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REVIEW

Renal cell carcinoma – summarising overview, biomarkers, metastases and new perspectives

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ABSTRACT
Kidney carcinoma is currently the tenth most diagnosed tumour in women and the sixth in men. It makes up about 4 % of all malignant tumours. In urology, it is the third most common malignant disease. It is most often diagnosed between the ages of 40 and 60, and its incidence is still rising. Risk factors include positive family history, high blood pressure, obesity, and smoking. In examining the samples of cancer tissues, histopathological examination methods were used, including biomarkers such as LRRC3B, TCF21, or cadherins and other markers. The use of imaging methods such as computer tomography and sonography improved the detection ability of an asymptomatic kidney tumour. Due to the expansion of diagnostic methods and the introduction of new techniques in surgical treatment, the paradigm in the surgical treatment of this disease has changed in recent years. In the case of a detailed study of the intracellular structures in the carcinogenic processes, more profound knowledge about them can eliminate the need for surgical resection in the future *(Tab. 7, Fig. 2, Ref. 48)*. Text in PDF *www.elis.sk*
KEYWORDS: kidney carcinoma, RCC, biomarkers, diagnostics, surgical treatment.

Introduction

Renal cell carcinoma (RCC) is currently the tenth most diagnosed tumour in women and the sixth most common in men. The tumour incidence is constantly rising, mainly due to the diagnosis of alleged tumours found during examinations of other organs (1) (Fig. 1). The rapid increase in the disease is observed in women in general as well as in the African and African – American population (2, 3). A high incidence was recorded in Central Europe, North America, and Australia. On the other hand, a low prevalence was observed mainly in Asia and Africa (4). The values recorded in developing countries may be skewed due to the low accessibility and the level of health care in those countries. Kidney cancer can be clinically manifested by haematuria, weight loss, or palpable pain. We can also see anaemia, fever, cachexia, and hypercalcaemia (5). The classification system, called Classification of Malignant Tumours (TNM), is used in scientific and clinical practice. At present, anatomical classification systems are often used to describe kidney cancer. These systems do not describe only the size of the tumour but also its excessive growth, the relationship of the tumour to the renal pelvis–calyx system, or the vascular supply of the kidney. PADUA system or the ABC scoring system is the most used classification system. It is used when the decision needs to be made for the type of surgical procedure – radical nephrectomy vs partial nephrectomy (6, 7). Table 1 shows the classification from 2017 (8), and Table 2 shows the clinical classification system (8).

Anatomical factors (tumour size, venous invasion, renal capsular invasion, adrenal involvement, and lymph node and distant metastasis) are commonly gathered in the universally used TNM classification system. Figure 2 presents pathological changes in some of the T stages of renal cancer.

Incidence

In 2020, the estimated global number of newly diagnosed cases was 431 288. The world-standardised incidence rate (ASR-W) of kidney cancer was 4.6 per 100,000 in the population (6.1 per 100,000 males and 3.2 per 100,000 females). Cancer of the kidney accounted for 4.2% of all malignant tumours diagnosed in the Slovak Republic in men and 2.7% in women in 2010, placing them seventh (men) and eighth (women) in the ranking of malignant tumours in the country (except for non-melanoma skin tumours) (9). The incidence of kidney cancer varies considerably according to the geographical area. Three regions with the highest incidence of kidney cancer globally were Central and Northern Europe (Scandinavia), North America, and Australia. The number of new cancer cases in 2020 is provided in Table 3 (10).

