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Long-term Survival in Renal Cell Cancer Patients

Symptoms, diagnostics and prognostic factors

ACADEMIC DISSERTATION
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Abstract

The object of this study was to investigate the long-term prognosis and prognostic factors, symptoms and change in diagnostics among renal cell carcinoma (RCC) patients diagnosed in the Pirkanmaa region. To this end, we collected information from the original medical records of 970 RCC patients diagnosed between 1963 and 1997. Follow-up was up to August 2007, the longest follow-up being 35 years.

RCC is a rare disease. During 2011, according to the most recent statistics in the Finnish Cancer Registry, new cases of kidney cancer were diagnosed in 415 females and 562 males nationwide. Of these, 42 females and 43 males were diagnosed in the Pirkanmaa Hospital District. Almost 40 years has passed since the last publication on the clinical presentation of RCC in Finland. Apart from this, we found no data on the current symptoms of RCC in the international literature. This lack of information prompted us to collect the present material.

RCC involves poor long-term survival. Here primarily metastatic disease was found in 26% of patients and 30% relapsed during follow-up, some of these even after a 20-year disease-free period. After 25 years only 26% of patients were alive. Fifty per cent of operated women and 43% of operated men remained disease-free; 47% of all women and 54% of all men died of RCC. Stage, age and symptomatic disease were the most important clinical prognostic factors. Also grade, gender, smoking status and body mass index (BMI) were significant. In terms of the order of importance of clinical factors, the clinical presentation proved a stronger prognostic factor than BMI. Obese patients had better survival (5.9 years) than normal or underweight patients (3.4 years and 12 months, respectively) with lower-stage, asymptomatic tumors. Smokers had poorer survival in localized tumors than non-smokers; in stage I tumors five-year overall survival was 71% vs. 89%, respectively. In cancer-spesific survival there was no difference between smoking status groups, even though smokers had more relapses and a shorter disease-free interval. There was no difference in patient-dependent delay. We found no other explanatory factors for recurrent disease than the smoking itself.

RCC tumors are nowadays more often small and of lower stage than those diagnosed before computed tomography (CT) and ultrasound came into general

use. However, in this study only 12% of tumors were <3.0 cm in diameter; most being found in recent study years. These tumors were more often asymptomatic and had better prognosis than larger tumors. The survival rate after 20 years was 67% vs. 30% in patients with small or large tumors, respectively. More imaging studies were needed to assess these small tumors, but the diagnostic accuracy was the same as with larger growths. The mean figure was 3.17 in the group with small tumors and 2.92 in large tumors. CT proved the best method.

The most common symptoms of RCC were flank pain, hematuria and high erythrocyte sedimentation rate (ESR). During the study period, the incidence of hematuria (from 39% to 26%) and high ESR (from 28% to 20%) decreased, but there was no change in other symptoms.

In conclusion, long-term survival in RCC was still poor regardless of the development of diagnostics and treatment; it was the cause of death in 47% of women and 54% of men. The previously known clinical prognostic factors, for example stage, age and clinical presentation, were valid also in Finnish patients. Of prognostic factors, symptomatic disease was stronger than high BMI, which normally signifies better prognosis. Symptoms of RCC changed only little during the study period; only the incidence of hematuria and high ESR decreased. The use of diagnostic imaging studies has changed substantially since CT and ultrasound became available. The use of angiography, cavography and urography has decreased along with this change.

Tiivistelmä

Tutkimuksen tarkoitus oli selvittää Pirkanmaalla todettujen munuaissyöpäpotilaiden pitkäaikaisennuste ja siihen vaikuttavat tekijät, taudin oireet ja diagnostiikan muutos. Tätä varten keräsimme alkuperäisistä potilaspapereista vuosina 1964-1997 diagnosoidun 970 munuaissyöpäpotilaan tiedot. Seuranta-aika oli elokuulle 2007, jolloin pisin seuranta oli 35.4 vuotta.

Munuaissyöpä on harvinainen sairaus. Tuoreimmissa Suomen Syöpärekisterin tilastoissa vuodelta 2011 uusia tapauksia diagnosoitiin 415 naisella ja 562 miehellä, näistä 42 naista ja 43 miestä Pirkanmaan sairaanhoitopiirin alueella. Edellisestä julkaisusta suomalaisen munuaissyövän kliinisestä kuvasta on kulunut lähes neljäkymmentä vuotta. Myöskään kansainvälisessä kirjallisuudessa ei ole munuaissyövän oireista julkaistu kattavaa materiaalia. Kyseinen tiedon puute sai aikaan tämän tutkimusaineiston keräämisen.

Munuaissyövällä on huono pitkäaikaisennuste. Toteamisvaiheessa levinnyt tauti löytyi 26 %:lla ja 30 %:lla syöpä uusiutui seurannassa. Osa uusiutumista tapahtui vielä 20 vuoden tautivapaan ajan jälkeen. Vain 26 % potilaista oli elossa 25 vuoden jälkeen. Tautivapaina operoiduista potilaista pysyi 50 % naisista ja 43 % miehistä; munuaissyöpään kuoli kaikista naisista 47 % ja miehistä 54 %. Levinnäisyysaste, ikä ja taudin oireisuus olivat tärkeimmät kliiniset ennustetekijät. Myös erilaistumisaste, sukupuoli, tupakointi ja painoindeksi olivat merkitseviä ennustetekijöitä. Verrattaessa ennustetekijöiden tärkeysjärjestystä, taudin oireisuus osoittautui tärkeämmäksi kuin painoindeksi. Ylipainoisilla potilailla oli pitempi elossaoloaika (5.9 vuotta) kuin normaali- tai alipainoisilla (3.4 vuotta ja 12 kk). Tauti oli myös matalampaa levinneisyyttä ja useammin oireeton löydös. Tupakoitsijoilla oli huonompi ennuste paikallisissa kasvaimissa kuin tupakoimattomilla: levinneisyysasteessa I viiden vuoden kuluttua elossa oli tupakoitsijoista 71 % ja tupakoimattomista 89 %. Syöpäspesifisessä elossaolossa ei ollut eroa tupakointiryhmien välillä, vaikkakin tupakoitsijoilla oli enemmän uusiutumia ja lyhyempi tautivapaa-aika. Potilaiden hoitoon hakeutumisajassa oireiden alusta ei kuitenkaan löytynyt eroa. Tässä tutkimuksessa tupakoitsijoiden huonompaan ennusteeseen ei löytynyt muita syitä kuin itse tupakointi.

Munuaissyöpä on yhä useammin pieni ja matalan levinneisyyden omaava kuin ennen tietokonetomografian ja ultraäänen yleistymistä. Tässä materiaalissa kuitenkin vain 12 % kasvaimista oli <3.0 cm läpimitaltaan; suurin osa näistä kuitenkin tutkimusjakson loppupuolella löytyneitä. Pienet kasvaimet olivat useammin oireettomia ja niillä oli parempi ennuste kuin isommilla kasvaimilla. Kahdenkymmenen vuoden päästä elossa oli 67 % potilaista, joilla oli ollut pieni kasvain ja 30 % ison kasvaimen takia hoidetuista. Diagnostiikassa tarvittiin enemmän radiologisia tutkimuksia, mutta näiden jälkeen diagnostinen tarkkuus oli samaa luokkaa kuin isommilla kasvaimilla. Keskimäärin pienille tuumoreille tehtiin 3,17 tutkimusta ja isoille 2,92. Tietokonetomografia oli paras diagnostinen kuvantamismenetelmä.

Yleisimmät munuaissyövän oireet olivat vatsakipu, verivirtsaisuus ja korkea lasko. Tutkimusajanjakson aikana verivirtsaisuus (39 %-26 %) ja korkean laskon (28 %-20 %) esiintyminen vähenivät, mutta muiden oireiden esiintyvyydessä ei ollut muutosta.

Tutkimuksen johtopäätöksenä on se, että huolimatta hoidon kehittymisestä, pitkäaikaisennuste oli edelleen huono; munuaissyöpä oli kuolinsyynä 47 %:lla naisista ja 54 %:lla miehistä. Tunnetut ennustetekijät, kuten levinneisyysaste, ikä ja taudin oireisuus, toimivat myös suomalaisilla potilailla. Näistä oireisuus oli voimakkaampi ennustetekijä kuin korkea painoindeksi, joka on hyvän ennusteen merkki. Oirekuva on muuttunut näiden vuosikymmenten aikana vain vähän, vain verivirtsaisuuden ja hypersedimentaation esiintyvyys pieneni. Diagnostiset kuvantamistutkimukset ovat muuttuneet voimakkaasti tieotokonetomografian ja ultraäänen käyttöönotulemisen jälkeen; angiografian, cavografian ja urografian käyttö on vähentynyt voimakkaasti tuon muutoksen myötä.

Contents

List of original communications

This thesis is based on the following publications, which are referred to in the text by their Roman numbers. In addition, previously unpublished results are presented.

I. Sunela KL, Kataja MJ, Lehtinen ET, Salminen TK, Kujala PM, Virman JP, Kellokumpu-Lehtinen P-LI (2009): Prognostic factors and long-term survival in renal cell cancer patients. Scand J Urol Nephrol 43(6): 454-460.

II. Sunela KL, Kataja MJ, Kellokumpu-Lehtinen P-LI (2010): Changes in symptoms of renal cell carcinoma over four decades. BJU Int; 106: 649-653.

III. Sunela KL, Kataja MJ, Kellokumpu-Lehtinen, P-LI: Influence of body mass index and smoking on the long-term survival of patients with renal cell cancer. Clin Genitourin Cancer, 2013 Jun 26. doi:10.1016/j.clgc.2013.04.017 [Epub ahead of print].

IV. Sunela KL, Lehtinen ET, Kataja MJ, Kujala PM, Soimakallio S, Kellokumpu-Lehtinen P-LI: Development of renal cell carcinoma (RCC) diagnostics and impact on prognosis. BJU Int, 2013 Jul 26. doi:10.1111/bju.12242 [Epub ahead of print].

The publishers of the original articles have kindly granted permission to reprint the papers.

Abbreviations

BID	bis in die; Latin; twice a day
BMI	body mass index
BRAF	proto-oncogene producing a protein called B-Raf.
CAIX	carbonic anhydrase IX
cc	clear cell
c-Kit	mast/ stem cell growth factor receptor; tyrosine-protein kinase CD117
c-MET	proto-oncogene encoding hepatocyte growth factor receptor
CR	complete response
CSS	cancer-specific survival
CT	computed tomography
CTL	cytotoxic T lymphocyte
CTLA-4	cytotoxic T lymphocyte antigen 4, a protein receptor which downregulates the immune system
CXCR3/4	gene that encodes C-X-C chemokine receptor type 3/4
DFI	disease-free interval
DFS	disease-free survival
DNA	deoxyribonucleic acid
ESR	erythrocyte sedimentation rate
18F-FDG PET	18F-fluoro-deoxy-glucose positron emission tomography
FGF(R)	fibroblast growth factor (receptor)
FH	fumarate hydratase
FLCN	tumor suppressor gene, folliculin
Flt3	FMS-like tyrosine kinase 3
5-FU	5-fluorouracil
GM-CSF	granulocyte macrophage colony stimulating factor
HIF	hypoxia induced factor
HLA	human leucocyte antigen
HRPT2	the tumor suppressor gene causing hyperparathyroidism-jaw syndrome (Cdc73)

HSS	high statistical significance
IFN	interferon
IGF-1	insulin-like growth factor-1
IL	interleukin
i.v.	intravenous
LAG-3	lymphocyte-activation gene 3
LOH	loss of heterogeneity
MDR	multi-drug resistance protein
MHC	major histocompatibility complex
(M)IU	(million) international units
mmHg	millimetres of mercury
MMP	matrix metalloproteinase
(m)PFS	(median) progression-free survival
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSKCC	Memorial Sloan-Kettering Cancer Center
MTD	maximal tolerated dose
mTOR	mammalian target of rapamycin
NA	not accessible
ORR	overall response rate
PD-1	programmed death-1, a cell-surface co-inhibotory receptor regulating negatively T-cell activation
PDGF(R)	platelet derived growth factor (receptor)
p.o.	per orally
OR	odds ratio
OS	overall survival
PR	partial response
SD	stable disease
SSIGN	stage size grade and necrosis –prognostic scoring system
RCC	renal cell cancer
RET	rearranged during transfection; proto-oncogene encoding a tyrosine kinase receptor for extracellular signaling
RF(A)	radiofrequency (ablation)
RR	risk ratio
s.c.	subcutaneusly
SDHB	succinate dehydrogenase complex, subunit B
TFE3	transcription factor E3
TGF(R)	transforming growth factor (receptor)

TIE	gene encoding tyrosine protein kinase, which has role in angiogenesis and blood vessel stability by inhibiting angiopoietin 1
TKI	tyrosine kinase inhibitor
TNM	tumor-node-metastasis; classification for cancers
TSC	tuberous sclerosis complex gene
UCLA	University of California, Los Angeles
UICC	Union Internationale Contre le Cancer
US	ultrasound
VEGF(R)	vascular endothelial growth factor (receptor)
VHL	von Hippel-Lindau

1 Introduction

Although the incidence of and mortality from renal cell carcinoma (RCC) have until recently continuously increased, the proportion of patients surviving for five years has improved (Pantuck et al. 2001, Ljungberg et al. 2011). The rising incidence is observed in every stage, but the greatest change is reported in localized tumors (Chow et al. 1999). In most reports, a trend towards lower stages is observed (Woldrich et al. 2008). One previous study of 43 807 patients diagnosed between 1988 and 2006 showed an incidence rising from 7.6 to 11.7 / 100 000 person-years. The increase was observed mostly in localized disease; the incidence of higher stages decreased. (Sun et al. 2011) This is not a global phenomenon; no such tendency was observed in an Australian study on surgically treated patients between 1993 and 2007. However, the proportion of stage I patients was already high (67%) at the beginning of that study period. (Doeuk et al. 2011)

The Finnish Cancer Registry has recorded cancer cases in Finland since 1952. The most recent figure for kidney cancer cases is from the year 2011, with 977 diagnoses nationwide; 85 of these were diagnosed in Pirkanmaa. Since however the register records all cancers of the kidney (including uroepithelial and other histologies) in the same statistic, specific information on RCC is not directly available from this database. The Finnish Cancer Registry publishes one- and five-year survival ratios for different cancer types. The recent statistic for the one-year relative overall survival (OS) is 77% for males with kidney cancer and 78% for females, the five-year relative OS being 61% and 63%, respectively. In our hospital district, the age-adjusted incidence and mortality (per 100 000 person-years) increased between the 1970s and 1990s. In females the incidence increased from 4.5 to 5.5 and mortality from 1.7 to 2.7, in males from 9.0 to 12.3 and mortality from 4.4 to 5.9. In concrete numbers, this indicates that in the former period, 35 patients were diagnosed and 16 died of kidney cancer per year, in the latter period 70 and 31. Among males in our hospital district, kidney cancer is currently the tenth most common cancer in the causes of death statistics, accounting for 3.4% of cancer-related deaths. (www.cancer.fi)

Reports of 25-year survival among adult cancer patients are rare in the literature. Among breast cancer patients with tumors less than five centimeters in diameter and no distant metastases, 25-year survival is from 39.7% to 43.8%

depending on local therapy (Simone et al. 2012). Another study with patients over 70 years with primary local breast cancer not surprisingly reported 28-year OS of 0% (Gazet and Sutcliffe 2011). Among prostate cancer patients treated with a ^{125}I prostate implant followed by external beam irradiation, the 25-year disease-free survival rate has been 73%, but OS was not reported (Critz et al. 2012). Patients with high-grade, localized osteosarcoma have a 25-year OS rate from 15% to 38% depending on whether they received adjuvant chemotherapy or not (Bernthal et al. 2012).

Prior to the present study local information on survival and prognosis of RCC patients has been lacking. In addition, there were no data on current symptoms of RCC. We thus feld it important to collect and present this information in order to chart the clinical picture of Finnish RCC patients. In the present study we focused on the survival, prognostic factors, symptoms and diagnostics of these patients in the Pirkanmaa Hospital District. We evaluated the long-term survival in this large, centrally treated RCC population according to different subgroups. Such a long follow-up as ours has rarely been reported. The present paper reviews the clinical presentation and management of RCC as currently presented in the literature.

2 Review of the literature

2.1 Etiology

Hereditary RCC syndromes are estimated to be a reason for 3-5% of RCC cases. To date, ten such syndromes have been described, all inherited with an autosomal dominant trait. Further mutations are nevertheless required to develop RCC: a susceptibility to cancer is inherited, not cancer per se. (Verine et al. 2010) However, most RCCs are sporadic and a number of potential risk factors have been identified in epidemiologic studies.

2.1.1 Risk and protective factors in sporadic RCC

Tobacco smoking and obesity are the most consistently established causal factors, with a dose-dependent effect and strength of the association (Dhote et al. 2004). Also male gender (Woldrich et al. 2008), hypertension (Navai and Wood 2012) and acquired renal cystic disease involve a marked risk (Maisonneuve et al. 1999). Weaker associations have been shown with a history of kidney disease, for example previous kidney stones and urinary tract infections, immunosuppressive medication, diuretic and analgesic medications, occupational exposure, ionizing radiation, diabetes, number of births, hysterectomy and oophorectomy (Penn 1999, Dhote et al. 2004, Lindblad 2004). The risk of RCC is higher in the lowest sosioeconomic status quintile, but this is associated with a higher prevalence of smoking and obesity and poorer diet (Hellenthal et al. 2012).

Tobacco consumption of over 20 pack-years has led to a significant association with odds ratios (OR) between 1.3 and 9.3 (Dhote et al. 2004). The risk is increased even after cessation, being 1.3-fold for former smokers and 1.6 for current smokers when compared to never-smokers (Chow et al. 2000). Also never-smokers with prolonged (>20 years) enviromental smoke exposure carry a 2- to 4-fold increased likelihood of having RCC (Navai and Wood 2012). The mechanism of carcinogenesis is discussed in paper III.

An association has been shown between obesity and RCC, with ORs between 1.1 and 4.6, the most obese cases being at greatest risk (Dhote et al. 2004). The highest risk increase has been found among obese non-smokers (Chow et al. 2000). It is estimated that 27% of RCC cases among American men and 29% among women could be related to obesity. The risk of RCC

increases by 7% for each unit increase in body mass index (BMI). (Bergström et al. 2001) Mechanisms of increased risk are discussed in paper III. Patients with diabetes own a 1.3-1.7 –fold increased risk of RCC, and combination of obesity and diabetes increases the risk to 3.2–fold. It remains unclear whether diabetes is an independent causal factor or only an intermediate step between obesity and RCC. (Lindblad et al. 1999)

RCC is diagnosed more in males: 62.3% vs. 37.7% in females (Woldrich et al. 2008). The reason for this is not fully understood, but men are more likely to have occupational exposure to chemicals associated with RCC (Dosemeci et al. 1999, Dhote et al. 2000). One further reason for the gender difference might be smoking (Woldrich et al. 2008).

Hypertension is associated with a 2.4–fold risk of RCC, with a dose-dependent increase with increasing blood pressure (Navai and Wood 2012). High diastolic pressure also has an association with cancer risk. The risk of RCC in men with a diastolic pressure of ≥90 mmHg is more than double than in men with a pressure below 70 mmHg. If systolic pressure is ≥150 mmHg, the risk is 1.6-1.7-fold compared to those with a pressure below 120 mmHg. This risk is independent of BMI. Change in blood pressure during surveillance affected the cancer risk. (Chow et al. 2000) Diuretic therapy is associated with a twofold risk of RCC, women being in greater danger than men. This risk is related to the duration of diuretic use, but not with dose. The association is weaker when other factors such as hypertension are controlled for. (Grossman et al. 1999)

Patients with end-stage renal disease and acquired renal cystic disease have been reported to evince a 3.6-fold higher incidence of RCC than the general population. This excess cancer risk is highest in the 0-34 –year age group and is dependent on the time the patient has been on dialysis. (Maisonneuve et al. 1999) The prevalence of acquired renal cystic disease in dialysis patients varies between 30% and 90% (Schwarz et al. 2007); among these patients a four per cent incidence and 19.4% prevalence of RCC has been reported (Gehrig et al. 1985, Schwarz et al. 2007). It is estimated that nine per cent of dialysis patients have renal tumors with a metastatic rate of six per cent. The tumors are often bilateral and multifocal. (Bretan et al. 1986, Schwarz et al. 2007) Although after transplantation acquired renal cystic disease has been reported to regress in native kidneys (Lien et al. 1993), the risk of RCC remains high (3.9%), with a mean interval from transplantation to tumor of 106 months. In this connection, no significant relationship to immunosuppressive therapy has emerged. (Doublet et al. 1997) The increase is more likely to be related to the underlying

cause of renal failure or to dialysis (Penn 1995), an immunosuppressed state of uremia or the accumulation of poorly excreted carcinogenic substances (Bretan et al. 1986). RCC occurrence has also been suggested to be dependent on deposition of oxalate crystals, a genetic mechanism (oncogene, antioncogene or mutagen), decreased immunology, increased free radical production related to inflammation, impaired anti-oxidant defense mechanisms or viral factors (Sassa et al. 2011, Shanbhogue et al. 2012). The histopathology and genetics of renal tumors in patients with end-stage renal disease may be unique: up to 87% of cancers are reported as papillary RCC compared to 10% in the general population. Patients receiving hemodialysis for over 10 years have more often RCCs with a sarcomatoid component. (Gulanikar et al. 1998, Sassa et al. 2011) Other kidney disorders such as kidney or bladder infections yield an OR 1.9 for RCC. The risk is modified by gender and smoking status, as the strongest risk was in male current smokers with OR 9.7. (Parker et al. 2004)

Immunosuppressive medication is a known risk factor for many cancers. RCC represents five per cent of all cancers in all transplant recipients, in contrast to two per cent in the general population (Penn 1999). The risk seems to be dependent on the type of transplanted organ and the immunosuppressive medication employed. The incidence of RCC in the native kidney of a renal transplant recipient is 0.68% and the overall prevalence is reported to be up to 3.9%. This is clearly increased (100-fold) compared with the general population, but much lower than for hemodialysis patients despite long-term immunosuppression due to regression of acquired renal cystic disease after uremia has improved. This is also the reason why most cancers are found in the native kidney and not in the graft. (Doublet et al. 1997, Ishikawa et al. 1998) The prevalence of RCC among cardiac allograft recipients is the same as in the general population (Penn 1995), but liver transplant patients have a relative risk of RCC 30-fold compared with the general population; 1.7% of patients developed RCC during 20 years surveillance (Haagsma et al. 2001). Also patients with human immunodefiency virus infection are reported to evince an 8.5 times greater prevalence of RCC than the general population, with an average age at occurrence approximately 15 years younger than others (Baynham et al. 1997).

The regular use of non-steroidal anti-inflammatory drugs other than aspirin was found to be associated with a 1.51-fold increased risk of RCC in one prospective study. The risk has a dose-response relationship: the increase was seen after four years' use. This association did not differ by levels of other risk factors. No increase in risk was now seen in connection with the use of acetaminophen, which has been associated with an increased risk in previous retrospective studies. Non-steroidal anti-inflammatory drugs inhibit the

synthesis of renal prostaglandins, resulting in injury-related deoxyribonucleic acid (DNA) damage and potentially leading to carcinogenesis. The difference between aspirin and other non-steroidal anti-inflammatory drugs may be explained by different dosages. (Cho et al. 2011)

In retrospective studies, nutritional factors such as daily intake of fat and proteins are positively correlated with the incidence of RCC. The variation in the worldwide incidence of RCC might be related to such dietary patterns. However, results on total fat or various types of fat intake and RCC risk in prospective studies have been inconsistent. (Ljungberg et al. 2011)

Occupational studies have linked RCC to occupations, for example textile or glass workers, dry cleaning, oil refining, metal working, truck driving, printing, firefighting, pulp and paper work and employment as physician, journalist, painter, architect, engineer, coke-oven operator and airline pilot. Also an association with agricultural work, particularly among female workers, has been suggested. Several agents encountered in these occupations, especially asbestos, iron, steel, polycyclic aromatic hydrocarbons, cadmium, lead, gasoline, benzidine, formaldehyde, glass fibres, brick dust and solvents (particularly trichloroethylene) have been linked to an increased risk. (Dosemeci et al. 1999, Dhote et al. 2004, Heck et al. 2010, Ljungberg et al. 2011) A number of studies have been published on trichloroethylene, an industrial solvent currently classified by the International Agency for Research on Cancer as a probable human carcinogen. Workers exposed to it have a 2- to 8-fold higher incidence of RCC than those not exposed. This solvent seems to induce mutations in the VHL pathway, but its position in carcinogenesis is not clear yet. (Navai and Wood 2012)

Various types of ionizing radiation have been associated with an excess risk of RCC: radiotherapy for cervical cancer, X-ray treatment for ankylosing spondylitis or bone tuberculosis and the use of Thorotoast, an α-emitting contrast medium (Lindblad 2004, Lipworth et al. 2006).

