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Metastases from Renal Cell Carcinoma

Recurrence Patterns, Detection and Management

SAEED DABESTANI
DEPARTMENT OF CLINICAL SCIENCES LUND | FACULTY OF MEDICINE | LUND UNIVERSITY

Renal cell carcinoma (RCC) is a diverse group of malignant tumors found in the kidney. When diagnosed, removal of the tumor is normally the best treatment but results in just over half of the patients with the disease being cured. The remainder either already have a spread or later experience a recurrence of the disease to other body sites, so called metastases, which are associated with poorer survival. The timely detection and, if possible, treatment of these metastases may provide a chance at prolonged survival or even cure for these patients. The aim of this thesis is to provide a modern introduction to the subject of RCC and to present new insights into the detection, recurrence patterns and management of metastases from RCC.

Saeed Dabestani is a graduate of Lund University where he attained his medical degree in 2007. He is a specialist in general surgery as of 2014 and also in urology as of 2016, receiving his training at Skåne University Hospital, Sweden. Since 2012 he has been a part of the European Association of Urology RCC Guidelines Panel, helping to provide evidence based recommendations for the diagnosis and management of RCC.

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Metastases from Renal Cell Carcinoma

Recurrence Patterns, Detection and Management

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M.D.

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UNIVERSITY

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Metastases from Renal Cell Carcinoma – Recurrence Patterns, Detection and Management

Abstract:

This thesis provides novel insights into the detection, recurrence patterns and management of metastases from renal cell carcinoma (RCC). In paper I the role of metastasectomy and other local therapies were clarified in a robust systematic review. Studies included showed a benefit in performing complete metastasectomy in terms of overall survival (OS) and cancer-specific survival (CSS). Some evidence suggested benefits in reaching local or symptomatic control of metastases using radiotherapy. Evidence quality was low with overall high risk of bias and confounding. In paper II a population-based cohort was presented in regards to RCC demographics and treatments. Incidence of primary metastatic RCC decreased from 2005 (23%) to 2009 (18%). Treatments for asynchronous recurrences were shown to be systemic in 50%, observational in 27% and metastasectomy in 17% (68% with curative intent). For Study III and IV a multinational database (RECUR) with non-metastatic RCC patients was established to provide evidence on the impact of follow-up on recurrence detection and survival. In study III analysing clear cell RCC recurrence patterns and survival, the low-risk group recurrences according to Leibovich score were found to be infrequent at follow-up and occurred later. OS after recurrence management was disappointing especially in the Leibovich score high-risk group which harbored most patients with potentially curable recurrences. Symptomatic at recurrence meant poorer survival irrespective of metastatic burden. Competing risk analysis suggested age as an important factor in follow-up protocols. In paper IV imaging modality (cross-sectional vs. conventional) and more frequent follow-up imaging for detection of RCC recurrences did not impact OS. Finally, use of excessive follow-up imaging compared to frequencies recommended by the EAU guidelines was unlikely to increase OS after recurrence. Higher level of evidence is needed as well as novel markers in the molecular era of RCC to develop better follow-up protocols and prognostic models.

Key words: Renal Cell Carcinoma, Follow-up, Recurrence, Metastasectomy, Local Therapy, Survival

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Metastases from Renal Cell Carcinoma

Recurrence Patterns, Detection and Management

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Front cover: Original illustration by Professor Paul Grawitz depicting a clear cell carcinoma of the kidney for the first time in his publication "Die sogenannten Lipome der Niere" from 1883.

Back cover: Portrait photography of the author. © Anna Stubbendorff 2016.

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"To the beaver spotter and the hedgehog in my life"

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Paper I **Dabestani S**, Marconi L, Hofmann F, Stewart F, Lam TB, Canfield SE, Staehler M, Powles T, Ljungberg B, Bex A. Local treatments for metastases of renal cell carcinoma: a systematic review. The Lancet Oncology. 2014 Nov;15(12):e549-61.

Paper II **Dabestani S**, Thorstenson A, Lindblad P, Harmenberg U, Ljungberg B, Lundstam S. Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: a population-based study. World Journal of Urology. 2016 Aug;34(8):1081-6.

Paper III **Dabestani S**, Beisland C, Stewart GD, Bensalah K, Gudmundsson EO, Lam TB, Gietzmann W, Zakikhani P, Marconi L, Fernandez-Pello S, Monagas S, Williams S, Torbrand C, Powles, Van Werkhoven E, Meijer RP, Volpe A, Ljungberg B, Bex A. Long term outcomes of follow-up for initially localised clear cell renal cell carcinoma: RECUR database analysis. Eur Urol Focus (2018), https://doi.org/10.1016/j.euf.2018.02.010 (article in press, Epub 2018-03-07).

Paper IV **Dabestani S**, Beisland C, Stewart GD, Bensalah K, Gudmundsson EO, Lam TB, Gietzmann W, Zakikhani P, Marconi L, Fernandez-Pello S, Monagas S, Williams S, Torbrand C, Powles, Van Werkhoven E, Meijer RP, Volpe A, Ljungberg B, Bex A. Impact of follow-up imaging on outcome of surgically treated non-metastatic RCC: a RECUR database analysis. (Manuscript)

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Publications Not Included in Thesis

1. Powles T, Albiges L, Staehler M, Bensalah K, **Dabestani S**, Giles RH, Hofmann F, Hora M, Kuczyk MA, Lam TB, Marconi L, Merseburger AS, Fernández-Pello S, Tahbaz R, Volpe A, Ljungberg B, Bex A. Updated European Association of Urology Guidelines Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer. Eur Urol. 2017 Dec 6. pii: S0302-2838(17)31001-1. [Epub ahead of print] Review.

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List of Abbreviations

124-IG	124-Iodine-Girentuximab
AJCC	American joint committee for cancer staging and end result reporting
AML	Angiomyolipoma
AS	Active surveillance
AUA	American Urological Association
BHD	Birt-Hogg-Dubé
BS	Bone scintigraphy
CA	Cryoablation
CB	Core biopsy
ccRCC	Clear cell renal cell carcinoma
CDC	Collecting duct carcinoma
CEUS	Contrast enhanced ultrasonography
chRCC	Chromophobe renal cell carcinoma
CN	Cytoreductive nephrectomy
CSI	Cross-sectional imaging
CSM	Cancer-specific mortality
CSS	Cancer-specific survival
CT	Computed tomography
CXR	Conventional chest X-ray
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
ENI	Estimated number of imaging
EORTC	European Organization for Research and Treatment of Cancer
FDG	2-Deoxy-2-[18F]-fluoro-D-glucose
FNA	Fine needle aspiration
FSRT	Fractionated stereotactic radiotherapy
GFR	Glomerular filtration rate
HIF	Hypoxia-inducible factor
IF	Imaging frequency
IFN-α	Interpheron-alpha
IL-2	Interleukin-2
IMDC	International Metastatic Renal-Cell Carcinoma Database Consortium
IR	Imaging ratio
ISUP	International Society of Urologic Pathologists
IVC	Inferior vena cava
KPS	Karnofsky performance status

LND	Lymph node dissection
LPN	Laparoscopic partial nephrectomy
LRN	Laparoscopic radical nephrectomy
LS	Leibovich risk score
MET	Mesenchymal to Epithelial Transition
MIT	Minimally invasive technique
mRCC	Metastatic renal cell carcinoma
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MTX	Metastasectomy
NED	No evidence of disease
non-ccRCC	Non clear cell renal cell carcinoma
NR	Not reported
NRS	Non-randomized study
NSKCR	National Swedish Kidney Cancer Register
OC	Oncocytoma
ORR	Objective response rate
OS	Overall survival
PC	Potentially curable
PET	Positron emission tomography
PFS	Progression free survival
PI	Probably incurable
PN	Partial nephrectomy
pRCC	Papillary renal cell carcinoma
PS	Performance status
QoL	Quality of life
RAPN	Robot-assisted partial nephrectomy
RCC	Renal cell carcinoma
RCT	Randomized controlled trial
RECUR	eu**R**op**E**an association of urology renal cell carcinoma guidelines panel **C**ollaborative multicenter consortium for the studies of follow-**U**p and recurrence patterns in **R**adically treated renal cell carcinoma patients
RFA	Radiofrequency ablation
RFS	Recurrence free survival
RG	Risk group
RMC	Renal medullary carcinoma
RN	Radical nephrectomy
RPA	Recursive partition analysis
RTB	Renal tumor biopsy
SBRT	Stereotactic body radiation therapy
SR	Systematic review
SRM	Small renal mass

SysT	Systemic therapy
TNI	Total number of imaging
TTR	Time to recurrence
UISS	University of California-Los Angeles Integrated Staging System
US	Ultrasonography
VTT	Venous tumor thrombus
WBRT	Whole-brain radiotherapy
WHO	World Health Organization

Introduction

A Brief History of Kidney Cancer Surgery

The first recorded successful nephrectomy was performed by German Professor Gustav Simon (Figure 1) in 1869 due to a ureteral fistula and interestingly he was also one year later the first to deliberately perform a partial kidney resection in a case of hydronephrosis.[1] The historical mainstay of Professor Simon's successful surgeries was that extirpation of a kidney, or part of one, was relatively safe and that patients could survive with the remaining kidney function. Therefore the upcoming last quarter of the 19th and beginning of the 20th century saw the expanding use of nephrectomy, which was at that time deemed safer than partial resection.[2] It was not until in 1963 when Charles J. Robson presented the results for 62 patients with kidney cancer who had undergone radical nephrectomy (RN), i.e. kidney vessel identification and ligation, removal of perinephritic fat and overlying peritoneum and where possible/applicable resection of loco-regional lymph nodes, that the modern surgical approach we see today was established.[3] Robson and colleagues updated these results in 1969, a century after the first elective nephrectomy, with 88 patients followed up for 3 to 15 years and for the first time showing that survival was dependent on tumor grade and stage with the results of the latter from the original publication shown in Table 1.[4]

Table 1 – Kidney cancer survival by Robson stages.

	3 years	5 years	10 years
Stage 1	24/33 (73%)	21/32 (66%)	9/15 (60%)
Stage 2	10/15 (67%)	9/14 (64%)	4/6 (67%)
Stage 3	16/27 (59%)	10/24 (42%)	5/13 (38%)
Stage 4	3/12 (25%)	1/9 (11%)	0/3 (0%)
Total	53/87 (61%)	41/79 (52%)	18/37 (49%)

Original data from the study by Robson et al 1969.[4] Stage 1 =Confined to kidney. Stage 2 =Perirenal fat involvement but confined to Gerota's fascia. Stage 3 = A: Gross renal vein or Inferior Vena Cava involvement or B: lymphatic involvement or C: both A and B. Stage 4 = A: Adjacent organs other than the adrenal involved or B: distant metastases.

Partial resection of the kidney, more familiar as partial nephrectomy (PN), was first performed for specific removal of a kidney tumor by Vincent Czerny in 1887 and for the next decades to come experimental studies by several others strengthened the feasibility of the procedure.[5, 6] Although PN was established as achievable to preserve renal function the extensive risk of perioperative and/or postoperative bleeding, persistent urinary fistulas and risk of metastases due to iatrogenic tumor cell dissemination positioned the procedure as inferior to nephrectomy even for smaller organ confined renal masses. As such for the greater half of the 20th century PN was reserved for selected cases where renal function preservation was necessary. In the mid-1970s the discussion about indications for PN heated up again and almost two decades of debate within the urological community pursued before more robust evidence of oncological safety for PN emerged, initially in 1993 when Licht and Novick reported on a collected series of PNs in 241 patients with a normal contralateral kidney. They showed a 95% disease free survival (DFS) rate and only two local recurrences; albeit the average tumor size was 3.5 cm and the follow-up period was only three years.[7] It wasn't until around the turn of the millennium when two pivotal studies shifted most urologists towards widely accepting elective PN as a legitimate option for renal tumors. These studies showed that long term survival outcomes, especially in unilateral renal masses ≤ four cm in diameter, were excellent with local recurrences being rare while also the benefit of preserving renal function was achieved.[8, 9] As a result, with the parallel development of more modern surgical techniques, several RCC curative treatment options are today available and will be described further down.

Figure 1 – Professor Gustav Simon (30 May 1824, Darmstadt – 21 August 1876, Heidelberg)

Epidemiology and Risk Factors

Incidence

The worldwide incidence of RCC is about 338 000 new cases annually. This translates into world age standardized rate (ASR) of 4.4 per 100 000 in incidence, making RCC the 14th most common malignancy. RCC is 1.5 times more frequent in men than women, peaks at age 60-70 years and has a great regional variation in estimated incidence with the lowest at ASR ≤1 per 100 000 in much of Africa and South-East Asia to the highest observed in the Czech Republic at ASR 16.7 per 100 000.[10, 11] For the last two decades the trend has been towards an increase in incidence in the highly developed countries with a falling trend only described in Sweden.[12] This trend increase has been attributed to several factors, most commonly the increased use of computed tomography (CT) accounting for more frequent detection of incidental renal tumors.[13]

Mortality

Worldwide mortality is estimated to 144 000 deaths annually and the ASR is 1.8 per 100 000 for both sexes, making RCC the 16th most common malignant cause of death. Men die 1.8 times more often than women in RCC and the mortality rates are again the lowest in Africa and South-East Asia and the highest in the highly developed countries with the Czech Republic on top at ASR 4.8 per 100 000.[11] While the incidence of RCC has seen an increase, the mortality rates have consolidated globally for the last decades and even decreased in Western and Northern Europe, the USA and Australia.[10] Simultaneously, the mortality rates show a trend increase in some European countries like Croatia, Estonia, Greece, Ireland and Slovakia. Most of the mortality trends seen are attributed to regional changes in several of the risk factors described below.[14]

Risk factors

Smoking, hypertension and obesity are well established risk factors for RCC. In a meta-analysis, the risk for RCC was increased by 50% in men and 20% in women who smoked compared to non-smokers.[15] For obesity, a large contemporary meta-analysis including 21 cohort studies analysing body mass index (BMI) showed that the relative risk of RCC was increased by 28% in patient with pre-obesity (BMI 25–29.99) and by 77% in patients with obesity (BMI ≥30) compared to normal weight (BMI 18.5–24.99). When adjusting for age, smoking, physical activity, alcohol consumption and hypertension respectively, the relative risks stayed about the same and the authors estimated an incremental RCC risk increase of 4% per kg/m^2.[16] Patients with hypertension, defined as ≥90 mmHg diastolic pressure or ≥140 mmHg systolic pressure, have been shown in several cohort studies to have about 1.5–2.5 times high-

er risk of developing RCC compared to those that are normotensive. However, these studies have also showed that with decline in blood pressure the RCC risk decreases.[17-19]

Dietary habits evaluated include red or processed meat, fruits and vegetables, coffee and alcohol. Intake of more fruits and vegetables containing antioxidants such as Vitamin A, C and E and carotenoids have been weakly associated with lowered risk while read meats, especially processed meats in women, have to some extent been associated with increased risk of RCC, albeit it is important to note that none of these results have been conclusive.[20-25] A newly published large case-control study comparing 669 RCC cases to 1001 matched controls suggested that coffee consumption compared to no coffee consumption was associated with a reduced risk of RCC (OR 0.74, 95%CI 0.57-0.99) but surprisingly that decaffeinated coffee consumption yielded an increased risk of RCC (OR 1.47, 95% CI 0.98–2.19).[26] However a recent systematic review (SR) analyzed 22 comparative studies in which coffee consumption versus no coffee consumption and the risk of RCC was analyzed. They concluded that the pooled relative risk (RR) was 0.99 (95% CI 0.89-1.11) suggesting that coffee does not affect risk of developing RCC.[27] Alcohol has also recently been evaluated in several SRs suggesting an inverse association between regular alcohol consumption and risk of developing RCC.[28-30] In a SR by Xu and colleagues they showed a pooled RR of 0.86 (95% CI 0.76-0.96) in favor of regular alcohol consumers compared to non- and or occasional alcohol consumers. They also estimated a dose-response inverse association showing that a 5g/day increase in alcohol consumption translated into 5% reduction in risk of RCC albeit the linear correlation was only up to 12.5g/day. Interestingly also a significant association to specific alcoholic beverages (wine for females and beer for males) was found in relation to the reduced risk of RCC.[30]

Several other factors have been associated with increased risk of RCC but with less established evidence. Trichloroethylene has been evaluated with findings suggesting an occupational exposure-response relationship to increased risk of RCC in humans.[31] Use of non-steroidal anti-inflammatory drugs and acetaminophen (paracetamol) have in a large meta-analysis been associated with an increased risk of RCC.[32] Excluding hereditary forms of RCC, patients with a history of a first degree relative with RCC have been associated with an increased risk of RCC, as have parous compared to non-parous women.[33, 34] Finally a recent SR showed a pooled estimate of 41% increased risk of RCC in men with a history of kidney stones compared to no such history.[35]

RCC Classification and Genetics

Historically the first subtype of RCC described in the literature has been attributed to Professor Paul Albert Grawitz who in 1883 published his pathological description of a clear cell renal tumor (ccRCC).[36] He hypothesized based on tumor morphology that the tumor originated from the adrenal gland hence naming it "hypernephroma". This was later proven wrong and since then more accurate pathophysiology, histology and genetic alterations of ccRCC, other RCC subtypes and benign tumors have been elucidated, underlining the heterogeneity of kidney tumors. Indeed heterogeneity is the imperative word when describing the advances in RCC classification for the last two decades. With the advent of more advanced molecular methods the genomic investigations of RCCs have clarified the molecular basis of several subtypes of RCC, mainly by the investigations into their hereditary forms.[37-39] Consequently a better understanding of the mutations and intra-cellular changes involved in oncogenesis and the molecular heterogeneity of many RCC subtypes has led to the next level of RCC sub-classification and advances in systemic treatment options.[39] Also mapping of human cancer genomes has created a better understanding of genetic intra-tumor heterogeneity, i.e. the occurrence of diversely mutated cells at different locations within the same tumor. In a pivotal study Gerlinger and colleagues applied a multiregion exome sequencing to ten ccRCC tumors and elegantly described spatial separation of different subclonal mutations within the same tumor, underlining the intra-tumor heterogeneity.[40] The recently updated 2016 World Health Organization (WHO) classification of tumors of the kidney currently recognizes no less than 55 different entities in adults and children of which 40 subtypes are malignant.[41] Accounting for all these is outside the scope of this thesis and therefore only the most relevant subtypes are discussed below.

