doi:10.25143/prom-rsu_2015-05_dts

RĪGAS STRADIŅA UNIVERSITĀTE

Māris Sperga

CICATRICIAL CHANGES IN THE KIDNEYS AND THEIR LINK TO RENAL TUMOURS

Summary of the Doctoral Thesis
for obtaining the degree of a Doctor of Medicine

Speciality – Pathology

Riga, 2015

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The Doctoral Thesis was carried out in the Department of Pathology of Rīga Stradiņš University

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The Doctoral Thesis will be defended on 14 April 2015, at 15.00 at an open meeting of the Doctoral Council of Medicine of Rīga Stradiņš University, at the Hippocrates Lecture Theatre, 16 Dzirciema Street, Rīga, Latvia.

The Doctoral Thesis is available in the library of RSU and RSU homepage: www.rsu.lv

The Doctoral Thesis was developed with the support of ESF project agreement No. 2013/0004/1DP/1.1.1.2.0/13/APIA/VIAA/020

Secretary of Doctoral Council
Dr. med., Associate Professor **Simona Doniņa**

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ABBREVIATIONS USED IN THE PAPER

AD – autosomal dominant inheritance

AML – angiomyolipoma

ARCD – acquired renal cystic disease

ESRD – end-stage renal disease

G I; G II; G III; G IV – degrees of malignancy of the tumour (grade I; grade II; grade III; grade IV)

H&E – haematoxylin and eosin

HIF – hypoxia-inducible factor

mTOR – mammalian target of rapamycin

RCCC – renal clear cell carcinoma

RCC – renal cell carcinoma

OA – oncocitary adenoma

PA – papillary adenoma

PRCC – papillary renal cell carcinoma

pRB – retinoblastoma gene

pT – local spread of primary resected tumour assessed by a pathologist

PTEN – phosphatase and tensin homologue

WHO – the World Health Organization

RAKUS – the Eastern Clinical University Hospital of Riga (*Rīgas Austrumu klīniskā universitātes slimnīca*)

RMI – renomedullary interstitial tumour

SFT – solitary fibrous tumour

TNM – classification of tumour growth and local spread: T – size of the tumour; N – regional lymph nodes; M – distant metastases (Latin for *tumori, noduli, metastasis)*

VEGF – vascular endothelial growth factor

VHL –Von Hippel-Lindau syndrome

INTRODUCTION

Topic of the Study

Two percent of the tumours diagnosed worldwide every year are renal tumours [*Parkin et al., 2003*]. Within this group of tumours, 85% are renal cell carcinomas [*Ahmedin et al., 2009*]. In Latvia, 4.4–4.9% of all diagnosed tumours are renal tumours, and renal tumour incidence rates tend to keep increasing [*Latvijas vēža slimnieku reģistrs, 2008; 2009*]. In Latvia, the age-standardised incidence rates in 2011 and 2012 were 6.9 and 7.0 cases for women, and 12.5 and 14.1 cases for men, respectively.

Renal cancer risk factors include obesity, diabetes and arterial hypertension. Taking into consideration patients' age, gender and risk factors, there is a possibility that these tumours will develop in the background of previous changes. Experimental studies on animals have undoubtedly proven the role various specific carinogens play in the development of renal tumours. It is known that clear renal cell carcinomas are associated with Von Hippel-Lindau Syndrome (VHL) and other syndromes [*Ornstein et al., 2000*]. A link has been observed between clear and papillary renal cell carcinomas as well as terminal changes in the kidneys during the end phase of chronic kidney diseases characterised by progressive loss of kidney function [*Levine et al., 1991*]. Among the population, the risk of developing renal tumours is forty times higher in patients with terminal kidney disease and also in patients with acquired renal cystic disease [*Tickoo et al., 2006*]. In the literature, little data exist on the direct effects of background changes on tumour development without systemic manifestations. Additionally, not much data examine how tumour incidence changes as background changes progress. There are a few studies that show what structural changes in the kidneys are most frequently associated with tumour development, how renal tumour incidence varies as the

extent and severity of these changes increases, and their biological aggressiveness but these topics have not been fully researched. Therefore, the factors discussed above illustrate the topic of this doctoral thesis and its fundamental and practical significance.

The Aim of this Paper

The aim of this paper is to research the link between renal tumour development and nephrosclerotic processes in the kidneys and to compare the predictor variables of this group with those of renal tumours without nephrosclerosis.

Enabling Objectives

In order to reach the objectives of this work, the following enabling objectives were set:

1) to analyse renal tumours and changes in the adjacent tissue;
2) to identify the role of nephrosclerosis of various origins in the process of renal tumour formation;
3) to select renal tumours that both show a link and those that do not to nephrosclerosis and to carry out an immunohistochemical analysis of the cell cycle and predictive markers.

Hypothesis

Cicatricial areas in renal tissue are associated with increased renal clear cell carcinoma formation, and their incidence in cicatricial areas far exceeds the incidence in other renal tumours.

The Scientific Novelty of this Paper

The scientific novelty of this paper lies in the fact that groups of renal tumours were analysed for background changes in the kidneys (nephrosclerosis), and whether these background changes affect the biological behaviour of the tumour were assessed in terms of the expression of predictive markers and grades of malignancy. This was the first study carried out in Latvia that analysed and compared renal tumours with and without background changes and identified differences in predictive marker expression. Literature on this topic is scarce; therefore, the present paper is novel in a number of ways.

The Clinical Significance of this Paper

As the average age of the world's population increases, the number of chronic diseases that affect both the functional status of and structural changes in the kidneys is growing. Pathological changes develop mostly in renal blood vessels. These changes can cause systemic diseases and local renal diseases. With an upward trend in renal tumour incidence among the population, for specific groups of patients, incidence is notably high. The present study will enable singling out at-risk patient groups and assess them, as well as determine the degree of risk of developing renal tumours; this can influence the way the patients are monitored in the future.

The Personal Contribution of the Author

In order to meet the enabling objectives, the author developed a plan and design for the research work and performed all the steps of the research process: processing of materials from primary renal tumour surgery, morphological diagnostics of renal tumours, diagnostic and explorative immunohistochemical visualisation, data acquisition and interpretation. Research work was completed in close conjuction with practical work. Thus, when performing the preparation work on the laboratory material of the present study, the author streamlined the protocol for primary processing of surgery material that had thus far been practiced by pathologists, as well as promoted the standardisation of immunohistochemical methodologies and participated in the laboratory's external control process. The author carried out statistical processing of the data together with statistics experts.

1. MATERIALS AND METHODS

In order to reach the goal of the study and to confirm or disprove the hypothesis, three subgroups, as depicted in *Illustration 2.1*, were included in the study design described below.

The selection criteria for the 304 renal tumour samples obtained through clinically well-grounded surgery were macroscopically visible tumours and renal tissue with their anatomic structure preserved after surgery.

A study group comprising 107 kidneys was gathered by obtaining samples both from clinically well-grounded surgery material and from material obtained during sections carried out at the Eastern Clinical University Hospital of Riga (RAKUS) Pathology Centre. The material was obtained in a retrospective and sequential manner. The main criterion for inclusion was renal tissue nephrosclerosis caused by various diseases.

The author of the present study examined the kidneys obtained as a result of clinically well-grounded surgery and during sections macroscopically and determined the following:

1) The dimensions of the kidney – length, thickness (in centimetres);
2) weight (in grams);
3) kidney surface changes (scars, their extent expressed as a percentage – the ratio of cicatricial surface changes to the total kidney surface area, granularity of the cortex).

The author classified the nephrosclerosis identified macroscopically into five stages. If a kidney was visually unchanged, its parameters ranged from 11 × 5 × 2.5 cm to 12 × 7 × 3 cm, its weight ranged from 115–170 g [*Kalbergs, 1971*], scars were not identified and the surface was smooth; the author considered the kidney nephrosclerotically unchanged. To include kidneys like these into the statistical analyses and measurements, it was classified as "0" stage nephrosclerosis.

4) The dimensions of the tumour – length, width, thickness (in centimetres), colour, shape, contours (sharply defined, blurred), presence/absence of a capsule and its thickness (in milimetres);
5) the necrosis of the tumour and scars in the tumour tissue were assessed according to a dichotomous scale;
6) the existence of other tumours, their dimensions – height, width, thickness (in centimetres).

Patients' age and gender were determined in accordance with medical documentation data.

To make histological preparations, tissue samples with renal tumours were cut out, as well as the adjacent renal parenchyma tissue, attempting to include from 70 to 100% of the parenchyma adjacent to the tumour. Therefore, depending on the place where the material was obtained from, 'adjacent changes' were defined as structures that were in the direct vicinity of the tumour, were in a capsule connected with it, both in the region of renal core and in the renal cortex layer.

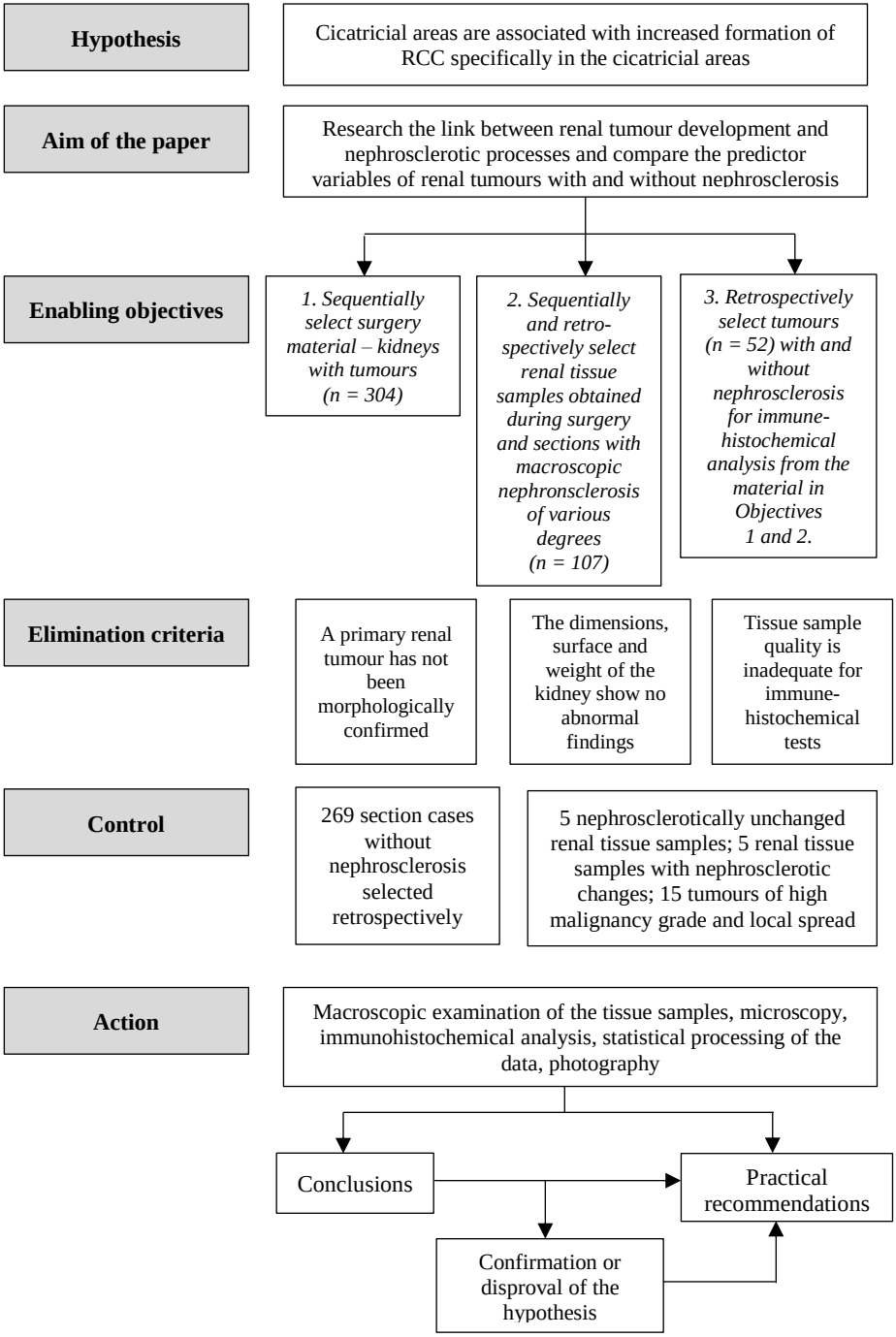
The tissue samples taken fom these kidneys were submitted for further processing at the laboratory to obtain histological preparations stained with haematoxylin and eosine (H&E stain). Microscopy of the preparations was carried out using a *NICON Eclipse 80i* microscope. Magnifications of 40×, 100×, 200×, and 400× were used with fields of view of 23.7 mm², 3.7 mm², 0.94 mm² and 0.24 mm² respectively to determine the following:

1) the histological type of tumour (according to the 2003 criteria of the WHO);
2) the grade of tumour malignancy according to Thoenes [*Thoenes et al., 1986*]. The grade of malignancy of the nuclei of chromophobe renal cell carcinomas was determined according to Paner [*Paner et al., 2010*]. To determine as precise an immunohistochemical interpretation as possible, grades of malignancy of renal clear cell

carcinomas and papillary renal cell carcinomas were determined accordinng to Furhman's methodology [*Fuhrman et al., 1982*];

3) changes in renal tissue adjacent to the tumour were determined: the extent of the fibrosis area was measured with a microscope ruler (in milimetres), the nature of the inflammation and its severity was made according to a scale of three stages (under a magnification of 200x with a field of view of 0.94 mm^2);
4) by assessing the tissue: nephrosclerosis with a corresponding stage of severity was identified according to the Banff classification [*Colvin et al., 2007*], which is used to assess changes in kidney transplants in case of chronic rejection. Thus, renal interstitial fibrosis, atrophy of renal tubules, glomeruloscrerosis or hyalonosis, and narrowing of arterial lumens were assessed. These changes were classified into four stages of severity with analogy to the Banff classification;
5) small cystic changes in renal collecting ducts and deposits of oxolate crystals in the renal stoma tissue were assessed, using a binary or dichotomous scale;
6) dysplastic changes in renal collecting ducts were assessed; epithelium that had enlarged nuclei and coarse chromatin were considered dysplastic renal tubule epithelium;
7) in the cases of additional tiny microscopic tumour findings, the same structural change interpretation was done as when analysing macroscopically identified tumours; additionally, the localisation of these tiny proliferations was determined in relation to the anatomic structures of the kidney, as well as the degree of nephrosclerosis in the tissue surrounding the tiny tumour.

Only the 269 section cases without nephrosclerosis selected during sections were used as control group material in the present study. Within the control group, one renal neoplasm was found by the author.