The risk of RCC may increase with each child born: compared with nulliparous women, everparous women are at a 1.4–fold risk of RCC. Each additional birth after the initial pregnancy is associated with a 15% increase in the risk and an already two-fold risk is estimated for women with more than five births. The hormonal changes associated with pregnancy or weight gain may be the reason for this increase. (Benichou et al. 1998, Lambe et al. 2002) Hysterectomy doubles the risk of RCC, even after comparing the parity and the use of estrogen. This increase might be a result of unintentional injury to the ureter, which results in renal cell damage. (Gago-Dominguez et al. 1999)

In addition, epidemiologic studies have shown that having one first-degree relative with RCC is associated with a significantly increased risk of RCC even when no genetic disorder is diagnosed. The familial risk of RCC is 1.75 when a parent and 2.61 when a sibling is diagnosed with kidney cancer. The risk is even higher for early-onset (<50 years of age) RCC patients: 2.07 and 2.80, respectively. (Liu et al. 2011)

Alcohol consumption has been found to be a protective factor in a meta-analysis of observational studies. A 10-20% reduced risk of RCC is associated with light to moderate alcohol drinking up to 50 g/day. Other known risk factors did not alter this protective effect. The mechanism involved here is thought to be the effect of alcohol on insulin sensitivity or its diuretic effect, which increases urine volume. (Bellocco et al. 2012) Also fruit and vegetable consumption is associated with a lower risk of RCC, but vitamins, minerals or other nutrients have not yielded consistent results (Ljungberg et al. 2011). In one large cohort study the use of oral contraceptives appeared to underlie a 20% reduction in risk among ever-users, more in never-smokers, and in young and overweight women (Kabat et al. 2007). Also physical activity reduces the risk of RCC: a clear inverse relationship with increasing leisure time physical activity has been found, but no association with occupational activity. This was also seen after adjustment for BMI, energy intake, smoking, hypertension, education and fruit and vegetable intake. The risk ratio (RR) of having RCC in light, moderate and heavy physical activity categories was 1.0, 0.89 and 0.46, respectively. (Mahabir et al. 2004) In addition, use of statins has been associated with a 48% reduction in the risk of RCC. The protective effect was seen across different age and sex groups and irrespective of the presence of obesity and smoking. (Khurana et al. 2008)

2.1.2 Von Hippel-Lindau disease

Von Hippel-Lindau (VHL) disease, first described in 1894, is the most common cause of inherited RCC. Other manifestations of the disease include pheochromocytomas, retinal angiomas, endolymphatic sac tumors, islet cell tumors, pancreatic cysts and central nervous system hemangioblastomas. Patients with VHL disease are at risk of developing up to 600 tumors in each kidney. (Arjumand and Sultana 2012) The syndrome is caused by germline mutations in the *VHL* tumor suppressor gene located on the short arm of chromosome 3 (3p25-26), having high penetrance (80-90% at 65 years of age) (Latif et al. 1993). The incidence is estimated to be 1 per 35 000 live births (Verine et al. 2010). De novo diagnoses are reported in up to 23% of patients, resulting from a new mutation occurring during oogenesis or spermatogenesis in the parent or if the seemingly unaffected parent is mosaic for the disease

(Sgambati et al. 2000). VHL-diseased families are divided into four phenotypes (1, 2A-C). Of these, type 2A individuals are at low risk of RCC development while type 2B patients are at clearly increased risk. (Arjumand and Sultana 2012)

The *VHL* gene product takes part in the regulation of hypoxia-induced factor-1α (HIF) and HIF2α to stabilize HIF under hypoxia and facilitates proteosomal degradation of HIF under normoxia. The gene product complex is sensitive to conditions of hypoxia. When oxygenation levels decrease, the complex is dissociated from HIF activating angionesis and proliferation through vascular endothelial growth factor (VEGF), transforming growth factor-α (TGF) and platelet- derived growth factor-β (PDGF). When this gene product is dysfunctional, as in VHL disease, dysregulation and overaccumulation of HIF1α and HIF2α can occur, causing pseudohypoxia and thus activation of angiogenesis. (Ohh et al. 2000) Clinical manifestations in the kidneys include typically multiple cysts and solid lesions (Poston et al. 1995). Most (85%) of the solid lesions are malignant. Often multifocal and bilateral clear cell RCCs are found in 35% to 55% of patients. (Levine et al. 1982, Malek et al. 1987, Solomon and Schwartz 1988) RCC is the first symptom of VHL disease in 10% of affected persons (Malek et al. 1987), mean age at diagnosis of RCC being 30 to 44 years (Chauveau et al. 1996). Metastatic clear cell (cc) RCC has become the most common cause of mortality in these patients (Verine et al. 2010).

All patients with a diagnosis of VHL disease should undergo screening with abdominal CT even in the absence of urological symptoms in view of the tendency of renal tumors to occur silently and at an early age (Loughlin and Gittes 1986). Screening is recommended yearly starting with ultrasound (US) from 11 or 15 years of age and CT yearly (alternatively every second or third year) from 18 to 20 years of age or earlier if clinically indicated (Choyke et al. 1995). Solid renal lesions should be removed when greater than 30 mm in diameter. Smaller neoplasms centrally located or adjacent to vital structures may be indications for earlier operations. (Walther et al. 1995)

2.1.3 Tuberous sclerosis

The tuberous sclerosis complex is characterized by widespread cutaneous and visceral hamartomas with highly variable clinical manifestations. A typical symptom triad is epilepsy, mental retardation and facial angiofibromas, but the condition may involve almost any organ system or tissue. Pathologically, it is a disorder of cellular migration, proliferation and differentiation. (Kwiatkowski and Short 1994) The birth incidence is 1/11 000; 60% of cases are sporadic,

representing new mutations. Inactivating mutations in two tumor suppressor genes, *tuberous sclerosis complex-1 (TSC1)* at 9q34.3 encoding for hamartin and *TSC2* at 16p13.3 encoding for tuberin, have been implicated in the development of the syndrome (Henske 2005): hamartin and tuberin bind to each other and this heterodimer inhibits the downstream pathways of the mammalian target of rapamycin (mTOR) (Verine et al. 2010). Renal lesions are seen in 50-80% of patients, being mostly angiomyolipomas, cysts and oncocytomas. RCC was linked to tuberous sclerosis as far back as 1922, occurring in 1-4% of patients at a mean age of 28-36 years, primarily in women. The predominant type is ccRCC, but 50% of tumors have high-grade sarcomatoid features. Also papillary and chromophobe histologies are seen. (Stillwell et al. 1987, Bjornsson et al. 1996, Rakowski et al. 2006, Verine et al. 2010)

All patients with tuberous sclerosis should undergo periodic renal investigation. The current recommendation is that pediatric patients have a baseline US before five years of age. If results are normal, follow-up should be arranged every two to three years. If masses are found, yearly US is recommended. If RCC is suspected, magnetic resonance imaging (MRI) should be applied with follow-up imaging at six-month intervals and interventions undertaken when needed. (Rakowski et al. 2006)

2.1.4 Other genetic disorders

Hereditary papillary RCC is characterized by the development of multifocal, bilateral papillary type-1 RCC: low-grade tumors with basophilic cells and a favorable prognosis. These tumors occur at late age (between 50 and 70 years of age), but an early form is also described. The disorder has high penetrance: patients have a 90% likelihood of developing RCC at 80 years of age. The *c-MET* proto-oncogene in chromosome 7q31 has been identified as the genetic defect in this disorder, but the incidence is unknown. (Schmidt et al. 1997, Zbar et al. 2003, Pavlovich and Schmidt 2004, Verine et al. 2010)

Hereditary leiomyomatosis and RCC predisposes to multiple cutaneous and uterine leiomyomas and early-onset solitary papillary type-2 RCC, which is a high-grade tumor with large eosinophilic cells, aggressive course and poor prognosis. Most patients die of metastatic disease within five years of diagnosis. Also collecting duct and clear cell tumors, Wilms' tumors and oncocytomas are reported. The syndrome is caused by a mutation in the tumor suppressor gene, *fumarate hydratase (FH)*, located in the long arm of chromosome 1 (1q42.3-43), having incomplete penetrance (20%). The incidence is unknown. Most of the families with this gene mutation have been reported from the United Kingdom, North America and Finland, but the disorder occurs worldwide. (Tomlinson et

al. 2002, Pavlovich and Schmidt 2004, Verine et al. 2010, Smit et al. 2011) Renal US and MRI are recommended to all *FH* germline mutation carriers to screen for RCC at the age of 20, followed by annual MRI and semi-annual US examinations (Smit et al. 2011).

The Birt-Hogg-Dubé syndrome, first described in 1977, is a genodermatosis which predisposes to benign cutaneous lesions of the face and neck, spontaneous recurrent pneumothorax and/or lung cysts and renal tumors. It occurs in about 1 in 200 000 persons with great clinical variability. Patients have a 7-fold increased risk of developing renal neoplasia, and RCC occurs in 15% to 30% of gene carriers, with a variable age at diagnosis (mean 50 years). Males develop renal tumors 2.5-fold more often than females. The tumors in question display various histological features, mostly chromophobe RCCs, but chromophobe-oncocytic hybrid RCCs, oncocytomas, ccRCCs and rarely papillary RCCs have also been observed. (Zbar et al. 2003, Pavlovich and Schmidt 2004, Schmidt et al. 2005, Verine et al. 2010) The genetic locus responsible for the syndrome has been linked to chromosome 17p11.2 in gene *FLCN,* which encodes folliculin. This gene is also infrequently (<10%) mutated in sporadic RCCs, suggesting a minor role in renal carcinogenesis. (Schmidt et al. 2005, Verine et al 2010)

The hyperparathyroidism-jaw tumor syndrome is a rare condition associated with parathyroid adenomas causing hyperparathyroidism, multiple ossifying jaw fibromas and unusual renal tumors (in 15% of patients): the malignant tumors are late-onset Wilms' tumors and RCCs. This syndrome is caused by germline mutations in tumor suppressor gene *HRPT2* (1q24-32). (Carpten et al. 2002, Verine et al. 2010) Familial papillary thyroid carcinoma predisposes to thyroid cancer, nodular thyroid disease, but also to papillary RCC and oncocytoma. The causative gene is unknown, but is located in 1q21. (Malchoff et al. 2000) The hereditary paraganglioma syndrome has recently also been associated with RCC. It is caused by a mutation in the *succinate dehydrogenase complex, subunit B (SDHB)* –gene, which encodes mitochondrial succinate dehydrogenase implicated in the Krebs cycle. When this mitochondrial function is impaired, a severe energy deficit occurs and oxygen-free radicals are generated. This is sensed by mitochondrias as hypoxia and HIFs are activated. Patients have extra-adrenal pheochromocytomas and early-onset RCCs, including ccRCCs and chromophobe histologies in addition to oncocytomas. (Vanharanta et al. 2004, Verine et al. 2010)

Several renal-cancer-associated syndromes have been identified for which no predisposing gene has been found. One of them carries a balanced

chromosome-3 translocation which predisposes to multifocal and bilateral ccRCCs in the absence of *VHL* inactivation (Bodmer et al. 1998). To date, 13 different constitutional translocations involving chromosome 3 have been described in association with RCC. In some of the affected families the lifetime risk of RCC is more than 80%. However, in the absence of a family history of RCC or evidence of disruption of a specific tumor suppressor gene, chromosome 3 translocation carriers are not at high risk of developing RCC and no annual renal surveillance is offered. (Verine et al. 2010, Woodward et al. 2010) Familial clear cell renal cell cancer is characterized by the inherited occurrence of ccRCC without any other clinical manifestations. First-degree relatives of these RCC patients are found to have a less than 1:141 -risk of developing RCC. Usually the diagnosis is made relatively late in life (>50 years in age) and tumors are generally solitary. More than 70 families have been reported. (Pavlovich and Schmidt 2004, Zbar et al. 2007, Verine et al. 2010)

2.2 Epidemiology

Worldwide, RCC is the 13th most common malignancy. Approximately 270 000 cases of kidney cancer are diagnosed every year and 116 000 patients die of their cancer. (Ljungberg et al. 2011) The kidney cancer incidence has been steadily increasing at a rate of about 2.5% per year during the last 50 years (Pantuck et al. 2001). Only in the most recent years has the incidence and mortality been declining in some European countries, including Finland (Ljungberg et al. 2011). This increase in incidence has occurred in all age and racial/ethnic groups, the most rapid increases being seen in localized stage disease and small tumors (<2 cm and 2-4 cm in diameter) in females and in black individuals, suggesting that factors contributing to the increasing incidence have affected the entire population rather than only certain subgroups over time. These factors may be the increased prevalence of obesity and hypertension and the increased availability and use of abdominal imaging. (Lipworth et al. 2006, Chow and Devesa 2008) Worldwide the incidence varies considerably: There is a 50-fold difference between the highest and lowest figures. The highest incidence (per 100 000 persons) was in the Czech Republic (20.0 in males, 10.2 in females) and the lowest in Gambia (0.4 in males, 1.0 in females) according to records between 1993 and 1997. In general the incidence is highest in several Western and Eastern European countries and lowest in Asia and Africa. In Finland the figure for this period was 11.0 in males and 6.2 in females. (Parkin et al. 2002, Lipworth et al. 2006) The highest incidence is in individuals in their seventh decade, with a median age at diagnosis of 66 years and a median age at death of 70 years (Pantuck et al. 2001).

2.2.1 Renal cell cancer in children

RCC in children is a rare disease, with a cumulative incidence of 2.2 per million, accounting for only 1.9% to 6% of pediatric malignant renal tumors and 0.1% to 0.3 % of all pediatric neoplasms. The incidence has been stable during the last few decades with no sex difference. (Geller and Dome 2004, Pastore et al. 2006, Indolfi et al. 2012) The median age at diagnosis is 10-16 years. In the second decade of life, RCC becomes more common than Wilms' tumor. These tumors cannot be confidently distinguished preoperatively. (Grabowski et al. 2009, Sausville et al. 2009) Most cases are symptomatic, only 15% of children have an incidental diagnosis. Flank or abdominal pain is seen in 55% of cases, hematuria in 30% and abdominal mass in 13%. General symptoms such as fever, weight loss, anemia or malaise are seen in 43% of children. T1 tumors are found in 44% of patients, lymph node metastasis in 29% and distant metastases in 20%. The pathologic subtypes differ from those in adults: 33-79% are papillary tumors, translocation type (Xp11.2 tumors) is found in 22-70% and only rarely ccRCC (6%). (Selle et al. 2006, Sausville et al. 2009, Indolfi et al. 2012)

In about every third child possibly RCC-related underlying disorders (e.g. tuberous sclerosis, VHL syndrome and chronic renal failure) or related diseases in their families are found. Papillary tumors are most frequent in children with underlying disorders. (Selle et al. 2006)

The five-year OS for localized RCC is 96%, for node positive tumors 75% and for metastatic disease 0-33%. The surgical resection of all tumor lesions, including lymph nodes and metastases, is the crucial mainstay of successful treatment in pediatric RCC and lies behind these better survival rates especially for node-positive cases. (Selle et al. 2006, Indolfi et al. 2012) Adjuvant therapy in node-positive patients does not improve the already good survival (Geller and Dome 2004). Pathologic parameters typically associated with poor outcome in adults, including high tumor stage or nuclear grade, angiolymphatic invasion and tumor necrosis, are not good prognostic factors for children (Wang et al. 2012).

2.2.2 Renal cell cancer in young adults

RCC in young adults, usually considered as 18 - (40) 45 years old, differs from the elderly patient's tumors. These tumors are relatively rare, among RCC cases 3.5% to 7.3% have been shown to occur in those younger than 40 years. (Gillett et al. 2005) The likelihood of ccRCC is the same when compared with

the elderly, but more chromophobe and fewer papillary tumors are seen than in older patients. No differences are found in sex, tumor size, TNM stage or multifocality, but young patients have locally symptomatic tumors more often; in systemic symptoms there is no difference. (Thompson et al. 2008) Despite modern imaging techniques the rate of symptomatic tumors at presentation in young adults has not decreased; the younger and generally healthier population rarely needs imaging studies for other reasons (Siemer et al. 2006). Compared to older patients, cancer-specific survival is similar (Thompson et al. 2008).

2.3 Signs and symptoms

RCC is notorious for its presentation with a diversity of symptoms. In one previous report paraneoplastic manifestations were present in 19% of patients. These symptoms included weight loss, fatigue, cachexia, anemia, fever, hypertension, hypercalcemia, hepatic dysfunction, erythrocytosis, amyloidosis, enteropathy, neuromyopathy, elevated alkaline phosphatase, galactorrhea and Cushing's syndrome. (Ou et al. 2003) In addition to these, the clinical presentations can be various, for example metabolic, hepatic, neuromuscular, hematologic, renal or cutaneous syndromes (Papac and Poo-Hwu 1999). These have been shown to be stage-dependent: five per cent of stage-I patients to 38.5% in stage IV (Ou et al. 2003). Symptoms are caused by various tumor-secreted hormones such as parathyroid hormone, prostaglandins, erythropoietin, prolactin, renin, insulin, glucagons, gonadotropins and glucocorticoids (Dayal and Wilkinson 1989). Reports have also suggested a possible role of interleukin (IL)-6-overexpression by the primary tumor, which has proved to be associated with anemia, thrombocytosis, C-reactive protein and haptoglobin increase, neutrophilia, monocytosis and decreased albumin (Blay et al. 1997, Walther et al. 1998). Elevated ferritin in the tumor is associated with RCC-related anemia (Kirkali et al. 1995).

The classic triad of Virchow (hematuria, palpable mass and abdominal pain) was present in nine per cent of patients in a report by Skinner and associates (1971), but it has since become more rare: a 3.8% to 5.5% incidence is reported (Sigalow et al. 1991, Jubelirer and Rubin 1993). The clinical presentation of RCC has changed along with the increased use of abdominal imaging. Nowadays incidental diagnoses with asymptomatic tumors may constitute up to 80% of cases. (Schips et al. 2003) The clinical presentation of RCC does not differ between young and elderly (over 70 years) patients (Doherty et al. 1999).

The most common symptoms of metastatic disease are asthenia (30%), bone pain (26%), fever (17%), weight loss (15%), abdominal pain (15%), dyspnea (11%), neurological disturbances (10%) and cough (6%). However, 22% of patients with metastatic diseases are asymptomatic. (Citterio et al. 1997)

Few modern series dealing with symptoms of RCC have been reported. In a Chinese study, 26% of patients were asymptomatic, 56% had local and 19% had paraneoplastic symptoms (Ou et al. 2003). In an older Finnish study (1968-1972), hematuria was seen in 25% of patients, 24% had pain, 4% a palpable tumor, <1% fever, 14% lowered general condition, and only 6% were asymptomatic (Mäntylä et al. 1977).

Hypercalcemia has been observed in up to nine per cent of patients (Magera et al. 2008). It is caused mostly by parathyroid hormone-related protein secreted from a primary tumor, more rarely by local osteolytic metastases or prostaglandin-mediated factors (Walther et al. 1997). Elevated ESR, if systematically recorded, can be found in 70% of RCC patients. It has been shown to rise significantly for six or more years before the diagnosis and the rise is marked during the last year before the malignancy becomes apparent. The mean ESR is 47 mm/h in men and 52 mm/h in women, but 20% of these patients had ESR over 100 mm/h. (Iversen et al. 1996) Varicocele is often a late sign of RCC, being the presenting symptom in 2.3-3.3% of cases (Skinner et al. 1971, El-Saeity and Sidhu 2006).

2.4 Diagnostics of RCC

2.4.1 Diagnostic imaging

There are many studies comparing results obtained with different radiological imaging techniques, especially from the 1980s, when these methods became more widely accessible. In these studies there have been some differences in approach, but mostly the availability of techniques affects the choice of imaging method. A marked change has taken place in the diagnostic protocol along with this evolution of methods. Nowadays the diagnostic algorithm is to perform abdominal US and then 2/3-phase helical CT with 5 mm collimation to minimize partial-volume artifacts (Heidenreich and Ravery 2004). Kidneys are scanned early during the corticomedullary phase and then during the tubular nephrogram phase approximately 90 seconds after the injection of contrast medium (Bosniak and Rofsky 1996).

Previously, parenchymal, especially central calcification in excretory urography was suggestive of a malignancy. The typical appearance was a focal, most often hypervascular bulge in the renal contour. Any lucent lesion which was not sharply defined with a thin wall, was an indication for further investigations. RCC may displace collecting structures, or invade them producing filling defects or obliteration. (Hilton 2000) This approach detected

only 10% of CT-confirmed renal masses less than 1 cm in diameter, but 85% of masses greater than 3 cm (Warshauer et al. 1988). In a retrospective study, six per cent of all tumors had been missed. Unless the tumor is large enough to effect a change in renal contour or distortion of the collecting system, it may be difficult to see. (Demos et al. 1985)

Arteriography has nowadays an extremely limited role in the diagnosis of renal masses. It can be used to evaluate the renal blood supply if this information is needed in planning a surgical procedure. Occasionally, arteriography is used for therapeutic embolization of renal neoplasms to reduce vascularity and blood loss during surgery and to facilitate surgery with huge renal tumors, when the renal vessels are difficult to reach, and to stop bleeding as a palliation for inoperable tumors. In current practice its use is mostly in the cure of complications of nephron-sparing surgery. (Bosniak 1993, Roy et al. 1999) In angiography, most RCCs yield characteristic findings: a hypervascular mass with abnormal vessels, which are irregular in outline and without normal tapering, randomly distributed, variable in size and branching. Arteriovenous shunting is also typical. Hypovascularity is seen in 20% of tumors. (Roy et al. 1999)

In US small tumors are more often homogeneous and hyperechoic. The latter is seen in 30% of tumors, causing the finding to mimic angiomyolipoma. Heterogeneity appears when tumors are growing, indicating degeneration of the tumor; only two per cent of tumors larger than three centrimeters have hyperechoic appearance. (Forman et al. 1993, Mihara et al. 1999) However, 39% of small lesions are iso- or hypoechoic. Solid tumors are seen more often than cystic. A hypoechoic rim indicating the capsule is characteristic of a small RCC, which facilitates their identification. Calcification is very rare, seen in only three per cent. (Yamashita et al. 1992) Protrusion from the kidney is seen in 71% (Mihara et al. 1999). The main limitations of US are known to emerge in the case of small isoechoic intraparenchymal tumors causing no deformity, and polar tumors with extrarenal growth which may be obscured by bowel gas (Hélénon et al. 2001). When comparing US in relation to CT, it detects only 26% of CT-confirmed renal masses less than one centrimeter, but 85% of lesions greater than three centimeters (Warshauer et al. 1988). US should detect all surgically verified tumors larger than 25 mm (Jamis-Dow et al. 1996). The use of color Doppler US does not increase the detection rate in the case of small tumors. With an US contrast agents the detection of small renal masses can be improved, especially in cases with an isoechoic pattern, as the normal renal vascular architecture is then altered. (Hélénon et al. 2001)

With CT RCC can be diagnosed with 95% accuracy (Hilton 2000). After the introduction of helical CT in 1989, more reliable measurements were achieved

by reducing volume-averaging and respiratory artifacts and allowing image acquisition during optimal contrast enhancement. In 1998 machines were equipped with multiple row detector arrays, dramatically increasing volume coverage speed and improving optimization of volume data sets and thus providing better resolution. (Sheth et al. 2001) A biphasic imaging protocol consisting of a corticonephrographic and a tubulonephrographic phase is most commonly applied. Small tumors may require the plain phase to be seen. Some authors recommend a fourth acquisition phase to visualize the collecting system. (Walter et al. 2003) In CT a common presentation of small RCC is a noncalcified homogeneous lesion with baseline attenuation >20 Hounsfield units enhancing by at least 10 units after intravenous (i.v.) contrast (Silverman et al. 1994). Larger tumors more commonly present with calcification. Other signs suggesting malignancy are absence of a sharp margin between mass and parenchyma and thickening or nodularity of the wall or septae in a predominantly cystic renal mass. (Hilton 2000) The greatest difficulty in diagnosing a renal mass is encountered in complicated cystic lesions, pseudotumors of the kidney (including anomalies, abscesses and hematomas), tumors of the kidney not treated surgically (lymphomas) and lesion of the kidney less than 1.5 cm in diameter (Bosniak 1993).

