Treatment selection in metastatic renal cell carcinoma

Towards an individualised approach

MARIA STENMAN
Renal cell carcinoma (RCC), a common malignancy worldwide, affects 1200 new patients yearly in Sweden. Metastatic RCC (mRCC) develops in one in three and is commonly incurable. Clear cell histology dominates followed by papillary histology. The mainstay of mRCC treatment is targeted agents (TA) against aberrantly signalling pro-angiogenic tyrosine kinase receptors, and recently also immune checkpoint inhibitors. Local metastatic therapy with stereotactic radiotherapy (SRT) or surgical metastasectomy may be considered for oligometastatic disease.

The aims of this thesis were (1) to identify clinically relevant factors useful for prognostication in real-world patients with mRCC treated in the TA era, (2) to deepen the understanding of papillary mRCC, and (3) to evaluate local metastatic therapy in mRCC. The papers of this thesis were based on retrospective data from regional databases or patient records from 2005 and onwards to reflect the contemporary therapeutic landscape.

Paper I was a single-centre study analysing inflammatory blood and clinical parameters in relation to overall survival (OS) in mRCC (n=84). Median OS (mOS) was 20 months. Hypoalbuminemia was a negative prognostic factor (HR 2.7), independently of patient performance status (PS) or Memorial Sloan Kettering Cancer Center risk criteria.

Paper II included solely patients with papillary mRCC (n=86) treated at three centres. mOS was 11 months. Age ≥60 years (HR 2.2), ≥3 metastatic sites (HR 2.7), and Eastern Cooperative Oncology Group (ECOG) PS ≥2 vs 1 (HR 3.0) were independently associated with worse OS.

Paper III included mRCC patients treated with local metastatic therapy (n=117). Survival was similar irrespective of SRT or surgical metastasectomy with a mOS of 51 months. Treatment with TA in close proximity to local therapy was well tolerated. ECOG PS 1 vs 0 (HR 2.9), intracranial treatment (HR 1.8), and watchful waiting ≥18 months prior to treatment (HR 0.3) were independently prognostic.

Paper IV was a follow-up of patients with ccRCC brain metastases treated with single fraction gamma knife radiosurgery (sf-GKRS) at three European centres (n=43). 1- and 3-year local control rates were 97% and 90%, and mOS was 16 months. Hypoalbuminemia (HR=5.3), corticosteroids prior to sf-GKRS (HR=5.8), and Karnofsky PS <80% (HR=9.1) were independently associated with worse OS, whereas previously described prognostic scores were not. Adverse radiation effects (ARE) were uncommon and associated with large target volumes and pre-treatment oedema.

In conclusion, this thesis identifies several factors potentially useful for prognostication in mRCC, and indicates the usefulness of local metastatic therapy, in particular SRT, in selected patients. The results should be validated prospectively.

Keywords: RCC, renal cell carcinoma, kidney cancer, stereotactic radiotherapy, srt, stereotactic body radiotherapy, sbt, gamma knife radiosurgery, gkrs, stereotactic radiosurgery, srs, radiotherapy, overall survival, prognostic factor, papillary

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To Peter, Hanna and Junia
“I can do all things through him who strengthens me.”
- Phillippians 4:13
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

*Medical Oncology*, 31(3):841

Metastatic papillary renal cell carcinoma in the era of targeted therapy – a retrospective study from three European academic centres.  
*Acta Oncologica*, 58(3):306-312

Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at two Swedish centres 2005-2014.  
*Radiotherapy and Oncology*, 127(3):501-506


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<td>Adverse event</td>
</tr>
<tr>
<td>AKT</td>
<td>Also known as protein kinase B</td>
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<td>ARE</td>
<td>Adverse radiation effect</td>
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<tr>
<td>AXL</td>
<td>Name of a tyrosine kinase inhibitor, derived from the Greek word anexeleko</td>
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<td>BAP1</td>
<td>BRCA1-associated protein 1</td>
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<td>BED</td>
<td>Biological effective dose</td>
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<td>BMs</td>
<td>Brain metastases</td>
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<td>ccRCC</td>
<td>Clear cell renal cell carcinoma</td>
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<td>CDKN2A</td>
<td>Cyclin-dependent kinase inhibitor 2A</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CITV</td>
<td>Cumulative intracranial tumour volume</td>
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<td>CITV-SIR</td>
<td>Cumulative Intracranial Tumour Volume Scored index for Radiosurgery</td>
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<tr>
<td>c-MET</td>
<td>The MET receptor</td>
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<td>CN</td>
<td>Cytoreductive nephrectomy</td>
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<td>CpG</td>
<td>Nucleotide C and G connected by a phosphodiester bond</td>
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<td>CPIs</td>
<td>Checkpoint inhibitors</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>CT</td>
<td>Computer tomography</td>
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<td>CTCAE</td>
<td>Common terminology criteria of adverse events</td>
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<td>CTLs</td>
<td>Cytotoxic T-lymphocytes</td>
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<td>CTLA4</td>
<td>Cytotoxic T-lymphocyte-associated antigen 4</td>
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<td>CTV</td>
<td>Clinical target volume</td>
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<tr>
<td>DS-GPA</td>
<td>Disease Specific Graded Prognostic Assessment</td>
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<td>ECOG PS</td>
<td>Eastern Cooperative Oncology Group performance status</td>
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<tr>
<td>eIF4E</td>
<td>Eukaryotic translation initiation factor 4E</td>
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<tr>
<td>EQD2</td>
<td>Equivalent dose in 2 Gy fractions</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Fluorodeoxyglucose positron emission tomography</td>
</tr>
<tr>
<td>FGF</td>
<td>Fibroblast growth factor</td>
</tr>
<tr>
<td>FH</td>
<td>Fumarate hydratase</td>
</tr>
<tr>
<td>FKBP12</td>
<td>12-kDa FK506-binding protein</td>
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<tr>
<td>GKRS</td>
<td>Gamma knife radiosurgery</td>
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<td>GPA</td>
<td>Graded Prognostic Assessment</td>
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<td>GTV</td>
<td>Gross tumour volume</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>HGF</td>
<td>Hepatocyte growth factor</td>
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<td>HIF</td>
<td>Hypoxia inducible factor</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>IFN-α</td>
<td>Interferon-α</td>
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<td>Interleukin-2</td>
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<td>IL-10</td>
<td>Interleukin-10</td>
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<tr>
<td>IMDC</td>
<td>International Metastatic RCC Database Consortium</td>
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<tr>
<td>KDM5C</td>
<td>Lysine-specific demethylase 5C</td>
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<td>KPS</td>
<td>Karnofsky performance status</td>
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<tr>
<td>LINAC</td>
<td>Linear accelerator</td>
</tr>
<tr>
<td>LLV</td>
<td>Largest lesion volume</td>
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<tr>
<td>LLV-SIR</td>
<td>Largest Lesion Volume Scored index for Radiosurgery</td>
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<tr>
<td>LQ-formula</td>
<td>Linear-quadratic formula</td>
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<tr>
<td>mccRCC</td>
<td>Metastatic clear cell renal cell carcinoma</td>
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<tr>
<td>MDSC</td>
<td>Myeloid-derived suppressor cells</td>
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<tr>
<td>MET</td>
<td>Mesenchymal-epithelial transition</td>
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<tr>
<td>mOS</td>
<td>Median overall survival</td>
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<td>mpRCC</td>
<td>Metastatic papillary renal cell carcinoma</td>
</tr>
<tr>
<td>mRCC</td>
<td>Metastatic renal cell carcinoma</td>
</tr>
<tr>
<td>MRT</td>
<td>Magnetic resonance tomography</td>
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<tr>
<td>MSKCC</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
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<tr>
<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
</tr>
<tr>
<td>mTORC</td>
<td>Mammalian target of rapamycin complex</td>
</tr>
<tr>
<td>nccRCC</td>
<td>Non-clear cell renal cell carcinoma</td>
</tr>
<tr>
<td>NLR</td>
<td>Neutrophil-to-lymphocyte ratio</td>
</tr>
<tr>
<td>NRF2-ARE</td>
<td>NF-E2-related factor 2-antioxidant responsive element</td>
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<tr>
<td>NSCLC</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td>OAR</td>
<td>Organs at risk</td>
</tr>
<tr>
<td>ORR</td>
<td>Overall response rate</td>
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<td>OS</td>
<td>Overall survival</td>
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<td>PBRM1</td>
<td>Polybromo 1</td>
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<td>PDGF</td>
<td>Platelet derived growth factor</td>
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<tr>
<td>PDL1</td>
<td>Programmed death receptor ligand 1</td>
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<tr>
<td>PDL2</td>
<td>Programmed death receptor ligand 2</td>
</tr>
<tr>
<td>PD1</td>
<td>Programmed death receptor 1</td>
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<tr>
<td>PFS</td>
<td>Progression free survival</td>
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<td>PI3K</td>
<td>Phosphoinositide-3-kinase</td>
</tr>
<tr>
<td>PS</td>
<td>Performance status</td>
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<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homolog</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning target volume</td>
</tr>
<tr>
<td>pRCC</td>
<td>Papillary renal cell carcinoma</td>
</tr>
<tr>
<td>pVHL</td>
<td>von Hippel Lindau protein</td>
</tr>
<tr>
<td>p1RCC</td>
<td>Type 1 papillary renal cell carcinoma</td>
</tr>
<tr>
<td>p2RCC</td>
<td>Type 2 papillary renal cell carcinoma</td>
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</table>
RCC Renal cell carcinoma
Rheb Ras homolog enriched in brain
SETD2 SET domain containing 2
sf-GKRS Single fraction gamma knife radiosurgery
SM Surgical metastasectomy
SRS Stereotactic radiosurgery
SRT Stereotactic radiotherapy
S6K1 Ribosomal protein S6 kinase beta-1
TA Targeted agents
TAM Tumour associated macrophage
T-cell T-lymphocyte
TCR T-cell receptor
TERT Telomerase reverse transcriptase
TGFβ Transforming growth factor β
Th2 cell T-helper-2 cell
TKIs Tyrosine kinase inhibitors
TKR Tyrosine kinase receptor
TLR Thrombocyte-to-lymphocyte ratio
TP53 Tumour protein 53
Treg T-regulatory cell
TSC Tuberous sclerosis complex
USC Universal survival curve
VEGF Vascular endothelial growth factor
VHL Von Hippel Lindau
WBRT Whole brain radiotherapy
3p The short arm of chromosome 3
7p The short arm of chromosome 7
9p The short arm of chromosome 9
14q The long arm of chromosome 14
17p The short arm of chromosome 17
Introduction

Epidemiology
Renal cell carcinoma (RCC) represents around 2% of all cancers in Sweden and over a 1200 new cases are diagnosed each year. Initially, most patients have a localised disease and are cured, commonly treated with surgery. Nevertheless, about 15% of patients have metastases at primary diagnosis (synchronous metastases) and a further 20% of those with localised disease, initially treated with a curative intent, experience metastatic relapse within five years (metachronous metastases) (1). Once metastatised, RCC is a lethal disease where cure is rare. In a study of Swedish patients treated for metastatic RCC (mRCC) in the years 2009-2012, using three national registries (n=1593), the median overall survival (mOS) was 18 months (2). Men have a higher incidence of RCC than women (66% in Sweden in the year 2016) and the median age at diagnosis is 68 years with few patients diagnosed before the age of 40. 30% of RCC can be explained by smoking and other predisposing factors include obesity and hypertension. Patients with chronic kidney disease, such as polycystic kidney disease also have increased risk of RCC (1,3).

