Renal cell carcinoma: Review of etiology, pathophysiology and risk factors

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Background and Aims. The global incidence of renal cell cancer is increasing annually and the causes are multifactorial. Early diagnosis and successful urological procedures with partial or total nephrectomy can be life-saving. However, only up to 10% of RCC patients present with characteristic clinical symptoms. Over 60% are detected incidentally in routine ultrasound examination. The question of screening and preventive measures greatly depends on the cause of the tumor development. For the latter reason, this review focuses on etiology, pathophysiology and risk factors for renal neoplasm.

Methods. A literature search using the databases Medscape, Pubmed, UpToDate and EBSCO from 1945 to 2015.

Results and Conclusions. Genetic predisposition/hereditary disorders, obesity, smoking, various nephrotoxic industrial chemicals, drugs and natural/manmade radioactivity all contribute and environmental risks are a serious concern in terms of prevention and the need to screen populations at risk. Apropos treatment, current oncological research is directed to blocking cancer cell division and inhibiting angiogenesis based on a knowledge of molecular pathways.

Key words: hereditary syndromes, nephrectomy, radioactivity, renal cell carcinoma, renal carcinogenesis, uranium toxicity

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INTRODUCTION

Renal cancer (RC) accounts for around 3% of all adult malignancies and is the twelfth most common cancer in the world, with 338,000 new cases diagnosed in 2012 and around 100,000 deaths annually^{1,2}. Cancers of the kidney are more common in men than in women, and over the last few decades, the incidence has been increasing in many parts of the world. About 59% of RC cases occur in more developed countries. The global incidence rates are highest in Europe, North America and Australia and lowest in Africa, India and China. The Czech Republic has the highest rate of RC in the world, followed by Lithuania and Slovakia. The incidence in the Czech Republic to 2012 was reported as 24.1 (men) and 10.5 (women) per 100,000 people per year¹. This accounts in the Czech Republic for around 2,000 partial or radical nephrectomies yearly. Renal cell carcinoma (RCC) accounts for 80-85% of kidney cancers. It is the most common kidney variety and the third most commonly diagnosed urogenital malignancy³.

The most frequent histological type of RCC is clear cell renal cell carcinoma (ccRCC), with a prevalence of 75% of all primary kidney cancers. Papillary and chromophobe RCC are two less common subtypes (ref.^{4,5}). Renal pelvic cancer accounts for the remaining 10%. Nephroblastoma (Wilms tumor), the primary renal carcinoma in children comprises about 1.1% of all kidney cancers⁶. Up to 10% of RCC patients present with characteristic clinical symptoms consisting of hematuria, lateral dorsal or flank pain and palpable abdominal mass. Over

60% of RCC are detected incidentally in routine ultrasound examination⁷. Despite the advances in diagnosis, especially improved imaging techniques, about 20–30% of all patients are diagnosed with metastatic disease. Patients with metastatic RCC have a median survival of around 13 months. The 5-year survival rate is under 10% (ref.⁸). More than 20% of patients undergoing nephrectomy will develop metastases during follow-up⁹. For those with metastatic disease, the prognosis is extremely poor despite advances in multimodal treatment. Therapeutic options for RCC are limited due to resistance to chemotherapy and radiotherapy and to the low efficiency and toxicity of immunotherapy^{10,11}.

CLASSIFICATION AND PATHOLOGY OF PRIMARY RENAL NEOPLASMS

The four most common malignant epithelial neoplasms in adults are clear cell, papillary, chromophobe RCC and collecting-duct carcinoma. The rare benign primary renal tumor with unique microscopic features is an oncocytoma.

Clear cell renal cell carcinoma

The genetic features most closely associated with ccRCC are mutation, hypermethylation, loss or biallelic inactivation of the tumor suppressor - von Hippel-Lindau gene (VHL) (ref.^{12,13}). The loss of the wild-type allele of VHL is found in hemangioblastomas, pancreatic neuroendocrine tumors, kidney cysts, and ccRCC in patients

with VHL. Inactivation of VHL results in upregulation of hypoxia inducible factors (HIF)-1 α and 2 α which drive angiogenesis and proliferation and has profound effects on energy metabolism^{14,16}. According to recent data, inactivation of VHL alone is not sufficient to cause ccRCC. Other genes are likely to be important in its development including: polybromol (PBRM1), BRCA1 associated protein-1, SET domain containing 2 (SETD2) and lysine K-specific demethylase 6A (KDM6A) (ref.¹⁷⁻²⁰). Histopathologically clear cell RCC appears as golden yellow but the color varies with tumor grade. Under light microscopy, the tissue can demonstrate a variety of growth patterns including solid, acinar and cystic papillary, pseudopapillary, tubular and sarcomatoid. The cytoplasm is typically clear or granular-eosinophilic²¹. The clear cell RCCs are highly vascularised tumors due to upregulation of vascular endothelial growth factor A (VEGFA or VEGF) and platelet-derived growth factor B (PDGFB) which both promote angiogenesis^{22,23}.