MRI has been shown to be slightly superior to CT: sensitivity is the same, but MRI is better in differential diagnosis (Kreft et al. 1997). Since MRI offers no clear advantage, it is most useful in patients with iodine allergy or renal failure and can be used during pregnancy (Hilton 2000). The performance of 18-F-fluorodeoxy-glucose positron emission tomography (18F-FDG PET) in the detection of primary disease is limited by reason of renal excretion of FDG, resulting in a high frequency of false-negative results (10-40%). This can be potentially avoided by hydration and diuretics. Diagnostic accuracy is also dependent on the degree of tumor differentiation; in general sensitivity is 60%. (Perini et al. 2008, Lawrentschuk et al. 2010) Recent progress has been achieved with other radiotracers. 124I-cG250 is a labeled chimeric girentuximab; cG250 functions as an epitope of carbonic anhydrase IX (CAIX), discussed in the Biomarkers section. PET is undertaken six to eight days after injection of this radiotracer. The sensitivity is 94% and specificity 100%, which clearly exceed the corresponding figures for 18F-FDG PET. 18F-fluorothymidine-PET is less promising by reason of the physiological uptake of this isotope in liver and bone; metastases in these sites cannot be reliably observed. ^{111}In-Bevacizumab PET has been studied to stratify patients for antiangiogenic therapy and for therapy monitoring, and 18F-fluoromisonidazole-PET has been evaluated as a

means to show hypoxia in metastatic RCC. However, this was less frequent and less pronounced than initially suspected. The data on 11C-acetate PET is limited and conflicting. (Khandani et al. 2012)

2.4.2 Preoperative staging

According to European Society of Medical Oncology and European Association of Urology staging of RCC is recommended to be done by abdominal and chest CT. Plain chest X-ray can be sufficient in low-risk patients. Bone scintigraphy is undertaken when clinically needed and cerebral CT is performed only upon suspicion of brain metastases. If a tumor is local, but there is a suspicion of a thrombus after primary imaging, MRI or Doppler US is recommended. (Ljungberg et al. 2010, Escudier et al. 2012) 18F-FDG PET and PET-CT evince good performance in the staging and diagnostics of metastases. In the majority of published studies the sensitivity is close to 100%. PET-CT can be used to stage bone metastases accurately and thus replace bone scintigraphy. A major advantage of imaging with PET is in the detection of occult lymph node or bone metastases or differentiation between tumor thrombus and coagulative thrombus. (Perini et al. 2008, Lawrentschuk et al. 2010)

In previous studies comparing different staging methods, the T stage was determined correctly by CT in 80%, by US in 74.5%, by angiography in 64% and by excretory urography in 56.5% of cases (Tammela et al. 1991). MRI and CT have yielded similar results in staging. However, MRI may be more sensitive in detecting venous extension, metastatic adenopathy and adjacent organ invasion. (Nishimura et al. 1988, Fritzsche 1989) Staging errors in imaging occur due to limitations in assessing microscopic invasion of the renal capsule and perinephric fat, detecting metastases in normal-sized lymph nodes and differentiating inflammatory hyperplastic lymph nodes from neoplastic (Nazim et al. 2011).

When detecting vena cava thrombus MRI and venacavography have a sensitivity of 100%; CT has 79% and US only 68% (Kallman et al. 1992). Extension in the vena cava has to be considered when a perihilar mass associated with a nonfunctioning kidney is seen on excretory urography, filling defects are noted in the venous phase of arteriography or involvement of the renal vein or vena cava is suspected on CT (Libertino et al. 1987). With contrast-enhanced CT and duplex Doppler US correct estimation of the extent of the thrombus is possible in 86% and 71% of patients, respectively (Bos and Mensink 1998). The most common reason for a false-negative CT is a poor bolus injection of i.v. contrast medium. The cranial extent of a tumor thrombus might be poorly evaluated because of the inhomogeneous contrast filling of the

inferior vena cava. (Kallman et al. 1992, Hélénon et al. 2001) Occasionally, large tumors obscure the imaging of the distal renal vein and vena cava due to compression and distortion. Metastatic lymphadenopathy can also simulate a renal vein tumor thrombus. On US, the most frequent causes of poor visualization of the renal vein include bowel gas, obesity and large tumors which compress and distort the vessels. (Kallman et al. 1992)

2.4.3 Preoperative biopsy

Previously preoperative cytology samples were not reliable, as only 40% of aspirations were reported to yield diagnostic malignant cells (Campbell et al. 1997). Nowadays the sensitivity of US-guided fine-needle aspirations for differentiating RCC is 90.6% (Schmidbauer et al. 2008). By means of helical CT-fluoroscopy, guided core biopsy is achieved with a success rate >90% and insufficient material is noted in only five per cent (Khan et al. 2007, Schmidbauer et al. 2008). Nonetheless multiple cystic kidney lesions in VHL patients are hard to diagnose; only 29% sensitivity is reported (Poston et al. 1995).

There are a number of occasions by which needle aspiration or biopsy is indicated. These include differentiating a chronic abscess from a cystic carcinoma, a new primary renal neoplasm from a metastatic one in a patient who has had a previous primary tumor in another organ, primary renal neoplasm from renal lymphoma in a patient with lymphoma, particularly when the lesion does not regress with treatment while the remaining lymphomatous disease does, and differential diagnosis of an indeterminate renal mass in a solitary kidney or bilateral renal masses. (Bosniak 1993, Khan et al. 2007) Also in ablative therapies a pretreament biopsy should be taken to ensure malignancy (Ljungberg et al. 2010). In these cases it must be remembered that spread of a tumor by needle puncture of the renal neoplasm has been reported (Shenoy et al. 1991).

2.4.4 Incidental diagnosis

In the modern world of easy diagnostic methods such as US, the incidental finding of asymptomatic RCC is quite common. In the era before CT and US, Skinner and colleagues (1971) first reported a seven per cent rate of incidentally detected tumors; only 38% of patients had the disease confined to the kidney (Robson et al. 1969). Nowadays the percentage of incidental diagnoses can be up to 80% of cases (Schips et al. 2003). This progressive increase has taken

place since the 1980s. Incidental tumors present with lower stage and grade, smaller tumor size and with less metastatic disease at diagnosis (Luciani et al. 2000).

Most incidental tumors are detected by US (81%), some with abdominal CT (11%) and excretory urography (8%). These imaging studies are undertaken mainly because of cardiovascular diseases, mostly hypertension, general health examination, hepatobiliary diseases and prostatic symptoms. (Bretheau et al. 1995) In another study most (65%) of incidental cases were found when gastrointestinal signs and symptoms were studied. Abdominal pain was the most common reason for imaging studies, then biliary colic symptoms and dyspepsia; other reasons were prostatic and other urologic symptoms. In gastrointestinal surgery 10% of these tumors were found and the rest in postoperative surveillance of other diseases. (Vallancien et al. 1990) More incidental tumors are found in women, possibly by reason of the more regular use of the health services. The male:female ratio is found to be in incidental tumors 50.5 : 49.5 and in symptomatic tumors 63.2 : 36.8. (Beisland et al. 2002) More incidental tumors are found on the right side, as US is frequently requested for hepatobiliary disease. Also US examination is easier in the right kidney than in the left; probably 15% of left renal cancers are missed during abdominal US scanning. (Vallancien et al. 1990)

2.4.5 Screening

The current European Society of Medical Oncology and European Association of Urology guidelines take no stance on screening (Ljungberg et al. 2010, Escudier et al. 2012). However, routine screening in asymptomatic patients is not considered cost-effective in view of the low prevalence of kidney cancer in the general population and the high cost and particular sophistication of US detection (Tosaka et al. 1990, Lilly 1991).

In US screening studies a malignant kidney tumor has been found in 0.08% to 0.09% of screened persons. Even in the high-risk group the incidence of RCC is low: a solid renal mass was found in 0.32% of smokers, mostly men aged over 50 years with a history of hypertension. (Tosaka et al. 1990, Malaeb et al. 2005) Fifty-four per cent of these cancers were in asymptomatic subjects. Over 2 170 scans were necessary to make each diagnosis and 355 CT scans were necessary to identify 19 malignancies in the asymptomatic group. However, primary tumor size and clinical stages were significantly smaller and lower and the five-year survival rates after nephrectomy were 94.7% and 60.9%, respectively, in asymptomatic and symptomatic patients. (Tosaka et al. 1990) In another study all tumors were local and 37.8% were < 25 mm. The survival rate was 97% at five years and 95% at 10 years. (Malaeb et al. 2005) The fee for

detecting one malignant case was equal to that for gastric cancer screening popularized in Japan, but for detecting one RCC it was four-fold this (Mihara et al. 1999).

The conception of low cost-effectiveness in screening is supported by autopsy series showing that only 20% of clinically unrecognized kidney cancers are the cause of death; metastases were found in 24% of these cases (Hellsten et al. 1990). In a study comprising over 23 000 autopsies RCC was the cause of death in 1.55% to 1.76%. This figure was constant, while the numbers of clinically detected cancers increased during study period. In the study in question 8.9% of patients with clinically unrecognized tumors died of RCC. (Wunderlich et al. 1998)

Conflicting opinions are on record as to the usefulness of US screening. When a US mass survey was made, in 0.31% of screened had been found a malignancy, including renal, hepatocellular, gall bladder and pancreatic cancers. Almost all of these RCCs were resectable and the 10-year survival rate was 99%. (Mihara et al. 1998) In a screening program for individuals older than 40 years, in 0.1% of screened had been found to have a renal mass; 69% of these were also histologically RCC. The detection rate was 10-fold greater than the annual incidence of RCC in the United States and three times more than expected. The sensitivity for detecting RCC was 82% and specificity 98%. (Filipas et al. 2003) In another study also a detection rate of 0.3% to 0.4 % has been reported (Spouge et al. 1996). The prevalence of preclinical renal cancer has ranged from 0.11% to 0.76%. Based on these figures it is estimated that in screening studies RCC is found 3.7 to 5.8 years before it would evince any clinical symptoms. (Fenton and Weiss 2004)

The difficulty in screening lies in the fact that small isoechoic renal tumors causing no deformity of the renal cavities or cortex are not well detected by routine US (Forman et al. 1993). When evaluating US against CT it was found that US detected 26% of CT-confirmed renal masses of less than one centimeter and 85% of lesions greater than three centimeters. While US is efficient in detecting larger lesions, the inability to detect small renal masses reduces its utility in screening for early RCC. (Warshauer et al. 1988) The potential benefits of screening and early detection must be weighed against the potential harm caused in detecting benign tumors. In cases of radiographically suspected and operated tumors, as many as 16.9% of final diagnoses are something other than RCCs (oncocytomas 10%, but also other malignant diagnoses). (Silver et al. 1997, Dechet et al. 1999) In incidental tumors less than

five centimeters in diameter, the rate of benign lesions is high and only half are malignant (Vasudevan et al. 2006).

In some risk groups, however, US screening is considered to be effective. In RCC syndrome patients the risk is so high that screening is part of the normal protocol (discussed in the Etiology section). Also in patients with acquired cystic renal disease the cancer detection rate is four per cent (Gehrig et al. 1985). The higher prevalence and the risk of cancer progression while on immunosuppressive medication justify screening in patients awaiting transplantation: a malignancy is found in 1.64% of cases. Transplanted patients with immunosuppressive medication and functioning transplant are at a greater risk of metastatic disease and cancer-related death than those in hemodialysis. In these cases, no distant metastases have been seen and most tumors have been less than four centimeters in diameter. (Pope et al. 1994, Farivar-Mohseni et al. 2006) Screening US is recommended for all patients before starting dialysis, after three years on dialysis and yearly thereafter (Bretan et al. 1986). Some authors recommend screening every other year after three years of dialysis, as only 50% of patients will have acquired renal cystic disease by this time (Farivar-Mohseni et al. 2006). The sensitivity of screening US in cystic kidneys is reduced to 36.3%, but the positive predictive value of a solid mass is 100% (Gulanikar et al. 1998). These tumors can be difficult to detect even with CT, and contrast enhancement of a tumor may not occur because of diminished blood supply to the parenchyma (Gehrig et al. 1985). A survival advantage of screening has been shown among dialysis patients: in the case of an incidentally found tumor there is a 35% reduced risk of death when compared with symptomatic patients (Ishikawa et al. 2004). However, the routine screening of old dialysis patients with numerous comorbidities and short life expectancy is not considered justifiable. In patients with a life expectancy of more than 25 years both CT and US may reduce cancer deaths by half. If the cancer incidence is seven per cent per year, the gain provided by screening may reach five years. (Sarasin et al. 1995)

Apart from the radiological imaging methods there are as yet no other means of screening in clinical use. Preliminary results of urine biomarkers aquaporin-1 and adipophilin have been published. Aquaporin-1 is a water channel protein present in the apical membrane of the proximal tubule, but it can increase the migration and metastatic potential of tumor cells. Adipophilin is a protein associated with lipid droplets, a feature of clear cell carcinoma and macrophages. Lipid-laden macrophages are associated with papillary renal cell carcinomas. Concentrations of these two are high in the urine of patients with clear cell or papillary renal cancer. (Morrissey et al. 2010)

2.4.6 Diagnostic delay

There are only two publications dealing with diagnostic delay in RCC patients. In Senegal patients are seen to seek treatment very late: the average patient-dependent delay has been 14 months. Already 25% had metastases, 15% had locally advanced inoperable disease and a radical operation could be undertaken in only 60% of cases. (Gueye et al. 1998) In an Italian study, again, the diagnostic delay was 4.5 months (Talamini et al. 1991).

2.5 Histopathology and grading

Historically RCC has been regarded as a single entity manifesting many possible histological forms. In 1997 progress was made toward standardization when the Union Internationale Contre le Cancer (UICC) and the American Joint Commission on Cancer released a combined work-group classification of RCC, known as the Heidelberg classification, which also took account of genetic studies and practical concerns such as simplicity and consistency in historical usage. The Heidelberg classification identifies five groups on the basis of histological features and genetic alterations. These are shown in Table 1. (Kovacs et al. 1997)

Sarcomatoid differentiation, typified by a spindle cell growth pattern, is seen in eight per cent of RCCs. It represents high-grade transformation and can be seen in any histologic subtype. Before the 1997 classification it was categorized as renal sarcoma or sarcomatoid renal carcinoma. Many epidemiologic parameters, e.g. age and sex, are common with classic RCC, but it has a higher metastatic rate and tends to recur locally; 69% of patients die of the disease. Most have primarily advanced disease. The median survival in metastatic disease is reported to be 6-19 months. (de Peralta-Venturina et al. 2001) Tubulocystic RCC may be a variant of papillary RCC. It is presumed to originate from the collecting duct and affects predominantly men in their 5th or 6th decade. The tumor has good prognosis and low malignant potential. (Shanbhogue et al. 2012)

A more recent classification of renal tumors is the World Health Organization Classification of Renal Parenchymal Tumours. It has returned the entity of ccRCC. Is also recognizes multilocular ccRCC, Xp11 translocation carcinomas, carcinomas associated with neuroblastoma, and mucinous tubular and spindle cell carcinomas in addition to the tumor types of the Heidelberg classification. (Eble et al. 2004)

Table 1 The Heidelberg classification and genetic defects associated with renal tumors (Kovacs et al. 1997).

+=duplication; -=deletion; LOH=loss of heterogeneity; NA=not accessible.

Histologic subtype	Percentage of RCCs	Genetic defects	Pathologic features and origin
Conventional	75	Mutation of *VHL* (LOH 3p25)	Clear cytoplasm, cysts may dominate. Originates from the proximal convoluted tubule.
Papillary	10	Trisomy 3q, 7, 8, 12, 16, 17, 20 -Y *MET* proto-oncogene mutation	Papillary; type I scarce cytoplasm, type II eosinophilic cytoplasm. Originates form the distal convoluted tubule.
Chromophobe	5	LOH 1, 2, 6, 10, 13, 17, 21 Hypodiploid DNA	Large solid sheets, pale or eosinophilic cytoplasm. Hale's colloidal iron stain helpful. Originates from intercalated cells.
Collecting duct (incl. medullary carcinoma)	1	Inconsistent	Hobnail appearance, Ulex europaeus staining positive. Arises in the caliceal epithelium or near the renal papillae.
Unclassified	3-5	NA	NA

Of the rare tumor types, renal medullary carcinoma develops typically in black American men with sickle cell trait or sickle cell disease, but Caucasian and female patients are also sporadically seen (Kennedy et al. 1990, Davis et al. 1995). The tumor tends to develop in young patients with a mean age at diagnosis of 22 to 24 years, but the age range reported is wide. No consistent pattern of genetic abnormalities has been established. (Kovacs et al. 1997) Average survival after surgery is only 15 weeks. This tumor type tends to develop systemic metastases rapidly and is usually already metastasized when first discovered. (Kennedy et al. 1990, Davis et al. 1995) Radical nephrectomy, radiotherapy or chemotherapy have not been shown to change the outcome or slow the progression of this disease (Sathyamoorthy et al. 2006). Collecting duct carcinoma affects patients over a wide age range, more men than women. These tumors have typically a poor prognosis, many being metastatic at presentation. Some two thirds of patients die of their disease within two years of diagnosis. (Eble et al. 2004)

Multilocular cystic RCC is composed entirely of numerous cysts, the septa of which contain small groups of clear cell carcinoma cells. The age range of patients is wide and there is a slight male predominance. This tumor has low malignant potential and the prognosis is excellent. (Suzigan et al. 2006) Renal carcinomas associated with Xp11.2 translocations, resulting in gene fusions involving *the transcription factor E3 (TFE3)* gene, comprise at least one-third of pediatric RCCs, but 160 adult cases are also reported. The age range is wide, with an average of 25 years, with a marked female predominance. These tumors usually present with advanced stage, but their clinical course appears to be indolent in children. Some adult patients have rapidly progressive disease. (Argani et al. 2007, Shanbhogue et al. 2012) Oncocytoid RCC associated with neuroblastoma occurs only in long-term survivors of childhood neuroblastoma after an average of 15 years after the first malignant diagnosis. These patients have a more than 300-fold increased risk of developing RCC. Genetic susceptibility, familial cancer syndromes and exposure to chemo-radiation are implicated in this increased risk. Prognosis correlates with stage and grade, as in other RCCs. (Fleitz et al. 2003, Shanbhogue et al. 2012) Mucinous tubular and spindle cell carcinoma is a low-grade tumor originating from cells of the loop of Henle or more probably from the collecting duct epithelium. Multiple genetic alterations are reported. It is associated with nephrolithiasis. Patients are of wide age range, with a 1:4 male-to-female ratio. The prognosis seems to be favorable, with very low rates of recurrence or metastases, unless tumor exhibits sarcomatoid change. (Paner et al. 2006, Yang et al. 2010, Shanbhogue et al. 2012)

The rarest subtype of RCC is leiomyomatous RCC, which has only very recently been described in the literature, with only few cases reported so far. It can affect a wide age group of patients. The clinical and imaging manifestations are not specific and indistinguishable from the common RCC. (Shanbhogue et al. 2012)

Primary renal sarcoma represents less than one per cent of all primary tumors of the kidney, 47% of these being leiomyosarcomas (Vogelzang et al. 1993). Also malignant fibrous histiocytoma, clear cell-, extraskeletal osteo-, angio-, Ewing's and synovial sarcoma have been recognized (Eble et al. 2004). The prognosis is not good; most patients suffer recurrence of the disease. Radical surgery is still a corner-stone in treatment. (Spellman et al. 1995)

Nowadays renal tumors are graded with the Fuhrman system, which uses histopathological characteristics of cells found by light microscopy to stratify renal tumors as grade I through IV in order of increasing nuclear size,

irregularity and nucleolar prominence (Table 2) (Fuhrman et al. 1982). This system has proved to be inappropriate in chromophobe (Delahunt et al. 2007) and papillary RCCs (Sika-Paotonu et al. 2006), which currently have no functional grading system working as an indicator of prognosis.

Table 2 Defining features of the Fuhrman grading classification (Fuhrman et al. 1982).

	Nuclear diameter	Nuclear shape	Nucleoli
Grade 1	Small (10 μm)	Round, uniform	Absent, inconspicuous
Grade 2	Larger (15 μm)	Irregularities in outline	Visible at x 400
Grade 3	Even larger (20 μm)	Obvious irregular outline	Prominent at x 100
Grade 4	As for grade 3 with bizarre, often multilobed nuclei ± spindle cells		

2.6 Staging systems

The first formal staging system was proposed by Flocks and Kadesky in 1958. It was based on physical tumor characteristics and the location of tumor spread. A closely similar classification was published by Petkovic in 1959. Greater emphasis was placed on intrarenal tumors by dividing stage I tumors of the former systems into stages I and II. (Delahunt 2009) Robson and associates (1969) modified these criteria by proposing that staging should also consider vascular involvement.

Currently the most commonly used staging system is the Tumor Nodes Metastasis (TNM) system first introduced in 1978. The TNM system was initially considered too complex and hampered by an excessive number of categories. It was refined and simplified in 1987 and again in 1992 by organizing tumors according to tumor size, vascular spread, lymph node and metastasis. In 1997 the TNM system was again altered to mirror the improved results attained in the management of RCC. The T1 stage was expanded from less than 2.5 cm to less than seven centimeters, since it was noted that the lower size cut-off did not generate statistically significant survival differences. Again, in 2002 T1 was divided into two subgroups: tumor less or greater than four centimeters in diameter. This was proposed as it was considered that tumors less than four centimeters are more likely to be organ-confined and localized and thus amenable to partial nephrectomy. (Delahunt 2009) The current 2009 TNM system is shown in Table 3.

Table 3 Current 2009 TNM system for RCC, from UICC (TNM Classification of Malignant Tumours. 7th Edition. Wiley-Blackwell 2010).

T1 Confined to kidney T1a: ≤ 4.0 cm T1b: 4.1-7.0 cm	N0 No regional lymph node metastases	M0 No distant metastasis
T2 Confined to kidney T2a: 7.1-10 cm T2b: >10 cm	N1 Metastasis in regional lymph node(s)	M1 Distant metastasis c=clinically proven p= biopsy-proven
T3 Outside renal capsule T3a: Invades renal vein, perirenal or renal sinus fat T3b: Extends into vena cava below diaphragm T3c: Extends into vena cava above the diaphragm or Invades the wall of the vena cava		
T4 Outside Gerota fascia		
T0 No evidence of primary tumor TX Primary tumor cannot be assessed	Nx Regional lymph nodes cannot be assessed	Mx Distant metastases cannot be assessed

2.7 Prognosis

Even nowadays, almost 40% of patients with RCC will die from their cancer within five years from diagnosis. Approximately 20 to 30% of patients present primarily with metastatic disease. Of those who undergo nephrectomy for clinically localized RCC, 20% to 40% will subsequently develop distant metastases. (Janzen et al. 2003) RCC can develop particularly late recurrences. These can be found anywhere, but the lung is the most frequent location. After 10 years' surveillance 6.4% of patients still relapse; the disease-free survival (DFS) rate in patients not relapsing before 10 years was at 15 and 20 years 89.5% and 78.4%, respectively. Primary lymph node metastasis is the only known factor predictive of late recurrences. (Miyao et al. 2011)

In the 1950s five-year survival was only 34%, in the 1970s 51% and in the 1990s already 67% (Pantuck et al. 2001, Jemal et al. 2009). Since the 1950s many factors have improved survival. In the 1960s progress probably resulted from modifications in the surgical approach to nephrectomy introduced by Robson (1963). In the 1980s more smaller, lower-stage, incidental tumors were diagnosed as a consequence of increased use of US, CT and MRI. In addition,

in the 1980s immunotherapy for metastatic RCC became available. Since 2005 tyrosine kinase inhibitors (TKI) and VEGF-inhibitors have altered the results of therapy for metastatic RCC.

