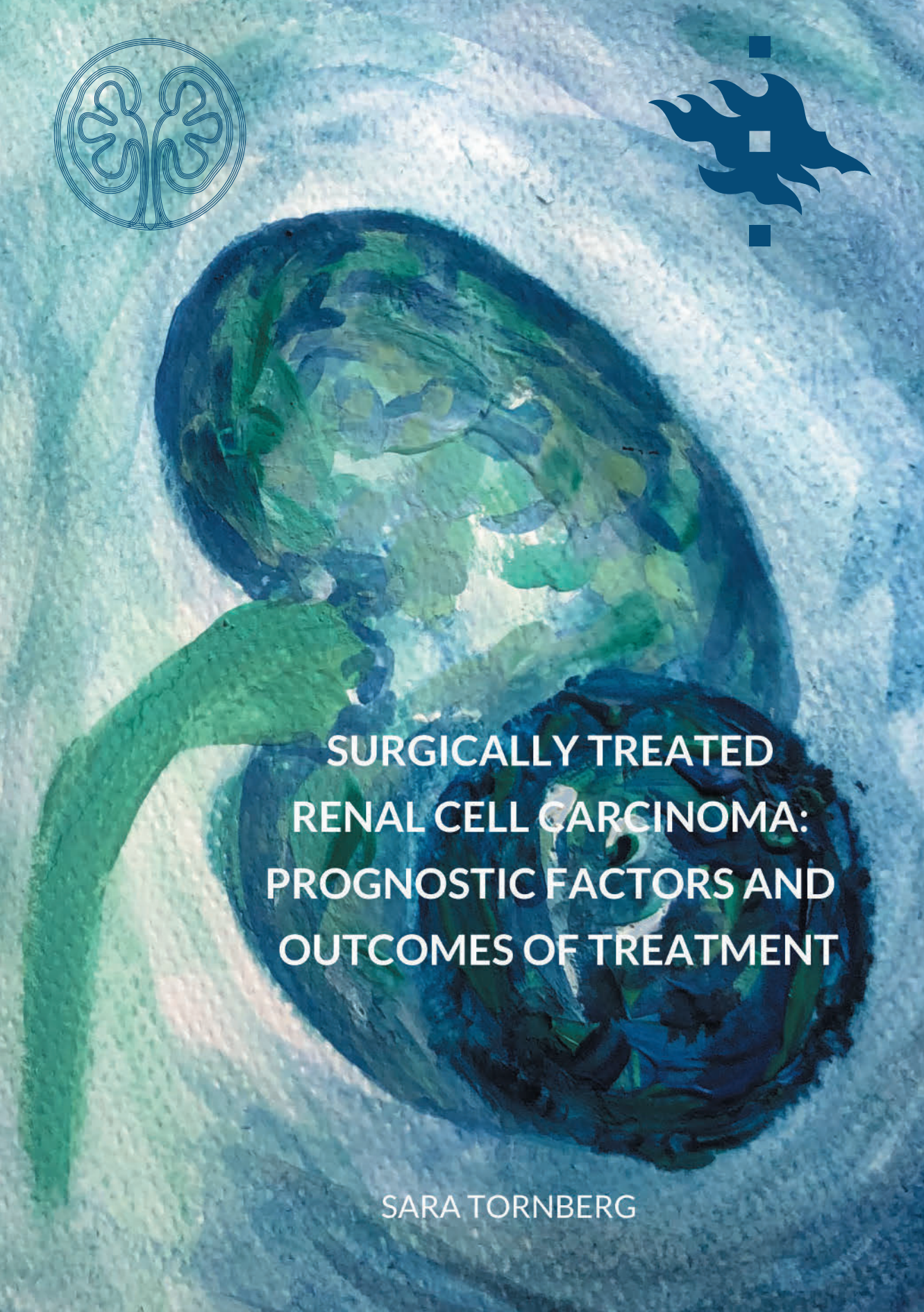

SURGICALLY TREATED RENAL CELL CARCINOMA: PROGNOSTIC FACTORS AND OUTCOMES OF TREATMENT

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SURGICALLY TREATED RENAL CELL CARCINOMA: PROGNOSTIC FACTORS AND OUTCOMES OF TREATMENT

Sara Tornberg

ACADEMIC DISSERTATION

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Dedicated to patients suffering
from renal cell carcinoma.

ABSTRACT

Background

Kidney cancer is the 12th most common malignancy worldwide, accounting for over 400,000 new cases in 2018 (1). As renal cell carcinoma (RCC) incidence and mortality, as well as treatment patterns, vary widely in Europe, to plan strategies for the future, we need to comprehend the current situation in Finland.

Accurate prognostic tools are essential for detecting cancers amongst the tumours noted in imaging studies and choosing optimal treatment for cancer patients. The Tumor, Node, Metastasis (TNM) staging system and International Society of Urologic Pathology (ISUP)/Fuhrman grading system are the most commonly used prognostic parameters for RCC. Currently, risk stratification relies on prognostic nomograms or risk stratification tools combining clinical, anatomical and histopathological data. However, these models have well-known limitations.

Treatment for RCC is changing. Over the last decades, more incidental RCCs were found, and more minor lesions were operated on using less invasive techniques. At the opposite end of the disease spectrum, selected metastatic RCC patients receive a combined treatment consisting of nephrectomy, metastasectomy and oncologic therapies. Surgery for locally advanced and metastasised tumours must be justified by the prospect of an improved outcome or quality of life. Decisions to operate on metastatic RCCs are currently based on expert opinions and nomograms designed for targeted therapy survival estimations only. Thus, better prognostic markers and diagnostic tools are needed.

Aims

The aims of this PhD study were to evaluate the current changes in the clinical picture, treatment and outcomes of RCC in Helsinki University Hospital district. Further analysis was done to determine the clinical outcomes of surgically treated RCC with tumour thrombus and metastasised RCC (mRCC). The authors aimed to externally validate the performance of the Leuven-Udine (LU) prognostic group model for mRCC and to evaluate the prognostic value

of serum concentration of tumour-associated trypsin inhibitor (TATI). The performance of renal tumour diameter and parenchymal invasion depth was compared with more complex classifications to assess their accuracy in predicting the nephrectomy performed.

Patients and methods

All patients studied were either suspected to have RCC or had RCC, and the majority of patients underwent nephrectomy at the Helsinki University Hospital (HUH). There were 1,719 patients with tumours suspected of RCC evaluated in four periods from 2006 to 2016 for clinical characteristics and treatments offered. From 2006–2014, 142 RCC patients with tumour thrombus (TT) were operated on at HUH. In total, using computed tomography (CT) or magnetic resonance imaging (MRI) images of 915 patients, tumour maximum diameter, depth of invasion, Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) score and Renal Tumour Invasion Index (RTII) were estimated. There were 97 patients with metastatic RCC undergoing surgery for metastases. Preoperative and postoperative serum levels of tumour associated trypsin inhibitor (S-TATI) of 132 RCC patients were determined by time-resolved immunofluorescence assay in 2006-2010.

Main results and conclusions

During the study period, the proportions of frail and co-morbid patients increased significantly as did the percentage of small (diameter ≤4 cm) and asymptomatic tumours. The use of surveillance as treatment increased significantly while the use of cytoreductive nephrectomies (CNs) decreased to 54%. However, CN combined with tyrosine kinase inhibitors remained the primary option in patients with metastatic RCC. However, the changing landscape of RCCs has already affected and will increasingly affect the treatments given.

For RCC patients with TT, no statistically significant difference in survival was found amongst the different levels of the venous extension. The prognosis for operated RCC patients with TT was good in the absence of papillary histology of primary tumour, lymphoid or distant metastases. Surgery remains a feasible option for selected patients in the era of modern oncologic therapy.

In predicting the type of nephrectomy, partial or radical, the simple measurements of tumour diameter and parenchymal invasion, were superior to the more complex classification. Hence, all of them were significant predictors for nephrectomy type. Our results recommend that potential anatomical classifications should be tested against these user-friendly measurements, diameter and parenchymal invasion.

Overall survival (OS) was more favourable for patients undergoing complete metastasectomy than patients with non-complete metastasectomy and time to systemic therapy was longer. Patients with skeletal metastases had shorter survival than patients with other metastatic sites whereas patients with lung metastases had the most favourable prognosis. In this study population, the performance of the LU prognostic group model could not be validated. Despite the abundant amount of inauspicious prognostic factors in our patient cohort, survival rates were reasonable.

Significant associations with preoperative S-TATI and Chronic Kidney Disease Stage (CKD grade), tumour stage, lymph-node involvement, metastatic status and preoperative C-reactive protein (CRP) level were noted. S-TATI, as a continuous variable, however, significantly predicted OS and cancer-specific survival (CSS). Prognostic significance of S-TATI should be further studied in larger patient cohorts and prospective settings.

TABLE OF CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Erkkilä K, Tornberg SV, Järvinen P, Järvinen R, Kilpeläinen TP, Visapää H, Hervonen P, Taari K, Nisen H. Evolving clinical picture of renal cell carcinoma: A population-based study from Helsinki. *Urol Int.* 102(4): 390–398, 2019.

II Tornberg SV, Nisen H, Visapää H, Kilpeläinen TP, Järvinen R, Mirtti T, Kantonen I, Simpanen J, Bono P, Taari K, Järvinen P. Outcome of surgery for patients with renal cell carcinoma and tumour thrombus in the era of modern targeted therapy. *Scand J Urol.* Oct; 50(5): 380–386, 2016.

III Tornberg SV, Kilpeläinen TP, Järvinen P, Visapää H, Järvinen R, Taari K, Nisén H. Renal tumor invasion depth and diameter are the two most accurate anatomical features regarding the choice of radical versus partial Nephrectomy. *Scand J Surg*. Mar; 107(1): 54–61, 2018.

IV Tornberg SV, Visapää H, Kilpeläinen TP, Taari K, Järvinen R, Erkkilä K, Nisen H, Järvinen P. Surgery for metastases of renal cell carcinoma: Outcome of treatments and preliminary assessment of Leuven-Udine prognostic groups in the targeted therapy era. *Scand J Urol*. Oct-Dec; 52(5-6): 419–426, 2018.

V Tornberg SV, Nisen H, Järvinen P, Järvinen R, Kilpeläinen TP, Taari K, Stenman U-H, Visapää H. Serum tumour associated trypsin as a biomarker for survival in renal cell carcinoma. Accepted for publication in *Scand J Urol* 15.7.2020.

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

ANCR	Association of the Nordic Cancer Registries
ASSURE	Adjuvant Sorafenib or Sunitinib for Unfavourable Renal Carcinoma
AUC	Area under the curve
BHD	Birt-Hogg-Dubé syndrome
CAIX	Carbonic anhydrase IX
ccRCC	Clear cell renal cell carcinoma
CEUS	Contrast-enhanced ultrasound
chroRCC	Chromophobe renal cell carcinoma
CI	Confidence interval
CKD	Chronic kidney disease
CN	Cytoreductive nephrectomy
CRP	C-reactive protein
CSA	Contact surface area
CSS	Cancer-specific survival
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte associated antigen 4
DAP	Diameter-axial-polar
DISSRM	Delayed Intervention and Surveillance for Small Renal Masses
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
GFR	Glomerular filtration rate
HIF1 α	Hypoxia-induced 1 alpha
HLRCC	Hereditary leiomyomatosis and renal cell cancer
HPRC	Hereditary papillary renal cancer
HU	Hounsfield units
HUH	Helsinki University Hospital
IARC	International Agency for Research on Cancer
IMDC	International Metastatic Renal Cancer Database Consortium
IQR	Interquartile range
ISUP	International Society of Urological Pathology
LDH	Lactate dehydrogenase
LU	Leuven-Udine
MDT	Metastasis-directed therapy
miRNA	MicroRNA
mRCC	Metastatic renal cell carcinoma

MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	Mammalian target of rapamycin
NePhRO	Nearness, Physical location, Radius and Organization of tumour
NLR	Neutrophil-lymphocyte ratio
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
OS	Overall survival
PADUA	Preoperative Aspects and Dimensions Used for an Anatomical Classification
PD-1	Programmed death-1 receptor
PDGF	Platelet-derived growth factor
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PN	Partial nephrectomy
pRCC	Papillary renal cell carcinoma
PSM	Positive surgical margin
PTEN	Phosphatase and tensin homolog
QOL	Quality of life
RAIV	Resected and ischemic volume
RCC	Renal cell carcinoma
RFS	Recurrence-free survival
RN	Radical nephrectomy
ROC	Receiver operating characteristic
RTB	Renal tumour biopsy
RTII	Renal tumour invasion index
SARR	Surgical approach renal ranking
SRM	Small renal mass
SSIGN	Stage, size, grade and necrosis
S-TATI	Serum tumour-associated trypsin inhibitor
S-TRAC	Sunitinib as Adjuvant Treatment for Patients at High Risk of Recurrence of Renal Cell Carcinoma Following Nephrectomy
TATI	Tumour-associated trypsin inhibitor
TKI	Tyrosine kinase inhibitor
TNM	Tumour, node and metastasis
TSC	Tuberous sclerosis complex
TT	Tumour thrombus
UISS	University of California Integrated Staging System
VEGF	Vascular endothelial growth factor
VHL	Von Hippel-Lindau
WHO	World Health Organization

1 INTRODUCTION

Renal cell carcinoma (RCC) is the most lethal urological malignancy; however, reliable prognostic tools to recognise the 'killer tumours' from indolent ones are lacking. Being a highly heterogenic disease, the clinical course of RCC is strikingly unpredictable.

As up to half of newly diagnosed RCCs are incidental findings (2, 3), we are often faced with the clinical challenge of an unclassified tumour susceptible to malignancy which is found in an imaging study. Peak incidence of RCC is from 60 to 70 years of age, meaning that RCC patients are often frail, have co-morbidities and a limited life expectancy. Therefore, operations for indolent or slowly progressing tumours may easily turn into overtreatment. Renal tumour biopsies (RTBs) are used to distinguish malignant tumours from benign ones. The sensitivity of an RTB for detecting renal malignancy is excellent in experienced centres (93-99.5%) (4, 5), but the accuracy of defining the grade is poor (67%) (4). Although severe complications associated with RTBs are rare (4), there is a definite need for less invasive and more precise tools to predict the course of yet unclassified renal tumours.

The five year overall survival (OS) for all RCCs was reported to be as low as 40% by a Swedish population-based study and merely 13% for metastatic RCC (6). Of local tumours operated on with curative intention, 20-40% commonly recur (7). When considering who benefits from nephrectomy or metastasectomy, estimating survival is important. The tumour, node and metastasis (TNM) classification is one of the most common and robust predictors of oncological outcomes (8). TNM classification and other prognostic factors for RCC, such as Fuhrman grade, tumour necrosis, histologic subtype and performance status of the patient, are not sufficiently accurate prognosticators when used alone (9). Hence, these prognostic factors are combined to numerous prognostic models or nomograms both for localised and metastatic RCCs. The follow-up recommendations and treatment decisions are based on these nomograms and models estimating recurrence and survival. Still, as clinicians and researchers, we are in great need of more accurate prognostic information to facilitate patient counselling, plan individual surveillance schemes and select optimal treatments for each patient (9).

To improve the prognostic accuracy, the further research and development of prognostic biomarkers has become a priority. The increased understanding of gene technology, proteomics, molecular biology and immunology of cancer has raised great hope for finding a 'true prognostic biomarker'. Despite the exhaustive efforts made in marker research, no molecular biomarker has been able to significantly improve the prognostic accuracy of existing models (10).

Surgery is always prone to complications, and complication rates vary amongst centres and procedures. Knowing the results of one's own centre is a benefit when planning more complicated surgery. After recent improvements in targeted therapy and immuno-oncology, doubts have been raised about the role and sequence of surgery in metastasised cases (11, 12). As metastasectomy or cytoreductive nephrectomy may also be used for palliation, the risk of complications, the recovery time from surgery and delay in commencing systematic treatments must be tolerable. For local tumours, mini-invasive surgery is the treatment of choice in all T1 tumours (13) as the oncologic safety of partial nephrectomy (PN) seems to be similar when compared with radical nephrectomy (RN) (13). Still, 22% of pT1a tumours are removed by RN in Northern European countries (14), inferring that more than just the diameter affects our decisions.

2 REVIEW OF LITERATURE

2.1 EPIDEMIOLOGY OF RENAL CELL CARCINOMA

RCC accounts for 2-3% of all cancers (15, 16), representing the ninth most common cancer in men and the sixteenth in women (17). For men, the lifetime risk for developing kidney cancer is about 1 in 48. In Finland, the reported number of new cases of RCC in 2018 was 1,010, ranking 10th in all newly diagnosed cancers (18).

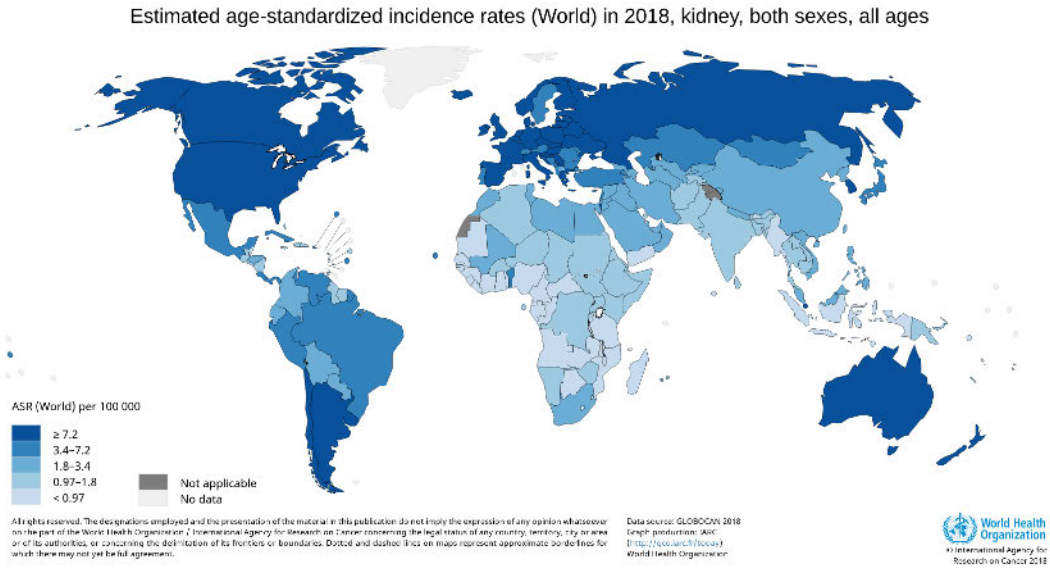


Figure 1 Estimated age-standardized rates of incidence for both sexes (per 100,000 persons) in 2018. In developed countries, the incidence is generally higher than in developing countries. Reprinted with the permission from the World Health Organization.

The number of incidental RCCs, usually smaller and of lower stage, have increased due to the increased use of imaging techniques. The proportion of small renal masses (SRMs) is currently up to 40% of overall incidence (19). Over the last decade, the RCC incidence has been rising worldwide, although this is less pronounced in women (18). However, a great disparity exists concerning RCC incidence globally (Figure 1). The incidence of RCC is highest in Western countries (16, 18). Differences are also profound in Europe: male incidence in Sweden and Malta is as low as 7.1/100,000 but is 22/100,000 in

the Czech Republic (16). Amongst the countries of Northern Europe, only in Finland and Estonia is male RCC incidence stabilised (18) (Figure 2).

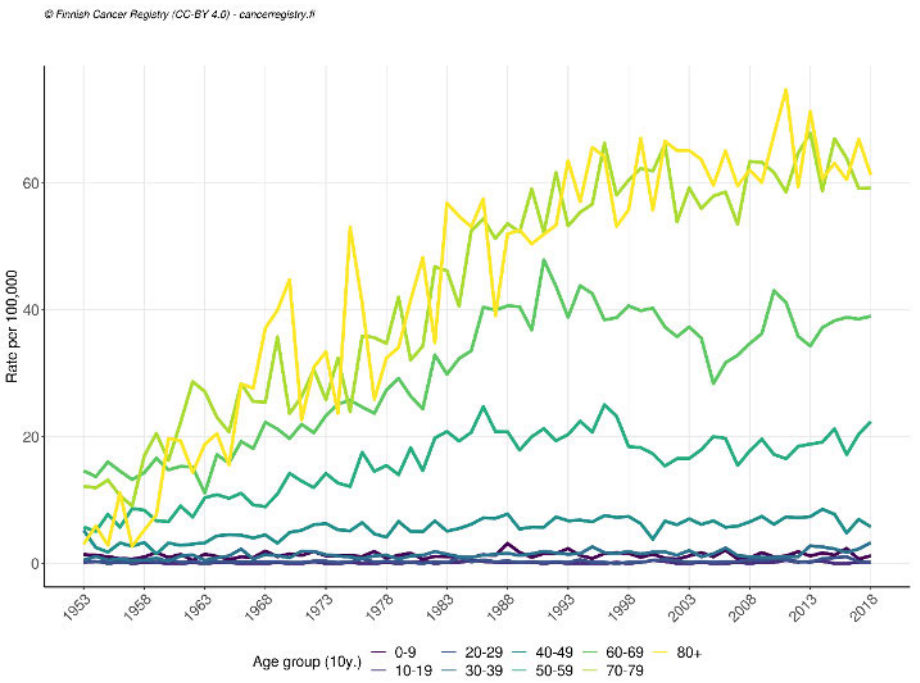


Figure 2 RCC incidence by age group in Finland from 1953 to 2018. Data from Finnish Cancer Registry. https://tilastot.syoparekisteri.fi/syovat, data from 2020-04-02, version 2020-04-17-004. Reprinted with the permission of Finnish Cancer Registry.