Papillary renal cell carcinoma

This type of kidney tumor comprises approximately 10% of all RCCs (ref.^{24,25}). Two familial syndromes are associated with increased risk of papillary-type RCC: hereditary papillary RCC is an autosomal dominant syndrome characterized by multifocal, bilateral, type 1 - RCC caused by mutation of the MET gene on 7q31. The papillary type 2 - RCC is the pathological type most commonly associated with Hereditary Leiomyomatosis (HLRCC) and tends to have an early age of onset. Mutation of the fumarate hydratase (FH) gene which encodes the enzyme that converts fumarate to malate in the Krebs cycle, is mutated in HLRCC. It should be noted that mutations in FH also occur in fumarate hydratase deficiency (FHD). Homozygous or compound heterozygous FH germline mutations cause autosomal recessive FHD, a metabolic disease characterised by neurological impairment and encephalopathy^{26,27}. Multifocal disease is a pathological feature of papillary RCC and under light microscopy, necrosis is often seen. The cancer cells associated with HLRCC have typically large nuclei with inclusion-like orangiophilic or eosinophilic nucleoli and hemosiderin pigment in the cytoplasm^{16,21,28}.

Chromophobe renal cell carcinoma

Chromophobe renal cell carcinoma is a distinct subtype of renal cell carcinoma that accounts for 5% of all renal neoplasms. This subtype is further subdivided into two variants, classic and eosinophilic (oncocytic).

The hereditary disease associated with chromophobe RCC (chRCC) is an autosomal dominant Birt-Hogg-Dubé (BHD) syndrome which is caused by germline mutations in the folliculin gene - FLCN maps to chromosome 17 and was subsequently identified at 17p11.2 (ref.²⁹). This gene acts as a tumor suppressor and interacts with mTOR and AMP activated protein-kinase signalling pathways³⁰. Patients with the BHD syndrome tend to develop fibrofolliculomas, lung cysts, spontaneous pneumothorax, renal cysts, cancers and skin manifestations as multiple fibrofolliculomas, trichodiscomas and acrochordons³¹. Few other

mutations in tumor suppressor genes have been identified in chromophobe RCC. One example is dismutations in PTEN located in 10q23 and TP53 located at 17p13 (ref.¹³).

Collecting-duct carcinoma

This rare type of renal neoplasm comprises less than 1% of primary renal tumors and is also known as Bellini duct carcinoma, medullary renal carcinoma, distal renal tubular carcinoma and distal nephron carcinoma^{21,32}. The tumor arises from the collecting duct in the renal medulla, is highly aggressive and most patients present with metastatic disease. Typically, the metastasis is to regional lymph nodes in approximately 80% of cases, to the lung or adrenal gland and to the liver^{32,33}. Associated chromosomal abnormalities are losses of various chromosomal regions on chromosomes: -1p, -8p, -9p, and gains on chromosome at-13q (ref.³⁴).

Renal oncocytoma

The incidence of oncocytomas ranges from 3% to 7% of all primary renal neoplasms. Oncocytoma has a wide age distribution, with a peak incidence in the seventh decade of life. Men are affected twice as commonly as females³⁵. Renal oncocytoma is rare. Benign renal epithelial tumors are composed of large cells with mitochondria-rich cytoplasm thought to arise from intercalated cells of the collecting duct. The cytological features of renal oncocytoma show overlap with other renal entities³⁶. Pathologically, classic renal oncocytomas have been described as circumscribed solid tumors with a central stellate scar, with focal cystification reported in 20% to 37% of cases^{37,38}. Pathological differentiation between an oncocytoma and an RCC with oncocytic features is difficult. The most recently published study described the usefulness of immunohistochemical markers: DOG1 (discovered on GIST 1), cyclin D1, CK7, CD117 and vimentin in the differential diagnosis of renal epithelial tumors. The results showed that of these markers, DOG1 is a very sensitive and very specific marker for distinguishing chRCC from ccRCC; Cyclin D1 is useful in discriminating between chRCC and renal oncocytoma; CK7 and CD117 are useful markers for distinguishing chRCC from renal oncocytoma and ccRCC; and vimentin is helpful for distinguishing clear cell RCC from chromophobe RCC and oncocytoma³⁹.

ETIOLOGY

Demographics, cigarette smoking, use of phenacetin-containing analgetics, obesity, lack of physical activity, exposure to industrial or environmental agents and comorbidities such as hypertension, hyperglycemia and hypertriglyceridemia belonging to the metabolic syndrome (MS) have been associated with RCC (ref.⁶). From observational studies, almost half of all kidney tumors are linked to obesity with a BMI > 30 kg/m² and renal cancer risk is between 20-35% higher for every 5 kg/m² of higher BMI. This association suggests that obesity is the chief factor in a diverse array of fatal conditions from malignancies to

cardiovascular and renal diseases^{40,41}. The mechanisms that underlie the role of the MS in RCC carcinogenesis are complex, involving insulin resistance (IR), inflammation, angiogenesis, cell-stroma interaction, and other factors⁴². The insulin-like growth factor (IGF) family and changes in its components that result from IR play a crucial role in tumor development and progression. Through activation of mitogen-activated protein kinase and phosphatidylinositol-3 kinase signaling pathways, IGF-1 may play a role in the promotion of mitosis, cell migration and apoptosis suppression. In addition, IGF-1 can stimulate tumor angiogenesis by increasing VEGF levels⁴³. In the case of the MS, elevated levels of reactive oxygen species (ROS) together with pro-inflammatory cytokines and mediators of inflammation, such as NF- κ B are known to affect cell apoptosis, proliferation and invasion⁴².