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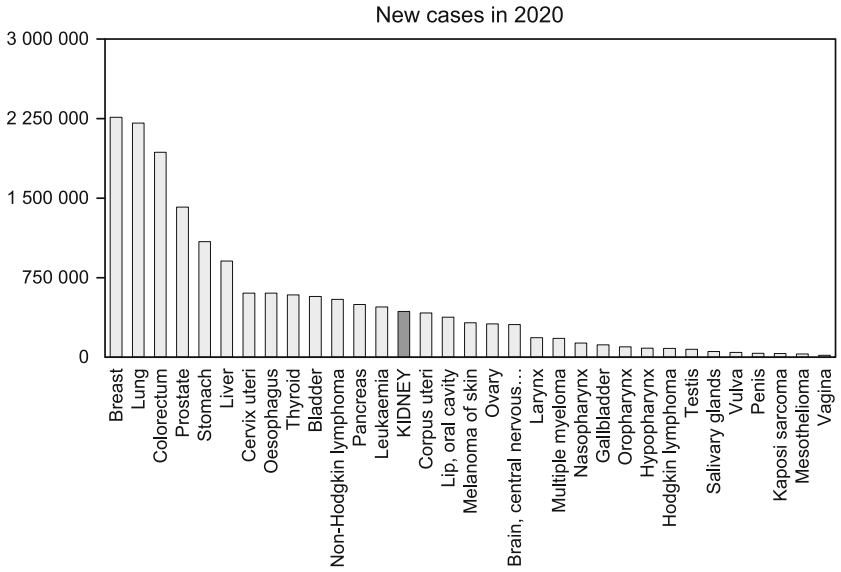


Fig. 1. Incidence of cancer types.

Risk factors

High blood pressure, obesity, and smoking increase the risk of renal carcinoma. Smoking increases the RCC risk by approximately 54 % in men and 22 % in women. There is a direct correlation between the daily number of cigarettes, smoking time, and kidney cancer incidence for both men and women. Increased risks of RCC have been reported with an increase in body weight of 5 kg/m^2. Patients with renal insufficiency and in the terminal stage of the disease are four times more likely to develop kidney cancer. The essential factors in the primary prevention of RCC are the elimination of smoking, reduction of Body Mass Index (BMI), and control of hypertension. A positive family history occurs in approximately 5–10 % of the patients with RCC. Those with a suspected hereditary RCC are recommended to undergo genetic testing (11–17).

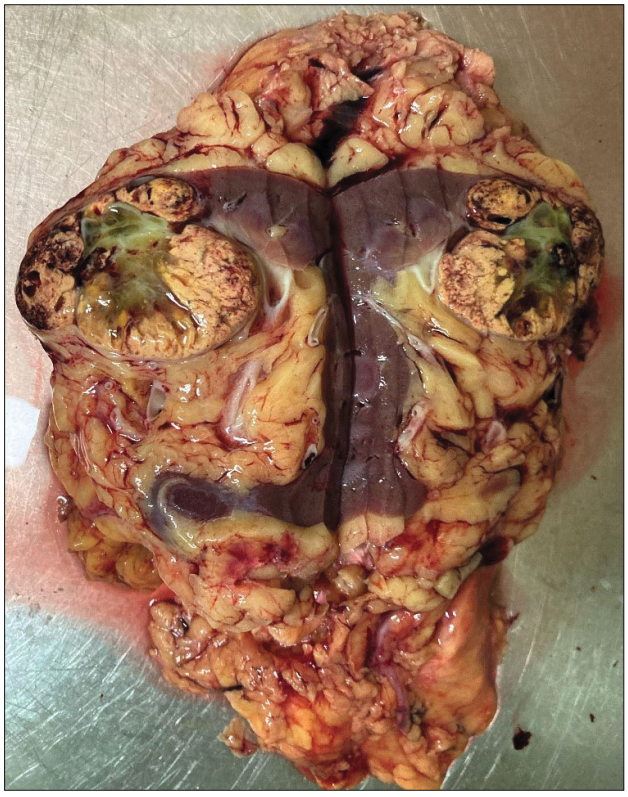
RCC and bone metastases

RCC often metastasises into lungs, bones, lymphatic nodes, liver, and suprarenal glands. The median survival in patients with metastases is eight months, with a 50 % mortality rate during the first year, and 5-years survival is 10 % (18). Bone metastases are destructive, and osteolytic lesions disrupt the integrity of bones. These patients suffer from pain, pathological fractures, nerve compression, and hypercalcemia. The pathological fractures should be managed surgically. The bone metastases most often involve the vertebrae, pelvic bones, and proximal part of the femur. The presence of metastases worsens the prognosis of patients with RCC (18).

