Localised and Metastatic Renal Cell Carcinoma

Aspects of Treatment

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Till Min Emma…

”Vad stort sker, det sker tyst.”

ur ”Odalbonden” (1811), Erik Gustaf Geijer (1783-1847)

ABSTRACT

David Lyrdal

Localised and Metastatic Renal Cell Carcinoma. Aspects of Treatment.

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Aims:

Paper I To assess the long-term results in patients operated with NSS in situ for RCC, with special reference to their dependence on tumour grade and stage.

Paper II To investigate 18-FDG-PET/CT as an option to evaluate treatment effects in patients with MRCC treated with targeted therapy, as sorafenib.

Paper III To assess optimal dose, efficacy and the tolerability for long-term treatment, when treating MRCC patients with Peg-interferon alfa-2b.

Paper IV To disclose imaging characteristics, predictive factors for local recurrence and repeated treatment in small renal masses treated with RFA.

Patients and methods:

Paper I Records of 87 patients subjected to NSS performed between 1980 and 1999 were reviewed, survival rate was determined with reference to grade stage and multiplicity of renal cell carcinoma (RCC).

Paper II Fifty-two lesions (39 soft and 13 bone lesions) in ten patients with MRCC, were evaluated. The 18-FDG-PET/CT was performed prior to treatment (sorafenib (Nexavar® Bayer HealthCare Ltd) 400mg twice daily) and 1–2 months after treatment start-up. The soft lesions were also measured and analysed according to Response Evaluation Criteria in Solid Tumors (RECIST) on CT images.

Paper III Twenty-eight patients with MRCC were treated with Peginterferon (Pegintron® Schering-Plough) in escalating doses of 0.5 μg/kg subcutaneously (s.c) weekly until 2 μg/kg was reached or prohibited toxicity occurred. Lesions were evaluated according to RECIST and toxicity according to National Cancer Institute's common toxicity criteria (NCI-CTC).

Paper IV Forty-six tumours in 43 patients were consecutively assessed for possible predictive factors after RFA treatment. At follow-up with CT or magnetic resonance imaging (MRI) possible predictive factors were analysed.

Results and conclusion:

Paper I Cancer-specific survival in M0 patients, regardless of stage and grade was 80% and 75% at 5 and 10 years, respectively. Stage and grade had a significant impact on long-term survival. The technique can be recommended in imperative indication and in selected cases with patients with normal contra-lateral kidney.

Paper II The mean glucose uptake in soft lesions decreased to 71% (32-108%) and to 82% (53-101%) in bone lesions of initial value measured by FDG-PET. Evaluated with RECIST the soft lesions diameter decreased to 80% (57-94%) of initial value. FDG-PET appears to be valuable for evaluation as it is possible to assess both soft and skeletal lesions.

Paper III The maximum dose of Peginterferon 2 μg/kg was reached by 46% (n=13) of the patients. Mean dose during long-term treatment was 1.5μg/kg. Median survival in all patients was 19.5 months. Partial response (PR) was seen in 4/11 patients with only intrathoracic lesions. Most side effects were grade 1-2/4, only two patients stopped the treatment due to toxicity.

Paper IV Thirty-eight (83%) tumours were completely ablated after the first treatment and 42 (91%) after repeated treatment. Nine patients (21%) showed local recurrence on follow-up, six of those were reablated, mean time to recurrence was 24 months. Maximum tumour diameter and volume were significantly larger and mean necrosis index lower in tumours with incomplete ablation compared to those completely ablated initially. Ultrasound-guided percutaneous RFA is a feasible and repeatable minimal invasive technique under development, for treatment of small renal tumours in selected patients.

Keywords:

renal cell carcinoma; nephron-sparing surgery; [^{18}F]-2-flouro-2-deoxyglucose; positron emission tomography; metastatic renal cell carcinoma, Peg-interferon alfa-2b; radiofrequency; ablation; percutaneous; ultrasound

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LIST OF PUBLICATIONS

This thesis is based on the following papers. They will, in the text, be referred to either by direct reference, e.g. **paper I**, or by their respective Roman numerals, e.g. **(I)**.

I. **Nephron-sparing Surgery for Renal Cell Carcinoma. Long-term Results**
S Lundstam, O Jonsson, D Lyrdal, R Peeker, S Pettersson
Scand J Urol Nephrol. 2003;37(4) 299-304

II. **Evaluation of Sorafenib Treatment in Metastatic Renal Cell Carcinoma with Positron Emission Tomography and Computed Tomography (18-FDG PET/CT)**
D Lyrdal, M Boijsen, M Suurküla, S Lundstam, U Stierner
Nucl Med Commun. 2009 Jul;30(7):519-24

III. **Metastatic Renal Cell Carcinoma Treated with Peg-interferon alfa-2b**
D Lyrdal, U Stierner, S Lundstam
Acta Oncol. 2009;48(6):901-8

IV. **Ultrasound-guided Percutaneous Radiofrequency Ablation of Small Renal Tumours: Clinical Results and Radiological Evolution During Follow-up**
D Lyrdal, M Andersson, M Hellström, J Sternal and S Lundstam
In Manuscript

ABBREVIATIONS IN THE TEXT IN ALPHABETICAL ORDER

AJCC	American Joint Committee on Cancer
ALAT	Alanin aminotransferase
AUC	Area under the curve
BHD	Birt-Hogg-Dubé
bw	Bodyweight
ccRCC	Clear cell renal cell carcinoma
CEUS	Contrast enhanced ultrasound
CHC	Chronic hepatitis C
CR	Complete response
CSS	Cancer specific survival
CT	Computed tomography
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
FDG	[^{18}F]-2-flouro-2-deoxyglucose
FH	Fumarate hydratase
FPTV	Fractional percentage of tumour volume
HIF	Hypoxia-inducible factor
HLRC	Hereditary leiomyomatosis and RCC syndrome
HPRC	Hereditary papillary renal cell carcinoma
IFN	Interferon
IL-2	Interleukin-2
IV	Intravenous
MBq	MegaBecquerel
MRCC	Metastatic renal cell carcinoma
MRI	Magnetic resonance imaging
MTD	Maximum tolerable dose
mTOR	Mammalian target of rapamycin

NCI-CTC	National Cancer Institute's common toxicity criteria
NSS	Nephron-sparing surgery
OR	Odds Ratio
PD	Progressive disease
PDGF	Platelet derived growth factor
PET	Positron emission tomography
PFS	Progression free survival
PR	Partial response
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radio frequency ablation
ROI	Region of interest
SC	Subcutaneously
SD	Stable disease
SPSS	Statistical Package for the Social Sciences
SRM	Small renal mass
TGFα	Transforming growth factor alpha
SUV	Standard uptake value
TKI	Tyrosine kinase inhibitor
TTP	Time to progression
UICC	Union Internationale Contre le Cancer
US	Ultrasound
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

TABLE OF CONTENTS

INTRODUCTION

Historical Background

Renal tumours are a heterogeneous group of lesions that in early attempts of surgical treatment were mistaken for other diseases. The first nephrectomy was reported to have been performed by accident by Wolcott in 1861, assuming the tumour wrongly to be a hepatoma. In 1869, Simon successfully accomplished an elective nephrectomy due to ureteral fistula; a surgical intervention which the patient survived (1).

Accordingly, the first accurate macroscopical description of kidney tumours was made by Konig in 1826 (2). Robson suggested in 1855 (later supported by Waldeyer's observations in 1867) that renal cell carcinoma originated from the renal tubular epithelium. However, the German pathologist PA Grawitz associated the fatty content of cancer cells to adrenal cells and suggested that the adrenal glands were the origin of the tumour. Subsequent investigators and fellow colleagues of Grawitz' era supported this idea of origin and Lubarch introduced the term "hypernephroid tumor" in 1894. This was followed by the term "hypernephroma". However, with time Grawitz' hypothesis of the cells' origin from the adrenal cortex was abandoned for the more general view stated by Allen, that the tumours derive from the tubular epithelium.

Epidemiology / Incidence / Risk factors

Kidney malignancy accounts for almost 2% of all malignancies worldwide. Renal cell carcinoma (RCC) accounts for approximately 80%. The highest rates for the disease are found in developed countries, i.e. Europe, Australia, North America, Japan and Scandinavia. In the USA, renal cancer is now the 7:th leading malignant condition or 2.6% of all cancers (3). Across the world there are over 200 000 new cases and more than 100 000 deaths annually from renal cancer (4). In the western world the incidence of kidney cancer has increased during the past four decades, specifically there is an increase of small RCC (4, 5), apart from Sweden and Denmark where the incidence has levelled out and slightly decreased since 1980 (6, 7). The incidence over the past 40 years in Sweden is illustrated in *Fig 1*. There is a male predominance of 2:1 and a peak incidence in the sixth and seventh decades (3, 8). Risk factors such as smoking, obesity and hypertension(9), as well as acquired cystic kidney disease associated with end-stage renal disease, have been identified. Other possible risk factors that need further investigation are analgesics, occupational exposures, reproductive factors and hormonal factors (7).

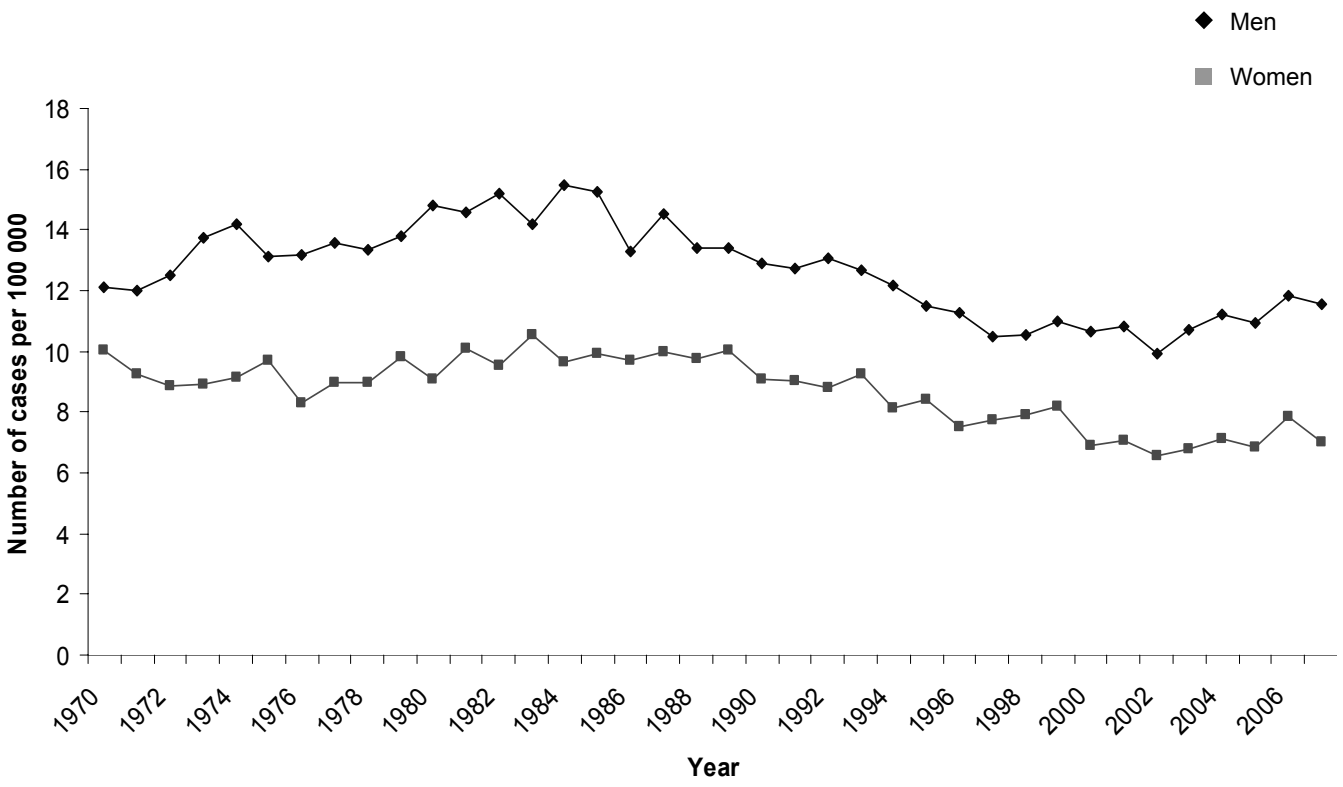

Fig 1 Incidence of kidney tumour in Sweden. (Courtesy SoS Epicenter, Sweden)

Classification

The RCC was, until the 1990s divided into four histological subtypes: clear cell, granular cell, tubulopapillary and sarcomatoid tumours based on cytomorphological characteristics and assumed origins of the cells (10). In 1993, Kovacs suggested a new classification based on a more fine interpretation of histological ultrastructure and genetics (11). After a revision in 1995 and the presentation of the Heidelberg document in 1997 (12), where a proposition of a histological classification based on genetic lesions was introduced, the system was finally approved and generally accepted in 1997 at the joint workshop by UICC and AJCC(13, 14).
Since then the following subgroups of malignant RCC are recognised (*Table 1*):

Conventional (clear cell) renal cell carcinoma (ccRCC), the most common type of carcinoma derived from the renal tubular epithelium, with a frequency of 70-75% and a male predominance of approximately 2:1. The tumours are mainly comprised by cells of clear cytoplasm, with a normally solid or cystic architecture. Bilateral involvement is seen in 2-4% of sporadic RCC, either synchronous or asynchronous, however more frequent in hereditary von Hippel-Lindau (VHL) tumour disease.
The von Hippel-Lindau (VHL) gene is a tumour suppressor gene in 3p, identified in1993 (15, 16). When a biallelic gene inactivation occurs a tumour phenotype is promoted. One allele may be inactivated through deletion (loss of material: heterozygosity), this is seen in 90% of sporadic ccRCC (17). The other gene may be inactivated through mutation (in approximately 50% of ccRCC) or through methylation (5-10% of the cases). The VHL is important for the transcription

factor: hypoxia-inducible factor (HIF) through an ubiquitin ligase complex which leads to the degradation of HIF. When the VHL gene is inactivated, the degradation of HIF will fail. The activated HIF translocates in the nucleus which will lead to transcription into different genes that in turn play part in the tumour progression. HIF targets both vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and transforming growth factor alpha (TGFα).
When the VHL gene was elucidated a number of pathways in the tumour biology was revealed and opened for new potential targets in treating RCC.

Papillary renal cell carcinoma represents approximately 12-15% and is hence the second largest group of renal tubular epithelium tumours in the entire group of RCC. The predominance is 5:1 for males and the papillary architecture is significant. Genetically they are characterised by trisomies in chromoses 3q, 7, 12, 16, 17, 20 and loss of the Y-chromosome. The chromosome 7 that hosts the MET proto-oncogene is duplicated in 75% of the sporadic papillary RCC. Two subtypes are identified as papillary RCC, type 1 and 2 (18). They differ in their structure and type 2 tumours are more heterogeneous genetically with less favourable prognosis and may emerge from type 1 (19). The MET gene causing type1 was identified in 1997 (20) and the fumarate hydratase (FH) gene, contributing to type 2 papillary RCC, was revealed in 2002 (21).
Hereditary papillary renal cell carcinoma (HPRC) is caused by mutation in the chromosome 7 that encodes for MET and leads to MET mutations. Subsequently this will express for MET protein (a tyrosine kinase receptor for hepatocytes growth factor). The hereditary leiomyomatosis and RCC syndrome (HLRC) increase the risk of cutaneous and uterine leiomyomas and solitary papillary RCC type 2. This autosomal dominant syndrome is caused by the FH gene encoding for fumarate hydratase, an enzyme in the Krebs cycle.

Chromophobe RCC is the third biggest entity among the RCC deriving from the renal tubular epithelium, intercalated cells type B, allegedly in most reports accounting for about 4-5%. The tumours mainly comprise of solid architecture. The genetics are characterised by monosomy (loss of heterozygosity) engaging multiple chromosomes (1, 2, 6, 10, 13, 17 and 21) hypodiploidy. The Birt-Hogg-Dubé (BHD) gene was identified in 2002, being the cause of the BHD-syndrome characterized by hair-follicle hamartomas on the face and neck (22). Approximately 15% of these patients have multiple renal tumours, mainly chromophobe or mixed chromophobe-oncocytomas (8).

Collecting duct carcinoma or Bellini's duct carcinoma is the smallest entity of the RCC group with less than 1%. The tumours derive from the medulla but may extend into the cortex. Their architecture is somewhat of cobblestone appearance. Genetically they present deletions on chromosome 1q and monosomy of chromosomes 6, 14, 15, and 22. However, the number of tumours yet presented is

limited and they are morphologically heterogeneous, thus the pattern of genetic abnormalities is inconsistent (1, 13).

Unclassified RCC are tumours that do not qualify for any of the other entities. They are reported to account for 3-5% of all RCC. Since the group contains a variety of morphological appearances and genetic lesions, limiting definitions are troublesome. Nevertheless, certain morphology will be recognised in this cohort as sarcomatoid tumours without recognisable epithelial elements, mucin production, mixtures of epithelial and stromal elements as well unidentifiable cell types.