Recent studies have also suggested that circulating vitamin D-binding protein (VDBP) concentration plays a role in the etiology of several cancers, directly or by modifying the association between circulating vitamin D and risk of disease^{44,45}. VDBP can directly impact carcinogenesis via membership of the extracellular actin scavenger system and by playing a role in macrophage activation, apoptosis and angiogenesis^{45,46}. In a prospective study, Mondul et al. investigated 262 RCC male patients to determine whether circulating VDBP concentration was associated with risk of renal cell carcinoma and whether this modified the association with 25(OH)vitaminD. Men with higher serum concentrations of VDBP had lower risk of RCC, whereas the 25(OH)vitaminD:VDBPratio, a proxy for free circulating 25(OH)vitaminD, showed a possible positive risk association. Thus, the VDBP association may reflect a biological mechanism unrelated to vitamin D status⁴⁷.

Anticancer properties are especially attributed to vitamin D3 which binds to the VDR receptor. Vitamin D3 and its analogues inhibit cell proliferation and promote apoptosis in cancer cells in culture. The major site for the synthesis of vitamin D3 is the kidney. Biological and epidemiological data suggest that vitamin D3 levels have an impact on the development of renal cancer. However, gene polymorphism of the vitamin D receptor may play the most important role in its development⁴⁸.

The association between *FokI* polymorphism (ff genotype) of VDR and higher renal cancer risk has been confirmed in two unrelated studies: in Central- Eastern European and North Indian populations. In a recent research study of a North Indian population, an increased number of *FokI* polymorphism alleles have been linked to a high risk of renal cell cancer, also taking into consideration other risk factors such as hypertension, smoking and high body mass index⁴⁸⁻⁵⁰.

Several studies have suggested that gene-environment interactions in connection to RCC are linked to genes that underlie enzymes involved in metabolism. Polymorphism in genes encoding carcinogen metabolizing enzymes with altered expression and function may increase or decrease carcinogen activation or deactivation. The most widely studied has been cytochrome P450 especially in relation to CYP1A1. This plays a key role in the metabolism of drugs and environmental chemicals e.g. polycyclic aro-

matic hydrocarbons that may contribute to carcinogenesis and in estrogen metabolism^{51,52}. The results of a metaanalysis by Chinese authors showed that CYP1A1 MspI polymorphism was significantly associated with increased risk of RCC using three genetic comparison models (allele model: OR=1.49, 95% CI 1.03-2.16; homozygous model: OR=1.64, 95% CI 1.13-2.40; dominant model: OR=1.72, 95% CI 1.07-2.76). Obvious heterogeneity was observed in an allele model and a dominant model⁵³.

Other studies have highlighted the impact and risk for tumor development associated with nutrition, especially with intake of ochratoxins and citrinin. These mycotoxins or their metabolites could significantly contribute to this disease of the kidney in the Czech population. The accumulation of ochratoxins, citrinin (CIT) and of their metabolites in the human organism could initiate cancer and negatively affect either the rest of the kidney or to increasing the risk of recurrence or accelerate ongoing cancer. Ochratoxins and citrinin are toxicological and agriculturally important mycotoxins. Ochratoxins and citrinin are produced by several fungi of the genera *Penicillium*, which contaminate foodstuffs, food and feed⁵⁴. Citrinin, often found in the same food as ochratoxin A (OTA), is a powerful nephrotoxin. After exposure, ochratoxins show nephrotoxic, hepatotoxic, immunotoxic, neurotoxic, embryotoxic, teratogenic, genotoxic and carcinogenic effects in laboratory and farm animals⁵⁵.

Ochratoxin A is an important nephrotoxin with carcinogenic effects (IARC, WHO, 1993) (ref.⁵⁶), a possible human carcinogen, which is now even considered as both an initiator and promoter of carcinogenesis. However, the mechanism of OTA carcinogenicity is currently the subject of scientific debate and there are opposing views⁵⁷⁻⁶⁰. According to some authors, OTA is a direct genotoxic carcinogen which forms covalent adducts at carbon level 8 (C8) guanine C8-dG-OTA (ref.⁶¹). Some recent data show that OTA reduces superoxide dismutase activity in porcine kidney proximal tubular cells and might decrease cellular glutathione with inhibited detoxification⁶².

In animal studies, CIT has similar toxic properties to OTA especially nephrotoxic ones. Citrinin modifies the distribution and excretion of OTA and increases its toxic effects. Co-administration of OTA 25 mg/kg and CIT 200 mg/kg increased the incidence of renal tumors in male mice⁵⁶. This co-occurrence of CIT and OTA in foods have raised concerns over possible risks for human health too⁶¹. Recent CIT research is oriented toward nephrotoxicity; both additive and synergistic effects have been described in combination with OTA (ref.^{61,63-65}). With regard to the nephrotoxicity of CIT, the situation may be complicated by the fact that CIT interacts with other naturally occurring mycotoxins e.g. OTA. This aside CIT and OTA are also associated with alterations in renal function and/or with development of renal pathologies. It has been demonstrated that co-exposure to CIT and OTA simultaneously modifies DNA adduct formation with increasing formation of the C-C8dG-OTA adduct⁶¹.