Benign Renal Tumors

The 2016 WHO classification of tumors of the kidney lists 14 different subtypes of benign renal neoplasms in adults and children.[41] Roughly 20% of all enhancing small renal masses are benign and of these, renal angiomyolipoma (AML) and oncocytoma (OC) are by far the most common, accounting for about 13% of all kidney tumors removed.[42, 43]

Angiomyolipoma

AML is the most common benign solid renal tumor, is composed of fat, smooth muscle and blood vessels, and most commonly distinguished through imaging where its fatty content is pathognomonic. An AML subset called "AML with minimal fat" is challenging to diagnose through imaging and often mistaken for RCC while another

rare variant, so called Epithelioid AML, possesses metastatic potential.[44, 45] AML is four times more common in women, ≤ four cm in 90% of cases found and asymptomatic at diagnosis in about 90% of cases. In those who are symptomatic abdominal pain and gross hematuria are the most common clinical features.[46-48] AML is sporadic in most cases but has been found in 10% to be associated with hereditary forms, mainly tuberous simplex complex (TSC).[46] In a contemporary retrospective study by Bhatt and colleagues, they showed in 447 patients with ≥ three imaging studies and long term follow-up, that the growth rate of AML tumors was 0.02cm per year in 91% of cases while the remaining 9% had a growth rate of >0.25cm per year, independent of initial size.[47] Furthermore they showed that bleeding, i.e. retroperitoneal hemorrhage or hematuria, due to tumor rupture was relatively rare in their series compared to other studies and more common in patients with TSC and in fast growing tumors.[47] Currently the European Association of Urology (EAU) guidelines on RCC recommends active surveillance (AS) as the most appropriate option, offering intervention only to fertile women, those with persistent pain or acute bleeding, when suspected low compliance to AS or when AML size reaches >4-5cm. Nephron sparing surgery is the recommended technique while selective arterial embolization is preferred in emergency cases and where elective surgery is not suitable. For patients with TSC, a size reduction of the AML is seen with everolimus which is currently recommended as systemic therapy (SysT) option.[49]

Oncocytoma

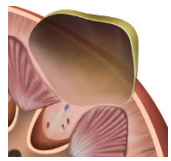
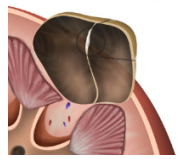
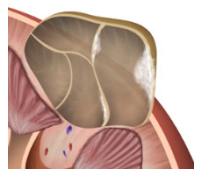
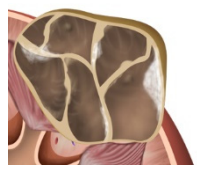
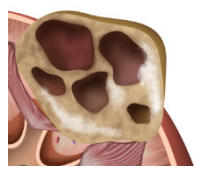
Renal OC is a benign tumor originating from the cortical collecting ducts, has a higher prevalence in men and accounts for approximately 3-7% of removed tumors.[42, 50] OC is found in both kidneys in 10% of cases and should then raise suspicion of the hereditary Birt-Hogg-Dubé (BHD) syndrome.[51, 52] The dilemma in OC diagnosis is that imaging does not allow differentiation between OC and RCC, especially chromophobe RCC (chRCC).[53, 54] Furthermore the growth rate of OC is estimated to 0.14cm annually, with lesions > four cm having even higher growth rates, again making differentiation challenging. Therefore the standard treatment recommended by the EAU Guidelines is surgical removal of the tumor but based on a retrospective study by Richard and colleagues AS may also be a feasible option if it is preceded by a renal tumor biopsy (RTB) histologically verifying OC.[49, 54]

Renal Cysts and Cystic Tumors

Simple renal cysts are common, increase in incidence with age and are found in 27-50% of the population over 50 years of age.[55, 56] More complex cysts have a potential of being malignant and in 1986 Morton A. Bosniak introduced, and later on modified, the Bosniak classification system for defining renal cysts complexity based on computed tomography (CT) findings.[57, 58] The diagnostics and management of renal cysts are closely intertwined based on radiological categorization and proper differentiation between benign and malign lesions making it clinically important when determining which patients should be offered surgical intervention. As shown in Table 2 the Bosniak five-tier classification system has the purpose of alleviating this management. Findings in a recent SR including 39 studies showed that the estimated risk of renal cysts being malignant was 0% for Bosniak category I-II cysts and <1% for Bosniak category IIF (F for follow-up) not being upgraded to a category III or IV after follow-up imaging. Interestingly the investigators found that about 12% of IIF cysts were re-classified to III or IV at follow-up, of which an estimated 85% were shown to be malignant. The SR also showed that the overall estimated malignancy risk increased to 51% in category III cysts and to 89% in category IV cysts.[59]

The imaging gold standard for renal cyst diagnostics is still contrast enhanced CT (CECT) but with advances in magnetic resonance imaging (MRI) and contrast enhanced ultrasonography (CEUS) techniques the diagnostic accuracy of these imaging modalities have improved making both feasible alternatives to CT.[60] Regardless of imaging modality used, it is the foundation for deciding on discontinuation of follow-up, additional follow-up or active intervention of any renal cyst. Bosniak category I and II cysts do not require any follow-up. Follow-up for Bosniak category IIF are recommended to be performed four to six months after initial imaging and with regular increasing intervals up to five years if needed to demonstrate stability of the cyst as proof of benignity. The current recommendations for both Bosniak category III and IV are surgical treatment of the tumors albeit active surveillance has been suggested for the former.[49] In several studies the surgical outcomes for renal cysts with RCC have revealed a low risk of local recurrence or metastases, especially for the newly classified histological entity "multilocular cystic renal neoplasm of low malignant potential".[61-65] Finally regarding survival, in the largest retrospective study to date analysing 687 renal cysts with RCC treated with surgical removal, the cancer-specific mortality (CSM) at a median follow-up of 40 months was only 1.8%.[66]

Table 2 – The Bosniak classification system, features and management

Category	Features	Management	Illustration
I	A benign simple cyst. with a hairline thin wall that does not contain septa, calcifications, or solid components. It measures water density and does not enhance.	No Follow-up	
II	A benign cyst. May contain a few hairline thin septa in which "perceived" enhancement may be present. Fine calcification or short segment of slightly thickened calcification may be present in the wall or septa. Uniformly high attenuation lesions <3cm, well marginated and do not enhance.	No Follow-up	
IIF	May contain multiple hairline thin septa or minimal smooth thickening of their wall or septa. Perceived enhancement of their septa or wall may be present. The cyst may contain calcification which may be thick and nodular, with no contrast enhancement. Generally well marginated. Totally intrarenal nonenhancing high attenuation renal lesions >3 cm are also included in this category.	Follow-up up to 5 years to demonstrate stability as proof of benignity.	
III	"Indeterminate" cystic masses that have thickened irregular or smooth walls or septa in which measurable enhancement is present. These are surgical lesions, although some will prove to be benign (eg, hemorrhagic cysts, chronic infected cysts, and multiloculated cystic nephroma), some will be malignant, such as cystic renal cell carcinoma and multiloculated cystic renal cell carcinoma.	Surgery in most cases, Active surveillance an option.	
IV	These are clearly malignant cystic masses that can have all the criteria of category III, but also contain enhancing soft-tissue components adjacent to, but independent of, the wall or septum. These lesions include cystic carcinomas and require surgical removal.	Surgery	

Adapted from Israel and Bosniak 2005.[58]

Illustrations courtesy of Dr Matt Skalski, Radiopaedia.org, rID: 20989

RCC Subtypes and Pathophysiology

Clear cell RCC

The most common histological subtype is ccRCC accounting for 70-75% of all malignant renal tumors and is associated with mutations in the Von Hippel-Lindau (VHL) gene in 91% of sporadic cases.[67] The VHL gene, found on chromosome 3p25 is a tumor suppressor gene first described in 1993 by Linehan and colleagues who determined its association to Von Hippel-Lindau syndrome, an autosomal dominant inherited disease hallmarked by hemangioblastomas of the retina, brain and/or spinal cord, pheochromocytomas, pancreatic cysts or neuroendocrine tumors, cystadenomas of the epididymis or broad ligament, and bilateral, multifocal kidney cysts or tumors.[68] The main pathway of ccRCC pathology is through the double hit deletion of the VHL gene which in turn deregulates the hypoxia-inducible factor (HIF) protein, in particular HIF2α, resulting in upregulation of downstream factors.[69] Other frequently associated genes with sporadic ccRCC oncogenesis include PBRM1, SETD2, JARID1C and BAP1.[70] Gross features of ccRCC are globular growths from the renal cortex with tumor borders being sharp against the normal parenchyma. The tumor itself is yellow in color, often showing areas of hemorrhage and necrosis and with larger tumors presenting with renal sinus or renal vein involvement. Microscopically a typical clear cytoplasm due to lipid and glycogen deposits is seen.[41] In a large cohort analysis by Leibovich and colleagues the estimated overall five year distant metastasis-free and cancer specific survival for localized ccRCC curatively treated was found to be 71% and 76% respectively with the corresponding 10 year survival rates estimated to 61% and 69% respectively. Based on multivariate analysis, they also showed that compared to papillary RCC (pRCC) and chromophobe RCC (chRCC) combined, ccRCC had a 2.76 higher risk of metastasis ($p<0.001$) and a 1.77 higher risk of cancer specific death ($p<0.001$).[71]

Papillary RCC

The second most common subtype is pRCC that is seen in 10-15% of cases.[72, 73] The 2016 WHO classification distinguishes between two groups; pRCC type-1 and type-2. Gross features of both pRCC tumor types show a varying cystic and/or solid consistency with a reddish-brown color and a pseudocapsule. Microscopically both tumor types display papillary or tubulopapillary architecture with occurrence of calcifications, necrosis, and foamy macrophage infiltration. Distinct microscopic features of type-1 tumors are thin basophilic papillae with clear cytoplasm while type-2 tumors appear with heterogeneous thicker papillae and eosinophilic cytoplasm. Recently Linehan and colleagues performed an extensive molecular characterization of pRCC concluding that 81% of type-1 pRCCs have a gain in chromosome seven which includes the Mesenchymal to Epithelial Transition (MET) proto-oncogene. They further analyzed type-2 pRCC genomics finding at least three type-2 subtypes with mu-

tations found mainly in the NRF2-ARE pathway genes. In their analysis type-1 pRCC was found to have a more favorable prognosis than type-2.[74] In a long-term survival analysis Steffens and colleagues compared pRCC survival to that of ccRCC in a total of 4941 patients. For localized disease both cancer-specific survival (CSS) and overall survival (OS) analysis favored pRCC compared to ccRCC with hazard ratio (HR) 0.45 (95%CI 0.31–0.65, p<0.001) and HR 0.58 (95%CI 0.45–0.74, p<0.001) respectively. Interestingly for patient with nodal or distant metastases at treatment start, CSS and OS analysis favored ccRCC compared to pRCC with HR 1.37 (95%CI 1.016–1.856, p=0.039) for CSS and HR 1.38 (95%CI 1.027–1.846, p=0.032) for OS.[73] A larger cohort including more than 11500 RCC patients compared subtype survival outcomes and showed similar CSS when comparing pRCC to ccRCC favoring the former with HR 0.64 (95% CI not reported, p=0.007).[75]

Chromophobe RCC

Being the third most common subtype, chRCC originates from the renal collecting ducts cells and accounts for approximately 5% of RCC cases.[41, 76] Classic and eosinophilic chRCC are the two variants that have been described, sharing features of being tan-brown, often large tumors with occasional central scar and well-circumscribed. Microscopically both variants have distinct cell borders and a voluminous cytoplasm with perinuclear halos and frequent binucleation. Separating histological features for the classic variant is that it has pale cytoplasm while the eosinophilic variant has large tumor cells with fine eosinophilic granules.[41] The genomics of sporadic chRCC accredits alterations, deletions in chromosomes 1, 2, 6, 10, 13 and 17, to the oncogenesis of these tumors.[39] When compared to ccRCC, univariate survival analysis of a large cohort showed that chRCC had a more favorable CSS with HR 0.24 (95% CI not reported, p=0.02).[75]

Other subtypes

The three RCC subtypes above account for ~98% of cases but some summarizing aspects of less frequent RCC subtypes are noteworthy. Both collecting duct carcinoma (CDC) and renal medullary carcinoma (RMC) are found in <0.5% of cases each and merit attention because of their extremely aggressive nature.[39] Both arise in the renal medulla, will frequently be diagnosed having large tumors with high histological grades and often perinephritic extension at presentation. These RCCs are more frequent in men (2.3:1 for CDC and 10:1 for RMC) and have extremely poor survival (median 17 weeks for RMC and 44 weeks for CDC). RMC has interestingly been noted to more commonly afflict young individuals of African descent with sickle cell hemoglobinopathy.[77]

Finally, although sarcoma of the kidney is no longer recognized as renal tumor entity, sarcomatoid differentiation is important to recognize as it can arise in any RCC subtype. It is estimated to occur in 5% of cases and with a median OS ranging from 4 to

12 months it is a strong indicator of poor prognosis even when compared to other high grade RCCs.[78] In a recent study by Trudeau and colleagues, on multivariate analysis comparing ccRCC to RCCs with sarcomatoid differentiation, the CSM risk was significantly higher for the latter with HR 3.15 (95%CI 2.49–3.99, p<0.001).[79] Similarly RCCs with rhabdoid differentiation are found in multiple subtypes, have an incidence estimated to 3-7% of cases, are generally aggressive with a 70% rate of distant metastases and associated with a poor median OS ranging from 8 to 31 months.[80]

Hereditary RCC and Genetic Considerations

Hereditary syndromes with RCC currently include Von Hippel-Lindau syndrome (VHLS), Birt-Hogg-Dubé syndrome (BHDS), Hereditary papillary RCC (HPRC), Hereditary leiomyomatosis and RCC (HLRCC), Tuberous sclerosis complex (TSC), Hereditary pheochromocytoma and paraganglioma (HPP), Non-polyposis colorectal cancer syndrome, Hyperparathyroidism jaw tumor syndrome, Cowden syndrome (also known as phosphatase and tensin homolog hamartoma syndrome) and finally Constitutional chromosome three translocation.[41]

The hereditary subtypes of RCC are estimated to comprise 5-8% of all RCC cases, are usually multifocal and bilateral and with the most common forms listed in Table 3 together with involved genes, chromosome location and tumor type histology.[38, 81, 82] In a national registry based analysis of more than 106 000 RCC records reviewed by Shuch and colleagues, the sensitivity of finding hereditary RCCs in patients who were ≤46 years was 70% with a specificity of 90%.[82] Age at RCC diagnosis is therefore, apart from family history, occurrence of bilateral and or multifocal renal tumors, presence of syndrome associated clinical manifestations and tumor histology, considered a major indicator of possible hereditary form of RCC. As such patients 46 years or younger diagnosed with RCC as well as their relevant family members should strongly be considered for genetic testing.[49]

Regarding management of hereditary RCCs, due to the frequent multifocality and bilaterality of these tumors, historically these patients have undergone bilateral nephrectomy with subsequent lifelong need of dialysis or in recurrence free cases renal transplantation.[83] With better understanding of the tumor biology of these hereditary forms, a “3-cm rule” has been developed for VHL, BHD and HPRC tumors with the principles that only lesions reaching three cm or larger should be removed preferably by tumor enucleation, that the systematic order of resection should be from most to least accessible and that based on follow-up imaging a repeat resection should be performed whenever any new lesion reaches three cm or larger.[84] In a study by Singer and colleagues including 128 patients with bilateral renal masses and a minimum ten-

year follow-up of applying the strategy above, they showed 97% CSS and 88% OS with 95% of patients avoiding dialysis.[85]

For patients with HLRCC and HPP related renal tumors on the other hand the "3-cm rule" cannot be applied due to the aggressive nature of these hereditary subtypes. Consequently early detection and wide margin resection of the lesions are advocated.[38, 86]

Table 3 – Most common hereditary forms of RCC

Hereditary syndrome	Gene(s)	Chromosome	Histology
Von Hippel Lindau	VHL	3p25	Clear cell
Hereditary papillary RCC	MET	7q31	Papillary type 1
Hereditary leiomyomatosis RCC	FH	1p42	Papillary type 2
Birt-Hogg-Dubé	FLCN	17p11	Hybrid oncocytic, chromophobe, oncocytoma
Tuberous sclerosis complex	TSC 1/2	9q34/16p13	Clear cell, papillary, chromophobe, bilateral angiomyolipomas
Cowden syndrome	PTEN	10q23	Clear cell, papillary, chromophobe
Hereditary pheochromocytoma and paraganglioma	SDH B/C/D	1q36/1q23/11q23	Clear cell, unclassified/eosinophilic variant

Table shows the most common hereditary forms of RCC, the identified genes and specific chromosomes involved and the histological subtype(s) of RCC they render. VHL = Von Hippel-Lindau, MET = Mesenchymal to Epithelial Transition, FH = Furamate hydratase, FLCN = Folliculin, TSC = Tuberous sclerosis complex, PTEN = Phosphatase and tensin, SDH = Succinate dehydogenase, p = Short arm of a chromosome, q = Long arm of a chromosome.