Hypothesis
Cicatricial areas are associated with increased formation of RCC specifically in the cicatricial areas
Aim of the paper
Research the link between renal tumour development and nephrosclerotic processes and compare the predictor variables of renal tumours with and without nephrosclerosis
Enabling objectives
1. Sequentially select surgery material – kidneys with tumours (n = 304)
2. Sequentially and retro-spectively select renal tissue samples obtained during surgery and sections with macroscopic nephronsclerosis of various degrees (n = 107)
3. Retrospectively select tumours (n = 52) with and without nephrosclerosis for immune-histochemical analysis from the material in Objectives 1 and 2.
Elimination criteria
A primary renal tumour has not been morphologically confirmed
The dimensions, surface and weight of the kidney show no abnormal findings
Tissue sample quality is inadequate for immune-histochemical tests
Control
269 section cases without nephrosclerosis selected retrospectively
5 nephrosclerotically unchanged renal tissue samples; 5 renal tissue samples with nephrosclerotic changes; 15 tumours of high malignancy grade and local spread
Action
Macroscopic examination of the tissue samples, microscopy, immunohistochemical analysis, statistical processing of the data, photography
Conclusions
Practical recommendations
Confirmation or disproval of the hypothesis

A third group was gathered for the immunohistochemical study from the groups that comprised 304 renal tumour cases and 107 cases of kidneys changed due to nephrosclerosis of various stages. This group comprised 52 kidneys with tumours that were found both in kidneys with and without nephrosclerosis. Of these 52 renal tumours, 25 were found in renal tissue with nephrosclerosis and 27 in tissue without nephrosclerosis. Tumours with/without nephrosclerosis were selected according to case-control methodology so that the groups were identical. Characterisation of the selected case paramaters is presented in Table 1.2.

Table 1.2.

Characterisation of the tumours used in the immunohistochemical study by patient's age, gender, histological type of the tumour, degree of malignancy, as well as the stage of local spread

Neoplasm	Number of cases	Patients' age (in years)	Males: Females (number)	Grade of malig-nancy according to Fuhrman (number)	Diame-ter of the tumour (mm)	pT stage (num-ber)
PRCC with nephroscler osis	5	72. ± 1.2	2 : 3	G I : 3 G II : 2	7.5 ± 3.5	pT1a : 5
PRCCC without nephron-sclerosis	8	70.2 ± 3.6	5 : 3	G I : 4 G II : 4	19.0 ± 9	pT1a : 7 pT1b : 1
PA with nephron-sclerosis	7	76.5 ± 1.0	2 : 5	was not deter-mined	2.04 ± 0.36	was not deter-mined

Table 1.2. continued

Neoplasm	Number of cases	Patients' age (in years)	Males: Females (number)	Grade of malig-nancy according to Fuhrman (number)	Diame-ter of the tumour (mm)	pT stage (num-ber)
PA without nephron-sclerosis	6	68.5 ± 4.0	2 : 4	was not deter-mined	2.5 ± 0.3	was not deter-mined
RCCC with nephron-sclerosis	13	71.3 ± 7.0	6: 7	G I : 10 G II : 3	12.9 ± 4.0	pT1a:13
RCCC without nephron-sclerosis	13	66.7 ± 3.4	8 : 5	G I : 7 G II : 6	16.4 ± 10.2	pT1a : 9 pT1b : 4

Abbreviations used in table: PRCC – papillary renal cell carcinoma; PA – papillary adenoma; RCCC – renal clear cell carcinoma; pT – local spread of primary resected tumour; pT1a – tumour is limited in the kidney with a size up to 4 cm in diameter; pTb – tumour limited in kidney ranging from 4–7 cm; G I – small nuclei up to 10 mkm in size; G II – nucleui with little polymorphism up to 15 mkm in size visible nucleoli in high magnification (400×).

To set up a control group for the immunohistochemical study, the author used tissue from five nephrosclerotically unchanged kidneys and five nephrosclerotically changed kidneys and also set up a comparative group comprising 16 renal cell carcinomas with a high grade of malignancy and a stage of local spread. In this group, the author included 13 renal clear cell carcinomas (RCCC): 9 cases with the G III grade of malignancy and four cases with the G IV grade of malignancy. All the tumours in the group were in the pT3a stage. Also, three G III malignancy grade and pT3a stage papillary renal cell carcinoma cases were included.

For immunohistochemical tests, the author selected 52 renal tumour samples and carried out immunohistochemical staining with prognostic

markers: E-cadherin (clone NCH-38 DAKO, *Glostrup, Denmark*), CD44 (clone DF 1485, DAKO, *Glostrup, Denmark*), Cyclin D1 (clone SP4, Ventana, *Tuscon, USA*), pRb (Ventana, *Tucson, USA*, p16 (clone 2D9A12, JC8, Ventana, *Tucson, USA*), Ki-67 (clone MIB1, DAKO, *Glostrup, Denmark*). In two cases, the author used CK7 (clone OV-TL12/30, DAKO *Glostrup, Denmark*) and CD10 (clone 56C6, DAKO *Glostrup, Denmark*). A method created by the manufacturer of LSAB (*labeled streptavidin biotin*) and *EnVision* for formalin-fixed tissue samples laid in paraffin was used.

When carrying out microscopy on the preparations with a *NICON Eclipse 80i* microscope, the author assessed the reactions both in a quantitative and qualitative manner depending on the specificity of the reaction of the primary antibodies (the reaction of cell cycle markers was assessed by studying the cell nuclei and prognostic markers – cell membranes).

The author considered the staining of specific cell structures in brown a positive reaction (stain of diaminobenzidine substrate and peroxidase reaction). The positivity of cell cycle markers was expressed as a percentage, assessing the total amount of cells in four fields of view with a magnification of 200×. The staining of the membranes was assessed qualitatively, either as negative or positive. In the case of positivity, the intensity of the reaction was assessed according to a three-stage system – weak, moderate, or strong intensity. Both negative and positive controls were used in order to determine the quality of the immunohistochemical antibody reactions.

The author collected the obtained data using *IBM SPSS 16* software and carried out statistical processing using the descriptive statistical method to characterise the central tendencies and dispersion indicators. Tendencies in frequency distribution of variable data were determined by calculating frequencies or by representing them graphically in histograms. Table 1.3. shows the statistical methods that were used.

Table 1.3.

Statistical methods used in data processing

Parameter to be determined	Statistical indicator
Patient age groups	*t* (the Student's t test), ANOVA test
Immunohistochemical indicators	*Mann-Whitney U* test
The stage of nephrosclerosis found macroscopically and the incidence of neoplasia	*Mann-Whitney U* test
Pathogenetic types of nephrosclerosis and their link to tumours	*Kolmogorov-Smirnov* test
Correlation between immunohistochemical qualitative indicators and tumours with and without nephrosclerosis, with a high grade of malignancy and stage of local spread	*Fisher* test
Correlation between immunohistochemical qualitative indicators and the grades of malignancy	*Chi-square (χ^2) test*
Distribution of the feature	*Chi-square (χ^2) test*
Determining statistical independence of two groups	*Spearman's correlation coefficient* *Kendell's correlation coefficient*
Determining the percentage ratio of a feature within a 95% confidence interval	*Confidence interval (CI)*

The author photographed the selected macroscopic and histologic preparations with a *NIKON* camera and processed the images using the *NIS – Elements BR 3.1* software in a *Windows HP* environment.

The research was carried out taking into consideration the international provisions of the Helsinki Declaration and provisions of the relevant Regulations of the Cabinet of Ministers of the Republic of Latvia. The ethics commission of the Rīga Stradiņš University approved the study in February 2010 (Decision No E-9 (2) of February 11, 2010 of the Ethics Commission of Rīga Stradiņš University (RSU).

2. RESULTS

2.1. Renal Tumours and Changes in Adjacent Tissue

During the study, 304 cases of renal tumours were analysed. In 151 cases (49.7%; 95% CI = 44.1–55.1), tumours were found in males and in 153 cases (50.3%; 95% CI = 44.7–55.9) in females. The patients were aged between 22 and 81, with an average age of 61.5 ± 11.8 years. For the males, the average age was 60.0 ± 11.2; for the females it was 62.9 ± 12.2 years. According to an independent sample *t*-test, the age differences were statistically significant, with a significance level of $p < 0.05$ ($t = 2.227$; $p = 0.027$).

Table 2.1.1. shows the number and relative frequency of renal tumours by morphological type.

Table 2.1.1.

Breakdown of the morphological types of renal tumours

Morphological type of tumour	Absolute number of cases	Relative frequency (%)	95% CI
Renal clear cell carcinoma	206	67.8	62.3–72.8
Oncocytoma	30	9.9	6.9–13.8
Papillary carcinoma	22	7.2	4.8–10.8
Chromophobe cell carcinoma	23	7.6	5.1–11.1
Other	23	7.5	5.1–11.1
Total	304	100	–

Abbreviations used in table: CI – Confidence interval.

2.1.1. Renal Clear Cell Carcinomas

RCCC were found in 67.8% (n = 206) of the cases. The average age of the patients was 61.9 ± 10.5 years. In 111 cases (53.9%; 95% CI = 47.1–60.6)

the patients were males, in 95 cases (46.1%; 95% CI = 39.4–52.9) the patients were females. Table 2.1.1.1. shows a breakdown of tumours by grade of malignancy (according to Thoenes).

Table 2.1.1.1.

Grades of malignancy of RCCC

Grades of malignancy	Absolute number of cases	Relative frequency (%)	95% CI
G I	71	34.5	28.3–41.2
G II	89	43.2	36.6–50.0
G III	46	22.3	17.2–28.5
Total	206	100	

Abbreviations used in the table: G I – small nuclei up to 10 mkm in size; G II – nucleus with little polymorphism up to 15 mkm in size, visible nucleoli in high magnification (400×); G III – nucleus with expressed polymorphism up to 20 mkm, nucleoli is visble at 100× magnification; CI – interval of confidence; RCCC – renal clear cell carcinomas.

In 26.7% (95% CI = 21.0–33.0) of the cases, the intensity of inflammation in the tumour capsule and in the adjacent tissue of renal parenchyma was Stage 1. In 43.7% (95% CI = 37.1–50.0) of cases it was Grade 2, and in 29.6% (95% CI = 23.8–36.2) of the cases inflammation was strong. By comparing the grades of tumour malignancy and the stage of severity of macroscopic nephrosclerosis, the following results were obtained (see Table 2.1.1.2.)

Table 2.1.1.2.

Breakdown of stages of severity of macroscopically identified nephroscleroses and the grades of malignancy of RCCC

Stage of nephrosclerosis	Grades of malignancy of RCC (according to Thoenes)			Total
	G I	G II	G III	
0	0	1	0	1
1	31	47	29	107
2	19	26	15	60
3	16	14	2	32
4	4	1	0	5
5	1	0	0	1
Total	71	89	46	206

Abbreviations used in the table: G I – small nuclei up to 10 mkm in size; G II – nucleus with little polymorphism up to 15 mkm in size, visible nucleoli in high magnification (400×); G III – nucleus with expressed polymorphism up to 20 mkm, nucleoli is visble at 100× magnification; RCCC – renal clear cell carcinomas; RCC – renal cell carcinoma.

Microscopic cicatricial changes were found by the author in all cases (100%; 95% CI = 97.8–100.0) (see Table 3.1.5.1.), also when nephrosclerosis was not found macroscopically.

When examining kidneys with clear cell carcinoma, tiny neoplastic proliferations that looked like clear cell papillary – eosinophil cell proliferations and dysplastic changes in the epithelium of renal tubules were often found in kidney capsules and in areas outside the capsule. Dysplastic changes were found in 87 kidneys (38.8%; 95% CI = 35.7–49.1) with clear cell carcinomas. Dysplastic changes were most often found in the renal tumour capsule or in its vicinity – in 87.0% (95% CI = 81.6–90.9) of the cases. The

remaining 13.0% (95% CI = 9.0–18.5) of cases were found in the renal parenchyma outside the tumour with severe Stage 3 microscopic nephrosis and Stages 3, 4 and 5 nephrosclerosis macroscopically. The histologically most common types of tumours were papillary adenoma, clear cell carcinoma, oncocytary adenoma and angiomyolipoma.

When examining RCCC, papillary adenomas were found in their capsules and in peritumoral renal parenchyma in 29 cases (14.1%; 95% CI = 9.9–19.5) (Image 2.1.1.1.).

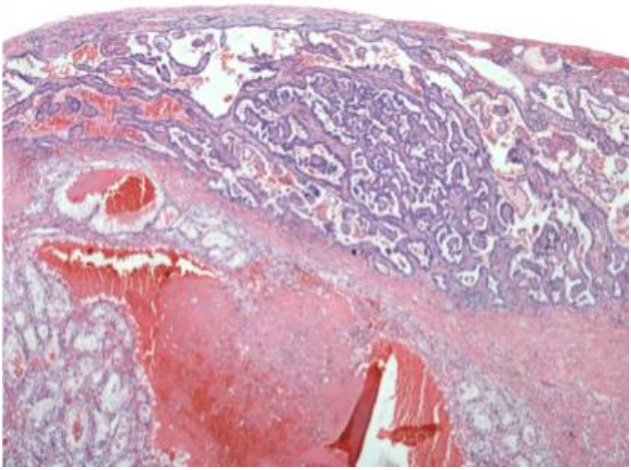


Image. 2.1.1.1. **Papillary renal cell adenoma (top of the image), alongside a RCCC (bottom of the image). H&E, 40× magnification**

In all the cases when adenomas were located inside the tumour capsule, the surrounding microscopic changes corresponded to Stage 3 nephrosclerosis. Table 2.1.1.3. shows a breakdown of papillary adenomas by their localisation.

Table 2.1.1.3.

Localisation of papillary adenomas and their link to the grades of malignancy of RCCC

Grade of malignancy of RCCC	Localisation of adenomas			
	subcapsular, next to the tumour	medullary, next to the tumour	subcapsular, outside the tumour	medullary, outside the tumour
G I	7	4	1	0
G II	3	2	5	2
G III	1	1	3	0
Total	11	7	9	2

Abbreviations used in the table: G I – small nuclei up to 10 mkm in size; G II – nucleus with little polymorphism up to 15 mkm in size, visible nucleoli in high magnification (400×); G III – nucleus with expressed polymorphism up to 20 mkm, nucleoli is visble at 100× magnification; RCCC – renal clear cell carcinomas.

In 68% (95% CI = 61.0–74.0) of cases, small cystic changes were found in the convoluted tubules in the immediate vicinity of papillary adenomas. In 15% of cases, dysplastic changes were found in the epithelium, and calcium oxalate crystals were found in 34% (95% CI = 27.9–40.6) of the cases.