More information from randomized controlled studies are necessary for accurate understanding of the direct nephrotoxicity of OTA, CIT and other mycotoxins on renal cells.

RCC can exist as hereditary or sporadic entities. Hereditary forms of kidney cancer usually present with multifocal, bilateral tumors in younger patients. Familial RCC is noted when more than one family member has a single malignancy or several tumors. Other sporadic forms of RCC often present as a solitary lesions in older patients⁶⁶.

INHERITED RENAL CELL CARCINOMA AND GENETIC ABNORMALITIES

An hereditary predisposition to renal cancer is likely whenever an individual who is diagnosed with renal cancer has a close relative also diagnosed with the disease, and/or when an individual presents with multifocal renal tumors or a history of previous renal tumors. A family

history should be obtained and a pedigree created, paying specific attention to relatives with a known history of cancer. Multifocal and bilateral renal tumors are commonly found in RCC associated with hereditary syndromes (with the exception of HLRCC), and extra-renal manifestations of disease, such as uterine tumors in HLRCC, pancreatic cysts, tumors and adrenal pheochromocytomas in VHL, should also be noted⁶⁷. A summary of hereditary syndromes associated with renal neoplasia is shown in Table 1.

RENAL CARCINOGENESIS

The most comprehensive review on spontaneous and experimental renal carcinogenesis from the 1970s is that of Hamilton⁸². Albeit the published data were mainly from

Table 1. Hereditary syndromes associated with renal neoplasia.

Syndrome / Inheritance pattern	Gene / Locus / Type / Protein	Type of renal Tumor	Ref.
Von Hippel-Lindau / AD	VHL / 3p25 / Tumor suppressor / (pVHL)	ccRCC	31,66-68
Birt-Hogg-Dubé / AD	FLCN / 17p12q11.2 / Tumor suppressor / (folliculin)	oncocytic/chRCC/pRCC	31,66-68
Hereditary leiomyomatosis/renal cell cancer / AD	FH / 1q42.1 / Tumor suppressor / (fumarate hydratase)	pRCC (HLRCC)	31,66-68
Hereditary papillary renal cancer / AD	MET / 7q31,1q21 / Proto-oncogene / c-MET	pRCC	16,31,66-68
Familial paraganglioma syndrome / AD	SDHA, B, C, D / 5p15, 11q13.1, 1p36, 1q21, 11q23 / tumor suppressor / -	ccRCC, chRCC, pRCC, oncocytoma	31,69
Familial papillary thyroid and renal cancer syndrome / AD	fPTC / PRN / 1q21 / - / -	pRCC	31,69,70
Familial oncocytoma / AD	Partial loss of chromosome 1, FLCN/ t(9:11) 11q13, p23:q23 t(8:9), (q24.1; q34.3), reciprocal translocation / -	Oncocytoma	31,36,69,71
Tuberous sclerosis complex / AD	TSC1, TSC2 / 9q34, 16p13.3 / Tumor suppressor / (mTOR pathway, hamartin, tuberin)	Angiomyolipomas, ccRCC	31,69,72
Hereditary nonpolyposis colon cancer (Lynch Syndrome) / AD	MLH1, MSH2, MSH6, PMS2 / 2p22, 3p22,2q31, 2p16 / mismatch repair / -	ccRCC	16,31,69,73-75
Autosomal recessive renal cancer/ AR	- / - / - / -	Non-specified, ccRCC	76
PTEN hamartoma tumor syndrome (Cowden disease) / AD	PTEN / - / tumor suppressor / phosphatase	ccRCC	16,77,78
BAP1 (BRCA-associated Protein 1) Mutations and familial kidney cancer / -	BAP1 / 3p21.1 / tumor suppressor / deubiquitinase	ccRCC	16,79
Familial nonsyndromic clear cell RCC / AD	- / - / - / -	ccRCC	80,81

AD – autosomal dominant, AR – autosomal recessive, BAP1 – BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase), ccRCC – clear cell renal cell carcinoma, HLRCC – hereditary leiomyomatosis and renal cell carcinoma, chRCC – chromophobe renal cell carcinoma, FH – fumarate hydratase, FLCN – folliculin, fPTC/PRN – familial papillary thyroid and papillary renal neoplasia, MET – MET gene, MLH1 – human mutL homolog 1, MSH – MutS protein homolog, PMS2 – postmeiotic segregation increased 2, pRCC – papillary renal cell carcinoma, PTEN – phosphatase and tensin homolog, pVHL – Von Hippel-Lindau protein, SDHA,B,C,D – succinate dehydrogenase subunit A,B,C,D, TSC – tuberous sclerosis complex, VHL – Von Hippel-Lindau

animal studies, they may reflect the same in the human organism. Experimental renal tumors were induced by hormones, viruses, chemicals and radiation. Induction of renal tumors in hamsters can be achieved by subcutaneous implantation or injection of estrogens: namely stilbestrol or diethylstilbestrol⁸³. However, Algard et al. described cells from an estrogen-dependent renal tumor that could be grown in a hormone-free media and in which the addition of crystalline hormone did not enhance growth or survival⁸⁴. The exact genesis of the estrogen-induced renal tumors was unclear though it was assumed it was via the pituitary or through the direct action of estrogen. Surprisingly, progesterone inhibited tumor induction^{82,85}. An exact explanation for this phenomenon has not been sufficiently confirmed.