Sporadic RCC				RCC in inherited syndrome	
Subtype	**Cell origin**	**Frequency (%)**	**Chromosome, gene**	**Syndrome**	**Gene**
Clear cell (conventional)	Proximal convoluted tubule	70-75	3p VHL	VHL disease FCRC	VHL Chromosome 3p translocation
Papillary	Distal convoluted tubule	12-15	3, 7, 12, 16, 17, Y MET TFE3	HPRC HLRCC	MET FH
Chromophobe	Intercalated cells, cortex	4-5		BHD	BHD
Collecting duct	Collecting duct	< 1			
Unclassified		3-5			

Table 1 *Sporadic and inherited syndrome of Renal cell carcinoma with cells origin, frequency and genetic origin. VHL: von Hippel-Lindau, FCRC: familial clear cell renal carcinoma, HPRC: Hereditary papillary renal cell carcinoma, HLRCC; hereditary leiomyomatosis and renal cell carcinoma, BHD: Birt-Hogg-Dubé, FH: fumarate hydratase gene, MET: MET proto-oncogene.*

Grade and stage

In 1932, Hand and Broders showed that grade of differentiation of the tumour cells in RCC is connected with the oncological outcome (23). A number of different grading systems (24-30) have since then appeared, reviewed by Novara et al.(31). The main part of these grading systems is based on the nuclear and nucleolar appearance with 1-4 grades. Jointly, for the different systems were survival that decreased with increasing grade as did high stage at diagnosis, metastases and local recurrence. At times there were many grading systems that led to controversies and in 1971 Skinner pointed out that it is "easier to invent one's own classification than to abide by another's" (28).

A generally accepted grading system was warranted and in 1997 at the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC), a document (32) was presented at the workshop in Rochester,

Minnesota, that recommended grading according to Fuhrman (26). This is now the most established and widespread nuclear grading system (*Table 2*) in North America as well as in Europe and acknowledged by the WHO. Even though the nuclear grading system is well accepted there are limitations to be considered in the clinical practice. The overall reported 5-year cancer specific survival is very variable. Stratified by grade, it differs between 65-100% in grade 1, 30-90% in grade 2 and 21-78% in grade 3 and 10-66% in grade 4 (26, 33-37). The inter-observer reproducibility is moderate likewise for intra-observer. The heterogeneity of the RCC tumour may contain areas of different grades and hence reflect the different survival probabilities stratified by grade. Quality of tissue fixation may also differ and affect the grading(38).

The staging system of kidney cancer was until the 1990:s mainly used according to the system implemented by Robson and co-workers in 1963 and updated in 1969 (39). The system originated from the scheme of Flocks and Kadesky (40) in 1958. Retrospectively the Robson system was limited, particularly at stage III where lymphatic nodes and venous involvement were not separated (*Table 3*). Hence the prognostic significance was lost and some authors reported similar survival for patients with stage II and III (28).

With the TNM system proposed by UICC the venous engagement was separated from those with lymphatic spread. At the previously mentioned workshop in 1997, the TNM system of 1997 was adopted and revised as the T1 was divided into T1a (tumor ≤ 4 cm confined to the kidney) and T1b (tumor > 4 cm but ≤ 7 cm confined to the kidney) (41, 42) (*Table 4a and 4b*).

Fuhrman's classification for nuclear grade in renal cell carcinoma

Grade	Nuclear Size	Nuclear Outline	Nucleoli
1	10 μm	Round, uniform	Absent or inconspicious
2	15 μm	Irregular	Small (visible at x400 magnification)
3	20 μm	Irregular	Prominent
4	≥20 μm	Bizarre, often multilobed	Prominent, heavy chromatin clumps present

Table 2 *Data from Fuhrman et al: Prognostic significance of morphologic parmeters in renal cell carcinoma. Am J Surg Pathol 1982;6:655-663.*

Tumor Status	Robson Stage	TNM Stage (1997)
Tumor ≤7 cm, confined to kidney	I	T1
Tumor >7 cm, confined to kidney	I	T2
Extension to adrenal gland or perinephric fat	II	T3a
Renal vein or vena caval involvement	IIIa	T3b
Vena caval involvement above diaphragm	IIIa	T3c
Single lymph node involved	IIIb	N1
More than one lymph node involved	IIIb	N2
Combination of venous and nodal involvement	IIIc	T3b or c, N1 or 2
Local extension beyond Gerota's fascia	IVa	T4
Distant metastasis	IVb	M1

Table 3 *Comparison of Robson and TNM staging systems for renal cell carcinoma. TNM; tumour, nodes, metastasis.*

Table 4a

TNM staging	
T –	**Primary tumour**
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1a	Tumour ≤ 4 cm, limited to the kidney
T1b	Tumour > 4 cm but ≤ 7 cm, limited to the kidney
T2	Tumour > 7 cm, limited to the kidney
T3a	Tumour invades adrenal gland or perinephric tissues, not beyond Gerota fascia
T3b	Tumour grossly extends into renal vein(s) or vena cava below diaphragm
T3c	Tumour grossly extends into vena cava above diaphragm
T4	Tumour invades beyond Gerota fascia
N –	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node
N2	Metastasis in more than one regional lymph node
M –	**Distant Metastasis**
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 4b

Stage Grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0, N1	M0
Stage IV	T4	N0, N1	M0
	Any T	N2	M0
	Any T	Any N	M1

Table 4a and 4b *– Revised TNM staging of 1997 and stage grouping.*

Prognosis – cancer specific survival

The probability for 5-year survival according to the TNM stage of 1997 has been reported to 91-95%, 74-90%, 59-67% and 20-32% for stage I, II, III and IV respectively (35, 42, 43), without subdivision to histological type. For MRCC the probability for 5-year survival drops dramatically to less than 10% (44).There are differences in survival regarding histological subtypes (45, 46) with a generally slightly higher 5-year survival in papillary and chromophobe tumours compared to ccRCC, however none of the references here had subdivided papillary tumours. The overall 5-year survival has improved both in Europe from 41% to 57% between 1978 and 1989 and in the United States it has increased from 52% to 63% between 1974 and 1999 (7). Possibly the change is accounted more for earlier detection and improved surgical technique than introduction of systemic therapy (47).

Treatment

Surgical treatment

Localised disease

Surgery is still the only way to treat RCC with curative intent if the disease is localised. After initially performing simple nephrectomy, Robson et al (39) presented improved survival by perifascial nephrectomy (including the Gerota's fascia, perirenal fat and adrenal) in 1969. This technique is since long the accepted procedure when performing nephrectomy. At the introduction of the laparoscopic technique, the nephrectomy was soon incorporated to the possible procedures to be performed with this less invasive technique. In 2007 a prospective randomised trial with laparoscopic versus open nephrectomy was performed, suggesting a lower morbidity for the patients, even though there was no statistical power for concluding the oncological outcome on follow-up (48). However, retrospective study of tumours of pT1-pT4 has shown promising results on seven years follow-up (49). Though, some reports suggest an increase in complications when nephrectomising larger tumours laparoscopically (50).

A possible venous thrombus should be resected at the time of nephrectomy (51). Ipsilateral adrenalectomy is normally performed if the tumour is positioned in the cranial part of the kidney even if the benefit of adrenalectomy has been under debate (52). Lymph node dissection is recommended if there is a suspicion of regional lymph node metastases on pre-operative imaging or per-operatively (53, 54).

If the disease is localised and extirpation judged feasible, i.e the tumour is favourably localised, partial nephrectomy is today performed in many centres where the competence is available (55-57). The tumour is resected with a brim of normal kidney tissue in order to be radical but still with the intention to save nephrons. This procedure may be performed laparoscopically in selected cases and 5-year survival data coming from high volume centres is promising.

Metastatic disease (metastasectomy and debulking / cytoreductive surgery)

Metastasectomy in RCC is generally recommended in case of solitary metastases. A clear disease-specific survival benefit, among the patients with a metastasis-free interval of over two years from diagnosis to metastasectomy has been shown, in comparison with those presented with metastases within two years (58). In many patients subjected to metastasectomy the intent is palliative, but may be of rather immediate necessity, such as maintaining musculoskeletal integrity when a pathological fracture has occurred or to control overwhelming pain (59), hematuria or possible a paraneoplastic syndrome. There are reports on survival after metastasectomy in lungs with an overall 5-year survival of 36% as well as 22 months of average survival after surgery of osseous metastases (60). Thus, metastasectomy may provide long-term survival in selected cases.

One rationale for debulking surgery (cytoreductive surgery as nephrectomy in MRCC) was the unique behaviour of MRCC where metastases, in the lungs, may

undergo spontaneous regress after nephrectomy, due to possible factors such as cytokines and vascular endothelial growth factors released by the renal cell carcinoma. However, this phenomenon is seen in less than 2% of the patients.
In a study, the volume of the primary tumour and of the metastases was measured on radiographs and the fractional percentage of tumour volume removed (FPTV) by nephrectomy was calculated (61). A difference was seen between those patients that had >90% and those with <90% removed in PFS with 11.6 and 2.9 months respectively. Two prospective randomised trials have been performed where the patients were randomised to cytoreductive surgery plus post-operative immuno-therapy (IFN) or immuno-therapy (IFN) alone. The median survival for surgery plus IFN was 11.1 and 17 months respectively, 8.1 and 7 months for IFN alone for the two trials, statistically significant (62, 63). A combination analysis of the trials showed a median survival of 13.6 and 7.8 months, which was statistically significant (64). It is now acknowledged to offer nephrectomy to selected patients with MRCC. The role for nephrectomy prior to other forms of systemic therapy is still unknown.

Ablative techniques

Ablative techniques were the next techniques to emerge as a possible treatment option for small kidney tumours. Patients that are prone to these treatments are highly selected. The tumour is treated with induced heating, e.g. by radiofrequency ablation (RFA), high intensity focused ultrasound (HIFU) or freezing by cryosurgical ablation (CA) and left in situ after treatment. The techniques (RFA and CA) can be performed either openly, laparoscopically, percutaneously or extra corporeally (HIFU), the latter being the most minimal-invasive procedure.

RFA is based on the deployment of energy leading to thermally caused damage, through an electrode introduced into the tissue (65). A generator of 150-200W is needed for sufficient ablation. The systems can either be temperature or impedance-based. The temperature-based systems measure the tissue temperature at the tip of the needles (66), whereas impedance-based systems measure the tissue resistance around the electrode (67). Resistive forces in the tissue produce heat through electrode near ionic agitation, which results in molecular friction, producing heat. Between 60^{o}C and 100^{o}C induction of protein coagulation with irreversible damage, e.g. coagulation of cytosolic and mitochondrial enzymes, will occur. Thus, electrode temperatures at approximately 100^{o}C are generally required to assure at least 60^{o}C at the periphery of the ablation zone (66, 68).

A temperature rise to, or in excess of 105^{o}C will result in tissue boiling, vaporisation and carbonisation will be the result (69). This phenomenon will decrease the ablation effect due to reduced energy transmission (70). It may be possible to subdue this by cooling the tissue nearby the electrode, e.g. internally cooled electrodes with chilled perfusate. The heterogeneity of heat deposition with a rapid energy falloff from the probe and poor heat conduction in the tissue is a

negative important factor to overcome to reach a successful ablation. The gas that is produced by the vaporisation also contributes to isolate the tissue, precluding further heat spread. Besides tissue limitations, the design of the electrode device itself may serve as a restrictive variable i.e. a single electrode produces coagulation up to 1.6 cm in diameter (69).
To increase energy deposition, it is possible to use repeated insertion of a single electrode or electrodes with expandable tines that unfolded in the lesion to reach overlapping ablation. Pulsating energy deposition also contributes to more favourable tissue destruction.
Well vascularised tissue with its' blood-flow is a negative factor in ablation therapy, which adds to heat-sink. Modulation of blood-flow may be explored through angiographic balloon occlusion and embolotherapy, pharmacological modulation and antiangiogenic therapy are also theoretically possible but not a routine in ablation procedures.
Imaging techniques in the ablation setting should fulfil three tasks; targeting of the lesion, guidance of energy deposition during the treatment and assessment of follow-up. Initially, most ablations were performed in ultrasound (US) guidance, however most reports on treatment with RFA are performed with CT today. With US the interventionist will have a real-time visualisation, the cost is low, the technique is portable and the availability is universal, performance with contrast enhancement is also possible. Repeat treatment is reasonably easy but occasionally US will give poor lesion visualisation. MR imaging normally gives a better tumour-to-tissue conspicuity and allows for multiplanar guidance. The technique is rather costly and requires equipment compatible with high magnetic field. Morevoer, it is less available than US. Radiofrequency ablation under CT guidance is today the most frequent form of guidance. Follow-up is primarily performed by contrast-enhanced CT to discriminate between ablated and residual viable tumour even though the need for post-ablation biopsies on follow-up has been proposed (71). In spite of increased use of RFA the technique should still be considered as a technique under development.

Cryosurgical ablation is a cycle of freeze and thaw performed with either liquid nitrogen or argon gas, circulating in the probes placed in the tissue. The extracellular space freezes, the osmolarity increases resulting in an oedema in the extracellular compartment. A change in pH, protein denaturation and the hypertonic intracellular milieu damages the cells, apart from the damage caused by mechanical disruption of the cell membrane. Tissue injury continues due to microvascular injury, in the hours and days post-ablation (72, 73). The technique is primarily performed via laparoscopy (74).

HIFU may also be used to induce tissue lesions. The focusing of energy increases the temperature to 90^{o}C. A thermal and a cavitational lesion are caused. There are difficulties in imaging lesions for the precise targeting destruction (75). Even though the technique is the most minimal-invasive treatment as it is performed

completely extracorporeally, it is far from general availability. However, the development of HIFU as a potential minimal-invasive treatment modality in the future is anticipated (76).

Systemic therapy

Only patients with MRCC are subjected to systemic therapy.

Cytokines

Five years ago patients with MRCC were mainly referred to treatment with either Interferon-alpha (INF-α) or Interleukin-2 (IL-2). Interferon is a glycoprotein divided into three major groups: INF-α, INF-β and INF-γ, derived from leukocytes, fibroblasts and T-lymphocytes respectively. INF-α has appeared as the most efficient in the group of INF in antitumour RCC (77). INF:s have an immunological effect with activation of host mononuclear immune cells, natural killer cells or macrophage tumoricidal properties (78). INF also have an antiangiogenic (79) as well as a directly antiproloferaitve (80) effect. Pyrhonene et al (81) showed in 1999 in a randomised trial with INF plus vinblastine (VBL) versus VBL alone a response rate (RR) of 16.5% versus 2.5% with benfit of overall survival of 7 months in favour of INF plus VBL and an overall survival of 56% versus 38%. Collaborators MRCRC (82) tried INF versus medroxyprogesterone (MPA) in a randomised study which gave a survival benefit for INF of 2.5 months and an overall one-year survival of 43% versus 31%.

A systemic Cochrane review (83) for immunotherapy, totally 58 trials, in advanced RCC was performed in 2005. Four trials, 644 patients, verified the superiority of INF-α in comparison to control, a pooled analysis demonstrated a significantly reduced one-year mortality (odds ratio (OR) for death at one year was 0.56, 95% CI 0.40 to 0.77). However, INF-α as monotherapy only showed a modest survival benefit, neither was there any improvement after adding low-dose interleukin-2 intravenously or subcutaneously regarding overall survival in comparison to INF-α as monotherapy, even though the response rate was increased (83).

The plasma half time of interferon is approximately 3-7 hours. Interferon is preferably administrated subcutaneously in dosages of 3-5MU. The half time requires drug administration of 3-4 occasions weekly (79).

By conjugating interferon through pegylation (attaching polyethylene glycol), the pharmacokinetic properties and pharmacodynamics are modified (84). These changes result in prolonged plasma half time, to approximately 40 hrs (85). The increased area under the curve (AUC) may suggest a better inhibition of angiogenesis as repeated injections of the conventional form of interferon (86, 87). The Peg-interferon allows for once weekly subcutaneous administration with acceptable safety (85). However, the tolerable dose in patients with MRCC is still not known.

Interleukin-2 (IL-2) also belongs to the group of cytokines that have proved to be efficient in the treatment of MRCC. IL-2 is secreted by T-lymphocytes stimulating the activity of macrophages, killer T cells and B cells. IL-2 is administrated both as high-dose intravenously (iv) and as low-dose subcutaneously. A number of trials have included high dose IL-2 arms, (88-91). However, these studies were restricted to patients with high performance status due to the toxicity of the drug. Toxicity in

patients treated with high dose IL-2 is bothersome, specifically when administering iv bolus doses (92). In a study 4% were suspected to have died due to adverse events related to IL-2 and 15% were in need of treatment in the intensive care unit. However, subcutaneous (sc) administration of low dose IL-2, in self-administration outpatient clinic has proved to be feasible treatment with documented safety (93).
Even though it is acknowledged that IL-2 is the only reported therapy with occasionally durable CR (88, 91, 94), the occurrences are infrequent and seen in a highly selected population.
No up-front studies have been performed that directly compare high dose IL-2 with INF-α. There are studies that compare INF-α versus IL-2 at reduced dose ("low dose") (95, 96). No difference in remission was seen analysing these studies but the toxicity was remarkably higher for IL-2 than for INF-α. For the role of nephrectomy prior to cytokine treatment please see the subtitle of debulking surgery under the section of "Surgical treatment", (page 21).