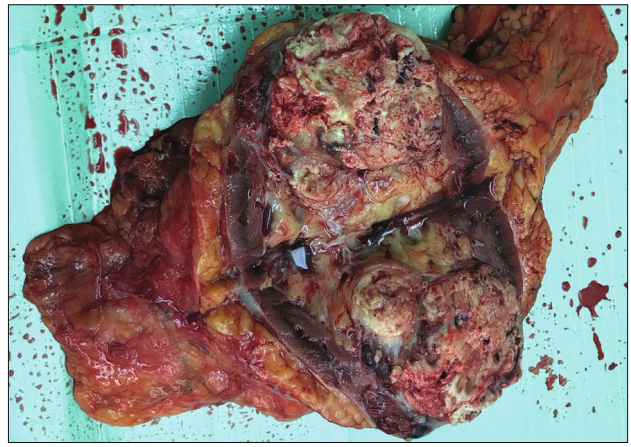
Bone remodelling is the continuous process of osteoclasis and osteogenesis, running all lifelong. The cycle of bone remodelling comprises a series of perfectly regulated processes by hormones, cytokines, prostaglandins, and growth factors. The system RANK/RANKL and osteoprotegerin (OPG) regulate the control of bone turnover. RANK (receptor activator of nuclear factor kappa-B) is the receptor expressed in pre-osteoclasts. In osteoblasts, the RANKL (receptor activator of nuclear factor kappa-B ligand) is synthesised. RANKL is the ligand of RANK and OPG. The interaction between RANK and RANKL is significant for the differentiation and maturation of the osteoclasts. The action of RANKL is

Tab. 1. TNM classification system.

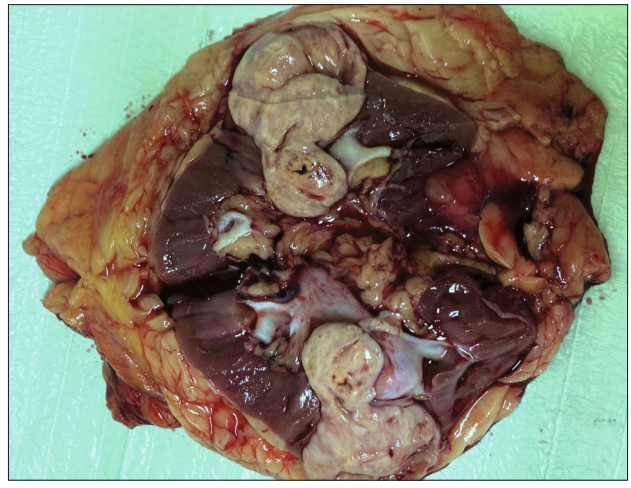
	T stage
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour < 7 cm in greatest dimension, limited to the kidney
T1a	Tumour < 4 cm in greatest dimension, limited to the kidney
T1b	Tumour > 4 cm but < 7 cm in greatest dimension
T2	Tumour > 7 cm in greatest dimension, limited to the kidney
T2a	Tumour > 7 cm but < 10 cm in greatest dimension
T2b	Tumours > 10 cm limited to the kidney
T3	Tumour extends into major veins or directly invades adrenal gland or perinephric tissues, but not into the ipsilateral adrenal gland
T3a	Tumour grossly extends into the renal vein or its segmental
T3b	Tumour grossly extends into the vena cava below the diaphragm
T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
	N stage
NX	Regional lymph nodes cannot be assessed
N0	Regional lymph nodes cannot be assessed
N1	Metastasis in a single regional lymph node
	M stage
M0	Metastasis in a single regional lymph node
M1	Distant metastasis