Before the era of immunotherapy, 43% of patients with metastatic RCC were alive at one year and 13% at five years (deKernion et al. 1978). After immunotherapy was introduced the median survival was eight months and one-year survival the same 43% (Medical Research Council collaborators 1999). In the current era of targeted therapies, the reported OS rates are from 10.9 months with temsirolimus to 26.4 months with sunitinib (Coppin et al. 2011). An improvement in OS is also reported in a population-based study from Sweden, where the median OS was 19.4 months in metastatic RCC when treated with TKIs compared to 9.7 months in patients treated with other agents, mostly interferon (IFN) (Wahlgren et al. 2013).

2.7.1 Prognostic factors

Stage, tumor size and bilaterality

Initially, in 1938 Bell reported an association of tumor size with prognosis, noting an increased propensity to metastasize associated with tumors greater than three centimeters. For each centimeter increase in tumor size the risk of cancer death is increased by 20%. Patients with tumors greater than four centimeters are significantly more likely to die of the disease than those with smaller tumors. (Fergany et al. 2000)

Stage of RCC is one of the most important considerations in the matter of prognosis. When compared to T1 tumors, patients with T3a tumors are four times more likely and patients with T3b tumors eight times more likely to die of their cancer. (Fergany et al. 2000) However, 12% of T1 tumors and 13% of T2 tumors disseminate, this lowering the prognostic value of T classification (Tsui et al. 2000). The mean time to recurrence is influenced by the initial pathological tumor stage: 70 months for stage T1a tumors versus 29 months for T3b tumors (Fergany et al. 2000). The current TNM system does not recognize the importance of microvascular invasion or tumor invasion of the collecting system. However, microvascular invasion occurs in as many as 18% of patients and is associated with larger tumor size, higher grade and more advanced T stage, lymph node and distant metastases. In univariate analysis it correlates with cancer-specific survival (CSS), but by reason of the stronger prognostic factors associated with it, its statistical significance is lost in multivariate analysis. (Kroeger et al. 2012) The tumor invasion of the collecting system worsens prognosis in localized tumors. In T2 tumors it is a more significant prognostic factor than tumor size. (Brookman-May et al. 2011)

The survival of patients with regional lymph node involvement only is identical to that of patients with distant metastases (Pantuck et al. 2003a). Even in the case of metastatic disease, the presence of lymph node metastases worsens prognosis (median OS 10.5 vs. 20.4 months) while the degree of lymphadenopathy is predictive of survival (Vasselli et al. 2001, Pantuck et al. 2003).

Synchronous bilateral RCCs have been found in 1.5% of patients. These were more frequently multifocal than unilateral tumors and papillary subtype. (Klatte et al. 2007) The prognosis varies, as survival has in some studies been better with asynchronous than with metachronous lesions (Smith et al. 1984). In another study patients with asynchronous tumors carried an over five-fold and patients with metachronous tumors a three-fold risk of dying of the RCC as againts those with unilateral disease (Fergany et al. 2000). In addition, in a more recent study the survival of patients with synchronous tumors was similar to that in unilateral RCC (Klatte et al. 2007). Some authors find no difference between synchronous and asynchronous bilateral tumors, but in the case of unilateral tumors a difference is noted. In stage I tumors five-year survival rates have been 100% for unilateral, 79% for bilateral synchronous and 82% for bilateral asynchronous RCC. (Novick et al. 1989) In one review of synchronous bilateral RCC the five-year survival rate was 69%, which is better than in unilateral disease (Jacobs et al. 1980).

Histology and grade

Clear cell RCCs present more often with high stage and grade and are more likely to develop distant metastases than papillary or chromophobe tumors. These non-cc histologies carry a favorable prognosis after nephrectomy for a localized tumor. The cystic variant of ccRCC seems to be an indolent tumor. (Beck et al. 2003, Cheville et al. 2003) Papillary RCC with scanty cytoplasm and small cells (type 1) behaves less aggressively than papillary tumors with eosinophilic cytoplasm and large cells (type 2) (Moch et al. 2000). In the metastatic setting, however, both papillary and chromophobe RCC are characterized by poor prognosis and a resistance to most conventional treatments. Patients with chromophobe RCC have longer survival, as it has a more indolent metastatic potential: the median time from nephrectomy to metastasis and from metastasis to death is twice that for ccRCC. In patients with papillary tumors the median survival is only eight months. (Motzer et al. 2002, Beck et al. 2003, Ronnen et al. 2006) Tumor necrosis is significantly

associated with cancer-related death in clear cell and chromophobe RCCs, but not in papillary tumors (Cheville et al. 2003).

Sarcomatoid RCC is characterized by a locally aggressive nature, metastatic potential and poor prognosis (Tomera et al. 1983). The tumors are commonly already metastatic or locally advanced at diagnosis. With no treatment the reported median survival after diagnosis is only 3.8 to 6.8 months. (Farrow et al. 1968, Sella et al. 1987) The presence of rhabdoid differentiation is associated with poor prognosis; extrarenal tumor growth is twice more likely and over 70% of tumors develop metastases shortly after diagnosis; the mean survival is only eight months (Delahunt 2009).

The initial report of the correlation of grade with patient outcome was published in 1932 by Hand and Broders. Thereafter several grading systems were used, until Fuhrman and colleagues (1982) expanded observations into a four-tier scheme based on nuclear size, irregularity and nucleolar prominence, which to this day remains the most commonly used system (Novara et al. 2007, Delahunt 2009). However, no study unequivocally showed the predictive value of nuclear grading systems regardless of pathological tumor stage until 2000, when the University of California, Los Angeles (UCLA) group reported a multivariate analysis of RCC prognostic factors. In this study five-year CSS was reported to be 89% for Fuhrman grade one, 65% for grade two, and 46% for grades three to four. Low-grade lesions carry better survival than high-grade tumors within all tumor stages. (Tsui et al. 2000)

Clinical presentation

The impact of symptoms of cancer on prognosis has proved to be significant in a number of studies. The CSS is significantly higher in asymptomatic than in symptomatic patients. The only clinicopathological difference between these groups was that microscopic venous invasion was seen more often in symptomatic patients. (Harada et al. 2006)

Tumors larger than five centimeters are more likely to cause symptoms: below this tumor size 12.6% of patients evince symptoms compared with 35.4% above five centimeters. Symptomatic patients have a 1.9-fold greater risk of dying of cancer; CSS is decreased by one third. The five-year OS was 83% in asymptomatic and 60% in symptomatic patients. Symptomatic disease is a significant prognostic factor in terms of OS, progression-free survival (PFS) and CSS. (Schips et al. 2003) Among the groups of asymptomatic, patients with localized symptoms or with generalized symptoms the five-year survival rates are 89%, 72% and 35%, respectively (Patard et al. 2004). The respective figures for 10-year survival are 68.6%, 45.6% and 12.3% (Ou et al. 2003). Symptoms are also reflected in performance status, which is a prognostic factor in all

stages. Patients with a European Cancer and Oncology Group value of one or greater had a significantly lower five-year survival rate of 51% compared with 81% in those with value zero. (Pantuck et al. 2001) Especially cachexia is a sign of poor survival (Kim et al. 2004).

Anemia is one significant prognostic factor in most models (discussed below in Prognostic scoring systems). A high preoperative platelet count is associated with lowered OS and CSS. The platelet count is a measure of the systemic inflammatory response. Platelets may protect circulating tumor cells from detection or attack by the immune system. They may also facilitate cancer cell adhesion to the vascular endothelium and promote tumor growth by secreting angiogenic and tumor growth factors. For each increase of 100 x 10^9 cells/litre the risk of worsened OS and CSS is increased by 16% and 20%, respectively. (Wosnitzer et al. 2010)

Body mass index

Obesity is a known risk factor for RCC (Chow et al. 2000), but paradoxically it does not worsen prognosis. A significant advantage in terms of OS and PFS is reported for patients with a BMI more than 25 compared to normal-weight patients. (Schips et al. 2004) This is discussed in greater detail in paper III. The explanation here has not yet been found, but some authors think that the larger volume of fatty tissue in overweight patients could delay tumor cachexia (Yu et al. 1991).

Operation year

Patients operated more recently tend to have better prognosis when compared with those operated in previous decades. In one of many studies the cancer-specific survival rates were among patients operated between 1978 and 1987 71.5% and among those diagnosed between 1988 and 2000 60.7%. One explanation here might be the higher percentage of incidental tumors found during the latter period. (Beisland et al. 2002)

Biomarkers

Numerous markers have been investigated as prognostic variables, but none has been seen to improve the predictive accuracy of clinical prognostic systems (Ljungberg et al. 2010). These biomarkers include for example CAIX, VEGF, HIF, *CXCR3*, *CXCR4*, metallomatrix proteinase-2 (MMP), MMP-9, insulin-like growth factor II mRNA-binding protein, insulin-like growth factor-1 (IGF-1),

epithelial cell adhesion molecule, vimentin, fascin, survivin, serum amyloid A, Ki67 and p53 (Eichelberg et al. 2009).

The only biomarker available in clinical practice is Ki67. Tumors with a high (>10%) proliferating index carry a ten times higher risk of recurrence than tumors with lower index. Ki-67 is also associated with disease-free period. (Hofmockel et al. 1995) However, MIB-1 values (an antibody which detects Ki67 antigen in fixed and wax-embedded tissue sections) have no association with stage or Fuhrman grade and are of no prognostic value (Kallio et al. 2004).

Other biomarkers mentioned above are used only in research. CAIX has been shown to be a marker for survival in patients with metastatic RCC. This protein is thought to play a role in the regulation of cell proliferation in response to hypoxic conditions and may be involved in oncogenesis and tumor progression. It is absent in most normal tissues. It has been postulated that cell surface carbonic anhydrases regulate the acid-base balance to optimize conditions in tumor invasiveness. Further, there might be an association between loss of contact inhibition and the anchorage dependence of cancer cells. Low staining in immunohistochemical analysis predicts poor prognosis regardless of stage. (Bui et al. 2003)

The VEGF concentration in serum has correlated with stage, grade and poorer survival. High p53 protein staining likewise correlates with poor prognosis. Patients with high HIF expression have poorer survival than those with low expression. *CXCR3* is a predictor of PFS in localized ccRCC. A correlation of strong *CXCR4* expression in ccRCC with a poor CSS is also reported. Elevations of MMP-2 and MMP-9 correlate with tumor aggressiveness, grade and poor survival. (Eichelberg et al. 2009) In addition, significantly increased expressions of MMP-2 and MMP-9 are found in symptomatic patients, reflecting the increased invasive potential of cancer (Harada et al. 2006). Insulin-like growth factor II mRNA-binding protein correlates with higher stage, grade, sarcomatoid differentiation and decreased CSS. Positive epithelial cell adhesion molecule staining is a predictor of recurrence-free and CSS. Vimentin expression is associated with a poor prognosis. Fascin expression correlates with higher grade, stage, tumor size and sarcomatoid transformation. Positive survivin staining is associated with higher stage, and grade and lower CSS. Serum amyloid A levels are reported to correlate with distant metastases. A high IGF-1 level is an independent predictor of OS. (Eichelberg et al. 2009)

Prognostic scoring systems

The first of the prognostic scoring systems (shown in Table 4) was published by Elson and associates (1988). The study population involved was composed

Table 4 Prognostic scoring systems.

Scoring system (patients in the study)	Prognostic factors	Median survival according to number of prognostic factors (Percentage of patients)
Elson et al. 1988 (N=610)	Performance status ≥1 (2=2 points, etc.) Time since diagnosis ≤ 1 year Number of metastatic sites >1 Recent weight loss Prior chemotherapy	0/1 = 12.8 months (18.5%) 2 = 7.7 months (23.1%) 3 = 5.3 months (24.8%) 4 = 3.4 months (20.2%) ≥5 = 2.1 months (13.4%)
Citterio et al. 1997 (N=109)	European Cancer and Oncology Group status 2-3 Hemoglobin ≤ 100 g/l	0 = 21.7 months (58.7%) 1 = 8.6 months (31.2%) 2 = 3.5 months (10.1%)
Motzer et al. 1999 (N=670)	Karnofsky performance status < 80% Lactate dehydrogenase >1.5 x upper limit Lowered serum hemoglobin High corrected serum calcium Absence of nephrectomy	0 = 19.9 months (25%) 1-2 = 10.3 months (53%) ≥3 = 3.9 months (22%)
Heng et al. 2009 (N=645)	Karnofsky performance status < 80% Lowered serum hemoglobin High corrected serum calcium Time since diagnosis ≤ 1 year Neutrophils >upper limit of normal Platelets >upper limit of normal	0 = not reached (22.7%) two-year OS 75% 1-2 = 27 months (51.4%) ≥3 = 8.8 months (25.9%)
SSIGN Frank et al. 2002 (N=1801)	Stage Size of tumor, ≥ 5 cm Grade Necrosis in tumor	Normogram up to 15 points; five-year survival rates: 0-1 99.4% (22.3%) 2 94.8% (13.0%) 3 87.8% (11.0%) 4 79.1% (11.4%) 5 65.4% (8.5%) 6 54.0% (4.9%) 7 41.0% (11.1%) 8 23.6% (3.4%) 9 19.6% (5.6%) ≥10 7.4% (8.7%)
UCLA Integrated Staging System Zisman et al. 2001 (N=661)	TNM stage Fuhrman's grade European Cancer and Oncology Group performance status	Normogram dividing into five groups, five-year survival rates: I 96% (20%) II 89% (18%) III 66% (14%) IV 42% (42%) V 9% (6%)

of patients treated with chemotherapy and none with immunotherapy. A group under Citterio (1997) developed an easier classification based on the European Cancer and Oncology Group performance status and serum hemoglobin. During the era of immunotherapy the standard system was the Memorial Sloan-Kettering Cancer Center (MSKCC) model for metastatic RCC (Motzer et al. 1999). This score has now been validated and updated for use in the current era of targeted therapies as the Heng criteria (Heng et al. 2009).

In localized tumors, two systems can be used to assess the risk of progression: SSIGN (Frank et al. 2002) and the UCLA Integrated Staging System (Zisman et al. 2001) scores. The SSIGN score might be more accurate (Escudier et al. 2012).

2.7.2 Recurrence of renal cell cancer

Local or contralateral renal recurrence

Local recurrence in the renal bed after nephrectomy is rare in localized tumors without primary lymph node metastases, the incidence being 1.8% in five years and 2.3% in 10 years. Most (43%) recurrent primary tumors are T1 or T2 with a mean time to recurrence of 2.8 years. Metastatic disease develops in 63% of these patients with a mean time of 1.6 years after local recurrence. A long disease-free interval (DFI) after nephrectomy is associated with improved survival. One third of recurrences have been operated with a five-year survival rate of 51%. In the patients in question, a local re-recurrence was noted in 50%, metastatic disease in 30% and only 20% remained disease-free. In the rest, medically treated patients had a five-year survival rate of 18% and in patients without any oncological treatment the rate was 12%. The cause of death was RCC in 83% of all patients; CSS at one and five years was 66% and 28%, respectively. (Itano et al. 2000)

After partial nephrectomy, the reported local recurrence rate is from seven to nine per cent with a mean interval of 4.6 years; for patients undergoing enucleation five per cent (Novick et al. 1989, Morgan and Zincke 1990). Local recurrence is more common in patients with VHL disease; recurrences are seen in 24% of patients at 31 months (Chauveau et al. 1996). Local recurrences tend to appear significantly later than distant metastases: 79.5 months vs. 35.4 months, respectively (Fergany et al. 2000). The risk of recurrence is highest within the initial three to five years postoperatively depending on pathological stage: percentages of recurrences increase and the intervals shorten according to

increasing T class (Hafez et al. 1997, Fergany et al. 2000). Bilaterality affects the recurrence rate: seven per cent of unilateral, 25% of bilateral synchronous and 46% of bilateral asynchronous tumors develop local recurrences (Novick et al. 1989).

In surveillance, 1.6% of RCC patients develop an asynchronous tumor in the contralateral kidney (Klatte et al. 2007). Patients with multifocal ccRCC are more likely to suffer a contralateral recurrence than those with a solitary tumor (DiMarco et al. 2004). Besides multifocality one significant predictor is a primary tumor of T2-3. All these tumors have been primarily node negative. (Dechet et al. 1998) The interval may be very long, patients having undergone contralateral radical nephrectomy 1 to 29 years previously; mean interval 9.9 years (Novick et al. 1989).

Metastatic disease

The risk of metastases grows when the primary tumor is greater than three centimeters in diameter (Bell 1938), but even primary tumors six millimeters in diameter have been reported to metastasize (Klatte et al. 2008). RCC can by nature metastasize to any site in the body and equally by both blood-borne and lymphatic routes. The most frequently involved sites the are lungs (29% to 54%), bone (16% to 27%), brain (2% to 10%) and liver (1% to 7%). (Janzen et al. 2003) The literature describes about 50 different sites of metastases. RCC is notorious for metastases to unusual sites such as the small bowel, thyroid and toe. (Pagano et al. 1996, Wahner-Roedler and Sebo 1997) Impairment of blood flow, due to the presence of the tumor thrombus in the renal vein and vena cava might be responsible for a higher rate of atypical metastatic sites. Also bypass routes of lymphogenous spread of the tumor or portasystemic venous shunts are more common in cases with a tumor thrombus, as the blood flow is inhibited in the renal vein and/or vena cava. (Saitoh 1982)

Most patients (71%) who develop metastatic disease do so within one year from diagnosis (deKernion et al. 1978); 78% of recurrences occur within five years, but as many as 22% of recurrences occur after this. One third of the late recurrences occur after ten years and a few even 20 years after nephrectomy. (McNichols et al. 1981) Small primary tumors are usually slower and less likely to develop metastases than tumors of higher T class (Levy et al. 1998, Ljungberg et al. 1999).

Occasionally metastatic renal carcinoma behaves in a variable and somewhat unpredictable manner. Although in most patients the tumor grows relentlessly until death, some may have periods of slow tumor growth or stability. The true

incidence of spontaneous tumor stabilization is unknown, but it may occur in up to 20% of patients (van der Werf-Messing and van Gilse 1971). This phenomenon is reported only in pulmonary parenchymal lesions, which may have these intervals of decreased growth rate and increased doubling times or even intervals of growth arrest (deKernion et al. 1978).

Inoperable RCC

In a series of patients medically unsuitable for nephrectomy, but without metastases and with a renal tumor technically operable, the primary tumor grew at a slow rate of 0 to 1.76 cm per year. In most cases the tumor size was unchanged during follow-up. Only one patient developed metastases 132 months after the initial diagnosis. The median time to death was nine months after diagnosis, none attributable to RCC. The most common reasons for not proceeding to nephrectomy were poor performance status (36%) and patients' reluctance to undergo the required postoperative dialysis (47%). Significant haematuria was successfully managed either conservatively or by embolization. (Lamb et al. 2004)

Truly inoperable RCC is very rare. It is estimated that only 0.4% of all kidney tumors cannot be operated. This figure is of course dependent on the urologist's capability. Reasons for inoperability are T4 tumor with infiltration to adjacent organs, bulky lymph node metastases, high thrombus in vena cava, bilateral large tumors and large tumor in a patient with only one kidney. (Ficarra and Novara 2010) In these cases neoadjuvant treatment is an option. This is discussed in the section on Targeted therapies.

2.8 Treatment

2.8.1 Surgery

Nephrectomy

Since the first nephrectomy for RCC was performed by Walcott in 1871, much progress has been made in the management of this tumor. In 1939 Mintz and Gaul reported only 13% five-year survival in patients treated with simple nephrectomy between 1900 and 1935. The principles of modern radical nephrectomy were annunciated in 1963 by Robson: early ligation of the renal vessels to minimize the risk of vascular tumor emboli, excision of Gerota´s fascia including the kidney and adrenal gland and extensive lymph node dissection including the para-aortic and paracaval nodes from the crus of the diaphragm to the bifurcation of the aorta. Background to this was that the ipsilateral adrenal gland was historically involved in 10% of cases. Also lymphatic metastases, which may diffuse through the perirenal fat, were

presumably removed. In addition, a more adequate margin was ensured. This approach was developed in the era when the diagnosis of a renal mass was based primarily on excretory urography and angiography, and the difficulty in accurately defining the status of the primary tumor and ipsilateral adrenal gland justified extensive excision of normal tissue with the tumor. Robson reported better results compared to a simple nephrectomy and showed a five-year OS rate of 52%. The survival rate was 66% in patients with localized disease. (Robson et al. 1969) These results were confirmed by Skinner and colleagues (1971), who described a 44% five-year OS and improved 10-year survival in patients who underwent radical versus simple nephrectomy.

The indications for operation are precisely defined: a solid enhancing mass without evidence of fat, a complex septated or multiloculated cyst and a cyst with irregular, enhancing margins (Bosniak 1993). Even locally advanced cancer can be cured by radical surgery with thrombectomy (O'Donohoe et al. 1987, Kallman et al. 1992).

In 1991, a group under Clayman first reported a laparoscopic radical nephrectomy. The operative technique has many advantages: decreased postoperative pain and hospital stay and shortened convalescence compared to the open approach (Abbou et al. 1999). It is an alternative to open surgery when the kidney tumor is less than eight centimeters in diameter or less than 850 g and there is no local invasion, renal vein involvement or lymphadenopathy (McDougall et al. 1996). The complication rate is lower for laparoscopic simple nephrectomy compared to laparoscopic radical nephrectomy (12% versus 34%, respectively). Conversion to the open procedure has been required in three per cent versus 16%, respectively. (Gill et al. 1995) The most widely discussed new side-effect is port site metastasis, but this is rare, reported in only 0.1% of cases. Most are port site seedings and related to the removal of high-grade tumors. Also deviation from oncological surgical principles, namely not using a plastic bag for specimen retrieval to avoid contact between malignant tissue and peritoneum or subcutis has proved a significant risk factor. (Micali et al. 2004)

Palliative nephrectomy

In the era of immunotherapy it was clear that patients would benefit from palliative nephrectomy. Surgery had an impact on survival in patients with good performance status: up-front nephrectomy improved median survival by 4.8 months over IFN-α alone. (Coppin et al. 2005) The Southern Western Oncology Group trial randomized patients with primarily metastatic RCC and

an operable primary tumor into two arms consisting of radical nephrectomy followed by IFN-α versus IFN-α alone. These groups had similar response rates, but the median survival was better in the group undergoing nephrectomy: 11 vs. 8 months. This difference was maintained across all stratification factors, including measurable disease, performance status and site of metastasis. (Flanigan et al. 2001) In the European Organization for Research and Treatment of Cancer study with similar protocol PFS and OS were statistically significantly improved in the surgical arm. Median survival was seven months in the IFN-α only arm, compared to 17 months in the surgery plus IFN-α arm. Response rates did not differ between the groups and complete responses (CR) were noted in both. (Mickisch et al. 2001) An advantage of palliative nephrectomy has also been shown for IL-2 –based therapy: one- and two-year survival rates have been 67% and 44%, compared with patients without nephrectomy: 29% and 4%, respectively (Belldegrun et al. 2000).

The reasons for this benefit are many. After cytoreductive surgery, serum immunosuppressive acidic protein decreases and natural killer activity increases significantly. The former is known to suppress various immune responses. These changes result in a shift from a predominantly inflammatory response to immune activation. (Fujikawa et al. 2000) Various defects in natural killer activity and lymphokine-activated killer cell generation are observed preoperatively, these slowly improving after the primary tumor is removed (Dadian et al. 1994). Also improved performance status and therefore better prognosis, reduced tumor burden enhancing the response to systemic treatment, better tolerance of treatment, removal of a trap for trafficking lymphocytes, source of growth factors and other molecules causing paraneoplastic symptoms, prevention of complications during therapy and removal of a source of future additional metastases are the rationale for surgery (Bennett et al. 1995, Fallick et al. 1997, Lam et al. 2004). Nephrectomy also seems to delay progression and increases the time to a lethal burden of metastatic disease. The mild renal failure after surgery causes metabolic acidosis, which is thought to reduce tumor progression. Along with removal of the primary tumor, also the source of VEGF and other angiogenic factors such as PDGF, fibroblast growth factor (FGF), TGF-β1, angiopoietins and hepatocyte growth factor, is removed. (Abel and Wood 2009) Potential disadvantages of palliative nephrectomy include perioperative morbidity and mortality as well as delay in starting systemic therapy, which involves a risk of progression (Bennett et al. 1995, Fallick et al. 1997, Lam et al. 2004).