The polyoma virus, SV 40 and adenovirus 7, aflatoxin, a number of chemicals (eg. N-nitrosodimethylnitrosamine, nitrosomethylurea, nitrosoethylurea, phosphate and acetate) and also γ -radiation can lead to renal tumorigenesis in animals⁸².

Radiation exposure

Informative data on carcinogenesis in humans has been acquired especially after exposure to radiation. In 1994, the first comprehensive report of cancer incidence from the Life Span Study (LSS) cohort of atomic bomb survivors in Japan (Hiroshima and Nagasaki) was published. This included data from 1958 to 1987 (ref.^{86,87}) and through 1998 (ref.⁸⁸). With the follow-up period for these analyses ending in December 1998, analyses were based on more than 40 years of cancer incidence data for members of the LSS. The LSS is one of the few radiation effect studies that is composed of a basically healthy general population, including males and females exposed to a wide range of radiation doses at all ages. The chance of surviving depends on factors such as age at the time of exposure and ability to survive the effects (heat, blast and radiation) of the bomb. In the full LSS cohort of 120,321 individuals, about 48% overall (52% of females and 43% of males) were still alive at the end of 1998. Among the 105,427 members of the LSS cohort included in this study, 17,448 first primary solid cancers were diagnosed from 1958-1998. Stomach cancer was the most common cancer in the cohort, accounting for more than 25% of all cases. Other commonly occurring cancers included lung (10%), liver (9%), colon (9%), rectum (5%), female breast (6%), and cervix (5%). Baseline renal cell cancer rates in the LSS tend to increase with age for men but did not increase very much for women. At age 70, the baseline rate for women was about one third that for men. The baseline rate models suggested that age-specific renal cancer baseline rates in the LSS have increased by about 20% per decade increase in year of birth and if radiation increased the RCC incidence, the magnitude decreased over time⁸⁸. However, in 2000, 13-years after the Chernobyl accident in Ukraine a higher incidence of RCC was found with an increase from 4.7 to 7.5 per 100,000 of the total population. The study was based on knowledge about ¹³⁷Cesium accounting for 90% of incorporated radioactivity and this is eliminated via the kidney. The Ukrainian population

has been exposed to long-term, low dose ionizing radiation since 1986. A study was carried out to evaluate the histopathological features and immunohistochemical status of proliferating cell nuclear antigen (PCNA) and K-ras in RCC of 236 Ukrainian patients in comparison to an analog of 112 patients in Spain. RCCs from Ukraine presented more frequently with sarcomatoid changes with significant differences and less frequent peritumor inflammatory response. The dramatic increase in aggressivity and proliferative activity presenting by PCNA level (83% in comparison to 69%) and K-ras expression (56% in comparison to 38%) of RCCs in Ukrainian groups showed good correlation with the duration of radiation exposure and confirmed the effect of chronic, regular and sustained low dose ionizing radiation on renal carcinogenesis in the Ukrainian population⁸⁹.

Low dose radiation

Prolonged low dose radiation is one major cause of human renal carcinogenesis? There is a difference between atomic bomb attack and survivors with different types of cancers and low-dose radiation over a longer period and its effects on the kidney. Maybe the answer to this question is based on the effects of low-dose radiation on living organisms and information on uranium nephrotoxicity.

Low dose radiation exposure is defined as doses up to ~100 mSv and usually has direct or indirect effects on DNA. Direct effects are based on adsorption of radiation energy with structural alteration of DNA. Induction of DNA damage by low-dose radiation has been quantified by foci formation, and over a range of few mGy up to 1000 mGy. A variety of changes in DNA have been identified: base damage, apyrimidic/apurinic sites, single-strand breaks, double-strand breaks and cross-linkages⁹⁰. DNA damage can lead to genomic instability that is a characteristic of most cancer cells with increased tendency to genome damage during cell division. Maintenance of genomic stability is essential for cellular integrity to prevent errors in DNA replication, endogenous genotoxic stress and exogenous carcinogen insult (ultraviolet light, ionizing radiation and DNA damaging chemicals). Genomic instability includes small structural variation such as increased frequencies of base pair mutations, microsatellite instability and significant structural variation such as chromosome number or structural changes⁹¹. The defence barrier against cancer are the well-known tumor suppressor genes. Three major pathways of regulatory control that are targeted by mutations in human neoplasia are: 1) Rb/p16 tumor suppressor pathway with two proto-oncogenes Cyclin D and Cdk4; 2) Apc/ β -Catenin pathway with Apc tumor-suppressor gene and β -Catenin as proto-oncogene; 3) p53/Mdm2 pathway with p53 tumor suppressor gene and Mdm2 proto-oncogene which binds and inhibits the transcriptional activation domain of p53 (ref.⁹²). In the other hand, one of the most important factors in gene expression and transcription is DNA methylation, a biochemical process where a methyl group is added to the cytosine or adenine DNA nucleotides. DNA methylation contributes to the adaptive response to ionizing radiation and was investigated on B-lymphoblast cells

in a study by Ye et al.⁹³ As a putative novel diagnostic biomarker in RCC genome-wide DNA methylation, profiling alterations in renal cell carcinoma of diverse histologies and benign adjacent kidney tissues were investigated in 96 patients. These authors found widespread methylation differences between malignant tumors and benign adjacent tissues, particularly in immune-, G-protein coupled receptor-, and metabolism-related genes⁹⁴.