Grading and Staging

Grading

Histological grading refers to the classification of a tumor according to the differentiation of its cellular morphology and with the purpose of predicting rate of progression for said tumor. Generally in grading systems, low grade tumors are well-differentiated, i.e. the tumor cells have a close resemblance to normal cells, and subsequently each incremental step up in grade classification indicates an increase in level of tumor cell abnormalities. The earliest suggested grading system for RCC was proposed by Hand and Broders in 1932 but soon abandoned because several non-RCC types of tumors were included in their cohort.[87, 88] In 1949 Griffiths and Thackray developed the first applicable RCC grading system.[89] It was a three-tiered classification system based on both overall microscopic tumor morphology and intra-cellular features in 42 patients who had undergone nephrectomy for RCC. They were able to show a 5 year CSS of 72% for grade 1, 33% for grade 2 and 28% for grade 3 tumors. Interestingly this was the grading system later applied by Robson in his RN series presented in 1969 showing similar results.[4] Although Griffiths and Thackray proved grade outcome differences the grading system was of a composite nature, i.e. a simultaneous microscopic overall tumor morphology and intra-cellular tumor assessment. Variations of this composite type of grading system were proposed by others as well, all of which were found to be problematic because of suboptimally defined grade criteria, failure to evenly weight the grades and finally interobserver interpretation errors.[88]

The next evolution of RCC grading was when Myers and colleagues introduced grading based on differentiation of tumor cell nuclei alone, a system that in 1971 was enhanced by Skinner and colleagues.[90, 91] The latter study defined a four-tiered system based on the worst nuclear morphology found in the tumor and showed a 5 year CSS of 75%, 65%, 56% and 26% in grades 1 through 4 (p=0.001) in 272 patients who had undergone nephrectomy for RCC.

In 1982 Susan A. Fuhrman and colleagues published a novel four-tier RCC nuclear grading system, as shown in Table 4, based on the simultaneous assessment of nuclear size, nuclear pleomorphism, and nucleolar prominence.[92] They retrospectively analyzed 103 patients with any subtype of RCC receiving any type of treatment and reported 5 year OS rates of 64%, 34%, 31% and 10% for grades 1 through 4 with survival rates of grades 2 and 3 non-significantly overlapping. For more than three decades the Fuhrman classification has been the most widely accepted grading system and proven to be an independent prognostic factor for RCC survival albeit in most studies a combination of grade groupings (most commonly grade 1+2 versus 3 versus 4 ,or grade 1+2 versus 3+4) have been used in the predictive models.[72, 93, 94]

The Fuhrman classification has not been without criticism though. Interobserver reproducibility has come into question by several investigators and has been attributed to the grading system's requirement of simultaneous assessment of three microscopic features.[94] The better understanding of RCC subtype and intra-tumor heterogeneity has also elucidated the weakness of the Fuhrman classification to prognosticate survival.[94-96]

In 2012 the International Society of Urologic Pathologists (ISUP) proposed a new four-tiered grading system for RCC based on the evaluation of the nucleoli alone as shown in Table 5.[80] The rationale behind a switch has been the aforementioned weaknesses of the Fuhrman classification in conjunction with evidence of stronger prognostic significance of the nucleolar grading system for ccRCC and pRCC.[97, 98] Most recently the WHO recommended the ISUP grading system at a consensus meeting in 2016 renaming it to the WHO/ISUP grading system.[41] The WHO/ISUP grading system has been validated for ccRCC and pRCC but not for other tumor subtypes although it can be applied in a descriptive manner.[99, 100]

Table 4 – Fuhrman grade classification

Grade	Nuclear diameter	Nuclear shape	Nucleoli
1	~10 µm	Round, uniform	Absent, inconspicuous
2	~15 µm	Irregularities in outline	Visible at x400
3	~20 µm	Obvious irregular outline	Prominent at x400
4	>20µm	Bizarre, often multilobed	Heavy chromatin clumps

Adapted from Fuhrman et al.[92]

Table 5 – ISUP/WHO grading system for ccRCC and pRCC

Grade*	Description
1	Nucleoli absent or inconspicuous and basophilic at x400 magnifiction
2	Nucleoli conspicuous and eosinophilic at x400 magnification, and visible but not prominent at x100 magnification
3	Nucleoli conspicuous and eosinophilic at x100 magnification
4	Extreme nuclear pleomorphism and/or multinucleate giant cells and/or rhabdoid and/or sarcomatoid differentiation

Adapted from Delahunt et al.[80] *The highest histological grade found in the RCC tumor should be noted in the pathology report but no consensus on the extent of tumor to be examined has been reached.

Staging

Tumor staging refers to the objective evaluation of tumor extent, more specifically the tumor size and anatomical location, nodal spread and presence of metastases at distant sites. The significance of any staging classification lies mainly in determining the best treatment option, the prognosis and the potential for inclusion into clinical trials. Historically the first two recognized staging classifications for RCC were suggested by Flocks and Kadesky in 1958 and by Petkovic in 1959.[101, 102] In 1969 the publication by Robson and colleagues gave rise to the Robson stage classification.[4] The important aspects of the Robson staging system were the subdivision of stage by extent of tumor growth, especially the extra-renal extent, and the significant differences in survival based on these stages (see Table 1). In 1978 the Union Internationale Contre le Cancer (UICC) and the American Joint Committee for Cancer Staging and End Result Reporting (AJCC) proposed, as a joint venture, a new Tumor, Nodes and Metastases (TNM) based staging classification for RCC.[103] Compared to the Robson classification the emphasis was put more on intra-renal rather than extra-renal tumor extent.[88] This was in order to create improved stage-classes which could better predict survival outcomes and since then the TNM classification has been modified in 1987, 1997, 2002, 2010, 2012, 2016 and in 2017 (Table 6) by both parties to further pursue this goal.[104, 105]

The latest TNM version from 2017 by the UICC remains unchanged from the 2010 classification which has been externally validated in regards to significant survival differences between different T-stages and overall TNM stages.[106, 107] Novara and colleagues showed the following significant estimated five year CSSs: 94.9% in pT1a, 92.6% in pT1b, 85.4% in pT2a, 70% in pT2b, 64.7% in pT3a, 54.7% in pT3b, 17.9% in pT3c and 27.1% in pT4 (overall $p<0.00001$). Pairwise CSS analysis showed a significant poorer survival ($p<0.05$) between each incremental T-stage step, except between pT2b and pT3a ($p=0.34$) and pT3c and pT4 ($p=0.26$). When using multivariate cox regression analysis T-stage was shown to be an independent predictor of CSS ($p<0.0001$) even when only considering N0M0 patients.[106] Kim and colleagues showed similar CSS between T-stages but with data for ten year survival rates. They also presented a concordance index (C-index) of 0.85 for overall TNM-stage as an independent prognostic variable for CSS.[107]

Interestingly differences have been identified between the latest versions of the AJCC (8th edition 2016) and UICC (8th edition 2017) TNM staging classifications for RCC. Delahunt and colleagues wrote a recent editorial on the topic pointing out that the UICC has overlooked novel prognostic factors that AJCC (in conjunction with WHO/ISUP) have considered in their 8th edition. In short the authors state that new evidence allows the presence of microscopic vein invasion, any type of hilar sinus invasion (not only hilar fat) or infiltration of the pelvicalyceal system to all qualify as pT3a as these features have been recognized as important new prognostic factors.[108]

Table 6 – 2017 TNM classification

T - Primary tumor		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1	Tumor ≤ 7 cm or less in greatest dimension, limited to the kidney	
	T1a	Tumor ≤ 4 cm
	T1b	Tumor > 4 cm but ≤ 7 cm
T2	Tumor > 7 cm in greatest dimension, limited to the kidney	
	T2a	Tumor > 7 cm but ≤ 10 cm
	T2b	Tumors > 10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia	
	T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia
	T3b	Tumor grossly extends into the vena cava below diaphragm
	T3c	Tumor grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)	
N - Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in regional lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	

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

Adapted from Brierley et al.[104]

Clinical Presentation and Diagnosis

Clinical Presentation, Physical Examination and Laboratory Work-up

RCC has been called the "internist's tumor" due to the diversity of signs and symptoms they cause although today an estimated 60% of renal tumors are detected incidentally due to increased use of imaging.[109] This has resulted in more frequently detection of smaller RCCs which consequently to a lesser degree elicit local symptoms at tumor detection.[110] Gross hematuria, a palpable abdominal mass and flank pain are the "classic triad" of symptoms in patients diagnosed with RCC and found in contemporary cohorts to be present in 39%, 23% and 13% of cases respectively.[111, 112] Being symptomatic at tumor detection is correlated to a more advanced disease and poorer survival but interestingly only between 6-10% of cases actually present with all three symptoms.[113, 114] Also adult debut of varicocele, especially on the right side, should raise suspicion of a renal mass, although it is rare and as a solitary symptom found in about 2% of RCCs in men.[115]

Paraneoplastic symptoms are present in about 30% of patients at diagnosis and are in general correlated to poorer survival. Proposed causes are thought to be mediated through tumor produced peptides, benign tissue reaction to malignancy, secondary to the immune system response or a combination of these mechanisms. The most common are hypertension (40%), cachexia (30%) and anemia (20%) while less frequent symptoms are fever (up to 20%), elevated liver enzymes in the absence of live metastases (Stauffer's syndrome) (3-20%) and hypercalcemia (13-20%). Infrequent and rare symptoms reported are mainly night fever (8%), polycythemia (1-8%), Amyloidosis (3-8%), beta-Human Chorionic Gonadotropin elevation and related symptoms (galactorrhea, gynecomastia, amenorrhea; 6% of cases), Cushing's syndrome (2%) and neuromyopathies.[69, 116]

Patient medical history and physical examination are, asides from relevant imaging, important parts of a rounded approach to RCC management and serve both the purpose of initially assessing extent of disease, but more importantly evaluating treatment options based on a patients' prognostic factors, comorbidities, age and wishes.[69] As part of this approach laboratory work-up helps to evaluate general condition, kidney function, coagulation function, nutritional status and prognostic biomarkers.[112] To that end currently the EAU guidelines recommend the work-up of the following laboratory parameters: glomerular filtration rate (GFR), creatinine, complete cell blood count, erythrocyte sedimentation rate, liver function study, alkaline phosphatase, lactate dehydrogenase, serum corrected calcium, coagulation study and finally urine analysis for infection and in relevant cases for cytology.[49]

Imaging Modalities

Imaging for renal tumor diagnostics and staging aim at differentiation between benign and malignant disease and precise determination of primary tumor extent before decision on treatment strategy. In RCC follow-up the goals of imaging are active surveillance (AS) of renal masses in patients unsuitable for surgery, recurrence detection after curative treatment of RCC or evaluation of progression in patients with recurrence or metastatic RCC (mRCC).[112] Imaging modalities with highest impact on diagnostics and surveillance in RCC are US, CT and MRI while positron emission tomography (PET), bone scan index (BSI) and conventional (plain) X-ray radiology play a more auxiliary role. Below these imaging modalities are briefly described and discussed.

Ultrasonography

Unenhanced US usually with color doppler allowing for vascular evaluation is the most commonly used modality for initial detection and evaluation (e.g. solid or cystic) of renal masses. This is explained by the frequent use of US for the general evaluation of the abdomen in asymptomatic patients where an estimated 0.18-0.80% of these examinations render an incidentally found RCC.[117] The modality is non-invasive, void of radiation exposure and cost efficient. Unenhanced US has low sensitivity and specificity for diagnosing RCC, especially in complex renal cysts and also limited staging accuracy. These limitations are partly user dependent but also due to bowel gas and body habitus which can asides from obscuring a renal mass also conceal major veins and retroperitoneal structures.[118] CEUS is an extension of US and uses microbubble contrast agents administered intravenously to increase the echogenicity in organs.[117] CEUS for RCC diagnostics has evolved for the last decade and in a recent SR was shown to have excellent overall median sensitivity of 93% with a moderate specificity of 73%. The evidence also suggested CEUS having superior diagnostic accuracy compared to CT in investigating complex renal cysts, renal masses <4cm and for differentiation between RCC and AML.[119] Currently CEUS is recommended as a valid alternative for diagnosing cases where CT or MRI show an equivocal renal mass.[49]

Computed Tomography

CECT is currently the gold standard for RCC diagnosis, staging and follow-up. Principally the modality uses multiphasic imaging after the administration of a single bolus of intravenous iodinated contrast in order to evaluate a renal tumor. The CECT phases usually include an unenhanced imaging phase, a corticomedullary phase (also known as angionephrographic phase or late arterial phase), a nephrographic phase (also known as parenchymal venous phase) and an excretory phase.[117] The unenhanced phase acts as baseline to which the other phases usually are compared. If an

enhancement (defined as >10-15 increase in Hounsfield Units compared to unenhanced images) is present it is a sign of a renal tumor. Furthermore the degree of enhancement has been correlated to different subtypes of RCC and benign renal tumors.[69, 117] In the contemporary SR by Vogel the CECT overall sensitivity and specificity of diagnosing RCC was estimated to 88% and 75% respectively but its diagnostic accuracy was lower in renal masses ≤ four cm and in complex renal cysts.[119] For TNM staging purposes CECT is still the most widely accepted modality with an overall estimated sensitivity of 87% and specificity of 75% albeit performing poorer than US and MRI in investigating venous tumor thrombus.[119]

Magnetic Resonance Imaging

MRI uses magnetic fields, electric field gradients and radio waves to generate images and therefore employs no radiation. For renal diagnostics MRI is suitable in cases with iodine-based CT contrast agent allergies and in pregnant women.[49] The modality has a high ability to show intrinsic soft tissue contrasts but similarly to CECT, the comparison of unenhanced images to that of gadolinium contrast agent enhanced ones are most commonly used for renal tumor evaluation.[117] Gadolinium contrast agents very rarely cause anaphylactic reactions but caution should be exercised in patients with impaired GFR of <30mL/min/1.73m^2 as the agents have been associated to nephrogenic systemic fibrosis.[69, 117] For diagnosing RCC an estimated overall median sensitivity of 88% and specificity of 89% was found in a contemporary SR in which also the ability of RCC staging using MRI was shown to be excellent. In particular MRI was shown to be superior to CECT in diagnosing RCC renal vein invasion and invasion of adjacent structures.[119] New MRI modalities are being developed such as diffusion-weighted imaging with suggested improvements on RCC diagnostic accuracy and subtype differentiation but no specific one is currently recommended.[49]

Conventional Radiography

Historically conventional radiography including urography, retrograde pyelography and renal angiography were used in the diagnosis and preoperative evaluation of suspected renal tumors. With the era of cross-sectional imaging these modalities have lost their role in assessing renal tumors. Urography and retrograde pyelography have been replaced by CECT which also holds true for renal angiography with the exception of the modality still being used as a prelude to renal artery embolization in selected cases.[117]