In all the cases, Stage 3 microscopic nephrosclerosis with an inflammatory component of varying intensity was found. Stage 3 nephrosclerosis was found macroscopically in 26 cases, Stage 4 in two cases, and Stage 5 in one case. Inflammation was found in 90% of the cases (95% CI = 84.9–93.0), and it corresponded with Stage 1. Clear cell proliferations were identified in the RCCC capsule in 26 cases (12.6%, 95% CI = 8.7–17.9). All the proliferations were G I tumours by grade of malignancy (Image 2.1.1.2.).

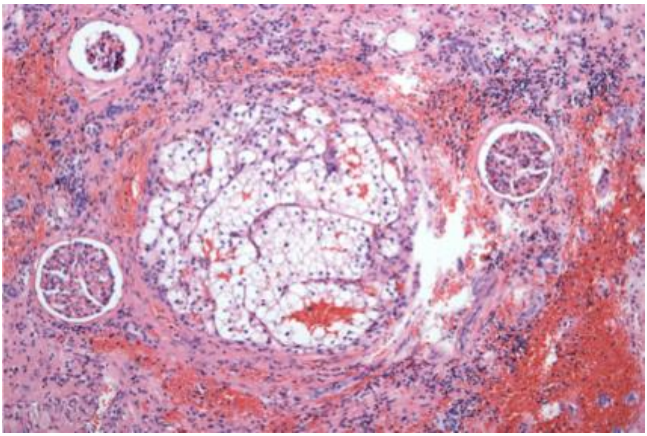


Image. 2.1.1.2. **G I RCCC with a compact structure in a nephrosclerotic area. H&E, 100× magnification.**

In 60% (95% CI = 42.5–77.5) of the cases, dysplastic changes in the adjacent tubular epithelium were identified in the clear cell proliferations. The dysplastic changes were characterised by early highlighting of the cell cytoplasm (Image 2.1.1.3.).

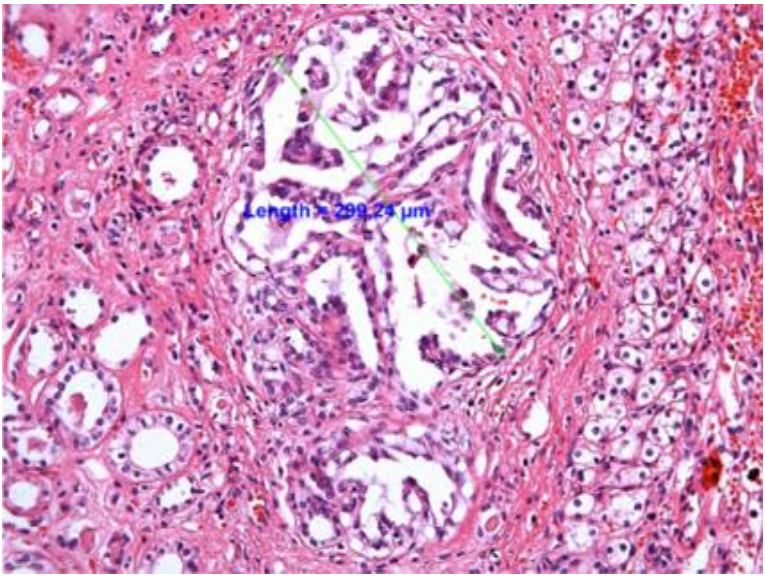


Image. 2.1.1.3**. RCCC focus in the scar area. Pre-existing tubule structures with dysplasia can be seen. H&E, 100× magnification**

In all the cases, a Stage 2 and 3 inflammatory infiltration was identified. There were Stages 2 and 3 microscopic nephrosclerosis. Oxalate crystals were not found.

Table 2.1.1.4. shows the grade of malignancy of primary tumour and the localisation of proliferations.

Table 2.1.1.4.

Localisation of clear cell proliferations and their link to grades of malignancy of RCCC

Grades of malignancy of RCCC	Localisation of clear cell proliferations			
	Subcapsular, next to the tumour	Medullary, next to the tumour	Subcapsular, outside the tumour	Medullary, outside the tumour
G I	1	3	2	2
G II	2	3	3	3
G III	1	2	3	1
Total	4	8	8	6

Abbreviations used in the table: RCCC – renal clear cell carcinomas; G I – small nuclei up to 10 mkm in size; G II – nucleus with little polymorphism up to 15 mkm in size, visible nucleoli in high magnification (400×); G III – nucleus with expressed polymorphism up to 20 mkm, nucleoli is visble at 100× magnification.

Macroscopically, the nephrosclerosis corresponded with Stages 2 and 3. Small cystic changes in renal tubules directly adjacent to these proliferations were found in three cases.

When examining the changes in tissue adjacent to clear cell carcinomas and in other areas of renal parenchyma, oncocytary adenomas were identified microscopically in three cases (1.5%; 95% CI = 0.3–4.4). In one case, the oncocytary adenoma was located inside the tumour capsule and the tumour itself was localised in the region of the renal cortex. In the other cases, the adenomas were localised distantly from the tumour in the renal cortex. In all cases, the nephrosclerosis that was identified macroscopically corresponded with Stage 2. Microscopically, the nephrosclerosis in the tissue surrounding the adenoma corresponded with Stage 3. In all cases, it was Grade II clear cell carcinoma in terms of malignancy. In one case, small cystic changes in the

tubules were found. Oxalate crystals were not found. In all cases, there was Stage 1 inflammation.

By histologically examining kidneys with clear cell carcinoma, in three cases (1.5%; 95% CI = 0.3–4.4) angiomyolipomas (AML) were found in the surrounding tissue. The localisation for all the AML was subcapsular, away from the tissue of clear cell carcinoma.

Macroscopically, in all cases nephrosclerosis corresponded with Stage 3. Histologically, tissue sclerosis next to the tumour was in Stages 2 and 3.

2.1.2. Oncocytary Adenomas

Oncocytary adenomas were identified in 30 cases out of the total 304 renal tumour cases that were analysed (9.9%). The average age of the patients was 64.6 ± 10.1; 11 patients were males, and 19 were females.

The stages of nephrosclerosis identified macrocsopically and microscopically are summarised below in Table 2.1.5.1. In one case of oncocytoma, an extensive renal oncocytosis was diagnosed with a pronounced shrinkage of renal stroma and fibrosis. The average thickness of the capsule was 0.6 mm with a Stage 2 inflammatory infiltration both into the tissue of the capsule and into the parenchyma.

In five cases (16.7%; 95% CI = 6.9–34.0), papillary adenoma was found in the vicinity of the oncocytary adenoma and in the renal parenchyma. Four foci out of the five cases were identified in the vicinity of the oncocitary adenoma capsule, and in one case a focus was found in the renal parenchyma more distantly from the tumour. In all the cases, histologically, the stage of nephrosclerosis in renal tissue stroma was Stage 3. Dysplastic changes in the tubules and oxalate crystals were not found. Small cystic changes in the tubules

were found. In all the cases, the severity of inflammation corresponded with Stage 1.

In one case, papillary adenoma was found outside the tumour capsule in the renal parenchyma. In the background, there were Stage 2 histological nephrosclerotic changes. In one case, there was a clear cell carcinoma proliferation (3.3%; 95% CI = 0–18.1) with severe (Stage 3) microscopic nephrosclerosis in the background. In one case (3.3%; 95% CI = 0–18.1), angiomyolipoma was found in the kidney together with oncocytary adenoma. Macroscopically and histologically, there was Stage 2 nephrosclerosis.

2.1.3. Papillary Renal Cell Carcinomas

In materials obtained from surgery, papillary renal cell carcinomas were identified in 22 cases (7.2% 95% CI = 4.8–10.8). The average age of the patients was 63.4 years. The male to female ratio was 1:1. The classification of the tumours in this group by grade of malignancy was as follows: four G I, 15 G II, and three G III papillary carcinoma cases.

A pronounced 2–4 mm thick capsule connected with the tumour was characteristic of papillary renal cell carcinoma. In all the cases, the tissue of the tumour capsule gradually transitioned into severely nephrosclerotically changed renal tissue. The inflammation was as intense as Stages 2 and 3.

Table 2.1.3.1. shows the macroscopically identified stages of nephrosleroses and a comparison of the grades of malignancy of papillary renal cell carcinoma.

Table 2.1.3.1.

Distribution of the stages of macroscopically identified nephroscleroses and the grades of malignancy of papillary carcinomas

Stage of nephrosclerosis	Grades of malignancy of RCC (according to Thoenes)			Total
	G I	G II	G III	
0	0	3	1	4
1	1	6	0	7
2	2	4	1	7
3	1	2	1	4
4	0	0	0	0
5	0	0	0	0
Total	4	15	3	22

Abbreviations used in the table: G I – small nuclei up to 10 mkm in size; G II – nucleus with little polymorphism up to 15 mkm in size, visible nucleoli in high magnification (400×); G III – nucleus with expressed polymorphism up to 20 mkm, nucleoli is visble at 100× magnification, RCC – renal cell carcinoma.

Neoplasms in the kidney capsule were also found in papillary renal carcinoma cases, as well as in renal parenchyma with Stages 2 and 3 macroscopic nephrosclerosis. Subcapsular papillary adenomas were identified next to a tumour in seven cases (31.8%; 95% CI = 16.2–52.8), in parenchyma next to a tumour in three cases (13.6%; 95% CI = 3.9–34.2). Small cystic changes in the tubules were found in nine cases. Oxalate crystals were found in two cases. In all the cases, there was Stage 3 microscopic nephrosclerosis.

2.1.4. Chromophobe Renal Cell Carcinomas

Of the 304 renal tumour cases that were researched, chromophobe carcinomas were identified in 23 cases or 7.6% (95% CI = 5.1 – 11.1). The average age of the patients was 57.5 ± 13.1 years. The male to female ratio was 1:1.1.

The chromophobe carcinomas were classified as follows by grade of malignancy (according to Paner): six G I malignancy tumours (26.1%; 95% CI = 12.3–46.8), 15 G II tumours (65.2%; 95% CI = 44.8–81.3), and two G III tumours were found (8.7%; 95% CI = 1.3–28.0).

When assessing the nephrosclerosis of renal parenchyma macroscopically, Stage 1 nephrosclerosis was identified in one case (4.4%; 95% CI = 0–22.7) of a G I tumour. Stage 2 nephrosclerosis was found in 11 carcinoma cases (47.8%; 95% CI = 29.2–67.0): G I tumours in two cases, G II in eight cases, and G III in one case respectively. Stage 1 nephrosclerosis was found in 11 cases as well (47.8%; 95% CI = 29.2–67.0), G I in three cases, G II in seven cases, and G III in one tumour case. The stages of microscopic nephrosclerosis are presented in Table 2.1.5.1. The thickness of the neoplasm capsule ranged from 0.3 to 1.6 mm.

When examining kidneys with chromophobe carcinomas, papillary adenomas were identified in the surrounding tissue in three cases (13.0%; 95% CI = 3.7–33.0). Histologically, they were papillary proliferations with fibrous stroma. In two cases (8.6%; 95% CI = 1.3–28.0) they were subcapsular in the immedate vicinity of the tumour (Image 2.1.4.2.); in one case (4.4%; 95% CI = 0–22.7), it was diagnosed as subcapsular, outside the tumour.

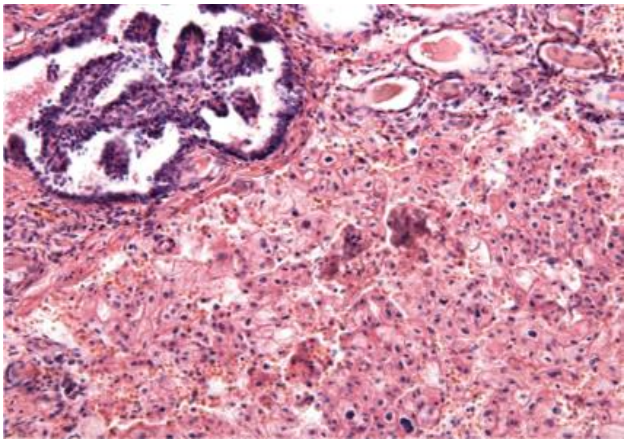


Image. 2.1.4.2. **Chromophobe renal cell carcinoma with a papillary adenoma focus in the tumour capsule. H&E, 200× magnification**

In two cases (8.6%; 95% CI = 1.3–28.0) they were located in the sclerotically changed (Stage 3 nephrosclerosis) stroma.

When examining chromophobe carcinomas, clear cell carcinomas were identified in the adjacent tissue in two cases (8.7%; 95% CI = 1.3–28.0). Oncocytary adenomas were diagnosed in five cases (21.7%; 95% CI = 9.2–42.3).

2.1.5. Angiomyolipomas

Of the 304 renal tumours analysed, six renal tumours were classified as AML comprising 2.0% (95% CI = 0.8–4.3) of all the renal tumours that were examined. The female to male ratio was 1:5; the average age of the patients was 37.5 ± 7.5 years.

Morphologically, the tumour had tissue structures of three different mesenchymal origins: those of adipose tissue, vascular, and smooth muscle *(*Image 2.1.5.1.).

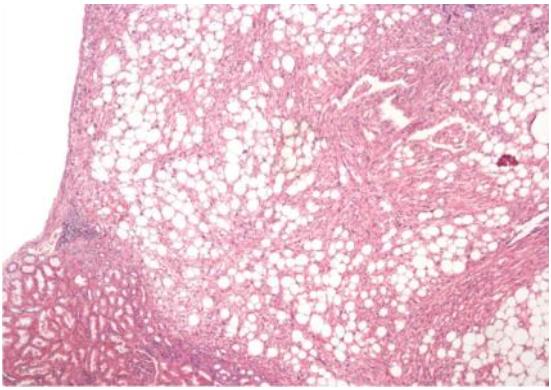


Image. 2.1.4.2. **Angiomyolipoma with three components. H&E, 40× magnification**

When examining the kidneys macroscopically, Stage 1 nephrosclerosis was present in four cases, and Stage 2 nephrosclerosis in two cases. When examining renal tissue outside the tumour and its capsule microscopically, unchanged renal parenchyma was identified in three cases. Stage 2 nephrosclerosis was identified microscopically in two cases, and Stage 3 in one case respectively.

Table 2.1.5.1. summarises the results regarding the parameters of the identified tumours that were analysed.

Table 2.1.5.1.