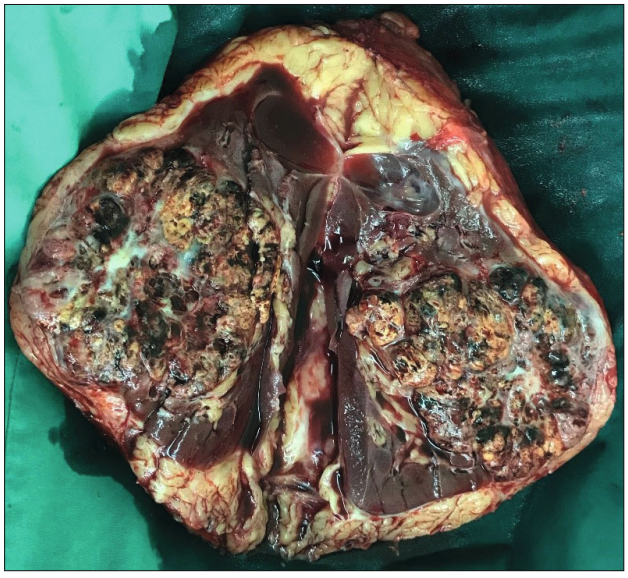
Stage T1 – T1b



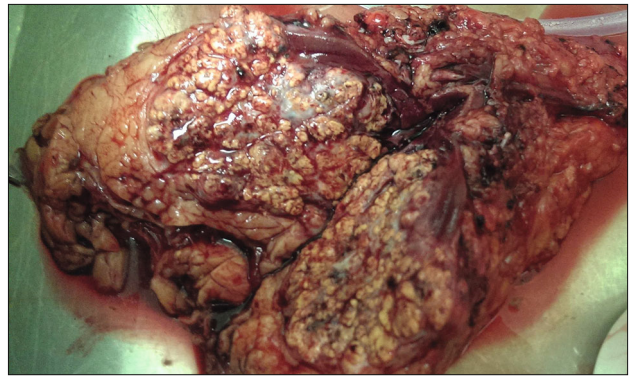
Stage T3 – T3a



Stage T3 – T3a



Stage T2 – T2b



Stage T4

Fig. 2. Illustration of some of the T stages of the kidney cancer

blocked by OPG, a soluble receptor for RANKL, and is blocking the interaction between RANKL and RANK. This leads to the reduction of maturation of the osteoclasts and a decrease in bone resorption. The RANKL/OPG ratio determines the speed of bone remodelling. The system RANK/RANKL/OPG is a physiological mechanism with a crucial role in bone metabolism, the immune system, and vascular biology. The disbalance of this system handles various bone diseases: for example, postmenopausal osteoporosis, osteoporosis induced by glucocorticoids, hyperparathyreosis, Morbus Paget, rheumatoid arthritis, and bone tumours. Nowa-

Tab. 2. TNM classification system.

Stage	Stage I	Stage II	Stage III	Stage IV
T	T1	T2	T3 T1, T2, T3	T4 Any T
N	N0	N0	N0 N1	Any N Any N
M	M0	M0	M0 M0	Any M M1

Tab. 3. Number of new cancer cases in 2020

Type of cancer	Global incidence
Breast	2 261 419
Lung	2 206 771
Colorectum	1 931 590
Prostate	1 414 259
Stomach	1 089 103
Liver	905 677
Cervix uteri	604 127
Oesophagus	604 100
Thyroid	586 202
Bladder	573 278
Non-Hodgkin lymphoma	544 352
Pancreas	495 773
Leukaemia	474 519
KIDNEY	431 228
Corpus uteri	417 367
Lip, oral cavity	377 713
Melanoma of skin	324 635
Ovary	313 959
Brain, central nervous system	308 102
Larynx	184 615
Multiple myeloma	176 404
Nasopharynx	133 354
Gallbladder	115 949
Oropharynx	98 412
Hypopharynx	84 254
Hodgkin lymphoma	83 087
Testis	74 458
Salivary glands	53 583
Vulva	45 240
Penis	36 068
Kaposi sarcoma	34 270
Mesothelioma	30 870
Vagina	17 908

days, in treating osteoporosis, we can use the antibody against the RANK (19).