Regarding imaging of the chest for RCC metastases evaluation at primary diagnostics, the use of conventional chest X-ray (CXR) is considered obsolete, favoring CT instead.[120] For follow-up in curatively treated RCC cases, the major guidelines with the exception of the EAU guidelines still recommend chest X-ray as part of their respective follow-up protocols but do advice on use of thoracic CT in patients with higher risk of recurrence.[121]

Bone Scintigraphy

Bone scintigraphy (BS) uses intravenous introduction of radioactive tracers, usually technetium-99m isotopes, which gather in sites with high metabolic activity (e.g. tumor cells) and emit radiation which is analyzed in regards to any potential bone metastasis. BS is superior to conventional radiography for detecting bone metastasis.[117] In RCC 30% of patients who have systemic symptoms at presentation are diagnosed with bone metastasis and therefore the current major guidelines recommend BS based on patient symptoms suggesting bone involvement.[49, 122, 123]

Positron Emission Tomography

For RCC diagnosis, staging and surveillance 2-Deoxy-2-[18F]-fluoro-D-glucose (FDG) and 124-Iodine-Girentuximab (124-IG) are two radioactive tracers recently established for positron emission tomography (PET). The tracers are introduced intravenously, are taken up to different extents based on type of tracer used and level of cellular activity. Finally a scanner detects the tracer radiation and an image is computed. PET uptake images are usually used in combination with an overlaid CT to create an enhanced spatial anatomy of lesions with high metabolic activity.[117, 124] In a study by Divgi and colleagues use of 124-IG-PET/CT was shown to have a sensitivity of 86% and a specificity of 86% in diagnosing RCC reaching a superior accuracy than CECT. Additionally in a recent SR use of FDG-PET/CT was evaluated for RCC diagnosis, showing a median sensitivity of 88% and specificity of 88%, albeit these results were from only two studies with small cohorts. Interestingly a study using dual-tracer PET/CT with both FDG and 11-carbon-acetate (11-AC) could show a 94% sensitivity and 98% specificity for differentiating AML with minimal fat from RCC.[125] All in all PET/CT is showing promise in RCC diagnostics but the role of the modality remains elusive due to the its limitations in detecting lesions smaller than two cm and that a negative result does not rule out a metastasis. Therefore currently no specific recommendations regarding their use are given by the major RCC guidelines.[49, 122, 123]

Renal Tumor Biopsy

The rationale of renal tumor biopsy (RTB) serves several purposes of which determining histology in a renal lesion with indeterminate radiological features being the most important. The biopsy is usually image guided using US or CT and performed percutaneously with fine needle aspiration (FNA) or Core Biopsy (CB). RTB is especially useful in a small renal mass (SRM) and highly recommended in patients who are candidates for active surveillance (AS) where tumor subtype can determine outcome. Furthermore the role of RTB is also to delineate tumor histology prior to any ablative treatment and in the RCC metastatic disease setting assist in establishing a treatment strategy.[126] Historically RTB has been associated with high risk of complications, risk

of tumor seeding and high rate (up to 18%) of false negative biopsies. With the advances in both imaging and biopsy techniques these risks have significantly diminished.[112] As such RTB has been revisited and extensively evaluated for the last two decades, most recently in a SR by Marconi and colleagues underpinning the RTB recommendations of the EAU guidelines.[49, 127] The SR analyzed the diagnostic accuracy of RTB in 5228 patients from the 57 included studies. The overall median accuracy rate of diagnostic RTBs was estimated to 92%. Diagnostic sensitivity and specificity of CBs for determining malignancy could be meta-analyzed in 17 studies and were 99.1% and 99.7% respectively. When using FNA instead, a meta-analysis was possible in 18 studies and showed a diagnostic sensitivity and specificity of 93.2% and 89.8% respectively. The diagnostic accuracy of finding malignancy in cystic renal lesion was meta-analyzed in four studies showing slightly lower diagnostic sensitivity and specificity of 83.6% and 98% respectively. Furthermore analysis of histological concordance between the RTB and the final pathology report after tumor resection was available in 14 studies showing an overall median concordance rate of 90.3% with interestingly a higher such rate of 96% when analysing the six studies only including SRMs. Finally complications were analyzed in 37 available studies with a median overall complication rate of 8.1% across all studies but with ≥ grade two Clavien-Dindo classification complications or tumor seeding being extremely rare.[127, 128]

Diagnostic Considerations in Metastatic RCC

Historically about 20-30% of RCCs have been metastatic at diagnosis but with the increase in incidentally found primary tumors the incidence of these synchronous mRCC cases has dropped to 15-17% during the last decades.[129, 130] Additionally about 20% of patients treated for localized RCC at diagnosis will develop an asynchronous recurrence within five years.[130] Timely detection of these metastases, with Table 7 showing the most common metastatic sites, is an important determinant of subsequent treatment strategy and outcome.[106, 131, 132] Therefore the current recommendations for mRCC evaluation are the use of the previously described imaging modalities for investigation of suspected metastatic sites (e.g. depending on suspected site; thoracic CT, MRI of the brain or conventional radiography or scintigraphy of bone etc.) together with laboratory work-up and other relevant clinical features. Thoracic evaluation using CT is currently strongly recommended as an integrated part of any RCC diagnostics (both localized and suspected mRCC) but none of the other imaging modalities are routinely recommended other than on a case by case basis.[49, 122, 123]

Table 7 – Most common sites of RCC metastases

Lung	45.2%
Bone	29.5%
Lymph node	21.8%
Liver	20.3%
Adrenal gland	8.9%
Brain	8.1%
Other*	18.2%

Adapted from Bianchi et al 2012.[131] Site distribution based on evaluation of 11 157 patients with metastatic renal cell carcinoma (RCC). *Includes small intestine, large intestine, other metastases in the digestive system, kidney, other metastases in the urinary system, ovary, pleura, mediastinum and other metastasis in the respiratory system.

Imaging During Follow-up

Regarding type of imaging performed for follow-up after curative treatment, thoracic and abdominal CECT are the current gold standard, especially for thoracic imaging where the cross-sectional topography allows for a more detailed evaluation and earlier detection of recurrences compared to conventional radiography.[133] Use of US and MRI are also recommended in all the major guidelines but play an auxiliary role to reduce radiation in patients who undergo frequent follow-up imaging or be used when CECT is contraindicated. Regarding brain and bone metastases most cases are symptomatic at detection and therefore follow-up imaging should be reserved for cases with neurologic symptoms or skeletal pain but not performed on a regular basis.[134] In a recent meta-analysis including 14 studies the use of FDG-PET alone for finding RCC distant metastases showed a pooled sensitivity and specificity of 79% and 90% respectively. Interestingly the meta-analysis also showed that combining FDG-PET with CT increased the above pooled sensitivity to 84% and specificity to 91%.[135] Also novel approaches with 124-IG-PET/CT are now showing promise in detecting occult regional lymph node metastases and distant metastases but remain to be further investigated.[136, 137]

Management of Localized and Locally Advanced RCC

Localized RCC is defined as TNM stage grouping I – II while locally advanced RCC is defined as TNM stage grouping III or IV without any sign of distant metastases (see TNM stage groupings in Table 6). Contemporary populations-based cohorts show about 71-77% of newly detected non-metastatic RCCs to be localized, with majority of those being T1 tumors (52-62%), while 24-27.5% are locally advanced.[75, 130] The principles of localized disease management are to optimize cancer treatment and to preserve renal function. If these two criteria are met the aim is then to implement a treatment strategy which is minimally invasive and with low risk of complications.[49, 122, 123] As such a pre-treatment assessment of patients' tumor extent, comorbidities, age and own wishes tie into the decision on treatment. The management options offered for localized RCC are described below with a separate section describing additional considerations in locally advanced RCC.

Active Surveillance

Active surveillance (AS) has mainly been developed for small renal masses (SRMs) defined as contrast enhancing renal tumors ≤ four cm.[138] The rationales for considering AS instead of active treatment are that in SRMs aggressive RCCs are rare while benign tumors are relatively frequent and most importantly that the remaining SRMs are mostly of an indolent nature.[42, 43, 139, 140] Based on multiple publications the current major guidelines recommend the use of AS to some extent, especially for SRMs. In general, patients with SRMs and high age, slow tumor growth rate, comorbidities contraindicating surgery, significantly reduced renal function or patients with multiple tumors due to hereditary forms of RCC are suitable candidates for AS. The guidelines for implementing AS are principally to, with informed consent from the patients, perform repeat imaging initially every 3-6 months to evaluate tumor size and growth rate and also weigh in the results from any RTB that may be performed. Based on the subsequent overall risk-benefit assessment a decision can be made to continue AS or opt for active treatment. If the disease is deemed stable an ongoing AS protocol every 6-12 months is implemented.[49, 122, 123]

Minimally Invasive Techniques

Currently there are two minimally invasive techniques (MITs) widely accepted for treating RCC: cryoablation (CA) and radiofrequency ablation (RFA). There are also other less established modalities such as high-intensity focused ultrasound, irreversible electroporation and laser ablation available but these are still under development.[49, 69, 112] In general MITs are valid alternative modalities compared to surgery for treatment

of mainly SRMs and considered in the elderly or those with significant comorbidities. Success of MITs in RCC treatment is operator dependent and the modalities should be used judiciously in highly selected patients. Pre-ablation RTB when applying MITs is well established in primarily confirming a malignant diagnosis but also detecting a potentially more aggressive RCC subtype in need of more extensive treatment. Conversely the role of post-ablation RTB is under debate and only recommended if a follow-up imaging shows suspected growth or contrast enhancement.[112] Finally in regards to follow-up after MIT treatment only one of the major guidelines recommends a protocol using CECT or MRI at 3 and 6 months after the procedure followed by annual imaging for five years total.[49, 123] The CA and RFA modalities are described below as they represent the most widely used MITs.

Cryoablation

In RCC the CA procedure is performed either through a percutaneous or laparoscopic approach by introducing a probe into the tumor and causing tissue destruction through two cycles of rapid freezing and thawing. Contemporary treatment uses argon gas based systems to freeze the tumor to a treatment temperature of at least minus 40˚C. The procedure is monitored with real time imaging and the CA part of the treatment usually takes about 20 minutes.[112] Several comparisons have been made between CA, RFA and PN with mixed results in terms of oncological, functional and complication outcomes.[49, 112] Recently in a large comparative study by Thompson and colleagues all three modalities were examined in patients with T1a RCC. They found no difference in recurrence free survival (RFS) in 1057 patients treated with PN compared to 187 patients treated with CA and 180 treated with RFA. However the study also showed a superior metastasis free survival (MFS) in the PN and CA patients compared to RFS suggesting both that CA is non-inferior compared to PN and should be favored instead of RFA for T1a RCCs.[141]

Radiofrequency Ablation

In RFA energy is converted, through vibration of ions in the target tissue, into heat which then causes tissue damage and cellular death. The vibrations are generated by use of alternating current at a frequency of 450-1200 kHz in the monopolar probe entered into the target tissue percutaneously or laparoscopically. Impedance or temperature-based systems are used to monitor the progress of treatment which aims at ≥60˚C at the periphery of the ablation zone and can be CT-guided.[112] For RCC treatment RFA outcomes have showed mixed oncological and functional results in several studies when compared to CA and PN although the treatment effect is convincing enough to be recommended by the major guidelines.[49, 122, 123]

Surgery

Surgical Techniques

The historical description of kidney cancer surgery in the initial section of this thesis illustrates the rationales for modern RN as described by Robson in 1969 but also the evolution of PN going from necessity to self-evident for the treatment of localized RCC. Today the current major guidelines are in agreement that when possible, renal function preservation should be prioritized when choosing surgical technique.[49, 122, 123] Open RN and PN have remained to date the gold standard procedures for localized RCC as they have been proven to offer best oncological control but with the advances of laparoscopy a multitude of less invasive options have emerged showing similar oncological results as open procedures.

Laparoscopic surgery for a renal mass saw its first clinical light on 25th of June 1990 when Dr Ralph V. Clayman and colleagues performed the first laparoscopic radical nephrectomy (LRN).[142] The procedure was performed at Washington University in St. Louis, USA, took six hours and 45 minutes with 300ml perioperative bleeding and with a 6 day postoperative in hospital stay before discharge.[143] Since then the laparoscopic techniques have evolved for the last two and a half decades to include retro- and transperitoneal approaches, laparoscopic partial nephrectomy (LPN), a hand-assisted laparoscopic technique, natural orifice transluminal endoscopic surgery (NOTES), laparoscopic single site surgery (LESS), and as of 2004 the introduction of the DaVinci® platform for robot-assisted procedures including robot-assisted partial nephrectomy (RAPN) as shown in Figure 2.[144-148] RAPN has lately gained more acceptance and use as the learning curve of the technique is steeper than that of LPN but also because more complex RCCs have become accessible with a minimal invasive approach.[149]

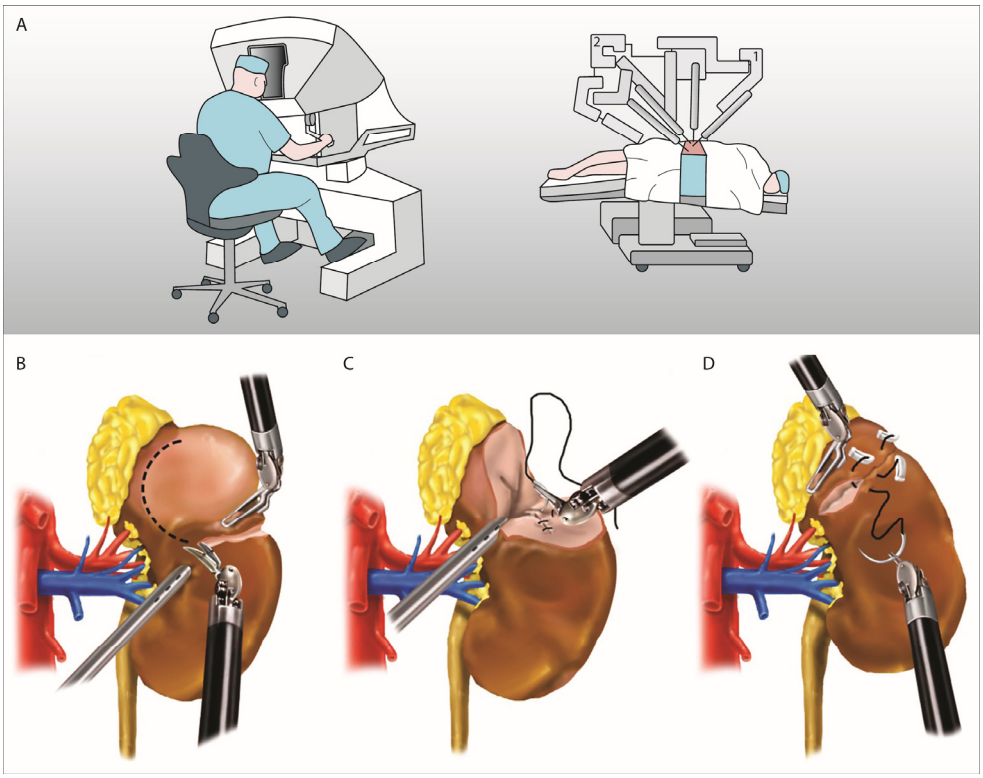


Figure 2 – Procedures in robot-assisted nephron-sparing surgery to remove renal cell carcinoma. (A) In robot-assisted surgery, instead of directly moving the instruments, the surgeon performs the normal movements associated with the surgery, and the robotic arms make those movements and use end-eff ectors and manipulators to perform the actual surgery on the patient. One arm is dedicated to the laparoscope and the two others hold forceps, monopolar curved scissors, a cautery hook, and a large needle driver. The patient is positioned in a modified flank position. Port configuration can vary based on tumor location to optimise the working angles. Surgical excision of the tumor is done by (B) kidney mobilisation, (C) tumor resection (with or without a rim of normal parenchyma according to anatomical and tumor features), and (D) final reconstruction (renorrhaphy). Figure illustration and text reprinted from The Lancet, Vol. 387, Capitanio and Montorsi, Renal Cancer, Pages No. 894-906, Copyright (2016), with permission from Elsevier.