Histological types
RCC comprises many different histological types with the updated classifications described by the International Society of Urological Pathology in 2013 and by the World Health Organization in 2016 (4,5). Clear cell histology (ccRCC) is the most common histological type (70-80%). The other renal tumours are often referred to as non-clear cell RCC (nccRCC), a heterogeneous category consisting of clearly distinct histologies; papillary (pRCC; 10-15%), or chromophobe (5-10%) being the most common but more than 15 different subtypes are described. For the purpose of this thesis, the in depth background is limited to ccRCC and pRCC histologies. Sarcomatoid histological features, a malignant mesenchymal-like spindle cell component, is a negative prognostic marker for all RCC histologies (6–9).
Clear cell renal cell carcinoma

The most common type of RCC is clear cell RCC (ccRCC), which derives from the proximal convoluted tubule and is characterised by aberrant angiogenesis. In ccRCC tumours there is typically an inactivation of the tumour suppressor gene von Hippel Lindau (VHL), commonly by chromosome loss and a second hit to the other chromosome by epigenetic silencing through promoter methylation (10). This inactivation is necessary but not sufficient for ccRCC development (11). In normal oxygen conditions (normoxia), the protein product of VHL (pVHL) can bind to the α-subunits of any of the transcription factors called hypoxia inducible factors (three isoforms: HIF-1α, HIF-2α, HIF-3α) leading to the degradation of the transcription factor. In the situation of low oxygen levels (hypoxia) pVHL is unable to bind the HIF α-subunit, and in ccRCC, where pVHL is scarce due to inactivating mutations, the HIF α-subunits cannot be degraded. Both situations result in rising levels of the HIF α-subunits. HIF-1α dominates in acute hypoxia and HIF-2α in chronic hypoxia (12). The two isoforms inhibit the expression of one another and have opposite effects in ccRCC. HIF-1α promotes apoptosis and is a tumour suppressor, whereas HIF-2α acts as an oncogene inducing tumour development in ccRCC (13). As HIF-2α accumulates it binds HIF-1β and form the transcription factor HIF-2. This transcription factor drives the transcription of several genes; the vascular endothelial growth factor (VEGF) and the platelet derived growth factor (PDGF) being particularly important for tumorigenesis. These induce angiogenesis through their respective tyrosine kinase receptors (TKR) (14–17). See Figure 1.

Another intracellular signal pathway commonly overstimulated in different cancers is the phosphoinositide-3-kinase/protein kinase B pathway (PI3K/AKT-pathway). The activation of a TKR at the cell surface in turn activates AKT which is important for starting numerous cellular processes for cell survival, proliferation and angiogenesis. A parallel regulator of the PI3K/AKT-pathway is the mammalian target of rapamycin (mTOR), where rapamycin is a compound from a bacteria found to inhibit mTOR after binding to the 12-kDa FK506-binding protein (FKBP12). mTOR is a serine-threonine protein kinase and can form two complexes, mTORC1 and mTORC2. mTORC1 is down-stream of AKT and drives protein synthesis important for cell growth. Nevertheless, through various yet inadequately understood signals, mTORC1 also stimulates mTORC2, which is an upstream activator of AKT (18–20). In at least 30% of ccRCC the PI3K/AKT-pathway is constitutively activated through excessive growth factor activation, mutation in the phosphatase and tensin homolog (PTEN) gene, the tuberous sclerosis complex (TSC1/TSC2) genes, or mTOR (21–26). Activated mTORC1 and mTORC2 also increase the expression of HIF-1α and HIF-2α, suggesting the complex
Figure 1. Hypoxia inducible factor (HIF) and its role in clear cell renal cell carcinoma.
feedback regulation of PI3K/AKT-pathway not yet fully understood (27–31). See Figure 2. A novel study links aberrant lipid homeostasis to key steps in ccRCC biology, including excessive mTOR signalling (32).

![Figure 2. The PI3K-AKT-pathway and its inhibition of rapamycin.](image)

Other common genes with somatic driver mutations in ccRCC include polybromo 1 (PBRM1; 30-40%), BRCA1-associated protein 1 (BAP1; 15%), SET domain containing 2 (SETD2; 10%), and lysine-specific demethylase 5C (KDM5C), all coding for chromatin-modelling proteins, as well as the gene for the tumour protein 53 (TP53), an important cellular protein with apoptotic effects (21,22,33,34). The PBRM1, BAP1, SETD2 genes are localised close to the VHL gene on the short arm of chromosome 3 (3p). Not surprisingly 3p loss is found in >90% of ccRCC (21). BAP1, SETD2 and TP53 alterations are generally looked upon as negative prognostic factors for ccRCC (35–42). In the metastatic setting, PBRM1 and KDM5C mutations, confer better survival in ccRCC patients (42–44).

Importantly, there is often substantial heterogeneity within ccRCC tumours implying different mutations in different tumour cells within a specific tumour
and between different metastases in the same patient (45–47). A recent study suggests that ccRCC follow different tumour evolutionary tracts, where some show little heterogeneity whereas others, developing by so called branched mutations, show pronounced heterogeneity. The differences predict the clinical and metastatic behaviour of the tumours. Loss of the short arm of chromosome 9 (9p) and the long arm of chromosome 14 (14q) appear to be important driver events for metastatic potential (48).

Papillary renal cell carcinoma

Papillary RCC (pRCC) is the second most common histological type of RCC and originates from the proximal convoluted tubule. pRCC can be further divided into type 1 (p1RCC) and type 2 (p2RCC), different not only in morphology but also in genetics and clinical characteristics (49–53). p1RCC is more common in localised disease whereas p2RCC is the more aggressive tumour and studies indicate a worse prognosis than ccRCC once metastasised (54,55).

p1RCC commonly exhibits mutations in or copy number gains in the short arm of chromosome 7 and 17 (7p and 17p), where mutations in the mesenchymal-epithelial transition (MET) gene is the most important (chromosome 7) (51,52,56–58). The MET gene codes for c-MET which is a TKR for the hepatocyte growth factor (HGF). It acts as an oncogene important for tumorigenesis, invasiveness, and metastatic potential. Nevertheless, copy number gains resulting in high MET expression can also be seen in p2RCC (51,58,59) and in vitro c-MET inhibition can show activity in ccRCC cells (60). The telomerase reverse transcriptase (TERT) gene, coding for a subunit of the telomerase complex that sustains the telomere of DNA preventing senescence, is the second most commonly mutated gene in p1RCC (30%) (61).

p2RCC tumours typically have a more heterogeneous genotype with allelic instability described in several chromosomes (62–64). Loss of the cyclin-dependent kinase inhibitor 2A (CDKN2A), activation of the NF-E2-related factor 2-antioxidant responsive element (NRF2-ARE) pathway and a C-phosphate-G (CpG) island methylator phenotype are some of the mutational changes observed in p2RCC, where the latter has been associated with worse survival (51,52,65). Similar to ccRCC, p2RCC show mutations in PBRM1, BAP1 and SETD2 (52). Inherited forms of p2RCC often show germline mutations in the fumarate hydratase (FH) gene, an enzyme involved in the Krebs cycle (66).
Biologically based targeted agents

In the early years of this millennium, a patient with mRCC diagnosis had an expected survival of less than a year. By then, the available systemic therapies, the first generation of immune therapies interleukin-2 (IL-2) and interferon-α (IFN-α), had effect in just a small minority of patients and were often accompanied with substantial side effects (67). Others were treated with hormone therapy with little evidence of effect (68,69).

Since 2005 mRCC is systemically treated with biologically based targeted agents (TA) that have been developed based on the specific ccRCC biology with VHL inactivation, see Figure 1. Hence, the majority of TA for mRCC are tyrosine kinase inhibitors (TKIs) acting on the VEGF receptor, PDGF receptor, FGF (fibroblast growth factor) receptor, AXL-receptor and/or c-MET. They include sorafenib (70), sunitinib (71), pazopanib (72), axitinib (73), tivozanib (74), lenvatinib (75) and cabozantinib (76). They all inhibit the downstream signalling from their respective TKR. Bevacizumab is a monoclonal antibody that block VEGF (77). For cellular targets of VEGF-directed TA, see Figure 3.

TA directed towards mTORC1 has also been studied for ccRCC. Temsirolimus (78) and everolimus (79) are two rapamycin analogs (rapalogs) that bind FKBP12 and inhibit mTORC1. The indirect effect of inhibition of mTORC1, leading to inhibition of mTORC2 and subsequently decreasing AKT activation, is thought to constitute the anti-tumoural effect of rapalogs. For cellular targets of mTOR rapalogs, see Figure 2 and Figure 3. Everolimus is the dominating mTOR inhibitor used for mRCC due to its oral administration. With some variation, treatment of metastatic ccRCC (mccRCC) patients with VEGF-directed TA and/or mTOR inhibitors has been associated with overall survival (OS) in the range of 15-30 months (70–74,76,77).
Clinical trials of different TA have often excluded patients with nccRCC histologies due to small numbers and heterogeneity (71,81). In the absence of biological therapies tailored to pRCC, these patients are commonly offered ccRCC-specific TA (82). Nevertheless, studies show a low hypoxic drive in pRCC corresponding to low prevalence of VHL alterations and lower VEGF levels in pRCC compared to ccRCC (65,83,84).

Single-arm studies have produced mOS ranging from 13 to 21 months for metastatic pRCC (mpRCC) patients treated with VEGF-directed TA and/or mTOR inhibitors (85–87). Data from a small prospective phase II study suggests that once metastasised, p1RCC and p2RCC may have a similar low overall response rate (ORR) to VEGF-directed TA (11-13%) while a slightly better OS was reported for p1RCC (86). A systematic review on the effectiveness of TA on metastatic nccRCC, including data from the two randomised prospective studies ESPN and ASPEN, showed a trend for better effect with VEGF-directed TA compared to mTOR inhibitors (88–90). Another review concluded that for nccRCC-studies, the higher the proportion of pRCC, the lower the response rates to TA (91).
Nevertheless, cabozantinib, through its potential pRCC specific target c-MET, has been retrospectively analysed for patients with nccRCC with modest yet hopeful results (92,93). A first in human phase I study of the MET inhibitor savolitinib suggested anti-tumour activity in pRCC patients (94) and other potential c-MET TA are crizotinib and foretinib (95,96). Prospective phase II studies of different c-MET TA, such as the multi-arm SWOG1500 trial, are currently recruiting mpRCC patients.

Irrespective of mRCC histology, treatment with TA remains palliative, offering a valuable yet transient disease control of variable length almost always followed by progression. The most dominating side effects of TA used for RCC are fatigue, hypertension, transaminitis, diarrhoea, hand-foot-syndrome, pneumonitis, and stomatitis, but they vary for each substance (80,81). A recent Swedish study shows TA to be increasingly cost-effective over time (97).
The immunologic microenvironment

Intense research on the immunologic microenvironment in cancer has revealed that in many tumour types the malignant cells are surrounded by abundant immune cells (98). In addition, the microenvironment also consists of several other cell types including fibroblasts, endothelial cells, and pericytes among others. They are all believed to communicate with the tumour cells as well as with the immune cells through cell-cell interactions and cytokines (99,100).

Under normal conditions, immune checkpoints serve to control and balance immune activation by inhibitory signals. Two such inhibitory interactions occur between programmed death receptor 1 (PD1) and its ligands (PDL1/PDL2) and between the cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and its ligand (CD80/CD86) (101,102). Through cytokines, tumour cells can increase the expression of PDL1 as well as stimulate antigen presenting cells to express CD80/CD86. When these ligands interact with PD1 and CTLA4 on a T-lymphocyte (T-cell), they inhibit the interactions with the T-cell, decreasing the antigen presentation and/or disabling the T-cell from killing the tumour cells. See Figure 4.

In ccRCC the level of inflammation often is prognostic (103). T-cells with a suppressor phenotype, T-helper-2 cells (Th2 cells) and T-regulatory cells (Tregs), activated through expression of transforming growth factor β (TGFβ) and interleukin-10 (IL-10), have been associated with worse survival (103–105). Furthermore tumour-promoting immune cells, such as myeloid-derived suppressor cells (MDSCs), that, directly or through differentiation into tumour associated macrophages (TAMs), support tumour angiogenesis, metastatic spread and tumour cell survival, have been associated worse outcome (44,106–110). The levels of different tumour-promoting immune cells, seem to correlate to specific ccRCC mutations (111).