Kidney cancer is the 16th most common cause of death worldwide. In Northern Europe, Scandinavia, North America and Australia, mortality has trended downward since the 1990s (Figure 3), while mortality has increased in Croatia, Greece, Slovenia and Portugal (16, 18, 20). Indeed, a worldwide gap in survival rates between high resource and low resource countries does exist and might even be widening following the introduction of immunotherapy (Figure 4).

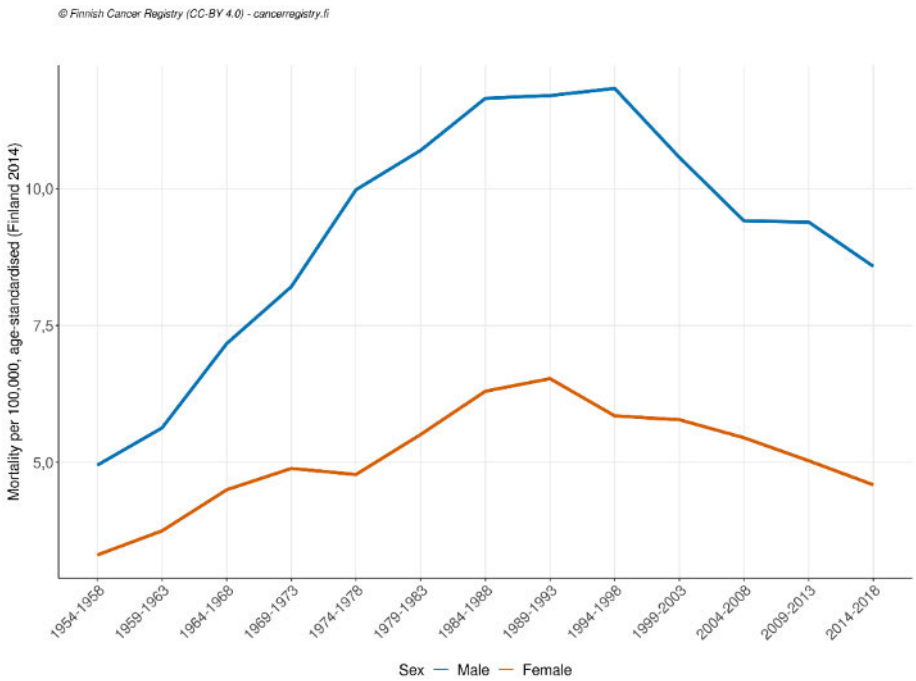


Figure 3 Age-standardised mortality rate (Finland 2014) per 100,000 for males and females from 1954 to 2018. Mortality started to decline in the 1990s. Data from Finnish Cancer Registry. https://tilastot.syoparekisteri.fi/syovat, data from 2020-04-02, version 2020-04-17-004. Reprinted with the permission of Finnish Cancer Registry.

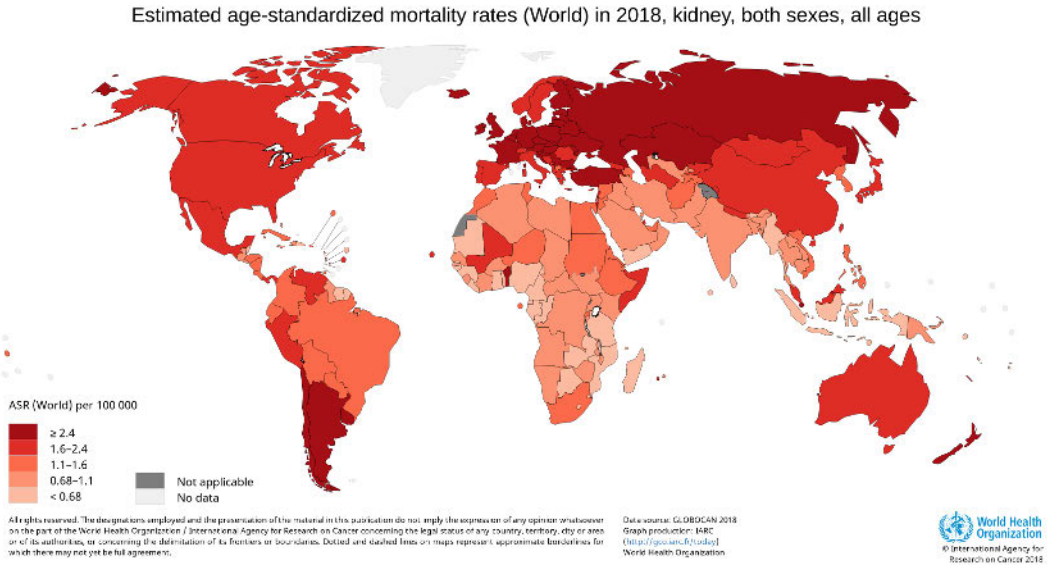


Figure 4 Estimated age-standardized rates of mortality (world standard population) for both sexes (per 100,000 persons) in 2018. The estimated age-standardised mortality rate in Finland equals the Danish figure (2.7/100,000) and is higher than in Sweden and Norway (2.3/100,000). Reprinted with the permission from the World Health Organization.

2.2 ETIOLOGY AND RISK FACTORS OF RENAL CELL CARCINOMA

Known risk factors for RCC are age, with peaks at 60-70 years, and gender, with a 1.5:1 male predominance. Common risk factors found in epidemiological studies include cigarette smoking (21), obesity (22), hypertension (21) and greater adult attained height (1). However, the importance of these risk factors may be biased by incidental cancer detection in imaging done due to illnesses associated with these risk factors (23). The presence of kidney disease, viral hepatitis, urinary stone in male patients and continuous use of paracetamol or non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) seem to increase the risk of RCC (21, 24). Having a first-degree relative with RCC has been associated in meta-analysis with a 2.2-fold and, in case-control analysis, a 4.3-fold significantly increased risk for RCC, 95% CI [1.6-2.9] and [1.6-11.9], respectively (25).

Kidney transplantation, end-stage renal disease and dialysis predispose patients to RCC (26-28). Several hereditary syndromes elevate the risk of RCC, accounting for 4% of all RCCs (25). Von Hippel-Lindau (VHL) disease, Birt-Hogg-Dubé syndrome (BHD), hereditary leiomyomatosis and renal cell cancer (HLRCC), hereditary papillary renal cancer (HPRC) and tuberous sclerosis complex (TSC) are the five most common autosomal dominantly inherited syndromes with distinct clinical manifestations and genetic alterations (29). However, most cases of TSC occur as sporadic cases, due to *de novo* mutation.

Physical activity and consumption of cruciferous vegetables associate with a lower risk of RCC (30, 31) as well as moderate alcohol consumption relative to abstinence (1, 32).

2.3 DIAGNOSING RENAL CELL CARCINOMA

2.3.1 CLINICAL PRESENTATION

Being located retroperitoneally and surrounded by fat, tumours of the kidney may enlarge significantly without presenting any symptoms. Due to the lack of early warning signs, as many as 25-30% of RCCs have already metastasised by the time of diagnosis (33). However, the recent population-based data from Sweden show the percentage of synchronous metastatic RCC to be as low as 19% (2).

The ‘classic triad’ of RCC, which includes abdominal pain, haematuria and palpable mass in the flank or abdomen, is especially rare today. Earlier, 6-10% of patients presented this triad (34, 35). Currently, up to 50% of RCC is detected incidentally (2, 3). However, the disease is sometimes accompanied by paraneoplastic symptoms such as fever, malaise, erythrocytosis and hypercalcemia.

No laboratory examinations, serum or urine are helpful in diagnosing whether a renal cell carcinoma exists. However, laboratory parameters, i.e. haemoglobin, neutrophils, thrombocytes, lactate dehydrogenase and calcium, are used to estimate prognosis of metastasised RCC.

2.3.2 RADIOLOGICAL EXAMINATIONS

Most renal masses are primarily diagnosed by imaging. Ultrasound imaging often raises suspicion about RCC, which is then followed by further imaging with computed tomography (CT) or magnetic resonance imaging (MRI). The paramount criterion for malignancy is the enhancement of contrast material within the tumour (36). An increase of 15 or more Hounsfield units (HUs) indicates solid tissue, which is most often malignant (37). However, fat-free angiomyolipomas and oncocytomas cannot be reliably differentiated from RCC. Recently, contrast-enhanced ultrasound (CEUS) has been used to differentiate cystic lesions from solid ones and has high sensitivity and specificity in characterising renal masses (38). For the purpose of staging RCC, thorax CT added to renal imaging by CT or MRI is recommended (13). CT of head and bone scans are performed only in the presence of symptoms or particular signs (13, 39). Position-emission tomography has a low sensitivity and specificity for detecting RCC and is not recommended by European Association of Urology (EAU) Guidelines (13) .

RTB is often considered non-necessary if the patient will undergo an operation based on radiology (13). Renal biopsies are strongly recommended prior to ablative treatment and for matching patients with the best medical therapy scheme, and they can be used to guide patient selection to active surveillance (13). Use of ultrasound or CT guidance provides similar results (40, 41). Even in experienced centres, up to 22% of biopsies are non-diagnostic, however (4, 42). Researchers found that the diagnostic rate was lowest when there was a long distance (>10 cm) from skin to tumour (73.1%), tumour

diameter was smaller than 4 cm (86.2%), enhancement on contrasted CT was less than 20 HU (57.9%) or the tumour was cystic (60.2%) (43). Also, biopsies of cystic tumours are not recommended (13).

In the literature, tumour seeding due to biopsy is anecdotal and is supposed to be avoided if biopsies are taken using the co-axial technique (4, 5, 44). In the co-axial technique, a larger needle, an introducer, is put in contact with target lesion and a smaller biopsy needle passes through it, multiple times if necessary, to avoid tumour contamination to surrounding tissues. However, a recent study by Macklin et al. has indicated that the risk of tumour seeding is minor but also real when using the co-axial technique (45). A patient case with tumour seeding and local recurrence is presented in Figure 5.

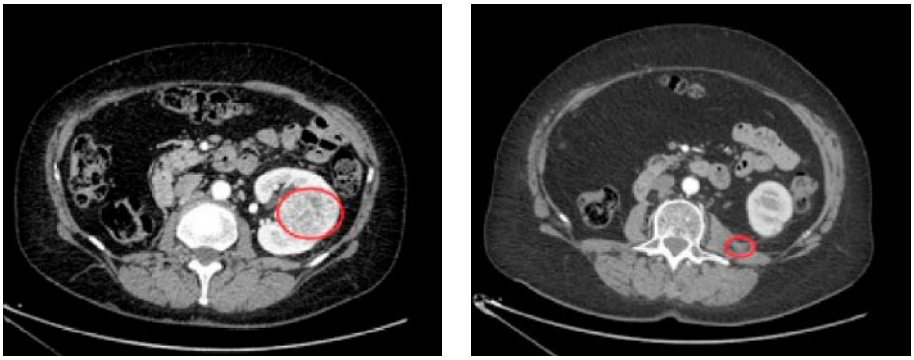


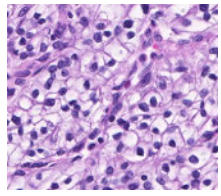
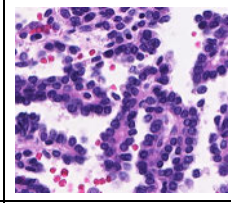
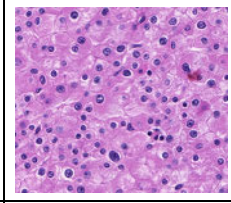
Figure 5 Radiological evidence of tumour recurrence after positive nephric margin and renal tumour biopsy. a) A preoperative image of left solitary renal tumour. b) Postoperative recurrence was noted on the tract of renal biopsy. Figure published with the permission of Elsevier: European Urology, 2019, May; 75(5):861-867, Macklin et al., 'Tumour Seeding in the Tract of Percutaneous Renal Tumour Biopsy: A Report on Seven Cases from UK Tertiary Referral Centre.'

2.3.3 HISTOLOPATHOLOGICAL CLASSIFICATIONS

RCC originates from renal tubular epithelial cells. RCC, being a highly heterogenous disease, comprises several genetic and histological subclasses as reported in the 2016 World Health Organization (WHO) classification (46). Three predominant subtypes are clear-cell RCC (ccRCC), papillary RCC (pRCC) and chromophobe RCC (chroRCC), together accounting for 85-90% of all renal malignancies (47). The three most common histologic subtypes and their features are presented in Table 1.

Oncocytomas comprise 7% of all renal tumours (48). As there are cases where oncocytoma has been noted to invade vascular structures and perinephric fat, although without altering the benign prognosis of oncocytoma, it could be considered as a tumour of a very low potential of malignancy instead of a strictly benign tumour (49) (50). Indeed, the EAU recommends that active surveillance should be offered as a treatment alternative for biopsy proven oncocytomas, as only 64.6% of those remained histologically oncocytomas after surgery, while 31% were classified as cancers (51).

Table 1. *The three most common histologic subtypes and their features (52-55). ccRCC=clear cell renal cell carcinoma, pRCC = papillary renal cell carcinoma, ISUP= International Society of Urological Pathology, Polypromo =PBRM, SETD =SET domain, nuclear respiratory factor =NRF, phosphate and tensin homolog =PTEN, folliculin =FLCN, succinate dehydrogenase deficient=SDH. Histologic pictures are of patients included in the Helsinki University Kidney Tumour Database and were photographed by Tuomas Mirtti and Anni Virtanen.*

Tumour histology	ccRCC	pRCC	Chromophobe RCC
Morphology			
Fuhrman/ISUP grading	Used	Used	Not used
Incidence (%)	75%	10%	5-7%
Alterations in chromosomes	3p loss (91%) 5q gain (67%) 14q loss (49%)	Type I: Gains of 7, 8q, 12q, 16p, 17, 20, and loss of 9p Type II: Gains of 8q, loss of 1p and 9p	Loss of chromosomes 1, 2, 6, 10, 13, 17 and 21
Gene mutations	VHL most common (54%) PBRM1 (40%) SETD2 (13%) BAP1 (10%) and others	Type I: MET mutations (81%) Type II: CDKN2A, SETD2 and NRF2	Low rate of somatic mutations. TP53, PTEN, FLCN gene
Hereditary syndromes	VHL, tuberous sclerosis, BAP1 mutant disease, SDH-associated kidney cancer	Heredital papillary kidney cancer, hereditary leiomyomatosis and RCC and Birt-Hogg-Dubé	Birt-Hogg-Dubé
Average age	64	60	58
Male: Female ratio	2:1	1.5:1	1.1:1

The remaining histologic subtypes are rare, each accounting for approximately 1% of total incidence (46). These minor subtypes include collecting duct RCCs, medullary RCC, clear-cell papillary RCC, microphthalmia-associated transcription factor (MiT) family translocation RCCs, hereditary leiomyomatosis and RCC, acquired cystic disease-associated RCC, tubulocystic RCC, succinate dehydrogenase-deficient RCC and mucinous tubular and spindle cell RCC. Up to 4% of RCCs fail to fit into any of these categories and are labelled as unclassified RCCs (52).

Pathological diagnosis does not only determine the subtypes of RCC, but also interprets the nuclear grade, tumour necrosis, lymphovascular invasion, sarcomatoid features and invasion to perirenal fat or venous system stage (53).

2.4 SURVIVAL AND PROGNOSTIC FACTORS

The clinical course of RCC is variable. After complete, curative-intended, surgical resection of local RCC, up to 30% recurred, according to a five-year follow-up, after being considered disease-free (56). The most fundamental prognosticator is whether the RCC is localised or advanced, at the time of diagnosis, as the hazard ratio of cancer-specific survival (CSS) in metastatic (M1) disease is 33.23 (95% CI [28.18-39.18]) compared with T1N0M0 disease (57). Prognostic factors can be labelled as clinical, anatomical, histopathological and molecular. Prognostic models which combine individual prognostic factors are needed to predict individual likelihood of recurrence and death when counselling patients and selecting patients for adjuvant therapy trials. Accurate and easy-to-use prognostic markers and models are needed, as detecting cancer as early as possible, finding the ones that will recur and deciding the right individual treatment for cancer patients are some of the great challenges of medicine today.

2.4.1 ANATOMICAL PROGNOSTIC FACTORS

2.4.1.1 TNM classification

The classic anatomic prognostic system is TNM classification (58) (Table 2). It was composed for scientific and clinical use (59). The current TNM classification was constructed in 1997 with global consensus (60) and is continuously updated by the Union for International Cancer Control. The

latest update was done in 2017. Tumour size, invasion of the renal capsule or venous system, adrenal involvement, lymph node status and existence of distant metastasis, all important prognostic factors, are included in TNM staging. The TNM classification is one of the most solid and reliable predictors of oncologic outcomes, as OS (Figure 6) and recurrence (8). The TNM classification from 2010 divided T2 into T2a and T2b and changed the pT3a and pT3b classifications. However, these changes have led to only modest improvements in predictive accuracy (8).

Table 2. *TNM Classification 2017 (58). Tumour =T, pathological tumour-node-metastasis =pTNM*

T		**Primary Tumour**	**pTNM Stage Group**
TX		Primary tumour cannot be assessed	
T0		No evidence of primary tumour	Stage I
T1		Tumour < 7 cm or less in greatest dimension, limited to the kidney	
	T1a	Tumour < 4 cm or less	
	T1b	Tumour > 4 cm but < 7 cm	
T2		Tumour > 7 cm in greatest dimension, limited to the kidney	Stage II
	T2a	Tumour > 7 cm but < 10 cm	
	T2b	Tumours > 10 cm, limited to the kidney	
T3		Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia	Stage III
	T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia	
	T3b	Tumour grossly extends into the vena cava below diaphragm	
	T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava	
T4		Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)	Stage IV
N		Regional Lymph Nodes	
NX		Regional lymph nodes cannot be assessed	
N0		No regional lymph node metastasis	
N1		Metastasis in regional lymph node(s)	Stage III (T1-3, M0)
M		Distant metastasis	
M0		No distant metastasis	
M1		Distant metastasis	Stage IV (Any T, any N)

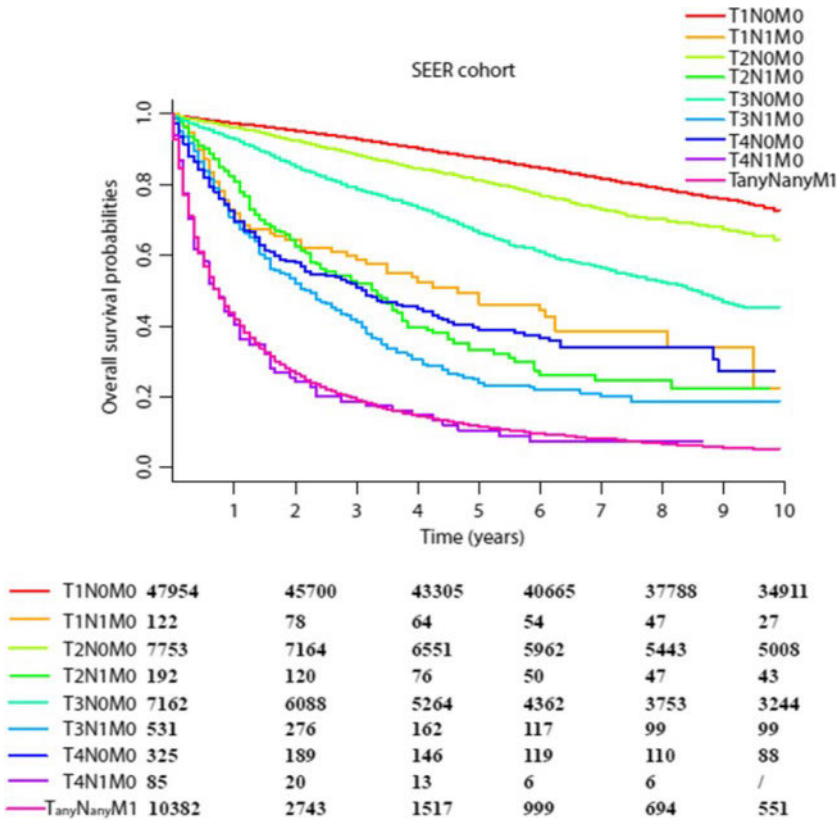


Figure 6 Kaplan-Meier survival curves for the patients of different TNM subgroups from the Surveillance, Epidemiology and End Results (SEER) cohort, affirming the clear differences in OS. Figure is reprinted by permission from Creative Commons, https://creativecommons.org/licenses/by/4.0/. Cancer Med. 2018 Nov; 7(11): 5431–5438. Shao et al., 'Modification of American Joint Committee on cancer prognostic groups for renal cell carcinoma'.

2.4.1.2 Other anatomic systems

Tumour diameter from the TNM classification (58) has been considered as insufficient to guide preoperative planning and to predict the perioperative outcome in terms of complications, operative time and renal function. A wide range of anatomical scorings has been introduced since 2009 to classify renal tumours more accurately, comprising the assessment of size, exo-/endophytic properties, measure of invasion, position in kidney and proximity to the collecting system and renal sinus.