Targeted therapies
After the discovery of the VHL gene the knowledge of the biological pathways and its underlying molecular biology of the RCC disease increased remarkably. As a result of this, the pathways of the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) were identified as possible therapeutic pathways for developing targeted therapies. Today five drugs targeting the pathways above are in clinical use for patients with MRCC. All are expensive.

Sorafenib (Nexavar®) is an inhibitor of the intracellular signalling enzyme raf kinase and against several receptors involved in vascularisation and tumour progression such as VEGFr-2 and -3 and PDGFβ (97). The drug is administrated orally, 400 mg twice daily. A phase III study showed a PFS of 5.5 months versus 2.6 months in the placebo group (98). Toxicity includes e.g. fatigue, hand-foot syndrome, diarrhoea, hypertension which is similar to that of Sunitinib but with less severity (99).

Sunitinib (Sutent®) is a small-molecule targeting the tyrosine-kinase part of the VEGF family of receptors inhibiting a number of receptors, e.g. VEGFr-1 and -2, platelet-derived growth factor receptors (PDGFr). The patients are treated with 50 mg for four weeks followed by two weeks off. In a phase III trial, sunitinib versus INF-α, the patients showed a progression-free survival (PFS) of 11 months vs 5 months (100). Toxicity is bothersome , including fatigue, hand-foot syndrome, diarrhoea, hypertension, hypothyroidism and decreased cardiac output (101).

Bevacizumab (Avastin®) is a monoclonal antibody binding to and neutralising circulating VEGF (102). Bevacizumab is administrated iv in a dosage of 10 mg/kg every two weeks. The drug is used in combination with interferon in the treatment of MRCC. In a phase III study bevacizumab plus INFα versus placebo plus INFα

showed a response rate of 31% versus 13% and PFS of 10.2 versus 5.4 months (103).

Temsirolimus (Torisel®) inhibits mammalian target of rapamycin (mTOR) which is a molecule implicated in several tumour-promoting intracellular signalling pathways. The activated mTOR leads to translation and phosphorylation which results in HIF production and regulators of cell-cycle. Temsirolimus prevents the activation of one subpopulation of mTOR proteins leading to a decrease in the production of HIF and influencing on cell growth (104). A phase III study with patients with MRCC and poor risk, Temsirolimus was tried alone (25 mg iv) versus interferon alone versus Temsirolimus 15 mg per week plus interferon. Patients on Temsirolimus had PFS of 3.8 months versus 1.6 months for INF alone. Serious toxicity as anaemia, asthenia and dyspnoe is seen and hypercholsterolaemia, hyperlipidaemia and hyperglycaemia are also common. The latter indicating the drugs inhibition of lipid and glucose metabolism.
Everolimus (Afinitor®) is an oral rapamycin inhibitor that has shown increased PFS versus placebo in patients previously treated with targeted therapy (105).

Adjuvant and neoadjuvant therapy

A number of different adjuvant approaches have been tried during decades. Radiation did not prove to be effective, RCC is largely resistant to radiation and this therapy is now mainly left for palliative treatment, of bone and cerebral lesions.
Medroxyprogesterone acetate (MPA) has been tried based on the rationale that RCC cells have hormonal receptors, however no benefits regarding recurrence-free survival, instead significant toxicity due to MPA was concluded (106).
Interferon has also been tried for adjuvant treatment however without signs of improvement on survival (107, 108).
Patient-derived vaccines have also been tried without any significant results that have had a general impact on treatment schedules (109), apart from one study showing significant PFS for the vaccine arm (110), however this has so far not been repeated and was criticised with regard to its performance. Neither has chemotherapy, alone or in combination had any significant effect (111).
Results from ongoing trials are anticipated in the next couple of years where adjuvant therapy (e.g. Sorafenib and Sunitinib) is used in locally advanced RCC (112).

The role of neoadjuvant (presurgical) therapy with targeted therapies in local disease is as yet unknown. However, neoadjuvant treatment in the context of locally advanced disease or MRCC is also being investigated in a number of phase 1-2 trials with targeted therapies. Neoadjuvant therapy may provide information of patient selection, i.e. which patient is responding to therapy and thus likely to benefit from the following surgery. The patient (and surgeon) may benefit from pre-operative down-staging of the tumour (113, 114). There is now data on neoadjuvant therapy (with bevacizumab, sunitinib and sorafenib) in patients with

MRCC. The patients were divided in two groups; one received up-front surgery and the other presurgical treatment. The results showed similar median cancer-specific survival between the two groups and no difference in co-morbidity. The authors suggest that the pre-surgical therapy is safe (115, 116).

AIMS OF THE STUDY

The objectives of this thesis were:

I. To assess the long-term results in patients operated with NSS in situ for RCC, with special reference to their dependence on tumour grade and stage.

II. To investigate 18-FDG-PET/CT as an option to evaluate treatment effects in patients with MRCC treated with targeted therapy, as sorafenib.

III. To assess tolerability, efficacy and the optimal dose for long-term treatment, when treating MRCC patients with Peg-interferon alfa-2b.

IV. To disclose imaging characteristics, predictive factors for local recurrence and repeated treatment in small renal masses treated with RFA.

PATIENTS AND METHODS

Paper I

Eighty-seven patients that had been subjected to nephron-sparing surgery (NSS) between 1980 and 1999 were analyzed according to stage, grade, synchronous / asynchronous metastases, uni- or bilateral tumours, single or normal contralateral kidney. Nine patients were in spite of their M+ stage subjected to surgery as metastatic surgery was being contemplated or systemic therapy in progress. Of the remaining 78 M- patients, 68 patients had one tumour in the kidney subjected to NSS and 10 had two or more. Forty-three patients had bilateral, 28 synchronous, and 44 had unilateral renal cell carcinoma (RCC).

The patient was treated with allopurinol preoperatively to decrease the formation of oxygen free radicals during reperfusion (117). As scavenger 15% mannitol (118, 119) was given before vascular clamping and before reperfusion. The kidney vessels were clamped and the kidney cooled with ice. After resection of the tumour with a 0.5 cm rim of normal tissue, the cavity was closed with interrupted suture or left open. In two cases enucleation was performed by splitting the pseudocapsule and in two cases the NSS was performed in a circulated normothermic kidney.

The patients were followed annually or every second year with computed tomography (CT) or in a few cases with ultrasound (US) of the abdomen and chest radiography. Case records and post-mortem reports were available for deceased patients. Tumours were mainly classified according to the 1992 WHO TNM system and not to the new classification of 1997(120). Grading was performed according to Skinner et al. (28). Survival analyses according to Kaplan-Meier were performed.

Paper II

Ten patients with progressive disease, eight after cytokine treatment, were enrolled in the study. Totally 52 lesions were studied, 39 soft tissue lesions were available for assessment with response evaluation criteria in solid tumours (RECIST)(121) and positron emission tomography (PET) as well. Thirteen skeletal lesions were assessed separately since they could not be evaluated with RECIST criteria.

[^{18}F]-2-flouro-2-deoxyglucose (FDG)-PET/CT was performed before treatment and after 1-2 months on all patients. Further follow-up was performed with contrast CT after 3, 6 and 9 months.

Sorafenib (Nexavar®, Bayer HealthCare Ltd) was given 400 mg bid orally. No dose reductions were done between first and second PET.

CT: The diagnostic CT performed before and after FDG-PET/CT was done with full-dose radiation and i v contrast, in full inspiration during the thoracic investigation.

Measurable lesions were identified and the largest diameters were measured in axial images. The sum of the largest diameters was calculated from CT images according to RECIST criteria.
Each patient's mean change in lesion size from baseline in the targeted lesions was calculated. Whilst evaluating with CT, before and after FDG-PET/CT, the multislice technique was used with a maximum thickness of 5 mm slices.
PET-CT: PET-CT-scans were obtained with a dedicated PET/CT system. Images were acquired from the skull base to the upper thigh close after intravenous injection of 5MBq 18F-FDG/kg/bw. A low-dose CT scan during quiet breathing was concurrently obtained and used for attenuation correction and anatomic localization and also for identifying measurable lesions where the largest diameters were measured in axial images and reconstructed. Imaging was repeated 1 month after treatment with sorafenib.
Glucose uptake: To evaluate the glucose uptake in the metastatic lesions, a region of interest (ROI) was applied to each lesion on the transverse section, where the lesion appeared to have the largest uptake according to size and intensity. The ROI (circular or ellipsoid or in a few cases polygonal) was drawn at a level that separated the lesion from the background activity. However, in low background areas it was drawn at a level of approximately 20% of maximal intensity in the ROI. The ROIs were copied and applied to the same lesion in the subsequent examination.
Indexes of glucose uptake were calculated by dividing the mean and maximal activity in the regions of interest with the mean cerebellar activity.
The mean cerebellar activity was calculated by visually assessed transverse sections through cerebellum, sections where it appeared to have the largest FDG uptake according to size and intensity was selected. Using the colour scale Step 10 a ROI was drawn around the cerebellum following the border between those levels in the colour scale that enclosed nothing more than activity in the cerebellum. The mean activity inside the ROI was regarded to represent the mean cerebellar glucose uptake.

Paper III

Patients with metastatic renal cell carcinoma (MRCC) were eligible for this study, they had either a single lesion with a diameter of ≥20mm or multiple lesions with a diameter of ≥10mm. No prior immunotherapy was allowed and preferably they should have been subject to nephrectomy but this was not a requirement. Life expectancy should be minimum 3 months. Performance status (PS) of >1 according to Easter Cooperative Oncology Group (ECOG) were not compatible with eligibility. Adequate haematological, renal and hepatic function was required.
Twenty-eight patients were enrolled in the study between 2002 until 2005 and followed until 2008. The main part of the patients had >1 metastatic site, eleven patients had their metastases limited to the lungs.

Peg-interferon alfa-2b was administrated subcutaneously at a starting dose of 0.5 µg/kg/w and was escalated in increments of 0.5 µg/kg every two weeks until a dose of 2 µg/kg /w was reached or prohibitive toxicity occurred. Treatment was continued at maximum tolerable dose (MTD), until progression of disease. Doses were adjusted to allow for long-term treatment with acceptable side effects and quality of life. The patients were able to administrate the treatment themselves.
Adverse events were graded for severity according to National Cancer Institute´s Common Toxicity Criteria (NCI-CTC) version 3.0 classification and managed by dose reduction until resolved (grade 0-1), at which time the dose was to be increased to MTD.
CT of abdomen and thorax was performed every three months and reviewed by an independent radiologist. Tumour response was calculated according to RECIST(121). Confirmation of stable disease (SD) and partial response (PR) was set to six months after the first dose of Pegintron®.
Blood samples for analysis of vascular endothelial growth factor (VEGF) were collected prior to first Pegintron® dose and every month throughout the treatment. The serum samples were stored at -80ºC until analysis, which was performed according to the established technique, using a commercial quantitative immunoassay kit for human $VEGF_{165}$ (Quantikine®, Human VEGF immunoassay, R & D Systems, Minneapolis, MN)(122).
The Gehan two-step procedure was used (123) to determine the size of the material. Initially, 14 patients were treated and accrual of further patients to the study continued if one responding patient was seen among the first 14 patients. Under these conditions the probability of rejecting a treatment with a response rate of 20% was less than 5%.
Response rates and adverse events were analysed with descriptive statistics. Survival rate was estimated with the Kaplan-Meier method. The non-parametric Mann-Whitney U test was used for testing the differences between groups.

Paper IV

Patients with co-morbidity and a substantially increased surgical risk and patients with solitary kidney that prior had been subject to surgery or had severely reduced renal function or hereditary predisposition to multiple RCCs were included.
The main co-morbidity was cardiovascular diseases (28 patients). Previous medical history of malignancy was found in 28 patients. Twelve of them had previously been treated for kidney cancer, all but one was nephrectomised and one had bilateral resection. Four of the nephrectomised patients had later undergone nephron-sparing surgery on the contralateral kidney, i.e. on the kidney exposed to radiofrequency ablation (RFA).
Patients with limited metastatic disease, were treated with RFA to achieve local tumour control and decrease the risk of decline in renal function.

Laboratory assessment was obtained in all patients and estimated glomerular filtration rate (GFR, ml/min/1.73m² body surface) (124) was calculated according to the National Kidney Foundation (125).
Forty-three consecutive patients (27 male, 16 female) were included for RFA treatment. The mean age of the patients was 68.8 years (range 27-86 years). In total, 46 tumours in 43 patients were treated with RFA *(Table 5)*.
Maximum pre-treatment tumour diameter was four cm, assessed with CT (n=34) or magnetic resonance imaging (MRI) (n=9). Pre-treatment the diameter was measured on the scan slice and the volume was analysed by manually delineating its borders, using the volume-application of a GE Advantage Windows workstation (GE Medical Systems, Milwaukee, Wis, USA).

		No of patients
Patients		43
Age in years, mean, (range)		69 (27-86)
Gender (F/M)		16 / 27
Side (Right/Left)		17 / 29
Position on kidney (n=45[1])	(cranial / middle / caudal)	13 / 18 / 14
Location in parenchyma (n=45[1])	(exophytic / parenchyma / central / mixed)	35 / 5 / 2 / 3
Co-morbidity	≤ 2 diagnoses	24
	> 2 diagnoses	19
	Cardiovascular diseases	28
	Pulmonary disease	3
	Renal impairment (unrelated to surgery)	4
	Cerebro Vascular Lesion	6
	Meningioma	1
	von Hippel Lindau	1
	Previous medical history with any type of malignancy	28
Prior kidney surgery		13[2]
History of kidney cancer		12
	Nephrectomised	7
	Nephrectomised + resected	4
	Resected bilaterally	1
	Metastatic RCC	6

[1]One patient had local recurrence after previous nephrectomy.
[2]One patient had lymphoma, all others kidney cancer.

Table 5 *Patient characteristics, n=43, (46 tumours).*

The location of the tumour in the kidney was classified by dividing the length of the kidney into thirds: upper 13(29%), middle 18(40%) and lower regions 14(31%) (126). The tumours were also categorised as being exophytic, parenchymal, central, or mixed, based on a previously described classification system (127). One tumour was a local recurrence in the cavity after previous nephrectomy.
All tumours were visualized with US and were assessed suitable for US-guided treatment except for two that were treated with CT-guidance.
The treatment was performed in general anaesthesia by one of two radiologists with former RFA experience on liver tumours. A percutaneous, 18-gauge biopsy was obtained immediately before the first RFA in all but two of the patients.
Most RFA sessions (n =49) were performed either using 17-gauge single (with a 3.0 cm electrode-tip) or cluster (with three 2.5cm tips) internally cooled probes (Cool-tip, Covidien, Boulder, CO, USA). Tumours 3 cm or smaller were treated with a single probe (127). If necessary, the probe was repositioned to create overlapping ablations. In 6 patients RFA was performed with an expandable, multitined 14-gauge probe (RITA StarBurst XL, AngioDynamics, Queensbury, NY, USA). The ablation was performed according to the manufacturer's operating recommendations, with consecutive deployment of electrode tips to create a lesion 0.5 to 1.0cm larger than the measured tumour diameter. Neither US, nor CT findings allow for prediction of the precise margins of the zone of ablation during RFA (127). The transient hyperechoic area seen at US during RFA and the lack of contrast enhancement following RFA at CT, was used to estimate the extent of tumour ablation induced.
On the day following RFA, CT or MRI before and after injection of intravenous (iv) contrast material was performed. Lack of enhancement on post-injection scans (<10 HU increase for CT or < 15% signal increase on MRI) was considered as evidence of complete tumour ablation (126). In accordance with the recommendations of the Working Group on Image-Guided Tumour Ablation (128), technical success of the RFA was considered to be present if the ablation zone covered the tumour completely. The volume of the RFA-induced coagulation necrosis was calculated using the volume-application of the GE Advantage Windows workstation. A necrosis index was obtained by dividing the volume of necrosis by the pre-treatment calculated tumour volume(129). A second observer, blinded to the results of the first observer, measured the volumes of tumours and necrosis in 20 of 43 randomly selected patients to allow for assessment of inter-observer agreement. No significant differences were detected.
Follow-up imaging with either CT or MRI was scheduled at 3, 6, 9 and 12 months after RFA and every 6-12 months thereafter (130). Local tumour recurrence was defined as growth of the tumour or any new enhancing portion demonstrated within or immediately next to the treated area, occurring after initial imaging had demonstrated complete tumour ablation. Repeat RFA session was considered for those patients. The primary technical success rate was the proportion of completely ablated tumours after the first ablation session assessed at the 3-month imaging.

The secondary technical success rate was the proportion of completely ablated tumours after repeated ablation session(s) (128).
Data are presented as mean, median, standard deviation and range. Progression-free survival rate was estimated with the Kaplan-Meier method. Intergroup comparison was performed by the use of the non-parametric Mann-Whitney test. Comparison between groups for categorical variables was made by chi-squared test or Fisher´s exact test, as appropriate. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 15.0 (SPSS Inc., Chicago, IL, USA). A p value of < 0.05 was considered to be statistically significant.