In many cancer types a pronounced tumour infiltration of CD8+ cytotoxic T-cells (CTLs) is associated with better prognosis, indicating that the immune system is actively killing tumour cells (105,112). Nevertheless, in RCC, as well as in Hodgkin lymphoma, follicular lymphoma, and prostate cancer, an opposite association of CTLs and prognosis has been reported (105,112,113). In RCC, this phenomenon has been explained by the abundance of Tregs and
high expression of PDL1, suppressing the activation of CTLs (114–116). Indeed, PDL1 expression is prognostic in RCC, with higher PDL1 expression associated with relapse in localised RCC and shorter survival in mRCC (115,117,118). Choueiri et al analysed the prognostic effect of PDL1 expression as well as CTLs in patients that were treated with sunitinib or pazopanib. They found a better survival for patients that had a low PDL1 expression, low levels of CTLs and the combination of both (119).

**Immune therapies**

The microenvironment of RCC, including the surrounding immune cells and other stroma cells, counteracts the ability of the immune system to discover and destroy the tumour cells. Before the advent of TA, the available systemic therapies for mRCC were the first generation immune therapies, IFN-α and IL-2, aiming to activate the immune system towards the tumour cells.

The development of VEGF-directed TA was initially focusing on its effect on the tumour angiogenesis in pVHL deficient tumours. Nevertheless, the effect on the blood vessels, stabilising their permeability, may also allow for the immune cells to better access the tumour (80). VEGF may also act immunosuppressive by enhancing the activity of MDSCs (120,121). Correspondingly, TKIs used for mRCC have proved to be capable of activating the innate immune system. Suggested mechanisms include reversing the immunosuppression through inactivating MDSCs or Tregs, lowering the levels of immunosuppressive cytokines, decreasing the levels of PDL1 expression on cell surfaces and increasing the levels of immune-stimulating cytokines (121–126).

Recently, second generation immune therapies, checkpoint inhibitors (CPIs), first successfully used for metastatic melanoma patients, have been introduced for mRCC. Nivolumab and pembrolizumab are monoclonal antibodies that block PD-1 on T-cells (127). Avelumab and atezolizumab are monoclonal antibodies that block PDL1 on tumour cells (128,129). The CTLA-4 inhibitory antibody ipilimumab, blocks CTLA-4 on T-cells and interrupts the inhibitory signal normally given by CD80/CD86 on the antigen presenting cells. CD80/CD86 is also expressed by T-regs, a cell subsequently inhibited with ipilimumab (80). See Figure 4. Due to the immune-stimulatory effect of CPIs the most common adverse events are auto-immune events, e.g. pneumonitis, colitis, thyroiditis, hepatitis and hypophysitis (80).
Nivolumab is approved in second-line as monotherapy based on the clinical trial Checkmate 025, where it compared favourable to everolimus in mRCC (130). Subsequent therapy combinations with immune therapies have caused a paradigm shift in the first-line therapy of mRCC. The phase III randomised controlled trial Checkmate 214 study compared the combination of nivolumab and ipilimumab vs sunitinib as first-line therapy for mRCC and was designed to detect an OS difference in non-favourable prognostic risk patients. For patients with non-favourable risk group the immune therapy arm had a better 24-month OS and ORR compared to sunitinib and a complete response rate of around 10% was seen in the immune therapy arm (131,132). The combination of ipilimumab and nivolumab was recently approved in the first-line setting and is now the standard of care in Sweden for non-favourable mRCC. Even more recently, the Federal Drug Agency approved the combination of pembrolizumab and axitinib as well as the combination of avelumab and axitinib in first-line setting for mRCC, based on the KEYNOTE-426 phase III trial and the JAVELIN Renal 101 phase III trial, respectively (128,133). The respective combinations compared favourably to sunitinib in patients with mRCC across all risk groups. Furthermore, other PD1-inhibitors and PDL1-inhibitors are currently evaluated in combination with TA in clinical mRCC trials such as IMmotion 151 (atezolizumab plus bevacizumab vs sunitinib), CHECKMATE 9ER (nivolumab plus cabozantinib vs sunitinib), and CLEAR (lenvatinib plus pembrolizumab vs lenvatinib plus everolimus vs sunitinib). These
are possibly yielding further choices in the first-line setting in the near future (129,134–136).

Data on CPIs in mpRCC are so far scarce. Studies suggest a PDL1 expression of 10-35% in pRCC, possibly more common in p2RCC than p1RCC (137,138). A meta-analysis suggests that PDL1 expression is a negative prognostic factor for OS in nccRCC and PDL1 expression was associated with distant metastases (139). Initial reports have demonstrated objective responses of immune therapy in some mpRCC patients (140–143). An ongoing randomised phase II trial SUNIFORECAST recruits patients with nccRCC to either ipilimumab and nivolumab or sunitinib (144).
Brain metastases

RCC is among the five solid cancer types that most commonly metastasise to the brain. Brain metastases (BMs) develop in 10-20% of patients with mRCC and around half of those patients seem to develop BMs early in the period of the disease (145,146). Nevertheless, brain imaging is not part of routine scanning, currently including computer tomography (CT) of the thorax and abdomen. Studies suggest that mRCC patients with lung or bone metastases or large primary tumours (>10 cm) are more prone to develop BMs compared to patients with abdominal metastases (147–149). BMs from RCC were found to be enriched in mutations in PTEN, PI3K and CDKN2A compared to the primary tumour (150).

Studies suggest that both VEGF-directed TA and CPIs can decrease the incidence of BMs (148,151–153). Nevertheless, mRCC patients with BMs have commonly been excluded from randomised clinical trials on TA. Two prospective studies suggest a modest effect on OS with TA (148,154). Undisputedly, TA is overall insufficient for those mRCC patients who develop BMs (145,146,151,155,156). An early study suggesting a similar situation for PD1 inhibitors (157). Nevertheless, several studies are recruiting mRCC patients with BMs for evaluating the effect of immune therapies in the central nervous system.
General aspects on radiotherapy

Conventional radiotherapy is one of the keystones in oncologic treatment. It is used with different therapeutical intentions: symptom palliation, local control, or curative intent, which may be definite radiotherapy or prior to (neoadjuvant) or after surgery (adjuvant). The linear accelerator (LINAC) is the method used for conventional radiotherapy and was developed by Fry in 1948 (158).

Conventional radiotherapy causes an ionisation of an atom or molecule leading to the removal of an electron. This gives rise to free radicals that causes DNA damages (159). As a consequence, the cell cycle progression is halted in order to allow for DNA repair, or, if that is not possible, cell death through mitotic catastrophe, apoptosis, necrosis or senescence occurs (159). This explains why cells that are dividing (mitotic) are more sensitive to radiotherapy as their DNA are more exposed (160).

The dose given at one radiotherapy session is referred to as a fraction and the dose of each fraction has the unit Gray (Gy, joule/kg). The cell killing effect of radiotherapy is dependent on numerous factors: the total dose given, the dose of each fraction, the interval between fractions, the irradiation volume, the dose distribution inside the target (homo- vs heterogeneous), the oxygen status of the tumour cells, the DNA repair capability of the tumour cells, what cell cycle phase the tumour cells are in, and the type of tumour (161). They are summarised in the 5 R’s of radiotherapy: repair of sublethal damage, redistribution of cells in the cell cycle, repopulation of cells within the tumour, reoxygenation of cells and the intrinsic radiosensitivity of cells (162–164). These commonly occur in both tumour cells and surrounding healthy cells in between two fractions and are of importance for both the damage to the tumour in subsequent fractions and the protection of surrounding tissues. The challenge in planning for radiotherapy is the balance between increasing doses for improved tumour control and decreasing doses to spare surrounding healthy tissues. In conventional radiotherapy a low dose per fraction given once daily in many fractions over several weeks is used to increase the repair of normal cells, which typically have better DNA repair capability compared to tumour cells. This decreases the level of late, often irreversible, toxicities in the healthy surrounding tissues (159).
When planning for radiotherapy a CT image or a magnetic resonance tomography (MRT) image is needed. It is important that the patient is thoroughly fixated in the treatment position when the planning imaging is done. The tumour volume on the scans, usually the contrast enhancing component, is the gross tumour volume (GTV). In conventional radiotherapy the target volume has to be enlarged to add margin in order to include microscopic disease (clinical target volume; CTV). Further margin is added (planning target volume; PTV) to control for internal or external uncertainties, e.g. organ movements, change of target size during treatment, patient positioning, equipment and experience of the radiotherapist (165). The prescribed dose is planned to an appropriate percentage isodose line and should ideally cover the PTV. If the dose distribution is homogenous, as is the case in conventional radiotherapy, the difference between the prescribed dose at the PTV and the maximum dose in the centre is small, yielding a high isodose at the periphery (proportion of the maximum dose given at the margin, usually 95%) (166).

The coverage is the proportion of the target that receives the prescribed dose, i.e. the higher the coverage, the more tumour cells are irradiated. Selectivity, on the other hand, is the proportion of the volume that receives the prescribed dose that constitutes the target, i.e. the higher the selectivity, the less normal tissue is irradiated (167). See Figure 5.

The linear-quadratic formula (LQ-formula) is the most commonly used equation to mathematically describe the cell killing effect of radiotherapy. It is based on the survival fraction of a certain dose being absorbed by a clonogenic population of cells (in vitro). It identifies the opportunity window for radiotherapy, the zone between 1.8 to 4 Gy per fraction where the best cell killing was seen with the least damage to normal healthy tissue (168). The LQ-formula includes the α/β value which reflects the ratio of DNA repair capability (lethal vs sublethal damage) and the sensitivity of the specific cell types and organs to radiation. A low α/β value (~1-3) is given to late responding tissues/tumours, whereas a higher α/β value (~8-10) reflect more acutely re-
sponding tissues/tumours. The $\alpha/\beta$ values of different tumours have been de-
bated (169,170) and for RCC it has been suggest to be between 2.5 and 7
(169,171). Tumours with higher $\alpha/\beta$ values are sensitive to small doses in in-
creased number of fractions. Tumours with lower $\alpha/\beta$ values, such as prostate
and breast, as well as RCC, are not sensitive to increased number of fractions,
but rather show increased cell death for single fraction or hypofractionation
(161,172). The equivalent dose in 2 Gy fractions (EQD2) is an expression of
the LQ-formula used in daily practice to recalculate the effect of a hypofrac-
tionated scheme to the equipotential effect of a 2 Gy per fraction (conventional
fractionation) schedule. To compare the biological effects in different sched-
ules the function is expressed as the biologically effective dose (BED) (173).
Local metastatic therapies

The idea of using local metastatic therapy is to provide patients with a single RCC metastasis or with oligometastatic RCC a potentially curative treatment. In addition it often aims to achieve local control in order to halt extracranial symptomatic progression or to salvage intracranial neurologic function. The definition of oligometastatic disease varies but commonly refers to a situation of one to three metastases.

In this section the use of conventional radiotherapy or cytoreductive nephrectomy (CN) in a mRCC setting are described followed by an in depth description of stereotactic radiotherapy (SRT) and how it compares to the oldest local metastatic therapy in use - surgical metastasectomy.

Conventional radiotherapy
RCC was early considered radioresistant (174,175). Studies on neoadjuvant and adjuvant radiotherapy for primary RCC did not improve relapse risk or survival, but the techniques and doses used are considered outdated (176,177). Nevertheless, palliative radiotherapy for mRCC has proven efficient if doses are escalated and it is commonly used to relieve pain from RCC bone metastases (176–178).