Pathophysiology of bone metastases

Bone metastases can be divided into osteolytic, osteoblastic, and combined lesions. The activity of osteoclasts creates osteolytic lesions, and their activation mechanism depends on the type of the primary tumour. Osteoclasts develop from haemopoietic stem cells (monocyte-macrophage lineage), responsible for the resorption of the mineralised bone matrix and for the development of the specific environment of the bone, where apoptosis has a crucial role. Stimulation factors, osteoblast, activated T-lymphocytes, malignant cells, and precursor cells of osteoclasts play an essential role in regulating the bone metabolism of the involved bone.

During the development of bone metastases, the malignant cells invade the bone erythropoietic system. The immune cells react and release the stimulating factors for osteoclasts, followed by bone destruction resulting in bone lesions (18). It is proven that the alteration of the RANK/RANKL/OPG system plays an important role in various diseases like rheumatoid arthritis, myeloma, osteolytic bone metastases, and osteoporosis (20).

Bone cells, immune system, and RCC

There is a complex system of interactions between the bone tissue and immune system of the organism organised at the molecular level. It is the system RANK, RANKL, and OPG. A higher ratio of serum levels of RANKL/OPG stimulates osteoclast genesis. The expression of RANKL and RANK is directly related to the stage of the primary lesion and metastasising into bones and other organs (18).

The pathogenesis of skeletal metastases in the RCC patients is like those in patients with breast cancer. Osteoclasts are activated, and the bone is destructed. The regulation of these processes is established by growth factors and cytokines that induce malignant cells' proliferation. In this group, we can find fibroblast growth factor (FGF) and transforming growth factor-beta (TGF-β), which are studied in association with osteosarcomas (21, 22). The malignant cells release prostaglandins, activated vitamin D, and tumour necrosis factor (TNF). These substances are responsible for the activation of osteoclasts (18).

RCC and biomarkers

Biomarkers with the ability to identify DNA methylation are helpful in the diagnostics in patients with renal tumours and RCC. They can also be used in the screening process in subpopulations at higher risk of RCC.

Lommen et al. (2019), in their paper, described the biomarkers which could identify the DNA methylation in RCC patients. It reviews the results and data from 19 papers devoted to this topic. In clinical settings, we could implement the biomarkers LRRC3B and TCF21. These two markers are the genes and transcription factors, and their role in the pathogenesis of RCC is significant. TCF21 is the transcription factor 21, also called pod-1, capsulin, or epicardin. It is a protein coded by the gene TCF21 in chromosome 6. It is expressed in various tissues, especially in the lungs and placenta. It also has a crucial role in renal embryogenesis. During malignancies, it is downregulated. LRRC3B is a gene often epigenetically activated in some epithelial malignancies, inhibiting cell growth and replication. It seems that the process of carcinogenesis acts as a tumour-suppressor gene in the pathogenesis of RCC and ovarian cancer (23, 24).

In the past, more authors in their papers described the LRRC3B. Losing chromosomal heterozygosity is a characteristic sign for more epithelial malignancies and RCC. The gene LRRC3B can be considered a tumour-suppressor gene. This is also confirmed in in-vitro experiments. We also know other biomarkers associated with RCC and other urinary tract tumours. It is a group of cadherins: E-cadherin, N-Cadherin, and P-Cadherin (25, 26). Other studied biomarkers in urogenital tumours (including RCC) are the markers associated with CD8+ T-lymphocytes, p53 a Ki-67 (27–30).

Genetic factors also contribute to RCC risk, as evidenced by individuals with a family history of renal cancer having an approximately twofold increased risk. Investigations into familial RCC have uncovered mutations in at least 11 genes (BAP1, FLCN, FH, MET, PTEN, SDHB, SDHC, SDHD, TSC1, TSC2, and VHL), some of which have also been implicated in sporadic RCC development. A notable example is VHL, a mutated gene underlying the von Hippel-Lindau disease, characterised by a high risk of developing ccRCC. The inactivation of the VHL protein leads to unchecked expression of oncogenic hypoxia-inducible factors (HIF-1 and HIF-2) is also a hallmark of sporadic ccRCC tumours. Genome-wide association studies (GWAS) of RCC identified six susceptibility loci to date on chromosome 2p21, 2q22.3, 8q24.21, 11q13.3, 12p11.23, and 12q24.31. The 2p21 locus maps to EPAS1, a gene encoding the HIF-2α subunit, whereas the biological effects underlying the 11q13.3 locus seem to be attributable to changes in the regulation of CCND1 (encoding cyclin D1, which is involved in cell cycle regulation (31).