The oncological and functional outcomes of the different surgical approaches have increasingly been evaluated in a vast number of studies for the last two decades and were summarized in two SRs with 4580 studies screened by Maclennan and colleagues in 2012.[150, 151] The first SR with 34 studies included analyzed the evidence regarding the oncological outcomes of surgical approaches options for localized RCC. The SR underpinned both the oncological survival benefits of PN for tumors ≤ four cm and the oncological survival non-inferiority of the PN approach in larger localized RCC tumors compared to RN. Furthermore they concluded that minimally invasive

alternatives, i.e. laparoscopic or robot-assisted approach, compared to an open approach were, when technically feasible, similar in CSS and OS.[150] In the second SR Maclennan and colleagues analyzed 29 studies providing data on functional outcomes of PN and RN both when performed open or laparoscopically. For PN there was a clear benefit in preserving renal function and better quality of life (QoL) compared to RN irrespective of open or laparoscopic approach. For RN a benefit in shorter hospital stay, shorter convalescence time and lower analgesic requirement was noted in patients undergoing laparoscopic compared to open surgery.[151] A more recent SR including 23 NRSs comparing perioperative outcomes between RAPN and LPN favored the prior in terms of length of hospital stay, risk of conversion to open surgery, warm ischemia time and changes in GFR before and after surgery.[152] These SRs and similar recent results have rendered the major RCC guidelines to recommend PN whenever technically available based on surgeon's expertise and skills and not only on tumor extent.[49, 122, 123]

Anatomical Classification Systems

Several scoring systems have been developed to assist in the objective decision making of whether open or laparoscopic PN or RN should be used. All are based on preoperative imaging elucidating the spatial anatomy of the tumor in relationship to the kidney and surrounding structures. The most recognized are the PADUA score, C-index Method, the RENAL nephrometry scoring system, the Arterial Based Complexity (ABC) Scoring System and the Zonal NePhRO scoring system.[153-157] The current major guidelines do not recommend any specific scoring system but emphasize the importance of objectifying tumor complexity to use together with surgeons experience and patient performance status, comorbidities, preferences and life expectancy when determining a suitable treatment option.[49, 123]

Roles of Lymph Node Dissection and Adrenalectomy

Lymph node dissection (LND) in RCC implies the removal of loco-regional lymph nodes at the same time as RN or PN. The rationale for LND has historically been to improve cancer control in those with suspected nodal spread but the use of LND has in contemporary cohorts dropped to less than 5% due to lack of evidence showing any benefit, decreasing risk of lymph node involvement due to stage migration and because of the challenges associated to performing LND laparoscopically.[158] Use of LND in localized RCC (T1-2) has been investigated in one randomized controlled trial (RCT) and sub-analyzed in regards to locally advanced RCC (>T2) in a SR by Bekema and colleagues.[159, 160] The trial randomized 772 patients to either RN with or without LND. In summary no significant survival benefit from LND was shown neither in patients with localized RCC nor in those with locally advanced RCC. Currently the major guidelines do not recommend LND in localized RCC without clinical evidence of lymph node involvement. However if pathological lymph nodes are

palpable at surgery or detected at preoperative imaging LND should be considered, especially if a patient's RCC indicates unfavorable features (e.g. sarcomatoid differentiation, high nuclear/nucleolar grade or tumor necrosis).[49, 122, 123]

In regards to adrenalectomy during RN or PN the rationale for such concurrent surgery is cancer control if adrenal gland invasion is present. A SR and recent prospective comparative non-randomized study (NRS) showed no difference in OS between those who underwent adrenalectomy and those who did not.[160, 161] Therefore the major guidelines recommend adrenalectomy if RCC invasion into the adrenal gland is suspected by imaging or clinically.[49, 122, 123]

Management Considerations in Locally Advanced RCC

Locally advanced RCCs can principally be summarized into being larger (>T2) and more aggressive (higher nuclear/nucleolar grade or invasive) with or without venous tumor thrombus (VTT) or loco-regional lymph node involvement.[49] As such these tumors require additional surgical considerations while also adjuvant systemic treatments have been suggested. Firstly LND may be more pressing as described in the previous section and secondly the larger size of these RCCs may warrant advanced open surgeries to a greater extent and in some cases even call for symptom control measures like arterial embolization in unresectable tumors.[112] Regarding the management of RCCs with VTT a poor prognosis has previously been noted but simultaneously through aggressive surgery with RN and thrombectomy patients have an estimated 45-69% five year survival rate if there is otherwise no evidence of distant metastases.[49, 112, 162] In a recent SR including 14 studies analyzing surgical outcomes of resection of VTT in the inferior Vena Cava (IVC) identified no superior surgical strategy offering any survival benefit and noted that the surgical method was more dependent on the extent of VTT being above or below the diaphragm and extent of IVC obstruction.[163]

Adjuvant Treatment in Locally Advanced RCC

About 20% of all non-metastatic RCC patients curatively treated will recur within five years and of these about half recur within the first two years.[164] At an attempt to prolong RFS in patients at high risk of recurrence (i.e. poor prognosis based on tumor morphology and histology corresponding chiefly to locally advanced RCC) adjuvant therapies have been assessed in a variety of studies since the mid-1980s.[112] There is currently no clear evidence on benefits of adjuvant treatment with recent results from phase III RCTs ASSURE and S-TRAC evaluating adjuvant targeted therapy in intermediate to high risk patients showing conflicting results.[165] Adjuvant therapy in high-risk patients will most likely play an essential future role in prolonging survival but is currently not recommended outside of clinical trials.[49, 122]

Management of Advanced RCC

Advanced RCC disease is defined as TNM stage grouping IV with metastases at diagnosis or asynchronous distant metastases of RCC developed in patients previously treated with curative intent for non-metastatic (M0) disease.[112] About 20-30% of newly diagnosed cases will present with mRCC (albeit with a decreasing incidence trend) while an additional 20% of localized RCC cases initially treated with curative intent will recur with distant metastases within five years.[129, 130, 134, 166] Interestingly a population-based study from Sweden showed the incidence of synchronous mRCC decreasing from 23% in 2005 to 15% in 2010 ($p<0.001$), attributing this to more frequent use of cross-sectional imaging.[130] Patients with advanced RCC generally have a poor prognosis but some treatment options have been made available aiming at prolonged survival or in some cases allowing for cure. These options include surgical removal of the primary tumor, local therapies for the metastatic lesions and systemic treatments. It is important to note that these options are primarily considered to be palliative measures and with the further possibility of combining these options the treatments can easily become complex. Therefore these advanced RCCs often require a multidisciplinary team of urologists, oncologists, pathologists and radiologists involved in deciding on treatment strategy.[112] Below the different aspects of advanced RCC management are discussed.

Cytoreductive Nephrectomy

Cytoreductive nephrectomy (CN) is the removal of the kidney containing the primary RCC in patients with mRCC. The rationale for CN has been to debulk overall tumor volume in patients with mRCC and improve immune response but also allow for possible regression of metastases.[112] The evidence for this approach has been based on two RCTs where mRCC patients were randomized to either receive interferon-alpha (IFN-α) systemic monotherapy or undergo CN and receive IFN-α.[167, 168] In 2004 Flanigan and colleagues performed a meta-analysis of these two RCTs totaling 331 mRCC patients demonstrating a 31% decreased risk of death in favor of the surgical arm ($p=0.002$) and with a median OS of 13.6 months for CN plus IFN-α compared to 7.8 months for IFN-α alone.[169] A population-based study by Thorstenson and colleagues showed that 55% of mRCC patients undergo CN in a contemporary cohort although other studies have shown that this seems to be decreasing since the introduction of targeted therapy.[130, 170] Currently the major guidelines recommend CN as part of a palliative treatment strategy but emphasize patient selection.[49, 122] The benefit of CN is largely dependent on the size and resectability of the primary tumor, the performance status (PS) and prognosis of the patient and the volume of metastases at time of diagnosis. More recently deferred CN has been proposed suggesting the need for the role of CN to be reevaluated, especially in the era of targeted therapy.[170]

Local Therapies for RCC Metastases

Metastasectomy (MTX) is the most frequently used local therapy for RCC metastases spread to parenchymal organs confined to the thorax or abdomen and is the only modality where a curative intent could be possible in mRCC patients. Radiotherapy (RT) is a palliative local therapy mainly used for brain and bone metastases while more recently also MITs aimed at metastases at various sites have been evaluated for this purpose as well.[69] Historically Barney and Churchill were in 1939 among the first to suggest a benefit of MTX in RCC by publishing a case report of one patient surviving 23 years after resection of pulmonary metastases.[171] During the 1970s and 1980s the role of MTX in mRCC grew stronger as several observational cohort studies could show that survival rates improved with MTX compared to no such treatment, especially in those with asynchronous metastases.[91, 172-175] Historically RCC has also been notoriously known for its resistance to RT but with more modern equipment and development of stereotactic body radiation therapy (SBRT) favorable outcomes in regards to symptom control and pain relief have been obtained.[132] Also MITs, mainly CA, for bone metastases have been evaluated in achieving local control.[176]

As highlighted in Table 7, data from a population-based study by Bianchi and colleagues showed the most frequent sites of RCC metastases to be lung, bone, lymph node, liver, adrenal gland and brain. Their study also showed that about two thirds of metastatic patients had one single site of metastasis but with the overwhelming majority being either inaccessible for surgery or having multiple lesions present. This suggested that number of metastases and location of metastatic sites for each patient were directly correlated with the possibility of performing MTX or RT and subsequently to prognosis of mRCC patients.[131] Furthermore investigations into complete MTX versus incomplete MTX have shown survival benefits in those undergoing complete resection both in RCC cases with synchronous and asynchronous metastases. In the case of the latter a survival benefit from repeat MTX has also been shown.[177, 178] In mRCC or for those with asynchronous metastases after curative RCC surgery, studies into the role of MTX and RT have revealed several patient, tumor, disease progress and metastatic site specific factors to be important for survival as shown in Table 8. Currently MTX for RCC metastases is recommended by the major guidelines in highly selected patients with favorable PS, tumor and metastatic features. RT on the other hand is reserved as a palliative option for bone and brain metastases.[49, 122] Finally in the era of targeted therapy the question of integrating MTX and/or RT with SysT has been evaluated but with most studies being retrospective and with small cohorts the results are difficult to interpret.[69]

Table 8 – Factors indicative of favorable outcome of local therapy for metastases from RCC

General factors			
Patient factors	• Good performance status (KPS, ECOG, WHO)	• MSKCC or IMDC favourable and intermediate risk	
Tumor biology	• Absence of sarcomatoid component	• Clear-cell subtype	• Low-to-moderate Fuhrman grade
Extent of disease	• Solitary (≤1) or oligometastatic (≤3) lesions	• Single organ site	• Absence of nodal metastases
Course of disease	• Asynchronous metastasis	• Disease-free interval of over two years	• No progression during treatment
Surgical factor	• Complete resection of metasteses possible or performed		
Site specific factors			
Lung	• Fewer than seven metastases, unilateral	• No mediastinal lymph node metastases	• Metastases less than four cm in diameter
Brain	• RTOG RPA class I*	• KPS ≥90 + single lesion	
Bone	• Peripheral location of metastases		

Adapted from Dabestani et al 2016.[132] ECOG = Eastern Cooperative Oncology Group, IMDC = International Metastatic Renal-Cell Carcinoma Database Consortium, KPS = Karnofsky performance status, MSKCC = Memorial Sloan Kettering Cancer Center, RPA = recursive partitioning analysis, RTOG = Radiation Therapy Oncology Group, WHO = World Health Organization. * RPA class I = KPS > 70, age < 65 years, absence of extracranial metastatic sites, control of primary tumor.

Systemic Therapy for RCC

With better understanding of the different histological and molecular subtypes of RCC, the last 20 years have seen some major breakthroughs in treatment of advanced RCC through SysT. Administered orally or intravenously SysT aims at hindering or diminishing RCC tumors and their metastases through various mechanisms. Simultaneously these potential benefits have to be weighed against the AEs of which fatigue, hypertension, nausea, diarrhea, dysphonia and palmar-plantar erythrodysaesthesia are most common.[179] Principally SysT treatments can be divided into chemotherapy, immunotherapy and targeted therapy for RCC with evidence for use of these drugs mainly established from phase III clinical trials.[49] Cellular pathways associated with development of RCC and treatment targets are depicted in Figure 3. The overall principles of SysT options in clinical use for mRCC are discussed below.

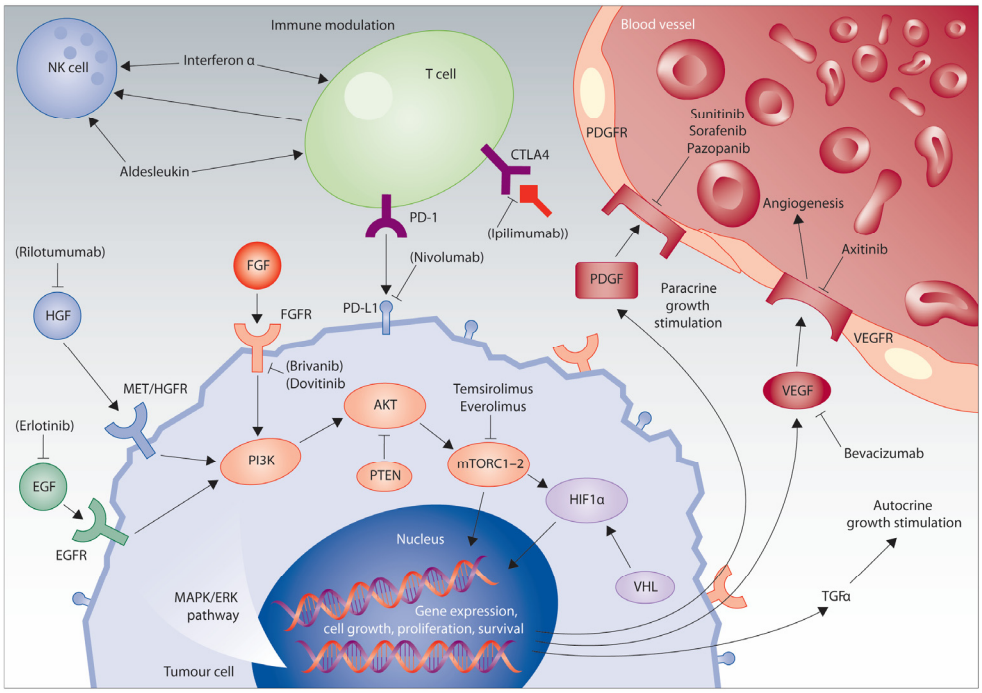


Figure 3 – Biological pathways related to development of renal cell carcinoma and treatment targets. EGF = epidermal growth factor, FGF = fibroblast growth factor, HGF = hepatocyte growth factor, NK = natural killer, PDGF = platelet-derived growth factor, VEGF = vascular endothelial growth factor. Figure illustration and text reprinted from The Lancet, Vol. 387, Capitanio and Montorsi, Renal Cancer, Pages No. 894-906, Copyright (2016), with permission from Elsevier.