The RENAL Nephrometry Score (61) and Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification (62) are the most frequently used and validated systems for guiding the choice of nephrectomy

and to predict complications, length of operation and hospital stay (63, 64). Other scoring systems are the zonal NePhRO scoring system (65), the surgical approach renal ranking (SARR) (66), centrality index (67), the Renal Tumor Invasion Index (RTII) (68), diameter-axial-polar (DAP) nephrometry (69), the renal tumour contact surface area (CSA) (70) and resected and ischemic volume (RAIV) (71), to name a few.

2.4.2 HISTOLOGICAL PROGNOSTIC FACTORS

The survival rates for ccRCC are the lowest, followed by pRCC and chroRCC (72, 73), but when stratifying histology to tumour grade or tumour stage (T-stage), the survival rate differences disappear in multivariable analysis, indicating that stage and grade determine prognosis more than histological subtype (74). Also, pRCCs consist of type 1 and type 2, with the first group being of lower grade and of favourable outcome, while latter group's tumours are of higher grade with an increased metastatic potential (75, 76). The prognostic difference between this subtyping is however debatable (75). Median survival of a rare subtype, carcinoma of the collecting duct, is 13 months, remarkably lower than for ccRCC, and the majority of tumours (70%) have metastasised by the time of diagnosis (77).

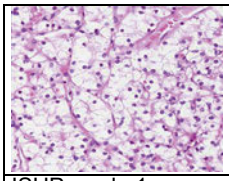
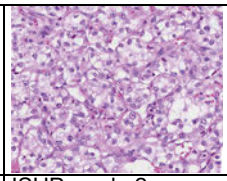
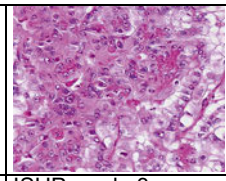
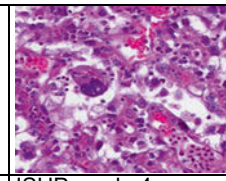
The presence of necrosis, sarcomatoid or rhabdoid features, microscopic venous or lymphaneous invasion and invasion in the collecting system are all associated with worse outcomes (78). Having a median survival of 4 to 13 months after diagnosis, sarcomatous carcinoma has a discouraging prognosis (79, 80). Of the relevant histological features, sarcomatoid differentiation also predicts a worse prognosis in metastatic renal cell carcinoma (mRCC) (81) as well as does non-ccRCC histology (82). For patients with rhabdoid features containing carcinoma, median survival is slightly better (8 to 45 months) than for sarcomatotic features. Rhabdoid features, as independent prognostic factors apart from Fuhrman grade, were not found to be associated with higher mortality (80, 83). Necrosis, however, is a predictor of CSS (84), recurrence (85) and progression to metastasis (86)

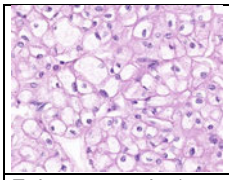
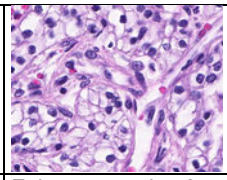
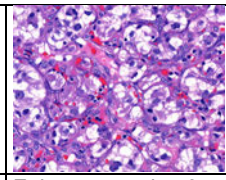
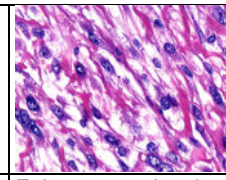
2.4.2.1 Fuhrman/ISUP grading system

The Fuhrman grading system has been one of most generally agreed upon independent prognostic markers for RCC (9, 87). Even though it is the most

popular grading system in clinical practice, it is suboptimal at best, and hence, it is being replaced by the WHO/International Society of Urological Pathology (ISUP) grading system (88). Allocating cancers to different Fuhrman grades has not been reliably repeatable. As no recommendation exists for stratifying the parameters when contradictory results are noted (75), some pathologists grade according to the nuclear prominence only, although this does not follow the grading criteria of Fuhrman. The new ISUP grading system is based only on nuclear prominence, and should be applied to ccRCC and pRCC, while chroRCC should not be graded (75). Table 3 presents the criteria for the ISUP and Fuhrman grading systems.

Table 3. *WHO/ISUP grading classification for RCC. Grade is assigned to the highest-grade cells present, not the most predominant.*

			
ISUP grade 1	ISUP grade 2	ISUP grade 3	ISUP grade 4
Tumour cell nucleoli inconspicuous or absent at 400x magnification.	Tumour cell nucleoli visible at 400x magnification but inconspicuous or invisible at 100x magnification.	Tumour cell nucleoli eosinophilic and conspicuous at 100x magnification.	Tumour presenting extreme nuclear pleomorphism, multinucleated cells, rhabdoid or sarcomatoid differentiation.
Rare	40% of tumours	30-40% of tumours	15% of tumours

			
Fuhrman grade 1	Fuhrman gradus 2	Fuhrman gradus 3	Fuhrman gradus 4
Nuclear diameter small (~10 µm)	Larger nuclear diameter (~15 µm)	Large nuclear diameter (~20 µm)	Mitoses; bizarre, multilobular, pleomorphic
Round uniform nucleus	Irregularities in nuclear outline	Obvious irregular outline	Giant cells, macronucleoli, extreme irregular outline
Absent, inconspicuous nucleoli	Visible at 400x	Prominent at 100x	
Very rare	40% of tumours	30-40% of tumours	15% of tumours

Data for table received from publication by Delahunt al. Grading of renal cell carcinoma. Histopathology. 2019;74(1):4-17. ISUP grading pictures are reformatted and republished with the permission of Springer New York: Genitourinary Pathology, 2015. Sukov W. et al. Classification of Adult Renal Tumors and Grading of Renal Cell Carcinoma. In: Magi-Galluzzi C., Przybycin C. (Eds). Histologic pictures of Fuhrman grading with 40.0 magnification received from Tuomas Mirtti and Anni Virtanen.

2.4.3 CLINICAL PROGNOSTIC FACTORS

With RCC, being symptomatic at the time of diagnosis is associated with worse survival (89). Moreover, cachexia, anaemia and low physical performance are independent markers for poor prognosis (90). The Eastern Cooperative Oncology Group (ECOG) or the Karnofsky scale are used to assess the performance status, and strongly correlate with prognosis (73).

Age is not an independent prognostic factor of RCC for surgically treated, localised RCC (91), and it is excluded from the commonly used prognostic models such as the Stage, Size, Grade and Necrosis (SSIGN) score and Memorial Sloan Kettering Cancer Center (MSKCC) nomogram. Age is strongly associated with other-cause mortality, meaning that septuagenarians, being at high risk for small renal tumour/RCC diagnosis, are also at high risk of other-cause mortality.

As age is only a number, the co-morbidity and disability of patients potentially play a more significant role when determining the outcomes of cancer treatments. In particular, the condition of frailty, meaning when an elderly person is a state of major vulnerability due to adverse health status changes because of a diminished physiological reserve capacity, is a major contributor to health outcomes. Studies of other cancers (92, 93) have pointed out that frailty is a predictor of complications after elective surgery, intolerance to chemotherapy, progression of disease and worse survival. To the best of my knowledge, no studies on the relationship between frailty and RCC exist at this point.

For mRCC patients, there is some evidence that socioeconomic status, older age and marital status (widowed, divorced or separated) are associated with higher cancer-specific mortality but not with overall mortality (94). However, these results may be biased by other factors, e.g. those who are married and have better socioeconomic status are more likely to receive cytoreductive nephrectomy (CN) (95, 96).

2.4.4 PROGNOSTIC BIOMARKERS

Cancer biomarkers are often defined as molecules that raise the suspicion of cancer or predict the future prognosis of cancer. But, a biomarker can be any medical sign that can be objectively measured and reproduced. Serum

prostate-specific antigen (S-PSA) is one of most widely used serum biomarkers for cancer, just as body temperature is a common biomarker for fever. Of commonly used laboratory markers, low haemoglobin level and high corrected serum calcium predict poor survival in patients with advanced RCC (97), and they are currently integrated into standard of care survival calculators. In addition, for patients receiving targeted therapy, hypertension and neutropenia are associated with favourable outcomes (98) and hyponatremia with poor outcomes (99).

Despite the increased interest in molecular biomarkers and the noted promising associations with outcomes, no biomarker has yet been externally validated or found to clearly improve the accuracy beyond the commonly used prognostic factors. Thus, they have not been accepted for use in routine clinical practice but are used in experimental settings only.

2.4.4.1 Markers of hypoxia-induced pathway

Proneness to inherited RCC arises from genes that participate in regulating cellular metabolism. In sporadic ccRCC, some molecular alterations are very common: both the inactivation of the von Hippel-Lindau tumour suppressor (VHL) gene and the loss of chromosome 3p (site of the VHL gene) are found in the majority of cases (100, 101). The VHL gene, which controls oxygen sensing, is encoded to protein (pVHL), which targets hypoxia-induced factor 1 alpha (HIF-1α). Accumulation of the hypoxia-inducible factors (HIF) leads to overexpression of angiogenic factors, platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), which promote neoangiogenesis (102). Commonly, HIF is inactive in an oxygenated environment but in cancer cells, with VHL mutation, HIF stays active although no hypoxemia exists.

The VHL alterations and HIF-1α have been associated with both better (103) and worse survival (104). High carbonic anhydrase IX (CAIX), a HIF-1 α regulated protein, has been demonstrated to predict better prognosis (105). VEGFs, working as regulators of angiogenesis, have been associated with worse survival (106). The best known stimulative and inhibitive pathways for RCC are presented in Figure 7.

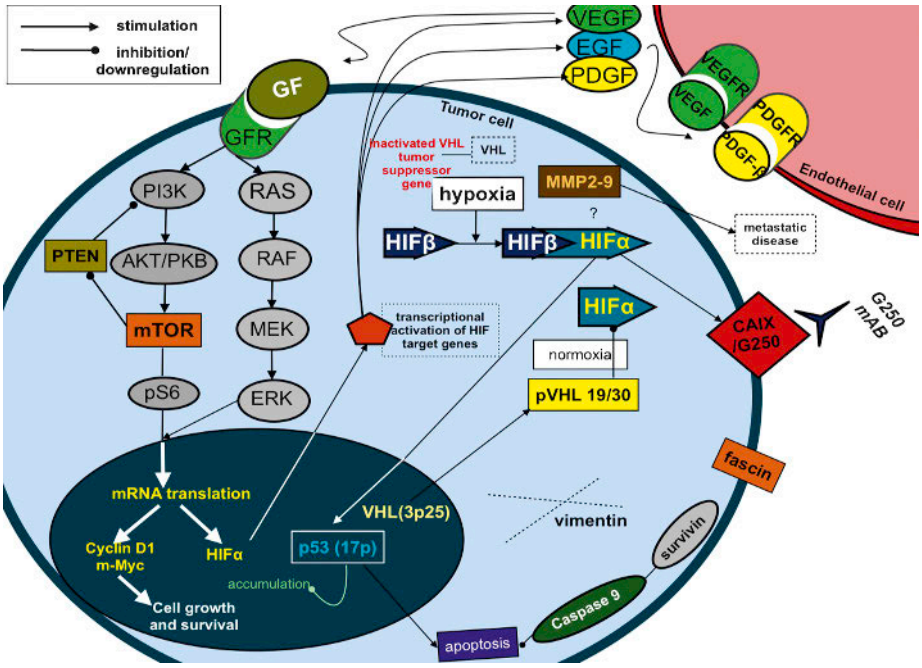


Figure 7 Biologic pathways and markers in renal cell carcinoma. AKT/PKB = akt/protein kinase B (gene); CAIX = carbonic anhydrase IX; EGF = endothelial growth factor; ERK = extracellular signal-regulated kinase; GF = growth factor; GFR = growth factor receptor; HIF = hypoxia-induced factor; MEK = methyl ethyl ketone; MMP = matrix metalloproteinase; mTOR = mammalian target of rapamycin; PDGF = platelet-derived growth factor; PDGFR = platelet-derived growth factor receptor; PTEN = phosphatase and tensin homolog; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; VHL = Von Hippel-Lindau. Republished with the permission of Elsevier, European Urology 2011 Oct;60(4):644-61. Sun, 'Prognostic Factors and Predictive Models in Renal Cell Carcinoma: A Contemporary Review'.

2.4.4.2 Immunological markers

Programmed death-ligand 1 (PD-L1), a ligand on a tumour cell binding to programmed death-1 (PD-1) receptor on activated T cells and assumedly preventing T cell-mediated tumour killing, is a potential biomarker for PD-1/PD-L1 blockage therapy. Overexpression of PD-L1, as seen in 30% of RCC patients, correlates with worse survival (107, 108). There is some evidence to support that PD-L1 expression correlates with higher response rates to anti-PD-L1 therapy at least in melanoma, but results are less clear for RCC (109). Many other immunological markers, as tumour DC8 T-cell density and PD-L2 expression, are actively being studied (110-112) .

2.4.4.3 Inflammatory markers of RCC

Some tumours are heavily infiltrated by immune cells of the host, and this process seems to mimic inflammatory responses of normal tissue (113). Previously, this immune reaction was seen as an attempt to erode tumours. However, currently, the inflammation process is considered to have the paradoxical effect of facilitating the tumour growth and progression (114). Inflammation is sometimes present in the earliest stages of progression from neoplasia to cancer (115, 116), suggesting that inflammation laboratory exams are possible prognostic markers.

A meta-analysis by Hu et al. noted that elevated C-reactive protein (CRP) correlated with poorer CSS and OS (117). The new and promising inflammation marker, neutrophil-lymphocyte ratio (NLR), was found to be associated with poorer prognosis in a recent meta-analysis (118). Elevated platelet and neutrophil counts are also suggested to be independent predictors for poor prognosis (119). In addition, the C-reactive protein to albumin ratio has been associated with worse OS and disease-free survival (DFS) in a recent meta-analysis (120).

Consequently, there is still interest in searching for other acute phase reactants that have a prognostic impact for RCC, such as lactate dehydrogenase (LD) (121) and tumour-associated trypsin inhibitor (TATI) (122, 123). TATI, a 6-kDa peptide, occurs in high concentrations in the pancreas and pancreatic fluid and in several tumours. As pancreatectomised patients have normal TATI concentrations (124), the liver is considered as a main source of TATI (122). Increased serum levels are noted in renal, ovarian, colorectal, bladder and pancreatic cancer and are associated with adverse outcomes (122, 123, 125). Renal excretion removes TATI from circulation. When renal dysfunction exists, serum TATI (s-TATI) becomes markedly elevated (126). The TATI molecule is shown in Figure 8.

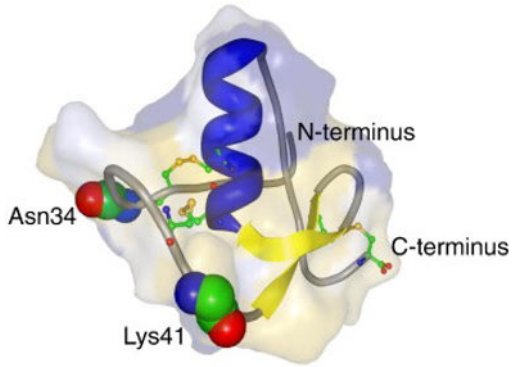


Figure 8 Ribbon diagram of recombinant TATI molecule as visualised by the Protein Workshop program with surface features. Reprinted with the permission of Elsevier: Clinica Chimica Acta, 2014 Apr 20;431:260-9, Itkonen et al., 'TATI as a biomarker'.

Inflammatory markers are widely available, already implemented in clinical practice as markers of infection and inexpensive to use; thus, they are ready to be introduced first in research settings and then in clinical practice.

2.4.4.4 Other markers of RCC

Results concerning ribosomal protein S6, phosphatase and tensin homolog (PTEN) and mammalian target of rapamycin (mTOR) are few, whereas expression of p53, Ki-67 and surviving and matrix metalloproteinases seems to be associated with impaired prognosis (105). However, BioScore, a combination of Ki-67, surviving and B7-H1, was recently externally validated, and it did not improve the prognostic accuracy of the SSIGN score (127). Serum microRNAs (miRNAs), especially miR21 and miR126, have shown promising preliminary results predicting prognosis in RCC (128).

2.4.5 PROGNOSTIC SYSTEMS AND NOMOGRAMS

Even the most important established prognostic factors, TNM stage and Fuhrman grade, are not sufficiently reliable prediction tools on their own, and therefore, there has been a growing call for other prognostic systems. The term 'prognostic model' is used for the clinical prediction model, predictive model or prediction index. A nomogram is a graphic illustration of a multivariable prognostic model and meant to be used for evaluating patients' individual risks and outcomes at certain time points (129). Usually, the TNM stage is included

in all models. The competence of a model is estimated by measuring discrimination using the concordance index (C-index) or area under the curve (AUC). Mathematic values of discrimination vary from pure hazard (0.5) to perfect prediction (1.0). However, no recommendation of an acceptable level of accuracy for allowing models to be introduced to clinical practice exists.

2.4.5.1 Prognostic systems and nomograms in localised disease

The first models to predict recurrence, the Kattan nomogram (130) and Cindolo model (89), included clinical presentation (asymptomatic vs symptomatic) at the time of diagnosis. More current models have excluded symptoms as the presentation of RCC has changed completely. Currently, up to 60% patients are asymptomatic (131), while two decades ago, when Cindolo model was introduced, up to 62% of patients were symptomatic at the time of diagnosis. (89)

Prognostic models that predict CSS, such as the SSIGN score (84) and the Karakiewicz nomogram (132), including all TNM stages, usually report better discrimination than models excluding the metastatic patients, since the metastatic stage is the most powerful prognosticator of CSS. The SSIGN score and Karakiewicz nomogram have a report accuracy of over 82-88% (133, 134) and 87-89% (132), respectively, thus being superior to the TNM stage alone (77%) (135). Despite the better (135, 136) discrimination, the models including all stages are mainly used for research purposes only because the endpoint (CSS) for such a variety of diseases should not guide clinical decision-making.

The Leibovich prognostic score (86) and University of California Integrated Staging System (UISS) (136) are the most generally used postoperative prognostic systems. The original purpose of the UISS score was to assess survival (136), but after few years, the UISS score was adopted to estimate recurrence-free survival (56), while the Leibovich score was used to estimate the metastasis-free survival. The Leibovich includes N+ patients and only ccRCC, but the UISS considers N+ patients as metastatic and accepts all RCC patients. The most common prognostic models both for local and metastasised RCC are shown in Table 4.

Table 4. *Most commonly used prognostic models for both local and metastasised RCC presenting studied outcomes and variables included.*

Prognostic models and studied outcomes						
	Localised disease				**Metastatic disease**	
	Leibovich prognostic score	**UISS**	**SSIGN**	**Postoperative Karakiewicz model**	**MKSCC prognostic system**	**Heng model**
Studied outcome	Metastases-free survival	Recurrence-free survival	CSS	CSS	OS	OS
Tumours accepted	ccRCC	RCC	ccRCC	RCC	RCC	RCC
Variables						
TNM stage	✔	✔	✔	✔		
ECOG performance status		✔				
Karnofsky performance status					✔	✔
RCC related symptoms				✔		
Fuhrman grade	✔	✔	✔	✔		
Tumour necrosis	✔		✔			
Tumour size	✔		✔	✔		
Delay between diagnosis and treatment					✔	✔
LDH					✔	
Corrected calcium					✔	✔
Haemoglobin					✔	✔
Neutrophil count						✔
Platelet count						✔

Data from Volpe et al. Prognostic factors in renal cell carcinoma. World J Urol. 2010;28(3):319-27.

The UISS divides patients into three risk groups: high, intermediate and low risk of recurrence, with the five-year recurrence rates being 90.4%, 61.8% and 41.9% (56), respectively, and the externally validated accuracy being 80% (137). The postoperative follow-up protocol recommended by the EAU guidelines is based on UISS risk groups (13). The recurrence usually emerges in the first five years following surgery. However, patients with higher UISS risk cancer were found to experience recurrence sooner, as median time to

recurrence in high, intermediate and low risk groups were 9.5 months (mean 21.9 ± SD: 26.2), 17.8 months (mean 25.5 ± SD: 23.9) and 28.9 months (mean 26.5 ± SD: 17.1), respectively (56). In addition, in a RECUR database analysis, 52.8% (n=28) of Leibovich low-risk patients recurring in a five-year follow-up time, 37.1% (n=39) of intermediate risk and 30.5% (n=39) of high-risk patients were considered potentially curable at the time of recurrence (138).

2.4.5.2 Prognostic systems and nomograms for metastasised disease

The earliest version of MSKCC prognostic model dates back to 1999 (139), and was updated in 2002 and 2004 (97, 140). In the era of interferon-α, high serum corrected calcium, high serum lactate dehydrogenase (LDH), low haemoglobin, low Karnofsky performance status and absence of prior nephrectomy were all recognised to be independent markers for poor prognosis (139). They all, except the absence of prior nephrectomy, combined with delay between diagnosis and treatment, have also continued to be markers of worse OS after the introduction of tyrosine kinase inhibitor (TKI) therapy. The importance of performance status assessed by the ECOG scale or Karnofsky index must be highlighted, as it is the most important patient-derived prognostic factor in mRCC. Criteria for grading the ECOG scale and Karnofsky index are presented in Table 5.

The MSKCC model is still used in recommendations of the EAU for CN, for example; however, as it was developed before the targeted therapy era, it is considered outdated by some (10). Choueiri et al. combined prognostic factors to predict progression-free survival after targeted therapy (141).

Heng et al. used the International Metastatic Renal Cancer Database Consortium (IMDC) data and developed Choueiri's model, proposing six prognostic factors for OS and dividing patients into three prognostic groups (poor, intermediate and good prognosis). The median OS for poor-risk, intermediate-risk and low-risk groups were determined to be 7.8, 22.5 and 43.3 months, respectively (142).