In ccRCC, the VHL tumour suppressor gene is the most frequently mutated, and its complete loss through genetic and/or epigenetic mechanisms constitutes the earliest truncal oncogenic driving event. VHL is the substrate recognition component of an E3 ligase complex that ubiquitinates HIF-1α and HIF-2 α for proteasome-mediated degradation. Therefore, loss of VHL leads to aberrant accumulation of HIF proteins despite an adequately oxygenated tissue microenvironment, resulting in uncontrolled activation of HIF target genes that regulate angiogenesis, glycolysis, and apoptosis. Human ccRCC tumours are rich in lipids and glycogens and are highly vascular, which underlies why agents that primarily inhibit VEGF and its receptor VEGFR are effective treatments for metastatic ccRCC. However, VHL loss alone does not induce ccRCC, evidenced by the long latency (>30 years) in individuals who harbour VHL germline mutations to develop ccRCC and by observing that *Vhl* loss in mice is usable to induce ccRCC. These results suggest that additional genetic and/or epigenetic events are probably needed for ccRCC to develop (31).

Tab. 4. Classification of RCC by WHO.

Histologic Subtype	Prevalence (%)	Putative Cell of Origin
Clear cell RCC	70%	Epithelium of proximal convoluted tubule
Papillary RCC	10%	Epithelium of proximal convoluted tubule
Chromophobe RCC	5%	Cortical collecting duct, type B interca-lated cell
Hereditary cancer syndromes	5%	
Multilocular cystic RCC	<1	
Collecting duct carcinoma	<1	Medullary collecting duct
Medullary carcinoma	<1	Medullary collecting duct
Mucinous tubular and spindle cell carcinoma	<1	Possibly the loop of Henle
Neuroblastoma-asociated RCC	<1	
Unclassified lesions	4	

Tab. 5. Types of the papillary RCC.

Type 1	Papillae are covered by a single raw of low nuclear grade tumour cells with scanty cytoplasm
Type 2	Shows a higher nuclear grade with pseudostratified nuclei and abundant eosinophilic cytoplasm

Types of kidney cancer (Renal Cell Carcinoma)

RCC is now considered a heterogeneous clinicopathological disease that can be classified into clear cell, papillary, chromophobe, collecting duct carcinoma, medullary carcinoma, and unclassified categories (32). Generally, the RCC types have different clinical courses and responses to therapy. The WHO classification of RCC is summarised in Table 4 (32, 33).

Clear cell renal cell carcinoma (ccRCC)

Clear cell RCC generally consists of solitary cortical neoplasms. It occurs equally in either kidney. It is the most frequent renal tumour subtype, accounting for 70 % of all the RCCs. It may exhibit a distinct golden yellow tumour surface due to the abundant lipid content of the cells (32). The tumour cells have a round nucleus. Depending on the tumour grade, the nucleus has evenly distributed chromatin and variable-sized nucleolus and has a clear or eosinophilic cytoplasm (34). Clear cell RCC commonly appears heterogeneous at imaging due to necrosis, cysts, and haemorrhage. Clear cell renal cell carcinoma originates from the renal cortex and typically exhibits an expansile growth pattern. Multicentricity and bilaterality are rare (< 5 %) in sporadic cases (35).

Papillary RCC

Chromophil RCC, also called papillary RCC, is the second most common histologic subtype, making up 10–15 % of RCCs. The tumour tissue is usually friable, bounded by a thick pseudocapsule and frequently shows fibrosis and haemorrhage.