Chemotherapy

Chemotherapy has been investigated extensively and only found to have an overall response rate in about 6% of cases.[180] Many such drugs including 5-Fluorouracil, platinum compounds, gemcitabine, vinblastine and bleomycin have been investigated without any significant clinical impact in mRCC.[112] The use of gemcitabine and doxorubicin in combination has been proposed in rapidly progressive mRCCs especially if sarcomatoid differentiation features are present.[181]

Immunotherapy

Historically immune-modulating cytokines such as IFN-α and interleukin-2 (IL-2) were the first drugs used in mRCC showing a 12% response rate with IFN-α and interestingly a high-dose IL-2 complete response in 5-10% of cases, but unfortunately both being associated with high levels of toxicity.[182-184] In the targeted therapy era IFN-α was recently re-evaluated in a Cochrane SR. They showed an estimated 30%

increase risk of death and 17% increased risk of serious adverse events (AE) using IFN-α compared to temsirolimus or sunitinib.[185]

Immune checkpoint blockade and vaccines also fall under immunotherapy but represent the newer generation of immune-modulating drugs for advanced RCC. Regarding vaccine therapy for mRCC, some promising trials are underway but no clinically approved treatment has been established yet.[69] The immune checkpoint inhibitors nivolumab and ipilimumab have recently emerged as novel clinical therapies. Both are human monoclonal antibodies with nivolumab being a programmed death ligand 1 (PD-L1) receptor inhibitor and ipilimumab a cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) receptor inhibitor. The principal mechanism of action for both drugs is to up-regulate the patients' immune response against tumor cells. When combined in a phase III RCT nivolumab plus ipilimumab showed a higher objective response rate (ORR) and OS compared to sunitinib alone in treatment-naïve advanced/metastatic RCC intermediate- to poor-risk patients.[186] Furthermore nivolumab monotherapy has previously been shown to also have favorable OS, better QoL and fewer AEs compared to everolimus in advanced ccRCC patients who had failed first or second line targeted therapy.[187]

Targeted Therapy

Oral intake tyrosine kinase inhibitors (TKIs) established for treatment of advanced RCC are sorafenib, sunitinib, pazopanib, axitinib and cabozantinib with less established drugs lenvatinib, tivozanib still under evaluation.[49] The principle mechanisms of action for these drugs are inhibition of platelet-derived growth factor (PDGF) and/or vascular endothelial growth factor (VEGF) or the receptors of respective factors. Both PDGF and VEGF are angiogenic proteins resulting from HIF overexpression in tumor cells with VHL-mutation found in 91% of ccRCC cases.[67, 69] While these drugs share the same principal mechanisms of action and have shown survival and/or progression benefits, based on various RCTs there are clear differences in their use as first, second and third line SysT for advanced RCC.[49]

Unlike TKIs, bevacizumab is a monoclonal antibody targeted therapy which directly inhibits VEGF and has been evaluated in RCTs in combination with INF-α compared to INF-α alone showing an overall higher ORR and PFS.[49]

Finally the mammalian target of rapamycin (mTOR) is an established oncologic target as it is a regulator of HIF. Both everolimus and temsirolimus are inhibitors of mTOR and induce antitumor effects by reducing angiogenesis in addition to possible direct negative effects on tumor cells.[69] While temsirolimus is administered intravenously and has shown limited potential in clinical trials, everolimus which is taken orally has shown potential in improving PFS as a second-line drug in VEGF-resistant mRCC patients.[188]

Systemic Therapy Strategies

Although objective response rates of 30-40% after targeted therapy have been observed, only 1-3% complete responses occur.[189-191] This suggests that there is a potential for improvement in type and timely use of these drugs. A reflection on this is the rapidly increasing number of drugs evaluated in RCTs comparing SysTs in different treatment settings (first, second or third line of therapy), patient groups (recurrent RCC or mRCC) and RCC subtypes (ccRCC or non-ccRCC). Furthermore the combination of different drugs and systemic treatment sequencing either with other drugs or with CN or MTX makes SysT strategies even more complex.[69] Through arduous work by experts the available evidence of the effects for each drug in different scenarios have been sorted out and summarized in the major guidelines.[49, 122] The most recent EAU guidelines recommendation on SysT for advanced ccRCCs is depicted in Figure 4. Finally regarding metastatic disease in non-ccRCC, in the absence of level 1 evidence, treatments have been based on retrospective analyses summarized in a recent SR suggesting, primarily for pRCC, some survival benefits from use of sunitinib or everolimus.[192]

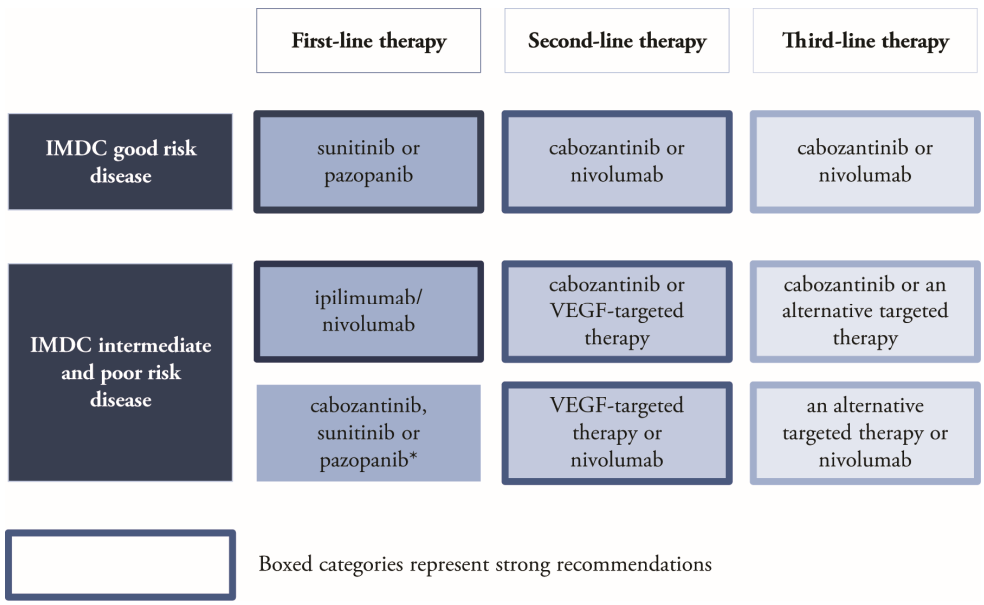


Figure 4 - EAU guidelines recommendations 2018 for the systemic treatment of metastatic clear-cell renal cell carcinoma. IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium, VEGF = vascular endothelial growth factor. *pazopanib for intermediate risk only. Reprinted with permission from the EAU Guidelines Office.

Prognostication and Follow-up in RCC

Prognostication

Since the turn of the millennia at least seven prognostic models using preoperative and eleven using postoperative parameters have been proposed. These models serve to determine likelihood of recurrence or survival based on clinical factors including laboratory findings and tumor morphology, extent and histology. Some prognostic models are presented in nomogram format (i.e. based on presence or absence of prognostic factors weighted points given which are then summarized and interpreted in a table into 1, 3, 5 or 10-year survival rates) while others are stratified into risk groups (i.e. based on presence or absence of prognostic factors, weighted points given which based on predetermined cut-offs stratify patients into risk groups; usually low, intermediate or high-risk).[112] Below the Leibovich score (LS) model is highlighted as an example in Table 9 while the most commonly used prognostic models are summarized in Table 10.[193, 194] More recently genetic and liquid prognostic biomarkers have been identified and are under investigation in novel integrated prognostic models.[194]

Table 9 – Leibovich score model for risk of recurrence stratification in ccRCC

Risk factor		Points
pT1a		0
pT1b		2
pT2		3
pT3a/b/c or pT4		4
pNx/pN0*		0
pN1-2**		2
Tumor size < 10 cm		0
Tumor size ≥10 cm		1
Fuhrman grade I-II		0
Fuhrman grade III		1
Fuhrman grade IV		3
Necrosis no		0
Necrosis yes		1
Leibovich Scores	**5-year metastasis-free survival**	**10-year metastasis-free survival**
0-1p = Low-risk	97.1%	92.5%
2-5 = Intermediate-risk	73.8%	64.3%
≥6p = High-risk	31.2%	23.6%

Adapted from Leibovich et al 2003.[193] Leibovich points are summed based on pathology variable asn patients receive a risk score as depicted together with 5- and 10-year metastasis-free survival from the original study including 1671 patients. ccRCC = clear cell RCC, p = according to pathology report. * Nx refers to no assessment of N-stage. ** N-stage based on the 2002 AJCC TNM classificaton.

Table 10 – Prognostic models for RCC

Study ID Model name (Center)	Setting / Prediction	N	Prognostic indicators	Outcome / Acurracy†
Preoperative				
Raj 2008 - **(MSKCC & Mayo Clinic)**	M0 all RCCs / Nomogram	2517	gender, tumor size by imaging, presentation (incidental, local, systemic), lymphadenopathy or necrosis by imaging	RFS / 80%
Kutikov 2010 - **(FCCC)**	M0 all RCCs / Nomogram	30801	tumor size, race, gender, age	CSS / 73%
Postoperative				
Zisman 2001 **UISS** **(UCLA)**	M0 and M1 all RCCs / Algorithm	661	1997 TNM classification, Fuhrman grade, ECOG performance status, metastasis	OS, CSS / 86%
Frank 2002 **SSIGN** **(Mayo Clinic)**	M0 and M1 ccRCC / Risk groups	1801	1997 TNM classification, tumor size, Fuhrman grade, histologic necrosis	CSS / 88%
Leibovich 2003 **Leibovich score** **(Mayo Clinic)**	M0 ccRCC / Risk groups	1671	2002 pathologic T-stage and N-stage, tumor size, Fuhrman grade, necrosis	RFS / 84%
Sorbellini 2005 **Kattan score** **(MSKCC)**	M0 ccRCC / Nomogram	701	2002 pathologic T-stage, presentation (incidental, local, systemic), tumor size, Fuhrman grade, necrosis, vascular invasion	RFS / 82%
Karakiewicz 2007 - **(Multiple)**	M0 all RCCs Nomogram	2530	2002 TNM classification, tumor size, Fuhrman grade, histologic subtype, local symptoms, age, gender	CSS / 86%

Adapted from Meskawi et al 2012.[194] ccRCC = clear cell RCC, CSS = cancer specific survival, ECOG = Eastern Cooperative Oncology Group, FCCC = Fox Chase Cancer Center, N = number for patients. MSKCC = Memorial Sloan Kettering Cancer Center, RFS = recurrence free survival, UISS = University of California Los Angeles (UCLA) Integrated Staging System. † = highest internal or external validation percentages for diagnostic accuracy.

Finally for prognostication in the mRCC setting several models have been proposed during the cytokine and targeted therapy era. Of these the Motzer, Memorial Sloan Kettering Cancer Center (MSKCC)/Motzer and the International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC)/Heng risk models are most recognized. They are summarized in Table 11 including the median OS outcomes of the early 1999 Motzer model from the cytokine era and the more modern IMDC/Heng prognostic model from the targeted therapy era.[195-197]

Table 11 – Prognostic models for metastatic RCC

Study ID Model name (Center)	Setting / Prediction	N	Adverse prognostic indicators	Outcome /Acurracy†
Motzer 1999 **Motzer** **(MSKCC)**	M1 RCC Risk groups	670	Karnofsky performance score <80% high lactate dehydrogenase low hemoglobin high corrected calcium No prior nephrectomy	OS/ Not reported
Motzer 2008 **MSKCC/Motzer** **(MSKCC)**	M1 ccRCC treated with sunitinb / Nomogram	375	ECOG performance status high lactate dehydrogenase low hemoglobin high corrected calcium ≤1year from diagnosis to systemic therapy presence of lung metastases prior nephrectomy high number of metastatic sites presence of liver metastases	PFS /63%
Heng 2013 **IMDC/Heng** **(Multiple)**	M1 all RCCs treated with VEGF-inhibitors (sunitib in 82%) / Risk groups	849	Karnofsky performance status <80% high neutrophile count low hemoglobin high corrected calcium thrombocytosis ≤1 year from diagnosis to targeted therapy	OS / 71%

Risk group stratification:	**Number of Risk factors:**	**Motzer 1999 median OS**	**IMDC/Heng 2013 median OS**
Favorable prognosis	0 risk factors	20 months	43 months
Intermediate prognosis	1-2 risk factors	10 months	23 months
Poor prognosis	≥3 risk factors	4 months	8 months

Adapted from Meskawi et al 2012, Motzer et al 1999 and Heng et al 2013.[194, 195, 197] ccRCC = clear cell RCC, OS = overall survival, ECOG = Eastern Cooperative Oncology Group, MSKCC = Memorial Sloan Kettering Cancer Center, N = number of patients, OS = overall survival, PFS = progression free survival. † = highest internal or external validation percentages for diagnostic accuracy.

Follow-up

Follow-up consists of visits to either the treating urologist or to a general practitioner (GP) on a periodical basis in which also laboratory work-ups and imaging is performed in conjunction with or between these visits. The aims of follow-up of RCC patients after they have received curative treatment are to monitor for any possible complications postoperatively, monitor renal function and for the timely detection of any local or distal recurrences.[49] Although most recurrences of initially non-metastatic curatively treated RCCs occur within the first two years, a recurrence can occur as late as 45 years after RN.[164, 198] A recent study by Frees and colleagues including 880 curatively treated non-metastatic RCC patients showed that just over 42% of recurrences were detected after five years of follow-up.[199] This suggests that a life-long risk of recurrence is possible and patients curatively treated for RCC should not easily be discharged from any surveillance protocol. Additionally prognostic factors such as age, kidney function after surgery, comorbidities and radiation exposure associated with follow-up imaging should be taken into account and balanced against the likelihood of a RCC recurrence. Currently there is no clear consensus on frequency and type of imaging to perform during follow-up but there is some evidence suggesting improved survival in patients who consistently attend their follow-ups compared to those who do not.[200] With the expanding use of prognostic models for curatively treated RCCs, a change in recommendations by the major RCC guidelines has been to endorse bespoke follow-up protocols based on risk of recurrence. While the AUA and NCCN guidelines recommend the TNM classification to stratify RCC patients into low-, intermediate-, and high risk groups for custom follow-up regimens, the EAU RCC guidelines uses the same three-tier stratification but specifies the University of California Los Angeles Integrated Staging System (UISS) prognostic model to stratify patients.[49, 122, 201, 202].

Two recent reviews conducted comparisons of the major guidelines in terms of recurrence detection, radiation exposure and cost.[121, 203] Lobo and colleagues evaluated these factors in a model simulating the protocols of the AUA, NCCN, EAU and Canadian Urological Association (CUA) follow-up guidelines for patients curatively treated for localized RCC. They concluded for one that the CUA and EAU guidelines to be more accurate in finding recurrences in low-risk patients (95%) using their protocols compared to the NCCN and AUA guidelines which missed about one third of the recurrences in low-risk patients, even when strictly following their respective protocols. Furthermore radiation exposure varied between guidelines depending on if a low-risk or high-risk protocol was followed, albeit the NCCN protocol rendered the highest exposure in both risk groups. Lastly a cost analysis revealed the CUA to be the most cost efficient protocol independent of risk group while the AUA and NCCN where the most expensive.[203] Williams and colleagues conducted a review with data until October 2015 also comparing the follow-up protocols in the four guidelines

above and in contemporary surveillance protocol studies published. Regarding type of imaging to use for follow-up the collected evidence suggested that same modalities available for RCC diagnostics can be considered during follow-up. They then analyzed follow-up visits and imaging protocols for low, intermediate and high risk patients treated for localized RCC, concluding that there was a great variation in type and frequency of imaging proposed by each guideline.[121]

Finally both age and comorbidities have been proposed to play a role in the competing risk of death by other cause in several recent publications with sensible levels of evidence but interestingly none of the major guidelines have currently included these factors in their recommendations.[204, 205] The most recently updated follow-up recommendations for localized RCC, where major changes have been removal of CXR (already in 2017 version) as imaging modality and addition of no upper limit of follow-up time, are found in the more streamlined 2018 version of the EAU guidelines as shown in Table 12.

Table 12 – EAU RCC guidelines on follow-up after curative treatment for localized disease

Risk profile	**Surveillance**				
	6 mo	1 y	2 y	3 y	> 3 y
Low	US	CT	US	CT	CT once every 2 years; Counsel about recurrence risk of ~10%
Intermediate / High	CT	CT	CT	CT	CT once every 2 years

Adapted from Ljungberg et al 2018.[49] EAU guidelines recommend using University of California Los Angeles Integrated Staging System (UISS) for risk stratification of patients treated with curative intent for localized RCC. CT = computed tomography, US = ultrasound.

Aims of Current Thesis

The general aim was to investigate which patients with recurrent RCC or mRCC at diagnosis would benefit the most from timely detection of metastases and what interventions would be most beneficial for their management.

Paper I

The aim was to address the question of whether integration of local treatment of metastases into the management of RCC with metastatic lesions is beneficial and, if so, what the best treatment modalities were.

Paper II

The aim was to present contemporary population-based data on RCC demographics in Sweden between 2005 and 2009 from the National Swedish Kidney Cancer Register (NSKCR), with focus on local recurrences and metastases in non-metastatic RCCs within five years of follow-up, subsequent treatments and in relation to performed primary surgery.

Paper III

Using a multi-institutional consortium database, the aim was to analyze recurrence patterns in patients with non-metastatic ccRCC based on risk group stratifications, recurrence treatments and subsequent outcomes.

Paper IV

Based on the same database as for paper III, the aim was to investigate potential effect on OS in association to imaging modality used, frequency of imaging and guidelines follow-up protocol adherence for detecting recurrences in patients with initally curatively treated non-metastatic RCCs.

Methods

Ethical considerations

Paper I was a SR and did not require any Ethical Review Board approval. Ethical Review Board approval for Swedish patients retrospectively included in papers II to IV was procured under the auspices of the Regional Ethical Review Board of Northern Sweden (Dnr 2012-418-31M). For patients from other European countries included in paper III and IV, appropriate institutional Ethical Review Board approvals were obtained through respective local institutional contributors.

Study Design and Statistical Analysis

Paper I

Using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, a SR was conducted in accordance with principles of Cochrane Handbook for Systematic Reviews of Interventions under the auspices of the EAU RCC guidelines panel.[206, 207] A paper by Knoll and colleagues detailing the robust process of conducting such a SR within the EAU guidelines was recently published.[208] To summarize the current SR methods, a multiple database search was conducted for any type of comparative studies published between 1st January 2000 and 30th September 2013 determining the benefits and harms of different local treatments for metastatic lesions of RCC. The search yielded 2180 studies to screen by two separate reviewers, subsequently leaving 189 full text studies to screen and finally including 16 studies for SR analysis. Also a risk of bias and confounding assessment was performed and a narrative synthesis was provided. Statistical analyses used were mainly descriptive for presenting baseline characteristics and patient outcomes. Where appropriate provided HRs and/or relative risks and 95% CIs were compared between studies using forest plots with statistical heterogeneity between studies assessed by visual inspection of plots, the chi-square test and the I^2 statistic.[209]

Paper II

The NSKCR was used for a contemporary analysis of RCC patients treated for localized, locally advanced or metastatic disease between 2005 and 2009 in Sweden. The NSKCR had 99% coverage of all RCC patients in Sweden when compared to the mandatory Swedish Cancer Register.[210] Patient and tumor characteristics, primary treatment and subsequent treatment at recurrence for initially non-metastatic RCCs,

treatment modalities and treatment outcomes were extracted from the NSKCR and analyzed. For comparing subgroups in the cohort, two-tailed student t-tests and chi-square were used, principally with the null-hypothesis that no difference between compared cohorts would exist. Two-tailed p value of <0.05 was considered statistically significant.