Symptoms related to the primary tumor are noted in 28% of patients. They are usually not difficult to manage. (Montie et al. 1977) However, sometimes nephrectomy in the palliative setting is needed when the patient experiences

pain related to a kidney mass not easily treated with medication, intractable hematuria, erythrocytosis or uncontrolled hypertension (Lam et al. 2004) or persistent hypercalcemia which does not respond to pharmacological agents. In most cases nephrectomy eliminates malignant hypercalcemia. (Walther et al. 1997)

The spontaneous regression of metastatic disease after nephrectomy alone is rare: only 0.8% of patients experience spontaneous regression (Montie et al. 1977). Most of the reported cases have been in the lung (Freed et al. 1977). However, more than half of all patients experiencing spontaneous regression had not undergone prior nephrectomy (Snow and Schellhammer 1982).

No prospective randomized trials have as yet been published on the effect of cytoreductive nephrectomy on the survival of patients with primarily metastasized RCC treated with targeted therapies. However, nephrectomy does not appear to be essential for benefit from these. In retrospective studies the treatment response or PFS does not differ between patients with or without nephrectomy. The reason for this may be better response of the primary tumor to the targeted therapies, which overrides the benefits of nephrectomy. In many cases the disease has also progressed during postoperative recovery. Patients with Karnofsky performance status less than 80, with tumors bearing sarcomatoid features, coagulative necrosis, tumor thrombus, Fuhrman grade 4 or non-cc histology, elderly patients (>75 years) or patients with poor risk in MSKCC scale derive no benefit from surgery. (Culp et al. 2010, Choueiri et al. 2011, You et al. 2011) Also patients with at least four out of seven preoperative factors (high lactate dehydrogenase level, low serum albumin, metastatic symptoms, liver metastasis, retroperitoneal or supradiaphragmatic adenopathy or T3/T4 tumor) do not benefit from nephrectomy. Conversely, optimal cases for cytoreductive nephrectomy are patients with good performance status in whom there is a possibility to remove a significant proportion (>75%) of the tumor burden, with adequate surgical resectability and no central nervous system, bone, liver or multiple-site metastases. (Culp et al. 2010)

Adrenalectomy

Since Robson's times the principles of routine adrenalectomy have changed. The recent guidelines no longer recommend routine adrenalectomy (Ljungberg et al. 2010). The procedure should only be undertaken with radiographic or intraoperative evidence of adrenal involvement (Weight et al. 2011). With accurate preoperative staging, the target population for adrenalectomy can be

specified. CT has greater than 99% specificity and almost 90% sensitivity to detect adrenal involvement preoperatively. (Tsui et al. 2000a)

Patients with upper pole tumor, tumor size more than seven centimeters, with tumor thrombus or metastatic disease have the highest risk of adrenal involvement. Even in this high-risk group the frequency of ipsilateral adrenal involvement is still quite low (<10%). Additionally, adrenalectomy does not lower the risk of subsequent adrenal metastasis, nor improve CSS. Asynchronous adrenal metastases are more often contralateral than ipsilateral. In the case of previous routine adrenalectomy, these patients would develop total adrenal insuffiency. If the adrenal is only site of metastasis, adrenalectomy cures 4.2% of patients. (Weight et al. 2011)

Altogether adrenal involvement is seen in 2.4% of patients (Weight et al 2011). This situation is mostly encountered when preoperative CT has shown the adrenal gland to be displaced, enlarged or not visible. Even in this group with adrenal abnormalities, malignant involvement has been found in only 26% of patients. Non-visualization can also occur due to sparse retroperitoneal fat, inappropriate scan interval or slice thickness, operator error or the presence of surgical clips in the vicinity. However, the most common reason has been the presence of a large upper pole renal tumor with extensive collateral blood vessels, which distorts, displaces or engulfs the ipsilateral adrenal gland. (Gill et al. 1994, Tsui et al. 2000a)

Lymphadenectomy

Routine lymphadenectomy is not nowadays done routinely as it does not improve survival (Ljungberg et al. 2010). The survival advantage of a systematic retroperitoneal lymph node dissection adjunctive to a radical nephrectomy is estimated to be at best about six per cent (Pizzocaro and Piva 1990). If a patient has palpable or CT-detected enlarged lymph nodes, lymphadenectomy should be performed to obtain adequate staging information (Ljungberg et al. 2010). Unlike other metastases, lymph node involvement is difficult to identify accurately with imaging: 30% of patients with pathologically positive lymph nodes have microscopic disease only (Waters and Richie 1979). Moreover, in patients with enlarged nodes at preoperative CT truly positive nodes have been found in 42%, the rest showing only inflammatory changes and/ or follicular hyperplasia. False-positive findings have been significantly more frequent in patients with renal vein involvement or tumor necrosis. The incidence of false-negative results has been 4.1%. (Studer et al. 1990) When lymph nodes are in preoperative imaging negative, but palpable to the operator's hand, metastases are found in 16%. In preoperatively negative and nonpalpable lymph nodes, the risk of metastases is only one per cent. (Blom et al. 1999)

The risk of lymph node involvement varies greatly depending upon primary tumor stage and size, renal vein involvement, presence of metastases and the extent of lymphadenectomy performed. The percentage of positive findings increases along with T class. In metastatic disease, positive lymph nodes are found in 62% of patients and even more if there is additionally renal vein invasion. (Giuliani et al. 1983) In a more recent study the overall risk of lymph node metastasis was 27% in patients with metastatic disease and seven per cent in local disease. In the former case the presence of positive lymph nodes was associated with larger sized, higher grade, locally advanced primary tumors which were more commonly associated with sarcomatoid features. (Pantuck et al. 2003a)

Prior to the advent of modern imaging technology, primary lymphadenectomy reduced local recurrences (Phillips and Messing 1993) and improved survival. Macroscopic renal vein invasion eliminates the effect of extended lymph node dissection. For patients with positive lymph nodes significantly better survival rates have been apparent only during the first three years postoperatively; thereafter the benefit disappeared. (Herrlinger et al. 1991) Only one fourth of patients with lymph node metastases are cured by radical nephrectomy; for the majority, regional extension is merely an indicator of systemic metastatic spread (Lieber et al. 1981). In the era of immunotherapy, survival advantage was achieved in metastatic disease when lymphadenectomy was performed with nephrectomy. Median survival in IL-2 treatment was approximately five months better in those undergoing lymphadenectomy. (Pantuck et al. 2003)

In more recent studies no survival advantage is found. In a comparison of patients undergoing nephrectomy and extensive lymphadenectomy, nephrectomy and lymphadenectomy for gross nodal disease only and nephrectomy only no significant survival advantage was obseved in any of these groups, but there was a tendency for patients with extensive lymphadenectomy to survive better (Schafhauser et al. 1999). The European Organization for Research and Treatment of Cancer has conducted the only prospective, randomized controlled study in this area. Patients with clinically localized disease were randomized to undergo nephrectomy with or without a standardized lymphadenectomy. Only 3.3% of preoperatively negative lymph nodes were found to be metastatic. After a median five-year follow-up there were no differences in complications, progression rate or survival between these groups; the five-year OS was 82%. (Blom et al. 1999)

Partial nephrectomy

Partial nephrectomy was first reported by Wells in 1884, undertaken for removal of a perirenal fibrolipoma. The initial enthusiasm for this approach abated after significant problems were encountered in the form of excessive postoperative morbidity (Novick 1987). Primarily nephron-sparing surgery was limited to imperative indications such as bilateral renal masses or tumor in a functionally or anatomically solitary kidney. Following the observations of Robson and colleagues (1969) of better survival after extrafascial nephrectomy, the use of partial nephrectomy fell into disfavor. Recent interest for nephron-sparing surgery has been stimulated by advances in imaging methods, experience with renal vascular surgery, improved methods of preventing ischemic renal damage, the growing incidence of incidentally discovered low-stage RCC and good long-term survival rates in patients treated by partial nephrectomy. (Novick 1993) After the re-introduction of the approach, indications widened to patients with impaired renal function from congenital anomalies such as ureteral reflux, nephropathy, or significant calculus disease, and to patients with comorbidities, such as diabetes, collagen disease, chronic pyelonephritis, nephritis, renal artery stenosis or hypertension (Novick et al. 1989, Lam et al. 2004).

Nowadays, partial nephrectomy has become the standard surgical treatment for T1a tumors (Van Poppel et al. 2011). The reason for this is the possibility of a metachronous tumor developing in the contralateral kidney, which is seen in some studies in six per cent of cases (Dechet et al. 1998). Absolute indications for nephron-sparing surgery are an anatomic or functional solitary kidney and a patient with hereditary RCC carrying a high risk of developing additional kidney tumors. A condition which might impair the function of the functioning opposite kidney in the future is a relative indication for partial nephrectomy. (Ljungberg et al. 2010)

Patients with extensive local tumors (minimal remaining normal renal parenchyma), regional adenopathy or renal vein or vena cava extension are not candidates for resection (Lam et al. 2004). The risk of small synchronous tumors is apparent even in small tumors, as none of the current radiological methods can detect these (Prati et al. 1993). In patients with VHL disease the results of nephron-sparing surgery are less satisfactory; there is a high recurrence rate due possibly to multifocality of the lesions associated with this syndrome (Chauveau et al 1996).

The effectiveness and safety of nephron-sparing surgery is well evinced in the treatment of renal tumors four centimeters or less. Local recurrences are seen in 2.6-7% of patients, but this may derive from tumor multifocality rather than real local recurrence. (Barbalias et al. 1999, Kunkle et al. 2008)

Multifocality is reported in 7-21.4% of RCC patients (Mukamel et al. 1988, Cheng et al. 1991, Campbell et al. 1996, Baltaci et al. 2000). In many cases the primary tumor has been less than four centimeters. Stage is a significant predictor of multifocality, whereas the histological pattern and the primary tumor diameter are not. (Baltaci et al. 2000)

The margin size is irrelevant in the case of local recurrence. Two thirds of margin-positive patients survive without recurrence; the rest developed metastatic disease without local relapse. (Sutherland et al. 2002)

CSS rates following radical and partial nephrectomy are comparable (Van Poppel et al. 2011). However, patients treated with radical nephrectomy are more likely to die of other causes when compared with patients treated with partial nephrectomy. This difference persists even after adjusting baseline comorbidity index and is caused by treatment-induced chronic kidney disease and related cardiovascular events. (Sun et al. 2012) Patients younger than 65 years have better survival after partial nephrectomy (Thompson et al. 2008). In patients undergoing partial nephrectomy, a risk reduction of 26% is noted in the development of at least one adverse renal outcome (Miller et al. 2008). The chance of kidney failure over time is significantly less in patients treated with partial resection compared to the radical nephrectomy group: in five years' surveillance none vs. 15%, respectively. The plateau was reached approximately four years after operation. (McKiernan et al. 2002) Patients with a greater than 50% reduction in overall renal mass are at greater risk of proteinuria, glomerulopathy and progressive renal failure. Structural or functional renal damage is usually antedated by the appearance of proteinuria, whose extent is inversely correlated with the amount of remaining renal tissue. The risk of progressive renal failure is highest in patients with over 75% reduction in renal mass. This can occur over 10 years after surgery. (Novick et al. 1991) In patients with risk factors for kidney failure partial resection provides many years of dialysis-free and tumor-free renal function: the mean time to dialysis is 9.8 years after the operation (Fergany et al. 2000). Preservation of nephrons has been suggested to be protective against hyperfiltration injury, which could otherwise lead to excessive renal blood flow and glomerular filtration rate, causing continuous activation of the preserved glomeruli of the outer cortex. This intrarenal hypertension is considered to be one of many causes of the progressive glomerular sclerosis seen in cases of surgical loss of renal mass. (Lau et al. 2000)

Partial nephrectomy can be performed laparoscopically. This is a technically challenging procedure, for which absolute contraindications are renal vein

thrombus, multiple renal tumors and central intra-renally located tumor. Relative contraindications include morbid obesity, a history of prior ipsilateral renal surgery and bleeding diathesis. (Lam et al. 2004) A 10% perioperative complication rate and four per cent conversion rate to open nephrectomy have been reported (Cadeddu et al. 1998). When compared to open partial nephrectomy, the laparoscopic procedure involves less surgical time and blood loss. Additionally, the analgesic requirement, hospital stay and average convalescence are smaller. (Gill et al. 2003)

Robot-assisted partial nephrectomy was first reported in 2004. The short-term oncologic outcome of this technique is comparable to the open operation, while morbidity is less. The procedure involves significantly smaller intraoperative blood loss, reduced length of stay in hospital and shortened warm ischemia time. In addition, surgeons have a relatively shorter learning curve when compared to the laparoscopic operation. The postoperative complication rate is 9.8%, 8.2% being major. This compares favorably to complications in both laparoscopic and open partial nephrectomy. (Babbar and Hemal 2012)

Other nephron-sparing procedures

Other nephron-sparing techniques include enucleation and as outpatient therapy percutaneous radiofrequency ablation (RFA), cryoablation, microwave ablation, laser ablation and high-intensity focused ultrasound ablation. The advantages of these newer, outpatient techniques are reduced morbidity and the possibility to treat high-risk surgical candidates. The current indications are small cortical lesions in elderly patients, tumors in patients with a genetic predisposition to develop multiple tumors, bilateral tumors and patients with a solitary kidney who are at high risk of complete loss of renal function. Absolute contraindications are irreversible coagulopathies and severe medical instability. Relative contraindications are tumors greater than three centimeters or located in the hilum, near the proximal ureter or the central collecting system. (Ljungberg et al. 2010)

Primary enucleation of kidney tumors is reserved for patients with VHL disease who have multiple diffuse carcinomas (Loughlin and Gittes 1986, Spencer et al. 1988) or patients with an encapsulated, hilar tumor directly overlying the major vessels with no interposed margin of uninvolved parenchyma (Novick et al. 1989). It is also favored in elderly patients with concurrent medical problems for whom the anesthesia time should be kept to a minimum and the microscopic residual cancer is unlikely to have an impact on survival. Enucleation is suitable for lesions throughout the kidney. (Morgan and Zincke 1990)

Laparoscopic cryoablation has been performed in many centers with promising results since 1995. Cryoablation involves rapid freeze and thaw cycles to produce tumor destruction and to cause movement of intracellular water, alterations in intracellular pH, protein denaturation and mechanical destruction of cell membranes. Delayed necrosis also occurs, as the injured miscovasculature causes decreased tissue perfusion and delayed cell death. (Aron and Gill 2007) In peripheral tumors no local, port site or distant recurrences have been found during a mean follow-up of 16 months. In post-treatment biopsy three to six months subsequently, histological analysis has been negative for viable cancer cells in all patients. The cryolesions are observed to contract in size over time. In an MRI scan at one year, no residual cryolesion could be identified in 25% of patients and in the remainder the mean size reduction was 66%. Potential complications are urine leakage secondary to caliceal cryoinjury, with resultant fistula formation and post-thaw hemorrhage. The careful selection of patients with peripherally located tumors and meticulous intraoperative US monitoring of the evolving cryolesion to protect the caliceal system are important in this regard. To minimize hemorrhage, gentle insertion and removal of the cryoprobe are essential. If during the follow-up an increase in the size of the cryolesion, no further decrease or abnormal MRI characteristics inconsistent with a contracting avascular cryolesion are seen, a needle biopsy and new evaluation of the lesion is recommend. (Gill et al. 2000) Local recurrence is reported in 4.6% of patients (Kunkle et al. 2008).

RFA was first described in treating kidney tumors in 1998 (McGovern et al. 1998). RF waves are converted to heat by ionic agitation, resulting in thermal tissue damage: as the target tissue temperature increases to approximately 50°C, cellular proteins become denaturated and lipid components melt, leading to disintegration of cell membranes and irreversible tissue destruction (Matlaga et al. 2002). The zone of coagulative necrosis is visible 24 to 48 hours after ablation, achieving maximal extent by seven days. This ablated tissue is eventually replaced by inflammation and fibrosis and is ultimately re-absorbed. (Schulman and Zlotta 1994) Laparoscopic RFA as a part of partial nephrectomy was first described in 2001 (Gettman et al.). RFA as a sole treatment was at first unreliable, but more recent publications have reported excellent results using high-wattage generators (Matlaga et al. 2002, Jacomides et al. 2003). In a meta-analysis with a mean follow-up of 47.1 months, local recurrence rate has been shown to be up to 11.7%, but no differences are detected in the incidence of

metastatic disease when compared to partial nephrectomy or cryoablation (Kunkle et al. 2008).

Microwave ablation is a thermal needle ablation treatment modality. However, it has resulted in poor oncological outcomes with a significant complication rate. The recurrence rate has been reported to be 38%, the intraoperative complication rate 20% and the postoperative complication rate 40%. (Castle et al. 2011) Laser ablation is done performed under general anesthesia percutaneusly using MRI-guidance. Laser fibers are placed on the tumor and the tumor is ablated under MRI control. The initial clinical experience has been promising; only one out of ten patients was not successfully ablated. One complication (myocardial infarction) occurred in the small study in question. (Kariniemi et al. 2010) High-intensity focused ultrasound is reported to be a safe, feasible and effective technique. It is administered with a non-invasive extracorporeal device under general anesthesia. Real-time diagnostic US is used for targeting and monitoring. No major complications are seen. Stable lesions are achieved in two thirds of patients. (Ritchie et al. 2010)

Metastasectomy

The incidence of solitary metastasis is only 2.5% (O'Dea et al. 1978). In 1939 Barney and Churchill excised single pulmonary metastases in a patient who had undergone nephrectomy for RCC. The patient died 23 years later of coronary artery disease (Wilkins et al. 1961). The success of this first reported case and the lack of effective nonoperative modalities until recent times, are factors which have promoted an aggressive surgical approach to the management of this small group of patients. Excision of metastatic foci significantly improves the survival of patients up to five years, after which most die due to recurrence. (deKernion et al. 1978) Very difficult surgical procedures can be undertaken to cure a patient: hemipelvectomy is reported in a patient with solitary bone metastasis six years after nephrectomy. This patient was alive and cancer-free 13 years after the metastasectomy. (McNichols et al. 1981)

There is no consensus as to factors prognostic of survival after metastasectomy. In some studies the presence or absence of a metastasis at diagnosis, the length of DFI after nephrectomy or the site of metastasis did not influence survival after excision of the single lesion (Dineen et al. 1988). In contrast, another study has reported patients with synchronous metastasis or DFI less than six months to have an average survival of approximately 10 months; only 44% survived one year and six per cent for five years. Patients with over two years DFI have a median survival time of 24 months in the metastatic phase. (Maldazys and deKernion 1986) In addition, another study

has shown a survival difference when patients with operated solitary metastasis are compared to those with multiple foci operated: the five-year OS is 54% vs. 29%, respectively. Those patients with isolated metastases to a glandular site (thyroid, salivary gland, pancreas, adrenal or ovary) have had the most favorable prognosis: 63% were alive five years after metastasectomy. The lung as a site is more favorable than the brain; five-year survival rates are 54% vs. 18%, respectively. In the study in question, patients with DFI longer than 12 months survived better, the five-year OS being 53% versus 33% in patients with a shorter interval. When metastases became apparent at an interval, no difference in survival after curative resection of second and third metastases was seen when compared with initial metastasectomy: five-year OS is 46%, 44% and 43%, respectively. (Kavolius et al. 1998)

In the era of immunotherapy, metastasectomy of residual disease was worthwhile. Patients who received high-dose IL-2-therapy and achieved a partial response (PR), underwent surgical resection of the residual tumor. The overall response rate (ORR) was 15.5%. Operated patients remained disease-free after a median follow-up of 21 months. If surgery was not done, most patients relapsed: 22% of patients with CR and 66% of patients with PR evinded progression. The median duration of response in these patients was only 10 months. (Kim and Louie 1992) Reports after targeted therapy are scarce. The median length of preoperative treatment has been almost one year (range 12-177 weeks). Half of the operated patients did not relapse during the one-year follow-up. Operation risks are not increased, but a need for careful hemostasis and lymphostasis is reported. (Karam et al. 2011)

2.8.2 Angioembolization

Angioinfarctation of the kidney was introduced in clinical practice in the early 1970s. Indications have been palliation of patients with persistent hemorrhage or resistant hypercalcemia due to RCC who were not surgical candidates, and reducion of tumor volume and blood loss to facilitate surgery in patients with large RCC. The optimal delay to operation seems to be one day. (Kalman and Varenhorst 1999) In some series a 30% decrease in tumor volume was noted in 75% of subjects after embolization (Mebust et al. 1984).

Since the introduction of this method, a total of 22 different embolization agents have been used, but since the beginning of the 1980s concentrated ethanol has become more common. In the preoperative devascularization of a tumor, short-acting agents such as an absorbable gelatine sponge and thrombin are also adequate, but ethanol as a permanent material produces a prolonged

occlusion and long-term palliation. It has also the lowest complication rate, but unintentional embolization is described with all agents. Mortality is reported to be 3.3% and the mean complication rate 9.8%. (Kalman and Varenhorst 1999) The reasons for death have been pulmonary embolus and perforation of a small aortic aneurysm with postoperative complications (Mebust et al. 1984). Other possible serious complications are embolization of non-target organs such as the large bowel, spinal cord, contralateral kidney or arteria testicularis. This can be usually prevented by means of a balloon occlusion catheter. Also tubular necrosis, renal abscess and alteration in blood pressure are reported. The complication rate is four-fold in palliative therapy when compared with preoperative procedure, as patients are in lower general condition and tumors are usually larger. (Kalman and Varenhorst 1999) As a milder complication almost all patients develop a postinfarctation syndrome involving pain, fever and gastrointestinal symptoms such as nausea, vomiting and hiccups. These symptoms begin almost immediately upon embolization and may persist for longer than three days in 25% of patients. (Swanson et al. 1980)

Nowadays, arterial embolization may still be indicated as a palliative ablation for inoperable patients with huge tumors, in emergency cases of acute hemorrhage, to reduce blood loss during surgery and to cure complications of nephron-sparing surgery related to bleeding or arteriovenous fistulas (Roy et al. 1999).

2.8.3 Oncological treatments

Oncological treatments are for patients with metastatic disease. As some metastatic RCCs are of particularly indolent nature, a period of observation before starting should be considered if the patient is almost asymptomatic. There is no recommended adjuvant treatment, although many adjuvant trials are ongoing. (Escudier et al. 2012)

Endocrine treatment

RCC can be induced experimentally in hamsters by administration of estrogens (Matthews et al. 1947). Inhibition of induced tumor growth in an experimental animal has been achieved with estrogen antagonists such as testosterone propionate (Riviere et al. 1961), progesterone and deoxycorticosterone (Kirkman 1959, 1959a). The effect of progesterone and high-dose tamoxifen on metastatic RCC was noted already 50 years ago. The mechanism of action is still unclear and efforts have been made to clarify the issue. When estrogen and progesterone receptors were determined in tissue samples obtained from tumors, surrounding kidney and from healthy subjects' kidneys, the tumor tissue had the lowest content of these receptors and the highest percentage was

in control kidneys of healthy persons. (Mukamel et al. 1984) Some studies have found a correlation between different sex steroid receptors and survival of patients. The survival rate of patients with one or more steroid receptors (estradiol, progestin or androgen) was significantly higher than that of patients negative for receptors. All receptor-negative patients died within 13 months; in the positive receptor status group the survival rate was 25% at 43 months. (Nakano et al. 1984)

Progesterone was observed to be a moderate competitor for dexamethasone and binding of medroxyprogesterone acetate to glucocorticoid receptors of cancer tissue was one assumed mechanism of action (Bojar et al. 1979). Medroxyprogesterone acetate may also interfere with IL-6 macrophage production, possibly causing a synergistic effect in association with IL-2 and IFN-α. IL-6 is considered to be a growth factor for RCC. Macrophage production causes immunosuppression in metastatic patients. (Naglieri et al. 2002) The most common side-effects of medroxyprogesterone acetate are loss of libido, weight gain, hypertension, hirsutism and amenorrhea. Treatment interruptions have been necessitated by toxic hepatitis and retinal damage. (Pizzocaro et al. 1983; 1987)

Chemotherapy

RCC is widely considered a chemorefractory disease. Many sytostatic drugs have been tested in metastatic disease, but the response rate has not been good (Motzer and Russo 2000). Overexpression of the multidrug-resistance protein-1 (*MDR-1*) gene is believed to be responsible for chemotherapy resistance, although the use of MDR modifiers with standard chemotherapeutic agents has not improved response rates. Multi-drug resistance-associated protein, the gene product of *MDR-1*, actively expels chemotherapy drugs from tumor cells by a molecular pump. *MDR-1* also accelerates drug secretion into the urine at the level of the luminal membrane of renal proximal tubules. (Mignogna et al. 2006)

Of tested chemotherapy drugs, 5-fluorouracil (5-FU) in continuous infusion has yielded less than 10% PRs (Kish et al. 1994). The newer per oral prodrug of 5-FU, capecitabine produces minor responses even in third-line therapy, but in most patients no response or only stable disease (SD) is observed (Pagliaro et al. 2006, Petrioli et al. 2007). The rationale behind the use of capecitabine is that kidney cancer cells contain a considerable amount of thymidine phosphorylase, a key enzyme converting capecitabine to active 5-FU (Miwa et al. 1998). The best results reported with chemotherapy are in the combinations with interferon or pegylated interferon, which increase intratumoral levels of

thymidine phosphorylase especially when given prior to fluoropyrimides. This increases the efficacy of chemotherapy (Eda et al. 1993, Morita and Tokue 1999). The combination of continuous infusion of 5-FU and IFN-α-2b produces a 43% response rate with 19% CRs, with mild toxicity. Responses have been durable, the mean duration being almost two years. (Gebrosky et al 1997) However, the response rates in multicenter randomized trials are similar to those for cytokines alone (Negrier et al. 2000). In a phase II study combining capecitabine and pegylated IFN-α-2a the response rate was 27%, with four per cent CRs (Sunela et al. 2010).