Macroscopically, papillary RCCs often contain areas of haemorrhage, necrosis, and cystic degeneration (32). Epithelial cells forming the papillae and tubules are its histological characteristics. We know two types of papillary RCC. Type 1 and type 2 are defined in pRCC (Tab. 5) (34).

Chromophobe RCC

ChRCC accounts for approximately 5 % of RCC. Chromophobe RCC is histo-patho-

Tab. 6. Hereditary renal cell tumours.

Hereditary syndrome	Histologic type of renal tumour	Gene	Chromosome
Von Hippel–Lindau	Clear cell RCC	VHL	3p26
Hereditary papillary RCC	Type 1 papillary RCC	c-MET	7q34
Hereditary leiomyoma-RCC	Type 2 papillary RCC	Fumarate hydratase	1q42-43
Birt-Hogg–Dube´	Multiple chromophobe RCC, oncocytoma, papillary RCC	BHD	17p11.2
Medullary carcinoma	Medullary carcinoma		11p

logically characterised by large polygonal cells with prominent cell membranes. Macroscopically, chromophobe RCCs are well-circumscribed, solid, tan-brown tumours with a mildly lobulated surface. Solitary tumours commonly occur with a homogeneous grey or grey-brown gross appearance. Compared with ccRCC and pRCC, this type of RCC has a better prognosis and mortality of less than 10 % (36).

Collecting duct carcinoma

It is a very aggressive renal tumour type accounting for < 1 % of all renal cancer types (34). Collecting duct carcinoma shows a female: male ratio of approximately 1:2. The age range is 13–83 years. Collecting duct carcinoma appears as a grey-white infiltrative neoplasm with some epicentre in the pelvicalyceal system. It usually occurs in the central region of the kidney (32). Collecting duct carcinoma is histologically characterised by tubulo-papillary architecture with a high nuclear grade and a characteristic desmoplastic stromal reaction (37).

Renal medullary carcinoma

Renal medullary carcinoma is an extremely rare malignant neoplasm occurring almost exclusively in patients with sickle cell traits (38). This type of carcinoma is always found in young patients. The typical range of age is between 10–40 years. The female-to-male ratio is 1:2 (32, 37). Histology of renal medullary carcinoma show sheets of poorly differentiated, mucin-producing eosinophilic cells associated with inflammatory, fibrous, or oedematous stroma (38). Haemorrhage and necrosis contribute to tumour heterogeneity. Renal medullary carcinoma is typically associated with caliectasis (39).

Hereditary renal cell carcinoma

Hereditary RCC syndrome is characterised by the early development of bilateral and multicentric renal neoplasms in both genders (40). Hereditary renal cell tumours are described in Table 6 (34).

Diagnostics

A large number of renal tumours are detected by non-invasive imaging procedures, such as computer tomography (CT) or ultrasound imaging (USG). Macroscopic haematuria, hip pain, and palpable resistance are medical findings that are very rare. A particular group of symptomatic patients can also present with symptoms caused by metastatic diseases, such as long-lasting cough or bone pain. In the patients diagnosed with the primary RCC, it needs to be preoperatively evaluated whether a CT scan should be performed to identify the staging of cancer prior to the nephron-saving surgery (16, 17).

Patients with RCC and, at the same time, with suspicion of tumours of the renal vein and/or lower vena cava should receive magnetic resonance imaging (MRI). If asymptomatic patients have a renal tumour greater than 3 cm, a thoracic CT scan is also recommended (16, 17). A Contrast MRI of the brain is indicated with suspected brain metastases. Tissue biopsy is contraindicated if there is a suspicion that the tumour is without metastasis. It is crucial to take two tissue samples. The tissue sample must be taken under the control of the CT or USG technique (16).

The kidney biopsy is performed in particular:

1) in the patients in whom a kidney mass of "uncertain nature» / "unknown consistency» is observed because of its ability to influence further treatment options;
2) in the patients before ablation therapy;
3) in the patients with metastatic RCC – prior to cytoreductive nephrectomy or prior to systemic therapy;
4) in the patients who are actively monitored for RCC.