Cytoreductive nephrectomy
Up until recently nephrectomy has in large been performed on most patients with RCC, including those with metastatic disease. This cytoreductive nephrectomy (CN) on mRCC patients was proven to prolong OS in patients treated with first generation immune therapies (179). In the more recent treatment era the recommendation has been to perform CN on mRCC patients with a good PS and the main tumour burden in the kidney (180). Two recent prospective studies, CARMENA and SURTIME, have evaluated the use of CN as well as the timing of CN (immediate vs deferred after initial systemic therapy). The results challenge the benefit of CN in patients with synchronous metastases (181,182). Rather an immediate start of systemic therapy seems to
prolong OS. CN should still be considered for patients with very limited metastatic tumour burden, especially those eligible for local metastatic therapies or active surveillance, as well as in patients with favourable risk group (182–185). It is debated whether RCC patients with BMs should be eligible for CN (149,186). The use of CN must be re-evaluated in the fast developing therapeutic landscape of second generation immune therapies.

Surgical metastasectomy

Surgical metastasectomy is the oldest practised local metastatic therapy and it is used primarily for extracranial metastases in mRCC (187). A wide range of OS figures, in the range of 36-142 months, has been reported (187–193). The European Association of Urology recommend that surgical metastasectomy is considered irrespective of metastatic site, possibly excluding bone metastases and multiple brain metastases (194). Meta-analyses of retrospective studies indicate a possible survival benefit for patients with lung, liver and pancreatic oligometastatic disease (193,195). When possible, complete surgical metastasectomy of all known metastases (in this thesis called ‘curative intent’), should be considered (196–198).

For BMs, surgical metastasectomy is suitable for surgically fit patients with a solitary metastasis, or for BMs otherwise not treatable with SRT such as large metastases >3-4 cm / >8-10 cm³. In these cases, neurosurgery followed by radiation to the surgical bed is the treatment of choice (199,200).

Stereotactic radiotherapy

As described, RCC is a relatively radioresistant tumour, implying it is less sensitive to lower doses per fraction of radiotherapy. It commonly has a better DNA repair capability than other more radiosensitive tumours, allowing for repair of sublethal damages from conventional radiotherapy in between fractions (201). In stereotactic radiotherapy, on the other hand, a single or a few large fractions are delivered in a short time period, resulting in a significant biological effect, rendering a potentially strong cytotoxic effect (151). This can be done as the tumour is irradiated with high precision (high coverage) and with small margins, exposing minimal volumes of normal tissue to the high doses (high selectivity). SRT has a profound effect in RCC which has substantially increased the rational of using radiotherapy in RCC. For metastases of RCC, SRT is regarded as a possible alternative to surgical metastasectomy (169,202).
There is considerable confusion with the denotations and definitions of SRT in the literature. For the purpose of this thesis the expression extracranial SRT refers to hypofractionated high-dose radiotherapy (≤10 fractions) towards extracranial metastases. In Paper IV the term stereotactic radiosurgery (SRS) was used to describe gamma knife radiosurgery of BMs, but for coherency in this summary the term intracranial SRT is used exclusively and refers to single fraction or hypofractionated high-dose radiotherapy towards intracranial metastases.

SRT utilises different fixation systems. For extracranial SRT a body-frame with stereotactic coordinates was originally used (203), but today other devices for fixation can be equally effective. Intracranial SRT with LINAC is mainly mask-based and a rigid frame is used in the case of GKRS. The thorough body or skull fixation, innovative planning techniques with heterogeneous dose distribution, a sharp dose fall off outside the PTV, as well as image guided treatments minimise the dose to normal tissue. This enables higher doses per fraction with a dose per fraction of 7-17 Gy for extracranial SRT and ≥15 Gy for single fraction intracranial SRT.

As movements of internal organs occur due to peristaltic movements of the gut and breathing motions, margins need to be added to the treatment plan of extracranial SRT (CTV and PTV margins are added outside of GTV). If the location of the tumour is close to organs at risk (OAR), the dose often needs to be adapted. In intracranial SRT with the LINAC a small margin is added to the CTV, but for GKRS, due to the thorough fixation of the skull, no margins need to be added (GTV=CTV=PTV). In SRT, the dose distribution in the target is commonly heterogeneous, i.e. the dose prescribed to the periphery and the maximum dose in the centre differ substantially, usually an isodose at the margin of around 50-80% (172,204). Another radiobiological concept used in intracranial SRT is the 10Gy-volume; i.e. the total volume outside of the tumour that receives a dose of at least 10 Gy.

The LINAC, used for conventional radiotherapy, has been further developed for hypofractionated SRT, both extra- and intracranial. It uses high energy photons and the radiation source, the gantry, is moving around the patient to emit radiation beams from different angles. The table where the patient is situated at can also be moving to allow for treatment from different angles (172,204).

Gamma knife radiosurgery (GKRS) is used to stereotactically treat BMs, benign/low grade skull base tumours, primary malignant brain tumours, vascular malformations, and functional disorders. GKRS was developed by professor Lars Leksell at the Karolinska Institute in Stockholm in 1967 (205). It uses a frame (called g-frame) that is surgically fixated to the skull. The g-frame is
the basis for the stereotactic coordinate system and is used to fixate the patient to the treatment device. The treatment device contains 192 cobalt sources that are collimated with Tungsten creating beams that intersect in a small focal point. This summarises to a high dose in the tumour but low doses to the surroundings (204). GKRS is delivered with MRT guidance. GKRS is usually given as a single fraction therapy (sf-GKRS). Nevertheless, hypofractionated GKRS has recently gained interest (206,207). The decision whether to deliver GKRS in a single fraction or hypofractionated depends on target localisation, volume, oedema, clinical status, and earlier radiotherapy to the brain.

Emerging signs of a new radiobiology

The radiobiology of hypofractionation is poorly understood. However, new radiobiological research on the biological effects of high doses per fraction is emerging. Substantial studies on how to mathematically describe the cell killing effect of radiotherapy have been performed and the LQ-formula, described earlier, is one of the most accepted and used (168). The use of the LQ-formula for hypofractionated SRT has been debated for over a decade, as it is not validated for fractionation schemes above 8-10 Gy (208–210). Nevertheless, the clinical applicability of the LQ-formula to predict cell killing for higher doses is promising (161,163). A new radiobiological model called the universal survival curve (USC) was published in 2008. This is supposed to provide a superior approximation of cell survival curve data in the high-dose range, however no final conclusion on the optimal calculation of dose is settled (211).

In parallel with the direct effect of tumour cell killing through unrepairable DNA damage, high doses of ionising radiation can cause damage to other cellular components that may lead to secondary or indirect effects. Vascular damage can occur with apoptosis of endothelial cells and increased permeability as a consequence. This theory is supported by experimental data but it is still much debated if it occurs in human tumours (212,213). Others have shown that high doses per fraction can optimise the reperfusion kinetics and thus enhance reoxygenation (214,215).

Furthermore, and very promising, an abscopal effect of hypofractionated radiotherapy is increasingly studied. The abscopal effect is when an out-of-field metastasis shows a regression after a local therapy of another metastasis, typically with radiotherapy. It was first described in 1953 (216) and has since been debated and different explanations have been proposed (217,218). In the context of SRT the potential for an abscopal effect is higher compared to conventional radiotherapy (219,220). Case reports of tumour regression after SRT of other, not treated, metastases of mRCC exist (221,222). Triggering of the immune system is one of the dominating explanations that is being proposed...
for the abscopal effect of SRT. The activation of the immune system can be divided roughly into three parts (217,218,223–227):

1. The tissue damage and cell death release cytokines and tumour-specific antigens, as well as increase the expression of the major histocompatibility complex class I. This recruits immune cells and allows the immune system to better detect other metastases of the same tumour through dendritic cell activation.
2. Vasculature normalisation improves the permeability of the blood vessels allowing for better penetration of the immune cells into the tumours.
3. The tumour killing alleviates the immune evasive pressure formerly imposed by the tumour and thus invigorates T-cells.

Results of stereotactic radiotherapy

There are today no prospective randomised studies in mRCC on the use of local metastatic therapy in general or SRT specifically. It can be disputed if the long-term survival seen for some mRCC patients is due to the local metastatic therapy itself, since retrospective studies are likely biased by the selection of patients with a more indolent tumour biology.

A meta-analysis of extra- and intracranial SRT in mRCC was performed in 2015 and concluded that there was a profound heterogeneity in the patient selection, doses, methods and measured variables (e.g. local control, and survival) (228). For intracranial SRT a one-year local control of 88% was found and factors associated with local control was dose and tumour volume. Median OS was 7-26 months. For extracranial SRT the one-year local control rate was 86% and mOS ranged from 12 to 22 months (228). Some retrospective studies have presented results of extracranial SRT from the TA era. They suggest a mOS of more than two years, and a local control above 90%. A BED of ≥100 Gy seem to be important to reach ablative doses and gain local control (229–231). For intracranial SRT some retrospective studies on patients treated from 2005 and onwards have been reported, with mOS in the range of 8-14 months (232–235). One large study showed that patients receiving intracranial SRT had a longer mOS compared to matched patients not treated with intracranial SRT (236). There are limited data on which prescription dose for sf-GKRS in mRCC is needed to achieve ablation. The prescription dose depends on site and size of the target but a dose of ≥20 Gy is commonly advocated (202,214,235,237,238). Nevertheless, we are still lacking in depth knowledge on the use of SRT in mRCC patients in the modern therapeutic era.

It is believed that the abscopal effects of SRT in alerting the immune system, could allow for a synergistic effect if SRT is combined with CPIs (225,227,239,240). In metastatic lung cancer, where this synergy has been
more studied, a recent systemic review reported a mean abscopal response rate of 41%, when CPIs were combined with SRT (241). Some retrospective studies have found such an effect in mRCC patients and the concept is now addressed in several clinical phase II studies recruiting patients with mRCC (153,242).

Earlier, whole brain radiotherapy (WBRT) was the gold standard of palliative treatment of RCC BMs (243). Studies have investigated the effect of adjuvant WBRT after intracranial SRT or neurosurgery and found that it decreases the number of local recurrences in the brain but does not affect OS (244,245). As WBRT has limited effect and can cause cognitive side effects, the use of adjuvant WBRT after SRT has decreased and is mainly used as a palliative therapy when intracranial SRT is not an option (243,246).

Toxicity and adverse radiation effects after stereotactic radiotherapy

Adverse events (AE), caused by for example cancer treatment, are graded according to common terminology criteria (CTCAE, last version 5.0 from 2017) also known as ‘common toxicity criteria’:

“An adverse event is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure” (247).

Each AE is graded from 1 to 5 with increasing severity (grade 1 being the most mild AE and grade 5 being death related to AE).

For extracranial SRT toxicities occur if significant doses are delivered to OAR close to the target. Dose constrains and dose adaptations are used to avoid significant damage to OAR. Data, mostly from SRT for non-small cell lung cancer (NSCLC), show that the toxicity of extracranial SRT is generally mild (248). Two studies on RCC patients reported a low incidence of toxicity, primarily grade 1 and 2, after extracranial SRT (249,250) and a meta-analysis reported grade 3 and 4 toxicities in the range of 0-4% (228). Nevertheless, as extracranial SRT is pushed further with increased doses and treatment of targets closer to OAR, the risk for toxicities increase (251–253). In a meta-analysis of intracranial SRT in mRCC patients 5% grade 3-4 toxicities were reported (228).

Other than the CTCAE grading system, the term adverse radiation effect (ARE) is used for intracranial SRT. It is a post radiotherapy unwanted change on a radiology image that can be reversible or irreversible and may or may not
be symptomatic (254). The definition of ARE can vary between different centres. As to the clinical practice at the included GKRS centres in this thesis, ARE was defined from findings on follow-up MRT images (usually done every three months) of an increase in contrast enhancement post sf-GKRS, commonly with perilesional oedema and/or development of necrosis where tumour progression had radiologically been ruled out.