Also vinblastine was previously widely used in the treatment of RCC. However, the ORR for vinblastine is only 2.5% and OS 38 weeks. When combined with IFN, ORR is increased to 16.5% and OS to 68 weeks without significant increase in toxicity. (Pyrhönen et al. 1999)

Immunological treatments

The first real possibilities to treat metastatic kidney cancer were IFN and IL-2. IFN was already reported to evince antitumor activity against RCC in 1983, producing PRs to 26% of patients in the early studies (Quesada et al. 1983). A few years later came reports of a dramatic response of patients with advanced cancer treated with IL-2, a glycoprotein first defined as a T cell growth factor, and lymphokine-activated killer cells, generated by the in vitro culture of peripheral blood lymphocytes in the presence of IL-2. Of three reported RCC patients all achieved partial responses. (Rosenberg et al. 1985)

Interferons are glycoproteins produced by a variety of human cells in response to viral infections or other inducers. They have been demonstrated to have antiviral and antioneoplastic activity, the latter possibly mediated by direct tumor toxicity and/or indirect cytotoxicity. The mechanisms of action of interferon are various and still partly unclear; IFN modulates cancer cell growth and differentiation by regulation of the cell cycle; it affects cellular communication and intracellular signaling, causing cells to undergo apoptosis, but also induces nonapoptotic cell death. It also upregulates the expression of major histocompatibility complex (MHC) class I antigens, which favors tumor cell recognition by specific cytolytic T cells as well as the activation of natural killer cells. IFN has postgenomic effects based on the regulation of protein synthesis and on the selective translation of proteins participating in growth arrest and apoptosis. IFN also produces a link between innate and adaptive immune responses and interferes with tumor-mediated angiogenesis. (Tagliaferri et al. 2005)

In initial reports of IFN-α, the response rate was 15% to 26%, including a few CRs with a duration up to 19 months. The greatest benefit was achieved in

selected patients, namely those with good performance status, previous nephrectomy, long DFI and lung being predominant metastatic site. (deKernion et al. 1983, Quesada et al. 1983 and 1985, Kellokumpu-Lehtinen and Nordman 1988) Improved one-year survival compared to medroxyprogesterone acetate was reported (43% versus 31%, respectively); median survival was 8.5 vs. six months. CRs were found in two per cent (vs. 0%) and PRs in 12% of interferon-treated (vs. seven per cent); these remained at six months control. The typical side-effects of IFN are fever, lack of appetite, tiredness, nausea, lack of energy, shivering and dry mouth. (Medical Research Council Renal Cancer Collaborators 1999) However, in most studies the duration of the treatment with IFN has been only 6-12 weeks by reason of the side-effects, and reported responses have been observed after two to four months' treatment. Intermittent (three weeks on, one week off) and prolonged use of IFN up to doses of 18 million international units (MIU) three times a week has proved to be feasible for up to two years, producing an ORR of 17% with four per cent CRs, PFS 12 months and OS 19 months. All these responses were observed in patients treated with a dose greater than 9 MIU three times a week. This was well tolerated in 88% of the patients. (Kankuri et al. 2001)

The Cochrane database systematic review includes 53 randomized controlled trials made between 1966 and 2003, involving 6 117 patients. PRs or CRs were seen in 12.9% compared to 2.5% in non-immunotherapy control arms and 4.3% in placebo arms; 28% of the responses seen in immunotherapy arms were complete. Median survival averaged 13.3 months; the improvement was 3.8 months. The difference in remission rate correlated poorly with the difference in median survival. The addition of a variety of enhancers, including low-dose intravenous or subcutaneous IL-2, has failed to improve survival compared to IFN-α alone. (Coppin et al. 2005) In addition, the combination of subcutaneus IL-2 and IFN is reported to be rather toxic, 70% of patients having grade 3 or 4 adverse effects (Vuoristo et al. 1994). Lymph node-positive patients rarely respond to immunotherapy (Pantuck et al. 2003a). IFN yields only modest benefit in metastatic RCC with other than clear cell histology (Dutcher et al. 2009).

IFN has moderate toxicity and the dosing is three to five times a week given as subcutaneous injections. New formulations have therefore been developed and pegylated IFN-α-2a and -2b are commercially available. These are chemically modified by covalent linkage of a polyethylene glycol polymer to enhance pharmacokinetic characteristics and reduce immunogenicity. In phase II studies of pegylated IFN-α-2a the response rate has been 13%; CR was

observed in 2.5%. The toxicity was mostly mild to moderate; grade 3-4 toxicity was seen as neutropenia, fatigue, nausea/vomiting and elevated hepatic transaminase values. (Motzer et al. 2002a) In a phase II study with pegylated IFN-α-2b, ORR was 13.6% with 4.5% CRs. Median OS was 13 months; in 9% of patients the response remained over six months. In this study fatigue was the major dose-limiting factor, grade 3-4 fatigue being reported in 22.7% of patients. No grade 3-4 hematologic toxicity or liver enzyme elevations were seen, but 55% of patients required dose reductions. (Bex et al. 2005)

With IL-2 the best results are achieved with high-dose bolus i.v. dosage: patients are treated with 600 000 or 720 000 IU/kg by i.v. bolus infusion every eight hours for 14 doses during five days' hospitalization, followed by an identical repeated treatment cycle after a 10 days' resting interval. With this protocol seven per cent of CRs and eight per cent of PRs are reported. The median duration of response has been 53 months; in CRs the median was not reached, this being at least 80 months. Median survival was 16 months. Significantly, a small subset of responding patients have remained alive for 11 years after therapy. As this treatment produces many side-effects, patient selection remains of paramount importance and should focus on European Cancer and Oncology Group status, absence of concomitant underlying disease and good cardiac, respiratory and renal function. (Dutcher et al. 1997) All patients have in varying degrees hypotension, peripheral edema and oliguria (Fleischmann and Kim 1991). When reduced-dose IL-2 is given by i.v. bolus or by subcutaneous injection survival equivalent to high-dose IL-2 is seen, with less toxicity (Coppin et al. 2005).

Cancer vaccines have a potential for focusing immune reactions toward tumor-specific and tumor-associated antigens. Dendritic cells are loaded with relevant antigens, which stimulate these cells to mature and migrate to lymph nodes, where they prime tumor antigen-specific T and B lymphocytes. The activated T cells penetrate metastases to kill tumor cells. Stimulated B cells differentiate into plasma cells which produce anti-tumor antibodies. Development of the optimal protocol is still in progress and studies on the choice of antigens, the use of granulocyte macrophage colony-stimulating factor (GM-CSF) or low-dose cyclophosphamide to reduce the number of T regulator cells, the combination of sunitinib or other targeted therapy with the addition of immunomodulatory antibodies are ongoing. (Dranoff 2012) The immunological therapies under investigation are shown in Table 5.

In 2000 was published the first series of RCC patients refractory to cytokine therapy and treated with allogeneic stem cell transplant from a human leucocyte antigen (HLA)-identical sibling donor. ORR was 53% and CRs were seen. Responses are often delayed in onset, frequently associated with graft-versus-

host disease or cyclosporine withdrawal, or with infusion of donor lymphocytes. The prognostic factors are C-reactive protein, lactate dehydrogenase and performance status. The use of an allogenic transplant decreased dramatically after the introduction of targeted therapies. However, 20% of these cytokine-refractory patients were alive five years after transplant. This treatment is an option only for patients aged less than 60 years, with the availability of an HLA-compatible sibling donor and with no significant comorbidities. (Bregni et al. 2009)

Targeted therapies

After the discovery of the *VHL* gene in 1993 and its role in sporadic RCC in 1994, investigators were able to demonstrate regulation of tumor growth and angiogenesis through HIF-1α and HIF-2α. Several agents which disrupt angiogenesis and cell growth pathways have since been developed and are being used successfully. (Abel and Wood 2009) Since 2005 there have been seven drugs commercially available. According to the European Society of Medical Oncology guidelines, in patients with a good or intermediate MSKCC risk rating sunitinib, bevacizumab + IFN or pazopanib are choices for first-line treatment, and temsirolimus for patients with poor prognosis. For patients with non-cc histology the recommedation is not so clear, but temsirolimus, sunitinib and sorafenib are possibilities. For second-line treatment everolimus and axitinib are recommended, sorafenib being an option, and for third-line everolimus is recommended if the patient is still in good general condition. (Escudier et al. 2012) Further drugs are under development; these are shown in Table 5.

Bevacizumab is a humanized anti-VEGF monoclonal antibody. In a phase III first-line study bevazicumab in combination with IFN-α-2a was compared to IFN alone. Bevazicumab is administered i.v. every two weeks. The combination has resulted in a significant improvement in PFS (10.2 months vs. 5.4 months). The respective response rates were 31% vs. 13%. OS data were not mature when the paper was published. Typical side-effects of bevacizumab are proteinuria, hypertension and thromboembolic events. (Escudier et al. 2007a)

Sunitinib is an orally and once-daily administered TKI, inhibiting VEGFR and PDGFR. The treatment is taken for four weeks, followed by two weeks' rest. The typical side-effects are diarrhea, vomiting, hypertension, hand-foot syndrome and hematologic events. In first-line therapy when compared with IFN-α, sunitinib has been associated with a higher response rate (31% vs. 6%)

and longer progression-free survival (11 months vs. 5 months). (Motzer et al. 2007)

Sorafenib is an oral multikinase inhibitor with effects on tumor-cell proliferation and tumor angiogenesis. It inhibits Raf-kinases, VEGFR-1, -2 and -3, PDGFR-β, FMS-like tyrosine kinase 3 (Flt3), c-Kit protein and *RET* receptor tyrosine kinases. (Wilhelm et al. 2004, Carlomagno et al. 2006) In one phase III study sorafenib was compared to placebo as second-line treatment in ccRCC. Sorafenib is taken twice daily perorally and continuously. The median PFS was 5.5 months compared to 2.8 months in the placebo group. PRs were seen in 10% and two per cent of patients, respectively. One CR was observed in the sorafenib group. Most patients (74%) had SD, which is typical of TKIs. The median duration of response was six months. Diarrhea, rash, fatigue and hand-foot skin reaction are the most common adverse effects. (Escudier et al. 2007) In the first-line setting a randomized phase II study reported no significant PFS or response rate advantage over IFN, even if there were higher rates of tumor size reduction, better quality of life and improved tolerability with sorafenib treatment (Escudier et al. 2009).

Pazopanib is an inhibitor of VEGFR-1, -2 and -3, PDGFR-α and –β, c-Kit, FGFR-1 and -3, IL-2 receptor-inducible T-cell kinase and transmembrane glycoprotein receptor tyrosine kinase. It is taken once daily orally. Common adverse effects include diarrhea, rash, hand-foot syndrome, fatigue, hypertension and elevation of liver enzymes. Hepatotoxicity may be fatal in rare cases (0.2%). (Keisner and Shah 2011)

Azitinib is a selective inhibitor of VEGR-1, -2 and -3. Its relative potency is 40-450 greater than that of the first-generation inhibitors, e.g. sunitinib. It is taken orally twice daily. The most common adverse effects are diarrhea, hypertension, decreased appetite, nausea, dysphonia and fatigue. As a second-line treatment when compared to sorafenib the median PFS has been better (6.7 months vs. 4.7 months, respectively). Respective ORRs have been 19% vs. 9%. (Rini et al. 2011)

mTOR is an intracellular kinase which acts as a central controller of multiple signaling pathways regulating mRNA translation of key growth-regulating proteins. It is an important anticancer drug target instrumental in driving tumor cell growth, proliferation, survival, angiogenesis and the response to hypoxic stress. mTOR inhibitors are semi-synthetic derivatives of the antifungal agent sirolimus, a product of a Streptomyces species discovered in a soil sample collected on Easter Island. Temsirolimus is a highly specific inhibitor of mTOR, inhibiting the synthesis of various proteins of the cell cycle and tumorigenesis such as HIF-1 and VEGFR. Temsirolimus is administered as a once-weekly i.v. infusion at a flat dose. This drug is cleared predominantly by

the liver and eliminated in the feces; dose reductions are thus likely in patients with hepatic dysfunction. (Boni et al. 2009) In one phase III trial temsirolimus improved the OS and PFS of RCC patients with poor MSKCC prognostic factors over against IFN-α. The most common side-effects were asthenia, anemia, nausea, dyspnea, diarrhea, rash, peripheral edema, stomatitis, hyperglycemia and hyperlipidemia. (Hudes et al. 2007) Temsirolimus has also proved effective in patients with metastatic papillary or chromophobe RCC (Dutcher et al. 2009).

Another mTOR inhibitor, everolimus, is an orally and once-daily administered drug. In a phase III study among patients progressing on VEGF-receptor inhibitors, the PFS was improved over placebo, 4.9 months vs. 1.9 months, respectively. By reason of cross-over in treatment groups, no survival advantage could be shown. SD was achieved in 67%, PR in 1.8%, no CRs were seen. The most common adverse events were infections, dyspnea and fatigue. Pneumonitis is a drug-specific side-effect. (Motzer et al. 2008, Motzer et al. 2010)

There is currently no published randomized phase III study of neoadjuvant treatment with tyrosine kinases, but investigations are ongoing. In phase II studies undertaken in patients with metastatic disease, the most promising agent to date has been sunitinib. PR in a primary tumor is achieved in six per cent of patients and the median size decrease is 12%. The best response is seen during two to four months' treatment. (Powles et al. 2011) A withdrawal period of at least two to three half-lives of medication is needed before and after surgery (Ficarra and Novara 2010). During this pause, progression is seen in 25% of patients. Postoperative complications are seen in 27%, most of them wound healing problems. (Powles et al. 2011) When comparing bevacizumab, sunitinib and sorafenib there was no difference in complications. With neoadjuvant treatment the possibility of multiple complications is greater. The incidence of major complications is no higher than in patients without neoadjuvant treatment. Wound healing problems may be delayed and come three months after nephrectomy. (Bex et al. 2010)

Radiotherapy

RCC is often considered to be resistant to radiotherapy. The approach has no role in adjuvant or neo-adjuvant treatment of RCC. However, it can be used to treat unresectable primary or recurrent disease to improve local control. (Escudier et al. 2012) In most cases, this treatment modality is used for

symptomatic patients with nonresectable brain or osseous lesions who do not respond to systemic treatment efforts (Ljungberg et al. 2010).

Table 5 New drugs currently studied in metastatic RCC (Eisen et al. 2012, Escudier 2012, Figlin et al. 2012, Schmidinger et al. 2012).

Abbreviations:

BID=bis in die - twice a day;

BRAF=proto-oncogene producing a protein called B-Raf ;

CTL=cytotoxic T leucocyte;

CTLA-4= cytotoxic T lymphocyte antigen 4;

LAG-3= lymphocyte-activation gene 3;

mPFS= median progression-free survival;

MTD=maximal tolerated dose;

PD-1=programmed death 1;

p.o.= per orally;

s.c.= subcutaneusly;

TIE=gene encoding tyrosine protein kinase, which inhibits angiopoietin 1.

Therapy	Mechanism of action	Dosing	Efficacy	Number of patients	Side-effects
Tivozanib	Inhibitor of VEGFR-1, -2, -3.	1.5 mg p.o. daily, 3 weeks on, 1 week off.	First line; ORR 30%. mPFS 11.7 months.	272	Hypertension, dysphonia.
Dovitinib	Inhibitor of VEGFR-1, -2, -3, FGFR-1,-2, -3 and PDGFR.	400 mg p.o. daily.	Second line; PR 8%, SD >4 months 37%.	51	Nausea, diarrhea, vomiting, asthenia, fatigue.
Cediranib	Inhibitor of VEGFR-1, -2, -3.	45 mg p.o. daily.	First line; PR 38%, SD 47%, mPFS 8.7 months.	43	Hypertension, dysphonia, nausea, diarrhea, fatigue.
MK-2206	Allosteric inhibitor of Akt (regulator of tumor growth and angiogenesis).	Once weekly. MTD 60 mg.	NA.	Phase I 30 (phase II ongoing)	Rash, fatigue, nausea, pruritus, stomatitis, hyperglycemia, diarrhea.
BIBF 1120	Inhibitor of VEGFRs, PDGFRs and FGFRs.	200 mg p.o. BID.	First line; NA.	Phase I 10 (phase II ongoing)	Nausea, vomiting, diarrhea.
Lenvatinib	Inhibitor of VEGFRs, PDGFR-β, c-Kit.	MTD 25 mg x1 p.o. 2 weeks on, 1 week off.	Second line; NA.	Phase I 27 (phase II ongoing)	Hematuria, fatigue, diarrhea, hypertension, elevated liver values, headache, proteinuria.
AMG 386	Peptide-Fc fusion protein, neutralizes angiopoietin 1 and 2.	Once weekly 3 or 10 mg/ kg i.v.	Second line; ORR 37-38%.	32	Fatigue, peripheral edema.
Aflibercept	Soluble decoy receptor comprising portions of VEGFR-1 and -2 fused to the Fc portion of human IgG (neutralizes VEGF ligands).	0.3-7.0 mg/kg i.v. every 2 weeks/ s.c. 50-1600 mcg/kg once weekly.	Phase I studies, SD more than 1 year in one patient.	In phase I (phase II ongoing)	Diarrhea, fatigue, stomatitis, proteinuria, hypertension, neutropenia.
Regorafenib	Inhibitor of VEGFR-1, -2, -3, *TIE2*, PDGF β, c-Kit, *RET*, *BRAF* and FGFR.	160 mg x1 p.o. 3 weeks on, 1 week off.	First line; PR 40%, SD 42%. Median duration of response 14 months.	49	Hand-foot syndrome, renal failure, fatigue, hypertension, cardiac ischemia, diarrhea.
Enzastaurin	Serine/threonine kinase inhibitor of protein kinase Cβ (development and progression of RCC, angiogenesis).	In combination with sunitinib: 500 mg day 1 p.o., then 125 mg x2.	First line; PR 24%, SD 65%. Development discontinued.	17	Anemia, neutropenia, thrombocytopenia. Dose reductions common.
Ramucirumab	Fully human monoclonal antibody to the extracellular	8 mg/kg i.v. biweekly.	Second line; PR 5%, SD >5 months	39	Headache, fatigue, nausea.

	ligand binding domain of VEGFR-2 (prevent VEGF binding and receptor activation).		38%.		
IMA901	Cancer vaccine, synthetic RCC tumor-associated peptides which activate T cells. Selection of 9 HLA-class I and 1 HLA-class II-binding tumor-associated peptides.	17 intradermal vaccinations during 9 months with single dose of cyclophosphamide.	Second line; Disease-control rate 12% in TKI refractory. 6-month OS 87%.	30 and 40	Local injection site reactions.
MDX-1106	Fully human monoclonal PD1 antibody (expressed on T cells, which regulate immune responses)	Single i.v. infusion/ every three weeks (up to 10 mg /kg).	PR 31%, SD >4 months 38%.	39	Lymphopenia, fatigue, musculoskeletal events.
BMS-936558	Anti-PD-1 antibody.	0.1-10 mg /kg biweekly i.v.	PR 31%, SD >6 months 19%.	33	Grade 3/4 adverse effects in 17%. Deaths from pulmonary toxicity.
AGS-003	Dendritic cells obtained with leukapheresis and loaded with autologous amplified tumour RNA. Induces proliferation of sytotoxic T cells, which target RCC cells expressing autologous tumor antigens.	In combination with sunitinib, intradermal injections every 3 weeks 5 doses, then every 3 months until progression.	First line; PR 10%, SD 52%. mPFS 11.9 months.	21	Mild injection site reactions.
Reniale®	Autologous tumor cell lysate, vaccination.	Intradermal injection every 4 weeks x 3-30.	Improvement in PFS among patients with pT3 RCC. 10 years OS 53.6% vs. 36.2% in those without Reniale.	1267	Injection site reactions.
Ipilimumab	Anti-CTLA-4 antibody. Disrupts T cell proliferation and function and the maintenance of peripheral tolerance.	3 mg/kg i.v. every 3 weeks.	PR 13%, duration of response 7 – 21 months.	40	Grade 3/4 adverse effects in 42%, most commonly enteritis.
Tremelimumab	Anti-CTLA-4 antibody.	MTD 6 mg /kg i.v. Q12 weeks, in combination with sunitinib.	PR 43%.	16	With 10 mg/kg: acute renal toxicity, one sudden death.
Denileukin diftitox	Fusion protein of diphtheria toxin and human IL-2; functions to deplete cells expressing the CD25 component of the IL-2 receptor.	In combination with IL-2, 9 mg/kg i.v.	ORR 33%.	18	Not increased when compared with IL-2 alone.
IMP321	Soluble *LAG-3*. Agonist of MHC class II-driven dendritic cell activation, enhances expansion of tumor-specific CTLs (in vitro).	0.5 to 30 mg i.v. biweekly up to 6 injections. Effective with doses > 6 mg.	At high doses SD 88% at 3 months.	21	No clinically important adverse events.

3 Aims of the study

This retrospective study was conducted to evaluate prognostic factors, survival and symptoms in RCC patients in a local perspective and in different decades and to evaluate the use of different radiological imaging methods and their effect on prognosis.

The specific aims in each study were:

1. To study the long-term survival of RCC patients (paper I).
2. To study the significance of known clinical prognostic factors in a large centrally treated Finnish RCC population and to study the possible change in prognosis in Finnish RCC patients since the 1960s (paper I)
3. To determine whether there has been a change in typical RCC symptoms during four study decades (paper II).
4. To study the influence of smoking and BMI on the long-term survival of RCC patients and explanatory factors related to the survival difference (paper III).
5. To evaluate the use of imaging methods and the effect on prognosis of small RCCs compared with larger tumors according to era of diagnostics (paper IV).

4 Patients and methods

From the Finnish Cancer Registry we collected 970 RCC cases from the Pirkanmaa hospital district (Tampere University Hospital and four secondary centres); demographics are shown in Table 6. These patients were diagnosed between the years 1964 and 1997. Wilms, uroepithelial and benign tumors and lymphomas were excluded. Also patients whose treatment was conducted only partially in our hospital district or whose medical records had already been destroyed 20 years after death were excluded. A total of 204 patients were excluded from the first study years for this reason. In the case of survival analysis 22 cases with tumor diagnosed post mortem were excluded. Follow-up was maintained according to clinical practice at the time of diagnosis. The Pirkanmaa Hospital District Ethical Committee gave permission to collect the relevant information. Follow-up was until death or August 2007. The mean follow-up time was 76.9 months (range 0 days to 35.4 years). At close of follow-up 83% of subjects had died, 61% due to RCC, and 10% of surviving patients had relapsed.