RESULTS

Paper I

At the time of writing the manuscript, 54 patients (62%) were alive, 90% of them without signs of recurrent disease. Twenty patients (61%) had died from RCC and 13 (39%) from intercurrent diseases. Cancer-specific survival (CSS) was 80% and 75% at 5 and 10 years respectively in M0 patients whereas the 5-year CSS in patients with bilateral disease was 70%, regardless of synchronous or asynchronous tumours. Crude 5- and 10-year survival was 70% and 50% respectively.

Survival was strongly correlated to stage and grade. No patient in stage 1 died within 10 years, whereas 7/12 patients in stage 3 had died from cancer within 5 years (*Fig 2a*). No patient with grade 1 disease died from RCC, while the 5-year survival for grade 3 disease was only 65% (*Fig 2b*). No patients with M0 and single tumour had died from cancer within 5 years, in contrast to patients with multiple tumours. Approximately 25% of the patients with M+ disease were alive after 5 years.

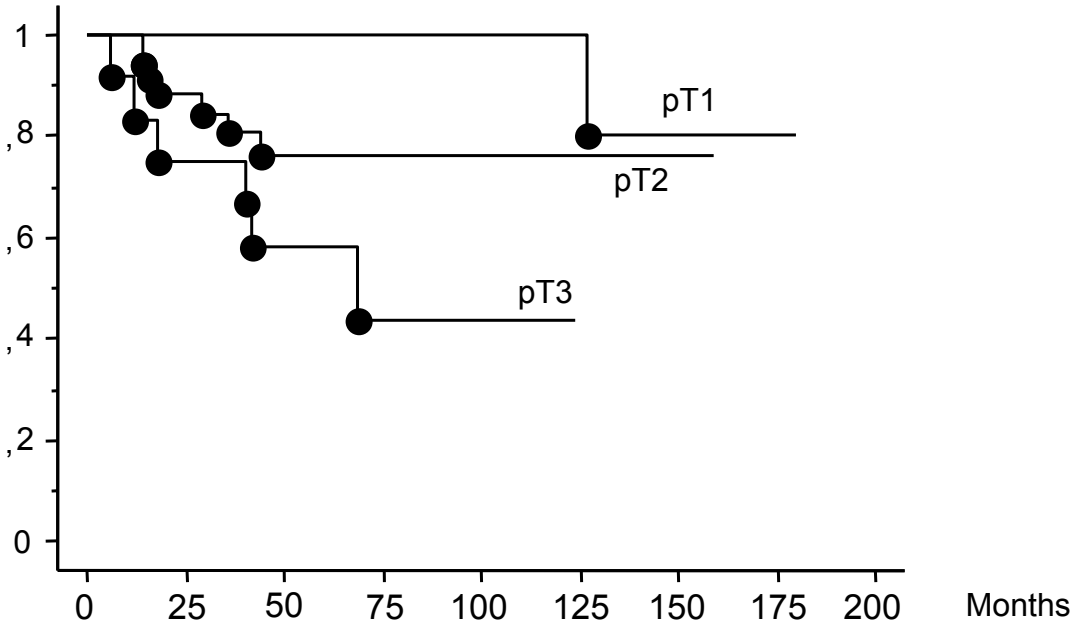

Fig 2a *Cancer-specific survival in the 78 M0 patients related to stage: pT1 (n=32), 14 patients are at risk after 5 years and five after 10 years; pT2 (n=34), 15 patients patients are at risk after 5 years and five after 10 years; pT3 (n=12),five patients are at risk after 5 years and one after 10 years.*

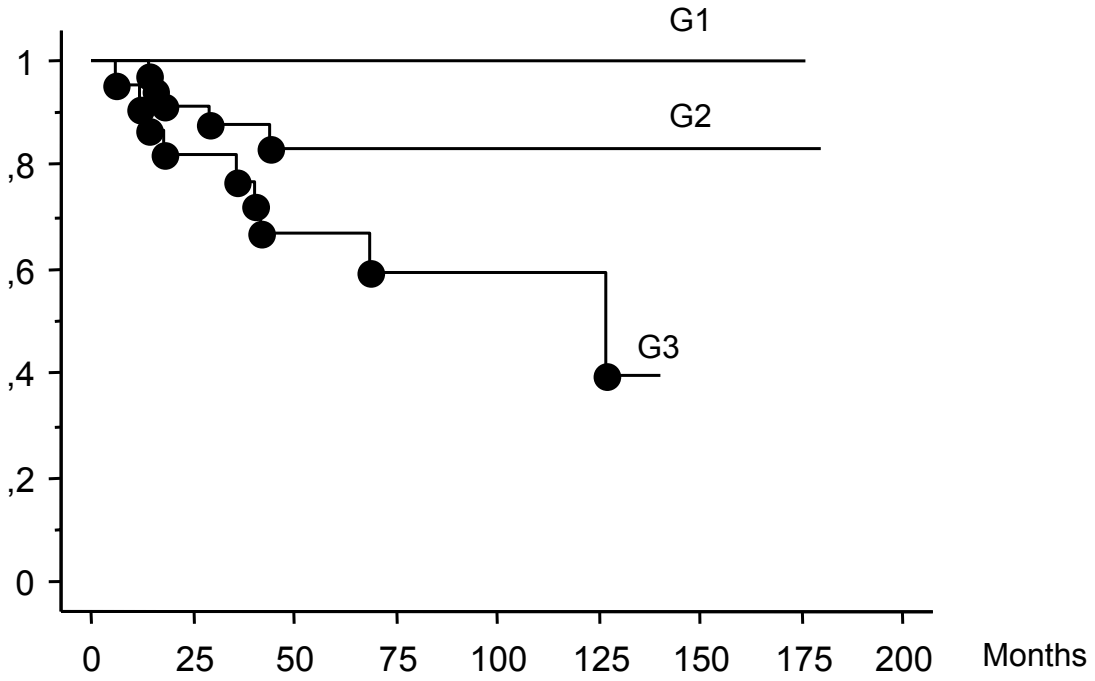

Fig 2b *Cancer-specific survival in the 78 M0 patients related to grade: G1 (n=19), eight patients are at risk after 5 years and four after 10 years; G2 (n=37), 16 patients are at risk after 5 years and four after 10 years; G3 (n=22),10 patients are at risk after 5 years and three after 10 years.*

Paper II

After 1-2 months (median 39.5 days), the sum of the diameters of *soft lesions* measured by CT was mean 80% (57-94%) of the initial value (*Table 6*). In corresponding lesions the mean and the maximum glucose uptake decreased to 71% (32-108%) and 80% (23-131%) respectively of the initial values as measured by FDG-PET (Table 2). The change in uptake between different metastatic sites in the individual patients varied more when the maximum uptake of the ROI was used compared to the mean uptake. In all lesions (soft and skeletal) the mean uptake decreased to 75% (32-105%) and the maximum uptake to 86% (46-131%) compared with the initial values. The reduction in glucose uptake was similar in the peripheral and the central parts of the lesions.

In *skeletal lesions* (*Fig 3*) the mean glucose uptake was 82% (53-101%) and the maximum uptake was 90% (72-101%) after 1-2 months' treatment (*Table 6*).

The five best responders with a decrease of ≥20% according to FDG-PET, had an overall survival of mean 18.1 (15-21) months compared to 12.9 (11-21) months for the five patients with least response. The decrease in glucose uptake did not correspond to an increased progression free survival (PFS).

Eight patients had reached a state of progression, CT-verified, according to RECIST or clinically after median 7.3 months (3-12 months). One patient was still in SD after 18 months and one had only skeletal lesions, thus not possible to assess according to RECIST.

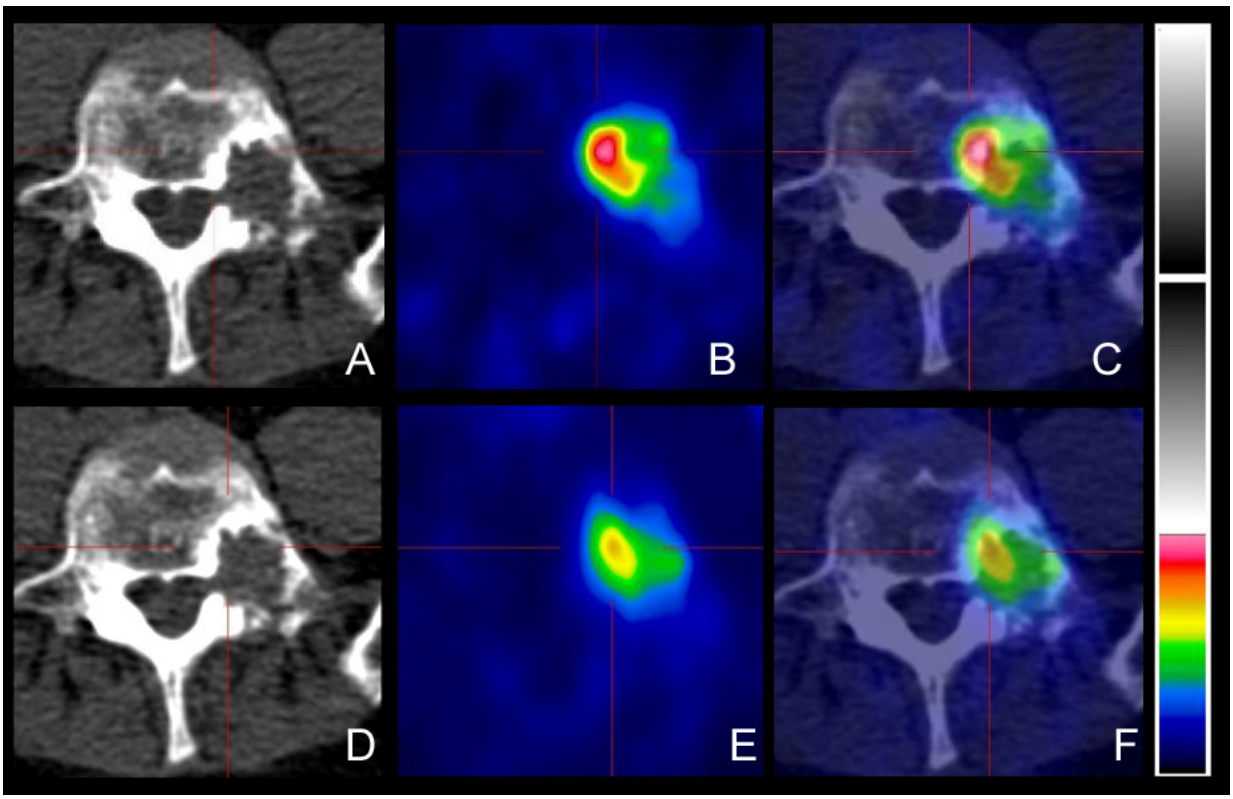

Fig 3 *Bone lesion lumbar vertebrae, L3, CT, PET and fusion of CT and PET. Pretreatment: (a-c) and posttreatment: (d-f). Mean glucose uptake decreased to 74% of pretreatment value. CT, computed tomography; PET, positron emission tomography*

Pat	CT	PET			
		Soft Lesions		Skeletal Lesions	
	Soft Lesions[a]	Max[b]	Mean[b]	Max[b]	Mean[b]
1	87	46	33	NA	NA
2	92	98	94	NA	NA
3	86	71	74	95	85
4	67	23	32	101	101
5	83	83	79	NA	NA
6	94	106	84	72	74
7	NA	NA	NA	94	81
8	83	55	61	76	53
9	73	106	108	100	99
10	57	131	72	NA	NA
Average	80 (p=0.008)*	80 (p=0.173)*	71 (p=0.015)*	90 (p=0.080)*	82 (p=0.058)*
n	9	9	9	6	6
Range	57-94	23-131	32-108	72-101	53-101

[a]Average change in diameters in all evaluable soft lesions in each patient
[b]Average percentage in glucose uptake in all evaluable lesions in each patient.
*P value according to the Wilcoxon rank test.

Table 6 *Changes on CT according RECIST and in glucose uptake measured by PET at 1-2 months. (Percentage (%) of initial value). CT, computed tomography; Max, maximum; NA, not available; PET, positron emission tomography; RECIST, Evaluation Criteria in Solid Tumors.*

Paper III

Thirteen patients (46%) managed to reach a weekly dose of 2 µg/kg/week. Nine patients (32%) reached the interval of ≥ 1.5 < 2.0 µg/kg/week and two patients the interval of ≥ 1.0 < 1.5 µg/kg/week. 13/28 patients (46%) needed a dose reduction at some time.

Sixteen patients continued the treatment for 6 months or longer and of these 11 (69%) needed dose reduction at some stage. This subgroup had an average dose of 1.5µg/kg weekly for the entire treatment period. Among these 16 patients the dose at the end of the treatment was average 1.2 µg/kg/week. The twelve patients that were assessed as progressive disease (PD)<6 months had an average dose of 1.1 µg/kg/week. Four of these never reached 1.0 µg/kg/week.

Totally 24 patients managed to reach ≥ 1.0 µg/kg/week at some time.

Fatigue, nausea, fever and rigor/chills, mostly grade 1-2 according to NCI-CTC, were the most commonly reported side effects. There were four grade 3 and no grade 4 adverse events reported.

Two patients stopped treatment due to toxicity. Three patients had elevated alaninaminotransferase (ALAT) (> 2.5 x upper reference limit) and creatinine (>200 µmol/L) due to treatment. They all improved after dose reduction and the elevated values subsided.

Four patients (14%) were evaluated having a PR at six months, no later PR was observed in the treatment. At six months 12 patients were also evaluated to have SD. At 12 months eight patients (29%) were assessed as SD. Twelve patients had PD before six months, out of which six had PD before three months.

Time to progression (TTP) (*Fig 4)* in all patients was median 8 (1- 40+) months. TTP in patients with disease control (PR and SD) was 13 months.

In the subgroup of PR and SD, 14/16 (88%) patients had performance status ECOG 0 and 7 (44%) patients had only one metastatic site. The corresponding data for the group of PD< 6 months were 7/12 (58%) with ECOG 0 and 2/12 (17%) patients with one metastatic site respectively.

After discontinuing Pegintron® seven patients received second-line treatment with targeted drugs and seven endocrine treatment with Tamoxifen.

The median overall survival (n=28) was 19.5 (1-88.5) months. Survival for PR and patients with SD at six months was median 28 (15-88.5) months, six of the patients received targeted drugs second line. Median overall survival was 9.3 (1-30) months for patients with PD < 6 months, one of these patients received targeted drugs.

Patients with only pulmonary and mediastinal metastases (n=11) had a median TTP of 9.5 (3-32+) months and a response rate of 4/11 (36%) with PR at six months and median survival of 25.5 (9-33) months.

The pre-treatment s-VEGF was 594 (85-1742) pg/ml in the overall group, 565 (128-1575) pg/ml in the disease control group, PR and SD and 632 (97-1742) pg/ml in the non-responders´ group, NS. During treatment there was no statistical significance between patients with PR and SD, versus non-responders.

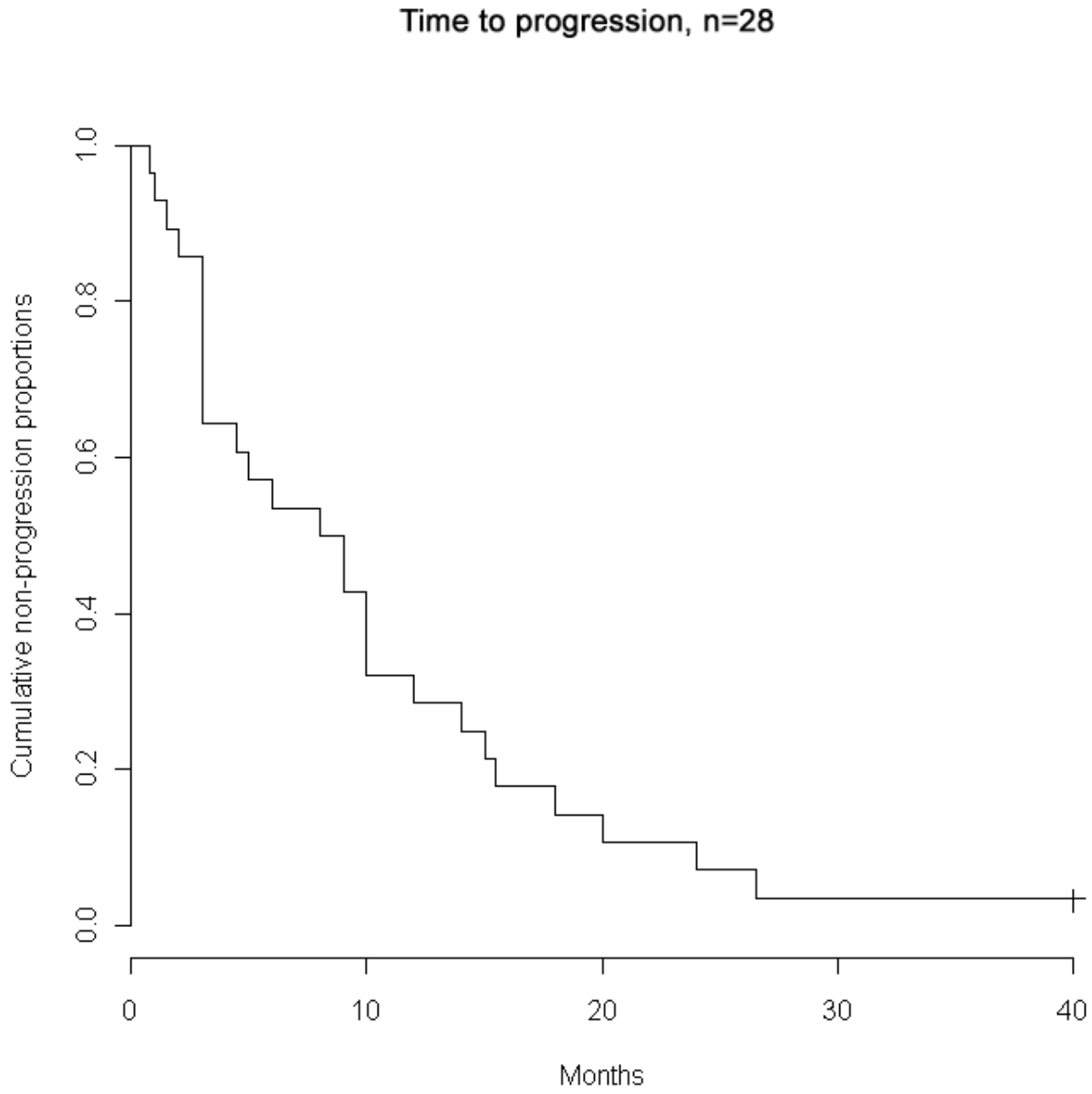

Fig 4 *Kaplan-Meier curve for time to progression (TTP), n=28. Median TTP 8 months for the entire study population. One patient had not reached PD at the time of evaluation. Censored patient is shown by a vertical tick mark.*

Paper IV

Biopsies were performed in 41 patients revealing 27 (65.9 %) clear-cell RCCs, two (4.9 %) papillary RCCs and four (9.8%) oncocytomas. Eight (19.4 %) biopsies were inconclusive.