Surgical treatment

Until the end of the 20th century, the standard of surgical treatment was considered an open radical nephrectomy (ORN) (41). The principle of radical nephrectomy is a transabdominal approach to the kidney, which allows the identification and primary ligation of the kidney vessels prior to manipulating the kidney itself. This prevents – the dissemination of tumour cells into the systemic circulation. The kidney is also removed with the fat capsule bounded by the Gerot fascia (along) with the adrenal gland and the regional paraaortic, paracaval, and inter-aortocaval lymph nodes. This procedure is different from a simple nephrectomy. In simple nephrectomy, the adrenal glands remain, and the affected kidney is removed without perirenal adipose tissue. Adrenalectomy is also a part of radical nephrectomy, which is indicated if metastatic adrenal involvement can be detected using imaging

Tab. 7. The survival of patients – 5 years after their treatment.

Five years after treatment without lymph node invasion and distant metastases	70–90 %
Without lymph node invasion and metastases – tumour smaller than 4 cm	90–100 %
Survival of patients (5 years) with a tumour larger than 7 cm	70–80 %

(EAU Guidelines)

methods. Adrenalectomy may be indicated if a kidney tumour affects the upper pole or a large part of the whole kidney (17, 42). The standard treatment for kidney cancer is radical nephrectomy.

The technique and approach of the operation depend on:

A: tumour size and location

B: metastatic involvement of the abdominal organs

The disadvantage of the trans-abdominal approach is the extended period of postoperative intestines paralysis. A thoracoabdominal approach can be used if the upper part of the kidney is affected by the tumour. This approach is rarely used. The lumbotomic approach is used in smaller tumours. Complications of radical nephrectomy occur in approximately 20 % of cases. The survival of the patients after the radical nephrectomy for renal cell carcinoma depends on the pathological stage of the disease. The 5-year survival after the individual treatment is shown in Table 7 (43).

Partial nephrectomy is a surgical procedure where only the kidney tumour is removed, and healthy parenchyma is left. This operation can also be called nephron-sparing surgery (NSS). The high morbidity and complexity of the operation PNF were performed only in the imperative indications – e.g., bilateral tumours or chronic kidney disease. The indication of PNF is currently extended to stage T1 and T2 tumours. This development was indicated for improving surgical techniques and developing diagnostic methods (MR and CT). Many studies compare the results of partial and radical nephrectomy (44, 45).

A tumour with a border of healthy parenchyma is usually removed in partial nephrectomy. Therefore, it is necessary to temporarily interrupt blood flow through the kidney to maintain good visualisation in the operating field. This is an advantage for a complete assessment of the tumour and the vascular structures. The operation can be performed without occlusion of the renal vessels in warm or cold ischemia. Partial nephrectomy without ischemia is indicated for small tumours in the renal cortex. Removing the tumour safely and reconfiguring the kidney surface in these cases are possible. Warm ischemia should not be longer than 20–25 minutes (46). There will be no irreversible damage to the renal parenchyma in this case. It is usually enough to close the main artery and leave the vein free. If the tumour resection takes longer than 35 minutes, the blood flow must be stopped entirely, and the kidney must be cooled.

The introduction of robotic-assisted surgery and the development of laparoscopic techniques in urology have started to evolve the surgical treatment of kidney tumours in partial nephrectomy. Comparative studies dealing with robotic, laparoscopic, and open PNF have pointed to the advantages of robotic surgery. This surgical technique reduces morbidity, hospitalisation time, blood transfusion, and complications (47, 48).

Conclusion

The size of the tumour, the stage of the disease, and the surgeon's experience are the fundamental factors influencing the choice of the optimal treatment method. The standard open surgical approach is gradually replaced by robotic-assisted partial nephrectomy. The open surgical approach is still reserved for locally advanced illnesses like lymphadenopathy or the venous system. New prognostic and predictive markers are currently being investigated, which may help make decisions in managing RCC patients in the future.

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