Uranium

The nephrotoxic effects of uranium are known from the uranium industry around the world from human^{95,96} and animal studies⁹⁷. Biologically soluble uranium compounds such as uranyl nitrate [$\text{UO}_2(\text{NO}_3)_2$] and ammonium diuranate ($\text{NH}_4\text{-UO}_3\text{-H}_2\text{O}$) are filtered rapidly through the renal glomeruli and are toxic to the renal proximal tubules. The lesions in the proximal convoluted tubules result in the appearance of glucose, low-molecular-weight proteins and amino acids in the urine. These substances, under normal conditions are reabsorbed from the tubular fluid. Acute damage to the proximal tubular cells and reduced proximal tubular reabsorption are consistent with uranium nephrotoxicity^{98,99}. Thun et al. showed significant excretion of beta-2-microglobulin and amino acids in 39 uranium industry workers⁹⁹. However, proteinuria in the case of uranium nephrotoxicity was low and had no value in predicting kidney damage. A more sensitive approach for urinalysis in uranium detection is the fluorophotometric method¹⁰⁰. Chronic exposure to soluble uranium and the harmful effects of low-dose radiation can be predicted in countries with a uranium industry. The Czech Republic's mine at Rozna is the only operating uranium mine in the European Union and the only one currently operating in Europe. It is not known if there is an association between increase in RCC cases and the uranium mining and its chemical industry in the Czech Republic.

DIAGNOSIS OF RENAL CELL CARCINOMA

The detection and diagnosis of RCC have evolved in recent years. At present, the majority of RCCs are found incidentally from abdominal ultrasound or computer tomography examinations undertaken for various reasons. Significantly less frequent are visible signs and symptoms of RCC. The most common are: microscopic or macroscopic hematuria, lateral dorsal or flank pain and palpable abdominal mass. Important information for physicians is that RCC can become very large without any symptoms, due to the retroperitoneal position of the kidney¹⁰¹. Paraneoplastic manifestations of RCC, including hypercalcemia, production of adrenocorticotrophic hormone, polycythemia, hepatic dysfunction, amyloidosis, fever and weight loss are present in up to 20% of patients. Hypercalcemia is caused by release of parathyroid hormone-related peptide (PTHrP), interleukins IL-6, IL-1 and tumor necrosis factor α (TNF α) from cancer tissue¹⁰¹. The mechanism by which PTHrP causes hypercalcemia involves many of the normal hormonal pathways of cal-

cium homeostasis. PTHrP binds to the PTH receptor in both bone and renal tissue. This binding leads to increased bone resorption and decreased renal clearance of calcium as well as increased phosphorus excretion¹⁰².

Wells syndrome, a less common paraneoplastic manifestation of metastatic RCC was reported by Rajpara et al. who described a 58-year old man suffering from diffuse granulomatous dermatitis with eosinophilia¹⁰³, first reported by Wells in 1971 as eosinophilic cellulitis¹⁰⁴. Nonmetastatic nephrogenic hepatic dysfunction syndrome (Stauffer's syndrome) is a unique and rare paraneoplastic manifestation of renal cell carcinoma that usually manifests as anicteric cholestasis. This syndrome, originally described in 1961 by M. H. Stauffer, is characterized by elevated alkaline phosphatase, erythrocyte sedimentation rate, α -2-globulin, and γ -glutamyltransferase, thrombocytosis, prolongation of prothrombin time, and hepatosplenomegaly, the absence of hepatic metastasis and jaundice due to the possible role of IL-6 overexpression by the primary tumor^{105,106}. Polycythemia (or erythrocytosis) which has been noted in patients with RCC is believed to be caused by ectopic production of erythropoietin by cancer cells¹⁰¹. Nonspecific symptoms such as fever, weight loss, and fatigue common to many malignancies, are thought to be mediated by cytokines especially TNF α and IL-6 (ref.¹⁰⁷). Many other endocrine abnormalities are associated with RCC, such as elevated human chorionic gonadotropin and adrenocorticotrophic hormone, manifesting themselves as clinical syndromes such as Cushing's syndrome and hyper/hypoglycaemia. Other conditions associated with RCC include amyloidosis due to pathological production and deposition of AA protein with typical clinical presentation related to the specific organ systems affected including the cardiovascular, renal and gastrointestinal systems. A number of other syndromes such as light chain nephropathy, vasculitis, coagulopathies, neuromyopathies have been also described in patients with RCC (ref.¹⁰⁷). Most pulmonary and neurological symptoms result from lung or intracranial metastases and have a poor prognosis.