Table 5. *Comparison of ECOG/WHO scoring system versus the Karnofsky scoring system.*

ECOG scoring system versus the Karnofsky scoring system			
ECOG/WHO score		**Karnofsky score**	
Asymptomatic, fully active, no restrictions	0	Normal, no evidence of disease	100
		Able to perform normal activity with only minor symptoms	90
Symptomatic, restricted in strenuous activity but completely ambulatory Can carry out work	1	Normal activity with effort	80
		Able to care for self but unable to do normal activities	70
Symptomatic, ambulatory >50% of the time Capable of self-care	2	Requires occasional assistance, cares for most needs	60
		Require considerable assistance	50
Symptomatic, ambulatory <50% of the time Capable of limited self-care only	3	Disabled, requires special assistance	40
		Severely disabled	30
Confined to chair or bed No self-care	4	Very sick, requires active support	20
		Moribund	10

Currently, evidence-based recommendations, such as the EAU Guidelines, use the IMDC model when targeted therapy is concerned (13). The external validation of the IMDC model has shown somewhat similar concordance indices for both the IMDC and MSKCC models at 0.664 and 0.657, respectively, proving that the MKSCC model is still valid (142). The use of these prognostic models is widespread and highly recommended because they are the best available. As the majority of known prognostic markers have already been tested in different combinations, to gain better discriminancy, the current prognostic systems with clinical factors need to be reinforced with novel prognostic biomarkers.

2.4.6 COMPLETE RESECTABILITY AND SURGICAL RESULTS

Traditional surgical standards demand that there must be a clear margin of healthy tissue surrounding the tumour which is removed with the tumour. Partial resections, especially enucleations, have challenged this way of thinking. Enucleation means blunt dissection along the capsule with no visible

layer of normal tissue covering the tumour. Also, in partial resections, the healthy tissue margin has been getting smaller. Recently, a meta-analysis confirmed that enucleation is as safe as PN concerning progression-free survival (PFS) and CSS in a relatively short follow-up time (7.2-54.4 months in studies of meta-analysis) and in T1 tumours (143, 144).

Positive surgical margins (PSMs), usually meaning that cancer cells are present in an inked surface, is seen as a risk of oncologic failure, recurrence or metastasis. Avoiding PSM is of paramount importance in all cancer surgery. However, results are confusing. Some studies have argued that PSM might be prognostically significant only with aggressive cancers, if at all (145). Yet, some recent studies have been able to demonstrate PSM to be a significant factor predicting recurrence (146). The role of PSMs remains debatable, but until more conclusive evidence exists, they should be vigorously avoided.

2.5 TREATMENT OPTIONS FOR LOCAL AND LOCALLY ADVANCED RENAL CELL CARCINOMA

2.5.1 ACTIVE SURVEILLANCE

More widespread use of imaging has led to an increasing number of incidentally diagnosed SRMs. Non-symptomatic tumours, less than 4 cm in size, are considered as SRMs. Treating all these SRMs aggressively would lead to overtreatment as approximately 20-30% of them are of benign origin (147). Most SRMs are diagnosed in the elderly and co-morbid population, making postponing the treatment a possible option. Active surveillance is a treatment plan for monitoring patients' condition but giving treatment only if the surveilled condition deteriorates. To be included in active surveillance, patients have to be sufficiently fit to endure the operative or other active treatment.

The success story of active surveillance of prostatic grade group 1 prostate cancer has prompted the interest in surveilling low-stage RCC patients. Both cancers are local, slowly growing tumours which are more prevalent in the elderly. But distinct features do differ. In active surveillance of SRMs, patients are monitored by serial abdominal imaging. Information on histology, grade and pathologic stage might be missing as renal biopsy is not mandatory before designating patients with SRMs for active surveillance. No serum test, such as

S-PSA for prostate cancer, is available for follow-up. Added to this, intervention for prostate cancer causes more functional consequences while RN or PN is considered having only a minimal effect on quality of life (QOL) (148). However, it has been affirmed that preserving nephrons by PN leads to better QOL (149) (150). This might suggest that, by choosing not to operate, i.e. 'choosing the ultimate nephron sparing treatment', might have a beneficial influence on certain aspects of QOL. Additionally, no adverse changes in mental health were noted when comparing active surveillance to operative surgery, according to one multicentre study (151).

Despite fervent discussions, no agreed-on instructions as to when to move from active surveillance to active treatment exist. Arbitrary values of SRM diameter growing larger than 4 cm and growing faster than 0.5 cm/year have been used (152, 153). Recent results of the multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry affirmed that active surveillance, when tumour diameter is less than 4 cm, was not predictive for cancer-specific or OS during a 5-year follow-up time (152).

However, a meta-analysis by Smaldone et al. determined that almost half of the actively surveilled patients (45.4%) ended up having delayed intervention at a mean of 30.5 months (range 6-143 months, SD 21.8 months), mainly due to patients' wishes (57.2%), but also as a result of tumour growth (35.7%) (154). Of the SRMs actively surveilled, 2% metastasised at a mean of 40.2 months (154).

Currently, according to EAU guidelines, following young and healthy patients with active surveillance protocol is against recommendations.

2.5.2 OPERATIVE TREATMENT OF RCC

Over a century, operative removal of local and locally advanced renal tumour has been the treatment of choice. In 1876, Carl Johan Langenbuch performed the first successful nephrectomy on a human patient because of a malignant tumour. It was not long after this that Spencer Wells in 1884 and Vincenz Cerny in 1887 published the first PN results. Although active surveillance has been introduced and focal therapies exist, surgery is still the first-line treatment for local tumours.

RN entails the removal of the entire kidney and surrounding perinephric fat. PN is recommended for T1 tumours and is an option for larger tumours if

technically feasible (155, 156). The indication and possibly gained benefit from lymphadenectomy is still controversial. In a recent systematic review by Bindi, lymphadenactomy was found not to increase survival either in M0 or M1 RCC (157), but contributing studies were sparse and contained risk of bias as only one randomised controlled trial was investigated (158). However, when adverse clinical features exist, extended lymphadenectomy should be considered according to EAU guidelines (13) as a knowledge gap of possible survival benefit for subgroups of high-risk M0 RCC still exists.

The actual procedures (RN or PN) can be performed as conventional open procedures or mini-invasive ones using laparoscopic technology with or without the 3D technique, robotic assistance or the more rarely used hand assistance. Significant debate and research have been ongoing about the best practice, previously about the RN vs PN and more recently about the open or mini-invasive approaches.

As was made evident in a randomised, multicentre study by van Poppel et al., both PN and RN provide excellent and equal results in terms of oncological safety (156). PN, compared with RN, is superior when it comes to renal function and QOL after the operation, but similar to CSS and recurrence-free survival (RFS), although the OS question remains unanswered (13). Since oncologic results are pointed out to be similar, and RN deteriorates kidney function more, PN is the first-line treatment for all T1 tumours if no contraindications exist (13). In 2015, in all Nordic countries, 55% of all kidney tumour treatments were RNs and only 37% PNs (14).

In comparing mini-invasive with open RN, researchers found no differences in CSS, OS or RFS (159, 160). The length of hospital stay, blood loss during operation and requirements for anaesthetics were lower for laparoscopic RN patients (160). In experienced centres, conventional laparoscopic and robot-assisted PN yielded similar results to open PN when looking at OS, RFS and severe complications (159, 161). Blood loss was lower in mini-invasive PN (161) (159). Operation time and warm ischaemia time were longer in laparoscopic PN but not in robot-assisted PN compared with open PN (159, 161, 162). Results concerning glomerular filtration rate (GFR) decline were somewhat contradictory: at least no long-term difference in GFR decline was reported (163, 164). However, the conventional laparoscopic PN is a challenging procedure and comes with a long surgical learning curve. Robot-assisted PN, with articulated

wrist instrument motion, has lessened these technical challenges, reduced the learning curve and reduced the use on laparoscopic PN (165, 166). Robot-assisted PN must still be regarded as a demanding procedure. As shown by Larcher et al., the learning curve for robot-assisted PN, with respect to complications, appears to be endless, without reaching a plateau even after 300 cases (167). Also, amongst hospital regions, there is assumedly a marked variance in the use of mini-invasive techniques, as the choice is dependent of financial resources, patient volume and experience of surgeons.

2.5.3 RENAL CARCINOMA WITH TUMOUR THROMBUS

Tumour thrombus (TT) reaching the vena cava inferior is a considerable adverse prognostic factor for RCC. At the time of diagnosis, up to 10% of RCC patients have venous extension added to the primary tumour (168).

For treating RCC with TT, nephrectomy, combined with thrombectomy, is considered the only curative option and sizable surgical resections are accepted for curative intention. Evidence to support this is based only on case series with limited sample sizes, often with a single-centre design and inhomogeneous population (169-171). Results concerning the prognostic significance of the TT level have been somewhat controversial as some studies have found the level of TT as an independent prognostic factor (172, 173), while some have not (174, 175). In the presence of non-metastatic disease, surgical removal of the tumour and TT are strongly recommended (13), while systemic treatment has been reserved for metastatic disease only.

In a recent retrospective series by Field et al., patients with locally-advanced or metastatic RCC with TT had improved CSS and reduction in tumour and thrombus size after receiving neoadjuvant sunitinib (176). Older studies, with smaller patient populations and with a selection of targeted therapy offered, have had contrasting results (177, 178), however. More studies are needed to confirm if patients who are not able to undergo up-front surgical treatment could benefit from neoadjuvant sunitinib prior to surgery.

Compared with that of localised disease, long-term survival of TT patients remains poor (169-171). Survival has been outstandingly poor for patients with lymph node metastases. Isolated lymph node disease seemed to predict shorter survival (CSS) than single distant metastasis in a large multicentre database study by Tilki (170), with the 5-year CSS estimates for lymph node positive

disease and single distant metastases being 17.3 (95% CI [9.3–27.4]) and 36.8% (95% CI [27.0–46.5]), respectively. Patients with TT and tumours with papillary histology seemed to be associated with significantly worse outcomes as 5-year estimates for pRCC and ccRCC were 36.8% (95% CI [27.0–46.5]) and 54.8% (95% CI [51.8–57.8]), respectively (172).

Being major surgery, the surgery of RCC with TT is prone to complications. According to a large study by Tilki et al., the overall 30-day postoperative complication rate was 34%, and the major complication rate (Clavien 3-5) was 13% (169).

2.5.4 ABLATIVE THERAPIES

Ablation techniques have not gained wide popularity in Finland nor in Nordic Countries as initial treatment for kidney tumours (5% and 8%, respectively) (14). Ablation therapy options are cryoablation and radiofrequency ablation, done percutaneously or laparoscopically. High-quality data to prove oncologic outcome or morbidity of ablative therapies is lacking (13). Population-based study results about oncologic safety are mixed, but no study has proven ablative therapies to be superior to PN (179, 180). A recent meta-analysis found that lower morbidity rates and lower GFR reduction favour ablative therapies, while CSS and OS do favour PN, and local recurrences and appearances of metastasis do not differ between the two treatments (181). Ablative therapies are recommended for old and fragile patients as an alternative to PN or active surveillance (13).

2.5.5 ADJUVANT THERAPY

Surgery is the therapy of choice in non-metastasised RCC. Survival after surgery, in locally advanced disease, remains modest, however, since 5-year disease-free survival (DFS) for UISS intermediate and high-risk patients has been determined to be 64% and 37%, respectively, after nephrectomy (182). Also, a number of targeted therapies have been studied for reducing recurrence of cancer.

The findings of the newly published, important trials for Adjuvant Sorafenib or Sunitinib for Unfavourable Renal Carcinoma (ASSURE) (183), Sunitinib as Adjuvant Treatment for Patients at High Risk of Recurrence of

Renal Cell Cancer (S-TRAC) (184), PROTECT (185) and ATLAS (186) are mixed. The largest trials to date, ASSURE and PROTECT defined no differences between the placebo and treatment arm in DFS or OS, but S-TRAC could prove a DFS difference. ASSURE also enrolled patients with T1b and pT2 disease, whereas S-TRAC only accepted patients with pT3-4 disease. The EAU guidelines recommend not to offer adjuvant therapy with sorafenib, pazopanib or axitinib (strength of rating: strong) and recommend against sunitinib adjuvant therapy in surgically resected high-grade ccRCC (strength of rating: weak). Recent meta-analysis did prove a DFS benefit, but without a significant improvement in OS, for patients treated with adjuvant TKIs (187). This meta-analysis comprised all these four studies, also the ATLAS study which was missing from the most recent version of guidelines. Patients with greater tumour size, T3-T4 tumours and/or nodal metastases did benefit more (187). The biological rationale behind the effect of TKIs in an adjuvant setting is unknown as is whether or not adjuvant TKI just delays metastases or can if it actually prevent recurrence and metastasis. Immune check-point inhibitors have been proven to have promising efficacy in metastatic settings, and several adjuvant studies on immune check-point inhibitors (PROSPER, IMMotion, KEYNOTE and CheckMate) are still recruiting or ongoing, and their results scheduled for 2022 to 2024 are eagerly awaited.

2.6 TREATMENT OF METASTASISED RENAL CELL CARCINOMA

2.6.1 CYTOREDUCTIVE NEPHRECTOMY

Prior to immunotherapy, nephrectomy for metastatic RCC patients was used for the palliation of symptoms (e.g. unendurable pain, bleeding, uncontrolled hypertension or hypercalcemia). As well as the option of palliative nephrectomy, mRCC patients can undergo cytoreductive nephrectomy, meant for reducing of tumour burden, or nephrectomy combined with metastasectomy for oligo-metastatic disease aiming to reach a state where there is no evidence of disease status.

During the last decade, the efficacy of CN was proven in two trials by the former Southwest Oncology Group (SWOG) (188) and the European Organisation for Research and Treatment of Cancer (EORTC), respectively

(189). CN followed by interferon α-2b improved survival compared with interferon treatment alone (OS 11.1 vs 8.1 months and 17 vs 7 months, respectively). Since then, CN has been a routine procedure for patients with a large primary tumour, restricted amount of metastases and good performance status. However, the use of CN has declined over time. According to recent Swedish Cancer Registry, 55% of mRCC patients underwent nephrectomy (2). However, contemporary demographic data from the US has indicated that distinctly fewer patients, only 30% of those receiving targeted therapy, underwent CN (96).

In the era of targeted therapy, the role and sequence of CN remains an unanswered question. Two large prospective and randomised trials, CARMENA (11) and EORTC SURTIME (43), tried to answer this question. CARMENA compared the efficiency of sunitinib alone with immediate CN followed by sunitinib in mRCC patients. Although the trial failed to reach its accrual goals, it still had enough power in the intention-to-treat population to prove the non-inferiority of sunitinib alone vs CN followed by sunitinib. Although OS for sunitinib alone patients was longer (18.4 vs 13.9 months), the results of CARMENA cannot prove superiority of sunitinib alone. Nevertheless, the CARMENA trial lacks real-world applicability, as operated patients were mainly MSKCC intermediate and high-risk patients. The proportion of high-risk patients was as high as 43%, although, according to earlier evidence, CN for poor-risk patients is discouraged (190). Also, the groups did differ as to the proportion of locally advanced tumours (T3 and T4), 51% and 70.1% for sunitinib alone vs CN-sunitinib group, respectively.

Bex A et al. studied immediate CN followed by sunitinib versus sunitinib followed by deferred CN in a SURTIME trial (43). Results of SURTIME lack statistical power to draw any conclusions because of early termination due to slow accrual. The main finding of SURTIME was that patients undergoing deferred compared with immediate nephrectomy had longer OS, suggesting that selecting patients for nephrectomy with a trial phase sunitinib treatment might be useful. Because of slow recruiting, the time has almost passed for these results from CARMENA and SURTIME to be of any relevance as a newer and potentially more efficient option, immunotherapy, has been invented and trials with immunotherapy are now ongoing.

Based on current evidence, CN does not additionally benefit all mRCC patients receiving targeted therapy. Immediate CN still has a role for patients with good performance and no need for immediate systemic therapy, patients with oligo-metastatic disease when complete removal of metastases can be achieved (13) and for intermediate risk patients by MKSCC criteria in the absence of progressing disease during systemic therapy. For high-risk patients, CN should probably be reserved only for palliation (13). In addition, patients with ccRCC without sarcomatous features and whose tumour burden could be reduced markedly (>90% of tumour burden removed) by CN are those who are likely to benefit from CN (191) (192). Furthermore, tumour shrinkage of >10% after initial oncological treatment and the shrinkage taking place during the first 60 days are good prognostic signs and favour CN (193).

Currently, the combination of the patients' MKSCC risk score, disease progression, amount of metastatic burden and response to systemic therapy define those who might benefit from CN. As insightfully stated by Dr Lara et al. in *JAMA Oncology* (194), 'Ultimately, it may be that the disease rather than the physician decides who should undergo surgery.'

2.6.2 METASTASECTOMY AND METASTASES-DIRECTED THERAPIES

No evidence of disease status can also be achieved with operative treatment for patients with single- or oligo-metastatic resectable disease. More often, surgery is only palliative and targeted therapy is needed. Metastasectomy remains an option for carefully selected patients although evidence from randomised controlled trials is lacking. Most studies comprise only patients with ccRCC, so little is known about the benefits for other types of RCC.

Complete removal of metastases improves survival of mRCC patients according to recent systematic reviews (195, 196), although results might be affected by patient and tumour-derived factors, since randomised trials are lacking. Retrospective works, however, have suggested that both OS and CSS are better for complete metastasectomy versus incomplete metastasectomy or no metastasectomy at all (195, 197-199). Some small retrospective series suggested that survival benefit might be gained even after incomplete resection of metastasis compared with no resection patients (197, 198).

Metastasectomy does also have a role in palliation and postponing the initiation of targeted treatment to avoid associated toxicity (195, 200). To avoid the complications of surgery, non-surgical metastases directed-therapies, i.e. stereotactic radiotherapy and thermal ablation, have been used to treat metastases and symptoms of metastases.

The most common sites of metastasis in RCC are the lungs (45%), bones (30%), lymph nodes (22%), liver (20%), brain (8%) and adrenal glands (8%), but any site is practically possible (201). The primary recurrence sites are the lungs (54-64%), lymph nodes (22%) and bones (15-20%) (138, 202). Less common sites include distant lymph nodes, adrenal glands, local recurrences, pancreas, liver and brain. Metastasectomy is the most relevant local treatment to all metastatic sites, except brain and possibly bones. Many prognostic factors for metastasectomy are presented in Figure 9, including patient-derived factors, features of cancer and completeness of surgery (195) (203). Factors associated with favourable outcomes after metastasectomy include good performance status and cancer risk status of good or intermediate risk (by MSKCC or Heng risk score), metastasis being metachronous with primary tumour, recurrence-free interval being over two years, metastasis being solitary or oligo-metastatic, metastasis emerging in a single organ, absence of nodal metastasis, clear-cell histology, absence of a sarcomatoid component and low-to-moderate Fuhrman grade (199).

EAU guidelines recommend metastasectomy if complete resection is achievable and beneficial prognostic factors exist or for mere palliation (13). Other local therapies can be used for palliative purposes; for example, stereotactic radiotherapy comes with low toxicity and can significantly improve local symptoms caused by brain and bone metastasis (204).

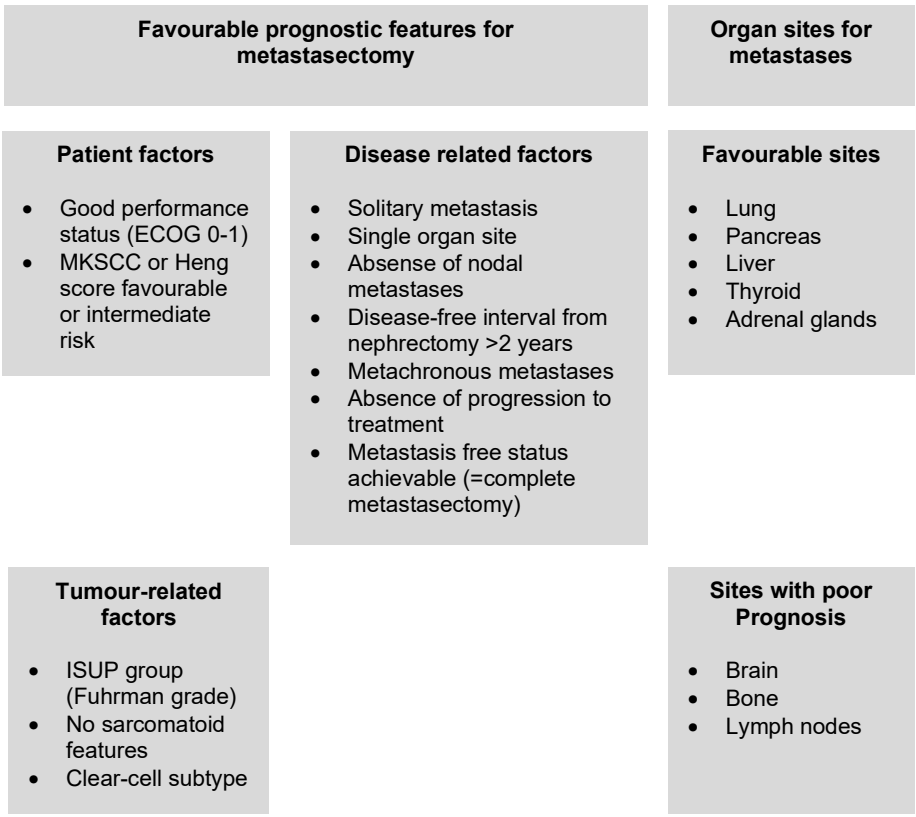


Figure 9 Prognostic factors for surgery of RCC metastasis. Data from publications Dabestani et al. Local treatments for metastases of renal cell carcinoma: a systematic review. Lancet Oncol. 2014 Nov; 15(12):e549-61 and Dabestani S. et al. Metastasis therapies for renal cancer. Curr Opin Urol. 2016 Nov; 26(6):566-72.