Summary of the examined parameters of the identified renal tumours

Histological type of the tumour	Number and relative incidence (%)	Breakdown of tumours by grade of malignancy incidence (%); (95%CI)	Stages of macroscopic nephrosclerosis (number) incidence (%); (95%CI)	Stages of microscopic nephrosclerosis (number) incidence (%); (95%CI)	Tiny tumours found in adjacent tissue (number) incidence (%); (95%CI)
Oncocitary adenomas	30 (9.9%)	non-malignant tumours	Stage 1.–13 43.4%; (27.4–60.8) Stage 2.–9 30.0%; (16.5–48.0) Stage 3.–7 23.3%; (11.5–41.2) Stage 4.–1 3.3%; (0–18.1)	Stage 0.–7 23.8%; (11.5–41.2) Stage 1.–8 26.7%; (14.0–44.7) Stage 2.–8 26.7%; (14.0–44.7) Stage 3.–7 23.8%; (11.5–41.2)	Hybridtumours-2 6.7%; (0.8–22.4) PA-5 16.7%; (6.9–34.0) RCCC-1 3.3%; (0–18.1) AML-1 3.3%; (0–18.1)
RCCC	206 (67.8%)	G I-71 34.5%; (28.3–41.2) G II-89 43.2%; (36.6–50.0) G III-46 22.3%; (17.2–28.5)	Stage 1.–107 51.9%; (45.2–58.7) Stage 2.–60 29%; (23.3–35.7) Stage 3.–32 15.5%; (11.2–21.2) Stage 4.–5 2.5%; (0.9–5.7) Stage 5.–1 2.1%; (0–3.0)	Stage 1.–73 35.5%; (29.2–42.2) Stage 2.–53 25.7%; (20.2–32.1) Stage 3.–80 38.8%; (32.4–45.6)	PA-29 14.1%; (9.9–19.5) RCCC-26 12.6%; (8.7–17.9) AML-3 1.5%; (0.3–4.4) OA-3 1.5%; (0.3–4.4)

Table 2.1.5.1. continued

Histological type of the tumour	Number and relative incidence (%)	Breakdown of tumours by grade of malignancy incidence (%); (95%CI)	Stages of macroscopic nephrosclerosis (number) incidence (%); (95%CI)	Stages of microscopic nephrosclerosis (number) incidence (%); (95%CI)	Tiny tumours found in adjacent tissue (number) incidence (%); (95%CI)
Papillary renal cell carcinoma	22 (7.2%)	G I-4 18.2%; (6.7–39.1) G II-15 68.2%; (47.2–83.8) G III-3 13.6%; (3.9–34.2)	Stage 0.–4 18.2%; (6.7–39.1) Stage 1.–7 31.8%; (16.2–52.9) Stage 2.–11. 50.0%; (30.7–69.3) Stage 3.–4 18.2%; (6.7–39.1)	Stage 1.–8 36.4%; (19.6–57.1) Stage 2.–3. 13.6%; (3.9–34.2) Stage 3.–11 50.0%; (30.7–69.3)	PA-10 45.5%; (26.9–65.4)
Chromophobe renal cell carcinoma	23 (7.6%)	G I-6 26.1%; (12.3–46.8) G II-15 65.2%; (44.8–81.3) G III-2 8.7%; (1.3–28.0)	Stage 1.–11 47.8%; (29.2–67.0) Stage 2.–11 47.8%; (29.2–67.0) Stage 3.–1 4.4%; (0–22.7)	Stage 0.–3 13.1%; (3.7–33.0) Stage 1.–3 13.1%; (3.7–33.0) Stage 2.–7 30.3%; (15.0–51.1) Stage 3.–10 43.5%; (26.0–63.0)	PA-3 13.1%; (3.7–33.0) OA-5 21.6%; (9.2–42.3)
AML	6 (2.0%)	non-malignant tumours	Stage 1.–4 66.7%; (25.6–90.8) Stage 2.–2 33.3%; (9.3–70.4)	Stage 1.–3 50.0%; (18.8–81.2) Stage 2.–2 33.3%; (9.3–70.4) Stage 3.–1 16.7%; (1.1–58.2)	was not determined

Abbreviations used in the table: G I – small nuclei up to 10 mkm in size; G II – nucleus with little polymorphism up to 15 mkm in size, visible nucleoli in high magnification (400×); G III – nucleus with expressed polymorphism up to 20 mkm, nucleoli is visble at 100× magnification; PA – papillary adenoma; RCCC – renal clear cell carcinoma; AML – angiomyolipoma; OA – oncocitary adenoma.

When collecting kidney surgery material, in 29.0% of the cases, other renal neoplasms were also identified. There was no mathematical correlation between the incidence of neoplasm findings and the histological type of the tumour, $p > 0.05$. A correlation between the grade of tumour malignancy and the incidence of neoplasm findings was not found either, $p > 0.05$. A positive correlation between the incidence of adenoma findings and the stage of macroscopic nephrosclerosis was found, $R = 0.3$, $p < 0.01$. A moderately close correlation was found between papillary adenoma findings and cystic changes in the collecting ducts (Spearman's coefficient $R = 0.52$, $p = 0.01$).

In comparison with the control group that comprised 269 section cases without nephrosclerosis in which four renal neoplasms were identified by the author (in three cases, histologically they were of metastatic origins, and in one case the neoplasm was a RCCC), neoplasms in kidneys with pre-existing tumours were 92 times more common than in the control group.

2.2. The Link between Nephrosclerosis of Various Origins and Renal Tumours

107 section and surgery cases were analysed with Stages 2, 3, 4 and 5 macroscopic nephrosclerosis. The number of males and females was 51 (47.7%; 95% CI = 38.5–57.0) and 56 (52.3%; 95% CI = 43.0–61.6) respectively (Table 2.2.1.). The average age was 64.5 ± 1.0 years. The distribution of the stages of severity of the macroscopic nephroscleroses among females and males is presented in Table 2.2.1.

Table 2.2.1.

Stages of severity of macroscopic nephroscleroses and their distribution among males and females

Gender	Stage of nephrosclerosis				Total
	2	3	4	5	
Males	11	21	14	5	51
Females	8	29	14	5	56
Total	19	50	28	10	107

There was no correlation between age indicators, gender and the stages of severity of nephrosclerosis. The kidney weight indicators were as follows: the average weight of the kidney was 137 ± 14.5 grams, with 50 grams as the lowest weight and 950 grams as the highest weight. The most frequently identified type of nephrosclerosis was that of vascular origins.

2.2.1. Nephrosclerosis of Vascular Origins

Cicatricial changes in the kidneys of vascular origins were identified in 54 cases, comprising 50.5% (95% CI = 41.1–59.8) of the material examined. Vascular nephrosclerosis of various degrees was found in 28 (51.8%; 95% CI = 38.9–64.6) males and in 26 (48.2%; 95% CI = 35.4–61.2) females. The average age was 66.12 ± 1.2 years. Analysis of variance (ANOVA) showed that there were no significant age differences between stages of severity of vascular nephrosclerosis with a 95% probability level with a p value of 0.764 and an actual Fisher value of F = 0.271 with a factor group homogeneity p value of 0.446. Changes of the following two types were characteristic of nephrosclerosis of macroscopically vascular origins: focal cicatricial changes that looked like retracted scarred areas on the kidney surface, as well as diffuse

granularity of the renal cortex *(*Image 2.2.2.1.) in bluish-pink (‘the red granulation’).

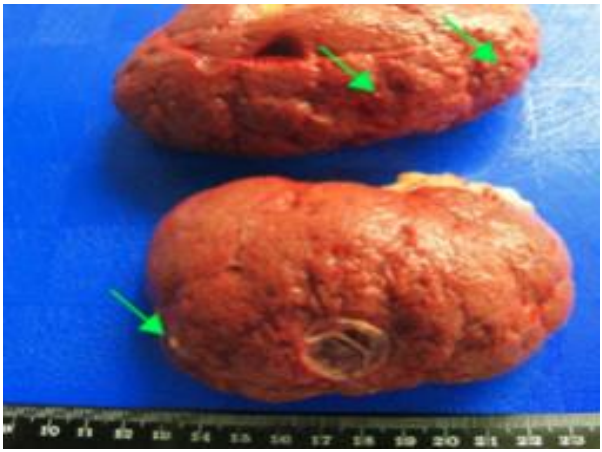


Image. 2.2.1.1. **Macroscopic Stage 3 nephrosclerosis of vascular origins with a solitary cyst. The kidney surface is granular with tiny tumour foci (indicated by the small arrows)**

Most often, the weight and dimensions of the kidney were unchanged. The average weight of the kidney was 115 ± 2.44 grams. The lowest kidney weight was 80 grams. The stages of severity of nephrosclerosis of macroscopically vascular origins were distributed as follows: there were ten cases with Stage 2 (18.5%; 95% CI = 10.2–31.0), 35 cases with Stage 3 respectively (64.8%; 95% CI = 51.5–76.2), and nine cases with Stage 4 (16.7%; 95% CI = 8.8–29.0).

Histologically, in all cases, Stage 3 sclerotic changes were identified in low-caliber arterioles and arteries. In the cases of cicatricial changes, tapered scars in the renal cortex were observed microscopically.

Neoplasms were found in 34 cases (63.0%; 95% CI = 49.6–74.6) of nephrosclerosis of vascular origins. Papillary adenomas (Image 2.2.1.2.) were diagnosed in 23 (42.6%; 95% CI = 30.3–55.9) vascular nephrosclerosis cases.

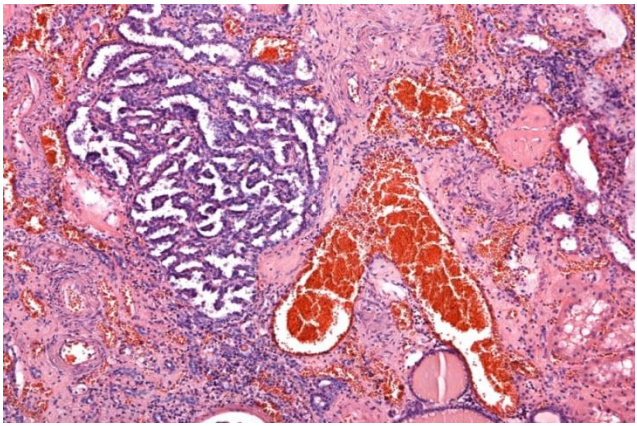


Image 2.2.1.2. **Papillary adenoma with tissue changed by Stage 3 nephrosclerosis next to it. H&E, 100× magnification**

The average age of the patients was 67.3 ± 2.2 years. In percentages, the distribution among male and female patients was 51.9% and 48.1% respectively. Comparing the average age indicators of the two samples, age indicators did not differ significantly with a 95% probability interval with an actual p value of 0.765.

In the kidneys with papillary adenomas, the severity of macroscopic nephrosclerosis was as follows: Stage 3 was identified in 18 cases (78.3%; 95% CI = 57.7–90.8), and Stage 4 in five cases (21.7%; 95% CI = 9.0–42.0). In all the cases, Stage 3 microscopic nephrosclerosis was identified. The average weight of the kidney was 111.6 ± 4.7 grams. The papillary adenomas were located in the renal cortex; most of them in the subcapsular area of the renal cortex. Stage 1 inflammation was identified adjacent to the papillary adenomas in the renal tissue in 31.8%, Stage 2 in 40.9%, and Stage 3 in 27.3% of the cases. In all cases, vascular sclerosis was also found. Small cystic changes in the renal tubules were found in

27.3% of the cases. In 22.7% of the cases, there were papillary adenomas with a multilocular growth pattern. Oxalate crystals were found in 17.4% of the cases.

In the cases when multilocular adenoma growth patterns were identified, Stage 4 macroscopic nephrosclerosis was identified in five cases and Stage 3 in four cases. It must be noted that there was a direct correlation between the severity of macroscopic nephrosclerosis and the multilocularity of papillary adenoma, R = 0.458 with a 95% probability level.

RCCC were identified in five cases, 9.3% (95% CI = 3.6–20.3) of all the examined material with vascular nephrosclerotic changes. In these cases, the average age of the patients was 62 ± 5 years. In all cases, renal clear cell tumours were found in males. The severity of macroscopic nephrosclerosis was as follows: Stage 4 in four cases (80.0%) and Stage 3 macroscopic nephrosclerosis in one case (20.0%). All the cases showed Stage 3 microscopic nephrosclerosis. In 20.0% of the cases, there were small cystic changes in the adjacent tissue. In 80.0% of the cases, there was Stage 3 inflammation, whereas in 20.0% of the cases, there was Stage 1 inflammation. Oxalate crystals were not found. The average weight of the kidneys was 95.0 ± 7.58 grams. In terms of localisation, RCCC proliferations were located in the renal cortex.

A solitary renal fibrous tumour was found in four cases, or 7.4% (95% CI = 2.4–18.1). The average patient age indicators were 72.0 ± 5.49 years. The male to female ratio was 3:1. The average weight of the kidneys was 121 ± 7.46 grams. Macroscopically, the severity of nephrosclerosis was as follows: Stage 2 in 25.0% (n = 1) and Stage 3 in 75.0% (n = 3) of the vascular nephrosclerosis cases.

Stage 1 microscopic nephrosclerosis predominated the material in 75.0% of the cases, and Stage 2 nephrosclerosis in 25.0% of the cases. In 75.0% of the cases, tumours were localised subcapsularly in the renal cortex layer. In 75% of the cases, the severity of the inflammation corresponded with Stage 1, whereas in 25% of the cases, inflammation had reached Stage 2.

2.2.2. Hydronephrosis

Hydronephrotic changes in the kidneys were found in 23 (21.5%; 95% CI = 14.7–30.3) of all the nephrosclerotically changed kidneys *(*Image 2.2.2.1.). The differences between the average ages of the patients in the various nephrosclerosis severity groups using an ANOVA test were not significant, with an F value of 0.336, an actual p value of 0.799 and a nephrosclerosis group homogeneity p value of 0.628 with a 95% probability level. The average age of the patients in this group was 64.0 ± 1.9 years; the youngest patient was 48 years old, the oldest was 78. The gender distribution was as follows: males in eight cases (34.8%; 95% CI = 18.7–55.2) and females in 15 cases (65.2%; 95% CI = 44.8–81.3). The average male and female age indicators were as follows: 68.2 ± 3.2 years for males, 61.7 ± 2.3 years for females.