Paper III

The study was conducted under the auspices of the euRopEan association of urology renal cell carcinoma guidelines panel Collaborative multicenter consortium for the studies of follow-Up and recurrence patterns in Radically treated renal cell carcinoma patients (RECUR). The RECUR database retrospectively collected data on consecutive non-metastatic RCC patients treated surgically with curative intent between 1st January 2006 and 31st Dec 2011. The inclusion dates allowed for at least four years of follow-up and also analysis of patients from the beginning of the targeted therapy era. Data lock for the current analysis was on May 1st 2017. Tumor characteristics, type of primary surgery, frequency and type of imaging to recurrence or last follow-up, patient and tumor recurrence characteristics and finally recurrence treatment intent and outcomes were recorded from medical records in non-metastatic RCC patients. All subtypes of sporadic RCCs were recorded according to the RECUR protocol and for this current study ccRCC was analyzed.

Patients with ccRCC were stratified into low-, intermediate- and high-risk groups according to LS and in patients with recurrence also grouped based on potentially curable (PC) or probably incurable (PI) metastatic extent at time of recurrence detection.[193, 211] Isolated local, solitary and oligometastatic (≤3 lesions at a single site) recurrences were considered PC by local therapeutic strategies while all others were regarded as PI (i.e. > three lesions at a single site or dissemination to ≥ two distant sites). For continuous and non-parametric data, independent samples t-test and Mann-Whitney U tests were used respectively. Kaplan-Meier (KM) method with Log-Rank test was performed for time to recurrence (TTR) for PC and PI groups stratified by Leibovich risk score and OS analyses between patients being symptomatic and asymptomatic at recurrence and finally between PC and PI groups stratified by Leibovich risk score. Also a competing risk analysis was performed stratifying patients by Leibovich risk score and age. Where relevant, univariate Cox regression models were used to obtain hazard ratios (HR) between groups. For all statistical comparisons, a two-tailed p-value of <0.05 was considered significant.

Paper IV

The RECUR database was used including all subtypes of RCCs for a retrospective analysis of OS after curative surgery for non-metastatic patients in relation to follow-up imaging modalities (cross-sectional imaging (CSI) vs. conventional imaging), imaging frequencies and also adherence to follow-up protocol of the EAU guidelines.[49]

All patients were assigned to a three-tier risk group (RG) with LS applied for ccRCC patients and an adapted TNM stratification used in a recent RCT based on the UISS model applied for non-ccRCC patients.[193, 212] For non-ccRCC the RGs were defines as low-risk patients being T1a and T1b Fuhrman grade 1-2/N0/M0, the intermediate-risk patients being T1b Fuhrman grade 3-4/N0/M0 and high-risk patients as ≥T2 Fuhrman $grade_{any}$/N0-1/M0. In cases of non-ccRCC subtypes did not allow for Fuhrman grade assessment the UICC TNM stage grouping was applied with stage I being low-risk, stage II intermediate-risk and stages III-IV being high-risk patients.[104]

Regarding imaging analysis the study collected data on all types of imaging used with CSI defined as any type of CT or MRI modalities while conventional imaging was any type of plain radiography or US during follow-up. Total number of imaging (TNI) was defined as all imaging performed during follow-up. Patients were divided into two groups depending on their percentage of CSI divided by TNI (≥50% compared <50%). Imaging frequency (IF) was defined as the TNI until recurrence detection or last follow-up divided by time from primary surgery to detection of recurrence or last follow-up (years) and patients were stratified by median IF-value into either high IF or low IF. Based on EAU guidelines risk stratified follow-up protocol for non-metastatic RCC, the estimated number of imaging (ENI) for each risk group following the guideline recommendations was calculated and compared to the TNI via a calculated imaging ratio (IR), based on ENI divided by TNI, and stratified into low IR and high IR groups. These imaging factors were scrutinized within each RG.

The three RGs were moreover stratified into three time groups (Early follow-up (0-2.49 years), Intermediate follow-up (2.5-5.49 years) and late follow-up (>5.5 years)) after initial surgical treatment with the relationship between IF and detection of recurrence within the follow-up protocol, non-symptomatic recurrence, and curability explored within the resulting nine groups.

Descriptive statistics were presented as categorical variables with percentages and continuous variables as median and interquartile range (IQR). For categorical and non-parametric data comparisons, exact Chi-square test, Mann-Whitney U test or Kruskal-Wallis tests were used. KM method with Log-Rank test was performed for overall survival (OS). Principally for all statistical calculations the null-hypothesis was that no differences would be found between compared groups and a two-tailed p-value of <0.05 was considered significant.

Results and Discussion

The introduction of this thesis is lengthy as to illustrate the extensive amount of factors coinciding to determine the outcomes of RCC treatments. Not only is the complexity of RCC founded on macroscopic, microscopic and molecular differences but the disease also carries with it intra-tumor heterogeneity with completely different mutations or RCC subtypes within different regions of the same tumor.[40, 213] These factors put together are therefore perhaps what make RCC particularly difficult to treat successfully in the metastatic setting, making it the urological cancer with the highest mortality rate.[129] Historically about 20-30% of patients have mRCC at diagnosis but interestingly paper II, based on a population-based cohort of 4527 patients (939 with mRCC and 3107 non-metastatic RCC at diagnosis) in the NSKCR, showed that for patients with mRCC at diagnosis the incidence dropped from 23% in 2005 to 18% in 2009, in line with previous publications.[129, 130] The decreasing trend was thought to be due to an increase in incidentally found RCCs.[130, 214] Also as shown in paper II 20% of non-metastatic RCCs had a recurrence detected within five years and of these 92% had undergone RN which suggested a more advanced T-stage correlating to higher risk of recurrence also as previously shown.[164] Indeed further evaluation showed that patients with recurrence within the five year follow-up had significantly larger tumor size ($p<0.0001$), a higher number of T2-T4 tumors ($p<0.0001$), were more often N1 disease ($p<0.0001$) and had a higher number of Fuhrman Grade 3-4 ($p<0.0001$) compared to the recurrence-free RCC patients. Historically patients with a synchronous or asynchronous RCC metastasis received palliative intent treatment with curative outcomes from CN, MTX and/or SysT being scarce.[215] Currently there is no curative systemic treatment available for RCC perhaps with the exception of high dose IL-2 in very few cases.[183] However since the dawn of targeted therapy in the mid-2000s and better understanding of the role of both CN and MTX, the improved survival rates compared to Robson's 1969 results are irrefutable.[4, 106, 216] As paper II also pointed out on a population level, the use of SysT with palliative intent in a contemporary setting was offered to about 50% of recurrent patients while MTX was offered to only 17% of those with recurrence after initially curative intent surgery. Interestingly the majority of these MTXs (68%) were performed with a curative intent, suggesting patient selection to be complex, perhaps accounting for the low numbers being considered for curative treatment but high percentage with curative intent in those actually offered one. The NSKCR had a 99% patient coverage which is excellent compared to other population-bases cohorts but nevertheless the results were still based on data registered by individual reporters

across Sweden (i.e. no central evaluation of tumor histology or imaging) and as such subject to reporting bias as the main limitation.[217]

While the demographics of contemporary RCCs and their treatments including treatment at recurrence were presented in paper II, the roles and benefits of MTX as a local therapy for metastasis of RCC had been analyzed and presented in paper I. This SR was at the time the first analysis of the role of local therapies for metastases of RCC performed using a robust methodology.[208] The mainstay survival benefits of MTX presented in paper I were based on seven of the 16 comparative studies included in the SR showing an improved OS or CSS in cases where complete MTX was performed compared to incomplete or no MTX (Figure 5).

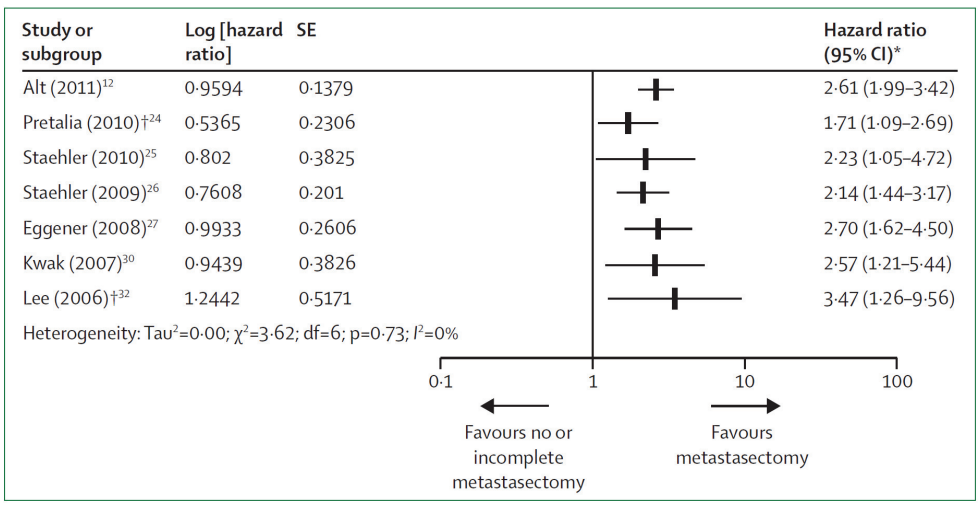


Figure 5 – Forest plot of hazard ratios for overall survival or cancer-specific survival in studies comparing incomplete or no metastasectomy versus complete metastasectomy. Superscripted reference numbers in figure represent those in the original publication (paper I). Figure illustration and text reprinted from The Lancet Oncology, Vol. 15, Dabestani et al, Local treatments for metastases of renal-cell carcinoma: a systematic review, Pages No. 549-561, Copyright (2014), with permission from Elsevier.

Also the role of RT as local therapy for metastases of RCC was evaluated showing whole-brain radiotherapy (WBRT) and stereotactic radiosurgery for RCC brain metastases in two studies and SBRT or conventional RT for bone metastases in three studies. In summary paper I revealed stereotactic RT modalities to offer no attempt at cure but symptom control and pain relief was noticed for most patients while a significant improved 2-year survival could be noticed in some with favorable tumor features.[218]

A risk of bias and confounding assessment of included studies in paper I showed all studies to be NRSs, mostly retrospective and with small cohorts and moderate to low

overall quality of evidence. Selection bias, i.e. whether the OS and CSS benefits of MTX were due to patients with more favorable tumor and performance status features being available for complete metastasectomy while poorer patients were not, was the principal limiting factor in nearly all included studies. Furthermore the included studies were seldom adjusted for important confounding factors as age, gender, Fuhrman grade, size and volume of metastases, number of metastases, previous treatment prior to MTX, performance status, different sites treated and tumor histology. Paper I also reviewed and discussed the level of evidence for local therapies of RCC metastases, underlining the general and site specific factors to consider prior to offering local therapy options to select patients. These recommendations were reiterated in a review article in 2016 and are presented in Table 8 above.[132]

The option of deferring from any treatment in the metastatic setting might be beneficial in some patients with an indolent RCC biology as this prolongs time to any strenuous SysT or MTX.[219] Indeed in paper II 27% of recurrent RCCs did not receive any tumor specific treatment indicative of possible indolent disease albeit it has to be recognized that this patient groups could very well contain patients who did not receive any active palliative treatment due to poor performance status or advanced disease with poor prognosis at recurrence detection.

While Paper I and II provided a view on primary mRCC and recurrence rates, metastatic sites and local treatment options, the focus of papers III and IV were on the timely detection, curability and subsequent treatments and outcomes of asynchronous RCC recurrences. The questions aimed to be answered were whether any recurrence detection and subsequent treatment resulted in improved survival for a certain group of patients with initially non-metastatic RCC and if imaging modality and frequency in the follow-up of these patients impacted said survival. As of May 1st 2017 the RECUR-database consisted of a retrospective cohort of 1889 (1265 ccRCCs, 400 non-ccRCCs and 224 excluded) non-metastatic RCC patients treated curatively and was created under the auspices of the EAU RCC guidelines panel to answer these questions. Paper III stratified 1265 ccRCC patients according to LS and curability (PC and PI) showing both the 131 PC and 155 PI ccRCC recurrences to independently differ significantly in TTR between LS risk groups in line with the original publication of Leibovich and colleagues.[193] Although the PC and PI definitions were established by a group of experts within the EAU RCC guidelines panel with a practical clinical setting in mind and have been previously published, it has to be recognized that they are not universally accepted.[211] TTR for PC recurrences was 25 months compared to 17 months for PI recurrences (p= 0.004) suggesting in line with previous publications that PC recurrences tend to occur later irrespective of LS risk group.[211, 220] Furthermore the risk of recurrence was significantly higher in the PI high-risk group compared to the PC high-risk group (HR 1.54, 95% CI 1.08–2.21, p=0.018). The treatment and outcomes of PC and PI patients are shown in Figure 6. When stratified by both curability and LS the end results showed only 2% (3/128) of high-

risk patients, i.e. the group harboring most patients with recurrence, alive with no evidence of disease (NED) after receiving curative intent treatment for recurrence. The corresponding percentages were 10% (10/105) and 25% (13/53) for the intermediate-risk and low-risk group respectively.

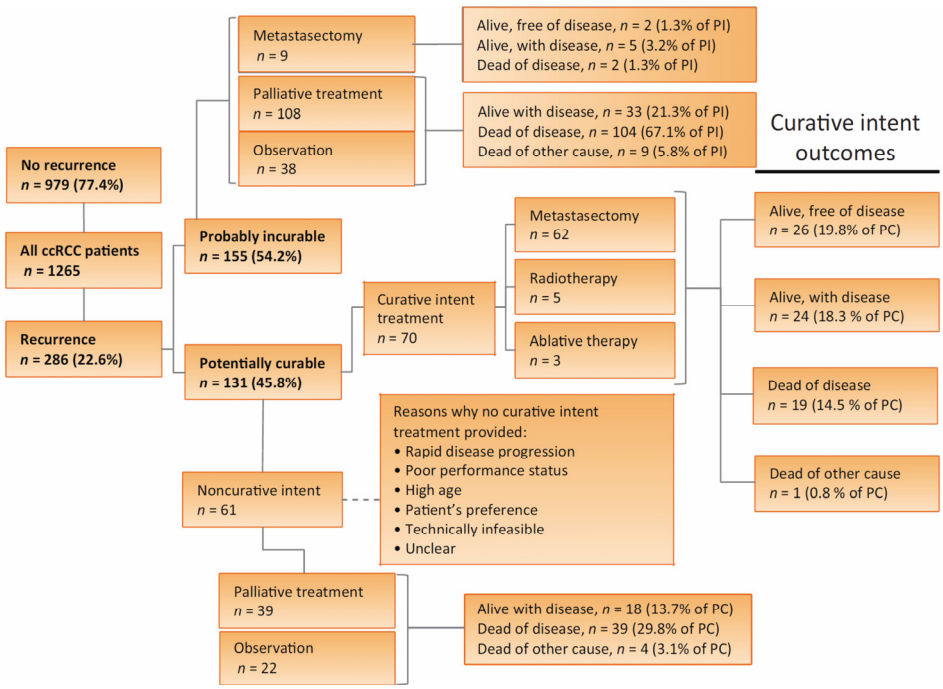


Figure 6 – Adapted from Dabestani 2018 (paper III). Flow chart of recurrence, curability, management and survival outcome in 1265 patients with ccRCC. Reasons for withholding therapy from potentially curable (PC) patients and type of treatment given to patients deemed as probably incurable (PI) are provided. Palliative treatment was defined as systemic therapy or best supportive care while observation refers to refraining from active palliative treatment due to no rapid progression of disease. Published with permission from Elsevier.