As stated earlier, MKSCC risk categories determine patients suitable for CN but no nomogram is agreed upon for choosing patients for metastasectomy. Tosco et al. proposed a clinical tool that could be helpful when deciding amongst treatment options for mRCC patients by assigning metastatic patients to different risk categories by their prognosis (205). The LU prognostic group system divides patients into four different prognostic groups (Figure 10). The system provides a useful clinical tool, but it needs external validation before it can be adopted to practise.

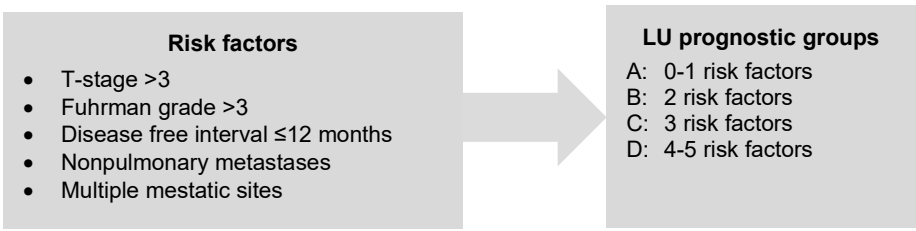


Figure 10 Leuven-Udine prognostic groups.

There are some ongoing prospective studies. One is the RESORT trial, which compares complete metastasectomy and targeted therapy vs metastasectomy and best supportive care until disease recurrence. An ongoing randomised controlled trial by National Cancer Institute (NCT01575548) compares metastasectomy and pazopanib vs metastasectomy and placebo. However, currently, complete metastasectomy remains the only possible cure for limited metastatic disease in the presence of favourable prognostic factors. It may also offer significantly longer CSS and OS, defers time to systematic treatment and relieves symptoms.

2.6.3 SYSTEMIC THERAPY

The first medications for RCC were immunotherapy preparations interferon-α (IFN-α) and interleukin-2 (IL-2). But, since the implementation of targeted therapy, the use of IFN- α and IL-2 has become limited.

Targeted therapies are intended to inhibit the critical signalling pathways of RCC. Targeted therapy comprises VEGF antibodies, tyrosine kinase and multikinase inhibitors and mTOR inhibitors (206). Sunitinib and pazopanib, both TKIs, are the first-line treatment options for treatment-naïve mRCC of IMDC favourable risk (13). Targeted therapies have proven survival benefits compared with IFN-α, but durable remissions are rare (206) as cancer finally develops resistance to these medications. With sunitinib or pazopanib as a first-line treatment, the median PFS is from 8 to 11 months for all patients (207, 208). A more novel multi-kinase inhibitor, cabozantinib, is recommended as a first-line treatment for treatment-naïve mRCC of IMDC intermediate or poor risk (13)

By inhibiting immune cells of the host through overexpression of immune checkpoint molecules, cancer cells escape the immune reaction (209). By

weakening the negative regulation of immune defence, the immune reactions of the host are boosted to fight intruding cells (210). Cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) is a receptor, which turns off the activation of T cells to prevent excessive reaction. A more physiological and less expensive way is to unwind the downregulation of readily activated T cells by selectively blocking the interaction between programmed death 1 (PD1) receptor and programmed death-ligand 1 (PD-L1) (210).

The phase III trial CheckMate 214 (NCT 02231749) proved that a combination of ipilimumab (CTLA-4 inhibitor) and nivolumab (a PD-1 immune checkpoint inhibitor) in treatment-naïve advanced or mRCC patients to be superior to sunitinib in terms of response rate and OS but also in health-related QOL assessment (211). Therefore, the most recent recommendation by EAU is to use ipilimumab plus nivolumab as a treatment for IMDC intermediate and poor-risk previously untreated patients (13). However, widely removing the downregulation of the immune system is not innocuous: even life-threatening autoimmune reactions may happen, and more selective immunological medication is highly anticipated.

2.6.4 PRECISION MEDICINE – THE WAY OF THE FUTURE

Over its history, cancer has been perceived as a disease of an organ, and oncologic treatment has been chosen for the organ involved, e.g. TKIs for RCC. In addition, treatments have been traditionally designed for the 'average patient'. Consequently, treatments have been effective for some but not for all, and the effect of the treatment has been tested with a trial period for each cancer patient. By contrast, precision medicine, e.g. personalised medicine, is treatment taking into consideration genetics as well as molecular and cellular features of the tumour (212)

RCC is, however, not a single entity, but includes various subtypes of tumours. Also, intra- and inter-tumour heterogeneity is huge, being a major obstacle to selecting individual, and effective, treatment for mRCC. As demonstrated by Saaed et al., even cells form different tumour regions and respond differently to cancer medication (213). In clinical research, the bulk tumour has already been handled with surgery or one drug, and tumour subclones simultaneously with some other drug (214). Some promising tissue-based predictive biomarker studies for mRCC exist, but to validate the results,

larger studies are needed. Due to the heterogeneity of the index tumour and metastases, precision medicine will be essentially dependent on tissue samples for now until more accessible biomarkers emerge.

3 AIMS OF THE STUDY

Currently, the prognosis of an individual patient with a renal tumour still cannot be accurately predicted due to the heterogenous behaviour of tumours. The ongoing question concerning which patients should be designated for an operation is more relevant than ever when tumours are ranging from tiny, indolent tumours to life-threatening metastasised disease. Additionally, patients are getting older and more vulnerable. Thus, the low number of complications, good surgical quality and reasonably accurate estimate of life expectancy are of utmost importance when deciding on the treatment.

The aims of this study were to evaluate the contemporary landscape and quality of surgical treatment in the Helsinki metropolitan area and identify prognostic factors of RCC.

The specific aims were as follows:

1) To evaluate changes in the clinical picture and treatment of RCC (I)
2) To evaluate the efficacy of surgery in RCC patients with TT (II)
3) To ensure that anatomical factors and models predict the type of nephrectomy, and that they have impact on recurrence (III)
4) To evaluate the outcome of metastasectomy of RCC patients and assess the performance of the LU prognostic model (IV)
5) To appraise the value of s-TATI as a prognostic marker (IV).

4 PATIENTS AND METHODS

4.1 STUDY COHORTS AND TIMELINES

The patient cohorts are described in detail in the original publications (I-V). All patients studied had the clinical condition of RCC (II-V) or were suspected to have RCC (I). All patients in studies II-V underwent nephrectomy at the Helsinki University Hospital (HUH).

We searched the consecutive patients for each study from either the Helsinki University Kidney Tumour Database or Helsinki University Hospital urological and oncological outpatient registries. Statistics Finland provided the death certificates, but all other information was gathered from patient registries.

Tumours were histologically classified according to either WHO 2004 classification (II and III) (46) or WHO/ISUP 2013 classification (studies I, IV and V) (88) and staging of tumours according to TNM 2009 classification (58). For studies II and IV, we recorded postoperative complications occurring in the first 30 days after operation and graded them according to the Clavien-Dindo classification of surgical complications published by Dindo et al. (215). Patient and tumour characteristics of each substudy are presented in Table 6.

4.1.1 STUDY I

To describe the whole population with kidney tumours, the outpatient registries of urological and oncological departments and the institutional kidney tumour register, covering the entire Helsinki and Uusimaa Hospital District (HUH) of 1.67 million patients, were searched for ICD10 codes of D41.0 and C64.88. The intention was to single out all patients with tumours suspected of being RCC from 2006 to 2016. Having a publicly financed healthcare system and being the only referral institute for urology in the area, these registries comprise nearly all renal tumour patients of the metropolitan area of Helsinki, providing a comprehensive data collection on renal tumours in a current population.

We identified 1,719 patients who had either a solid or a cystic mass (Bosniak 3-4), with a maximum diameter ≥10 mm. We wanted to study the change in presentation and treatment patterns, especially the changing proportion of

active surveillance. Deciding the right treatment often demands some time, so treatments during the first six months after tumour diagnosis were included and meticulously collected from oncological and urological patient records. Patients received urologic treatment, oncologic treatment or observation due to their renal tumours. Not all the tumours being followed up had known histology, as is also the case in real life. The timeline of study was divided into four time periods, 2006-2008, 2009-2011, 2012-2014 and 2015-2016, to obtain better a perception of changes over time.

Table 6. *Clinicopathological data of substudies.*

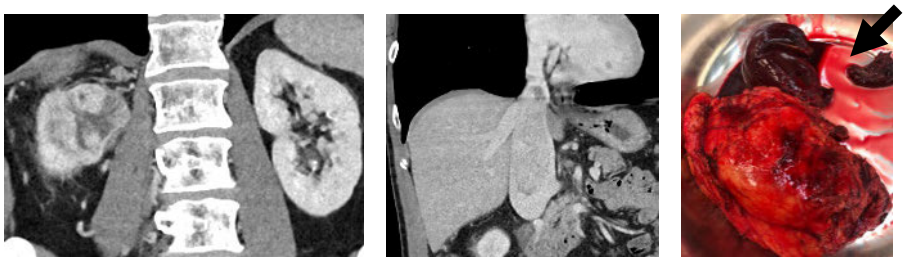
Clinicopathological data of substudies					
	Study I	**Study II**	**Study III**	**Study IV**	**Study V**
Patients (n)	1,719	142	915	97	132
Male (%)	988 (57)	95 (67)	499 (54)	57 (59)	62 (47)
Age (years), mean (SD)	66 (13)	65 (14)	63.4 (13)	64 (4)	64 (18)
When conducted (years)	2006-2016	2006-2014	2006-2014	2006-2017	2005-2010
Nephrectomies (n, %)	1107 (64)	142 (100)	915 (100)	97 (100)	132 (100)
PN/RN	482/625	0/142	388/527	7/93	NA
Malignant tumours (n, %)	1,103 (62)	142 (100)	764 (84)	97 (100)	132 (100)
ccRCC	803 (73)	129 (91)	546 (75)	86 (89)	114 (86)
pRCC	210 (19)	10 (7)	114 (16)	8 (8)	15 (11)
chroRCC	62 (6)	1 (0.7)	53 (7)	0 (0)	1 (0.8)
Fuhrman grading					
Grade 1-2		38 (27)	510 (71)	19 (20)	64 (48)
Grade 3-4		104 (73)	199 (28)	78 (80)	63 (48)
TNM grading					
T-stage 1-2	710 (64%)	0	584 (76%)	24 (25)	58 (44)
T-stage 3-4	393 (36%)	142 (100)	180 (24%)	73 (75)	74 (56)
Median diameter of tumour (mm), mean (SD)	55.5 (36.4)	103 (36)	53.6 (33.7)	80 (15.3)	N.A.
N=0		118 (83)	728 (99.6)	N.A. *	118 (89)
N=1		24 (817)	3 (0.4)	N.A. *	14 (11)
M=0		88 (62)	723 (99)	0	107 (81)
M=1		54 (38)	8 (1)	97 (100)	25 (19)

*N.A.= Information not available. *Only information of patients with removed metastatic lymph nodes (n=4) was available for metastatic patients. This was not included in the table because it is not comparable with other studies. As in other studies, lymph nodes, suspicious for malignancy in preoperative imaging, were also included. SD =standard deviation, PN = partial nephrectomy, RN= radical nephrectomy, ccRCC = clear cell renal cell carcinoma, pRCC = papillary RCC, chroRCC = chromophopic RCC.*

4.1.2 STUDY II

Study II comprised 142 patients with TT treated with nephrectomy from 2006 to 2014 in Helsinki University Hospital. Patients were identified from the Helsinki University Kidney Tumour Register. The majority were inhabitants of Helsinki University Hospital district, but some had been referred from other hospital districts. Follow-up details were collected from different hospitals and healthcare centres around Finland. Treatment intention, radical or cytoreductive, was not an exclusion criterion. The diagnosis of RCC and the level of TT were detected originally from the CT scans taken preoperatively and were further defined after the analysis of pathological specimen. The majority of the patients (95%) underwent whole-body CT and 4% underwent chest X-ray and abdominal CT/MRI.

Mainly studies with small patient populations were conducted during the era of targeted therapy, and the prognostic importance of the TT level was debatable at the time of this study. The study tested the prognostic importance of TT level after surgical management. This required reclassification of TT level according the current TNM classification (2009) and careful recording of adjuvant oncologic treatments. The proportion of patients with supradiaphragmatic TT was modest in our study (n=9, 6%). Figure 11 presents a rare case of supradiaphragmatic TT.



a) b) c)

Figure 11 Rare case of patient with tumour thrombus (TT) extending to the right atrium. Less than 1% of TTs reach the cardiac chambers. a) Preoperative CT: Necrotic 6 cm-sized primary tumour in right kidney was found when imaging patient due to recent pulmonary embolia. b) Preoperative CT of the TT. However, the cephalic level of the TT was best visualised with cardiac echo. c) TT broken into two pieces after resection, and kidney removed *en bloc*. Cardiac extension marked with an arrow. Cardiac bypass and cell-saving technique for blood were used. Only a resection of inferior vena cava was needed, as the TT was non-attached from its cephalic extension. CT images are received from HUS urology clinic patient archives'. Photo of TT was taken by the author.

4.1.3 STUDY III

Study III evaluated the performance of most fundamental tumour characteristics, tumour diameter and parenchymal invasion depth, compared with more compound classifications, such as PADUA classification and RTII, in predicting the type of nephrectomy performed. Nephrectomy types compared were PN (n=388, 42%) and RN (n=527, 58%). Patients underwent operations at Helsinki University Hospital from 1.1.2006 to 31.12.2014 for tumours suspicious for malignancy. The information was retrieved from Helsinki University Kidney Tumour Register.

Twenty-six consultant urologists performed or assisted in these 1,284 operations. The type of nephrectomy was ultimately decided by the primary surgeon based on CT or MRI imaging of the tumour and patient-derived factors. No anatomic classifications were used as a decision aid at the time of the study. For this study, tumour maximal diameter, the depth of parenchymal invasion, PADUA classification and RTII were assessed by one urologist only according to published methods (62, 68).

4.1.4 STUDY IV

Study IV was conducted to assess the safety and efficacy of metastasectomy for RCC patients and to test the performance of the previously published LU prognostic group model. The Helsinki University Kidney Tumour Register was searched for patients with surgically treated metastases of RCC, and it provided 97 patients with sporadic metastatic RCC treated from 2006 to 2017. All patients included in the study also ultimately underwent surgical treatment for the primary tumour. Medical oncologists planned oncological treatments according to prevailing practise when no curable surgical treatment existed. After nephrectomy and metastasectomy, patients were followed up with imaging, laboratory tests and physical examinations according to risk of recurrence. The LU prognostic groups comprised patients with 0 to 5 risk factors, and the patients were divided to groups according the original publication by Tosco et al. (205) (Figure 10).

4.1.5 STUDY V

Study V looked into the value of the serum marker TATI in predicting outcomes after nephrectomy. Patients (n=173) who had undergone either PN or RN at Helsinki University Hospital from 2005-2010 for any kind of renal tumour were included in this study. Patients with benign histology or non-RCC cancer as well as patients with severely reduced renal function were excluded from this study (n=41). No patient had acute infection or pancreatitis at the time of serum sample measurement. We used preoperative CT of the thorax, abdomen and pelvis to determine the metastatic status, but the status was updated if positive lymph nodes were seen in pathological examination.

Serum samples were taken preoperatively at a median of 1.0 day (range 0-50 days) prior to the operation and a minimum of 3 weeks after nephrectomy (median of 52 days, range 25-176 days), to avoid the effect of inflammatory response caused by surgery. Serum samples were stored at -20°C before the assay. S-TATI was determined by time-resolved immunofluorometry assay (TR-IFMA) according to methods previously described.

4.2 STATISTICAL ANALYSIS

All statistical analyses were performed with IBM SPSS Statistics versions 22-24 (IBM, Armonk, NY, USA). Statistical significance was set at $P<0.05$ in two sided-tests.

In studies I and III, the tests used to assess comparisons amongst clinicopathological factors were done with Student t-test and chi-squared test for continuous and categorical variables, respectively. In study V, associations between S-TATI and clinical variables were calculated using Spearman's rho, Mann-Whitney U test and Kruskall-Wallis test, when appropriate. The Wilcoxon signed-rank test was used to analyse differences of medians of pre- and postoperative S-TATI measurements.

In publications II, IV and V, the survival times (OS, CSS and RFS) were defined as the time from nephrectomy to death from any cause, to death from RCC or to first recurrence, respectively. In study IV, the OS and the RFS were calculated from the first surgery for metastases. The Kaplan-Meier estimate was used to analyse the median survival times with 95% CIs for all CSS, RFS and OS, and statistical significance amongst groups was analysed using a log-

rank test. Effects of clinicopathological data and other factors studied were assessed using uni- and multivariate Cox proportional hazard models. These results are expressed as odds ratios (ORs) with 95% CI.

In study III, we calculated the receiver operating characteristic (ROC) curves with areas under the curve (AUCs) to compare the effect of anatomical parameters in predicting the type of nephrectomy. We performed multivariable regression analyses for nephrectomy type using a backward stepwise likelihood ratio test. The anatomic variables correlated strongly. Therefore, we tested them separately and combined them with a constant group of independent non-anatomic cofactors (hypertension, age and year of surgery) aiming to recognise the real-life effect of a single anatomic factor. By expressing the observed results as a percentage of the expected results, the goodness of fit of the models was determined.

4.3 ETHICS

All data for studies I-IV were collected retrospectively from Helsinki University Kidney Tumour Database and Helsinki University urological and oncological patient registries, without requiring informed consent from patients. In study V, patients had given informed consent at enrolment before the planned nephrectomy. The Ethics Committee of the Helsinki and Uusimaa Hospital District approved all studies.

5 RESULTS

5.1 STUDY I

The study of 1,719 patients with kidney tumours suspected of malignancy showed that the field of renal surgery had changed markedly over the 10-year span of the study. The number of septuagenarians and older patients increased from period I (2006-2008) to period IV (2015-2016; p=0.067) (Figure 12). Operated on patients also became more ill and frailer, as the percentage of patients with CCI ≥2 and with ECOG ≥2 increased from 33% (period I) to 44% (period IV; p=0.019) and 19% (I) to 36% (IV; p<0.001), respectively. Tumours were more often incidental (p<0.001), and the percentage of small tumours (diameter ≤4 cm) diagnosed increased from 36% (I) to 54% (IV; p<0.001).

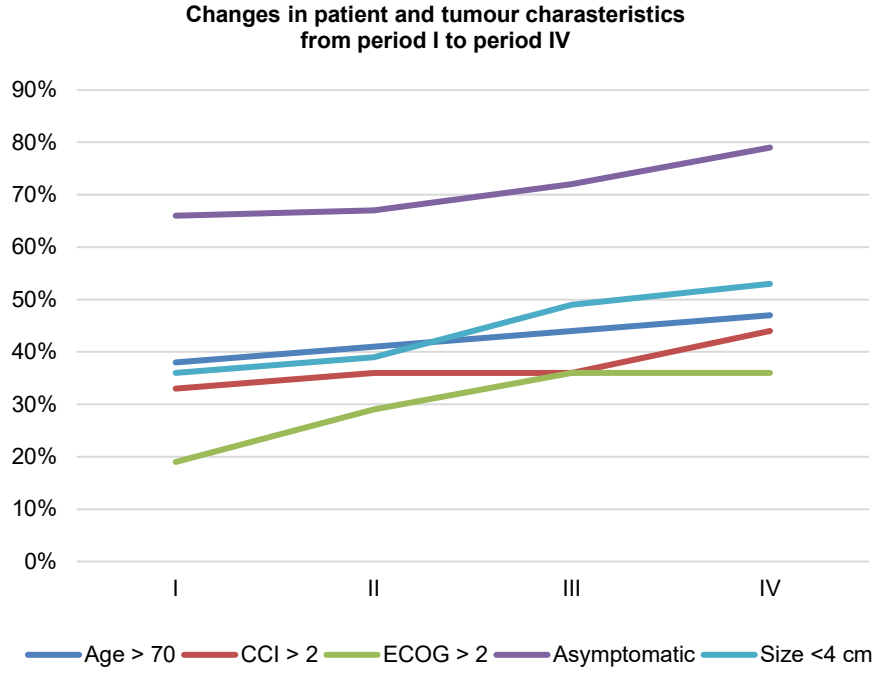


Figure 12 Increasing proportions of older and more fragile patients with smaller tumours during the study periods I-IV (from 2006-2008 to 2015-2016). Illustration previously unpublished by author.

As patients got older and more vulnerable with smaller tumours, the treatment pattern also changed. The use of observation, including both active surveillance and watchful waiting, as forms of urological treatment delivered within six months from diagnosis, increased significantly (Table 7). During period I, 8% of patients had a needle biopsy taken from the tumour compared with 19% in period IV (p<0.001). From period I to period IV, RN decreased from 66% to 30% (p>0.001), respectively. The use of CN decreased significantly as well from 72% (I) to 54% (IV; p=0.032).