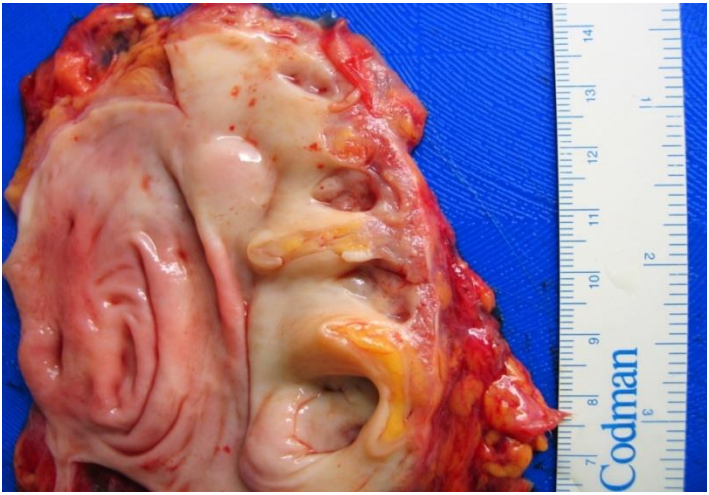


Image 2.2.2.1. **Kidney stone disease with hydronephrosis. Cystic dilatation of the renal pelvis with cortical atrophy**

In a cross-section, the renal pelvis and calyces were distinctly diluted, whereas the renal parenchyma was pronouncedly thin. The average weight of the kidneys was 89.0 ± 4 grams; the minimal weight of the kidneys was 50 grams. The severity of macroscopic nephroscleroses in hydronephrotically changed kidneys was distributed as follows: Stage 2 nephrosclerosis in one case (4.4%; 95% CI = 0–22.7) of all the hydronephrotically changed kidneys, Stage 3 in five cases (21.7%; 95% CI = 9.2–42.3) of the examined material, Stage 4 in 11 cases (47.8%; 95% CI = 29.2–67.0), and Stage 5 in six cases (26.1%; 95% CI = 12.3–46.8).

Examining the material histologically, Stage 3 nephrosclerotic changes in the interstitium with massive fibrosis of the interstitium and atrophy of renal tubules was observed in all the cases (Image 2.2.2.2.).

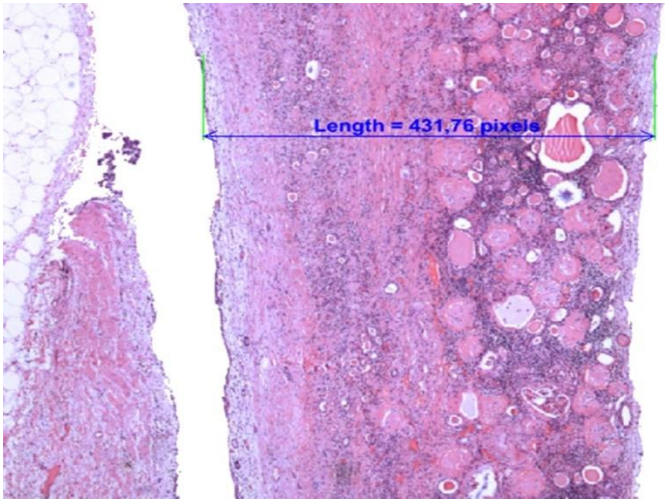


Image 2.2.2.2. **Hydronephrosis with Stage 3 fibrosis of the interstitium, glomerulosclerosis, chronic inflammation of intense nature and pronounced atrophy of the renal parenchyma (the blue arrow). H&E, 40× magnification**

In 39.1% cases (95% CI = 22.1–59.3), tumours were found in kidneys with hydronephrosis. By morphologic type there were five papillary adenomas

(21.6%; 95% CI = 9.1–42.2), two clear cell carcinomas (8.7%; 95% CI = 1.3–28.0), two solitary renal fibroid tumours (8.7%; 95% CI = 1.3–28.0). The average age of the patients in this group was 67.2 ± 5 years. Papillary adenomas were found in three males and in two females. Mutually independent samples *t*-test showed that at a 95% probability level, significant age differences did not exist between the age indicators of patients with papillary adenomas and the average age indicators in groups with hydronephrosis. The actual p value was 0.780, with an actual t value of 0.280.

The distribution of the severity of macroscopic nephroscleroses in papillary adenoma cases was as follows: Stage 4 nephrosclerosis in two cases (40.0%), Stage 5 in three cases (60.0%).

Severe nephrosclerotic changes that corresponded with kidney shrinkage were also found in histologically wide fields of view. Cystic changes in the renal tubules were also very pronounced in all the cases. Nephrosclerosis in conjunction with papillary adenomas was histologically very highly pronounced – Stage 3 – in all the cases. There was Stage 3 (100.0%) inflammation in the adjacent tissue and vascular wall sclerosis (100.0%); small cystic changes in the tubules were observed in 50.0% of the cases, whereas a tumour with a multilocular growth pattern was found in 80.0% of the cases.

RCCC in kidneys with hydronephrosis were identified in two cases (8.7%; 95% CI = 1.3–28.0). The average age indicators were 74.5 ± 1.5 years; there was one male and one female among the patients. In both cases, there was Stage 4 macroscopic nephrosclerosis, while microscopic nephrosclerosis was in Stage 3. In terms of localisation, both clear cell tumours were located in the renal cortex area. The following changes were highlighted in the tissue adjacent to the clear cell carcinoma foci: in both cases neoplasm foci were adjacent to tissue changed due to microscopic Stage 3 nephrosclerosis.

Solitary renal fibroid tumours were found in two cases (8.7%; 95% CI = 1.3–28.0) in kidneys with nephrosclerosis caused by hydronephrosis. The

tumours were found in a male and in a female aged 66 and 65 respectively. The weight of the kidneys was 80 and 95 grams, and they corresponded to macroscopic Stage 4 nephrosclerosis. The neoplasms were located in the renal cortex, sharply demarcated from the surrounding tissue.

2.2.3. Nephrosclerosis of Pyelonephritic Origins

Nephrosclerosis of this origin was found in 24 cases (22.4%; 95% CI = 15.1–31.3). The average age of the patients was 62.2 ± 1.0 years; the youngest was 44 years old and the oldest was 81 years old. When analysing the relationships between the age of the patients and the severity of macroscopic nephrosclerosis using an ANOVA, there was no relationship between the patients' age and the severity of nephrosclerosis, with an actual p value of 0.233, F = 1.448 and a nephrosclerosis group homogeneity p value of 0.375. The number of males in the pyelonephritic nephrosclerosis group was 11 (45.8%; 95% CI = 27.9–64.9), while the number of females was 13 (54.2%; 95% CI = 35.1–72.1). The female-male age difference was not significant, with an actual p value of 0.188. The average weight of the kidneys was 107.9 ± 5.74 grams. The smallest kidney weighed 60 grams, whereas the biggest kidney weighed 135 grams. Macroscopically, the dimensions of the kidneys were most often reduced. The renal surface had extensive retracted blue-pink scars, and the renal surface was also granular (Image 2.2.3.1.).

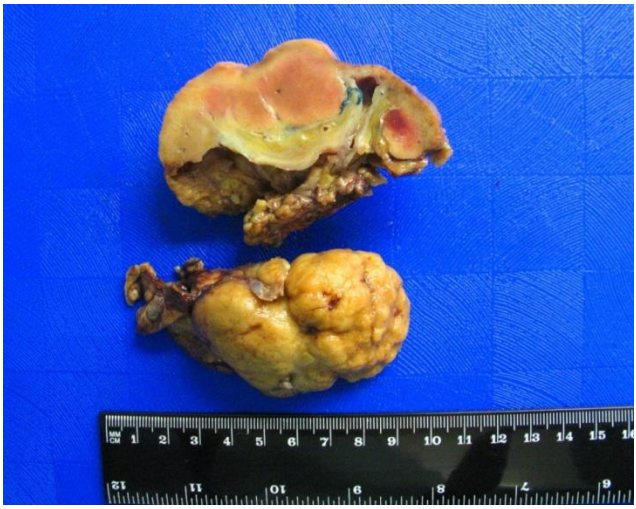


Image 2.2.3.1. **Kidney shrinkage of pyelonephritic origins**

The severity of macroscopic nephrosclerosis was distributed as follows: Stage 2 nephrosclerosis in eight cases (33.3%; 95% CI = 17.8–53.4), Stage 3 in nine cases (37.5%; 95% CI = 21.1–57.4), Stage 4 in four cases (16.7%; 95% CI = 6.1–36.5), and Stage 5 (pyelonephritic kidney shrinkage) in three cases (12.5%; 95% CI = 3.5–31.8).

The severity of microscopic nephrosclerosis was as follows: Stage 1 in two cases (8.3%; 95% CI = 1.2–27.0), Stage 2 in 12 cases (50.0%; 95% CI = 31.4–68.6), and Stage 3 in ten cases (41.7%; 95% CI = 2.4–61.2).

The following types of tumours in pyelonephritic nephrosclerotic kidneys were found: papillary adenomas in six cases (25%; 95% CI = 11.7–45.2), RCCC in three cases (12.5%; 95% CI = 3.5–31.8), and in one case (4.2%; 95% CI = 0–21.9) there was a medullar interstitial tumour localised in the renal cortex layer.

The average age of the patients with papillary adenomas was 64.7 ± 2.0 years. In three cases, there was Stage 4 macroscopic nephrosclerosis, and in three cases, Stage 5 nephrosclerosis.

In all the cases, histologically, there was Stage 3 nephrosclerosis in the tissue adjacent to papillary adenomas. In all cases, the inflammation in the adjacent tissue had reached Stage 3 intensity, and there were also small cystic changes with oxalate crystal deposits in three cases. In 50.0% of the cases, the adenomas had multilocular growth characteristics.

RCCC was identified in three kidneys changed by pyelonephritic nephrosclerosis. These constituted 12.5% of all the cases of pyelonephritic nephrosclerosis. The average age was 62.0 ± 3.0 years; the patients included two males and one female. In all the cases, microscopically, the tissue adjacent to RCCC had Stage 3 nephrosclerosis. The tumours were localised in the renal cortex. Small cystic changes in the tubules were not found. In all cases, the nuclei were G I in terms of malignancy and there was Stage 3 inflammatory infiltration. In one case, oxalate crystal deposits were found.

2.2.4. Renal Polycystosis

Five adult-type autosomal dominant inherited renal polycystosis cases and one acquired renal cystic disease case in a patient with an anamnesis of long-term haemodialysis, kidney shrinkage and acquired renal cysts were included in this group. Due to the different disease mechanisms and morphology, the two types of polycystosis have been discussed separately in this section.

Renal adult-type polycystosis was present in five cases (4.7%; 95% CI = 1.7–10.8) of the examined renal tissue material. Macroscopically, in all the

cases, the size and weight of the kidneys were pronouncedly enlarged. The average weight of the kidney was 726 ± 104.9 grams (Image 2.2.4.1.).

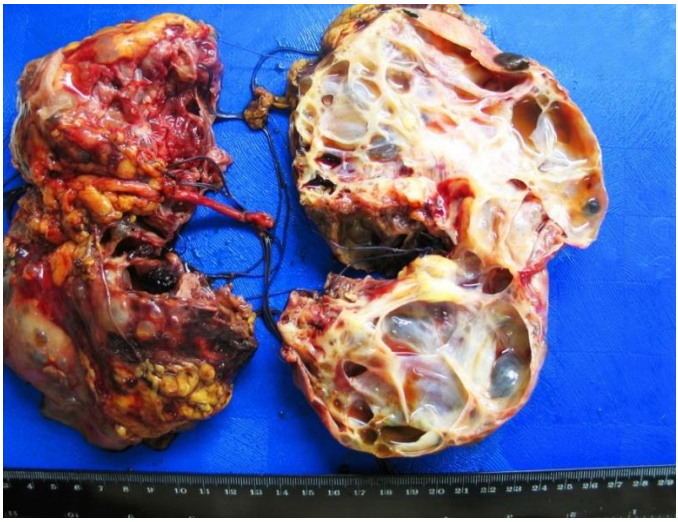


Image 2.2.4.1. **Renal polycystosis. Renal parenchyma with cysts of various sizes**

The average age of the patients was 54.4 ± 5.3 years. In an independent samples *t*-test with a 95% probability level, the average age of these patients significantly differed from the rest of the nephrosclerosis group with an actual p value of 0.025. In all cases, macroscopic Stage 4 nephrosclerosis was characteristic of adult-type polycystosis. Three males (60.0%) and two females (40.0%) had adult-type polycystosis; the average age of the males was 48.6 ± 2.6 years, while the average age of the females was 63.0 ± 12 years.

In all the cases of polycystosis, Stage 3 microscopic nephrosclerosis was found. In some cysts, there was increased epithelial proliferation with dysplastic changes in the epithelium. In two (40.0%; 95% CI = 11.6–77.1) of the five polycystosis cases, tumours were found – both were papillary adenomas, in one female and one male. The male was 53 years old; the female

was 51 years old. Neoplasms were localised in the renal cortical area. In tissue adjacent to the tumours, pronounced nephrosclerosis with oxalate crystal deposition, small cystic changes and Stage 2 inflammation were identified.

Acquired-type renal polycystosis was found in one case. The disease was diagnosed during a section performed on a male who was 74 years old, following five years of haemodialysis. The weight of the kidney was a mere 90 grams. The surface was scabrous with multiple tiny cysts of up to 6mm in diameter in the renal cortex. Macroscopically, the nephrosclerosis was in Stage 4. Hypertensive type vasculopathy and histologic Stage 3 nephrosclerosis, small cystic changes in the renal tubules and oxalate depositions were also found, as well as papillary adenomas with multilocular growth characteristics.

When the data about the diseases and neoplasms causing nephrosclerosis was collected, the following results were obtained as presented in Table 2.2.4.1.

Table 2.2.4.1.

Breakdown of diseases causing nephrosclerosis and the morphological types of tumours

Disease causing nephrosclerosis	**Morphological type of tumour**			
	Number of cases	**PA**	**RCCC**	**SFT**
Vascular diseases	54	23	5	4
Hydronephrosis	23	5	2	2
Pyelonephritis	24	6	3	0
Polycystosis	6	3	0	0
Total	107	37	10	6

Abbreviations used in the table: PA – papillary adenoma; RCCC – renal clear cell carcinoma; SFT – solitary fibrous tumour.

Table 2.2.4.2. shows the types of tumours and their incidence rates for various stages of macroscopically identified nephrosclerosis. There was a proportional moderately close correlation between the macroscopic stages of nephrosclerosis and neoplasm findings (Spearman's correlation coefficient $R = 0.596$; $p = 0.01$).

Table 2.2.4.2.

Macroscopic stages of nephrosclerosis and the incidence rates of various tumours

Neoplasm	Macroscopic stages of nephrosclerosis				Total (number)
	Stage 2	Stage 3	Stage 4	Stage 5	
PA	0	17	12	8	37
RCCC	0	5	5	0	10
SFT	1	3	2	0	6

Abbreviations used in the table: PA – papillary adenoma; RCCC – renal clear cell carcinoma; SFT – solitary fibrous tumour.