From the time point of recurrence to last follow-up the PC patients had a significantly longer median OS (27.4 months (IQR 11.1–48.3)) relative to PI patients (15.2 months (IQR 5.5–33.4); p<0.001) and being symptomatic meant higher risk of death compared to being asymptomatic at recurrence detection (HR 2.84, 95%CI 2.10–3.86, p<0.001). Finally paper III also analyzed the competing risk of dying from other causes than RCC. In short this analysis proposed risk of recurrence to always be higher than risk of death of other cause in the LS high-risk group while the opposite would hold true in the LS low-risk group. When stratified by age groups 18-60 years, 61-75 years and 76-90 years, the competing risk analysis demonstrated for low- and intermediate-risk groups that patients >75 years of age had a higher risk of death from

other causes than the risk of death from ccRCC recurrence. For high-risk patients, death from ccRCC recurrence was higher than death from other causes, independent of age. The recurrence rates and OS in paper III were in line with previous publications which also highlight the poorer outcomes associated with either high-risk of disease progression or poorer survival outcome in patients with extensive metastatic spread and in several recent publications the aspect of competing risks have been established as well.[131, 166, 200, 204, 221] The mainstay of paper III lays in determining curability in relation to LS risk groups. The results here indicated survival with NED was rare irrespective of risk group (i.e. low-risk patients with recurrence were few with recurrence but 25% could obtain NED if MTX was applied versus high-risk patient harboring most patients with recurrence but with only 2% with NED of curative intent treatment was applied) and therefore any future follow-up protocol should consider not only risk-group but also comorbidities, PS, rapid disease development and age when planning a follow-up strategy.[200] The rationale for excluding the non-ccRCCs patients from paper III was the more indolent nature of these tumors, especially type-1 pRCC and chRCC, with better survival shown in various studies.[71, 73-75] The use of the UISS risk score instead of the Leibovich score (LS) was justified by evidence showing that Fuhrman grade, an integral part of the LS model (see Table 10), has not been validated for other RCC subtypes.[75] Several limitations were considered in paper III mainly attributed to the retrospective nature of the study. About 12% of patients were excluded for lacking essential data, performance status was not evaluated allowing for risk of selection bias favoring MTX in patients with good PS and finally as discussed above the definitions of PC and PI were not fully established.

While paper III focused on recurrence patterns and survival in ccRCC, paper IV elucidated patterns in follow-up imaging for recurrence detection in relationship to survival after recurrence detection. Here the entire RECUR-database cohort was used with 1612 out of the 1889 patients having sufficient data for analysis of follow-up imaging modalities and frequency. Recurrence was detected in 336 patients of whom 152 were deemed PC and 184 PI. Of 17333 follow-up imaging procedures performed, 4929 (28%) and 3024 (17%) were abdominal CTs and thoracic CTs, respectively. Furthermore, 6540 (37.7%) CXR and 2651 (15.3%) abdominal US investigations were performed for follow-up. High-risk patients according to LS were more prone to undergo thoracic CTs compared to LS intermediate- and low-risk patients ($p<0.001$). When analyzing OS from recurrence detection to last follow-up within PC and PI groups respectively, no significant difference was found within respective group when stratified by type of imaging (CSI or conventional imaging) or when stratified by high or low CSI/TNI-ratio, i.e. proportion of CSI modalities used for follow-up per patient (Figure 7). Together with findings on significant OS differences between PC and PI patients from paper III, this suggests that those who will recur irrespective of low or high metastatic burden have OS differences between them but the type and main imaging modality used for follow-up does not affect this. Currently

the 2018 EAU guidelines have removed use of conventional imaging in their recommendations while other major guidelines still approve use of these modalities.[49, 121]

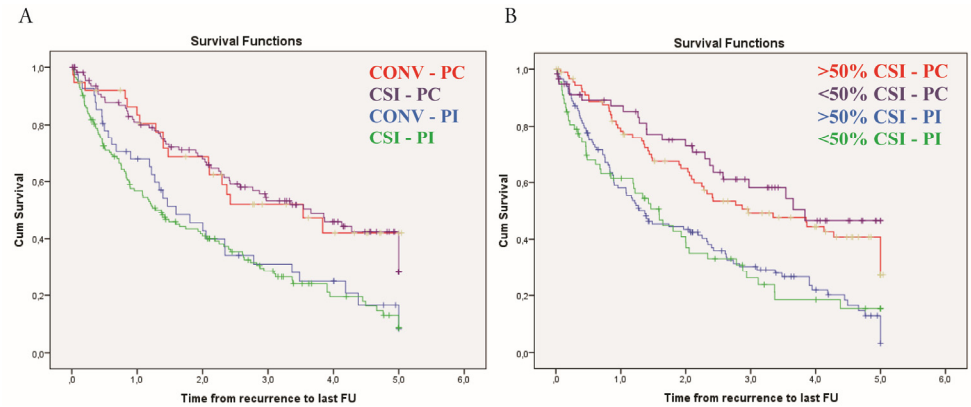


Figure 7 – A) Figure shows overall survival (OS) Kaplan-Meier (KM) plots for RCC patients stratified by curability and their recurrence detection by conventional methods or cross-sectional imaging. There were no significant difference in OS within PC and PI groups respectively.
B) Figure shows OS in KM plots after recurrences for patients stratified by curability and if the majority of follow-up imaging were by convential methods or cross-sectional imaging. There were no significant differences within the PC and PI groups respectively. >50% CSI = CSI/TNI-ratio above 50%, <50% CSI = CSI/TNI below 50%, CONV = conventional imaging, CSI = cross-sectional imaging, FU = follow-up, PC = potentially curable, PI = Probably incurable, TNI = Total number of imaging.

In paper IV the IF (defined as average number for imaging per year) in relation to RGs and length of follow-up was noted to significantly decrease over time in each RGs ($p<0.001$) and within each follow-up time group (early, intermediate and late) an increase in IF per incremental step in RG was noted. Furthermore, irrespective of length of follow-up and RG, no overall conclusive difference was noted in IF between those with and without a recurrence. Also when analyzing high and low IF (stratified using median IF as cut-off) within respective RG and time groups no overall conclusive differences in OS were found. Finally when comparing the IR (defined as TNI divided by ENI based on the EAU guidelines follow-up protocol for RCC) in different RGs and follow-up time groups, the RECUR-database cohort follow-up were in line with that of the guidelines but again no overall significant differences in OS were found.

In paper IV the RECUR-database cohort seems to coincide well with the recommendation on follow-up frequency proposed by the EAU guidelines which also is in line with all major RCC guidelines in using risk stratified protocols with higher intensity of follow-up imaging early after surgical treatment.[49, 122, 202] However paper IV also shows that higher intensity of imaging does not affect OS. In a recent study by Sohn and colleagues the absence of high-level evidence on optimal RCC follow-up was

pointed out and a retrospective registry based analysis revealed, in line with paper IV, that higher intensity of imaging did not result in improved CSS.[222] Interestingly none of the major guidelines recommend separate follow-up protocols for different RCC subtypes even though different long-time outcomes based on histology have been shown.[72, 75] Paper III accounted for this by only including ccRCCs while for paper IV the rationale for allowing all RCC subtypes into the analysis was that follow-up imaging variables (e.g. TNI, IF, IR) were deemed not to be affected by tumor histology. In a large cohort study earlier in 2009 by Siddiqui and colleagues a follow-up protocol accounting for RCC subtype was suggested but this protocol was never properly recognized.[223] Additional findings in paper IV also suggested that the imaging modality may not matter in affecting OS. A recent study showed similar results and concluded that follow-up outcomes seemed to be more dependent on follow-up duration and frequency rather than modality.[224] Still the issues of type of imaging modality for RCC follow-up remain unclear as other studies have shown clear benefits of using CSI, particularly for CT-based thoracic evaluation, arguing that the modality allows for a more detailed topographical evaluation and higher diagnostic accuracy.[133, 135] Of note is also the long-term follow-up study by Beisland and colleagues who used a LS stratified model for follow-up of radically treated non-metastatic RCC patients, and suggested an alternative approach with reduced number of follow-up CTs and also incorporating follow-up visits to a general practitioner instead of an urologist. Prospectively including 312 patients (63% with complete follow-up data) they showed a 59% reduction in number of visits at their department while maintaining a 65% detection rate of recurrence and with OS per LS risk group similar to other recent series.[200] Limitations of paper IV mainly concerned the retrospective nature of the RECUR-database same as described for limitations of paper III. Additionally analyzing up to 27 subgroups (e.g. IF and IR analyses) brought about a possible small-population bias, making any statistically significant findings difficult to interpret. Concerning other limitations of the RECUR-database, not collecting and adjusting for comorbidities and/or any type of performance status at time of diagnosis and recurrence detection limits the interpretation of survival outcomes. However the RECUR database did collect data on SysT considered primarily in patients with PI recurrences but this was unfortunately not analyzed in the contexts of papers III and IV, also potentially confounding the survival results. In the context of advances made both in understanding the complexity of RCC molecular subtypes as portrayed by Shuch and colleagues and in development of novel SysTs options, the ideal follow-up strategy for curatively treated RCCs is yet uncertain.[39, 165, 225] Also the biology of small metastatic lesions with suggested inherent dormant behavior and unpredictable progression patterns adds to the difficulty in optimizing follow-up.[226, 227] Finally irrespective of the possibility of detecting any recurrences, the competing risks of death by other causes are currently a hot topic as recent studies have shown age and comorbidities to be strong determinates of OS in curatively treated RCCs.[204, 221]

Conclusions and Future Perspectives

In conclusion the papers included in this thesis provided novel insight into contemporary management of patient with mRCC at diagnosis and those with asynchronous RCC recurrence. The role of metastasectomy and other local therapies were clarified in a robust SR where relevant studies included, albeit being of low level of evidence with high risk of bias and confounding, consistently showed a benefit in performing complete metastasectomy in terms of overall survival and cancer-specific survival. Also some evidence of local or symptomatic metastasis control using radiotherapy was established. The demographics of RCC in a modern population-based cohort were presented together with management outcomes showing a decreasing incidence of patients with mRCC at diagnosis. More importantly the treatments for asynchronous RCC recurrences were shown to be systemic oncological in 50%, observational/expectative in 27% and metastasectomy in 17% of patients with 68% of metastasectomy cases having curative treatment intent. The RECUR-database was established to provide evidence on the true impact of follow-up on survival, albeit being limited by its retrospective nature. Low-risk group recurrences according to LS were rare during follow-up but OS after recurrence management was disappointing especially in the LS high-risk group which harbored most patients with potentially curable recurrences. Patients symptomatic at recurrence had a poorer survival irrespective of metastatic burden at recurrence detection. Competing risk analysis suggested an age and risk score-dependent approach to follow-up protocols. The RECUR-database also concluded that imaging modality (cross-sectional vs. conventional) for detection of RCC recurrences did not seem to affect OS irrespective of metastatic burden. More frequent follow-up imaging for recurrence detection did not improve on OS after recurrence. Finally, use of excessive follow-up imaging compared to frequency recommended by the EAU guidelines was unlikely to increase OS after recurrence. For a higher level of evidence supporting the findings above there is a need for prospective, preferably randomized, comparative studies.

The rationale for follow-up of patients radically treated for non-metastatic RCC is the timely detection of a recurrence (local or distant) allowing for systemic or local therapy potentially leading to prolonged survival or even cure obtained with least amount of adverse events afflicting the patient. In patients with mRCC at diagnosis, with the addition of CN, the treatment goals and any ensuing follow-up are the same. Currently all accepted prognostic models allowing for a stratified risk approach, like the Leibovich score, are based on clinical features, TNM classification and histology. The diagnostic accuracy of these models as well as for those in the mRCC setting range

roughly from 60% to 85% and as suggested by Heng and colleagues an accuracy plateau may have been reached.[197] Therefore one future aspect is to bring about risk-group stratified follow-up with better accuracy based on new prognostic factors. As earlier suggested acknowledging RCC subtypes to have different natural histories and risks of recurrence is important and should be considered in future studies and recommendations on follow-up protocols.[223] Future analyses of the RECUR-database in regards to recurrence patterns in non-ccRCC are therefore planned. More importantly though are the advances in the molecular understanding of RCC subtypes and mutations which may serve to improve the prognostic accuracy of existing risk models and to help tailor genetically based follow-up protocols or treatment strategies in the metastatic setting.[39, 40] Gene signatures derived from tumor biopsies or the removed tumor itself are already in use and based on these several prognostic models have been proposed with more recently even a prognostic molecular subtyping for ccRCC established. These molecular models may also aid in optimizing any systemic treatment offered and in improving on prognostication in the mRCC setting.[228-230] As an example Rini and colleagues developed a 16-gene assay for ccRCC showing diagnostic accuracy of 79% in predicting recurrence with the genetic model alone.[231] Combining molecular and clinical data could in the future provide higher diagnostic accuracy in determining RCC progression or survival but need to be investigated further.

Moreover the use of competing risk models in tailoring follow-up protocols to both frequency and duration should be a major future goal. As Stewart-Merrill and colleagues point out in their RCC competing risk study there is a strong need to address follow-up strategies not only based on TNM classification and histological parameters but also on patient age and comorbidities.[204] Indeed life expectancy should play a major role in determining the frequency and duration of follow-up protocols and indirectly a determinant in reducing health care costs by reducing number of imaging. In addition, certain RCC sub-groups with low risk of recurrence may even benefit in QoL from reduced follow-up.[200]

Lastly, finding a unifying biomarker with potential for prognostic stratification of RCC patients, augmentation of the subsequent follow-up after curative treatment or the surveillance during SysT for mRCC may be most coveted. Serum and urine biomarkers could have this potential with circulating tumor DNA, VEGF and CA-IX and IL-6 among others currently being investigated.[232] Interestingly Gatto and colleagues have recently published exciting results using glycosaminoglycan profiles in both serum and urine in patient with any subtype and setting of RCC. A score system has been created to detect biochemical progression with preliminary results showing promise in independently predicting PFS and OS.[233, 234]

An optimal follow-up protocol based on super-accurate prognostic models may perhaps never be reached but as the martial artist Bruce Lee put it *"Don't fear failure. Not failure but low aim is the crime. In great attempts it is glorious even to fail"*.

Popular Science Summary in Swedish

Populärvetenskaplig sammanfattning

Njurcancer är en elakartad tumör i njuren, drabbar män oftare än kvinnor och är vanligare bland 60- till 70-åringar. Ofta saknas symtom och tumören upptäcks inte sällan slumpmässigt i samband med skiktröntgen som gjorts av andra skäl. Det finns olika typer av njurcancer men gemensamt för alla är att modertumören i den sjuka njuren kan skicka ifrån sig dottertumörer, s.k. metastaser, till andra delar av kroppen. Botande behandling kan ges till patienter där man kan operera bort modertumören i njuren, s.k. lokaliserad sjukdom, och i de fall där det finns ett fåtal lättåtkomliga metastaser kan även dessa opereras bort. Efter en operation är det viktigt att följa upp patienterna med regelbundna kontroller för att hitta återfall. Upptäcks dessa patienter i rätt tid kan man fortfarande bota dem genom ytterligare försök att ta bort metastaser medan om sjukdomen har spridit sig till flera svåråtkomliga ställen i kroppen går den sällan att bota. Bromsande behandlingar i form av tabletter eller dropp används hos de som har en spridd sjukdom men än så länge går det inte att bota sjukdomen på detta vis. Av 100 vuxna som får njurcancer kommer ungefär 30 att ha metastaser när sjukdomen upptäcks, 50 kommer botas genom operation medan resterande 20 patienter som till en början opererades i botande syfte kommer få ett återfall inom fem år.

Syftet med denna avhandling var att belysa hur vi bäst upptäcker och behandlar metastaser från njurcancer. Delarbete I: Genom en noggrann jämförelse av viktiga studier har vi sett att patienter med metastaser kan överleva längre genom att operera bort både modertumören och metastaserna jämfört med att avstå från detta. Dock fungerade detta bättre hos friska och yngre patienter med få metastaser. Delarbete II: En undersökning av den svenska befolkningen visade att njurcancer upptäcks i ett allt tidigare skede eftersom fler skiktröntgen genomförs inom vården. För de som får ett återfall visade studien att hälften får bromsande behandling och 1 av 5 får genomgå ny operation för metastaser. Delarbete III: Här granskades tre riskgrupper av njurcancer i en studie med njurcancerpatienter från 8 länder i Europa. Alla patienter hade opererats i botande syfte. De med låg risk för återfall var minst i antal och fick sina återfall sent under uppföljningen medan de med hög risk var flest, fick sitt återfall tidigare men hade sämst resultat av behandlingar de fick för sina återfall. Det gick sämre för dem med symtom av sin sjukdom vid återfallet jämfört med de utan symtom vid återfallet. Även patienters ålder vid insjuknande spelade roll där de som var över 75 år inom låg- och mellanriskgrupperna verkade ha större risk att hinna avlida av något annat än ett återfall av njurcancer. Delarbete IV: Samma patienter som studie III utvärderades med hänsyn till antalet kontroller som gjordes under uppföljningen. De med låg risk genomgick minst antal undersökningar och de med hög risk flest. Fler eller färre eller typ (t.ex. skikt- eller slätröntgen) av kontroll påverkade inte överlevnaden hos de med återfall.

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