Table 7. *Initial urological treatments (during first six months from diagnoses) for patients with small tumours suspected for RCC. a = Chi-square test between radical and partial nephrectomy. b = Chi-square test between active urological treatment and observation methods. RN=radical nephrectomy, PN= partial nephrectomy, RFA= radiofrequency ablation.*

Variable	All	2006-2008	2009-2011	2012-2014	2015-2016	p-value
	n=1,457 n (%)	n=265 n (%)	n=397 n (%)	n=462 n (%)	n=333 n (%)	
Initial urological treatment						
RN	625 (42.9)	176 (66.4)	194 (48.9)	156 (33.8)	99 (29.7)	<0.001a
PN	482 (33.1)	65 (24.5)	123 (31.0)	166 (35.9)	128 (38.4)	
RFA	5	1	3	0	1	
Active surveillance	260 (17.8)	22 (8.3)	59 (14.9)	98 (21.2)	81 (24.3)	<0.001b
Unfit for treatment	76 (5.2)	1 (0.4)	16 (4.0)	38 (8.2)	21 (6.3)	
Refusing to be treated	9	0	2	4		

Table modified from one published in Urologia Internationalis 102(4),390-398, 2019, Erkkilä et al., 'Evolving Clinical Picture of Renal Cell Carcinoma: A Population-Based Study from Helsinki' by permission from S. Karger Publishers Ltd.

5.2 STUDY II

Despite the evolved treatment of metastatic RCC, the long-term survival of patients with RCC and TT has remained modest. In our study, the 5-year CSS rate for non-metastatic patients was 59% and 38% for patients with distal metastases. The median CSS for patients with lymph node involvement was particularly poor, 10 months, whereas it was 63 months for patients with no disease (p<.01) (Figure 13).

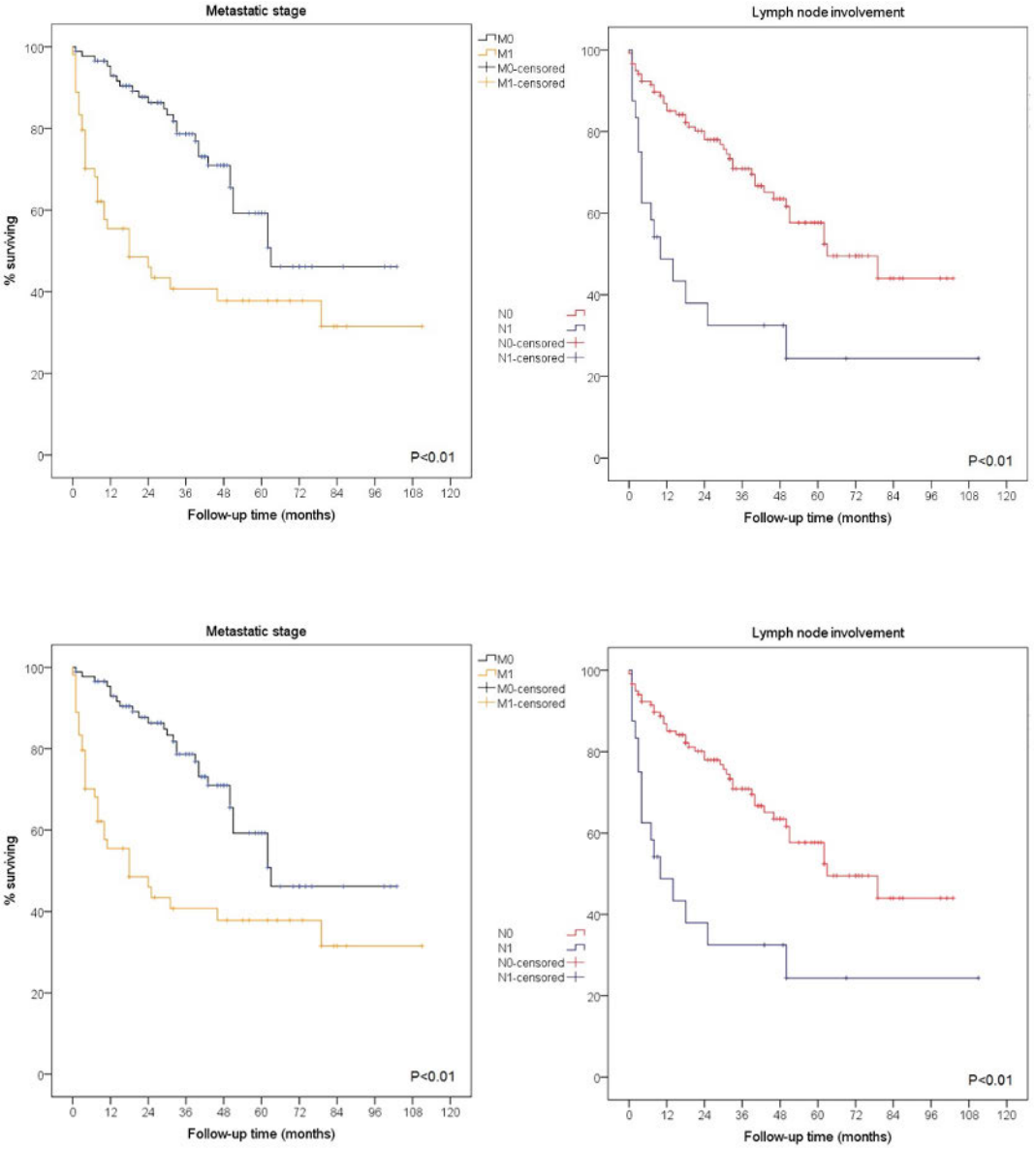


Figure 13 CSS by metastatic state and lymph node involvement. Figures reprinted by permission of Taylor & Francis Group. Scandinavian Journal of Urology 2016, 50(5), 380-386, Tornberg et al., 'Outcome of surgery for patients with renal cell carcinoma and tumour thrombus in the era of modern targeted therapy'.

The level of TT failed to be a significant prognostic predictor of survival in our study – the mean (median) CSS rates for renal vein, subdiaphragmatic vena cava and supradiaphragmatic vena cava were 68 (79) months, 56 (50) months and 43 (not acquired) months, respectively (p=.42).

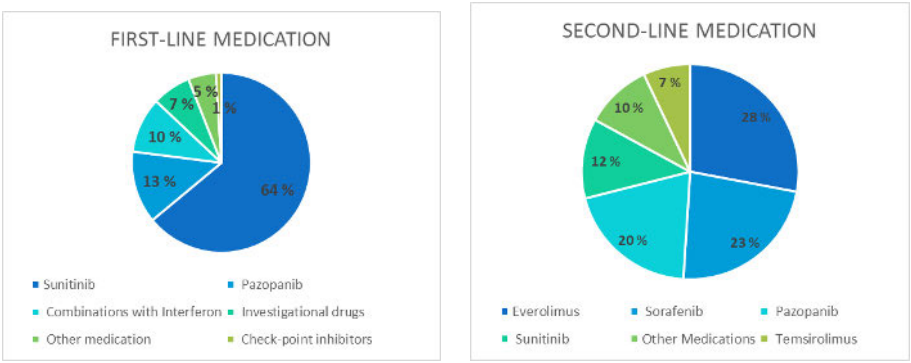


Figure 14 Systemic therapy delivered first- and second-line. Illustration previously unpublished by author.

The majority of patients (62%, 88/142) were operated on with radical intention and 38% (54/142) with cytoreductive intention. During the follow-up time, 73 patients (51%) received postoperative targeted therapy (Figure 14).

Major complications (Clavien-Dindo classification 3-5) were rare (Table 8). Two postoperative deaths occurred with the 30-day mortality being 1%. The overall complication rate was 34%.

5.3 STUDY III

In study III, the proportion of PN increased significantly, from 25% in 2006-2008 to 50% in 2012-2014 (p<0.001) for all tumours. In the last study period (2012-2014), patients with T1a tumour underwent PN in 87% of cases, which differed significantly from the first period (59%; p<0.001). In multivariable regression, younger age, absence of hypertension, later year of surgery, lower tumour invasion, smaller diameter and lower PADUA score were significantly associated with performance of PN.

Table 8. *Thirty-day complication rate according to Clavien-Dindo classification for complications for nephrectomy with tumour thrombectomy.*

Clavien-Dindo grade	All patients	TT reaching renal vein	TT reaching subdiaphragmatic vena cava	TT reaching supradiaphragmatic vena cava
	n (%)	n (%)	n (%)	n (%)
	142 (100%)	81 (100%)	52 (100%)	9 (100%)
No complications	94 (66.2)	61 (75.3)	29 (55.8)	4 (44.4)
1	1 (0.7)	0 (0)	0 (0)	1 (11.1)
2	34 (23.9)	14 (17.3)	17 (32.7)	3 (33.3)
3a	1 (0.7)	0 (0)	1 (1.9)	0 (0)
3b	6 (4.2)	2 (2.5)	4 (7.7)	0 (0)
4a	4 (2.8)	2 (2.5)	1 (1.9)	1 (11.1)
4b	0 (0)	0 (0)	0 (0)	0 (0)
5	2 (1.4)	2 (2.5)	0 (0)	0 (0)
Total number of complications	48 (33.8)	20 (24.7)	23 (44.2)	5 (55.5)
Number of major complications (Clavien-Dindo 3-5)	12 (8.5)	6 (7.4)	6 (11.5)	1 (11.1)

Table modified from one published in the Scandinavian Journal of Urology 50(5),380-386, 2016, Tornberg et al., 'Outcome of surgery for patients with renal cell carcinoma and tumour thrombus in the era of modern targeted therapy' with the permission of the Taylor & Francis Group.

When comparing the anatomical scores, in ROC/AUC analysis, the invasion (AUC 0.92, 95% CI [0.90-0.94]), as well as diameter and RTII, performed better at predicting the nephrectomy than PADUA (AUC 0.88, 95% CI [0.85-0.90]). In the multivariable regression model, adding one anatomic factor to the consistent group of non-anatomic factors was useful, but adding more anatomic factors did not improve the performance significantly. The best model with one anatomic factor was reached with invasion (Table 9).

Table 9. *Comparison of different multivariable regression models for best combination predicting performance of PN. RTII: Renal tumour invasion index; PADUA: Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification score.*

Modality	Anatomical factors included in the model	Percentage classified correctly (%)
Non-anatomic factors (age, hypertension, and year of surgery)	None	63.0
Non-anatomic factors combined with one anatomic factor	Invasion	85.6
	RTII	84.4
	Diameter	84.0
	PADUA	81.8
Non-anatomic factors combined with two anatomic factors	Invasion + Diameter	86.0
	Invasion+RTII	86.0
	Invasion+PADUA	85.6
Non-anatomic factors combined with three anatomic factors	Invasion+Diameter+RTII	86.7
	Invasion+Diameter+PADUA	86.3
Non-anatomic factors combined with four anatomic factors	Invasion+Diameter+RTII+PADUA	86.4

Table modified from one published in Scandinavian Journal of Surgery 2018 Mar; 107(1):54-61. Tornberg et al. 'Renal Tumor Invasion Depth and Diameter are the Two Most Accurate Anatomical Features Regarding the Choice of Radical Versus Partial Nephrectomy'.

Tumour stage, i.e. tumour size in local tumours, is the most important prognostic factor for RCC. However, no studies concerning invasion as a predictor of recurrence have been published to the best of my knowledge. Using the patient data of study II on patients with non-metastasised malignant tumours (N0M0) (n=731) who had undergone nephrectomy with radical intention, we investigated to determine if invasion could predict recurrence and survival. As expected, T-stage, dichotomised to T1 and T2, predicted recurrence in Kaplan-Meier analysis as did invasion (dichotomised in two groups, invasion being either <25 mm or ≥25 mm) ($p<0.005$) (unpublished finding by the author) (Figure 15). These results could be expected as these measurements are strongly correlated. Invasion, diameter and Fuhrman grade were statistically significant predictors of recurrence in univariate analysis, while histology was not. Also, invasion, Fuhrman grade and diameter all remained statistically significant in multivariable analysis predicting recurrence (unpublished finding by the author) (Table 10).

For predicting CSS or OS, invasion excelled in univariate analysis, but the effect was lost in multivariate analysis when compared with diameter or T-stage (dichotomised to T1a/T1b or T1/T2) and Fuhrman grade.

Table 10. *Results of univariate and multivariate analysis of recurrence of tumours with NoMo status at the time of operation.*

			Univariate analysis			**Multivariate analysis**		
		Patients (n)	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Invasion								
As a continuous variable		680	1.03	1.02-1.04	<0.001	1.013	1.00-1.02	0.005
Diameter								
As a continuous variable		680	1.01	1.01-1.01	<0.001	1.007	1.00-1.01	<0.001
Fuhrman grade								
	1	97	1			1		
	2	402	2.10	0.64-6.94	0.22	2.64	0.64-10.79	0.18
	3	166	10.07	3.12-32.47	<0.001	9.36	2.34-37.44	0.002
	4	19	31.72	9.02-111.49	<0.001	30.39	7.20-128.44	<0.001
Histology								
	ccRCC	537	1		0.04	1		0.02
	pRCC	112	0.42	0.19-0.91	0.03	0.52	0.24-1.13	0.10
	chroRCC	52	0.43	0.14-1.37	0.16	0.24	007-0.78	0.02

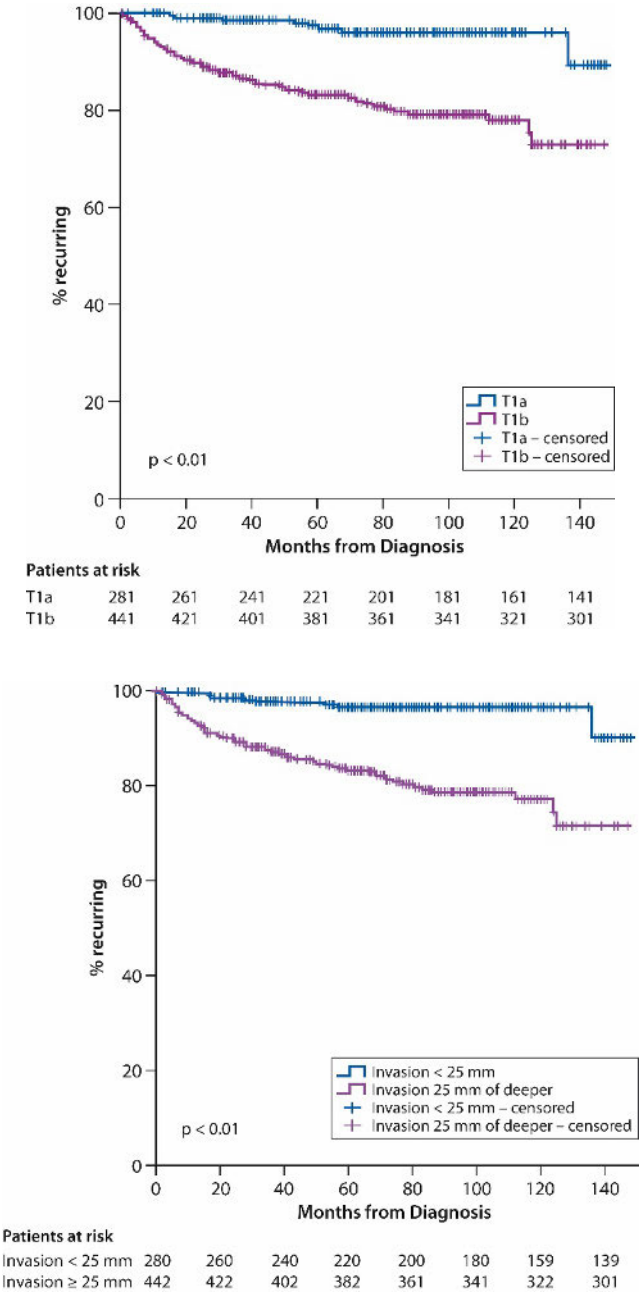


Figure 15 Recurrence by T-stage, divided into T1a and T1b, and invasion with the cut-off of 25 mm. Illustration previously unpublished by author.

5.4 STUDY IV

The 97 patients underwent 90 nephrectomies, 7 PNs and 128 operations for metastases. Only a minority (15%) of metastasectomies were performed simultaneously with the operation on the primary tumour. Most of patients (66/97) underwent one metastasectomy operation, and two operations and three or more operations were done to 24 and 7 patients, respectively. The majority of patients who had undergone metastasectomy had synchronous metastases (62%), and in 37% of patients the metastases emerged after radically intended nephrectomy. The thirty-day complication rate for overall major complications was 11%, and the 30-day mortality rate was 1 % (Table 11).

Table 11. *Thirty-day complications of metastasectomies with the Clavien-Dindo classification.*

Clavien-Dindo Grade	All patients	Initial metastasectomy	Complications in the operations after the first round of metastasectomy
	N (%)	N (%)	N (%)
No complications	84 (63%)	61 (63%)	23 (74%)
1	11 (9%)	9 (9%)	2 (7%)
2	19 (15%)	14 (14%)	5 (16%)
3a	4 (3%)	4 (4%)	0
3b	2 (2%)	2 (2%)	0
4a	6 (5%)	6 (6%)	0
4b	1 (1%)	1 (1%)	0
5	1 (1%)	0	1 (3%)
Total number of complications	44 (34%)	36 (37%)	8 (26%)
Number of major complications (Clavien-Dindo 3-5)	14 (11%)	13 (13%)	1 (3%)

Table reprinted by permission of the Taylor & Francis Group. Scandinavian Journal of Urology 2018 Oct - Dec;52(5-6):419-426.Tornberg et al., 'Surgery for metastases of renal *cell carcinoma: outcome of treatments and preliminary assessment of Leuven-Udine prognostic groups in the targeted therapy era'.*

The estimated median OS was 67 months (Interquartile range (IQR) = 30-130). Patients with complete metastasectomy had significantly better 5-year OS compared with those with non-complete metastasectomy, 59% and 45%, respectively (p=0.030). Figure 16 shows site-specific survival, median survival by sites being 35 (95% CI [16-53]), 77 (58-96), 60 (not available) and 58 (49-67) months for bone, lung, brain and adrenal metastases, respectively.

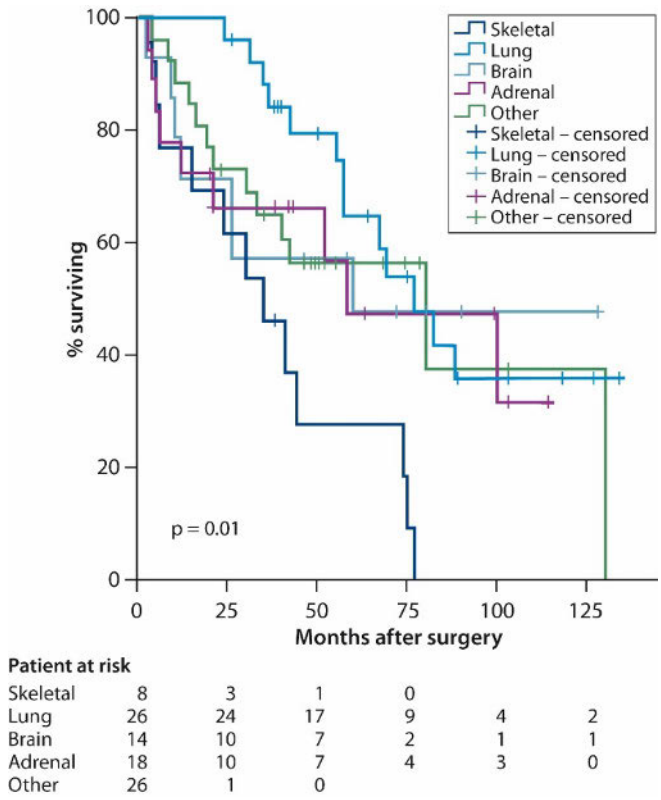


Figure 16 OS by different sites of surgery for RCC metastases. Illustration previously unpublished by author.

Up to 61% of patients, who had undergone complete initial metastasectomy, experienced recurrence and the median RFS after complete metastasectomy was 10 months (IQR = 3-37).

Half of the patients (57%) were on systemic therapy. The estimated median time from diagnosis to oncological treatment was shorter (p=0.006) for patients with non-complete metastasectomy, 19 (IQR = 1-71) months, but for those with complete metastasectomy, at the time of analysis, the median time was not achieved. Figure 17 presents the oncologic systemic treatments administered in the first- and second-line medication.

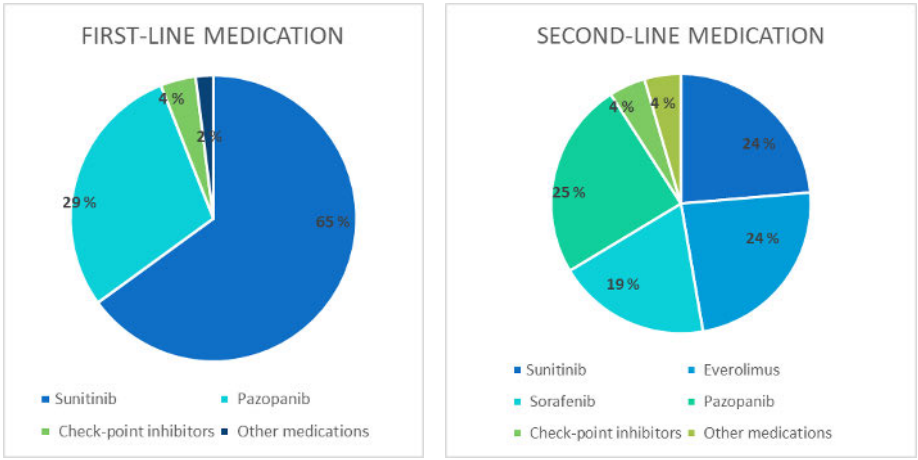


Figure 17 Targeted therapy administered in the first- and second-line for mRCC patients. Illustration previously unpublished by author.