There were no significant age differences between the groups of macroscopic stages of nephrosclerosis: the actual single-factor ANOVA p value was 0.286 (except for the adult-type renal polycystosis group). There was no significant difference between groups of nephroscleroses of various pathogenetic types with tumours (the actual p value of a Kolmogorov-Smirnov test was 0.608). In all cases, there were Stages 2 and 3 microscopic nephrosclerosis in the tissue adjacent to papillary adenomas and RCCC. Adenomas and RCCC have a distinct tendency to develop in a nephrosclerotic environment. The incidence rate of neoplasms found in nephroslerotically changed kidneys was significantly higher – 56 times higher and RCCC 10

times higher in comparison to the control group comprising 269 section cases with nephrosclerotically unchanged kidneys; among the neoplasms, there was one tumour – a RCCC. In relation to nephrosclerosis, all were G I neoplasms in terms of malignancy (according to Thoenes).

2.3. Immunohistochemical Characterisation of Renal Tumours

This paper examined immunohistochemical findings of prognostic markers e-cadherin, CD-44, Ki-67 and cyclin D1, pRb, p16, in order to simultaneously identify differences in expression between tumour groups with and without nephrosclerosis, as well as to compare the marker expression in this group with that in the group of high malignancy and local spread tumours. The results that were obtained are summarised in Tables 2.3.1. and 2.3.2.

Table 2.3.1.

Review of immunohistochemical test results in control group tissue samples

Antigen	Criteria assessed	Kidneys with nephrosclerosis (n = 5)		Kidneys without nephrosclerosis (n = 5)	
		Proximal tubules	Distal tubules	Proximal tubules	Distal tubules
E-cadherin	E	–	+	–	+
	Extent (%)	0	100.0	0	100.0
	I	0	3	0	3
CD44	E	+	+	–	–
	Extent (%)	15.0	20.0	0	0
	I	1	1	0	0

Table 2.3.1. continued

Antigen	Criteria assessed	Kidneys with nephrosclerosis (n = 5)		Kidneys without nephrosclerosis (n = 5)	
		Proximal tubules	Distal tubules	Proximal tubules	Distal tubules
Ki-67	Extent (%)	0.1–0.6	3.0–5.0	0.1–0.7	1.0–3.0
Cyclin D1	E	+	+	+	–
	Extent (%)	7.0	3.0–5.0	0.5	0
	I	2	1	0	0
pRb	E	+	+	+	+
	Extent (%)	30.0	80.0	70.0	40.0
	I	3	3	1	3
p16	E	+	+	+	+
	Extent (%)	10.0	40.0	3.0	5.0
	I	1	1	1	1

Abbreviations used in the table: E – expression; I – intensity; "+" means the presence of the indicated parameter, whereas a "–" means its absence.

Table 2.3.2.

Review of the immunohistochemical results for tumours with and without nephrosclerosis, as well as for tumours with a high malignancy grade

Antigen	Criteria assessed	Types of samples assessed							
		Renal tumours with nephrosclerosis (n = 25)			Renal tumours without nephrosclerosis (n = 27)			High malignancy and stage tumours (n = 16)	
		RCCC (n=13)	PRCC (n=5)	PA (n=7)	RCCC (n=13)	PRCC (n=8)	PA (n=6)	RCCC (n=13)	PRCC (n=3)
E-cadherin	E	+	+	+	+	+	+	+	+
	Extent (%)	0–30.0	0–60.0	20.0–80.0	1.0–70.0	1.0–18.0	10.0–90.0	6.0–100.0	0–22.0
	I	3	3	2	3	1	3	3	3
CD44	E	+	+	+	+	+	+	+	+
	Extent (%)	0–100.0	0–5.0	68.0	5.0–100.0	0–80.0	0–70.0	0–80.0	20.0–80.0
	I	1	1	2	3	2	1	3	3
Ki-67	Extent (%)	1.0–16	0.6–2.0	0.4–1.0	2.0–3.4	0.3–2.5	0.4–1.0	21.0	10.0–15.0
Cyclin D1	E	+	+	+	+	+	+	+	+
	Extent (%)	15.0–65.0	12.0	4.0–5.0	9.0–11.0	11.0	4.0–5.0	30.0–90.0	40.0
	I	3	1	2	3	2	2	3	3
pRb	E	+	+	+	+	+	+	+	+
	Extent (%)	60.0–90.0	75.0–80.0	65.0–80.0	55.0–88.0	30.0–40.0	40.0–70.0	30.0–90.0	80.0
	I	3	3	2	3	2	2	3	2

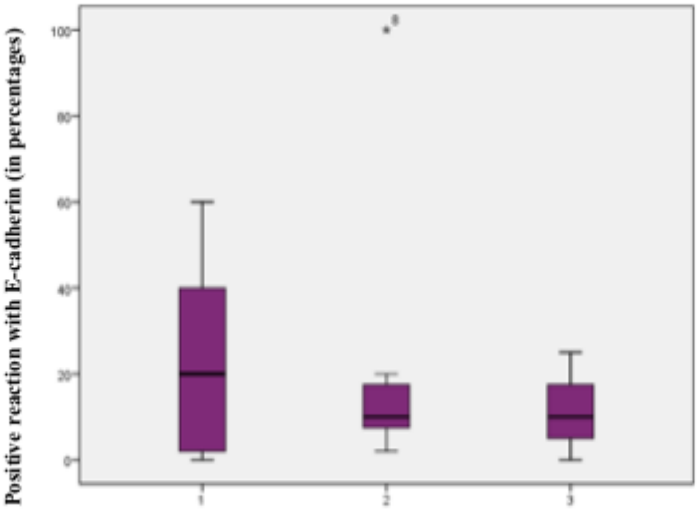
Table 2.3.2. continued

Antigen	Criteria assessed	Types of samples assessed							
		Renal tumours with nephrosclerosis (n = 25)			Renal tumours without nephrosclerosis (n = 27)			High malignancy and stage tumours (n = 16)	
		RCCC (n=13)	PRCC (n=5)	PA (n=7)	RCCC (n=13)	PRCC (n=8)	PA (n=6)	RCCC (n=13)	PRCC (n=3)
P16	E	+	+	+	+	+	+	+	+
	Extent (%)	5.0–70.0	60.0–80.0	90.0	20.0–80.0	20.0–30.0	70.0	10.0	90.0
	I	2	2	2	3	3	2	2	2

Abbreviations used in the table: E – expression; I – intensity; RCCC – renal clear cell carcinoma; PRCC – papillary renanal cell carcinoma; PA – papillary adenoma; "+" means the presence of the indicated parameter, whereas a "–" means its absence.

2.3.1. E-cadherin

Image 2.3.1.1. shows the relative extent of E-cadherin expression (% of the number of tumour cells) in groups of papillary carcinomas with and without nephrosclerosis, as well as in tumours with high grades of malignancy.



1 – papillary renal cell carcinomas with nephrosclerosis; 2 – papillary renal cell carcinomas without nephrosclerosis; 3 – high malignancy grade and stage papillary renal cell carcinomas

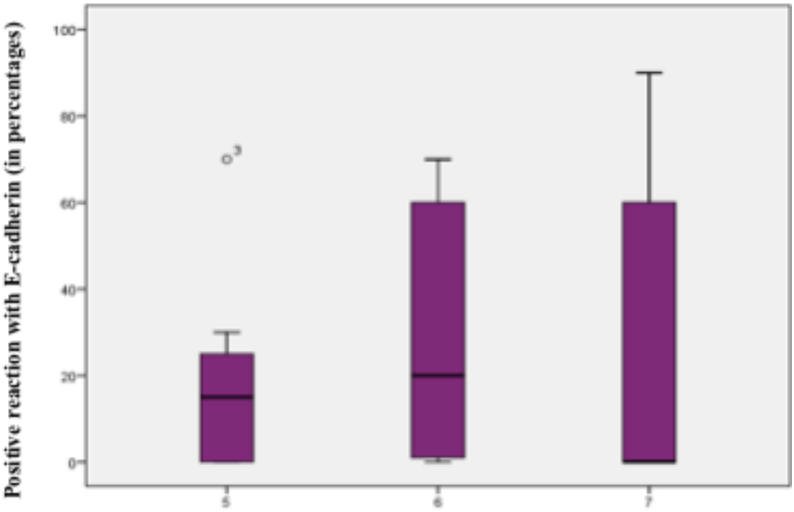
Image 2.3.1.1. **Expression of E-cadherin in papillary renal cell carcinomas. The star designates the extreme value**

There was no significant correlation between grades of malignancy of papillary carcinomas and the intensity and extent of E-cadherin expression in papillary carcinomas: $R = 0.386$; $p < 0.05$. Statistical analysis of E-cadherin expression in papillary carcinomas, depending on the grade of malignancy, stage of nephrosclerosis and the stage of local spread showed no significant differences between papillary carcinomas with nephrosclerosis, those without nephrosclerosis, as well as carcinomas of high malignancy grades and local spread, $p > 0.05$ (Fisher test, χ^2 test).

Statistically, there was no significant difference in reaction intensity in papillary adenomas with and without nephrosclerosis in a χ^2 test, 4.459 ($p = 0.216$). Statistical calculations showed no significant difference in expression intensity, with an actual χ^2 value of 5.486 ($p = 0.139$). A significant

difference in E-cadherin positivity between the two groups was not found either, with an actual Fisher test value of p = 0.383.

Image 2.3.1.2. shows E-cadherin expression in RCCC depending on nephrosclerosis, malignancy grade and local spread of the tumour. An uneven E-cadherin reaction in RCCC tumours with and without nephrosclerosis was observed.



5 – RCCC with nephrosclerosis; 6 – RCCC without nephrosclerosis; 7 – high malignancy grade and stage RCCC

Image 2.1.1.2. **E-cadherin expression in groups of RCCC. The circle designates the outlying value**

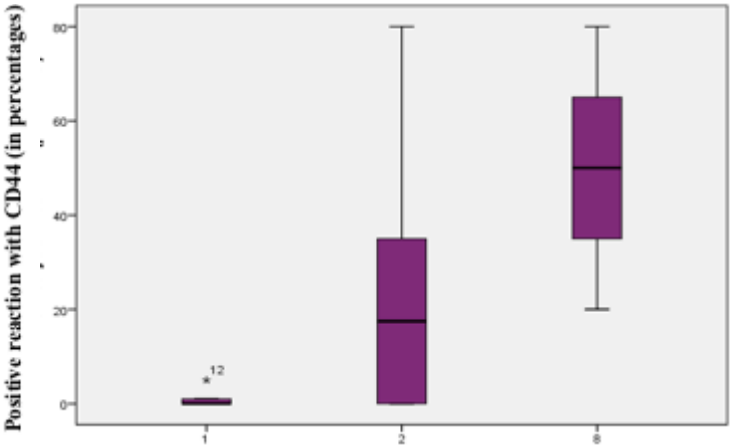
Statistical analysis of E-cadherin expression in RCCC, depending on nephrosclerosis and grade of malignancy, as well as local spread showed no significant difference, $p > 0.05$ (Fisher test, χ^2 test). High malignancy grade renal cell carcinomas reacted unevenly with E-cadherin.

No statistically significant correlation between the extent of E-cadherin expression and grade of malignancy according to Fuhrman was found, with an actual Spearman's correlation coefficient $R = -0.229$.

2.3.2. CD44

When examining renal tissue without nephrosclerotic changes as a control group, CD44 positivity in the renal tubules was not observed. In nephosclerotically changed tissue, a small increase in the intensity and extent of CD44 expression was observed in the renal tubules. A reaction of moderate and intense nature in the membranes of the tumour cells was observed in the high malignancy grade papillary carcinoma group.

Image 2.3.2.1. shows the CD44 reactivity of papillary carcinomas with and without nephrosclerosis and high malignancy groups. When comparing the groups, different reactivity with CD44 was observed among the groups.



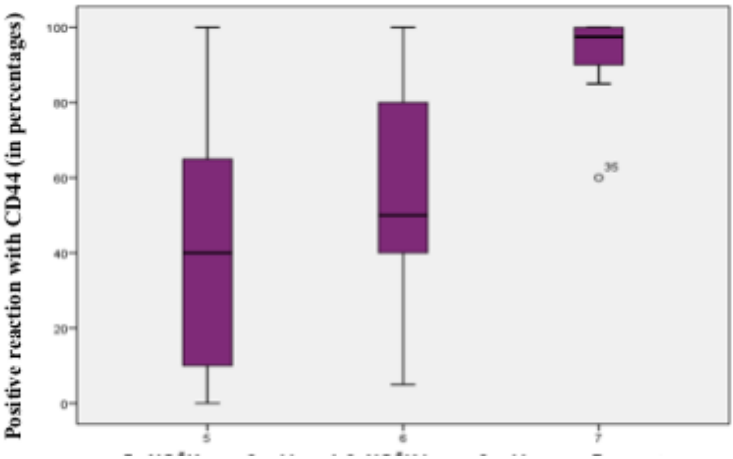
1 – papillary carcinomas with nephrosclerosis; 2 – papillary carcinomas without nephrosclerosis; 8 – high malignancy grade and stage papillary carcinomas

Image 2.3.2.1. **CD44 expression in papillary carcinomas depending on the stage and intensity of nephroscleros. The star designates the extreme value**

Analysis of CD44 expression in papillary carcinomas depending on stage of nephrosclerosis and the grade of malignancy showed no significant difference, $p > 0.05$ (Fisher test and χ^2 test). A statistically significant Spearman's correlation between the grades of malignancy of carcinomas according to Fuhrman and the extent of CD44 expression (%) must be noted, $R = 0.52$; $p = 0.05$.

There was no significant difference in positivity between papillary adenomas with and without nephrosclerosis, with an actual Fisher test value $p = 0.731$ at a significance level $p = 0.05$. There were no differences in the extent of positivity (%) and the stages of reaction intensity either, with a χ^2 test value of 2.026 ($p = 0.363$).

In clear cell carcinomas, pronounced CD44 expression was observed more frequently. CD44 reaction was vividly pronounced in the group of high malignancy grade carcinomas. Image 2.3.2.2. shows the reactivity of clear cell carcinomas with and without nephrosclerosis and those in the control group.



5 – RCCC with nephrosclerosis; 6 – RCCC without nephrosclerosis; 7 – high malignancy grade and stage RCCC

Image 2.3.2.2. **Extent of CD44 expression in RCCC tissue. The circle designates the outlying value**

When comparing the group of carcinomas associated with nephrosclerosis and the group of RCCC without nephrosclerosis, it was found that the positivity indicators did not differ significantly, with an actual Fisher test value of p = 0.5. When assessing the extent of CD44 expression in tumour cells (%) with an actual χ^2 test value of 10.53 with a p value of 0.569, reaction intensity χ^2 test value was 2.286, p = 0.515. Comparing CD44 expression in the RCCC group with nephrosclerosis and in the group of carcinomas with high malignancy grades and high stages of local spread, an actual Fisher test value of p = 0.260 was obtained; whereas, when assessing the positivity of CD44 expression in percent, an actual χ^2 value of p = 0.043 was obtained. The χ^2 test value of reaction intensity indicators was 5.660, p = 0.129.

