the kidney not affected by the RCC before and after radical nephrectomy.

**Materials and methods.** The study enrolled 49 patients. Group I included 37 patients with an initial diagnosis of RCC (on the right), Stage III of the disease, and without signs of chronic renal failure (GFR was  $\geq 90$  ml/min/1.73 m<sup>2</sup>).

In patients with RCC, six months after surgery, the RI increase in the contralateral kidney unaffected by the tumor was significantly associated with a significant reduction in GFR. Thus, RI can be potentially used to predict the development of CKD in this patient population.

**Key words: chronic kidney disease; renal cell carcinoma; radical nephrectomy; chronic renal failure**

### **Introduction**

Development and progression of chronic kidney disease (CKD) in patients with renal cell carcinoma (RCC) after radical nephrectomy remains an extremely pressing contemporary issue.

Postoperative changes of the ultrasound resistance index (RI) in the contralateral kidney not affected by the tumor after surgical treatment of RCC, as well as correlations between changes in IR and in glomerular filtration rate (GFR) remain far from being comprehensively investigated.

It is difficult to overestimate the current significance of changes in renal function, as well as the development and progression of chronic kidney disease in patients after radical nephrectomy (RN) for RCC. [1 - 3] The current range of diagnostic interventions is quite wide and includes such methods as dynamic renoscintigraphy, renal ultrasound in the Doppler scan mode, CT, MRI, laboratory assessments, etc. [4, 5]. For many years already, the following angle independent parameters are used to characterize arterial circulation: 1) RI = (S-Dy)/S (Pourcelot, 1974) resistance index; 2) PI = (S-Dy)/A (Gosling, 1976) pulsation index; 3) S/D (Smart, Drumm, 1980) peak systolic to end diastolic ratio; 4) D/A [6 - 8]. Of all angle independent indices, RI is the most widely used one. In a local hemodynamic assessment it can be assumed that RI is a variable that characterizes pulse volume in an isolated area of the vascular bed. RI may be accordingly viewed as a part of the loss in peak systolic blood flow velocity in an isolated area of major arterial circulation during the reduced filling phase. Taking into consideration the specific features of testing methodology, it is recommended to take mean RI values over several pulse cycles. It is also essential to take into account the RI calculation error, which is increased with the change in linear velocity of blood flow up to and over 100 cm/s from 4–5 to 13–15% [2]. In high peripheral resistance, diastolic

arterial blood flow is reduced, which leads to increased difference between systolic and diastolic blood flow velocities and to respective increase in the aforementioned indices [9, 10]. The blood flow depends on the pressure gradient; the pulsing pressure determined the pulsing pattern of blood flow, i.e. its changing velocity in different phases of the cardiac cycle. However, the velocity of pulse wave propagation exceeds blood flow velocity [11 - 14]. This is why in some vascular regions the distal propagation of the pulse wave leads to the fact that at some point in time the pressure in the distal area exceeds the pressure in the proximal portion and a reverse blood flow occurs. As a rule, the phase reverse blood flow occurs in locations with a strong formation of pulse wave peaks. This blood flow pattern is also typical for the femoral sections of arterial circulation, where the arteries are broad, but the peripheral resistance to the flow of blood is significant. In this respect, the peak value of negative diastolic wave can be used as a minimal value of linear blood flow velocity for calculation of angle independent indices. Renal arteries belong to arterial vessels with low peripheral resistance. Normal RI values for renal arteries in adults are within 0.6 to 0.7 with an upper limit of normal [15, 16, 2].

Calculation of RI for renal arteries may provide an additional characterization of blood flow in the renal artery and direct information about the hemodynamic changes in the vascular bed of renal parenchyma. It is a known fact that performing a renal transplant with an ultrasonographic  $RI > 0.8$  may lead to a significant increase in mortality levels in this patient population. It is known that in agenesis of a kidney or after one of the two kidneys is removed, there is development of compensatory hypertrophy of the remaining kidney. The hypertrophy is accompanied by an increased volume of renal blood flow for the reason that the hypertrophic process depends on the intensity of blood supply of the kidney [9, 17]. There have been moderately successful attempts at Doppler sonographic assessments of parameters of hemodynamic adjustment of the organ, as well as impairments in diseases of the remaining kidney [2, 18, 19].

RI assessments for the vessels of the remaining kidney produced ambiguous results. When studying hemodynamic parameters of renal blood flow in the hypertrophied kidney, which remained after a contralateral nephrectomy, reduced RI was found at the level of intra-renal vessels and negative correlations were found between RI and renal volume. As reported in a study [20], there was a correlation ( $r=0.67$ ,  $p<0.05$ ) between RI and renal volume in children after a mean period of 3.4 years after radical treatment of unilateral Wilm's tumor [16]. Comparison of data in this paper showed an increase in maximum blood flow velocity (by  $25 \pm 6.2\%$ ), an increase in RI (by  $18 \pm 3.4\%$ ), and an increase in volumetric blood flow