Our study population had more patients with inauspicious prognostic markers, e.g. a larger number of patients with synchronous metastases at the time of diagnosis ($p<0.001$), more patients with multiple metastatic sites ($p<0.001$) and worse ECOG scores compared with the patient population in the study by Tosco et al. ($p=0.003$) (Table 2 in original publication). The number of patients distributed in LU prognostic groups differed significantly between these two studies ($p>0.001$). In our study, we could not validate the performance of LU prognostic groups in predicting CSS. The 5-year CSS for LU prognostic groups A, B, C and D were 0%, 74%, 56% and 45%, respectively ($p=0.42$), and no difference was noted amongst groups B-D after exclusion of the minuscule group A of 2 patients ($p=0.220$).

5.5 STUDY V

The study's population of 132 patients was quite heterogenous, as 44% of patients had local disease (T1-T2), and 56% had locally advanced disease (T3a-T4). Of these patients, 11% had lymph node involvements, and 19% had metastatic disease. The median preoperative and postoperative concentrations of S-TATI for all patients were 13.0 µg/l (IQR = 9.9-19.5) and 18.3 µg/l (IQR = 13.6-24.3), respectively. Figure 18 shows the distribution of S-TATI in the cases of malignant and benign disease.

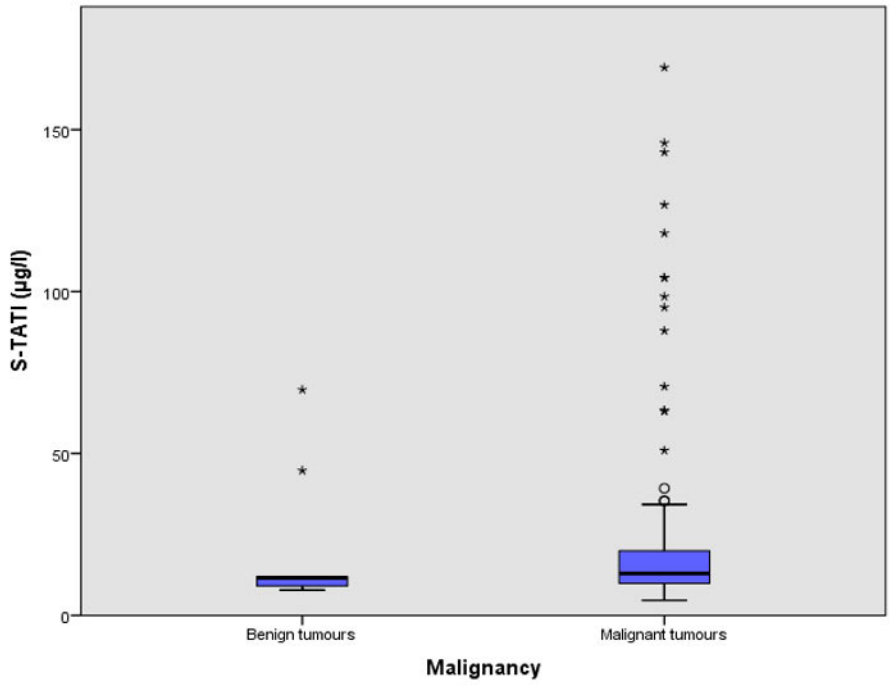


Figure 18 Distribution of S-TATI in malignant and benign diseases. Median preoperative S-TATI for malignant disease being 13.0 µg/l (IQR 10.0-20.0) and for benign disease 11.4 µg/l (IQR 8.7-14.1). Illustration previously unpublished by author.

Preoperative S-TATI measurements were significantly associated with several known prognostic markers for RCC, including T-stage (p=.006), lymph node involvement (p=.04), metastatic state (p=.94) and preoperative CRP level (p=.01). It was also associated with chronic kidney disease (CKD) grade (p<.001). The only significant association with postoperative S-TATI was noted between CKD grade and S-TATI (p<.001).

Postoperative S-TATI measurements were associated with both OS and CSS in the univariate Cox proportional hazards model (Table 2 in original publication). In multivariate analysis for OS, S-TATI remained statistically significant (p=.03) with age (p=.004), lymph node status (p<.001) and M-stage (p=.003). Additionally, for CSS, S-TATI (p=0.004), T-stage (p=.012), N-stage (p=.003) and M-stage (p=.001) remained significant (Table 3 in original publication) in multivariate analysis.

The cut-off of 16 µg/l seemed to predict OS and CSS significantly in the Kaplan-Meier analysis and univariate Cox proportional hazards model only (Figure 19).

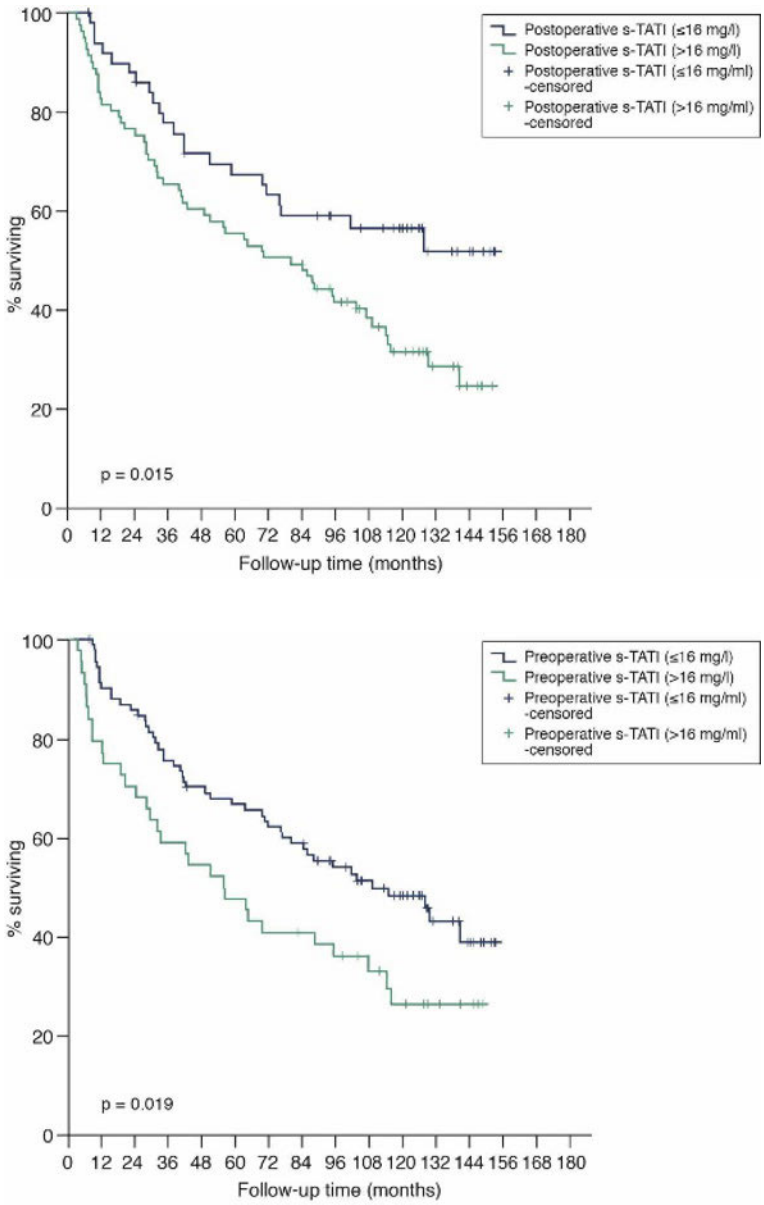


Figure 19 OS for patients with RCC after surgery according to pre- and postoperative S-TATI measurements.

Only 26 patients (26%) had disease recurrence after operations with radical intention. Also, we did not determine any association between postoperative dichotomous S-TATI with a cut-off of 16 µg/l and an increased risk of recurrence (p=.2).

6 DISCUSSION

The marked increase of incidentally found renal tumours has been estimated to have reached a plateau or even started to decline, at least in Europe (18). As the population ages, a larger proportion of renal tumours is found in elderly and co-morbid people. Not all patients with localised RCC who are fit for surgery undergo nephrectomy, but a growing proportion of patients are actively surveilled. In addition, first-line options for mRCC and advanced RCC are on the verge of a major change: the role of cytoreductive nephrectomy is being questioned, and there is a variety of systemic therapies to choose from. For finding the optimal follow-up and treatment protocol for each patient, the search for an optimal biomarker is of greater interest than ever. The growing understanding of immunogenic and molecular mechanisms of RCC has led us to this moment when we finally might be able to find truly predictive biomarkers or prognostic systems.

6.1 SUSPICIOUS MASS IN KIDNEY: ANY CHANGES IN TREATMENT PATTERNS?

The tumours suspected of being RCC are a major dilemma and pose serious questions: when to follow-up, is biopsy needed, when to operate and will the patient survive long enough to benefit from surgery. Our study (I) comprises practically all tumours suspected of being RCC in the HUH region. By restricting inclusion to tumours, not based on histology but suspicion of malignancy, we wanted to address this common clinical challenge: how to manage an unknown kidney mass identified radiologically. According to study (I), the proportion of active surveillance increased during the study period, although no commonly accepted protocol and admittance criteria exist. To support the decision about surveillance or operation, the proportion of tumour biopsies taken increased as well. During the study period, we aimed to familiarise urologists, radiologists and pathologists with the method. However, it must be remembered that RTB comes with morbidity. As it has been stated by Uzosike et al., RTB is appropriate only if it will change the treatment (152). And, due to tumour heterogeneity, Uzosike et al. does not recommend follow-up based on biopsy findings in young and healthy patients fit enough to undergo PN (152). Tumour seeding, especially when pRCC is concerned, is a

minor but existing risk, and it must be balanced against the usefulness of information received by tumour biopsy.

We counted as initial or first-line the treatments delivered during the first six months after the diagnosis because sometimes reaching the verdict takes time. It is important to note that, based on large studies, it might not always be wise to rush on selecting a definite treatment during the first six-month period (152, 154) as, reportedly, brief follow-up is considered safe and is needed for determining growth rate (152). Certainly, patients with an elevated growth rate need to be considered for active treatment.

The portion of mRCC diagnosed did not significantly decrease during the follow-up, although more incidental tumours were found. Our work, in line with other studies, determined that metastatic disease is still diagnosed in up to 20% of new RCC cases (2, 17). The rate of systemic treatments delivered have remained at the same level, but the rate of CN has decreased steadily. In Finland and Sweden, half of the mRCC patients currently receive CN. In the US, however, merely 30% of mRCC patients undergo nephrectomy (96). The American authors have speculated that the use of CN is lower in black, un-insured, unmarried patients and in those treated outside academic centres (96, 216). However, the role of CN might be changing. In light of the current data, CN is not being recommended for high-risk patients by MKSCC criteria or for intermediate-risk patients with progressing disease, despite oncological treatment (217).

6.2 TUMOUR SIZE, DOES IT MATTER?

At the time of the study III, anatomic classifications were widely studied and complex classifications were invented to add more information about diameter (T-stage). The efforts to develop a better nephrometry system are ongoing (218). Although many parameters of tumour, such as diameter, depth of tumour, location and proximity to hilar vessels and the urinary collecting system, do guide the type of nephrectomy chosen, only diameter (T-stage) exists in the guidelines (217). We wanted to see if simple invasion could outperform the diameter and more complex classifications (PADUA and RTII).

Invasion, measured as the distance the tumour invades from the surface of kidney cortex into the parenchyma, has been previously shown to be associated with operation time (219), warm ischaemia time (219), postoperative renal function (220) and postoperative complications (63). Our study investigated

whether invasion correlates with the type of nephrectomy performed. Invasion was superior to other models tested in predicting the type of nephrectomy chosen (III). Logically, the deeper the tumour invades, the more complicated the surgery becomes.

To test usefulness of invasion further, we showed that tumour invasion has the potential to predict recurrence (unpublished work by author). In the past, PADUA score and RENAL nephrometry have been used to predict local recurrence after ablative therapies (63, 221), and more complex tumours associated with higher growth rate in active surveillance (222). However, we found that patients with deeper invading tumours had recurrences more often after both RN and PN. Invasion also remained a significant predictor when combined with histology, diameter and Fuhrman grade. However, one might argue that increased recurrence might be due to unsuccessful surgery, i.e. positive surgical margins. As patients with deeper invasion more often undergo RN, it might instead be the tumour amenities that cause the recurrence than the tumour material left behind.

No previous studies concerning invasion as a predictor of recurrence exist as far as we are aware of. Invasion may have been overlooked as it might seem to be a composite of diameter. However, it remained significant in multivariable analysis, suggesting that it could have some predictive value on its own. It can be hypothesised that, the closer the tumour invades to the hilus or pelvis, the more prone it might be to metastasise.

Another interesting question is whether increased recurrence will translate to increased cancer mortality. In our data, there were no indications of this. Invasion did lose its significance when combined with Fuhrman grade and tumour diameter. According to the data, the majority of the recurrences occur within the first three years, and greatest risk for recurrence is within five years. Therefore, one could hypothesise that the median follow-up time of 5.6 years (67 months) would be enough for showing the effect of invasion on recurrence, but it would not be enough to show the true impact on CSS. A study with longer follow-up times would be needed to answer this question.

6.3 S-TATI, SHOULD WE MEASURE IT?

The main finding in study V was that elevated S-TATI values, both preoperatively and postoperatively measured, raised the risk of overall death

and death from RCC. Based on our data, postoperative S-TATI seemed to be a better predictor of OS than of CSS. This is convincing, as OS is often seen as a more significant and robust endpoint since it is not always clear when deciding if RCC is the ultimate cause of death or not.

Against our first assumption, postoperative S-TATI did not predict the recurrence significantly (V). There were only 26 N0M0 patients that did have recurrence, so it is possible that association might become visible only with larger patient populations.

S-TATI, or serine protease inhibitor 1 (SPINK1), acts as a protector of the pancreas against premature activation of trypsin, as an acute phase reactant, growth factor and inhibitor of apoptosis (223). In RCC, TATI is detected only in cell lines but not in RCC tissue (123), leaving the source of TATI in RCC unclear. In colorectal carcinoma, it is hypothesised that TATI has a role as an oncogene as well (224, 225). With all these functions, S-TATI has the potential to measure malignant behaviour of a tumour. However, having an acute phase reactant, such as TATI, as a prognostic marker of cancer poses many questions that must be addressed: how to exclude other acute infections, acute tissue damage caused by recent operation or impact of renal dysfunction (226). In study (V), we tried to address these points by excluding patients with severe renal dysfunction (CKD grade 4 to 5) or acute infections and by measuring the S-TATI minimum at three weeks after the operation based on previous publications (227).

S-TATI as a continuous variable seemed to predict mortality better than dichotomized S-TATI. Often, a continuous variable is considered to be less vulnerable to statistical errors than a dichotomised variable. However, being able to give a cut-off value predicting malignancy would be of utmost interest for clinicians. From the ROC analysis, the value of 16 μg/l seemed to be the best cut-off for indicating malignancy (sensitivity being 62% and specificity 63%). The same cut-off figure was proposed earlier for RCC (228) and colorectal carcinoma (229), and the reference interval of S-TATI in serum and plasma was suggested to be 5-15 μg/l (226). However, S-TATI did not excel in the ROC analysis, suggesting that using a biomarker with such a pleiotropic role might be challenging or even suboptimal for recognising cancer.

Based on these findings, we could speculate that in the future postoperative S-TATI measurements, in a combination with other markers, might be useful when selecting the intensity of postoperative follow-up controls but even when

estimating if high-risk patients would benefit from adjuvant or neo-adjuvant therapy. Räsänen et al. (15) have speculated that TATI might even have the potential for becoming a target for cancer therapy in the near future.

S-TATI is readily available, reproducible and inexpensive, making it a clinically applicable biomarker. To gain more information about the marker, it might easily be added into preoperative and postoperative laboratory protocol for patients undergoing nephrectomy. To properly examine the performance of S-TATI as a prognostic biomarker, a large prospective study is needed, and our study can be considered as a hypothesis-generating work.

6.4 LOCALLY ADVANCED, WHO SHOULD BE OPERATED?

We aimed to show that more extended TT would predict worse CSS after nephrectomy and thrombectomy, but thrombus level did not reach statistical significance when predicting survival (II). In our data, only 9 patients (6%) had supradiaphragmatic venous thrombus, and such a limited sample is vulnerable to results caused by pure chance. Before our data were gathered, the level of thrombus as a prognostic factor had been controversial (172-174), and there were speculations that the prognostic effect might become visible only in larger patient data sets. Just recently, a large meta-analysis by Gu et al. showed that the level of TT is a prognostic factor of CSS and OS for non-metastatic RCC with TT (171).

The main finding in study II, however, was that patients with RCC and venous thrombus with lymph node metastasis had a poor prognosis after nephrectomy and thrombectomy. Indeed, the median survival of N1 patients was shorter even than that of patients with distant metastases, at 10 months and 18 months, respectively. This finding concurs with that of other studies (170, 230). The reasons behind this phenomenon are unknown, and possibly the speculated hematogenous micrometastasis spread from TT is a less important factor than spreading through lymphatic system. In the systematic review by Gu et al., positive lymph nodes predicted both inferior OS and CSS (171).

The question that remains is whether the prognosis would improve by removing the pathological lymph nodes. A study by Tilki et al. showed superior 5-year CSS for N1 patients than our study did (5-year CSS 17.3% for Tilki and 0% for our population, respectively) (170). Our results might have been affected by the low number of N1 patients (n=24). Another difference was that,

in their study, all of the N1 patients received lymphadenectomy, whereas in our study II, positive lymph nodes might have been biopsied, resected with lumbectomy or removed with thorough lymphadenectomy (170). A recent study by Tilki et al. determined that up to 10% of clinically node-negative patients revealed positive lymph nodes in pathological analysis (231). Expectedly, clinically node-negative patients had better survival after thrombectomy and lymphadenectomy in Tilki et al.'s study. The important question is still unanswered as to whether node-negative patients benefit from prophylactic lymphadenectomy in comparison with just being observed until lymph nodes become visible in imaging studies.

Accurate and recent imaging before tumour thrombectomy is essential. Not only the level of TT markedly affects the selection of the operating technique, but also the personnel and equipment needed and the intensity and length of postoperative care. The metastatic state and the lymph-node status as well as other prognostic markers should be considered when deciding the treatment. In our study, the survival of mRCC patients with TT was surprisingly good. Compared with studies that had begun their patient gathering before the targeted therapy era, there was a clear survival benefit (170). This could imply that operations on mRCC with TT could be more advantageous when combined with targeted therapy or novel immunotherapy. Based on our study II, we would suggest considering operative treatment for mRCC patients with TT at least in the presence of solitary and/or resectable metastases. However, considering the poor prognosis of N1 patients, operative treatment as an obvious first-line treatment might need to be reconsidered.

When it comes to non-metastasised RCC with TT, after complete removal of tumour material, up to half of the patients experience recurrence in three years (232). Unfortunately, adjuvant therapy with TKIs does not have much to offer to this group of patients or N1 patients either, as adjuvant therapy does not provide an OS benefit according to recent meta-analysis (187). This group of patients showed a DFS benefit after adjuvant therapy however, but it is unclear if this would translate to OS benefit in the future. The possible benefit of adjuvant therapy must always be weighed against the risk of adverse effects.

The previously noted poor prognosis of patients with pRCC with TT compared with ccRCC (172) also existed in our study II. Being clearly less common than ccRCC, pRCC patients are often excluded from clinical trials for

cancer drugs (233, 234). Due to the lack of therapies targeted to pRCC, these patients receive medication targeted for ccRCC, albeit pRCC does not respond equally well (235). To improve the prognosis of locally advanced and metastasised pRCC patients, we need medical trials targeted specifically for pRCC patients.

6.5 METASTASISED RCC AND MODERN SYSTEMIC THERAPY, ANY POINT OF OPERATING?

Up to 200 retrospective studies about metastasectomy exist, but the patient populations are often small, and these are mainly from the cytokine era. As a handful of studies are from the targeted therapy era, there are arguments that the effect of targeted therapy might diminish the shown effect of metastasectomy on survival. Amongst these retrospective studies, our study IV has large patient population and is from the targeted therapy era.

Concurrent with our work (IV), recent works by Sun et al. and Lyon et al., suggest that the survival benefit of metastasectomy is consistent also in the era of targeted therapy (236, 237). A large database study by Sun et al. with 1,976 patients undergoing metastasectomy suggested that metastasectomy is associated with 17% decline of all-cause mortality (236). This propensity score-matched analysis showed that patients who underwent metastasectomy had superior OS than patients who did not (median OS: 24.1 vs 18.9 months) (236). A more recent study by Lyon et al. revealed all-cause mortality declined by nearly 60% amongst patients undergoing complete metastasectomy (237). The discrepancy in results might be explained by an inability to assess whether the metastasectomy was complete or non-complete leading to all metastasectomies being aggregated in a single group in the study by Sun (236).