The results of comparing the groups of renal cell carcinoma without nephrosclerosis and high malignancy grade and local spread stage were as follows: positivity Fisher test p = 0.520; extent of expression (%) χ^2 test value

p = 0.041; intensity χ^2 value p = 0.119. A statistically significant correlation between grades of malignancy according to Fuhrman and CD44 reactivity was found; Spearman's coefficient R = 0.614; p = 0.01.

2.3.3. Ki-67

In the control group, Ki-67 positivity in the proximal tubules ranged from 0.1 to 0.7% in renal tissue without nephrosclerosis. The reactivity of the cells of the distal tubules with Ki-67 ranged from 1.0 to 3.0%.

In kidneys with nephrosclerosis, a higher activity of Ki-67 proliferation in the distal renal tubules ranging from 3.0 to 5.0% was observed. By comparing the group of kidneys without nephrosclerosis and nephrosclerotically unchanged kidneys, the author found that the proliferative activity of distal tubules differed, with an actual Mann-Whitney U criterion p value of 0.008. On the other hand, the proliferative activity of the epithelium of the proximal tubules in the same groups did not differ significantly, with a Mann-Whitney U criterion p value of 0.421.

In papillary carcinomas, the extent of Ki-67 expression ranged from 0.6 to 2.0%. The statistical indicators of Ki-67 expression in groups of papillary renal cell carcinomas with and without nephrosclerosis showed a significant difference in comparison with high malignancy grade local spread stage tumours, $p < 0.05$ (the Mann-Whitney U criterion). Papillary carcinomas with and without nephrosclerosis did not show a significant difference in Ki-67 expression, $p > 0.05$ (the Mann-Whitney U criterion).

In papillary adenomas, Ki-67 expression ranged from 0.4 to 1.0% both in adenomas associated with nephrosclerosis and in those without it, and there was no statistically significant difference between them, with a Mann-Whitney U criterion Z = 1.554 (p = 0.120).

In comparison with the tumours discussed above, higher proliferative activity was characteristic of *RCCC*. In RCCC with nephrosclerosis, Ki-67 expression measured 1.6% in tumour cells, while in RCCC without nephrosclerosis Ki-67 expression was 2.0–3.4% in tumour cells. High proliferative activity was observed in RCCC with high malignancy grade and local spread stage – on average, 21.0% (95% CI = 14.2–30.1) of the tumour cells. A comparison of Ki-67 proliferative activity in the groups of RCCC with and without nephrosclerosis revealed a significant difference in expression, $p < 0.05$ (the Mann-Whitney U criterion), also when comparing these groups to high malignancy grade and local spread stage tumours, $p < 0.05$ (the Mann-Whitney U criterion).

2.3.4. Comparison of Cyclin D1, pRb, p16 Expression in Renal Tissue with and without Nephrosclerosis and in Renal Tumours

The expression of Cyclin D1 in nephrosclerotically unchanged renal proximal convoluted tubules was characterised by the presence of small foci, and this was observed in 0.5% of the cells. In nephrosclerotically changed renal collecting ducts, this was found in 3.0–5.0% of the epithelial cells, and for proximal tubules in 7.0% of the cells. A difference in cyclin D1 expression between renal proximal and distal ducts was not found ($p = 0.795$). A Mann-Whitney U test revealed a significant difference in cyclin D1 expression between nephrosclerotically changed and unchanged kidneys both in the proximal and in the distal and collecting ducts, with an actual p value of 0.009.

The expression of phosphorylated retinoblastoma protein (pRb) in renal tissue without nephrosclerosis had a low intensity reaction in the nuclei of epithelial cells of the proximal tubules, which covered 70.0% of the total number of epithelial cells. A stronger reaction (Stages 2 and 3 in intensity) was observed in the renal distal tubules. Here, positivity was observed in up to

40.0% of the cells. Statistical calculations showed a significant difference between renal proximal and distal tubules. The actual Z value of the Mann-Whitney U test was 2.522, $p = 0.012$.

In comparison with the previous group, a more intense reaction in renal proximal tubules was characteristic of pRb expression in kidneys with nephrosclerosis. As many as 30.0% of the epithelial cells were positive. Statistically, there were differences in pRb expression between kidneys with and without nephrosclerosis. The Mann-Whitney U criterion of the proximal tubules had a p value of 0.002, whereas the distal tubules had a p value of 0.003.

The expression of p16 antigen in kidneys without cicatricial changes was very diffuse. The Mann-Whitney U test did not show a statistically significant difference between the distal and proximal tubules in renal tissue without nephrosclerosis ($p = 0.079$).

The expression of p16 in the renal distal tubules with nephrosclerosis increased significantly. At the same time, an increase in p16 expression in the proximal tubules was not observed. The difference between the Mann-Whitney U criteria of these structures in the kidneys was significant, with a p value of 0.002.

A statistical comparison of the results for kidneys with and without nephrosclerosis yielded the following results: the reactivity of p16 in renal proximal epithelium did not differ significantly, with a p value of 0.546, whereas the reactivity of the epithelium of renal distal tubules showed a significant difference ($p = 0.008$).

An analysis of cyclin D1 expression in papillary carcinomas with and without nephrosclerosis did not show a significant statistical difference, with $p > 0.05$ (the Mann-Whitney U criterion, χ^2test). When comparing these groups with high malignancy grade local spread stage tumours, statistically there was a significant difference in D1 expression, $p < 0.05$ (the Mann-Whitney U criterion, χ^2test).

The extent of pRb expression in papillary carcinomas reached up to 80.0% in some areas. An analysis of pRb expression in papillary carcinomas with and without nephrosclerosis did not show a significant difference, $p > 0.05$ (the Mann-Whitney U criterion, χ^2test). When comparing these groups with high malignancy local spread stage tumours, statistical analysis showed a significant difference in expression, $p < 0.05$ (the Mann-Whitney U criterion).

Correlation calculations showed that there was a statistically significant correlation ($p = 0.01$) between malignancy grades of RCCC according to Fuhrman and the expression of pRb (Spearman's coefficient $R = 0.789$).

An analysis of p16 expression in papillary carcinomas with and without nephrosclerosis showed a significant diffference, $p < 0.05$ (the Mann-Whitney U criterion). When comparing papillary renal cell carcinomas with nephrosclerosis and high malignancy grade local spread stage tumours, statistical analysis showed a significant difference in expression, $p < 0.05$ (the Mann-Whitney U criterion).When comparing papillary renal cell carcinoma (PRCC) without nephrosclerozis and PRCC with a high malignancy grade local spread stage, the p value was found to be above 0.05: $p < 0.05$ (the Mann-Whitney U criterion, χ^2test).

Correlation analysis showed that there was a statistically significant inverse correlation $R = -0.509$ and $p = 0.05$ between the malignancy grades of PRCC according to Fuhrman and the extent of p16 expression (%).

The expression of cyclin D1 in renal papillary adenoma (PA) was focal. The relative extent of expression in PA cells was 5.0%. By comparing PA with and without nephroscleroses, the author found that there was no significant difference in cyclin D1 expression in these tumour groups with actual Z and p values as follows: $Z = 1.230$ and $p = 0.219$. The χ^2 square test comparing the indicators of reaction intensity in the tumour cells showed no significant difference ($\chi^2 = 2.026$; $p = 0.363$).

When examining PA, uneven positive pRb expression was found. In 70.0% of the cases, positive expression was observed, and its relative extent ranged from 20.0–80.0% of the cells. The indicators of reaction intensity varied as well. By comparing PA with and without nephrosclerosis, the author found that there was no significant statistical difference between the indicators of pRb expression ($Z = 0.646$; $p = 0.518$). The indicators of reaction intensity did not show any significant differences either ($p > 0.05$).

Positive expression of p16 in PA was found in 90% of the cases. Positivity ranged from 10 to 80% of the cells. Statistical calculations indicated no significant difference in p16 expression in PA with and without nephrosclerosis, with a Mann-Whitney U criterion value $Z = 0.504$ and a p value of 0.614.

In RCCC, positive immunohistochemical reaction of cyclin D1 was observed in the cells in all the cases, but the reaction intensity and extent varied. In RCCC with and without nephrosclerosis, the extent of cyclin D1 expression ranged from 15.0 – 65.0%. At the same time, in high malignancy grade renal clear cell tumours, positivity ranged from 30.0 – 90.0%.

An analysis of cyclin D1 expression in RCCC with and without nephrosclerosis showed no significant difference in expression, $p < 0.05$ (the Mann-Whitney U criterion, χ^2 test). When comparing these groups with high malignancy grade and local spread stage tumours, statistical analysis showed a significant difference, $p < 0.05$ (the Mann-Whitney U criterion, χ^2 test).

A distinct expression of pRb was observed in high malignancy grade and local spread stage RCCC. Mathematical calculations also showed a statistically significant correlation between grades of malignancy and the intensity of pRb expression ($R = 0.495$; $p = 0.001$).

A statistical analysis of pRb expression in RCCC with and without nephrosclerosis showed no significant difference in expression, $p > 0.05$ (the Mann-Whitney U criterion, χ^2 test). However, the results comparing these groups

with high malignancy grade and local spread stage tumours showed a statistically significant difference in expression, $p < 0.05$ (the Mann-Whitney U criterion).

In samples stained with p16, the extent of positive expression in RCCC with and without nephrosclerosis ranged from 5.0–80.0%. The prevalence of negativity indicators was very high in the high malignancy grade RCCC group. An inversely proportional correlation was found between p16 expression and the malignancy grades of RCCC according to Fuhrman, with a Spearman's correlation coefficient $R = -0.233$.

A statistical analysis of p16 expression in RCCC with and without nephrosclerosis showed a significant difference, $p < 0.05$ (the Mann-Whitney U criterion, χ^2 test). When comparing RCCC and high malignancy grade and local spread stage tumours, statistical analysis showed a significant difference, $p < 0.05$ (the Mann-Whitney U criterion, χ^2 test). When comparing RCCC without nephrosclerosis and RCCC with high malignancy grade, statistical analysis showed no significant difference in p16 expression, $p > 0.05$ (the Mann-Whitney U criterion, χ^2 test).

3. DISCUSSION

Renal tumours in the early stages were seen in the morphological material very rarely. Unique material that reflected the initial changes in renal tissue was obtained in Latvia. Very little data characterising peritumoral tissue structures were found in the relevant literature that would allow for systematising changes in renal tissue and classifying the stages of severity of the damage. Severity criteria were developed from scratch or adopted from changes of a cognate nature.

In some studies, the authors pointed out a link between tumours and background diseases [*Ganzen et al., 1989*]. End-stage renal disease has been clearly defined (*ESRD*) and the definition is based on changes in the glomerular filtration rate, as the parameter decreases to below 15 ml/min/1.73 m² [*Furness et al., 2003; Michael, 2007*]. Several signs of the disease are varied and depend on the disease-inducing factor, including diabetes mellitus, interstitial nephritis and others [*Riede et al., 2004*]. Changes affect all structures of the kidney [*Michael, 2007*]. Only a small number of the cases included in the present study corresponded to ESRD. The Banff classification [*Colvin et al., 2007*], that was designated for describing damage to kidney transplant (rejection) and shows microscopic changes in the kidneys was used in order to histologically determine the nature and stages of severity of renal tissue damage and their potential link to tumour formation, although some of the criteria were difficult to reproduce (a risk of different interpretations exists) with a *kappa degree* of 0.195–0.375 [*Serón et al., 2002; Furness et al., 2003*]. The microscopic signs of nephrosclerosis do not fully represent the extent of the process. Therefore, the author of the present paper developed severity criteria for macroscopic changes in the kidneys [*Sperga et al., 2009*]. The authors focused on groups of diseases that cause scarring. For example, in a study comprising 150 cases of renal cell carcinoma, in 64.7% of the cases, the

patients clinically had long-term anamnesis of a disease that was morphologically characterised by nephrosclerosis. In 26.9% of the cases, it was arterial hypertension and diabetes mellitus. Kidney stone disease and chronic pyelonephritis ranked second (17.9% of the cases). In this case, the authors did not indicate how extensive and severe the background changes had been [*Ganzen et al., 1989*].

The author's aim was to identify what changes to renal tissue structures were related to tumour formation. In the present study, 304 renal tumour cases were examined, and the severity of nephrosclerosis was defined both macroscopically and microscopically [*Sperga et al., 2009*]. Papillary renal cell carcinomas had the most pronounced relationship with nephrosclerosis (in 50.0% of the cases, the carcinomas had severe nephrosclerotic background changes). In the literature, there was data that highlighted high incidence rates of papillary renal cell carcinoma in kidneys with ESRD. In the literature, specifically in kidneys with nephrosclerosis, tumours of all histological types were found most often *[Hughson et al., 1996; Ikeda et al., 2002*]. Tumours – RCCC, chromophobe renal cell carcinoma, oncocytoma – were mostly found in kidneys with Stages 1 and 2 macroscopic nephrosclerotic changes. These results were not contrary to studies that specified that in 82.7% of the cases, renal cancers had been observed to have nephrosclerotic changes [*Ganzen et al., 1989*]. Background changes in the kidneys and the relationship between them and renal tumours have been mentioned in other publications as well [*Budin et al., 1984; Hughson et al., 1996*]. It must be noted that the author found no high malignancy grade tumours in any of the cases of severe nephrosclerosis (that corresponded to ESRD changes). Severe or end-stage changes in the kidneys were not related to a higher tumour stage than pT1. It is likely that renal cell carcinomas associated with ESRD might have a less aggressive biological potential. The author found partially similar conclusions in publications as well; however, renal cell carcinomas with these background

changes that progress in an aggressive manner and form metastases have also been described [*Ogata, 1990; Tickoo et al., 2006*].

When examining 304 renal tissue samples with tumours, other neoplasms and dysplastic changes in the epithelium of renal tubules were also found in 46.7% of the cases. In 1994, Mourad and colleagues described dysplastic changes in the epithelium of renal tubules around the foci of renal cell carcinomas. They found such changes in 30 cases out of 110 renal tissue samples [*Mourad et al., 1994*]. Changes of a similar nature were observed in patients with ARCD receiving kidney replacement therapy with haemodialysis [*Hughson et al., 1980*]. Also, in the present study, foci of epithelial dysplasia were most often found in sclerotically changed renal tissue regions adjacent to renal tumours. When focusing on neoplastic changes in these areas and comparing them to the incidence of neoplastic changes in other areas, the role of nephrosclerosis in the tumour formation process should be discussed in greater detail. Morphologically, these changes around the tumour corresponded to ESRD. There was a moderately close proportional correlation between the macroscopic stages of nephrosclerosis severity and neoplasm findings (Spearman's correlation coefficient $R = 0.596$; $p = 0.01$), which suggests that the risk of tumour formation is greater in extensive areas of cicatricial changes. There was a moderately close correlation between cystic changes in renal tubules and renal papillary adenomas (Spearman's coefficient $R = 0.52$; $p = 0.01$). In comparison to papillary adenomas, there was a weaker relationship between RCCC and small cystic changes in renal ducts.