(by  $87 \pm 12.3\%$ ) for the main renal artery of the solitary kidney. Intra-renal hemodynamics in children up to 10 years of age without heart failure and heart defects in the post-nephrectomy period was characterized by RI changes at the level of interlobar and arcuate arteries towards RI reduction due to increased diastolic blood flow velocity [21 - 24]. A substantial increase in the RI for the main renal artery was apparently occurring through a redistribution of total renal fraction of cardiac output in favor of the remaining kidney. In the meantime, the estimated values of the RI variable were changing at the expense of peak systolic blood flow velocity in the main renal artery [25, 26]. According to the authors, the increase of RI for the main renal arteries not only reflects the reduction in renal blood flow with age, but also is a collateral sign of kidney damage due to hyperfiltration [2, 27, 28]. When studying the filtration function of the solitary kidney in patients 3 to 16 years of age, an inverse correlation was found between creatinine clearance and RI at the level of interlobar arteries ( $r=-0.76$ ,  $p<0.001$ ) [17, 29, 30]. A protein challenge test in these patients has detected reduced amplitude of change in RI of the blood flow on the level of arcuate arteries compared to the control group [18, 19]. It is expected that with consideration for central hemodynamics, the RI values for the main renal artery can be used as the adequacy criteria of hemodynamic supply of the solitary kidney and its functional status.

The RI changes in the parenchyma of the intact (unaffected by the tumor) kidney before and after surgical treatment for RCC, and establishing correlations between RI changes and creatinine-dependent GFR remain unexplored issues.

### **Objective**

To assess the correlation between RI and GFR in the kidney not affected by the RCC before and after radical nephrectomy.

### **Materials and methods**

The study enrolled 49 patients. Group I included 37 patients with an initial diagnosis of RCC (on the right), Stage III of the disease, and without signs of chronic renal failure (GFR was  $\geq 90$  ml/min/1.73 m<sup>2</sup>).

Ultrasonographic findings. In all patients of Group I, the left renal artery originated from the aorta in a typical location; the renal arteries in visualizable segments were patent and with free lumens. There have been no data regarding stenosis. Depending on the RI changes during the observation period, the patients in Group I have been divided into subgroups Ia and Ib. Subgroup Ia included 11 patients who had a statistically significant change in RI during the 6 months of observation. Subgroup Ib included 26 patients who had no significant changes in RI during the above mentioned time period.

All patients in Group I had a therapeutic right-sided radical nephrectomy. Group II (control group) included 12 patients without signs of RCC and without signs of anatomical or functional disorders of the kidneys. In no cases the study subjects had any findings suggestive of cardiovascular disease.

Ultrasonographic findings. In all patients of Group II, renal arteries originated from the aorta in a typical location; the renal arteries in visualizable segments were patent and with free lumens. There have been no data regarding stenosis. The following clinical diagnostic parameters have been assessed: serum creatinine, GFR and RI. Assessment of results was conducted before surgical treatment and in 3 and 6 months after the completed treatment (or during the visit for the control group).

### **Results**

The mean RI values in patients of Group I (subgroups Ia and Ib) at primary examination were  $0.51 \pm 0.03$  and  $0.52 \pm 0.05$ , respectively ( $p > 0.05$ ). The mean RI value in patients of Group II (controls) in the same time period was  $0.49 \pm 0.03$  ( $p > 0.05$ ).

The respective mean GFR values in patients of Group I (subgroups Ia and Ib) were  $97 \pm 0.02$  ml/min/1.73 m<sup>2</sup> and  $93 \pm 0.04$  ml/min/1.73 m<sup>2</sup> ( $p > 0.05$ ). The mean GFR value in patients of Group II (controls) in the same time period was  $103 \pm 1.73$  ml/min/0.03 m<sup>2</sup> ( $p > 0.05$ ).

In 3 months after surgical treatment, 11 patients (29.73%) of Group I (subgroup Ia) had a statistically significant RI increase compared to baseline (mean value  $0.68 \pm 0.02$ ),  $p < 0.05$ . The rest of the patients (subgroup Ib) have not had any significant RI changes within 3 months following the initial visit (the mean value was  $0.53 \pm 0.03$ ),  $p > 0.05$ . The mean RI value in patients of Group II (controls) in the same time period was  $0.54 \pm 0.07$  ( $p > 0.05$ ).

In 3 months after surgical treatment, 11 patients (29.73%) of Group I (subgroup Ia) had a statistically significant GFR reduction compared to baseline (mean value  $93 \pm 0.07$  ml/min/1.73 m<sup>2</sup>)  $p < 0.05$ . The rest of the patients (subgroup Ib) have not had any significant GFR changes within 3 months following the initial visit (the mean value was  $93 \pm 0.01$  ml/min/1.73 m<sup>2</sup>),  $p > 0.05$ . The mean GFR value in patients of Group II (controls) in the same time period was  $107 \pm 0.01$  ml/min/1.73 m<sup>2</sup> ( $p > 0.05$ ).