Data as recorded in the original medical records, were collected on weight and height to constitute BMI, smoking, symptoms, investigations, surgery, histology, TNM stage and grade, recurrence date and type, site of metastases and treatment, last date of surveillance or death and cause of death. Symptoms were classified as local (hematuria, flank pain, palpable mass, varicocele) and systemic (anemia, erythrocytosis, weight loss, fever, hypercalcemia, high ESR, metastatic symptoms). If patients evinced both types of symptom, they were placed in the latter group. Patients were divided into 3 classes according to BMI: <18.5, 18.5-25 and >25 (i.e., underweight, normal weight and overweight), and into groups of ever-smokers, never-smokers, or patients with missing information regarding smoking status. Those yielding insufficient information (73 cases) to constitute BMI were excluded from calculations concerning this factor.

Tumors were restaged according to the 2002 TNM classification. The restaging was a combination of clinical (surgeon's estimate), pathological and/ or radiological measurements: the pathological measurement was the first choice, if available, then radiological and finally clinical measurement. Incomplete information for restaging was recorded in 41 tumors (4.2%); in 23 patients the primary tumor was not found or studied and 18 had kidney-

confined tumor with no measurements. The grade of 226 tumors diagnosed between the years 1985 and 1995 was re-evaluated by one uropathologist according to Fuhrman's grading. Re-evaluation of all 982 tumors was not possible for practical reasons such as the availability of tissue samples, as the study material was collected from five hospitals on diagnoses made during four decades. The National Authority for Medicolegal Affairs gave permission to re-evaluate the tissue samples.

Survival was analyzed using Bayesian multivariate analysis and the life-table method up to 25 years. Univariate analysis included seven variables: age, sex, stage, BMI, smoking status, symptoms and year of diagnosis. The likelihood ratio for five-year survival was calculated for each variable, and statistical dependencies within the groups were analyzed by chi-squared or Wilcoxon rank test using two-tailed interpretation. Five-year survival was analyzed as being the most common estimate of prognosis used in the literature. Other statistical differences were analyzed by Fisher's F test (one-tailed) or Kruskal-Wallis test. Multivariate analysis was made using an optimizing stepwise procedure based on the Bayesian approach, which is designed mainly for categorized variables and does not need a perfect variable matrix. It selects the combination of variables which best explains the selected outcome variable. No preselection or weighting of variables was applied. In the life-table method, the observed survival rates were here compared to the rates based on the year, sex- and age-specific survival tables for the whole Finnish population. The calculations are based on the individual life expectancies of the target population for the target years (Hakulinen 1977). The relative survival of the reference population would be 1.0. If the survival curve remains below this, there is excess mortality. The odds ratio (OR) curves for 5-year survival according to BMI were calculated using 5-unit windows for each BMI value. The resulting curves were then smoothed with a 3-point moving average. The result is not relative to the Finnish population, and the expected OR value for all three curves together is 1.00. Statistical significance was defined at a p value <0.05. The rating of high statistical significance (HSS) was given at a p value <0.000001; in paper II at a p value <0.001.

Table 6 Patient demography.

Patients (n=970)	532 males (54.8%) 438 females (45.2%) 3 von Hippel-Lindau syndromes, 1 tuberous sclerosis
Diagnosis in	
1964-1974	102 (10.5%)
1975-1984	233 (24.0%)
1985-1994	452 (46.6%)
1995-1997	183 (18.9%)
Age	
≤29	5 (0.5%)
30-39	27 (2.7%)
40-49	90 (9.3%)
50-59	214 (22.0%)
60-69	301 (31.3%)
70-79	251 (25.7%)
80-89	79 (8.1%)
≥90	3 (0.3%)
	median 62.7 years (range 6-93 years)
T-classification	
T1	408 (41.4%)
T2	169 (17.2%)
T3	319 (32.5%)
T4	45 (4.6%)
unclassified	41 (4.2%)
N +	125 (12.7%)
M1	259 (26.4%)
Stage	
I	330 (33.6%)
II	142 (14.5%)
III	172 (17.5%)
IV	338 (34.4%)
Histology (n=226)	
Clear cell carcinoma	205 (90.7%)
Papillary	11 (4.9%)
Chromophobe	4 (1.8%)
Sarcomatoid	2 (0.9%)
Collecting duct carcinoma	2 (0.9%)
Unclassified	2 (0.9%)
Grade (n=226)	
I	1 (0.4%)
II	22 (9.7%)
III	114 (50.2%)
IV	89 (39.4%)

Tumors (n=982)	right 49.6% left 50.4% 2 synchronous bilateral (0.2%) 10 asynchronous bilateral (1.0%) Size range 0.4 – 30 cm
Sites of metastases among M1 patients	
Single site	167 (64.5%)
Multiple sites	92 (35.5%)
Pulmonary	151 (58.3%)
Bone	81 (31.3%)
Liver	41 (15.8%)
Pleura	23 (8.9%)
Abdominal cavity, other	17 (6.6%)
Adrenal	15 (5.8%)
Brain	10 (3.9%)
Mediastinum	10 (3.9%)
Lymph nodes, distant	7 (2.7%)
Pancreas, spleen	6 (2.3%)
Skin, subcutis	6 (2.3%)
Genitourinary system	4 (1.5%)
Thyroid	3 (1.2%)
Breast	2 (0.8%)
Other	4 (1.6%)
Treatment	826 (85%) operated: 96.6% nephrectomies, 3.4% resections In relapse (56.5% of patients): 42% no treatment, 58% were treated: Radiotherapy to 75.5% Immunotherapy to 30% Chemotherapy to 35% Surgery to 16% Hormonal therapy to 24%
Smoking (Information available of 283 males and 140 females)	74% of males and 26% of females smoked 56.1% of stage I patients 60.4% of stage II patients 45.7% of stage III patients 57.9% of stage IV patients
Body mass index groups (BMI missing in 51 patients, 5.4%)	Underweight 24 (2.5%) Normal-weight 353 (37.2%) Overweight 520 (54.9%) Mean BMI 26.1 (SD 4.4). Median BMI 26 (range 11-51).

5 Summary of results

5.1 Demography of RCC patients (papers I-IV)

The median age of patients was 62.7 years. The age range was wide, from 6 to 93 years. The material included five patients (0.5%) less than 29 years old, two of them were children. Male gender was more common, 54.8% of patients. Most cases were sporadic, but one patient with tuberous sclerosis and three with von Hippel-Lindau–syndrome were recorded (altogether 0.4%). Two of these were father and daughter. Bilateral tumors were found in 12 patients (1.2%), 10 of them asynchronous.

The tumor size range was particularly wide, from 0.4 cm found in a renal cyst to a massive 30 cm tumor. Malignant kidney tumor was histologically confirmed in 92% of patients. Primarily, there were 399 adenocarcinomas, 191 renal cell carcinomas (one of them oncocytic and one chromophobic) and 294 clear-cell carcinomas. Other diagnoses (19 cases) included for example anaplastic, oncocytic, spindle cell, sarcomatoid and renal papillary carcinomas. Some of the tumors had only been classified as carcinomas. Operative removal of a primary tumor was performed in 85% of cases; in primary-metastatic disease, palliative nephrectomy was conducted in 64%.

5.2 Long-term survival in RCC patients (papers I and IV)

RCC patients evinced diminishing overall survival in the follow-up, with no plateau. The longest follow-up in this study was 35.4 years. The relative five-year, 10-year and 25-year OS rates were 56%, 44% and 26%, respectively. Primarily metastatic disease was diagnosed in 26.4% of patients, in 20% of operated and 62% of non-operated. Altogether, almost 57% of patients developed local recurrence or distant metastases even after very long DFI. Three patients had DFI >20 years, the longest interval being 21.9 years. RCC was the cause of death in 47% of women and 54% of men. At the time of analysis 83% of patients had died, 61% of them of RCC and 10% of the survivors had recurrent disease. In women diagnosed before 63 years of age excessive mortality was 36%.

The most common sites of metastases were lungs, bone and liver; other sites are listed in Table 6. A single site of metastasis was found in 64.5% of these patients, the rest having multiple sites.

Among small tumors no relapses were observed after 14 years of follow-up. Large tumors also relapsed after that time period. The 20-year OS was 67% in patients with small tumors and 30% in those with large tumors ($p<0.001$). RCC was the cause of death in 14.9% of patients with small tumors vs. 50.7% of patients with larger growths (HSS).

5.3 Prognostic factors for RCC (papers I, III, IV)

The most important explanatory prognostic factors were stage, age and clinical presentation of the tumor. Also gender, TNM class, BMI, smoking status and re-analyzed grade proved relevant for prognosis. In analysis of survival against these prognostic factors, the median survival in asymptomatic patients was 8.1 years, with local symptoms 9.1 years and with systemic symptoms only 1.7 years (HSS). Symptomatic disease also correlated with higher stage and metastatic disease, tumor size ($p<0.001$) and cancer-caused death (HSS). According to stage, the relative five-year OS was 88%, 63%, 65% and 15% in stages I to IV, respectively. Patients aged 40-49 had better prognosis than other age groups (HSS). The oldest patients obviously had the lowest survival, but also patients younger than 40 years of age had shorter survival times than patients aged 40-49. We also found a gender difference: female patients survived longer than males ($p<0.05$). According to T class the median overall survival was 9.0 years, 5.0 years, 2.3 years and 15 months in T1 to T4 tumors, respectively (HSS). However, up to 17% of T1 tumors were already primarily metastatic and lymph node metastases were seen in 4.4%. These figures increased with increasing T status. According to T stage there were also difference in DFS and CSS. According to grade the five-year OS rates were 91%, 74% and 45% in re-analyzed grade 1-2, grade 3 and grade 4 tumors, respectively ($p<0.001$). High-grade tumors evinced more lymph node metastases ($p<0.001$) and more severe T class ($p<0.001$) and stage ($p<0.0001$), and were more often symptomatic ($p<0.01$).

The year of diagnosis itself was not significant in respect of prognosis.

The mean BMI in this patient material was 26, which is categorized as overweight. Overweight patients had better prognosis and OS than normal or underweight subjects (median OS 5.9 years, 3.4 years and 12 months, respectively; HSS). There was no difference in tumor size between BMI groups which could explain the observation, but overweight patients had fewer lymph node (HSS) or distant metastases ($p<0.001$), lower stage ($p<0.001$) and a trend toward fewer relapses during follow-up. Underweight patients died in more cases because of RCC, but this did not reach statistical significance. We found a

trend for overweight patients also to have better CSS, but this reached statistical significance only in localized disease ($p<0.01$). The OR of five-year survival was already <1 in patients with BMI <24. In Bayesian analysis patients with BMI <20 had the lowest five-year survival likelihood ratio, while heavily obese patients (BMI>35) had the best ratio. In all BMI groups, women had better OS than men.

When comparing small and large tumors, the latter were higher grade ($p<0.05$) and stage (HSS); more lymph node ($p<0.05$) and distant metastases ($p<0.01$) were also observed. Small tumors were more often asymptomatic (HSS). Relapses occurred less frequently among patients with small tumors (HSS). However, 16% of these developed distant metastases; half of them were noted at time of diagnosis. In assessment of the importance of two major clinical prognostic factors, the clinical presentation of the tumor was a stronger prognostic factor than BMI. However, in symptomatic patients with low BMI survival was always poorer than among normal- or overweight symptomatic patients. Patients with local symptoms evinced good survival (OR >1) regardless of BMI. In patients with systemic symptoms the OR was <1 regardless of BMI. In underweight asymptomatic patients the OR for five-year survival was <1, in normal- and overweight patients OR was above this. Taking all symptom groups separately a BMI of 24 was always the cut-off value regarding OR for survival within each symptom group. With lower BMI the OR for OS was <1; with higher BMI the OR was >1.

Smokers had a poor prognosis. We found no difference in stage or tumor presentation at diagnosis between non-smokers and smokers; no difference in CSS was noted. However, the median OS was poorer among smokers (4.2 years compared with 6.6 years in non-smokers, $p<0.05$). This difference in OS was observed only in localized disease, but not between smoking status groups in stage III and IV disease. Smokers had more recurrences. The DFI was shorter in smokers than in non-smokers in localized disease, but in stage III longer ($p<0.01$).

5.4 Symptoms of RCC (papers II - IV)

Flank pain was the most common symptom, observed in 35% of patients. Other common symptoms were hematuria (30%), high ESR (26%), anemia (15%), weight loss (14%) and metastatic symptoms (13%). Fever and abdominal mass were seen in eight per cent. Non-frequent symptoms were fatigue (2.2%), urinary infections such as recurrent pyelonephritis and urosepticemia (1.6%), varicocele (1%), erythrocytosis (1%), hypertension (1%), pathologic fracture (0.6%), increase in serum creatinine (0.6%), edema in the legs (0.6%) and in the hands (0.1%), thromboembolic events (0.2%), pruritus

(0.1%), hypercalcemia (0.1%) and pollacisuria (0.1%). Only 0.7% presented with the whole classic Wirchow triad. Asymptomatic RCC was found in 11% of patients diagnosed before 1980, in 12% of those diagnosed in the 1980s and in 19% of patients diagnosed thereafter ($p<0.01$).

Stage and tumor class correlated markedly with symptoms: systemic symptoms increased and asymptomatic tumors became rarer with increasing stage (HSS). Patients with T1 tumors were more often asymptomatic than those with other tumor classes (HSS). However, as many as 33% of T1 tumors presented with systemic symptoms or signs. Hematuria was more common in male patients, anemia and flank pain in women (HSS). No difference in symptom groups or number of symptoms was noted between the genders. Tumors with local symptoms presented with fewer manifestations than tumors with systemic symptoms, the respective mean symptom number count being 1.3 and 2.4 (HSS).

Of patients with primarily metastatic RCC only 38% had symptoms of metastases. In this study eight per cent of patients with metastases were totally asymptomatic in their disease.

Aged patients were more often asymptomatic than younger ($p<0.01$), 80-89-year-olds being the least symptomatic. The corrections of paper II are shown in Table 7. Of asymptomatic tumors, 56% were found in men and 44% in women. Acute symptoms were seen in 40% of patients, subchronic symptoms in 14% and chronic in 31%, with no difference between the genders.

Table 7 Incidental and symptomatic patients according to age groups.

		Symptoms, n (%)		
Age, years	Incidental	Local	Systemic	Together
≤29	1 (20)	4 (80)	0	5 (0.5)
30-39	2 (7)	11 (41)	14 (52)	27 (3)
40-49	8 (9)	44 (49)	38 (42)	90 (9)
50-59	27 (13)	82 (38)	105 (49)	214 (22)
60-69	41 (14)	127 (42)	133 (44)	301 (31)
70-79	47 (19)	79 (31)	125 (13)	251 (26)
80-89	16 (20)	26 (33)	37 (47)	79 (8)
≥90	1 (33)	1 (33)	1 (33)	3 (0.3)
Total	143 (15)	374 (39)	453 (47)	970 (100)

Overweight patients had systemic symptoms less often and were more often asymptomatic ($p<0.001$). Systemic symptoms were observed in 80.8% of underweight, in 49.6% of normal-weight and in 41.6% of overweight patients. Weight loss was a common primary symptom in underweight patients.

Underweight patients also more often had symptoms which had lasted over one month ($p<0.05$). The median duration of symptoms, that is patient-dependent delay, was significantly longer in underweight patients: 44 days vs. normal-weight subjects 14 days and overweight seven days ($p<0.05$). These delays were also studied according to smoking status: patient-dependent delay and doctor-dependent delay were seven days in both smoking status groups.

Small tumors were more often asymptomatic and presented with fewer symptoms than large tumors (HSS). Large tumors were associated with more hematuria ($p<0.001$), elevated ESR ($p<0.01$) and abdominal mass ($p<0.01$). Two thirds of patients with small tumors had symptoms (vs. 88.4% in large tumors, HSS). Among patients with symptoms the mean number of these was 1.5 with small and 1.85 with large tumors.

5.5 Diagnostics of RCC (paper IV)

In this material 784 patients had been evaluated with one or many imaging methods and had confirmed tumor size. Altogether, 1481 imaging studies had been made to diagnose renal tumors. In addition, there were 833 thorax and bone X-rays. Preoperatively RCC was diagnosed in most patients with three imaging methods depending on tumor size. Over 70% of small tumors were studied with three or four methods, while large tumors needed one method less. The mean number of studies made was 3.17 in small tumors and 2.92 in large. The indication for imaging studies had been suspicion of RCC in 17.0% of small tumors and 35.7% of large ($p<0.001$). Small tumors were more often incidental findings, as 35.1% were totally asymptomatic compared to 11.6% of large tumors (HSS).

A preoperative malignant imaging result had been obtained in 93.6% of patients with small tumors and in 96.7% of patients with larger tumors, with no statistically significant difference. Uncertain diagnoses of RCC before operation were mostly due to cystic kidney tumors. CT proved to be the most reliable method. As expected, CT, US and urography proved superior in large tumors when compared to study results for small tumors ($p<0.001$).

Between 1985 and 1989, CT was used in the diagnosis of 25% of RCC cases, but between 1990 and 1994 as many as 55% of patients were examined with CT. US became more common five years earlier than CT; in the early 1980s 64% of patients were examined with US, and 94% in the late 1980s. Kidney biopsy was undertaken in only 31 cases (3.3% of all patients), most of these in cases of large tumors.

In this study population 12.0% of tumors were $\leq$ 3.0 cm in diameter. We found that the median time from the first diagnostic imaging study to operation was longer in small tumors: 57 days vs. 27 days (HSS).

5.6 Observed changes in RCC cases and prognosis during the study period (papers I-IV)

The symptoms of RCC remained almost stable during these study years. Only hematuria (from 39% to 26%) and elevated ESR (from 28% to 20%) became less common (HSS). No change was seen in other symptoms. However, more recent cases evinced fewer symptoms than earlier cohorts. Before 1980, operated patients presented with a mean of 1.7 symptoms, in the 1980s 1.6 and in the 1990s 1.5 symptoms ($p<0.01$). Incidental diagnoses increased from 12% to 19% in the study period ($p<0.01$). More recently fewer chronic or systemic symptoms were noted (HSS).

No difference was found in the percentages of BMI groups over the study period or between genders in BMI groups. Additionally, we found no change in the proportion of females during the study period.

The diagnostics of RCC changed notably. While in the first study years only native X-rays, urography, cavography and arteriography were available, since 1984 also US and since 1989 CT came into general use. Also MRI offered further imaging possibilities, but its use remained rare. The use of the old imaging methods decreased along with this change, this seen first when studying small tumors.

Even if the year of diagnosis was not significant in prognosis, the best prognosis was noted among patients with small tumors diagnosed in the CT era. No differences were seen between small tumors diagnosed in the first or US era, but in larger tumors the five-year OS difference was statistically significant ($p<0.001$). When comparing the US with the CT era improvement was observed in both patient groups ($p<0.001$). In the first diagnostic era there was no survival difference according to tumor size. In the US era patients with small tumors survived better after five years ($p<0.01$), whereas the situation was reversed after 10 years ($p<0.001$). In the CT era patients with small tumors had better five- and 10-year survival than those with large tumors (HSS and $p<0.001$, respectively).

The proportion of patients with small tumors and primarily metastatic disease decreased during the study period, being only two per cent in the CT era as againts 29 % in the first diagnostic era ($p<0.01$). The CSS showed a trend towards improvement, but by reason of small numbers of cases it did not reach statistical significance. The cause of death in patients with tumors less than three centimeters was RCC in 43%, 30% and 15%, in the respective diagnostic eras. No difference in DFS was observed.

6 Discussion

6.1 Methods

This was a retrospective study where information was collected from original medical records. This is the strength and the weakness of the study. Our survey presents real-life patient material, rather than highly selected study cases. These reports are scarce in the literature. As long follow-up as in the current study is not commonly reported. In addition, most reports of 25-year survival are final reports of undertaken studies (Gazet and Sutcliffe 2011, Bernthal et al. 2012, Critz et al. 2012, Simone et al. 2012). However, as laboratory values were not the same for every patient, we cannot be sure that every hypercalcemia and high ESR had been recorded. Also medical records were sometimes somewhat unspecific as to the onset of symptoms. Information on smoking status was available in only 423 patients, even if this figure is high enough to draw conclusions with Bayesian analysis. Neither could we record the real smoking status at the time of diagnosis, so that smokers are only categorized into ever- or never-smokers instead of current and former smokers and according to duration or cessation of smoking.

This was not a nationwide study. However, our hospital district represents the normal population of Finland, being the second largest province with nine per cent of the total population. This allows the possibility to gain realistic results regarding changes in prognoses. There was some difference in patient numbers studied here compared to those in the Finnish Cancer Registry. In this registry, there were 464 patients diagnosed in the 1980s and 484 patients in the 1990s, these including Wilms tumors and other excluded histologies. Our figures were 360 and 420, respectively. In recent decades, this difference is probably due to other histologies, late reports of malignancies to the registry and patients with treatments conducted in private hospitals or in other hospital districts.

Our data collection began in 1994. This might result in a bias in the patient population, as the oldest patients and those with the poorest prognosis were automatically excluded from the study years 1964-1974, since the medical records were destroyed 20 years after their death. For this reason we also calculated survival without this oldest subpopulation. There were no significant changes to the results presented.

Bayesian analysis is not a method commonly used in calculating survival rates in oncological studies. However, in a retrospective study such as this, where it is not possible to obtain all information on all patients, this method was considered by a statistician to be the best. The approach can be used with statistics with up to 60 different variables which do not have all perfect information (Hakulinen 1977); in logistic regression the limit is 10 different variables and the information must be perfect.

6.2 Prognostic factors and long-term survival of RCC patients

The significant prognostic factors stage, age and clinical presentation have also proved significant in previous studies (Fergany et al. 2000, Schips et al. 2003). Finnish patients do not differ in this respect from other patient materials. The symptom classification used here has previously been validated multi-institutionally and asymptomatic disease is a known prognostic factor (Patard et al. 2004).

We found no difference in prognosis according to study year. Even if this can be explained by inefficient oncological therapies, we decided to study the matter more closely. When patients were divided into subgroups, those operated in the 1990s had improved OS and DFS compared with patients operated in the earlier study decades, as more tumors were diagnosed incidentally. This improvement was observed among asymptomatic patients but not in those with systemic symptoms or primarily metastatic disease. Also more recent stage I patients had better survival. The difference was already perceptible 18 months after operation, as there were fewer relapses. In addition, tumor size and stage decreased during the study period. More T1A tumors were diagnosed in the 1990s and T4 tumors became rarer. The mean tumor diameter decreased from 8.7 cm to 7.4 cm; in T1 tumors before the 1980s the tumor size was 5.8 cm, in the 1990s 4.8 cm. However, no changes in primary lymph node or distant metastases were found. Fewer patients diagnosed in the 1990s relapsed in the surveillance, but there was no statistically significant difference in the mortality rates. Metastases developed in 70% of patients diagnosed before 1980 compared to 48% of patients diagnosed in the 1990s. Some of these may of course have relapsed after a long DFI, as this group had the shortest follow-up period. As also here more asymptomatic tumors were found in patients diagnosed in the 1990s, it is possible that if the data collection and follow-up could be updated, it might have been possible to establish a survival

difference according to the year of diagnosis. However, we decided to keep to this material to obtain especially long-term results.

In primarily metastatic disease we found no difference in survival or incidence in the whole study group during the study period; only in small tumors did the incidence of primarily metastatic disease decrease. More than half of the small tumors developing distant metastases already evinced them at the time of diagnosis. In the previous literature even 6 mm primary tumors have been reported to have metastases (Klatte et al 2008). In most patients IFN does not improve survival (Medical Research Council collaborators 1999). TKIs were not available during the study period, as these only became more common in Finland in 2008. IFN was first administered in this hospital district in 1988. It was the first-line choice in metastatic disease until 2007 and the end of the follow-up of our patient material.