One study on 86 RCC BMs treated with GKRS reported a 1-year cumulative incidence of ARE of 15%. ARE was developed after a median time of seven months. 52% were symptomatic generally corresponding to larger targets (>1.5 cm) (255). Kano et al reported detection of ARE in 10% of mRCC patients treated with GKRS (202). Target size is a known risk factor for ARE as well as the dose distribution to healthy perilesional tissues (10Gy- or 12Gy-volumes) (255–259). Similarly ARE seem to correlate with perifocal oedema prior to intracranial SRT (255,260). The association between treatment with VEGF-directed TA and ARE is debated. It is well established that VEGF-directed TA have a stabilising effect on the tumour vasculature making vessels less permeable (261,262). Studies have shown a neuroprotective role of bevacizumab at intracranial SRT for glioblastoma for which it is increasingly used in the clinical (263). Nevertheless, other studies have suggested that concurrent VEGF-directed TA and intracranial SRT may be associated with an increased incidence of radionecrosis (264,265). Treatment with CPIs in close proximity to SRT seems to be safe (266).
Prognostic and predictive factors

For the oncologist, as well as the patient, it is a hard task to make treatment choices. All therapies come with the risk of more or less pronounced side effects for the patients, including a small risk of lethality (267). Some patients have a rapid and aggressive tumour biology, whereas others have a slow and indolent disease, suggesting prognostic differences that are tumour specific. Other factors affecting the prognosis has to do with the specific patient, they are host specific. Furthermore, some patients respond significantly to the therapies whereas others experience severe side effects and/or progress rapidly. There has been excessive search for both prognostic and treatment response predictive factors in mRCC. In the literature significant confusion exist on the difference between a prognostic and a predictive factor. The following explanations of a prognostic and predictive factor, respectively, are proposed by Clark et al:

“A prognostic factor is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy that patients are likely to receive. It can be thought of as a measure of the natural history of the disease. A control group from a randomized clinical trial is an ideal setting for evaluating the prognostic significance of a biomarker.” (268)

“A predictive factor is a measurement that is associated with response or lack of response to a particular therapy. Response can be defined using any of the clinical endpoints commonly used in clinical trials. A predictive factor implies a differential benefit from the therapy that depends on the status of the predictive biomarker. In statistical terms, this constitutes an interaction between treatment benefit and biomarker status that is best evaluated in a randomized clinical trial with a control group.” (268)

The confusion is partly because many factors have not been validated in prospective randomised trials with a control arm and partly because many factors probably convey both prognostic and predictive information. A positive biomarker status can appear to convey a better response to a treatment compared to patients with negative biomarker status, but nevertheless both groups benefit, making the distinction between prognostic and predictive markers unclear. For the purpose of this thesis, based on retrospective data, only hypotheses on potential prognostic and predictive markers can be made.
Performance status

The most used prognostic factor for all cancers is a measure of the patient’s general condition called performance status (PS). There are two scores used to assess PS; Karnofsky performance status (KPS) (269) and Eastern Cooperative Oncology Group performance status (ECOG PS) (270). They both describe to what extent the patient is affected by the disease and how well they can perform everyday activities and self-care. Importantly, it is not an assessment done by the patient herself, but rather an assessment done by the clinician after having heard the patient’s history and observing her during the clinical consultation. For a comparison of KPS and ECOG PS, see Table 1.

In this thesis ECOG PS was used for Paper I-III as it was the grading system commonly used for mRCC by oncologists during the study period. In Paper IV KPS was used as it is the grading system commonly preferred and used by neurosurgeons (typically performing GKRS).

Table 1. Comparison of Karnofsky (269) and ECOG performance status (270)

<table>
<thead>
<tr>
<th>Karnofsky criteria</th>
<th>Karnofsky grade (%)</th>
<th>ECOG grade</th>
<th>ECOG criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal. No complaints.</td>
<td>100</td>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>Able to carry on normal activities. Minor signs or symptoms of disease.</td>
<td>90</td>
<td>1</td>
<td>Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.</td>
</tr>
<tr>
<td>Normal activity with effort.</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Care for self. Unable to carry on normal activity or to do active work. Requires occasional assistance, but able to care for most of his needs.</td>
<td>70</td>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>Requires considerable assistance and frequent medical care. Disabled, requires special care and assistance.</td>
<td>50</td>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>Severely disabled, hospitalisation indicated though death non-imminent. Very sick. Hospitalisation necessary, active supportive treatment necessary.</td>
<td>30</td>
<td>4</td>
<td>Completely disabled, cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td>Moribund.</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead.</td>
<td>0</td>
<td>5</td>
<td>Dead.</td>
</tr>
</tbody>
</table>
Prognostic scores

The most used prognostic score for prognostication of mRCC patients is the Memorial Sloan-Kettering Cancer Center (MSKCC) score, presented in 1999 by Motzer for patients treated with first generation immune therapy, see Table 2 (271). The MSKCC score has also been used in clinical trials of many of the modern TA and was confirmed applicable in patients treated with sunitinib where the mOS of the favourable, intermediate and poor risk group were not reached, 21 months and 5 months, respectively (272,273).

Table 2. Memorial Sloan-Kettering Cancer Center score (MSKCC score) (271)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin &lt;lower limit of normal</td>
<td></td>
</tr>
<tr>
<td>Calcium (albumin corrected) &gt;2.5 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase &gt;1.5 x upper limit of normal</td>
<td></td>
</tr>
<tr>
<td>KPS &lt;80% / ECOG PS ≥2</td>
<td></td>
</tr>
<tr>
<td>Time from diagnosis of RCC to start of metastatic systemic therapy &lt;1 year</td>
<td></td>
</tr>
<tr>
<td>Prognosis: Favourable: 0 risk factors, Intermediate: 1-2 risk factors, Poor: &gt;2 risk factors</td>
<td></td>
</tr>
</tbody>
</table>

Later, the International Metastatic RCC Database Consortium (IMDC) score (also known as the Heng score) has been shown to provide even more accurate prognostic information in patients eligible for treatment with TA, see Table 3 (274,275). It has further been confirmed useful in second- and third-line with TA (276,277). Hence, the IMDC score has succeeded the MSKCC score as a gold standard for prognostication in mRCC patients.

Table 3. International Metastatic RCC Database Consortium score (IMDC score) (274)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin &lt;lower limit of normal</td>
<td></td>
</tr>
<tr>
<td>Calcium (albumin corrected) &gt;2.5 mmol/L</td>
<td></td>
</tr>
<tr>
<td>KPS &lt;80% / ECOG PS ≥2</td>
<td></td>
</tr>
<tr>
<td>Time from diagnosis of RCC to start of metastatic systemic therapy &lt;1 year</td>
<td></td>
</tr>
<tr>
<td>Neutrophil level &gt;upper limit of normal</td>
<td></td>
</tr>
<tr>
<td>Thrombocyte level &gt;upper limit of normal</td>
<td></td>
</tr>
<tr>
<td>Prognosis: Favourable: 0 risk factors, Intermediate: 1-2 risk factors, Poor: &gt;2 risk factors</td>
<td></td>
</tr>
</tbody>
</table>

Based on the number of IMDC risk factors, the patients are considered to have favourable (mOS 43 months), intermediate (mOS 23 months) or poor (mOS 8 months) prognosis (275). The IMDC score have been validated for metastatic nccRCC, including mpRCC (54,140,278). For patients treated with immune
therapies in second or subsequent lines, the IMDC score have also been validated (279).

Other prognostic factors

Clinical factors other than those included in the MSKCC or IMDC score have been studied. Metachronous metastases have been associated with better prognosis than synchronous metastases in ccRCC in the TA era (280). Similarly, bone, liver and brain metastases seem to predict a poorer survival in mRCC (145,281,282).

Based on the immunogenic nature of RCC, several inflammatory factors have been studied for their potential prognostic value and they are summarised below:

The neutrophil-to-lymphocyte ratio (NLR) and the thrombocyte-to-lymphocyte ratio (TLR) have been suggested to add further prognostic accuracy than the respective levels themselves for patients treated with TA (283–286). This has been repeated for patients treated with nivolumab (287,288).

C-reactive protein (CRP) has been found prognostic in mRCC patients treated with sunitinib or sorafenib in first-line (289–292), in the second-line setting with either a TKI or a mTOR inhibitor (293) as well as for nivolumab (288). Normalisation of CRP after CN seem to predict a better prognosis (294). Some small studies suggest that baseline CRP is also predictive of response (292,295,296), but it is non-specific and not used clinically when choosing treatment.

Hypoalbuminemia is common in later stages of many cancers as a sign of a general inflammatory and catabolic situation. Hypoalbuminemia was surprisingly not included in studies leading to the MSKCC or IMDC scores but other studies have suggested its prognostic usefulness when estimating progression free survival (PFS) and OS, respectively (297,298). CRP and hypoalbuminemia have been combined in the modified Glasgow prognostic score. It was first described in the cytokine treatment era (299) but has later been evaluated for TA (300,301).

Weight loss, unintended and pronounced, is fairly common for patients prior to diagnosis of advanced cancer (302). In mRCC patients treated with IFN-α, patient-reported weight loss prior to diagnosis was a negative prognostic factor (303). Weight loss has not been evaluated as a prognostic factor in the current therapeutic era, but Ishihara found sarcopenia, a potential indicator for
weight loss, to be an independent prognostic factor for PFS but not OS in patients treated with first-line sunitinib (300).

Prognostic factors for brain metastases

Presence of BMs have long been considered a negative prognostic sign in mRCC and BMs are often accompanied with other negative prognostic factors (145,282). BM-specific prognostic scores have been developed over the years. Many of them were initially not RCC-specific but have thereafter been evaluated in mRCC patients. Others have been validated in patients receiving intracranial SRT. Generally, the scores include similar variants of factors in different combinations: age, PS, control of primary tumour and/or extracranial disease burden, number of BMs and/or volume of BMs. The most used prognostic score for mRCC patients with BMs is the Disease specific graded prognostic assessment (DS-GPA) or its expanded score, the modified Renal-GPA. For RCC patients with BMs treated with radiosurgery, the Largest Lesion Volume Scored Index for Radiosurgery (LLV-SIR) or its modification into Cumulative Intracranial Tumour Volume Scored Index for Radiosurgery (CITV-SIR) are suggested useful for prognostication. These scores are further described below.

In the therapeutic era prior to TA, Sperduto et al developed the DS-GPA score for mRCC patients with BMs, and the score included KPS and number of BMs (304). In the follow-up cohort of mRCC patients with BMs treated in the TA era the mOS was improved (305). In this cohort they developed the improved and expanded prognostic index Renal-GPA, see Table 4. The mOS of the different groups of Renal-GPA was: 4 months, 12 months, 17 months, and 35 months respectively (306). The DS-GPA has been validated in mRCC patients treated with intracranial SRT (307).

Table 4. Renal Graded Prognostic Assessment (Renal-GPA) (305)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Scoring criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS (%)</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Extracranial metastases</td>
<td>Present</td>
</tr>
<tr>
<td>Hemoglobin (g/l)</td>
<td>≤110</td>
</tr>
<tr>
<td>Number of brain metastases</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Score</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factor</th>
<th>Scoring criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>90-100</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>111-125</td>
</tr>
<tr>
<td></td>
<td>&gt;125</td>
</tr>
<tr>
<td></td>
<td>1-4</td>
</tr>
</tbody>
</table>

Group 1: 0-1 points, Group 2: 1.5-2 points, Group 3: 2.5-3 points, Group 4: 3.5-4 points

LLV-SIR was initially developed by Weltman et al and used for prognostication in patients receiving intracranial SRT for BMs, (308,309) and modified by Hirshman et al to better predict prognosis by changing the criteria LLV into CITV, see Table 5 (310).
Table 5. CITV-modified Scored Index for Radiosurgery (CITV-SIR) (310)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Scoring criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0 ≥60 51-59 ≤50</td>
</tr>
<tr>
<td>KPS (%)</td>
<td>0 ≤50</td>
</tr>
<tr>
<td>Systemic disease status</td>
<td>Progressive disease Partial response or Stable disease Complete response or No evidence of disease</td>
</tr>
<tr>
<td>Cumulative intracranial</td>
<td>&gt;13 3.5-13 &lt;3.5</td>
</tr>
<tr>
<td>tumour volume (cm³)</td>
<td>≥3 2 1</td>
</tr>
<tr>
<td>Number of brain metastases</td>
<td></td>
</tr>
</tbody>
</table>

Class 1: 0-3 points, Class 2: 4-7 points, and Class 3 8-10 points

Predictive factors

There is an ongoing vigorous search for predictive factors for mRCC therapies (311,312). It is of immense importance to be able to choose the right treatment for the right patient to improve survival, avoid unnecessary toxicity, as well as to use therapies in a cost-effective way. Several potentially predictive factors have been studied for the therapies of ccRCC.