The mean follow-up time was 24±17 months (range 3-59), compliance on follow-up was 100%. The primary technical success rate was 83% (38/46). Eight patients were assessed as incompletely treated after the first ablation session. Six of the eight (6/8) tumours with initially incomplete ablation were re-treated, four of those (4/6) successfully. The secondary technical success rate was 91 % (42/46). In two patients enhancing tumour persisted after a second RFA.

Local tumour recurrence was evenly distributed during follow-up (mean time 24 months, range 3-59) and diagnosed in nine (21%) of the 42 tumours treated with primary or secondary technical success. Six of those patients had repeat RFA performed, five were successfully treated and one had persistent enhancement on follow-up imaging. One of the patients that were successfully treated after recurrence had another local recurrence 13 months later, no more RFA was performed due to proximity to colon. Three of the patients with recurrence were withheld from treatment due to tumour proximity to colon, development of new tumours in the contra-lateral kidney or progressive disease with deteriorating health, suggesting that the patient would not benefit from further treatment. Thirty-seven (80%) of the originally 46 treated tumours irrespectively of first or second ablation were free of local recurrence, corresponding to 34 (79%) of 43 patients at the end of the follow-up. Of the 42 tumours that were completely ablated (after one or two RFA:s), 37 (88%) were free of tumour recurrence at the end of follow-up.

The maximum diameter of all tumours treated was mean 28mm (range 13-46mm) and their mean volume was 11.8 ml (range 1.3-39.6 ml). The mean volume of the ablation zone after the primary RFA was 17.3 ml and the mean necrosis index was 2.3. Maximum tumour diameter and tumour volume were found to be significantly larger, and the necrosis index significantly lower, in the group of tumours with incomplete initial RFA compared to tumours that showed complete ablation (*Table 7*). No significant difference between these variables or any other was found, when comparing groups of tumours with or without signs during follow-up of local recurrence after initial complete ablation.

Average pre- and post-treatment estimated GFR for all patients, excluding three patients with s-creatinine > 400µmol/L, was 55.3±2.9 and 52.7±3.1 ml/min/1.73m² (mean ± SE), respectively (ns). The three patients with s-creatinine > 400µmol/L had mean estimated GFR 10.8 ± 1.3 and 8.1 ± 2.9 ml/min/1.73m² pre- and post-treatment, respectively (ns).

Nine (21%) patients had side effects or complications within 30 days post-treatment. Four had minor side effects and were managed as outpatients. Another four patients required re-admittance. Two of those had fever, both resolved with conservative treatment. Two patients developed pneumaturia, both had previously been subjected to a partial nephrectomy. In one of them, pneumaturia resolved on

antibiotics, the other needed surgical intervention with a temporary pyelostomy and ileostomy for resolution of a renocolic fistula. The discharge of one patient, treated with a second RFA for local recurrence/or incomplete primary RFA, was delayed for two days due to post-treatment fever with signs of pyelitis at CT, although urine culture was negative.

Predictive factor	Complete ablation (n=38)	Incomplete ablation (n=8)	p-value
BMI (kg / m²)	26.7 ± 4.0	28.0 ± 4.8	0.69[1]
Distance, tumour to skin-surface (cm)	5.8 ± 2.0	6.2 ± 2.3	0.66[1]
Max diameter of tumour (mm)	26.7 ± 7.8	34.9 ± 7.6	0.016[1]
Tumour volume (ml)	10.7 ± 8.7	20.8 ± 12.4	0.032[1]
Volume of ablation zone (ml)	16.9 ± 9.8	19.2 ± 9.5	0.61[1]
Necrosis index	2.5 ± 2.9	1.2 ± 0.60	0.034[1]
Location[3]: Exofytic / Parenchymal / Central / Mixed	29 / 4 / 2 / 2	6 / 1 / 0 / 1	0.87[2]
Position[3]: Cranial / Middle / Caudal	10 / 13 / 14	3 / 5 / 0	0.23[2]

P-value according to [1]Mann-Whitney U-test and [2]Pearson Chi²-test
[3]One tumour was localised in the renal fossa after previous nephrectomy

Table 7 *Analysis of possible predictive factors for completeness of ablation after first treatment, mean ± SD.*

DISCUSSION

Paper I

The reported results from our material appear to be equivalent to perifascial nephrectomy for RCC(131, 132) as well as in accordance with earlier reported series of NSS for RCC(132-136). The surgical technique for NSS, enucleation or resection with a rim of normal tissue, has been debated throughout the years. In our material two cases of the enucleation technique was applied, both patients later developed generalized disease. This is not the technique of choice today in our department as reports have shown tumour extension through the pseudocapsule in enucleated specimens (137, 138).

It has been argued that watchful waiting may be an option for patients with small renal masses. However, as pointed out by previous authors(139), small adenocarcinomas in the kidney with at least high stage/high grade can be associated with both multifocality and metastatic disease. Ljungberg et al.(140) found that 43% of tumours with a diameter of <3 cm were aneuploid and moreover those tumours presented a higher degree of invasion into surrounding kidney tissue than diploid tumours. This argues against watchful waiting. On the contrary, Bosniak et al.(141) reported a series of selected and a partly retrospective study of 40 tumours ≤3.5 cm with slow growth rate (≤0.35 cm annually) and no metastasis on a mean follow-up of 3.5 years. This argues for watchful waiting – at least among elderly patients with incidentally detected small RCC.

To optimize the selection of tumours in order for the hosting patient to benefit from the followed procedure, an easy test is warranted. Studies on cytokines, signal molecules and genetic mechanism in the RCC may in the future unveil the secret of discriminating between low-grade and proliferative tumours with metastatic potential. Vascular endothelial growth factor, VEGF, in serum has promisingly been reported to correlate with clinical stage and histopathological grade of RCC. Levels of VEGF below median correlated to improved survival (122). The prognostic value was however not independent of stage and grade.

Ten of the 78 patients with M0 had more than one tumour resected. The incidence of multifocality in our material is unclear. Previously reported data claim a 5% frequency of small RCCs in the normal-appearing portion of the kidney if the primary tumour was ≤4 cm (142). This emphasizes the importance of correct selection of tumour and patient. The recurrence rate in contra-lateral kidney has been reported to 6%, with mean primary tumour size of seven cm. Significant predictors were ipsilateral multifocality and TNM stage(143). Higher recurrence rate has been reported in patients followed 10-43 years. Thus, multifocality may be bilateral in patients with non-hereditary RCC, this would argue in favour of performing NSS contra nephrectomy and the importance of long-term follow-up.

Comment, Paper I

The study is limited to its nature of retrospectivity.

However, the number of patients, 87, was at the time of analysing data a considerable population for a single centre.

When the study was performed NSS was accepted on imperative indications as single kidney, bilateral tumours, patients with multifocal tumours and renal insufficiency but it was still controversial regarding applying the procedure in patients with normal contralateral kidney(144). The main objections for not performing NSS on the latter indication was allegedly the risk of local recurrence (2%-12%) (145-147), the lack of complete specimen to be analysed for possible microscopic perirenal growth, the presence of regional lymph node metastases, risk of tumour spill, undetected microscopic multifocality and the complexity of the procedure afflicted by the risk of complications.

However, as follow-up after NSS have presented survival data that are in line with those retrieved from patients subjected to nephrectomy, the opinion has turned in favour of NSS and expanded its indications (132, 142, 148, 149). Moreover, reports on renal impairment on long term follow-up after nephrectomy supports the utilisation of NSS (150-152). Through the EAU-guidelines, 2008, Ljungberg et al. recommend the NSS to be an established curative approach for treatment of RCC that are feasible (153). Today the use of resections are more widespread but probably the procedure is still underused as an option to nephrectomy. This may be reflected in the Nationella njurcancerregistret, 2005-2007 (154), where it is stated that the regional differences in performing resections are between 12.5% and 35.5% on tumours ≤ 4 cm.

Paper II

After treatment with sorafenib, the mean uptake decreased in all lesions to 75% (32-105%) compared with the maximum uptake which decreased to 86% (46-131%) of the initial value. The latter only reflects the most intense part of ROI. Sorafenib decreased the FDG uptake in a heterogeneous way in the ROI but the uptake is not completely extinguished as in GIST tumours treated with imitanib. We therefore consider that the mean rather than the maximum uptake better reflects the effect of sorafenib in the lesion. The maximum uptake also showed a larger variation in different metastases compared to mean uptake, which may also support the use of the latter.

We used the uptake in cerebellum as reference to calculate indexes of mean and maximum FDG uptake instead of standard uptake value (SUV). The FDG uptake in the lesions was normalised to the cerebellar FDG uptake. We thus circumvent the sometimes large differences in SUV-results that may origin from the use of different equipment and algorithms. There are still no generally accepted cut-off values between responders and non-responders even though a change in 20% of FDG uptake (SUV) has been suggested to relate to therapy (155). In future studies the uptake using cerebellum as a reference will be compared with the SUV.

Utilising the cut-off 20%, a possible prolonged survival in responders in comparison to non-responders in our study was indicated. However, responders did not have an increased PFS as evaluated by RECIST. This may be explained by a small-sized study population and strict RECIST criteria may not necessarily reflect the patients´ clinical benefit when treated with targeted therapies (156). Increasing FDG uptake could be another possible criterion for progression.

In this study we used FDG-PET which is the most well known and tested radiotracer for solid tumours, based on the fact that many tumours metabolize glucose to a higher degree than surrounding tissue (157). This may not always be true in heterogeneous tumours like RCC. One has to remember that the measures calculated are the total activity in the apparent tumour volume, including unmetabolised FDG in the blood and in the intercellular spaces (158). Another possibility to evaluate tumour activity would be to use a tracer such as ^{18}F-fluorothymidine, reflecting the deoxyribonucleic acid (DNA) synthesis (159). This could be an optional index of early response. However, the experience from fluorothymidine is still limited (160).

Sorafenib inhibits tumour growth and the antiangiogenic effects may cause necrosis in the center part of the metastases but do not necessarily cause a reduction in tumour volume or diameter of the lesion (161, 162). In our study, a diffuse reduction in glucose uptake was found after one month's treatment and the metabolic effect was thus not more marked in the central part of the tumours. Our results support the use of changes in FDG-PET as an alternative to traditional criteria since it measures metabolism and not the size of the tumour.

Aware of the study's restrictions, with a small study population we are inclined to believe that PET/CT technique is a promising modality to evaluate treatment with targeted therapies especially in both soft and skeletal metastases difficult to evaluate with CT. Even in skeletal lesions, not measurable according to RECIST, the uptake decreased to 80%. Larger studies are required to analyse the outcome on different histological subgroups as well as using other radiotracers.

Paper III

In the present study we used Pegintron® with the intention of finding an acceptable dose for long-term treatment (≥ 6months) and still reaching clinical benefit as with conventional interferon (IFN) alpha 2b treatment.

In our study with Pegintron® the overall response rate (PR) was 14% (at six months) and 43% had SD. At 12 months 29% (n=8) were still assessed as SD and two patients were still at SD after 24 months.

The median overall survival was 19.5 (1-88.5) months (after second-line treatment with tyrosine kinase inhibitors (TKI) in seven patients) and at one year 71% of the patients were still alive. These data are in line with former phase I/II trials (163, 164). However, in those studies the patients were treated with pegylated interferon alfa-2b doses of 4.5-7.5 μg/kg/week. One of the studies (164) contained patients with MRCC where all (100%) had been subject to nephrectomy, in comparison to our group where 5/28 (18%) never were under surgery. The other study (163) was a

mixed study-population with different solid tumours even though most of them were MRCC, several of which had received previous treatment. Both of those studies presented patients with complete response (CR) but also more frequently severe adverse events. We have here presented the results from treating a group of severely ill patients from MRCC, treated with low average-dose of Peg-interferon (1.5 μg/kg/w among those who stayed on the treatment for ≥ 6 months) and still reaching acceptable response and minimising the toxicity. In studies with INF in combination with targeted therapies, Sorafenib, Bevacizumab, reduction of INF has shown to be a way to manage toxicity and yet maintaining efficacy(165, 166).

The baseline characteristics of the patients with PR or SD (n=16) contains a larger proportion of patients with only one metastatic site (n=7) and more frequently ECOG 0 (n=14) than among the patients of PD < 6 months, hence predicting PR and SD. These data could be expected concerning prognostic factors and are in accordance with a previously performed interferon study (167).

In the group of patients with only lung metastases, TTP was 9.5 months, median survival 25.5 and four of eleven patients (36%) had PR. Increased survival has been demonstrated in patients with lung metastases only compared to patients with other metastatic sites during interferon treatment of MRCC irrespectively if nephrectomy was performed or not (63).

Four patients progressed (PD) after one month only. Two of those had a performance status (PS) of ECOG 1. Two were synchronously metastatic and two asynchronously. One patient had a papillary tumour with growth in the perirenal fat. These patients presented high-grade tumours Fuhrman 4. All four had either two or three metastatic sites. Previous trials have shown high ECOG (168, 169) and time from diagnosis to treatment (<2 years) to be independent adverse prognostic factors for progression-free survival (PFS) (63). The number of metastatic sites is also a negative prognostic factor (170).

VEGF in serum taken before planned nephrectomy has a prognostic value in RCC (122) but in MRCC a significantly increased survival with low s-VEGF was shown only in patients with the best PS (171). In our study pre-treatment s-VEGF had no prognostic value. We found an increased VEGF in serum during the first month of treatment among patients with PD< 6 months as well as patients with PR and SD. This is similar to those findings Bukowski et al (172) presented on analysing S-VEGF in connection to treatment with sorafenib, where the levels of s-VEGF increased during treatment. In the study by Bukowski, baseline VEGF (mean 209 pg/mL) was recognised as an independent prognostic factor for overall survival. Patients with high baseline VEGF had a significantly shorter PFS than those with low VEGF. Notably, the levels for high VEGF were set to >131pg/mL and low to ≤131pg/mL. In our study, the levels of VEGF were higher at baseline, mean s-VEGF was 594 (85-1742) pg/mL in the overall group, 565 (128-1575) pg/mL in the SD and PR group and 632 (97-1742) pg/mL, which might indicate patients with more advanced disease. Alamdari (171) analysed baseline VEGF-levels before nephrectomy (mean 582.5, range: 47.8-2261.0 pg/mL) in 120 patients at diagnosis

of MRCC and found significant correlation to those patients with best PS and low VEGF and their survival.
To designate the early or late adverse events, toxicity was analysed at two months to give the patients a chance to reach full dose since Pegintron® was escalated 0.5µg every 2 weeks to reach 2 µg/kg/week and thereafter throughout the study.
Toxicity, grade 3/4 was very rare. However, dose reduction at some time during the study was frequent, 13/28 (46%), and four patients (age range 49-72 years) never even reached the dose of 1.0µg/kg/weekly before discontinuing the study. The optimal dose for treating patients with MRCC is still not known, however we have in our study population a group of 16 patients that had clinical benefit of the treatment. Those were treated with an average dose of 1.5 µg/kg/week.
Pharmacokinetic studies on pegylated interferon, analyzing accumulation, have been performed with interferon alpha 2a and in combination with other drugs and in clinical settings such as Chronic Hepatitis C (CHC) (85, 173). For doses of 0.7-1.4 µg/kg administrated weekly, a slight accumulation was observed over one month calculating from the area under the curve of concentration (AUC). The main part of our study group had been subject to nephrectomy. Thus, the pharmacokinetics may be different in our study group than in patients with CHC, neither does any long-term data exist on this matter. T½ is prolonged if the renal function decreases to CL_{cr} to 20-40 mL/min which is not unusual in nephrectomised patients (173). Thus drug accumulation cannot be excluded in our patient material during long-term treatment. Late-appearing side effects which called for dose reduction could support this hypothesis.
In the era of TKIs we see combination trials and sequential trials in treating MRCC. One combination in different trials is TKI + IFN. The prolonged exposure with pegylated interferon mimic the repeated injection of interferon and may increase the antiangiogenic effect of the drug. Our results indicate that there is room for the use of Peginterferon in the treatment of MRCC as monotherapy in selected patients and in combination with targeted drugs.