Our study IV suggested a survival benefit for patients undergoing complete metastasectomy vs patients with incomplete metastasectomy, which is in line with other studies (195) (237). However, our survival rates were surprisingly good, as the median overall survival was 77 months for complete and 57 months for incomplete metastasectomy. The increasing use of targeted therapy might explain some of the survival benefit compared with that of the study of Alt et al. with a median OS of 47 months and 15.6 months for complete and incomplete metastasectomy, respectively (197). In Alt et al.'s study of patients receiving systemic therapy, only 13% received targeted therapy, while 89%

(49/55) in our study received targeted therapy and one patient received novel immunological treatment.

One might argue that the beneficial results from metastasectomy are due to selection bias, i.e. only patients with favourable prognosis undergo an operation. Although Sun et al. tried to eliminate the effects of potential bias by propensity score adjustments (236), in the absence of RCTs, it is always possible that confounding factors exist and affect the results.

When it comes to performance status, patients accepted for clinical medical trials (e.g. CARMENA) have to have good performance status (ECOG performance score of 0 or 1) (11). It is noteworthy that, in our study, 21% of patients had low performance status (ECOG 2-5) (IV). This is markedly more frequent than in the study of Lyon et al. (ECOG 2-5: 6%)(237) or the older one by Vogl et al. (Karnofsky score ≤80%: 12.1%)(198). When compared with patients in the study of Tosco et al. (205), our patients had poorer prognostic markers in terms of a longer interval between nephrectomy and metastases, solitary metastatic lesions and performance status (42).

Indeed, considering the poor prognostic features of our metastasectomy population, the survival was surprisingly good. We do not have analogous OS figures from the current era for comparison, however. Lyon et al. reported only CSS figures with a shorter follow-up time, and in the study of Sun et al., median OS of 24.1 months for metastasectomy and 18.9 months for no-metastasectomy were affected by aggregation of complete and non-complete metastasectomies. Even the median survival of non-complete resection in our study surpassed those achieved with targeted therapy as the median OS of 26 months for sunitinib was noted, and for the nivolumab-plus-ipilimumab group, it was not reached during the median follow-up of 25 months (211).

Poor prognostic features may have caused the relatively large number of patients (71%) recurring soon (RFS ≤ 12 months) in our study IV. This emphasises that patient selection for operative treatment is of utmost importance. Maybe all recurring patients in our study did not personally benefit from the surgery, although the survival of the whole population was improved. Here, the patient's preference also comes into question. To find the patients who will benefit from metastasectomy, we need better prognostic systems and predictive markers. Yet, our study failed to prove the accuracy of LU prognostic groups as a tool for stratifying mRCC patients according to their

prognosis. As mentioned earlier, our population was different in terms of known prognostic factors. However, an accurate prognostic tool has to work in all kinds of populations.

Not all metastasectomies aim for longer survival. In our study, one-third of metastasectomies were cytoreductive in nature, and 62% of the operations for bone metastases were palliative (IV). In a study by Vogl et al. from the era of immunotherapy and IFN-α, 65% of patients had metastasectomy done for palliative reasons, i.e. for pain control or maintenance of skeletal integrity (198). The authors also pointed out that incomplete resection was a predictor of survival. Figure 20 presents a clinical scenario leading to CN.

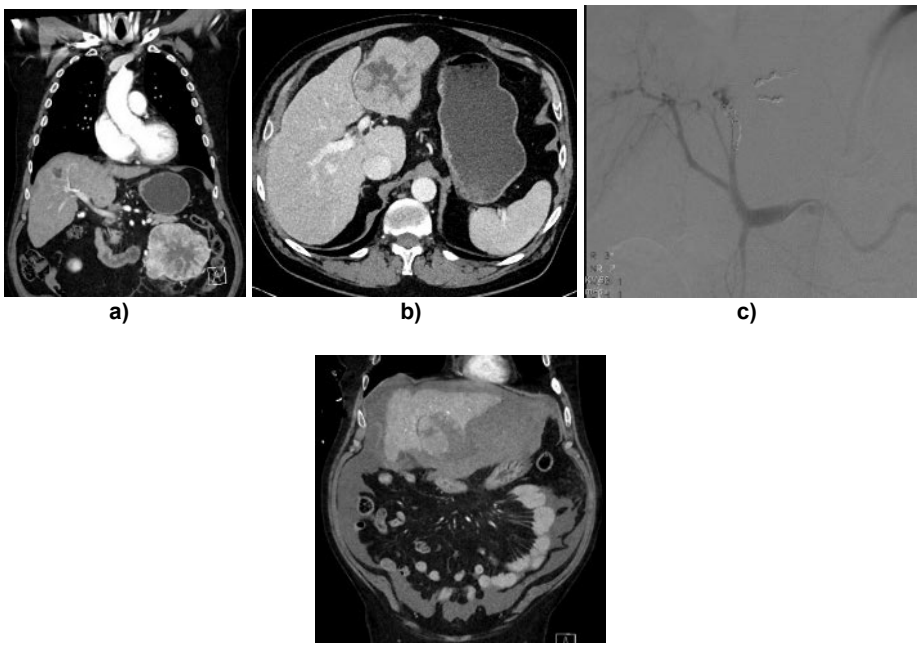


Figure 20 Incidentally found synchronous liver metastasis of RCC which ended up being treated by angioembolisation due to acute bleeding. a) Preoperative CT image: 16 cm tumour in left kidney. b) Preoperative CT image: Large 6.5 cm metastasis in liver. c) Before consultation of urologist, the patient arrived at the ER due to stomach pain. Active, life-threatening, bleeding from liver metastasis was noted in the CT. d) Emergency angioembolisation was made and stopped the bleeding. Liver resection and nephrectomy were planned as the patient had Heng risk status of good/intermediate risk. CT images were provided by the HUS urology clinic patient archives.

Our data concurs with other available data suggesting that metastasectomy still plays a part in this era of targeted therapy and check-point inhibitors. Apart from palliation, only a subgroup of patients benefits from metastasectomy. However, for some patients, metastasectomy offers clearly prolonged survival and delays the initiation of systemic treatment. The value of time without systemic therapy should not be underestimated as cancer drugs come with side effects. Metastasectomy, having acceptable morbidity in selected patients, might be gaining popularity as a part of a multimodality setting, especially if on-going randomised trials prove its efficacy (NCT00918775 and NCT01444807). Before that becomes a reality, however, decisions to operate should be done in co-operation with oncologists, and appropriate patient selection should be based on the prognostic factors, while considering the risks of treatments remains of ultimate importance.

6.6 BIG OPERATIONS, BIG CENTRES AND BIG RISKS?

Although the data of studies II and IV included patients with locally advanced or metastasized disease and technically challenged surgery, the complication rate was not that high. We noted a 30-day complication rate of 34% for operations on TT and 36% for initial metastasectomies, similar to the rates documented in the literature, but with fewer major complications (169, 238). The 30-day mortality was 1% for RCC with TT, being 0% for initial metastasectomies, but 0.8% for all metastasectomies, which was in line with the literature (169, 238). Patients undergoing CN have had more wound complications and more delayed (>90 days) complications after initiation of systemic therapy (239), but no differences in 30-day complications or severe complications (Clavien-Dindo ≥3) were noted (239, 240). An association with metastasectomy complications after commencement of targeted therapy has not been ascertained in the era of targeted therapy (238).

Operating RCC with extensive TT is challenging and has a high risk of vascular and major complications, and it is considered as safe when being performed in high-volume centres with the help of vascular surgeons, thoracic surgeons and anaesthesiologists. Interestingly, in a recent study of Meyer et al., no difference in complications of metastasectomy was noted regardless of the type of hospital or annual volume of cancer cases (238).

The team constellation, knowledgeability and volume of the centre may also affect implementing new treatment recommendations into the clinical practice. The 2001 EAU Guidelines on RCC stated the final evaluation of oncologic efficacy to be uncertain for T1a tumours (241). However, by the time the next fully updated version of the Guidelines was published in 2007, PN had already become the treatment of choice for all T1a tumours (242). Accordingly, the rate of PN increased markedly during the study period: in 2006-2008, only 57% of T1a patients underwent PN, but in 2012-2014, 87% did (III). The low adherence to guidelines in the first years of study might seem disheartening in a high-volume centre such as ours. At the time of the study, renal surgery was seen as a common operation suitable for all urologists and residents, and in study II, there were 26 urologist and/or residents who performed or assisted in 915 operations. Since the days of the study, we have gradually centralised the renal surgery to a limited number of urologists in our clinic. We assume that not only the volume of the clinic matters; we presumably also need high-volume urologists. In the future, we expect new treatment recommendations to be promptly accepted and followed in our clinic.

6.7 LIMITATIONS

The limitations of these studies (I-IV) include the nature of retrospective, single-centre study design, meaning that the results might not be generalizable to other populations. Due to the centralised system, only sporadic patients are missing from these patient cohorts gathered from the district of 1.67 million people. Despite the comprehensive patient cohort, for rare diseases, the volume of patients was too limited to offer sufficient distribution of patients amongst different categories. The unequal distribution of patients between LU prognostic groups (IV) and groups by level of TT involvement (II) may have affected our results.

No re-evaluations were done concerning the pathological examinations. At the beginning of these study periods (I-V), pathologists did not use any structured report form, which might mean that some information about necrosis, rhabdoid features, and sarcomatoid features might be missing from reports. As a structured report is now commonly used, this format requires that the pathologist always comment on these features. The ECOG performance status, CCI and Clavien-Dindo complication score should be determined at the

time of diagnosis or complications, but in these studies, many of them were assigned retrospectively by investigators. The limitations of these studies also include the continually improving imaging accuracy, meaning that the quality of imagines done at the beginning of study do not match the standards of today.

The main limitation of study V was minor and heterogenous patient data, which might have lessened the value of S-TATI as a prognosticator. We had to exclude many patients from the final analyses due to a disease of benign origin or urothelial carcinoma.

Unfortunately, at the time of study planning, neutrophils, lymphocytes and calcium were not seen as valuable prognostic markers for RCC in our clinic and were not routinely measured. This precluded us from including the Heng score or MKSCC nomogram in study IV. While in study V, comparing S-TATI with other inflammation markers with proven prognostic significance, as the neutrophil-lymphocyte ratio, would have been of significant interest. S-TATI was not measured repeatedly, which would have been relevant, especially considering the cases that recurred.

6.8 RCC, WHAT'S AHEAD?

Since the beginning of these studies, the treatment of RCC has changed substantially as we are moving from targeted therapy to novel immunotherapy. In addition, the substance of our work, the patient cohort, is changing. The patient population with small renal tumours is getting older, frailer and more prone to co-morbidities (I) (243, 244). Web-based, easy-to-use prediction nomograms, similar to the ones for prostate cancer created by MSKCC (245) to predict the risk of death and cancer-specific death of an individual patient, are eagerly anticipated. One key issue for creating prediction tools is how to define frailty. Co-morbidities or even performance status systems (i.e. ECOG) do not paint the whole picture of the recovering ability of an elderly person, while thorough geriatric questionnaires are often too detailed to use in daily practice.

The increase in incidentally found small tumours has not led to a decrease of newly diagnosed mRCC. Being the most lethal urological malignancy, but curatively manageable when diagnosed early, RCC screening seems a credible option. At the moment, no recommendations against or for RCC screening exist. Since RCC has a relatively low incidence rate, screening subpopulations,

i.e. patients older than 70 years of age, might be more rewarding while they are at an increased risk for high-stage and high-grade renal carcinoma (246)

The potential effect of screening is based on the assumption that early treatment should yield better survival. Indeed, the increase of RCC mortality has stabilised or even declined in recent years in many countries in Scandinavia (16). However, treating small incidental tumours may not lower overall mortality, which is more dependent on aging, frailty and co-morbidity. Fenton et al. estimated a sojourn time for RCC (mean duration of the detectable preclinical period) to be from 3.7 to 5.8 years, meaning that screened RCC of people under 65 would usually progress to clinical diagnosis during their life (247).

In one recent meta-analysis, which has presumably underestimated the true prevalence of histologically proven RCC, Rossi et al. (248) speculated that screening of RCC might even be as effective as the screening of abdominal aortal aneurysm or colorectal cancer, both of which have established screening programmes in UK. However, due to the different nature of diseases, comparing diseases is spurious. While healthcare costs are continuously increasing, screening cannot just be effective, but cost-effective as well. Rossi et al. recently published a cost-effectiveness analysis, where ultrasound screening seemed to be cost-efficient in 60-year old males (249). We must remember that the true prevalence of RCC by age/sex is still unknown as current figures may underestimate it due to uneven distribution of studies worldwide. For screening purposes, there is a need for inexpensive but accurate biomarkers, such as the ones measured from urine or blood.

Cancer treatment has made great progress. However, many of these treatments, such as metastasectomy, CN and many systemic therapies are effective only for some patients with good prognostic markers or for patients expressing specific biomarkers predicting responsiveness to therapy. In the future, the genetic and molecular analysis of tumour might be the base for treatment. This author believes that nephrectomies and metastasectomies might be needed in future not only for tumour histology but also for receiving enough tissue material to test the effects of various drugs on heterogenous tumour tissue (250).

In the future, treatment of RCC, especially when locally advanced or metastasised, has to be customised concerning cancer amenities, patient

derived factors, possible side effects of treatments and treatment efficacy. To offer the surgical and oncological treatments in the right sequence, we will need tight collaboration between urologists and oncologists. When planning the personalised treatment, we have to bear in mind the goal of each patient whether it is the longest survival or maintaining best possible QOL. This means that multidisciplinary teams should not just consider the tissue specimen but also take into account the whole individual affected by the disease.

Multiple tissue-based predictive biomarkers for metastatic ccRCC are emerging currently, but need to be validated, while non-ccRCC lacks candidates for potential biomarkers. No other prognostic marker is superior to tumour stage, despite the fervent search for a perfect prognostic marker. In the future, all potential prognostic markers should be compared with the TNM stage, the most substantial conventional prognostic marker, to prove their accuracy. The anatomical, histological and clinical prognostic factors combined have reached their ceiling in prediction accuracy (251). What we should be looking for is a combination of clinical and histological markers together with laboratory parameters, as genetic, molecular and tissue-based markers, to obtain more precise prognosticators.

6.9 FUTURE SCIENTIFIC CONSIDERATIONS

Over the past few decades, several biomarkers have been studied to estimate the prognosis of RCC. We are aiming to use the Helsinki Biobank RCC tissue samples to test a variety of known histochemical and immunohistochemical prognostic tissue markers in tumour microarrays (TMAs). To determine if any markers seem to predict recurrence or death, we are comparing them with prognostic data from the Helsinki University Kidney tumour database.

For this thesis, I ran further analyses to test the performance of tumour invasion in predicting RCC recurrence. In these preliminary analyses, invasion also seemed to be an independent prognostic marker when compared with tumour diameter, histology and Fuhrman grade. This is an important result as we can easily measure invasion using CT images. I intend to rerun the analyses, with additional clinical parameters, e.g. tumour necrosis, to see if this effect remains and to see if adding invasion to well-established prognostic scores, as the Leibovich score, would improve the accuracy of prognostication. Indeed, it

would be valuable to see if the effect of invasion is lost when a tumour becomes locally advanced, i.e. reaches the perirenal fat or pelvis.

One limitation of my studies (II, IV) was the small size of patient subcohorts. Despite the fact that our hospital is amongst the largest RCC centres in Northern European countries, when it comes to rare diseases as supradiaphragmatic TT, we do not have enough patients to run reliable analysis. After the initiation of my substudies, new collaboration groups for RCC researchers have been founded. Our study group is active in FinnKidney, a Finnish working group, and in NORENCA, a collaboration of RCC researchers in Nordic countries. A multicentre approach allows us to enrol more patients, making it possible to study rare diseases as well as to compare differences amongst different centres or nationalities.

Preoperative and non-invasive prognostic prediction methods are urgently needed to either replace or to be used with renal tumour biopsies. Today, the prognostic nomograms rely heavily on histology, which is only gained by invasive methods. As RCC patients get older and frailer, to operate or not to operate becomes a fundamental question. Despite the small and heterogenous patient number, TATI expression seems to be associated with adverse prognosis. In the future, it would be of value to use serum and urine samples of RCC patients from the Helsinki biobank to test the prognostic accuracy of promising up-to-date biomarkers.

7 CONCLUSIONS

On the basis of the present studies, the following conclusions can be drawn concerning the RCC patients treated surgically at Helsinki University Hospital.

1. RCC patients generally are getting older and more fragile. We are finding smaller and smaller tumours and more asymptomatic tumours. Mini-invasive treatments are becoming more popular, and we are treating more patients with active surveillance and taking biopsies of tumours more often. The proportion of newly diagnosed M1 patients did not change during the surveillance period. A shift in oncological treatments from targeted therapy to immunotherapy was not yet clearly observed in these studies. The number of CNs has declined.

2. The level of TT seems to be a prognostic marker only in large cohorts. The improved survival and feasible complication rate of mRCC patients after nephrectomy and thrombectomy makes operating on mRCC patients with TT a reasonable choice in the era of targeted therapy. The survival of the patients with pRCC and TT as well as N1 patients has been dismal.

3. Parenchymal invasion as well as diameter outperformed the more complex classifications, PADUA and RTII, in predicting the type of nephrectomy performed. Invasion seems to be an independent prognostic marker of recurrence, also when compared with tumour diameter.

4. Survival of all mRCC patients after metastasectomy was favourable, although the patient cohort lacked prosperous features for survival after metastasectomy. Assumedly, survival was superior for patients with complete metastasectomy compared with incomplete surgery. Complete metastasectomy led to longer systemic treatment-free time as well. Previously published LU prognostic groups did not predict the survival in this patient cohort.

5. S-TATI was able to predict CSS and OS as well as longer therapy-free intervals. The earlier suggested cut-off point of 16 μg/l seemed to be a

sensible cut-off value for survival. To validate these results, S-TATI should be investigated in large, prospective series, and the confounding effects should be addressed more thoroughly.

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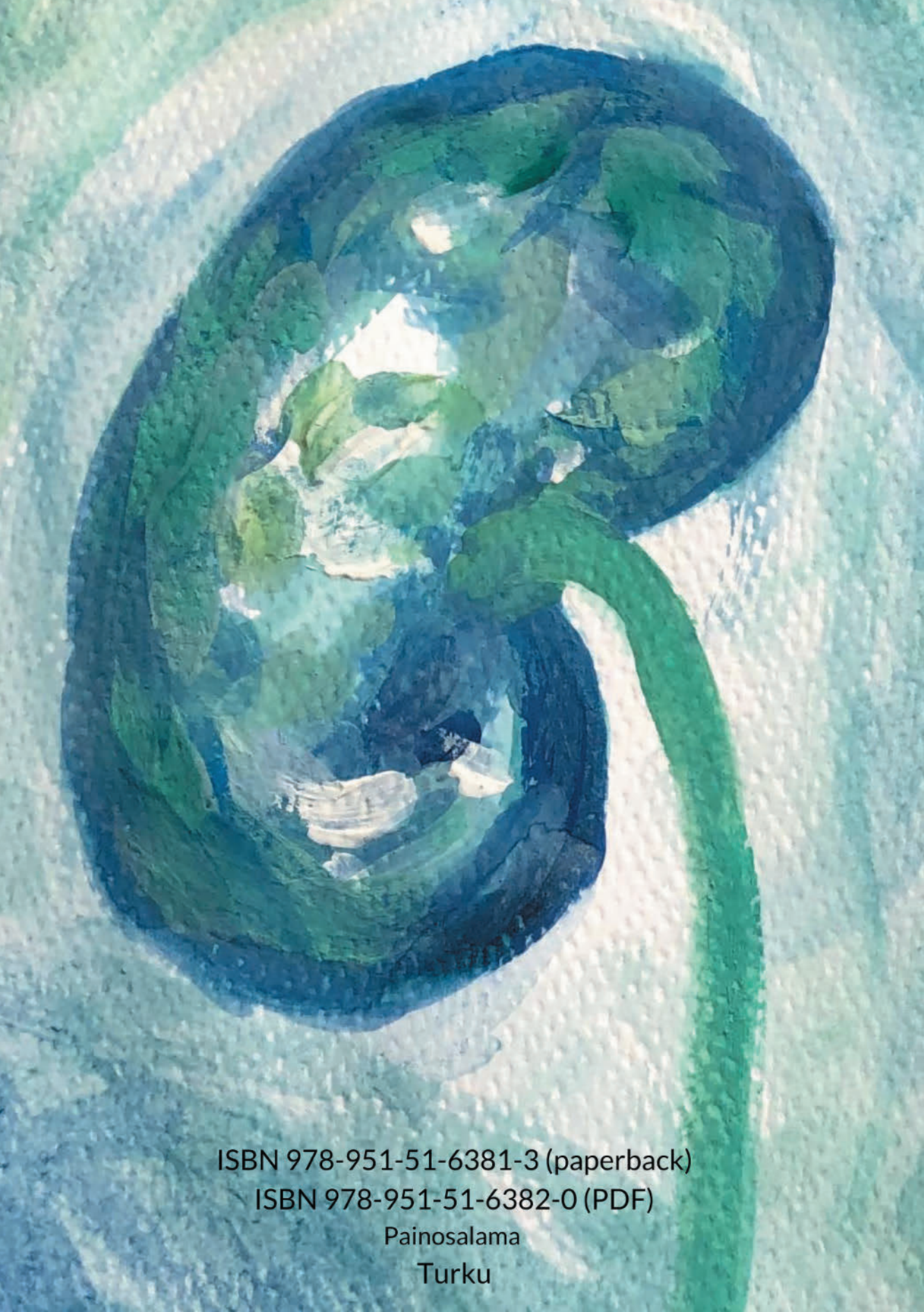

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