In the randomised CABOSUN trial where cabozantinib, among others targeting the receptor c-MET, was compared to sunitinib in first-line. MET positive patients treated with cabozantinib had significantly better PFS compared to sunitinib, whereas no significant difference in PFS was detected in MET negative patients (76). Somewhat surprisingly, a meta-analysis on the predictive value of mutations in VHL did not show any correlation to response on TKIs (313). Similarly, studies on the correlation between response to TKIs and the levels of VEGF and VEGF receptors in tumour tissues as well as serum VEGF have shown contradictory results (314). Hsieh et al studied the gene expression of patients treated with either sunitinib or everolimus in first-line and found that ccRCC patients treated with sunitinib had longer PFS if they had mutations in KDM5C, while for the everolimus arm a corresponding correlation was found for PBRM1 mutations (42). Another study suggests an existing subgroup of ccRCC patients with higher angiogenesis gene expression, frequently harbouring PBRM1 mutations but seldom BAP1 mutations, to have better ORR and survival when treated with sunitinib or pazopanib (44). In the Checkmate-214 study, patients with non-favourable IMDC risk group were more likely to respond to the combination of nivolumab and ipililumab, whereas patients with favourable risk group had better outcome if treated in the control arm with sunitinib (131). Reports on mutations in the PI3K/AKT-
pathway and mTOR are contradictive on their ability to predict response to everolimus (25,26,315).

PDL1 has been a strong candidate as to predict response to immune therapies and it is used for treatment selection (pembrolizumab) in NSCLC (316). Hakimi et al recently published results where they clustered patients treated with TKIs according to mutation expression. The cluster with the worst prognosis, encompassing more patients with poor risk features and responding less well to TKIs, had higher immune infiltration (especially macrophages) and PDL1 expression, suggesting a subgroup that could potentially respond well to immune therapies (44). In Checkmate 214, PDL1 expression was strongly associated with better response to the ipilimumab and nivolumab combination, with better PFS and ORR for PDL1+ patients. However, both PDL1+ and PDL1- patients in IMDC non-favourable risk groups benefitted from the immune therapies compared to sunitinib. In contrast, PDL1 expression (≥ 1%) was associated with poorer PFS for sunitinib in the same study. (131). Neither in KEYNOTE-426, nor in the JAVELIN Renal 101, was PDL1 expression a predictive factor for response to the respective immune therapy plus TA arm (128,133). Increased expression of PD-L2, the other ligand of PD1 and much less studied and understood, is one additional potential predictive marker of interest (317,318).

Interestingly, RCC tumours with sarcomatoid histological features, a known poor prognosis marker, appear to have increased PDL1 expression compared to non-sarcomatoid RCC tumours (319,320). The IMmotion151 trial showed a higher expression of PDL1 in sarcomatoid tumours and patients with sarcomatoid tumours and high PDL1 expression showed the greatest benefit in PFS for atezolizumab plus bevacizumab vs sunitinib (129). In a post-hoc subgroup analysis of the Checkmate 214 cohort, patients with sarcomatoid histological features had a significant benefit from ipilimumab plus nivolumab compared to sunitinib and an impressive ORR of 56% was presented for the CPI combination (321).

Furthermore, Beuselinck et al divided mRCC patients into four molecular subtypes, called ccrc1-4. The molecular subtypes have been shown to predict response to sunitinib and pazopanib (322,323). They also divide patients with different immune signatures as well as sarcomatoid histology and are therefore suggested to help in selecting patients for immune therapies (324). Interestingly, the molecular subtypes also appear to predict patients with longer disease free interval after complete surgical metastasectomy (325).

In summary, the answer to whether a single biomarker will be able to predict a response to a particular mRCC therapy or if a combination of many biomarkers is needed is not there yet (326).
Early response markers

As no easily available predictive markers have been found, especially not for TA, efforts have been made to identify early treatment response markers.

Several studies have demonstrated the associations between toxicity from different TKIs and ORR, PFS and OS, and the findings were summarised in two reviews as well as in a study on pooled data (327–329). Hypertension, hand-foot syndrome, neutropenia, thrombocytopenia and hypothyroidism, were the toxicities of TKIs with the most convincing correlation to outcome. Development of pneumonitis has been suggested to predict for a better response for everolimus (330). There is also evidence that the more toxicities a patient experience, the better the prognosis (328,331–333). Differences in toxicity and outcome are suggested to reflect a large variation in the concentration of TA between patients (334–336,333). This suggests the need for individualised dosing, aiming for a clinical response and an acceptable toxicity level for each patient (337). Furthermore, clinicians need to have thorough knowledge on how to manage toxicities, to allow patients to benefit maximally from TA (338). For CPIs, two studies on mRCC patients suggest an association between auto-immune toxicity and response to therapy (339,340).

Similarly, changes in inflammatory and blood parameters after start of TA have shown potential as early response markers. Decline in CRP (294) or NLR (285) and total lymphocytes (341) have been associated with good response to TKIs. Improvement in the IMDC risk group after first-line therapy predicted for better response to TKIs in second-line (342). Normalisation of hyponatremia was associated with better outcome for patients treated with everolimus (343). Decline in NLR seems to predict response to immune therapies (344).

Angiogenic factors have been suggested as potential early response markers to VEGF-directed TA. In one study the vessel density in the primary tumour, as measured with CD31 expression, decreased upon treatment with neo-adjuvant VEGF-directed TA and correlated with PFS (123). Changes in serum levels of VEGF and VEGF receptors correlated to response to sunitinib in one study but other studies have shown contradictory results (314,345).

For both TA and CPIs the evaluation of response is done through radiology follow up, CT being the routine imaging technique. Tumour response on CT scans after a short period of TKI therapy has been reported a potential response marker (346,347). Nevertheless, the radiological responses differ from those seen with cytotoxic therapies used in other cancers. Radiological response to TKIs are often seen as stable disease, or modest shrinkage, whereas for CPIs,
some patients first react with radiological progression and thereafter show tumour shrinkage (referred to as pseudoprogression) (348,349). Therefore different studies have investigated the use of volumetric fluorodeoxyglucose positron emission tomography (FDG-PET), dynamic contrast-enhanced CT blood flow and blood volume, and molecular targeted MRT directed to the vasculature, in order to detect changes after start of therapy that could potentially predict an early response to TKIs (350–352). The use of functional imaging is not used in the clinic and the limitations of utility and reproducibility needs to be addressed (353).
Aims

The general aim of this thesis is to identify clinically relevant factors that can be used for prognostic evaluation and therapy selection in patients with metastatic renal cell carcinoma treated in the era of targeted agents.

This aim is approached in four papers where I:

(a) study whether inflammatory blood and clinical parameters that are easily available in routine outpatient setting, are relevant as prognostic factors in addition to the established risk score (Paper I).

(b) study a cohort of metastatic papillary renal cell carcinoma patients and attempt to deepen the clinical understanding of this particular subgroup and identify disease-specific prognostic factors (Paper II).

(c) study the effect of intracranial and extracranial stereotactic radiotherapy or surgical metastasectomy on overall survival as well as tumour control and attempt to identify clinical variables associated with long-term survival and toxicity (Paper III and Paper IV).
Patients and Methods

Table 6. Summary of Patients and Methods

<table>
<thead>
<tr>
<th>Paper</th>
<th>No of patients</th>
<th>Histology</th>
<th>Type</th>
<th>Years</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>84</td>
<td>Clear cell 74%</td>
<td>Retrospective, single centre</td>
<td>2005-2012</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>II</td>
<td>86</td>
<td>Papillary 100%</td>
<td>Retrospective, multi centre</td>
<td>2005-2015</td>
<td>OS</td>
</tr>
<tr>
<td>III</td>
<td>117</td>
<td>Clear cell 88%</td>
<td>Retrospective, multi centre</td>
<td>2005-2014</td>
<td>OS, local control, toxicity</td>
</tr>
<tr>
<td>IV</td>
<td>43</td>
<td>Clear cell 100%</td>
<td>Retrospective, multi centre</td>
<td>2005-2014</td>
<td>OS, local control, toxicity, ARE</td>
</tr>
</tbody>
</table>

Paper I

Includes patients with metastatic RCC (n=84) referred to the Uppsala University Hospital. General data on diagnosis, tumour and host specific factors, as well as therapy were collected from patient records. The analysed factors of prognostic significance were MSKCC risk group, albumin, CRP, platelet count, and weight loss prior to treatment.

Paper II

Includes patients with metastatic papillary RCC referred to one of three academic centres, two in Sweden (the Karolinska University Hospital in Stockholm or the Uppsala University Hospital, n=44) and one in Germany (the Ludwig–Maximilian’s University Clinic in Munich, n=42). General data on diagnosis, tumour and host specific factors, as well as therapy were collected from patient records or institutional data bases. The median follow-up of patients alive was 33 months. The analysed factors of possible prognostic significance were age, sex, nephrectomy, metachronous or synchronous metastases, number of metastatic sites, involved organs (bone, liver, lung, lymph nodes and brain), ECOG performance status, MSKCC risk group, and use of targeted agents.
Paper III

Includes patients with metastatic RCC (n=117) treated with local metastatic therapy: either stereotactic radiotherapy (n=57), surgical metastasectomy (n=30) or both treatment modalities (n=30). Patients were referred to one of two academic centres in Sweden, (the Karolinska University Hospital in Stockholm or the Uppsala University Hospital). General data on diagnosis, tumour and host specific factors, as well as therapy (systemic and local) were collected from patient records or institutional data bases. These were supplemented with data on local tumour control and toxicity. The median follow-up of patients alive was 63 months. The analysed factors of possible prognostic significance were age, histology, tumour grade, metachronous or synchronous metastases, ECOG performance status, MSKCC risk group, target location, curative intent, and time to local metastatic therapy.

Paper IV

Includes patients with metastatic clear cell RCC that had received single fraction gamma knife radiosurgery against brain metastases (n=43). Patients were both from the Paper III cohort (the Karolinska University Hospital in Stockholm; n=29), as well as additional patients from two other academic centres (CUF Infante Santo Hospital, Lisbon, Portugal, and Bezmialem Vakif University Medical School Hospital, Istanbul, Turkey; n=14). General data on diagnosis, tumour and host specific factors, as well as therapy (systemic and local) were collected from patient records or institutional data bases. These were supplemented with radiobiological and technical data, need for corticosteroids, local tumour control, detection of adverse radiation effects, and toxicity. The median follow-up of patients alive was 56 months. The analysed factors of possible prognostic significance were age, Karnofsky performance status, MSKCC risk group, metachronous or synchronous metastases, brain metastases at mRCC diagnosis, extracranial disease status as well as blood parameters (albumin, haemoglobin, platelet count, lactate dehydrogenase, and calcium), number of intracranial targets, need for corticosteroids, tumour volumes, neurosurgery, treatment with TA, and specific risk group for BMs or intracranial SRT (DS-GPA, Renal-GPA, LLV-SIR and CITV-SIR).
Statistics
For all four papers the following statistical methods were used when applicable:

- Descriptive statistics were presented as median values and range.
- ROC-curves were used to identify optimal cut-offs when testing the effects of continuous variables on the probability of survival.
- Chi-squared test or Fischer’s exact test for comparing frequencies of categorical variables.
- Mann-Whitney U-test to compare means of values between two independent groups.
- Kaplan-Meier curves for probability of survival estimations with time, including values of median survival.
- Cox proportional hazards regression model for univariate and multivariate analysis of significance of putative prognostic variables, generating hazard ratios (HR) with 95% confidence intervals (CI).
- A p-value of <0.05 was considered statistically significant.
- All statistical analyses were performed using STATISTICA version 13 (StatSoft Inc, Tulsa, USA).