Paper IV

Percutaneous RFA is an attractive approach for ablation of small renal tumours as it allows preservation of renal parenchyma, is well tolerated and seems to have acceptable risks. Unlike partial nephrectomy, RFA allows for repeated treatment sessions with no substantial increase in technical difficulty.
When using treatments where no resected tissue is available for analysis, percutaneous biopsy is mandatory to confirm malignancy.
In our series we performed 56 core biopsies in 41 patients (15 patients had two biopsies taken and 26 had a single biopsy) yielding diagnostic material in 81% of the cases, while the biopsies were nondiagnostic in 19%, which is in line with the reported proportion of 10-20% of nondiagnostic biopsies, in previous studies (174). Wang et al, using multiple core biopsies in each tumour, reported that 91% had sufficient tissue for diagnosis. Thirty-five per cent of those with sufficient biopsies were benign, while in our study four lesions (9.8%) were benign. This suggests that

our material comprised a different selection of patients, where 12 of 43 (28%) patients had previously known kidney cancer, six of whom had inconclusive biopsies.

At the discretion of the radiologists we chose to perform the percutaneous RFA:s with US guidance, since substantial experience using this guidance method has been gained in treating liver tumours with RFA at our centre. Our primary technical success rate of 83% and a secondary success rate of 91% are in line with results from series using CT guidance (126) as well as series using ultrasound guidance (175) or both guiding methods (176, 177).

Advantages of US-guided RFA include real-time imaging of the needle electrode as it is advanced and positioned into the tumour. However, in our and the experience of others, some tumours may be difficult to visualize with US (127). During US-guided RFA, a hyperechoic focus appears a few minutes into the ablation process and progressively surrounds the electrode tip, secondary to microbubble formation in the ablated tissue. This transient hyperechoic zone is used as a rough guide to the extent of cellular damage induced (128). However, this zone does not always correlate with the extent of tumour necrosis demonstrated at pathologic examination (178). Additionally, this hyperechoic area may obscure the tumour and increase the difficulty of repositioning the electrode for subsequent, overlapping ablations. We also tried contrast-enhanced US (CEUS) but we found it to be of little help in demonstrating residual tumour, as tumour and normal renal tissue often show similar degree of contrast enhancement (179).
Although our primary technical success rate was comparable to series using CT-guidance (126, 129, 180), the recurrence rate was higher in our study. This may be explained by our relatively high rate of patients with malignant as opposed to benign renal lesions (10%). Also, our follow-up time was longer than in most studies and follow-up compliance was 100%. However, it cannot be excluded that the inferior image quality using US-guidance may have resulted in suboptimal probe positioning and microscopic foci of residual disease. As a consequence, a combined US- and CT-guided approach should be contemplated, to utilize the advantages of the respective techniques(177). Since technical factors and experience of the operator are important for the results, RFA treatment of renal tumors should be centralised.

Small tumour size (<3cm), exophytic tumour location and complete necrosis after ablation have been shown to be predictors of technical success after percutaneous RFA of RCC (181). Analysing possible predictive factors in our study, we found that the necrosis index may be a useful indicator to evaluate whether the coagulated tissue volume is sufficiently large as compared to the tumour volume (129). In our study, the mean necrosis index was 2.3, meaning that the induced coagulation necrosis was, on average, at least two-fold larger than the tumour volume. Tumour location could not be shown to be a predictive factor for primary technical success

in our study, bearing in mind that we had few central tumours. No other factors were found to correlate with incomplete tumour ablation.

Local recurrence, totally nine (21%), occurred throughout the whole follow-up time period, which underscores the need for sustained, close follow-up with imaging even after the first year has passed. Late local recurrence has also been reported by others (176, 180, 182, 183). We were not able to isolate any single significant predictive factor for tumour recurrence, but the tumour volume was slightly larger (n.s) in the group of patients with recurrence. In order to achieve a larger ablation volume, we have changed our policy to primarily using a cluster electrode on tumours with diameter larger than 2 cm. Although a certain proportion of tumours will be incompletely ablated by RFA or may recur, the minimal-invasiveness of percutaneous RFA allows repeated ablations to be performed with low morbidity.

Renal RFA is not free of risks; side effects and complications after RFA have been reported in 0-28% (181, 184, 185). We found that three of our patients had fever post-treatment without positive culture of urine. These conditions are consistent with the so called post-ablation syndrome, which is related to the size of the ablation zone. We experienced two cases of transient pneumaturia, both patients had been subjected to earlier parenchymal resection. In case of kidney resection, one should also consider to thoroughly embed the resection area with fatty tissue if future RFA treatment is anticipated. Likewise, one needs to be attentive to the difficulties in performing RFA on previously resected kidneys. A negative impact on kidney function after RFA, partial nephrectomy and radical nephrectomy has previously been reported (186). In our material the kidney function was generally below normal at baseline and a slight but statistically insignificant decrease was seen at follow-up. Thus, mild to moderate kidney disease does not seem to be an obstacle for RFA (125, 176).

The incidence of small renal masses (SRM) has increased during the last decades following the increased access to CT, US and MRI (5). Improved survival after treatment has also been reported (187). Although surgical resection remains the standard of care, not all patients with suspected RCC are optimal surgical candidates, due to significant chronic comorbidity, previous renal surgery and/or poor renal reserve. It might be that the longevity of many elderly patients is limited more by their comorbidity than by incidental SRM, and that the risk of treating a localised RCC is greater than just observing the lesion (188). However, as the life expectancy in an individual patient is difficult to predict and metastases occur in 2-6% of patients with tumours < 4 cm in diameter (189) incentives to treat selected SRM remain (190).

This study was limited by its retrospective nature and the fact that the treatment effect was assessed by radiological findings only, and not by biopsy. The technical success rate in our study, using US-guidance for the RFA procedure and CT and MRI for treatment evaluation, compares well with that of other experienced centres. RFA for small kidney tumours should be regarded as a procedure under

development. Thorough long- term follow-up appears mandatory as a substantial proportion of the patients will develop late local recurrence and will be in need of more than one RFA treatment session. The key to success is a close collaboration between the interventional radiologist and urologist.

CONCLUSIONS

Paper I

Nephron sparing surgery can be performed on imperative indication with good results and as well in selected cases with normal contralateral kidney.

Paper II

An early decrease in glucose uptake is measurable in both soft and skeletal lesions after treatment with sorafenib. With FDG-PET-CT it is possible to evaluate both soft and skeletal lesions, which is an advantage.

Paper III

We conclude that with an average dose of 1.5µg/kg sc and weekly, patients with MRCC were able to stay on long-term (≥6 months) treatment with Peg-interferon alfa-2b. Fourteen percent had PR and 43% SD at six months with tolerable toxicity.

Paper IV

Percutaneous RFA is a repeatable treatment for SRM in selected patients, long-term follow-up is needed as late local recurrences may be anticipated.
Tumour volume diameter, tumour volume and necrosis index are factors that predict the risk of incomplete treatment.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Lokaliserad och Metastaserad Njurcancer.
Aspekter på Behandling.

Förekomsten av njurcancer i västvärlden är ungefär 2% av all malignitet. I Sverige diagnostiseras knappt 1000 nya fall per år. Årligen avlider cirka 600 personer till följd av njurcancer.
Kirurgi – är den enda metoden för bot. Antingen opererar man bort den njure (s k nefrektomi) där tumören sitter eller tumören med en del av njuren, det senare kallas nefronsparande kirurgi. Syftet med den senare tekniken är att spara så mycket frisk njurvävnad som möjligt. Det har tidigare framför allt varit patienter som av någon orsak har haft nedsatt njurfunktion som har varit aktuell för nefronsparande kirurgi. Det kirurgiska ingreppet, både nefrektomi och nefronsparande kirurgi är omfattande för patienten.
Det senaste decenniet har man börjat pröva att behandla små (<4cm) njurtumörer med s k ablationsteknik. Det innebär att man oskadliggör tumören med värme, vilket man kan alstra med radiovågor som förs in i tumören via en sond, s k radiofrekvensablation (RFA). Data från resultat, prediktiva faktorer och långtidsuppföljning efter RFA behandling av njurtumörer är mycket begränsat.

Spridd njurcancer är svårbehandlad. I Sverige har man framför allt använt kortverkande interferon. Preparatet ges i injektionsform flera gånger i veckan. Behandlingen anses stärka immunförsvaret. Ett fåtal patienter svarar på behandlingen men med besvärande biverkningar. Nu finns även långverkande interferon, Peginterferon, dock är doseringen oklar. Sedan cirka fem år finns dessutom nya preparat som är direkt målsökande mot själva tumörcellerna, t ex sorafenib. De gör att nybildningen av kärl till tumören och metastaserna hämmas men behandlingen är inte botande. Dessa preparat är dyra och behäftade med biverkningar som kan vara besvärliga. För både interferon och målsökande behandling gäller att sjukdomen finns kvar men kan försvinna temporärt för att återkomma så småningom.

I denna avhandling, som omfattas av fyra kliniska delarbeten, presenteras ett antal behandlingsalternativ för patienter med såväl avancerad som lokaliserad sjukdom.

Delarbete I
Syftet var att fastställa långtidsresultatet efter nefronsparande kirurgi. Åttiosju patienter genomgick nefronsparande kirurgi mellan 1980 och 1999. Sjuttioåtta patienter hade lokaliserad sjukdom och nio patienter hade avancerad sjukdom.

Fem år efter operationen levde 80% respektive 25% av de med lokaliserad respektive avancerad sjukdom. Sammanfattningsvis kan man konstatera att resultatet vad gäller överlevnad för patienter som har genomgått nefronsparande kirurgi inte är sämre än för de som genomgår nefrektomi, enligt litteraturen.

Delarbete II

Syftet med arbetet var att bedöma om det går att använda 18-FDG-PET/CT teknik för att värdera effekten av sorafenib vid behandling av metastaserad njurcancer. Tekniken innebär att man på ett tidigt stadium kan bedöma effekten såväl i icke-skelett metastaser som i skelettmetastaser genom att evaluera upptaget av radioaktiva socker molekyler i metastaserna. En minskning i upptag tyder på effekt av behandlingen.
Undersökningen visade att medelupptaget i metastaserna hade minskat till 71% och 82% i icke-skelett respektive skelettmetastaser.
FDG-PET/CT verkar vara en teknik som lämpar sig för evaluering av effekten av den målriktade terapin med sorafenib, i synnerhet lämplig för bedömning av skelettmetastaser vilket man inte kan göra med CT eller konventionell röntgen.

Delarbete III

Studien handlar om doseringen av Peginterferon, under långtidsbehandling. Syftet med att ge Peginterferon istället för konventionellt interferon är att det dels är lindrigare med en injektion per vecka än tre-sju injektioner, dels att få en jämnare nivå av medicinen i blodet vilket både borde ge en lindrigare biverkningsprofil och eventuellt ge bättre effekt.
Tjugoåtta patienter med metastaserande njurcancer inkluderades och fick 0,5 mikrogram/kg och vecka, dosen ökades varannan vecka till maxdosen 2 mikrogram/kg uppnåddes.
Medeldosen för de som klarade behandlingen ≥6 månader var 1,5 mikrogram/kg och vecka. Femtiosju procent svarade på behandlingen eller hade en stabil sjukdomsbild. Peginterferon bedöms kunna användas i dos om 1,5mikrogram/kg och vecka för långtidsbehandling. Effekten verkar vara likartade som vid behandling med kortverkande interferon.

Delarbete IV

I denna studie behandlades 46 njurtumörer hos 43 patienter med ultraljudsledd radiofrekvensablation (RFA). Man mätte olika faktorer i syfte att förutsäga risken för ofullständig behandling av tumören samt för lokalt recidiv. Åttiotre procent var komplett behandlade efter första ablationen och totalt 42 tumörer (91%) efter andra behandlingen. Nio patienter uppvisade lokalt recidiv vid uppföljningen varav sex fick förnyad behandling, medeltid till uppföljningen var 24 månader. Tumördiameter och volym var signifikant större och tumörnekrosindex, (ablationsvolymen delad med tumörvolymen innan behandlingen), signifikant lägre

hos de initialt inkomplett behandlade tumörerna. Motsvarande skillnader kunde inte påvisas vid jämförelse mellan de tumörer som fick återfall jämfört med dem som inte fick detta.

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REFERENCES

1. Novick AC, Campbell SC. Renal Tumors. In: Walsh PC, editor. Campbell's Urology. Eighth ed. Philadelphia: Saunders; 2002. p. 2672-731.
2. Carson WJ. Solitary Cysts of the Kidney. Ann Surg. 1928 Feb;87(2):250-6.
3. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009 Jul-Aug;59(4):225-49.
4. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005 Mar-Apr;55(2):74-108.
5. Jayson M, Sanders H. Increased incidence of serendipitously discovered renal cell carcinoma. Urology. 1998 Feb;51(2):203-5.
6. Mathew A, Devesa SS, Fraumeni JF, Jr., Chow WH. Global increases in kidney cancer incidence, 1973-1992. Eur J Cancer Prev. 2002 Apr;11(2):171-8.
7. Lindblad P. Epidemiology of renal cell carcinoma. Scand J Surg. 2004;93(2):88-96.
8. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med. 2005 Dec 8;353(23):2477-90.
9. Chow WH, Gridley G, Fraumeni JF, Jr., Jarvholm B. Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med. 2000 Nov 2;343(18):1305-11.
10. Walsh P.C RAB, Vaughan E.D, Wein A.J. Cambell's Urology. 8th ed. Andrew C Novick SCC, editor. Philadelphia: Saunders; 2002.
11. Kovacs G. Molecular differential pathology of renal cell tumours. Histopathology. 1993 Jan;22(1):1-8.
12. Kovacs G, Akhtar M, Beckwith BJ, Bugert P, Cooper CS, Delahunt B, et al. The Heidelberg classification of renal cell tumours. J Pathol. 1997 Oct;183(2):131-3.
13. Storkel S, Eble JN, Adlakha K, Amin M, Blute ML, Bostwick DG, et al. Classification of renal cell carcinoma: Workgroup No. 1. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer. 1997 Sep 1;80(5):987-9.
14. Reuter VE, Presti JC, Jr. Contemporary approach to the classification of renal epithelial tumors. Semin Oncol. 2000 Apr;27(2):124-37.
15. Latif F, Tory K, Gnarra J, Yao M, Duh FM, Orcutt ML, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. Science. 1993 May 28;260(5112):1317-20.
16. Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. J Clin Oncol. 2004 Dec 15;22(24):4991-5004.
17. Gnarra JR, Tory K, Weng Y, Schmidt L, Wei MH, Li H, et al. Mutations of the VHL tumour suppressor gene in renal carcinoma. Nat Genet. 1994 May;7(1):85-90.
18. Delahunt B, Eble JN. Papillary renal cell carcinoma: a clinicopathologic and immunohistochemical study of 105 tumors. Mod Pathol. 1997 Jun;10(6):537-44.
19. Gunawan B, von Heydebreck A, Fritsch T, Huber W, Ringert RH, Jakse G, et al. Cytogenetic and morphologic typing of 58 papillary renal cell carcinomas: evidence for a cytogenetic evolution of type 2 from type 1 tumors. Cancer Res. 2003 Oct 1;63(19):6200-5.

20. Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, Choyke P, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet. 1997 May;16(1):68-73.
21. Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet. 2002 Apr;30(4):406-10.
22. Khoo SK, Kahnoski K, Sugimura J, Petillo D, Chen J, Shockley K, et al. Inactivation of BHD in sporadic renal tumors. Cancer Res. 2003 Aug 1;63(15):4583-7.
23. Hand JR BA. Carcinoma of the kidney: the degree of malignancy in relation to factors bearing on prognosis. J Urol. 1932;28:199-216.
24. Delahunt B, Nacey JN. Renal cell carcinoma. II. Histological indicators of prognosis. Pathology. 1987 Jul;19(3):258-63.
25. Arner O, Blanck C, von Schreeb T. Renal adenocarcinoma; morphology--grading of malignancy--prognosis. A study of 197 cases. Acta Chir Scand Suppl. 1965;346:1-51.
26. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982 Oct;6(7):655-63.
27. Kagawa S, Takigawa H, Kurokawa K, Akagi G. The correlation between the grading and nuclear size of renal cell carcinoma. Tokushima J Exp Med. 1985 Dec;32(3-4):45-8.
28. Skinner DG, Colvin RB, Vermillion CD, Pfister RC, Leadbetter WF. Diagnosis and management of renal cell carcinoma. A clinical and pathologic study of 309 cases. Cancer. 1971 Nov;28(5):1165-77.
29. Syrjanen K, Hjelt L. Grading of human renal adenocarcinoma. Scand J Urol Nephrol. 1978;12(1):49-55.
30. Lohse CM, Blute ML, Zincke H, Weaver AL, Cheville JC. Comparison of standardized and nonstandardized nuclear grade of renal cell carcinoma to predict outcome among 2,042 patients. Am J Clin Pathol. 2002 Dec;118(6):877-86.
31. Novara G, Martignoni G, Artibani W, Ficarra V. Grading systems in renal cell carcinoma. J Urol. 2007 Feb;177(2):430-6.
32. Medeiros LJ, Jones EC, Aizawa S, Aldape HC, Cheville JC, Goldstein NS, et al. Grading of renal cell carcinoma: Workgroup No. 2. Union Internationale Contre le Cancer and the American Joint Committee on Cancer (AJCC). Cancer. 1997 Sep 1;80(5):990-1.
33. Ficarra V, Martignoni G, Maffei N, Brunelli M, Novara G, Zanolla L, et al. Original and reviewed nuclear grading according to the Fuhrman system: a multivariate analysis of 388 patients with conventional renal cell carcinoma. Cancer. 2005 Jan 1;103(1):68-75.
34. Bretheau D, Lechevallier E, de Fromont M, Sault MC, Rampal M, Coulange C. Prognostic value of nuclear grade of renal cell carcinoma. Cancer. 1995 Dec 15;76(12):2543-9.
35. Tsui KH, Shvarts O, Smith RB, Figlin RA, deKernion JB, Belldegrun A. Prognostic indicators for renal cell carcinoma: a multivariate analysis of 643 patients using the revised 1997 TNM staging criteria. J Urol. 2000 Apr;163(4):1090-5; quiz 295.
36. Usubutun A, Uygur MC, Ayhan A, Toklu C, Sahin A, Ozen H, et al. Comparison of grading systems for estimating the prognosis of renal cell carcinoma. Int Urol Nephrol. 1998;30(4):391-7.

37. Ficarra V, Righetti R, Martignoni G, D'Amico A, Pilloni S, Rubilotta E, et al. Prognostic value of renal cell carcinoma nuclear grading: multivariate analysis of 333 cases. Urol Int. 2001;67(2):130-4.
38. Goldstein NS. The current state of renal cell carcinoma grading. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer. 1997 Sep 1;80(5):977-80.
39. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. J Urol. 1969 Mar;101(3):297-301.
40. Flocks RH, and Kadesky, M. C. Malignant neoplasm of the kidney - An analysis of 353 patients followed 5 years or more. J Urol. 1958;79:196-201.
41. Guinan P, Sobin LH, Algaba F, Badellino F, Kameyama S, MacLennan G, et al. TNM staging of renal cell carcinoma: Workgroup No. 3. Union International Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer. 1997 Sep 1;80(5):992-3.
42. Javidan J, Stricker HJ, Tamboli P, Amin MB, Peabody JO, Deshpande A, et al. Prognostic significance of the 1997 TNM classification of renal cell carcinoma. J Urol. 1999 Oct;162(4):1277-81.
43. Ficarra V, Righetti R, Pilloni S, D'Amico A, Maffei N, Novella G, et al. Prognostic factors in patients with renal cell carcinoma: retrospective analysis of 675 cases. Eur Urol. 2002 Feb;41(2):190-8.
44. Chow WH, Devesa SS, Warren JL, Fraumeni JF, Jr. Rising incidence of renal cell cancer in the United States. Jama. 1999 May 5;281(17):1628-31.
45. Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am J Surg Pathol. 2003 May;27(5):612-24.
46. Amin MB, Tamboli P, Javidan J, Stricker H, de-Peralta Venturina M, Deshpande A, et al. Prognostic impact of histologic subtyping of adult renal epithelial neoplasms: an experience of 405 cases. Am J Surg Pathol. 2002 Mar;26(3):281-91.
47. Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. J Urol. 2000 Feb;163(2):408-17.
48. Burgess NA, Koo BC, Calvert RC, Hindmarsh A, Donaldson PJ, Rhodes M. Randomized trial of laparoscopic v open nephrectomy. J Endourol. 2007 Jun;21(6):610-3.
49. Colombo JR, Jr., Haber GP, Jelovsek JE, Lane B, Novick AC, Gill IS. Seven years after laparoscopic radical nephrectomy: oncologic and renal functional outcomes. Urology. 2008 Jun;71(6):1149-54.
50. Gong EM, Lyon MB, Orvieto MA, Lucioni A, Gerber GS, Shalhav AL. Laparoscopic radical nephrectomy: comparison of clinical Stage T1 and T2 renal tumors. Urology. 2006 Dec;68(6):1183-7.
51. Wotkowicz C, Wszolek MF, Libertino JA. Resection of renal tumors invading the vena cava. Urol Clin North Am. 2008 Nov;35(4):657-71; viii.
52. Alamdari FI, Ljungberg B. Adrenal metastasis in renal cell carcinoma: a recommendation for adjustment of the TNM staging system. Scand J Urol Nephrol. 2005;39(4):277-82.
53. Godoy G, O'Malley RL, Taneja SS. Lymph node dissection during the surgical treatment of renal cancer in the modern era. Int Braz J Urol. 2008 Mar-Apr;34(2):132-42.
54. Margulis V, Wood CG. The role of lymph node dissection in renal cell carcinoma: the pendulum swings back. Cancer J. 2008 Sep-Oct;14(5):308-14.

55. Herr HW. Partial nephrectomy for incidental renal cell carcinoma. Br J Urol. 1994 Oct;74(4):431-3.
56. Herr HW. Partial nephrectomy for renal cell carcinoma with a normal opposite kidney. Cancer. 1994 Jan 1;73(1):160-2.
57. Campbell SC, Novick AC. Surgical technique and morbidity of elective partial nephrectomy. Semin Urol Oncol. 1995 Nov;13(4):281-7.
58. van der Poel HG, Roukema JA, Horenblas S, van Geel AN, Debruyne FM. Metastasectomy in renal cell carcinoma: A multicenter retrospective analysis. Eur Urol. 1999;35(3):197-203.
59. Vogl UM, Zehetgruber H, Dominkus M, Hejna M, Zielinski CC, Haitel A, et al. Prognostic factors in metastatic renal cell carcinoma: metastasectomy as independent prognostic variable. Br J Cancer. 2006 Sep 18;95(6):691-8.
60. Cerfolio RJ, Allen MS, Deschamps C, Daly RC, Wallrichs SL, Trastek VF, et al. Pulmonary resection of metastatic renal cell carcinoma. Ann Thorac Surg. 1994 Feb;57(2):339-44.
61. Pierorazio PM, McKiernan JM, McCann TR, Mohile S, Petrylak D, Benson MC. Outcome after cytoreductive nephrectomy for metastatic renal cell carcinoma is predicted by fractional percentage of tumour volume removed. BJU Int. 2007 Oct;100(4):755-9.
62. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet. 2001 Sep 22;358(9286):966-70.
63. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med. 2001 Dec 6;345(23):1655-9.
64. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol. 2004 Mar;171(3):1071-6.
65. Zlotta AR, Wildschutz T, Raviv G, Peny MO, van Gansbeke D, Noel JC, et al. Radiofrequency interstitial tumor ablation (RITA) is a possible new modality for treatment of renal cancer: ex vivo and in vivo experience. J Endourol. 1997 Aug;11(4):251-8.
66. Walther MC, Shawker TH, Libutti SK, Lubensky I, Choyke PL, Venzon D, et al. A phase 2 study of radio frequency interstitial tissue ablation of localized renal tumors. J Urol. 2000 May;163(5):1424-7.
67. Crowley JD, Shelton J, Iverson AJ, Burton MP, Dalrymple NC, Bishoff JT. Laparoscopic and computed tomography-guided percutaneous radiofrequency ablation of renal tissue: acute and chronic effects in an animal model. Urology. 2001 May;57(5):976-80.
68. Perry K, Zisman A, Pantuck AJ, Janzen N, Schulam P, Belldegrun AS. Laparoscopic and percutaneous ablative techniques in the treatment of renal cell carcinoma. Rev Urol. 2002 Summer;4(3):103-11.
69. Goldberg SN, Gazelle GS, Mueller PR. Thermal ablation therapy for focal malignancy: a unified approach to underlying principles, techniques, and diagnostic imaging guidance. AJR Am J Roentgenol. 2000 Feb;174(2):323-31.
70. Goldberg SN, Gazelle GS, Halpern EF, Rittman WJ, Mueller PR, Rosenthal DI. Radiofrequency tissue ablation: importance of local temperature along the electrode tip exposure in determining lesion shape and size. Acad Radiol. 1996 Mar;3(3):212-8.

71. Kunkle DA, Egleston BL, Uzzo RG. Excise, ablate or observe: the small renal mass dilemma--a meta-analysis and review. J Urol. 2008 Apr;179(4):1227-33; discussion 33-4.
72. Gill IS, Novick AC. Renal cryosurgery. Urology. 1999 Aug;54(2):215-9.
73. Berger A, Kamoi K, Gill IS, Aron M. Cryoablation for renal tumors: current status. Curr Opin Urol. 2009 Mar;19(2):138-42.
74. Kutikov A, Kunkle DA, Uzzo RG. Focal therapy for kidney cancer: a systematic review. Curr Opin Urol. 2009 Mar;19(2):148-53.
75. Klingler HC, Susani M, Seip R, Mauermann J, Sanghvi N, Marberger MJ. A novel approach to energy ablative therapy of small renal tumours: laparoscopic high-intensity focused ultrasound. Eur Urol. 2008 Apr;53(4):810-6; discussion 7-8.
76. Klatte T, Marberger M. High-intensity focused ultrasound for the treatment of renal masses: current status and future potential. Curr Opin Urol. 2009 Mar;19(2):188-91.
77. Horoszewicz JS, Murphy GP. An assessment of the current use of human interferons in therapy of urological cancers. J Urol. 1989 Nov;142(5):1173-80.
78. Fidler IJ, Heicappell R, Saiki I, Grutter MG, Horisberger MA, Nuesch J. Direct antiproliferative effects of recombinant human interferon-alpha B/D hybrids on human tumor cell lines. Cancer Res. 1987 Apr 15;47(8):2020-7.
79. Chang E, Boyd A, Nelson CC, Crowley D, Law T, Keough KM, et al. Successful treatment of infantile hemangiomas with interferon-alpha-2b. J Pediatr Hematol Oncol. 1997 May-Jun;19(3):237-44.
80. Nanus DM, Pfeffer LM, Bander NH, Bahri S, Albino AP. Antiproliferative and antitumor effects of alpha-interferon in renal cell carcinomas: correlation with the expression of a kidney-associated differentiation glycoprotein. Cancer Res. 1990 Jul 15;50(14):4190-4.
81. Pyrhonen S, Salminen E, Ruutu M, Lehtonen T, Nurmi M, Tammela T, et al. Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. J Clin Oncol. 1999 Sep;17(9):2859-67.
82. Collaborators MRCRC. Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Medical Research Council Renal Cancer Collaborators. Lancet. 1999 Jan 2;353(9146):14-7.
83. Coppin C, Porzsolt F, Awa A, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. Cochrane Database Syst Rev. 2005(1):CD001425.
84. Harris JM, Martin NE, Modi M. Pegylation: a novel process for modifying pharmacokinetics. Clin Pharmacokinet. 2001;40(7):539-51.
85. Glue P, Fang JW, Rouzier-Panis R, Raffanel C, Sabo R, Gupta SK, et al. Pegylated interferon-alpha2b: pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data. Hepatitis C Intervention Therapy Group. Clin Pharmacol Ther. 2000 Nov;68(5):556-67.
86. Berg WJ, Divgi CR, Nanus DM, Motzer RJ. Novel investigative approaches for advanced renal cell carcinoma. Semin Oncol. 2000 Apr;27(2):234-9.
87. Motzer RJ, Rakhit A, Thompson J, Gurney H, Selby P, Figlin R, et al. Phase II trial of branched peginterferon-alpha 2a (40 kDa) for patients with advanced renal cell carcinoma. Ann Oncol. 2002 Nov;13(11):1799-805.
88. McDermott DF, Regan MM, Clark JI, Flaherty LE, Weiss GR, Logan TF, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous

interleukin-2 and interferon in patients with metastatic renal cell carcinoma. J Clin Oncol. 2005 Jan 1;23(1):133-41.

89. Rosenberg SA, Lotze MT, Yang JC, Topalian SL, Chang AE, Schwartzentruber DJ, et al. Prospective randomized trial of high-dose interleukin-2 alone or in conjunction with lymphokine-activated killer cells for the treatment of patients with advanced cancer. J Natl Cancer Inst. 1993 Apr 21;85(8):622-32.

90. Yang JC, Topalian SL, Schwartzentruber DJ, Parkinson DR, Marincola FM, Weber JS, et al. The use of polyethylene glycol-modified interleukin-2 (PEG-IL-2) in the treatment of patients with metastatic renal cell carcinoma and melanoma. A phase I study and a randomized prospective study comparing IL-2 alone versus IL-2 combined with PEG-IL-2. Cancer. 1995 Aug 15;76(4):687-94.

91. Yang JC, Sherry RM, Steinberg SM, Topalian SL, Schwartzentruber DJ, Hwu P, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol. 2003 Aug 15;21(16):3127-32.

92. Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol. 1995 Mar;13(3):688-96.

93. Donskov F, Middleton M, Fode K, Meldgaard P, Mansoor W, Lawrance J, et al. Two randomised phase II trials of subcutaneous interleukin-2 and histamine dihydrochloride in patients with metastatic renal cell carcinoma. Br J Cancer. 2005 Oct 3;93(7):757-62.

94. Fyfe GA, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Long-term response data for 255 patients with metastatic renal cell carcinoma treated with high-dose recombinant interleukin-2 therapy. J Clin Oncol. 1996 Aug;14(8):2410-1.

95. Boccardo F, Rubagotti A, Canobbio L, Galligioni E, Sorio R, Lucenti A, et al. Interleukin-2, interferon-alpha and interleukin-2 plus interferon-alpha in renal cell carcinoma. A randomized phase II trial. Tumori. 1998 Sep-Oct;84(5):534-9.

96. Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Francais d'Immunotherapie. N Engl J Med. 1998 Apr 30;338(18):1272-8.

97. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004 Oct 1;64(19):7099-109.

98. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007 Jan 11;356(2):125-34.

99. Hutson TE, Figlin RA, Kuhn JG, Motzer RJ. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. Oncologist. 2008 Oct;13(10):1084-96.

100. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007 Jan 11;356(2):115-24.

101. Papaetis GS, Syrigos KN. Sunitinib: a multitargeted receptor tyrosine kinase inhibitor in the era of molecular cancer therapies. BioDrugs. 2009;23(6):377-89.
102. Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res. 1997 Oct 15;57(20):4593-9.
103. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. 2007 Dec 22;370(9605):2103-11.
104. Rini BI. Temsirolimus, an inhibitor of mammalian target of rapamycin. Clin Cancer Res. 2008 Mar 1;14(5):1286-90.
105. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008 Aug 9;372(9637):449-56.
106. Pizzocaro G, Piva L, Di Fronzo G, Giongo A, Cozzoli A, Dormia E, et al. Adjuvant medroxyprogesterone acetate to radical nephrectomy in renal cancer: 5-year results of a prospective randomized study. J Urol. 1987 Dec;138(6):1379-81.
107. Messing EM, Manola J, Wilding G, Propert K, Fleischmann J, Crawford ED, et al. Phase III study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma: an Eastern Cooperative Oncology Group/Intergroup trial. J Clin Oncol. 2003 Apr 1;21(7):1214-22.
108. Pizzocaro G, Piva L, Colavita M, Ferri S, Artusi R, Boracchi P, et al. Interferon adjuvant to radical nephrectomy in Robson stages II and III renal cell carcinoma: a multicentric randomized study. J Clin Oncol. 2001 Jan 15;19(2):425-31.
109. Anigenics I. Press release, New York, NY. 2006.
110. Jocham D, Richter A, Hoffmann L, Iwig K, Fahlenkamp D, Zakrzewski G, et al. Adjuvant autologous renal tumour cell vaccine and risk of tumour progression in patients with renal-cell carcinoma after radical nephrectomy: phase III, randomised controlled trial. Lancet. 2004 Feb 21;363(9409):594-9.
111. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. N Engl J Med. 1996 Sep 19;335(12):865-75.
112. Haas. Update on targeted adjuvant trials (ECOG/MRC). As presented at the Fifth International Symposium of the Kidney Cancer Association, 2006, Chicago, Illinois. 2006.
113. Jonasch E. Presurgical therapy in metastatic renal cell carcinoma. Expert Rev Anticancer Ther. 2007 Jan;7(1):73-8.
114. Wood CG. Multimodal approaches in the management of locally advanced and metastatic renal cell carcinoma: combining surgery and systemic therapies to improve patient outcome. Clin Cancer Res. 2007 Jan 15;13(2 Pt 2):697s-702s.
115. Margulis V, Matin SF, Tannir N, Tamboli P, Swanson DA, Jonasch E, et al. Surgical morbidity associated with administration of targeted molecular therapies before cytoreductive nephrectomy or resection of locally recurrent renal cell carcinoma. J Urol. 2008 Jul;180(1):94-8.
116. Wood CG, Margulis V. Neoadjuvant (presurgical) therapy for renal cell carcinoma: a new treatment paradigm for locally advanced and metastatic disease. Cancer. 2009 May 15;115(10 Suppl):2355-60.