The author found that tumour incidence was 56 times higher in tumour groups with nephrosclerosis than in the control group of nephrosclerotically unchanged kidneys. In the scientific literature, the risk of renal tumours was high in the case of two severe interconnected kidney pathologies – ESRD and ARCD [*Woldu et al., 2014*]. The development of the disease was related to the duration of haemodialysis. As early as after five to ten years of haemodialysis,

ARCD was found in 60–90% of the patients [*Matson, 1990*]. The incidence of renal cell carcinoma in the ARCD group was registered six times more often than in the group with ESRD. In this group, patients with tumours were 10 to 12 years younger [*Hughson et al., 1986; Port et al., 1989; MacDougall et al., 1990; Levine et al., 1991*]. Renal cell carcinomas were found in 4.2% of the ESRD cases [*Denton et al., 2002; Doublet et al., 1997*]. Renal tumour incidence (both benevolent and malignant) in the study group comprising 107 nephrosclerosis cases increased fifty-six fold. Such results must be assessed critically, because the study group was small and Stage 5 nephrosclerosis was identified by the author and observed in conjunction with renal diseases of vascular origins and caused by pyelonephritis corresponding with ESRD. There was found a significant correlation between the stages of severity of nephrosclerosis and the incidence of neoplasm findings. Several authors pointed out the presence of oxalate crystal deposits in tumour tissue that were not related to necrosis or the proliferative activity of the tumour. The author considered oxalate crystal findings highly relevant, because the extent of their deposition correlated with the duration of renal insufficiency [*Sule et al., 2005*]. Oxalate crystals are secreted in the kidneys during physiological processes, and their concentration in plasma increases with increasing uremia [*Michael, 2007*]. Presence of oxalate crystals in nephrosclerotically changed renal tissue was found in 23.4% of the cases. This indicates that the functions of the majority of the nephrosclerotically changed kidneys analysed during the study were still being compensated. Thus, it can be concluded that the formation of neoplastic proliferations is directly linked to specific morphological background changes in renal parenchyma rather than to the functional indicators of the kidneys. The incidence rates of the histological forms of the neoplasms were the following: papillary renal adenomas were found most often, as well as RCCC.

In the scientific literature, there was a lot of data about tumour-specific indicators and immunohistochemical indicators in relation to grades of malignancy, progress in tumour grade and metastases [*Kim et al., 2004; Kim et al., 2005; Pantuck et al., 2006; Djordjevic et al., 2007; Lane et al., 2008; Kluger et al., 2008; Bensalah et al., 2008; Inoue et al., 2012*]. In these articles, the authors highlighted the following prognostic markers: hypoxia-induced markers (HIF1alfa, VEGF-vascular endothelium growth factor), cell adhesion markers (E-cadherin, catenine-6, EpCAM), proliferation markers (Ki-67, MCM2), cell cycle regulating factors (cyclin, p27), apoptosis regulators (p53, Bcl-2), proteins involved in the mTOR (mammalian target of rapamycin) reaction chain (PTEN, akt). These immunohistochemical markers have been researched in relation to changes in tumour prognostic factors. The authors did not include in the study renal cell carcinomas of various malignancy grades and stages. Due to the case-control design used in the immunohistochemical section of the present study, the malignancy grades in groups of renal cell carcinomas and tumour stages in groups with and without nephrosclerosis had no significant statistical difference, which enabled the author to assess in detail the molecular events in renal tumour genesis attributable specifically to nephrosclerosis. RCCC did not indicate significant differences in the expression of proliferation marker Ki-67, CD44, pRB, cyclin D1 and E-cadherin in groups of tumours with and without background tissue nephrosclerosis, and neither did papillary renal cell carcinomas and papillary renal cell adenomas. A significant difference in the expression of Ki-67, CD44, cyclin D1, pRb was found by comparing renal cell carcinomas with a high malignancy grade and high stage carcinomas of a corresponding histological type with and without nephrosclerosis. In the literature, the author failed to find data which examined an immunohistochemical comparison of such tumours. By comparing low grade carcinomas to groups of high malignancy grade carcinomas, the author found that there were no significant changes in

E-cadherin expression. In the scientific literature, data pertaining to E-cadherin expression was contradictory [*Fisher et al., 1999; Heicapell, 1999; Langner et al., 2004; Gervais et al., 2007*]. The results of the present study were more consistent with the data that showed no correlation between E-cadherin and malignancy grades of renal tumours [*Katagiri et al., 1995; Jin et al., 1995; Tani et al., 1995*].

CD44 plays a highly relevant role as a transmembrane glycoprotein in the process of tumour malignancy [*Naor et al., 1997; Goodison et al., 1999*]. In the literature, there was a lot of data on changes in CD44 in relation to an increase in renal tumour malignancy grade [*Terpe et al., 1993; Heider et al., 1996; Kabiri et al., 2006*]. This was consistent with the author's observations that there was a significant increase in CD44 reactivity in high malignancy grade and high stage renal cell cell carcinomas.

It must be noted that cyclins D1 and pRb are highly important in such cell processes as hypertrophy, proliferation and apoptosis [*Shankland et al., 2000*]. The authors pointed out that cyclin D1 expression varied in tumours of various histological types *[Hedberg et al., 1999; Hedberg et al., 2002; Hedberg et al., 2003*]. On the other hand, an increase in cyclin D1 both in proximal and distal renal tubules was observed in nephrosclerotically changed kidneys, which coincided with indications in the scientific literature that the proliferative activity of the cells increased in the cases of kidney damage and hypoxic damage [*Shankland et al., 2000*]. The expression of phosphorylated retinoblastoma antigen in renal cell carcinomas has been sparsely covered in the scientific literature [*Ikuerowo et al., 2007*]. It correlated with the expression of cyclin D1. The results of the present study corresponded with the data discussed in the scientific literature.

By examining renal tumours with and without nephroslerosis, the author obtained various statistically reliable indicators of p16 expression. Of all the cell cycle markers included in the study, p16 was the only protein to show a

difference in expression when comparing renal tumours with and without nephrosclerosis. In scientific data, there were practically no publications discussing the immunohistochemical expression of p16 in these tumour groups [*Ikuerowo et al., 2007*]. The authors pointed out a possible relationship between p16 and the prognostic markers and the fact that p16 expression decreased in renal cell carcinomas. The author of the present study found a decrease in and loss of p16 reaction in high malignancy grade tumours. By comparing this group with renal tumours that formed in nephrosclerotically changed kidneys, the author found a statistically reliable difference. On the other hand, the group of tumours without nephrosclerosis showed no statistically reliable difference. The biological function of p16 is to slow down (inhibit) the cell cycle, inactivating cyclin kinases, thus not allowing them to phosphorylate the retinoblastoma antigen. An overproduction of p16 is observed in cervical carcinomas due to a functional inactivation of pRb caused by E7 protein of the human papilloma virus [*Sano et al., 1998*]. The scientific literature showed a correlation between p16 and the levels of pRb [*Benedict et al., 1999*]. Such a correlation was not convincingly found in the other studies [*Kamel et al., 1994; Furihita et al., 1995; Grce et al., 1997; Hodges et al., 2006*]. The most pronounced positivity indicators were obtained with clone 2D9A12, which indicates varying reactivity among various clones. A different expression of p16 was observed in nephrosclerotically changed and unchanged kidneys. It increased significantly in kidneys with severe nephrosclerosis both in distal and proximal tubules. To a large extent, the results corresponded to the results of other authors' studies [*Melk et al., 2004*] that researched p16 expression in relation to cell ageing processes. In the scientific literature, p16 expression increased significantly in the cortical layer of the kidneys as the age of the patients increased, and its expression was inversely proportional to Ki-67 expression in normal renal tissue. In the present study, the author interestingly found an increase in p16 expression not only in nephrosclerotically changed

areas of the kidneys, which, considering the molecular nature of the damage, can be considered a region involved in accelerated ageing, increased expression was also observed in renal tumours, in comparison to tumours without nephrosclerosis. Although the authors have noted that they have found an inverse correlation between the expression of p16 and the expression of Ki-67 in normal or 'aged' kidneys, the author of the present paper did not find such a convincing relationship. There were no differences in Ki-67 expression between renal tumours with and without nephrosclerosis. All of these were G I and T1 tumours. This fact suggests that in the case of a tumour, p16 starts to lose the cell cycle inhibition role and the proliferative activity becomes less dependent on p16. To a degree, this belief contradicts other authors' data [*Hiroyasu et al., 2002*], because the authors assign the loss of p16 in the gene locus a relevant role in cancerogenesis in renal tumours caused after oxidative stress. Other researchers pointed at a loss of heterogeneity and methylation of the p16 gene in the process of renal cell carcinoma development [*Sanz-Casla et al., 2003*].

The author of the present paper found an inverse correlation between tumour malignancy grades and the degree of p16 expression ($R = 0.509$; $p = 0.05$). As a type of tissue damage and an equivalent of tissue ageing, nephrosclerosis activates the p16 gene followed by a stopping of the cell cycle, thus the risk of the neoplastic process decreases. Nephrosclerosis together with a changed renal function, with an accumulation of metabolites and toxins in the renal interstitium are mutagenic factors that initiate tumour formation. Tumours that have developed alongside these background changes were observed to have a more pronounced p16 expression. It is possible that p16 could be one of the reasons why renal cell tumours in association with ARCD and ESRD have a better prognosis than renal cell tumours without an associated disease [*Ratcliffe et al., 1983; Gehrig et al., 1985*]. Interestingly, in the case of severe nephrosclerosis, changes in the immunohistological profile were often observed

alongside tumours, in comparison to unchanged kidneys. These changes often resembled low malignancy grade renal tumours (Ki-67, E-cadherin, CD44, cyclin D1, p16, pRB) in renal tubules as well, which did not have dysplastic changes, indicating that changes in the immunohistochemical profile take place not only in dysplastically changed renal tissue. Normal renal cells have a low proliferative activity [*Olsen et al., 1997*). These findings were compounded by an interesting study that claimed that genetic changes characteristic of papillary renal cell carcinomas had been found in renal tissue [*Hes et al., 2008*]. The authors pointed out that genetic changes taking place in renal tissue were the same as those in renal tumours during the initial stages of their development.

In the present study, the author found that regardless of the disease that caused it, nephrosclerosis was a significant factor in the process of tumour formation. High risk for tumour formation was directly related to the extent of nephrosclerosis and the stage of severity of tissue damage. Changes in the immunohistochemical profile were observed in this tissue characterised by changes in the expression of cell cycle and adhesion markers. These observations suggest significant molecular changes in the cells in the circumstances of nephrosclerotic damage. Morphologically, tumour tissue in direct relation to scarring and cystic changes in the tubules were often observed, which suggests that structural changes could also be involved in the formation process. Such tumours did not show a different immunohistochemical profile in comparison to a group of tumours of the same stage, morphological type and malignancy grade not associated with nephrosclerosis. Differences were only found in the expression of p16 – it was significantly higher in tumours associated with nephrosclerosis. It is possible that this explains why prognostic indicators are better in the early stage of disease in this group of tumours. As the functional indicators of the kidneys decline, the risk of tumour development increases manifold.

4. CONCLUSIONS

1. In cicatricial areas of the renal tissue, clear cell carcinoma was found much more frequently in comparison to the control group (26 times more frequently in kidneys with tumours and 10 times more frequently in nephrosclerotically changed kidneys).
2. In practically all the renal tumour cases, macroscopic and microscopic sclerotic changes in the renal parenchyma were found, which shows their impact on tumour formation and development, as well as a mutual impact that renal tumours and parenchyma have on each other.
3. There was no significant difference in patient ages among various groups of nephroscleroses of various stages of severity ($p > 0.05$), and comparing the difference in patients' ages among groups of nephroscleroses of various pathogenetic types, the group with adult-type polycystosis showed a significant difference in patients' ages ($p < 0.05$).
4. Papillary adenoma was the tumour type most frequently found in cicatricial renal areas. There was a positive correlation between the incidence of adenoma findings and the stages of severity of nephrosclerosis ($p = 0.01$).
5. There was an inverse correlation between the malignancy grades of RCCC and the macroscopic stages of nephrosclerosis.
6. Papillary adenoma, RCCC and papillary renal cell carcinoma were found to have the most pronounced relationship with background changes in the kidney (nephrosclerosis, inflammatory infiltration, cystic tubular dilation).
7. There was no correlation between disease causing nephrosclerosis and the morphological type or the incidence rate of tumours.

8. There was a statistically reliable difference in Ki-67 expression between RCCC associated with nephrosclerosis and RCCC without nephrosclerosis.
9. There was a significant difference in p16 expression between renal tumours associated with nephrosclerosis and tumours without nephrosclerosis.
10. There was no difference in the expression of immunohistological markers with CD44, E-cadherin, cyclin D1 and pRb in renal cell carcinomas and adenomas that were not associated with nephrosclerosis and those associated with it.

5. PRACTICAL RECOMMENDATIONS

The development of this research work has led to the following recommendations. When examining the operation and biopsy material:

1. There is a need to pay attention to primary processing stage for foci of cicatrical, cystic changes. The tissue samples must fully contain the above mentioned changes. In cases of polycystic kidneys, the samples must be taken from cyst inner surface with thickening, another shade or growths pattern.
2. By histological investigation, the data about cystic ductuli with epithelial hyperplasia and dysplasia should be noted. The displastic changes were often observed near the tumours.
3. Immunohistochemistry was not suitable for the differential diagnosis between initial neoplasia and background changes. The immunohistochemical reactions can change in nephrosclerotic area and mimic initial neoplasia.

Within the framework of the scientific paper, the following groups of patients have been identified as needing monitoring. The spreading of the tumour and lethal outcomes can be reduced by carrying out regular monitoring.

1. Patients who have had partial nephrectomies are at an increased risk of tumour formation in the scarring areas of the resection.
2. Patients with chronic renal diseases are at an increased risk of renal tumours, and it increases as a renal disease progresses. Patients with end-stage renal failure and patients with acquired haemodialysis cystic disease are at a very high risk of tumour formation.
3. In the case of kidney transplantation, the non-functioning kidney must be controlled continuously.

4. As the average age of the population increases, the number of cases of damage to the kidneys associated with extrarenal diseases is increasing. Individuals who are over sixty, as well as patients with diabetes mellitus, hypertensive disease and chronic pyelonephritis regardless of age require controlling the condition of the kidneys.

6. PUBLICATIONS

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