Ethical considerations
The studies in this thesis were approved by the ethical committees in Stockholm (dnr 2015/2147-31/1), Uppsala (dnr 2012/419), and Umeå (dnr 2012-418-31 and 2016-330-32), all Sweden, as well as acquired ethical certificates from Munich, Lisbon and Istanbul, respectively.
Results

Paper I
Median OS of all mRCC patients (n=84) was 20 months. The MSKCC score could be validated for OS in terms of separating poor risk patients from intermediate risk patients, while favourable risk patients did not differ statistically from intermediate risk patients. Hypoalbuminemia (<30 g/L), elevated platelet count (>360 x10^9/L), and weight loss prior to treatment were associated with OS in univariate analysis, after controlling for ECOG PS. CRP was not significant in univariate analysis. The multivariate analysis identified hypoalbuminemia as an independent prognostic factor for worse OS (HR 2.7). In the subgroup analysis of patients treated with TA (n=47) an association with PFS was found for albumin and platelet count in univariate analysis. Hypoalbuminemia alone remained associated with PFS in multivariate analysis (HR 3.9). Notably, MSKCC risk group was not associated with PFS.

Paper II
Median OS in the cohort of metastatic papillary RCC patients (n=86) was 11.2 months. Papillary subtype 2 dominated. Brain metastases at metastatic diagnosis were common (28%). Factors associated with OS in univariate analysis included age, number of metastatic sites, brain metastases, ECOG PS, and TA use. In contrast, nephrectomy, synchronous metastases at diagnosis, MSKCC risk group, or organ site other than brain were not associated with OS. In multivariate analysis, age ≥60 years (HR 2.2), ≥3 metastatic sites (HR 2.7), or an ECOG PS ≥2 vs 1 (HR 3.0) remained associated with poor OS. ECOG 0 vs 1 (HR 0.5) was borderline significant for association with better OS (p=0.056). In the subgroup analysis of patients treated with TA (n=66) age, lymph node metastasis, number of metastatic sites and ECOG PS were independent prognostic factors.
Paper III

Median OS in the whole cohort of patients treated with local metastatic therapies (n=117) was 51 months. There were no significant differences in survival with respect to treatment modality (SRT or surgical metastasectomy or both). Treatment with SRT or surgical metastasectomy was the first treatment for 87% of patients in this cohort, although 65% also received systemic therapy.

Local control of extracranial targets was similar for SRT (76%) and surgical metastasectomy (67%). For extracranial SRT various fractionation schemes were used depending on site and size of target (15 Gy x 3, 15 Gy x 2 and 7 Gy x 8 the most common) and local control was better for targets treated with a total dose of >90 Gy (EQD2). Extracranial surgical metastasectomy was most commonly used for lung and soft-tissue metastases and local recurrences. For intracranial SRT, 28 patients had single fraction GKRS delivered with a median dose to the periphery of 22 Gy, whereas three patients had hypofractionated LINAC (8 Gy x 5 or 6 Gy x 5). In total 167 intracranial SRT targets were treated and only six targets progressed (local control 96%, missing data for 30 targets). Eleven intracranial targets were removed with neurosurgery. Of patients treated with curative intent (n=60), 15% were relapse-free at last follow-up. Toxicity upon treatment with TA in close proximity to SRT or surgical metastasectomy was mild.

Prognostic factors in univariate analysis included MSKCC risk group, ECOG PS, treatment of intracranial vs extracranial metastases, and time from metastatic diagnosis to first SRT or surgical metastasectomy. In multivariate analysis, ECOG PS 1 vs 0 (HR 2.9), intracranial treatment targets (HR 1.8), and watchful waiting ≥18 months (HR 0.3) were associated with OS.

Paper IV

In the GKRS treated cohort (n=43), 70 single fraction GKRS (sf-GKRS) sessions were performed against a total of 194 targets (in median two targets per session). The median prescription dose to the periphery was 22 Gy. Only three targets progressed in-field, yielding local control rates at 12 and 36 months of 97% and 90%, respectively. Patients with out-of-field intracranial progression (n=18) were commonly re-treated with sf-GKRS upon progression (maximum six sf-GKRS sessions).

Median OS was 15.7 months from first sf-GKRS. Albumin <30 g/L (HR=5.3), need for corticosteroids prior to sf-GKRS (HR=5.8), and KPS <80% (HR=9.1)
were independently associated with worse OS in multivariate analysis. Number of intracranial targets, presence or absence of extracranial disease as well as LLV and CITV gave prognostic information in univariate analysis but not in multivariate analysis. Age, MSKCC risk group, upfront brain metastasis at mRCC diagnosis or blood parameters other than albumin did not add prognostic information. Neither were systemic therapies nor neurosurgery associated with survival. Specific risk scores for BMs or intracranial SRT (DS-GPA, Renal-GPA, LLV-SIR and CITV-SIR) were not prognostic in our cohort.

ARE was identified in 16% of the sf-GKRS treated targets, commonly after six months, and most were non-symptomatic. Larger targets and targets with pre-GKRS perifocal oedema as well as targets with larger 10Gy-volume were associated with a higher risk of developing ARE. Patients receiving TA within ±1 month from sf-GKRS had lower incidence of ARE.
Conclusions

This thesis aimed to identify clinically relevant factors useful for prognostic evaluation and therapy selection in patients with metastatic renal cell carcinoma treated in the era of targeted agents. The following factors have been retrospectively found to affect survival:

- Performance status (Paper I-IV).
- Hypoalbuminemia (Paper I and IV).
- Age (Paper II, papillary patients).
- Number of metastatic sites (Paper II, papillary patients).
- Intracranial metastases (Paper III, patients treated with local metastatic therapies).
- Time from metastatic diagnosis to treatment with stereotactic radiotherapy or surgical metastasectomy (Paper III).
- Need for corticosteroids prior to gamma knife radiosurgery (Paper IV).

The established MSKCC prognostic score (at routine during the study period, nowadays often exchanged with IMDC prognostic score) did not provide independent prognostic information for real-world mRCC patients in general (Paper I), or specifically for mpRCC patients (Paper II) or oligometastatic RCC patients treated with SRT or surgical metastasectomy (Paper III and IV).

In Paper II, mpRCC patients had a dismal prognosis despite treatment with TA. Brain metastases were unexpectedly common at metastatic diagnosis.

In Paper III, oligometastatic RCC patients treated with SRT or surgical metastasectomy had a very long mOS of more than four years. Local control for intracranial SRT was excellent and about two thirds of the SRT or surgical metastasectomy treated extracranial metastases had local control. At follow-up, the rate of patients without evidence of disease was comparable to results for the latest combinations of systemic therapies. Treatment with TA in close proximity of SRT or surgical metastasectomy caused no significant toxicity.

In Paper IV, GKRS treated RCC patients had a long mOS and the local control was excellent. The use of GKRS was safe and most ARE were non-symptomatic. Larger tumour volume, larger 10Gy-volume and presence of perifocal oedema prior to GKRS were positively associated with ARE, whereas treatment with TA in close proximity to GKRS seemed to be protective of ARE.
Individualised therapy of mRCC patients – thesis discussion and future perspectives

This thesis attempts to identify clinical factors that can help with prognostication and possibly with individualised treatment selection for mRCC patients. It presents real-world data in unselected mRCC patients treated in a general clinical setting. The retrospective design of the studies allow for hypotheses to arise for further prospective validation.

The importance of performance status and hypoalbuminemia as prognostic factors

Today, we have close to ten available targeted agents and a few approved CPIs and more so in the pipe-line. Although it remains to be seen which treatment will be preferred in the near future, the combination of CPIs plus TA is particularly promising. Still, there is so far a lack of predictive markers and the clinician is settled with the current clinical prognostic score (the IMDC score that succeeded the previously used MSKCC score) to prognosticate the patient and try to select the best possible treatment. The two most striking findings of this thesis were the usefulness of PS and hypoalbuminemia, respectively, for prognostication in mRCC patients.

Throughout all four papers in this thesis, the potent prognostic value of PS is clearly shown. This emphasises the importance of taking a thorough clinical history, carefully evaluating how the patient is affected by the disease in everyday life. This can improve the accuracy of prognostication but possibly also support the choice of treatment. Paper I and II suggest that PS is a prognostic marker in both mccRCC and mpRCC patients, which aligns with the IMDC risk score (274,278). Paper III and IV suggest that PS can predict the prognosis of patients considered for local metastatic therapy (SRT or surgical metastasectomy). This is supported by a recent meta-analysis on surgical metastasectomy in mRCC (193). Notably, all prognostic scores for BMs and intracranial SRT include PS (304,306,309,310).

Paper I and IV assess serum albumin as a potential prognostic marker. In these two cohorts of mainly mccRCC patients, hypoalbuminemia (<30 g/L) is found
to be a negative prognostic factor independent of PS, suggesting that it does not only reflect a fragile patient with poor nutritional status. We suggest that, albumin could be viewed as a simple to use composite indicator of both general metabolic as well as inflammatory status. As shown in Paper I, albumin provides more robust prognostic information than other inflammatory markers such as CRP or platelet count.

The Glasgow prognostic score, combining elevated CRP and hypoalbuminemia, has been suggested prognostic in the TA era (300,301,354). One retrospective study found serum albumin to be a prognostic factor for PFS in patients treated with bevacizumab and interferon, a combination nowadays rarely used (297). Another study analysed albumin as a prognostic factor for patients treated with sunitinib in univariate analysis but did not perform multivariate analysis to control for other potential risk factors (298). Notably, hypoalbuminemia was not analysed in the pivotal studies that gave rise to the MSKCC and IMDC scores (271,274,275). After our publication, Kattan et al verified hypoalbuminemia as a prognostic factor of PFS in patients treated with pazopanib (355). Moreover, in the study by Cai et al hypoalbuminemia was an independent prognostic factor for both PFS and OS in patients treated with sunitinib or sorafenib in first-line, thus confirming our results (356). Furthermore, Sacré et al showed hypoalbuminemia to be prognostic of OS in second-line treatment (357). Collectively, our results and the studies following, suggest that hypoalbuminemia in mRCC is a potential prognostic factor for mRCC patients, possibly adding information to the standard prognostic score used today. Importantly, this needs to be validated prospectively.

A deepened understanding of papillary renal cell carcinoma

The thesis also attempts to deepen the clinical understanding of the often omitted subgroup of mpRCC (Paper II). The currently available TA mainly target angiogenesis, being a hallmark of ccRCC, albeit the angiogenic and hypoxic drive in mpRCC is very limited (65,83,84). In line with other studies, the mOS in our papillary cohort was short and the benefit of TA seems limited bearing in mind the common toxicities of these therapies (54,55). This suggests the insufficiency of VEGF-directed TA for mpRCC and the aggressiveness of this disease entity once metastasised, recently confirmed in two studies on mpRCC patients treated with TA (358,359). As p1RCC tumours are often MET-driven, being sometimes also the case in p2RCC, several c-MET targeting TA are explored in clinical trials. In ccRCC, MET expression was predictive of a better response to the multi-kinase inhibitor cabozantinib which, among others inhibits c-MET. However, responses to cabozantinib have been seen in both
MET positive and MET negative patients (76). Notably, this association raises some hope for MET to be used as a predictive marker in mpRCC patients and two retrospective studies have shown promising results for cabozantinib in nccRCC (92,93). The SWOG1500 trial is recruiting mpRCC patients for the evaluation of savolitinib, crizotinib and cabozantinib, respectively, all targeting c-MET (94–96,360). Hopefully, this or upcoming studies on TA and/or immune therapies for mpRCC will contribute to improved treatment outcomes for mpRCC patients in the near future (144).