The retrospective analysis has found that in 6 months after surgical treatment in patients of subgroup Ia mean RI value was significantly different from preoperative values of this parameter, changing from  $0.51 \pm 0.03$  to  $0.71 \pm 0.02$  ( $p < 0.05$ ). At the same time, RI has changed insignificantly in subgroup Ib, from  $0.52 \pm 0.05$  to  $0.54 \pm 0.02$  ( $p > 0.05$ ). The

respective change in mean RI values in patients of Group II (controls) in the same time period was from  $0.49 \pm 0.03$  to  $0.50 \pm 0.02$  ( $p > 0.05$ ).

In 6 months following the initial visit, 11 patients (29.73%) of Group I (subgroup Ia) had a statistically significant GFR reduction compared to baseline, from  $97 \pm 0.02$  ml/min/1.73 m<sup>2</sup> to  $79 \pm 0.01$  ml/min/1.73 m<sup>2</sup> ( $p < 0.05$ ). The rest of the patients (subgroup Ib) have not had any significant GFR changes within 6 months following the initial visit. The mean GFR value in patients of Group II (controls) has changed from  $103 \pm 0.03$  ml/min/1.73 m<sup>2</sup> to  $102 \pm 0.07$  ml/min/1.73 m<sup>2</sup> ( $p > 0.05$ ) (Table 1).

When a correlation analysis was performed, a strong inverse correlation was obtained in subgroup Ia between the parameters of RI and GFR: the Pearson's coefficient was 0.764 ( $p < 0.05$ ).

Table 1. - Changes with time in RI and GFR parameters of the solitary kidney unaffected by the tumor in patients with RCC (in primary examination and in 3 and 6 months after the surgical treatment)

Observation period	RI					GFR ml/min/1.73 m <sup>2</sup>				
	In primary examination	In 3 months		In 6 months		In primary examination	In 3 months	In 6 months		
Group I (n=37)	$0.51 \pm 0.03$	Subgroup Ia (n=11)	$0.68 \pm 0.02$	Subgroup Ia (n=11)	$0.71 \pm 0.02$	$97 \pm 0.02$	Subgroup Ia (n=11)	$93 \pm 0.07$	Subgroup Ia (n=11)	$79 \pm 0.01$
	$0.52 \pm 0.05$	Subgroup Ib (n=26)	$0.53 \pm 0.03$	Subgroup Ib (n=26)	$0.54 \pm 0.02$	$93 \pm 0.04$	Subgroup Ib (n=26)	$93 \pm 0.01$	Subgroup Ib (n=26)	$93 \pm 0.02$
Group II (n=12)	$0.49 \pm 0.03$	$0.54 \pm 0.07$		$0.50 \pm 0.02$		$103 \pm 0.03$	$107 \pm 0.01$	$102 \pm 0.07$		

Note: RCC = renal-cell carcinoma; RI = resistance index, GFR = glomerular filtration rate, SD = standard deviation.

When a correlation analysis was performed, a strong inverse correlation was obtained in subgroup Ia between RI and GFR parameters: the Pearson's coefficient was - 0.764.

In 6 months after surgical treatment, the increase in the RI of the contralateral kidney (not affected by the tumor) in patients with RCC was statistically significantly dependent on the reduction in GFR (Table 2).

Table 2 - Renal blood flow parameters in 6 months after laparoscopic resection of the lower pole of the right kidney

Parameter	Right RA	Left RA
Blood flow in the orifice	Vps=82 cm/sec, RI=0.73	Vps=69 cm/sec, RI=0.71
Blood flow in renal hilum	Vps=67 cm/sec, RI=0.68	Vps=62 cm/sec, RI=0.67
Blood flow in the upper segmental artery	Vps=42 cm/sec, RI=0.62	Vps=40 cm/sec, RI=0.63
Blood flow in middle segmental artery	Vps=49 cm/sec, RI=0.64	Vps=46 cm/sec, RI=0.62
Blood flow in lower segmental artery	Vps=31 cm/sec, RI=0.67	Vps=42 cm/sec, RI=0.62

Note. RA = renal artery; Vps = peak systolic velocity; RI = resistance index.

The mean RI values in patients of Group I and Group II at the time of primary examination were  $0.51 \pm 0.52$  and  $0.49 \pm 0.13$ , respectively ( $p > 0.05$ ). At 6 months after surgery, 11 patients (29.73%) of Group I (subgroup Ia) had a statistically significant decrease in GFR compared to baseline (mean  $79 \pm 3.71$  ml/min/1.73 m<sup>2</sup>),  $p < 0.05$ . In the rest of the patients, no significant changes in GFR were observed within 6 months (subgroup Ib).

The retrospective analysis has found that 6 months after the operative treatment, the average RI values in patients of subgroup Ia were significantly different from those before surgery and were  $0.71 \pm 2.72$  and  $0.51 \pm 0.13$ , respectively ( $p < 0.05$ ). At the same time, there were no such differences in subgroup Ib ( $p > 0.05$ ). When conducting correlation analysis, a strong inverse correlation between RI and GFR was obtained in subgroup Ia: Pearson's correlation coefficient was 0.764 ( $p < 0.05$ ).

### Conclusions

In patients with RCC, six months after surgery, the RI increase in the contralateral kidney unaffected by the tumor was significantly associated with a significant reduction in GFR. Thus, RI can be potentially used to predict the development of CKD in this patient population.

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