Imaging tests

Radiological investigations of RCC should include CT imaging, before and after intravenous contrast to confirm the diagnosis. These will provide information on the function and morphology of the contralateral kidney and assess tumor extension, including extrarenal spread and venous involvement. Abdominal ultrasound and magnetic resonance imaging are alternatives to CT. Chest CT is the most accurate for tumor staging; a routine chest X-ray should be done as a minimum¹⁰⁸. Case dependant is evaluation of bone and brain metastases with diagnostic performance of bone scintigraphy and brain CT. Our clinical approach greatly depends on a patient's clinical status and tumor staging. Renal masses may be classified as solid or cystic by imaging criteria. For evaluating solid renal masses, the presence of enhancement is the most important criteria for differentiating malignant from benign lesions.

However, the best measure in differentiation malignant and benign lesions is a tumor biopsy, if technically or clinically (e.g. patient's status, solitary kidney, coagulopathies etc.) possible.

TNM CLASSIFICATION AND STAGING OF RENAL CELL CARCINOMA

International TNM classification according to American Joint Committee on Cancer (AJCC) 2010 is described in Table 2 (ref.¹⁰⁹).

TREATMENT OF RENAL CELL CARCINOMA

There are two treatment approaches to renal cell carcinoma according to RCC staging: 1) treatment of localised and 2) metastatic renal cell carcinoma.

Treatment of localised renal cell carcinoma

The first step in treating localised RCC is the urological measure which leads to eradication of the tumor mass by partial or total nephrectomy. Based on the available oncological and quality of life outcomes, the current evidence suggests that localised renal cancers T1a-b are best managed by nephron-sparing surgery (partial nephrec-

tomy) rather than by radical nephrectomy, irrespective of the surgical approach. However, the laparoscopic surgical approach usually takes longer than open laparotomy and complications may occur during the prolonged anaesthesia. When open partial nephrectomy was compared to open radical nephrectomy, the estimated cancer specific survival rates (CSS) at 5 years were comparable¹¹⁰. The selection of tumor mass for partial nephrectomy depends on anatomical location, staging, and other surgical features that can limit the option for tumor resection¹³. This is especially true in cases of bilateral renal tumor or chronic kidney disease prior to hospital admission with potential limitation for radical nephrectomy. Other additional treatment measures for localized tumors are ipsilateral adrenalectomy if needed, embolisation in massive hematuria or flank pain and extended lymphadenectomy if the lymph nodes are extended. According to the European Association of Urology (EAU) Guidelines on renal cell carcinoma: for solitary renal tumours up to a diameter of 7 cm, nephron-sparing surgery is the standard procedure, whenever technically feasible¹¹⁰. A minimal tumour-free surgical margin following partial resection of RCC is sufficient to avoid local recurrence. Treatments such as microwave ablation, stereotactic radiosurgery and laser ablation are experimental. Apart from these, the most commonly performed minimally invasive approaches include percutaneous radiofrequency ablation and laparoscopically

Table 2. TNM classification of RCC according to AJCC 2010.

Primary tumor (T)			
Tx Primary tumor cannot be assessed			
T0 No evidence of primary tumor			
T1 Tumor ≤ 7 cm in greatest dimension and limited to kidney			
T1a Tumor ≤ 4 cm			
T1b Tumor > 4 cm but ≤ 7 cm			
T2 Tumor > 7 cm in greatest dimension and limited to kidney			
T2a Tumor > 7 cm but ≤ 10 cm			
T2b Tumor > 10 cm			
T3 Tumor extends into major veins or perinephric tissues, but not beyond Gerota's fascia			
T3a Tumor extends into the renal vein or directly invades perinephric tissues, but not beyond Gerota's fascia			
T3b Tumor grossly extends into vena cava below the diaphragm			
T3c Tumor grossly extends into vena cava above diaphragm or invades wall of the vena cava			
T4 Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)			
Regional lymph nodes (N)			
Nx Regional lymph nodes cannot be assessed			
N0 No regional lymph node metastasis			
N1 Metastasis in regional lymph node			
Distant metastasis (M)			
M0 No distant metastasis			
M1 Distant metastasis			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T3	Any N	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

assisted cryoablation. Indications for thermal ablations are usually small renal masses in elderly more comorbid patients unable to undergo surgical intervention and patients with bilateral tumors or solitary kidney¹¹¹. Adjuvant therapy after nephrectomy has not been proven to prolong survival or to have any significant patient benefit^{110,111}.

Treatment of metastatic renal cell carcinoma

The treatment of metastatic disease is very difficult and greatly depends on histological subtype of renal tumour mass, the patient's clinical status and has changed over the last 10-15 years. Special emphasis is given to cytoreductive nephrectomy (CN) prior to the start of adjuvant therapy¹¹². The evidence for performing CN before cytokine therapy came from two randomized trials Southwest oncology group 8949 (SWOG 8949) and European Organisation for Research and Treatment of Cancer (EORTC 30947) where a survival benefit for CN followed by the immunotherapy with INF- α compared with INF- α alone was shown. The SWOG 8949 study reported the median survival of 120 eligible patients assigned to surgery followed by interferon as 11.1 months, and among the 121 eligible patients assigned to interferon alone it was 8.1 months ($P = 0.05$). The difference in median survival between the two groups was independent of performance status, metastatic site or presence or absence

of measurable metastatic lesion¹¹³. The EORTC 30947 study involved 40 (53%) of 75 patients receiving at least 16 weeks of INF- α treatment, which was the median duration of treatment. Time to progression (5 vs 3 months, hazard ratio 0.60, 95% CI 0.36-0.97) and median duration of survival were significantly better in patients than in controls (17 vs 7 months, 0.54, 0.31-0.94). Five patients responded completely to combined treatment and one to INF- α alone¹¹⁴.