117. Hansson R, Johansson S, Jonsson O, Pettersson S, Schersten T, Waldenstrom J. Kidney protection by pretreatment with free radical scavengers and allopurinol: renal function at recirculation after warm ischaemia in rabbits. Clin Sci (Lond). 1986 Sep;71(3):245-51.

118. Novick AC. Renal hypothermia: in vivo and ex vivo. Urol Clin North Am. 1983 Nov;10(4):637-44.

119. Pettersson. Renal Preservation in extracorporeal surgery. In: Marberger M DK, editor. Renal preservation. Baltimore MD: Williams & Wilkins; 1983. p. 139-63.

120. Sobin LH, Fleming ID. TNM Classification of Malignant Tumors, fifth edition (1997). Union Internationale Contre le Cancer and the American Joint Committee on Cancer. Cancer. 1997 Nov 1;80(9):1803-4.

121. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000 Feb 2;92(3):205-16.

122. Jacobsen J, Rasmuson T, Grankvist K, Ljungberg B. Vascular endothelial growth factor as prognostic factor in renal cell carcinoma. J Urol. 2000 Jan;163(1):343-7.

123. Gehan EA. The determinatio of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. J Chronic Dis. 1961 Apr;13:346-53.

124. Jelliffe RW. Letter: Creatinine clearance: bedside estimate. Ann Intern Med. 1973 Oct;79(4):604-5.

125. Eknoyan G, Levin NW. Impact of the new K/DOQI guidelines. Blood Purif. 2002;20(1):103-8.

126. Zagoria RJ, Traver MA, Werle DM, Perini M, Hayasaka S, Clark PE. Oncologic efficacy of CT-guided percutaneous radiofrequency ablation of renal cell carcinomas. AJR Am J Roentgenol. 2007 Aug;189(2):429-36.

127. Gervais DA, McGovern FJ, Wood BJ, Goldberg SN, McDougal WS, Mueller PR. Radio-frequency ablation of renal cell carcinoma: early clinical experience. Radiology. 2000 Dec;217(3):665-72.

128. Goldberg SN, Charboneau JW, Dodd GD, 3rd, Dupuy DE, Gervais DA, Gillams AR, et al. Image-guided tumor ablation: proposal for standardization of terms and reporting criteria. Radiology. 2003 Aug;228(2):335-45.

129. Memarsadeghi M, Schmook T, Remzi M, Weber M, Potscher G, Lammer J, et al. Percutaneous radiofrequency ablation of renal tumors: midterm results in 16 patients. Eur J Radiol. 2006 Aug;59(2):183-9.

130. Gervais DA, Arellano RS, Mueller PR. Percutaneous radiofrequency ablation of renal cell carcinoma. Eur Radiol. 2005 May;15(5):960-7.

131. Ljungberg B, Alamdari FI, Holmberg G, Granfors T, Duchek M. Radical nephrectomy is still preferable in the treatment of localized renal cell carcinoma. A long-term follow-up study. Eur Urol. 1998;33(1):79-85.

132. Novick AC. Nephron-sparing surgery for renal cell carcinoma. Annu Rev Med. 2002;53:393-407.

133. Belldegrun A, Tsui KH, deKernion JB, Smith RB. Efficacy of nephron-sparing surgery for renal cell carcinoma: analysis based on the new 1997 tumor-node-metastasis staging system. J Clin Oncol. 1999 Sep;17(9):2868-75.

134. Fergany AF, Hafez KS, Novick AC. Long-term results of nephron sparing surgery for localized renal cell carcinoma: 10-year followup. J Urol. 2000 Feb;163(2):442-5.
135. Marberger M, Pugh RC, Auvert J, Bertermann H, Costantini A, Gammelgaard PA, et al. Conservation surgery of renal carcinoma: the EIRSS experience. Br J Urol. 1981 Dec;53(6):528-32.
136. Van Poppel H, Bamelis B, Oyen R, Baert L. Partial nephrectomy for renal cell carcinoma can achieve long-term tumor control. J Urol. 1998 Sep;160(3 Pt 1):674-8.
137. Marshall FF, Taxy JB, Fishman EK, Chang R. The feasibility of surgical enucleation for renal cell carcinoma. J Urol. 1986 Feb;135(2):231-4.
138. Rosenthal CL, Kraft R, Zingg EJ. Organ-preserving surgery in renal cell carcinoma: tumor enucleation versus partial kidney resection. Eur Urol. 1984;10(4):222-8.
139. Eschwege P, Saussine C, Steichen G, Delepaul B, Drelon L, Jacqmin D. Radical nephrectomy for renal cell carcinoma 30 mm. or less: long-term follow results. J Urol. 1996 Apr;155(4):1196-9.
140. Ljungberg B, Mehle C, Stenling R, Roos G. Heterogeneity in renal cell carcinoma and its impact no prognosis--a flow cytometric study. Br J Cancer. 1996 Jul;74(1):123-7.
141. Bosniak MA, Birnbaum BA, Krinsky GA, Waisman J. Small renal parenchymal neoplasms: further observations on growth. Radiology. 1995 Dec;197(3):589-97.
142. Uzzo RG, Novick AC. Nephron sparing surgery for renal tumors: indications, techniques and outcomes. J Urol. 2001 Jul;166(1):6-18.
143. Dechet C BM, Zincke H. Nephron-preserving surgery for unilateral renal cell carcinoma: which variables contribute to contralateral renal tumor recurrence? J Urol. 1998;159((Suppl 5)):169.
144. Novick AC. The role of renal-sparing surgery for renal cell carcinoma. Semin Urol. 1992 Feb;10(1):12-5.
145. Brkovic D, Riedasch G, Waldherr R, Rohl L, Staehler G. [Local recurrence after organ saving kidney tumor surgery]. Urologe A. 1994 Mar;33(2):104-9.
146. Hafez KS, Novick AC, Campbell SC. Patterns of tumor recurrence and guidelines for followup after nephron sparing surgery for sporadic renal cell carcinoma. J Urol. 1997 Jun;157(6):2067-70.
147. Steinbach F, Stockle M, Hohenfellner R. Clinical experience with nephron-sparing surgery in the presence of a normal contralateral kidney. Semin Urol Oncol. 1995 Nov;13(4):288-91.
148. Delakas D, Karyotis I, Daskalopoulos G, Terhorst B, Lymberopoulos S, Cranidis A. Nephron-sparing surgery for localized renal cell carcinoma with a normal contralateral kidney: a European three-center experience. Urology. 2002 Dec;60(6):998-1002.
149. Lee CT, Katz J, Shi W, Thaler HT, Reuter VE, Russo P. Surgical management of renal tumors 4 cm. or less in a contemporary cohort. J Urol. 2000 Mar;163(3):730-6.
150. Lau WK, Blute ML, Weaver AL, Torres VE, Zincke H. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. Mayo Clin Proc. 2000 Dec;75(12):1236-42.

151. McKiernan J, Yossepowitch O, Kattan MW, Simmons R, Motzer RJ, Reuter VE, et al. Partial nephrectomy for renal cortical tumors: pathologic findings and impact on outcome. Urology. 2002 Dec;60(6):1003-9.
152. Matin SF, Gill IS, Worley S, Novick AC. Outcome of laparoscopic radical and open partial nephrectomy for the sporadic 4 cm. or less renal tumor with a normal contralateral kidney. J Urol. 2002 Oct;168(4 Pt 1):1356-9; discussion 9-60.
153. Ljungberg B. HDC, Kuczyk M.A., Merseburger A.S., Mulders P.F.A., Patard J-J., Sinescu I.C. EAU-Guidelines on Renal Cell Carcinoma. European Association of Urology Guidelines. 2009 ed. Arnhem: Drukkerij Gelderland bv; 2009. p. 1-28.
154. Onkologiskt Centrum S. Nationella njurcacerregistret. Rapport från åren 2005-2007. 2008.
155. Weber WA, Figlin R. Monitoring cancer treatment with PET/CT: does it make a difference? J Nucl Med. 2007 Jan;48 Suppl 1:36S-44S.
156. Gore ME, Escudier B. Emerging efficacy endpoints for targeted therapies in advanced renal cell carcinoma. Oncology (Williston Park). 2006 May;20(6 Suppl 5):19-24.
157. Avril N. GLUT1 expression in tissue and (18)F-FDG uptake. J Nucl Med. 2004 Jun;45(6):930-2.
158. Freedman NM, Sundaram SK, Kurdziel K, Carrasquillo JA, Whatley M, Carson JM, et al. Comparison of SUV and Patlak slope for monitoring of cancer therapy using serial PET scans. Eur J Nucl Med Mol Imaging. 2003 Jan;30(1):46-53.
159. Vansteenkiste JF, Stroobants SG. Positron emission tomography in the management of non-small cell lung cancer. Hematol Oncol Clin North Am. 2004 Feb;18(1):269-88.
160. Lawrentschuk N, Davis ID, Bolton DM, Scott AM. Positron emission tomography (PET), immuno-PET and radioimmunotherapy in renal cell carcinoma: a developing diagnostic and therapeutic relationship. BJU Int. 2006 May;97(5):916-22.
161. Ahmad T, Eisen T. Kinase inhibition with BAY 43-9006 in renal cell carcinoma. Clin Cancer Res. 2004 Sep 15;10(18 Pt 2):6388S-92S.
162. Hiles JJ, Kolesar JM. Role of sunitinib and sorafenib in the treatment of metastatic renal cell carcinoma. Am J Health Syst Pharm. 2008 Jan 15;65(2):123-31.
163. Bukowski R, Ernstoff MS, Gore ME, Nemunaitis JJ, Amato R, Gupta SK, et al. Pegylated interferon alfa-2b treatment for patients with solid tumors: a phase I/II study. J Clin Oncol. 2002 Sep 15;20(18):3841-9.
164. Bex A, Mallo H, Kerst M, Haanen J, Horenblas S, de Gast GC. A phase-II study of pegylated interferon alfa-2b for patients with metastatic renal cell carcinoma and removal of the primary tumor. Cancer Immunol Immunother. 2005 Jul;54(7):713-9.
165. Bracarda S ECea. Sorafenib Plus Interferon alpha-2b in Metastatic Renal Cell Carcinoma: Results from RAPSODY (GOIRC Study 0681) - A Randomized Prospective Phase II Trial of Two Different Treatment Schedules. EAU 2008 - 23rd Annual EAU Congress. 2008 2 April 2008.
166. Melichar B, Koralewski P, Ravaud A, Pluzanska A, Bracarda S, Szczylik C, et al. First-line bevacizumab combined with reduced dose interferon-{alpha}2a is active in patients with metastatic renal cell carcinoma. Ann Oncol. 2008 Apr 11;19(8):1470-6.

167. Fossa S, Jones M, Johnson P, Joffe J, Holdener E, Elson P, et al. Interferon-alpha and survival in renal cell cancer. Br J Urol. 1995 Sep;76(3):286-90.
168. Elson PJ, Witte RS, Trump DL. Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. Cancer Res. 1988 Dec 15;48(24 Pt 1):7310-3.
169. Fossa SD, Kramar A, Droz JP. Prognostic factors and survival in patients with metastatic renal cell carcinoma treated with chemotherapy or interferon-alpha. Eur J Cancer. 1994;30A(9):1310-4.
170. Negrier S, Escudier B, Gomez F, Douillard JY, Ravaud A, Chevreau C, et al. Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinomas treated by cytokines: a report from the Groupe Francais d'Immunotherapie. Ann Oncol. 2002 Sep;13(9):1460-8.
171. Alamdari FI, Rasmuson T, Grankvist K, Ljungberg B. Angiogenesis and other markers for prediction of survival in metastatic renal cell carcinoma. Scand J Urol Nephrol. 2007;41(1):5-9.
172. Bukowski RM, Tim Eisen, Cezary Szczylik, Walter M Stadler, Ronit Simantov, Minghua Shan, Jim Elting, Carol Pena, Bernard Escudier for the Sorafenib TARGET Group. Final Results of the Randomized Phase III Trial of Sorafenib in Advanced Renal Cell Carcinom: Survival and Biomarker Analysis. ASCO 2008; 2008; Chicago. 2008.
173. Glue P, Rouzier-Panis R, Raffanel C, Sabo R, Gupta SK, Salfi M, et al. A dose-ranging study of pegylated interferon alfa-2b and ribavirin in chronic hepatitis C. The Hepatitis C Intervention Therapy Group. Hepatology. 2000 Sep;32(3):647-53.
174. Wang R, Wolf JS, Jr., Wood DP, Jr., Higgins EJ, Hafez KS. Accuracy of percutaneous core biopsy in management of small renal masses. Urology. 2009 Mar;73(3):586-90; discussion 90-1.
175. Veltri A, Garetto I, Pagano E, Tosetti I, Sacchetto P, Fava C. Percutaneous RF thermal ablation of renal tumors: is US guidance really less favorable than other imaging guidance techniques? Cardiovasc Intervent Radiol. 2009 Jan-Feb;32(1):76-85.
176. Rouviere O, Badet L, Murat FJ, Marechal JM, Colombel M, Martin X, et al. Radiofrequency ablation of renal tumors with an expandable multitined electrode: results, complications, and pilot evaluation of cooled pyeloperfusion for collecting system protection. Cardiovasc Intervent Radiol. 2008 May-Jun;31(3):595-603.
177. Breen DJ, Rutherford EE, Stedman B, Roy-Choudhury SH, Cast JE, Hayes MC, et al. Management of renal tumors by image-guided radiofrequency ablation: experience in 105 tumors. Cardiovasc Intervent Radiol. 2007 Sep-Oct;30(5):936-42.
178. Goldberg SN, Gazelle GS, Compton CC, Mueller PR, Tanabe KK. Treatment of intrahepatic malignancy with radiofrequency ablation: radiologic-pathologic correlation. Cancer. 2000 Jun 1;88(11):2452-63.
179. Nilsson A. Contrast-enhanced ultrasound of the kidneys. Eur Radiol. 2004;14(Suppl 8):P104-P9.
180. Varkarakis IM, Allaf ME, Inagaki T, Bhayani SB, Chan DY, Su LM, et al. Percutaneous radio frequency ablation of renal masses: results at a 2-year mean followup. J Urol. 2005 Aug;174(2):456-60; discussion 60.
181. Gervais DA, McGovern FJ, Arellano RS, McDougal WS, Mueller PR. Radiofrequency ablation of renal cell carcinoma: part 1, Indications, results,

and role in patient management over a 6-year period and ablation of 100 tumors. AJR Am J Roentgenol. 2005 Jul;185(1):64-71.
182. Stern JM, Svatek R, Park S, Hermann M, Lotan Y, Sagalowsky AI, et al. Intermediate comparison of partial nephrectomy and radiofrequency ablation for clinical T1a renal tumours. BJU Int. 2007 Aug;100(2):287-90.
183. Levinson AW, Su LM, Agarwal D, Sroka M, Jarrett TW, Kavoussi LR, et al. Long-term oncological and overall outcomes of percutaneous radio frequency ablation in high risk surgical patients with a solitary small renal mass. J Urol. 2008 Aug;180(2):499-504; discussion
184. Mahnken AH, Rohde D, Brkovic D, Gunther RW, Tacke JA. Percutaneous radiofrequency ablation of renal cell carcinoma: preliminary results. Acta Radiol. 2005 Apr;46(2):208-14.
185. Farrell MA, Charboneau WJ, DiMarco DS, Chow GK, Zincke H, Callstrom MR, et al. Imaging-guided radiofrequency ablation of solid renal tumors. AJR Am J Roentgenol. 2003 Jun;180(6):1509-13.
186. Lucas SM, Stern JM, Adibi M, Zeltser IS, Cadeddu JA, Raj GV. Renal function outcomes in patients treated for renal masses smaller than 4 cm by ablative and extirpative techniques. J Urol. 2008 Jan;179(1):75-9; discussion 9-80.
187. Sweeney JP, Thornhill JA, Graiger R, McDermott TE, Butler MR. Incidentally detected renal cell carcinoma: pathological features, survival trends and implications for treatment. Br J Urol. 1996 Sep;78(3):351-3.
188. Crispen PL, Uzzo RG. The natural history of untreated renal masses. BJU Int. 2007 May;99(5 Pt B):1203-7.
189. Pahernik S, Ziegler S, Roos F, Melchior SW, Thuroff JW. Small renal tumors: correlation of clinical and pathological features with tumor size. J Urol. 2007 Aug;178(2):414-7; discussion 6-7.
190. Hsu RM, Chan DY, Siegelman SS. Small renal cell carcinomas: correlation of size with tumor stage, nuclear grade, and histologic subtype. AJR Am J Roentgenol. 2004 Mar;182(3):551-7.