The incidence of BMs was surprisingly high (28%) in our mpRCC cohort. For comparison the incidence of BMs at mRCC diagnosis in the histologically mixed population in Paper I was 5%. In a recent study by Bowman et al, BMs were described in 13% of RCC patients at initial evaluation for metastatic disease and another 10% had BMs diagnosed prior to or during first-line therapy (361). Sun et al observed a 12.0% incidence of BMs in a large real-world database in US (362). For mpRCC patients Connor Wells et al found an incidence of BMs of 3.6% (n=441) but our results suggest it can be more common (278). Notably, our Munich sub-cohort was scanned routinely for brain metastasis upfront in contrast to the standard diagnostic workup at the two Swedish centres that only undertook brain scanning if clinical symptoms of CNS spread were evident. However, this variation in procedure rather implies an underestimation of intracranial involvement, albeit referral bias must also be considered. Future studies need to validate our findings prospectively.

The usefulness of local metastatic therapies

In Paper III and IV the use of extracranial and intracranial SRT and surgical metastasectomy in general and GKRS of BMs in particular were studied. The median OS of all patients treated with SRT or surgical metastasectomy was more than four years, possibly suggesting a potent survival effect of local metastatic therapy. The true clinical survival benefit in our retrospective studies is difficult to assess since patients were inevitably selected for local metastatic therapy based on characteristics believed by the physicians to confer a benefit. This selection bias is reflected in the good PS and limited number of metastases in the patients treated with local metastatic therapies, possibly implying a less aggressive tumour biology. However the cohorts in Paper III and IV included patients in all MSKCC risk groups and around half of the patients had synchronous metastases, implying that the cohorts were fairly representative of a general mRCC population and that not all patients had an indolent disease. In patients with non-favourable prognostic characteristics, a sub-group analysis showed survival to be better than what would be expected from TA treatment alone, strengthening the case that the local metastatic therapies truly affected the survival.
For BMs (Paper III), intracranial SRT (mainly GKRS) was the treatment modality of choice for the majority of patients and the local control was excellent and well in line with earlier studies. In our cohort neurosurgery of BMs was performed in only seven patients (11 targets), not allowing for a deepened analysis. For the sf-GKRS treated ccRCC patients included in Paper IV, only three of 194 targets progressed in-field. We therefore suggest that intracranial SRT of RCC BMs allow for patients to have local tumour control, likely sustaining a fair quality of life, and rendering them fit enough to receive and benefit from systemic therapies.

The local control of extracranial metastases was comparable between SRT and surgical metastasectomy. Nevertheless, extracranial SRT was given to patients with worse general condition compared to surgical metastasectomy, suggesting its usefulness for more fragile patients being non-invasive compared to surgery, and thus possibly allowing for faster recovery and an earlier start (or resumption) of systemic therapy. As expected, extracranial surgical metastasectomy was most commonly performed on lung and soft-tissue metastases as well as local recurrences. The apparent inferior local control of extracranial SRT compared to intracranial SRT (76% vs 96% in Paper III) was not expected, albeit a thorough fixation of the target is easier accomplished for BMs compared to thoracic or abdominal metastases. Other studies have shown a local control of around 90% for extracranial SRT on RCC metastases (229–231,363). In our cohort, targets receiving a biologically equivalent dose (EQD2) of >90 Gy (corresponding to a BED of >126 Gy) had a better local control than those treated with an EQD2 of ≤90 Gy. This aligns well with other studies and suggests the importance of optimising treatment techniques and skills to reach ablative doses (172,176,228,249,364).

In the in-depth study of GKRS in Paper IV, GKRS appear to be more favourable for patients with a good PS, without need for corticosteroids prior to GKRS (likely a surrogate for non-symptomatic BMs), and normal albumin levels. Our study, along with others, suggest that mRCC patients with synchronous brain involvement, and more than four brain metastases could be considered for GKRS (365,366). Furthermore, patients with intracranial relapse after GKRS can be considered for repeated GKRS, especially patients with apparently less aggressive tumour biology (367). Surprisingly, previously described and used prognostic scores for BMs and intracranial SRT (DS-GPA, Renal-GPA, LLV-SIR and CITV-SIR) did not add independent prognostic information in our GKRS cohort.

The incidence of ARE post-GKRS was generally low and a minority were symptomatic. The usage of TA within ±1 month of sf-GKRS was well tolerated and our results rather suggest that TA can decrease the risk of developing ARE post-GKRS. Similarly, in Paper III, there was little toxicity associated
with TA in close proximity to SRT or surgical metastasectomy. We suggest that the neuroprotective role of VEGF-directed TA in intracranial SRT, as seen for bevacizumab in glioblastoma, should be studied prospectively in mRCC patients (263).

Analysing the results of local metastatic therapies in Paper III and IV, we believe that surgical metastasectomy and SRT meaningfully halt disease progression and is well-tolerated in mRCC patients. Importantly, cure was seen for 15% of patients treated with curative intent, a result comparing favourably to the complete response rates seen with the new combined systemic therapies (131,132). For patients not cured, local metastatic therapy may post-pone the need for systemic therapy, and, for others, allow for symptomatic relief necessary to enable systemic therapy (368). Our results align well with a recently published meta-analysis that discuss the potential use of surgical metastasectomy in oligometastatic RCC disease in the lung, adrenal gland, pancreatic gland, liver, bone, head/neck or brain. The authors suggest an individualised approach to treatment selection, where the potential for complete resection, the patients PS, the time from primary diagnosis to mRCC diagnosis and the metastatic burden should guide the treatment decision (193). In another meta-analysis on SRT younger age, good PS, fewer brain metastases, and no prior radiation to the brain or systemic therapy was prognostic for survival for intracranial SRT. For extracranial SRT the following factor were associated with survival: good PS, limited disease and SRT therapy to all known metastases (228).

Importantly, the patients in the Paper III and IV cohort were treated in the era of TA which is not the case for many earlier retrospective studies included in the meta-analyses mentioned above. This further implies the impact of Paper III and IV, albeit prospective validation is important. The next logical step would be to conduct a prospective study in mRCC patients with oligometastatic disease, with randomisation between local metastatic therapies and/or systemic therapy, in order to define the role for different local metastatic therapies, the optimal treatment technique and dosing as well as which patients benefit the most from them.

**Future perspectives**

The future of mRCC treatment appears to hold combinations of different immune therapies as well as combinations of immune therapies and TA (134). Furthermore, ongoing studies analyse if TA and/or immune therapies should be combined with SRT for synergistic effects (369–371). SRT is hypothesised to create a strong abscopal effect when high-dose radiation damage reveals
tumour antigens to activated immune cells relieved from tumour suppression through treatment with CPIs (153,242).

For successful usage of future therapeutic combinations, validated predictive markers are warranted. Studied putative predictive markers, such as MET and PDL1 status, have shown signs of predicting a better response to cabozantinib and ipiliilumab plus nivolumab, respectively (76,128,131). There is nevertheless an issue on the matter of biomarkers as to which marker to use and how and where to measure it. Possibly, MET and PDL1 status can predict response to different therapies, but the issue of heterogeneity between studies need to be settled to allow for comparisons (372). The significant heterogeneity within each tumour as well as in between the primary tumour and metastases raise further questions of methodology (45,47). Currently, the IMDC risk score is used to select patients for therapy with ipiliilumab plus nivolumab (131,132,311,312). The molecular subtypes of mRCC patients, discovered by Beuselinck et al, seem very promising in their ability to predict response to various therapies, both systemic and local (322–325). In the future, reliable predictive markers are necessary to individualise the therapy, but the increasing cost of advanced genetic and molecular analyses renders the question of whether biomarker detection will be affordable in the everyday clinic.
Svensk sammanfattning

Bakgrund

Njurcancer utgör cirka 2% av all cancer i Sverige och mer än 1200 nya fall diagnostiseras varje år. För de flesta patienter är njurcancer endast lokalisera till njuren och har inte spridit sig och njuren opereras bort. Tyvärr får 30% förr eller senare en spridd sjukdom. När njurcancer är spridd så är det en dödlig sjukdom och bot är ovanligt. Den mest använda prognostiska modellen för spridd njurcancer är MSKCCs, som på senare år har modifierats till IMDCs prognostiska modell. Njurcancer innefattar flera olika histologiska subtyper där klarcellig (70-80%) och papillär (10-15%) är de vanligaste. Behandlingen för spridd njurcancer är målriktad behandling och immunterapi. Utöver detta så används även lokala metastasbehandlingar, främst på patienter med en eller få metastaser. Dessa behandlingar kan erbjuda patienten en potentiellt botande behandling, alternativt syftar de till att ge lokal kontroll av en viss metastas.

Målet för denna avhandling var att (1) identifiera kliniskt relevanta faktorer som kan vara till hjälp i prognosbedömning och behandlingsval för patienter med spridd njurcancer som är aktuella för behandling med målriktade läkemedel, (2) fördjupa kunskapen om spridd njurcancer och (3) utvärdera användandet av lokal metastasbehandling vid njurcancer. Avhandlingen baseras på patientdata från databaser och journaler från år 2005 och framåt.

Delarbete 1

I det första delarbetet studerade jag det prognostiska värdet av olika blodvärden och kliniska parametrar som på olika sätt reflekterar graden av inflammation hos patienten. 84 patienter som behandlats för spridd njurcancer i Uppsala inkluderades. Den totala överlevnaden hos patienterna var 20 månader. Lågt albumin var en markör för sämre total överlevnad, oberoende av patientens allmäntillstånd och tidigare kända riskkriterier.
Delarbete II

I det andra delarbetet studerade jag 86 patienter med spridd papillär njurcancer som behandlats i antingen Uppsala, Stockholm eller München (Tyskland). Den totala överlevnaden hos patienterna var 11 månader. Hög ålder, tumörspridning till många av kroppens organ och dåligt allmäntillstånd hos patienten var prognostiskt egentliga faktorer för överlevnad i dessa patienter. Detta delarbete betonar den dåliga prognosen för denna patientgrupp och det är därför av stor vikt att fortsätta utveckla specifika målriktade läkemedel för papillär njurcancer.

Delarbete III


Delarbete IV

I fjärde delarbetet studerade jag 43 njurcancerpatienter som behandlats med en viss sorts lokal metastasbehandling, nämligen gammaknivsbehandling (GKRS) mot hjärnmetastaser, i Stockholm, Lissabon (Portugal) eller Istanbul (Turkiet). Den totala överlevnaden hos patienterna var 16 månader. Den lokala kontrollen efter behandlingarna var mycket bra. Albumin, behov av kortison innan först GKRS-behandlingen (sannolikt motsvarande symptomgivande hjärnmetastaser), och patientens allmäntillstånd var faktorer för sämre överlevnad efter GKRS, oberoende av tidigare kända prognostiska riskgrupperingar. Strålreaktioner sågs på röntgen hos 16% av patienterna efter GKRS men de flesta fick inte några symtom av strålreaktionerna.
Konklusion

I denna avhandling har flera kliniska faktorer identifierats som kan vara användbara för prognosbedömning för patienter med spridd njurcancer. I avhandlingen bekräftas Vikten av noggrann bedömning av patientens allmäntillstånd då detta har ett starkt prognostiskt värde i samtliga delarbeten. Därutöver är lågt albumin en stark prognostisk faktor både i en genomsnittlig njurcancerkohort (delarbete I) och i en kohort med njurcancer patienter behandlade med GKRS (delarbete IV). Albumin kan vara ett intressant tillägg till nuvarande prognostiska kriterier. Vidare synliggörs den sämre prognosen för patienter med spridd papillär njurcancer och det är av stor vikt att få fram målriktade läkemedel för denna subgrupp. Slutligen så framträder en tydlig bild av att lokal metastasbehandling i allmänhet och SRT i synnerhet, är användbara vid spridd njurcancer, med påtagligt höga överlevnadssifferor. Utöver detta framkommer en betydande lokal kontroll, inte minst gällande hjärnmetastaser behandlade med GKRS. Denna avhandling är av betydelse då vi i nuläget saknar bra markörer för val av behandling till njurcancerpatienter. Resultaten ska dock ses som hypotesgenererande och måste prövas och bekräftas i prospektiva studier.
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