These two studies were also been the motivation to perform CN in the targeted therapy era. However, cytoreductive nephrectomy is in principle not curative approach in case of metastatic disease and patients must have been able to undergo this surgical intervention. The rationale for CN performance is in better survival, removal of malignant renal mass, immunosuppressant cytokines and other hormones or molecules that underlie the paraneoplastic syndrome^{112, 115}. The palliative benefits of CN in case of tumor related pain and massive hematuria are also important for patient outcome.

Systemic metastatic RCC treatment has developed significantly: vascular endothelial growth factor as well as tyrosine kinase inhibitors and drugs that inhibit the mammalian target of rapamycin (mTOR) signaling pathway have become the mainstay for the management of advanced RCC. Possible treatment modalities in current

Table 3. Pharmacotherapeutic agents for systemic therapy in patients with metastatic RCC disease.

Pharmacotherapeutic Agent	Drug Classification and Categories	Mechanism of Drug Action	Ref.
5-fluorouracil	Pyrimidine analog - chemotherapeutic agent	- inhibition of DNA replication - irreversible inhibition of thymidylate synthase	108,110,111
Bevacizumab	Monoclonal antibody against circulating VEGF	- inhibition of angiogenesis	108,110,111
Temsirolimus Everolimus	Mammalian target of rapamycin (mTOR) inhibitors	- stimulates the degradation of cyclin D1, that inhibits the G1 to S-phase transition in the cell cycle, - downregulation phospho-p70 S6 kinase, is considered to be an indicator of the activated mTOR pathway	108,110,111, 116, 118
Interleukin 2 (IL-2)	Cytokine	- potent stimulator of T-cell proliferation, tumor-specific CTLs, NK cells, and possibly the subset of these that are intratumoral (tumor infiltrating lymphocytes) activated, and these leukocytes then kill the cancer cells	108,110,111, 117,118
Interferon- α (IFN- α)	Cytokine	- binding to cell surface receptors and activating the Jak protein family. Activated Jak1 and tyrosine kinase 2 phosphorylate signal transducers and activators of transcription - antiproliferative activity - activation of T-cells and NK cells - inhibition of cell cycle arrest	108,110,111, 116-119
Sorafenib Sunitinib Pazopanib Axitinib	Tyrosine kinase, VEGF, FGF, PDGF and angiogenesis inhibitor	- inhibition of tyrosine kinase pathway in modulation of growth factor signaling. Activated forms of these enzymes can cause increase in tumor cell proliferation and growth, induce antiapoptotic effects and promote angiogenesis and metastasis.	108,110,111, 115,120-122

CTLs – cytotoxic T-cells, FGF – fibroblast growth factor, Jak – Janus kinase, mTOR – mammalian target of rapamycin, NK cells – natural killer cells, PDGF – platelet-derived growth factor, VEGF – vascular endothelial growth factor

oncological and urological practice are described below in Table 3.

Unfortunately, systemic chemotherapy is not effective and monotherapy with INF- α and IL-2 is not recommended (except in lung metastases) as a 1st line therapy in patients with histopathologically verified metastatic clear cell RCC. According to the described pathophysiology of ccRCC in this group currently preferred and recommended in 1st line therapy are: 1) sunitinib (50 mg daily orally for a period of 4 weeks followed by 2 weeks of rest); 2) pazopanib (800 mg orally daily); 3) and the combination of INF- α (9 MU three times per week subcutaneously) + bevacizumab (10 mg/kg biweekly intravenously). In the 2nd line therapy is recommended axitinib, sorafenib and everolimus after prior tyrosine kinase inhibitors and sorafenib, axitinib and pazopanib after prior administration of cytokines^{110,111}. In the 3rd line are preferred everolimus after VEGF targeted therapy and sorafenib after mTOR treatment¹¹¹. However, the combination therapy has no benefit over single – agent use.

In patients with nonclear cell metastatic RCC recommended in 1st line therapy are: 1) sunitinib; 2) everolimus (10 mg daily orally) and 3) temsirolimus (25 mg weekly intravenously). In the 2nd line therapy any targeted agent can be used¹¹¹.

Patient surveillance after nephrectomy and RCC treatment is an important measure and allows physicians to make an early diagnosis of complications and/or assessment of local tumor progression and any metastasis. The basic measures should include abdominal ultrasound, CT or MRI imaging and thoracic X-ray/CT once yearly in the subsequent 5 years.

CONCLUSIONS

Renal cell cancer is usually a serious disease with poor prognosis, especially when there are metastasis. RCC tumors also are difficult to diagnose due to non-specific symptoms in the early stages of the disease. Current oncological research is directed to blocking cancer cell division or inhibiting angiogenesis based on knowledge of molecular pathways. Natural and manmade radioactivity, chemical nephrotoxicity and environmental risks are also a serious concern in terms of prevention and the need to screen populations at risk.

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