We confirmed that high BMI is a factor for better prognosis, but it has a positive association with survival only in organ-confined disease. This has also been shown elsewhere (Waalkes et al. 2010). Obesity gave no protection over against the major clinical prognostic factors reported in paper I, e.g. stage and symptomatic disease. Smoking was found to be a factor predicting recurrence with distant metastases. We found no other factors explaining this, as there was no difference in tumor stage or symptoms between smoking status groups. Smoking has already previously been linked not only to carcinogenesis, but also to disease progression. However, in previous studies smoking has been associated with advanced disease (Tsivian et al. 2011), not with shorter disease-free interval and more often recurrent disease. We found no difference in cancer-specific survival, but this may be due to severe comorbidities such as pulmonary or cardiac disease, which may be the cause of death before RCC. We also found a gender difference, as female patients had better survival than males. Gender has not always been a prognostic factor (Uno et al. 2004).

The five-year relative survival of patients diagnosed before 1980 was 52%, in the 1980s 51% and in the 1990s 60%. We had a possibility to compare our survival rates to corresponding figures in the Finland's Cancer Registry (Table 8). These are similar in the 1980s and 1990s. However, we have better survival figures for patients treated before 1980. This was contrary to our expectations, as this group included the oldest patients and those with the shortest survival excluded by reason of the destruction of medical records. The previous literature reports that 20-40% of RCCs develop metastases in surveillance (Janzen et al. 2003). Here, however, the figures were higher, as already 16% of patients with T1 tumors did not remain disease-free, and in T3 tumors metastatic disease occurred in 57% of patients. In comparison with five-year OS rates reported in the previous literature we had better rates (56%); in

Sweden between 2000 and 2008 the five-year OS rate for the whole RCC population was 49%. In the Swedish population 14% of patients were primarily metastatic and treated with TKIs in the metastatic situation. (Wahlgren et al. 2013)

The long-term survival reports of other cancer types are final reports of studies made in selected patient materials (Gazet and Sutcliffe 2011, Bernthal et al. 2012, Critz et al. 2012, Simone et al. 2012) and comparison is not equal or easy. Compared with these other cancer types, RCC has a poor OS, but the very aggressive osteosarcoma without adjuvant chemotherapy has an even lower OS (Bernthal et al 2012). RCC has currently no adjuvant therapy (Escudier et al. 2011), while in breast and prostate cancer and osteosarcoma this is in common use. RCC is a significant cause of excessive mortality and the cause of death in one half of patients.

Table 8 Five-year relative survival ratios (%) of kidney cancer patients according to Finland's Cancer Registry.

Period	Pirkanmaa		Finland	
	Males	Females	Males	Females
1960-1969	23	29	24	33
1970-1979	35	43	35	41
1980-1989	44	49	44	48
1990-1999	55	60	56	59

6.3 Demography, symptoms and diagnostics of RCC patients

The percentage of hereditary syndromes causing RCC was much lower here than the figure (3-5%) reported in the literature (Verine et al. 2010). No other reports are published about the prevalence of these syndromes among Finnish RCC patients. Also the incidence of synchronous bilateral renal tumors was much lower than previously reported (0.2% vs. 1.5%, Klatte et al. 2007). We have no explanation for these findings. Otherwise the patient material was the same. The age range here was particularly wide. The median age was the same as reported in RCC studies up to the end of this study period (62 years in Luciani et al. 2000). However, in previous reports the median age rose to 62 years while we had this in the whole material. We noticed the same rise, as patients were older at the time of diagnosis in the more recent decades. The median age was 61.9 years before 1980, 65.6 years in the 1980s and 67.2 years in the 1990s. Two of the patients were children. This is so small figure that we did not calculate separately prognostic factors for them. The percentage of

primarily metastatic disease was similar (26% vs. 20-30%) and the metastatic sites were typical of those reported in the literature (Janzen et al. 2003). The median BMI was categorized as overweight, which is a known risk factor for RCC (Dhote et al. 2004). In patients for whom information on smoking was available, most men and a high percentage of women smoked, which is also a known risk factor (Dhote et al. 2004). In addition, this patient material had a male predominance, even if this was less marked than previously reported (54.8% vs. 62.3% in Woldrich et al. 2008).

Even though women are commonly considered to be more active in seeking treatment, we found no change in the proportion of females during this period. This is contrary to other published results (Beisland et al. 2002). In the 1980s, 39% of asymptomatic patients were women; in other decades it was 46%. In addition, there was no difference between genders in the mean number of symptoms. We found that RCC patients were older at the time of diagnosis in the 1990s (61.9 years before 1980, 65.6 years in the 1980s and 67.2 years in the 1990s) as also recorded elsewhere (Luciani et al. 2000). This may be due to impact of imaging studies undertaken for other medical conditions. Further, the oldest patients were the least symptomatic. The youngest patients in this study were males diagnosed before the 1980; that is, before CT and US. In addition to incidental findings in older patiens, which raises the mean age at diagnosis, there might also be other reasons for this result. The incidence of smoking among men decreased during the study period, which may have lowered the risk of developing RCC.

The percentage of incidental tumors was lower than in many other studies (Schips et al. 2003). In part this is due to the long study period. Unfortunately, we did not record the causality of symptoms and cannot thus report how many of the remaining symptoms were actually caused by RCC. Flank pain might result from an abdominal disease other than RCC. The percentage of incidental findings may be greater than we report. Even if the percentage of asymptomatic patients did not reach the high figure previously reported (80%, Schips et al. 2003), it rose from 12% in patients diagnosed before 1980 to 19% in patients diagnosed in the 1990s. In addition, the mean symptom count decreased form 1.7 to 1.5, respectively.

When compared with a previous report on the symptoms of Finnish RCC patients (Mäntylä et al. 1977), more patients in this material had hematuria (25% vs. 30%), pain (24% vs. 35%), palpable tumor (4% vs. 8%) and fever (<1% vs. 8%). In addition, asymptomatic patients were more common (6% vs. 15%). Even in the patient group diagnosed in the 1990s, who had hematuria less commonly than others, the incidence of this symptom was 26%, that is, higher than in the previous report. The percentage of metastatic disease was higher

than in this study (34% vs. 26%). One explanation for the difference may be the smaller number of patients in the older Finnish study compared with this present (125 vs. 970). The percentage of whole classic Wirchow's triad was very small, 0.7%, when compared with older reports giving percentages of 3.8–9% (Skinner et al. 1971, Sigalow et al. 1991, Jubelirer et al. 1993).

The percentage of asymptomatic metastatic disease was only eight per cent compared with 22% reported in the previous literature (Citterio et a. 1997). Again, this may be due to the long study period and the low percentage of totally incidental diagnoses.

The incidence of hematuria decreased from 39% in patients diagnosed before 1980 to 26% diagnosed in the 1990s. This symptom was most common in patients with stage II or T2 tumors. The incidence of T2 tumors was greatest in the 1980s, decreasing thereafter (18.7%, 19.3%, 14.1%, respectively in the study decades), which might explain the change. Also the incidence of ESR decreased from 28% in patients diagnosed before 1980 to 20% in those diagnosed in the 1990s. This symptom was most common in patients with stage III or T3 tumors. Likewise the incidence of T3 tumors decreased during the study decades, the respective percentages being 34.3%, 35.3% and 31.2%.

The use of CT became more common in our hospital district at the beginning of the 1990s. We chose the cut-off point for a diagnostic era to be a year when at least 25% of patients were imaged with US and again with CT. These cut-off years were 1980 and 1989. As there were five hospitals included in this study, no clear limiting point was otherwise found.

Small tumors were diagnosed with a greater number of diagnostic studies. This might result from the need for more imaging studies to obtain a malignant diagnosis preoperatively. In addition, most of these small tumors were diagnosed more recently, when more methods were available.

The use of kidney biopsy was rare and only 58% of biopsies were diagnostic. Thus in practice the diagnostic methods for RCC were radiological imaging studies. The recommendation for the diagnostics of RCC is still based on radiological imaging studies (Heidenreich and Ravery 2004). The indications for operation of a kidney tumor are also radiological findings (Bosniak 1993).

6.4 Treatment of RCC

This was not a treatment study and our primary objective was not to report treatment choices or results of chosen therapies for metastatic RCC. However, we found that as many as 42% of patients received no oncological treatment when metastases were observed. During the study period, there were no

effective treatment modes to improve survival significantly (Medical Research Council Renal Cancer Collaborators 1999). IFN and IL-2 are toxic therapies (Fleischmann and Kim 1991, Vuoristo et al. 1994, Medical Research Council Renal Cancer Collaborators 1999), and these are not initiated in the case of patients with lowered general condition. In addition, patient materials must have been different from the present, with more systemic symptoms, cachexia and lowered performance status, all of which diminish OS and preclude instigation of therapy. Chemotherapy was a common choice in this material. It is not used at all nowadays by reason of low response rates (Motzer and Russo 2000). We have no figures for metastatic RCC patients treated in our clinic after this study period, but in practice there is rarely a situation when no oncological treatment is started at all.

As many as 15% of patients in the study population were not operated. Palliative nephrectomy was done in 64% of primarily metastatic cases. Nowadays most patients are first operated even when there is a metastatic situation. Low general condition, technical inoperability and profuse disease burden are situations where surgery is not generally done. As many as 16% of patients were operated in relapse. This high percentage reflects the poor possibilities of oncological treatments at that time. Nowadays metastatic surgery is not common, even if it should be remembered in the situation of a single metastasis in a technically operable site.

7 Summary and Conclusions

The present study set out to collect local information on the prognosis, symptoms and diagnostics of RCC patients.

The main findings were the following:

1. RCC patients evince diminishing overall survival in follow-up. RCC was the cause of death in 47% of women and 54% of men. Only patients with a tumor <3.0 cm achieve a survival plateau after 14 years.

2. The most important explanatory factors were stage, age and clinical presentation of the tumor. The prognosis declines along with increasing stage and symptomatic disease. Patients aged 40-49 have the best prognosis. The year of diagnosis was not in itself a prognostic factor.

3. Flank pain was the most common symptom. Others were hematuria, high ESR, anemia, weight loss and metastatic symptoms. Stage and tumor class correlated highly with symptoms. During the study period the incidence of hematuria and high ESR decreased.

4. Overweight RCC patients had better OS than normal- or underweight subjects, but this was found only in stage I and II tumors.

5. The clinical presentation of the tumor was a stronger prognostic factor than BMI. A BMI of 24 was always a cut-off value in respect of the odds ratio for survival within each symptom group.

6. Smokers had poorer survival than non-smokers, but this difference was observed only in localized disease, with no difference between groups in stage III and IV disease. In cancer-specific survival there was no difference, even if smokers had more recurrences with distant metastases and shorter disease-free survival.

7. The best prognosis was among patients with small tumors diagnosed in the CT era. The percentage of primarily metastatic disease in patients with small tumors decreased during the study period from 29% found in the first diagnostic era to the two per cent found in the CT era.

8. CT proved the most reliable method in diagnosing a kidney tumor. The reliability of radiological imaging studies was the same for small and large tumors, but small tumors usually needed more studies to achieve this result. The use of kidney biopsy was scant.

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ORIGINAL ARTICLE

Prognostic factors and long-term survival in renal cell cancer patients

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Abstract

Objective. The long-term survival of renal cell cancer (RCC) patients is not reported in the recent literature. This study evaluated the significance of known clinical prognostic factors and long-term survival in a large centrally treated Finnish RCC population. *Material and methods*. In 948 patients diagnosed between 1964 and 1997 the relative overall survival (OS) was calculated up to 25 years by Bayesian analysis and the life-table method. The effect of gender, age, cancer stage, TNM (tumour, node, metastasis) class, Fuhrman's grade, symptoms and year of diagnosis was studied. *Results*. Women and patients aged 40–49 years had better survival. Stage, TNM class and grade proved relevant for prognosis. The relative 5-year overall survival was 88%, 63%, 65% and 15% in stages I–IV, respectively. Asymptomatic patients had better survival, their median survival being 8.1 years as against 9.1 years in patients with local symptoms and only 1.7 years in patients with systemic symptoms. The year of diagnosis was not significant in prognosis. *Conclusions*. The most important explanatory factors were stage, age and clinical presentation of the tumour. RCC patients showed diminishing overall survival in the follow-up, with no plateau; almost 57% of patients developed local recurrence or distant metastases even after a very long disease-free interval.

Key Words: *Prognosis, renal cell carcinoma, survival*

Introduction

The prognosis of renal cell cancer (RCC) is poor; 20–40% of operated patients with localized disease develop metastases and approximately 20–30% present primarily with metastatic disease [1]. In localized tumours papillary or chromophobe histology indicates better prognosis than clear cell (cc) histology [2]. In the metastatic setting the former are characterized by poor prognosis and resistance to treatment [3]. Grade is a valuable prognostic indicator, Fuhrman's scheme remaining the most common system. Low-grade lesions entail better survival than high-grade tumours in all stages. Tumour classification has not always been a good prognostic factor; in disseminated disease even 12% of tumours are T1 [4]. After the growth reaches 4 cm in diameter, for each 1 cm increase the risk of cancer death increases by 20% [5]. The survival of patients with lymph-node involvement is identical to that in metastatic disease [6] and in the case of latter the presence of node metastases worsens the prognosis [7]. Young age is an independent predictor of relapse in localized RCC [8], but conflicting results are reported [9].

The impact of symptoms on prognosis is significant: cancer-specific survival (CSS) and overall survival (OS) are higher in asymptomatic than in symptomatic patients. The latter have a 1.9-fold greater risk of dying of cancer compared with asymptomatic, the 5-year OS rates being 83% and 60%, respectively [10,11]. When symptoms are divided into local and systemic, the 5-year OS rates are 55–72% and 27–35%, respectively [12,13]. Cachexia predicts poorer survival [14]. European Cancer and Oncology Group (ECOG) performance status of ≥1 might be the most important predictor of survival: the risk of death is 3.8-fold compared with patients with an ECOG of 0 [15]. A high erythrocyte sedimentation rate (ESR) is an independent prognostic factor [16];

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elevation of ESR is a systemic sign and associated with the most adverse pathological features of RCC [17].

During recent decades diagnostics and treatment have developed considerably. This study evaluated the long-term prognosis of 948 RCC patients over different decades.

Material and methods

RCC cases from the Pirkanmaa hospital district (Tampere University Hospital and four secondary centres) diagnosed between 1964 and 1997 were collected from the Finnish Cancer Registry (demographics in Tables I and II). Wilms', uroepithelial and benign tumours and lymphomas were excluded. In Finland throughout this study period, the standard operation has been radical (extrafascial) nephrectomy without formal lymphadenectomy, most commonly from lumbotomy excision and with ipsilateral adrenalectomy. Patients whose treatment was conducted only partially in this hospital district or whose medical records had already been destroyed 20 years after death were excluded. From survival analysis 22 cases whose tumour was diagnosed post mortem were excluded. Follow-up was performed according to clinical practice at the time of diagnosis.

Information, as it was recorded in original medical records, was collected on body mass index (BMI), smoking, symptoms, investigations, surgery, histology, tumour, node, metastasis (TNM) stage and grade, recurrence date and type, site of metastases and treatment, last date of surveillance or death and cause of death. Tumours were restaged according to the 2002 TNM classification. The restaging was a combination of clinical (surgeon's estimate), pathological and/or radiological measurements: the pathological measurement was the first choice, if available,

Table I. Patient demographics.

Patients (n = 970)	532 males (54.8%)
	438 females (45.2%)
	3 von Hippel–Lindau syndrome
	1 tuberous sclerosis
Treatment	826 (85%) operated
	806 (96.6%) nephrectomies
	28 (3.4%) kidney resections
	548 (56.5%) relapsed
	42% no treatment
	58% treatment to relapse
	Radiotherapy 75.5%
	Immunotherapy 30%
	Chemotherapy 35%
	Surgery 16%
	Hormonal therapy 24%
Diagnosis in	
1964–1969	29 (3.0%)
1970–1974	73 (7.5%)
1975–1979	90 (9.3%)
1980–1984	143 (14.7%)
1985–1989	225 (23.2%)
1990–1994	227 (23.4%)
1995–1997	183 (18.9%)
Age (years)	
≤29	5 (0.5%)
30–39	27 (2.9%)
40–49	90 (9.3%)
50–59	214 (22.0%)
60–69	301 (31.3%)
70–79	251 (25.7%)
80–89	79 (8.0%)
≥90	3 (0.3%)
	Mean 64.1 (SD 12.1) years
	In males 61.9 (SD 11.8) years
	In females 66.8 (SD 11.9) years
	Median 62.7 (range 6–93) years

Table II. Information on tumours.

Tumours (n=982)	Right 49.6%
	Left 50.4%
	2 synchronous bilateral (0.2%)
	10 asynchronous bilateral (1.0%)
	Size range 0.4–30 cm
Clinical presentation	Asymptomatic 14.8%
	Local symptoms 38.6%
	Systemic symptoms 44.6%
Tumour classification	
T1A	179 (18.2%)
T1B	229 (23.2%)
T2	169 (17.2%)
T3A	170 (17.3%)
T3B	146 (14.9%)
T3C	3 (0.3%)
T4	45 (4.6%)
Unclassified	41 (4.2%)
N1	24 (2.5%)
N2	101 (10.4%)
M1	259 (26.4%)
Sites of metastases among M1 patients	
Single site	167 (64.5%)
Multiple sites	92 (35.5%)
Pulmonary	151 (58.3%)
Bone	81 (31.3%)
Liver	41 (15.8%)
Pleura	23 (8.9%)
Abdominal cavity, other	17 (6.6%)
Adrenals	15 (5.8%)
Brain	10 (3.9%)
Mediastinum	10 (3.9%)
Lymph nodes, distant	7 (2.7%)
Pancreas, spleen	6 (2.3%)
Skin, subcutis	6 (2.3%)
Genitourinary system	4 (1.5%)
Thyroid	3 (1.2%)
Breast	2 (0.8%)
Other	4 (1.6%)
Stage	
I	330 (33.6%)
II	142 (14.5%)
III	172 (17.5%)
IV	338 (34.4%)

then radiological and finally clinical measurement. Of all tumours, 50% were assessed by pathological, 84% by radiological and 75% by clinical size measurement. After 1990 computed tomography (CT) was the most common radiological method. Ultrasound had become available 5 years earlier; most studies in the pre-CT era used angiography or urography without adequate measurements. However, only 41 (4.2%) tumours yielded incomplete information for restaging: in 23 patients the primary tumour was not found or studied (the diagnosis was made by biopsy of metastases) and 18 had kidney-confined tumour with no measurements. The grade of 226 tumours diagnosed between 1985 and 1995 was re-evaluated by one uropathologist (P.M.K.) according to Fuhrman's grading. The re-evaluation of all 982 tumours was not possible for practical reasons, such as the availability of these tissue samples as the study material was collected from five hospitals on diagnoses made during four decades. Survival was not analysed according to the original grade because primarily 30% of cases had non-specified grading and in the rest the original grading was mainly done in three grades. Symptoms were classified as local (haematuria, flank pain, palpable mass, varicocele) and systemic (anaemia, erythrocytosis, weight loss, fever, hypercalcaemia, high ESR, metastatic symptoms). If patients had both, they were placed in the latter group. This classification is validated multi-institutionally [13]. The Pirkanmaa hospital district ethics committee gave permission to collect information. The National Authority for Medicolegal Affairs gave permission to re-evaluate the tissue samples. Follow-up was until death or August 2007. The mean follow-up time was 76.9 months (range 0 days to 35.4 years). At the moment of analysis 83% of subjects had died, 61% due to RCC, and 10% of surviving patients had relapsed.

Survival was analysed using Bayesian multivariate analysis and the life-table method up to 25 years. The univariate analysis included seven variables: age, gender, stage, BMI, smoking status, symptoms and year of diagnosis. The likelihood ratio of 5-year survival (LRS) was calculated for each variable, and statistical dependencies within the groups were analysed by the chi-squared or Wilcoxon rank test using two-tailed interpretation. Five-year survival was analysed as it is the most common estimate of prognosis used in the literature. Other statistical differences were analysed by Fisher's *F* test (one tailed) or the Kruskal–Wallis test. The multivariate analysis was performed using an optimizing stepwise procedure based on the Bayesian approach, which is designed mainly for categorized variables and does not need a perfect variable matrix. It selects the combination of variables which best explains the selected outcome variable. No preselection or weighting of variables was applied. In the life-table method, the observed survival rates were compared with the rates based on the year, gender- and age-specific survival tables for the whole Finnish population. The calculations are based on the individual life expectancies of the target population for the target years [18]. The relative survival of the reference population would be 1.0. If the survival curve remains below this, there is excess mortality. In the whole study group the survival is shown up to 25 years, whereas in analysis of prognostic factors the survival is shown up to 10 years. Statistical significance was noted at a p value < 0.05. The rating highly statistically significant (HSS) is given for a p value < 0.000001.

Results

In the study population, the relative 5-, 10- and 25-year OS rates were 56%, 44% and 26%, respectively. Late relapses were seen: three patients had a disease-free interval (DFI) >20 years; the longest interval was 21.9 years. In Bayesian analysis, women had better LRS than men (Table III) and this remained the case throughout the study period (Figure 1). Fifty per cent of operated women and 43% of men remained disease free ($p < 0.05$); 47% of women and 54% of men died of RCC ($p < 0.05$). T1–T2 tumours were more common in women and T3–T4 tumours in men ($p < 0.05$). Grade 3 and 4 tumours (re-evaluated) were more often seen in men ($p < 0.01$). No difference was seen in tumour size, stage, nodal or distant metastases. Age was a significant prognostic factor (Table III), patients aged 40–49 having the best LRS (HSS). The year of diagnosis had no statistical significance.

The relative 5-year OS was 88%, 63%, 65% and 15% in stages I–IV, respectively (Figure 2). The group of kidney-confined tumours with no measurements was included in stage II, as their survival was similar. The median survival was 10.6 years in stage I, 6.3 years in stage II, 5.8 years in stage III and only 13 months in stage IV (HSS). The LRS was very similar in stages II and III, while stage I had the best and stage IV the lowest ratio (Table III). According to T classes, the relative 5-year OS was 74%, 55%, 40% and 19% in T1–T4, respectively and in the group of unclassified tumours 22% (Figure 3). The median survival was 9.0 years, 5.0 years, 2.3 years, and 15 months in T1–T4 tumours, respectively (HSS) and only 13 months among unclassified tumours. Altogether 4.4%, 7.1%, 26.3% and 20.0% of T1–T4 tumours had nodal metastases, respectively (HSS), and distant metastases were seen primarily in 17%, 23%, 35% and 36%, respectively ($p < 0.001$). Of the patients, 84%,

Table III. Bayesian likelihood ratio of 5-year survival (LRS).

Variable	LRS	95% CI	p (χ^2 test)
Age (years)			
<40	1.44	0.71–2.92	
40–49	1.65	1.06–2.56	
50–59	1.32	0.98–1.77	HSS*
60–69	1.17	0.90–1.51	
70–79	0.73	0.55–0.97	
≥ 80	0.24	0.14–0.43	
Gender			
Male	0.87	0.70–1.08	<0.05*
Female	1.19	0.94–1.49	
Stage			
I	3.53	2.67–4.67	
II	1.34	0.93–1.92	HSS*
III	1.41	1.01–1.95	
IV	0.17	0.12–0.23	
Symptoms			
Flank pain vs none	1.34 vs 0.85	1.04–1.72/0.69–1.04	<0.001*
Abdominal mass vs none	0.42 vs 1.08	0.26–0.69/0.90–1.30	<0.001*
High ESR vs none	0.46 vs 1.30	0.35–0.62/1.07–1.59	HSS*
Metastatic symptoms vs none	0.06 vs 1.30	0.04–0.12/1.08–1.57	<0.00001*
Symptom group			
No symptoms	2.45	1.65–3.64	
Local only	2.03	1.59–2.60	HSS*
Systemic	0.42	0.33–0.53	
Year of diagnosis			
–1974	0.80	0.53–1.21	
1975–1979	1.21	0.73–1.73	
1980–1984	0.96	0.67–1.37	ns
1985–1989	0.80	0.60–1.08	
1990–1994	1.30	0.97–1.74	
1995–	1.05	0.76–1.45	

ESR = erythrocyte sedimentation rate; HSS = highly statistically significant ($p < 0.000001$); ns = not significant.

52%, 43% and 6% remained disease free, respectively (HSS). RCC was the cause of death in 13%, 48%, 52% and 91% of the different T classes (HSS).

In re-evaluated tumours, grade 1 and 2 tumours were analysed together, as there was only one grade 1 tumour. The 5-year OS rates were 91%, 74% and

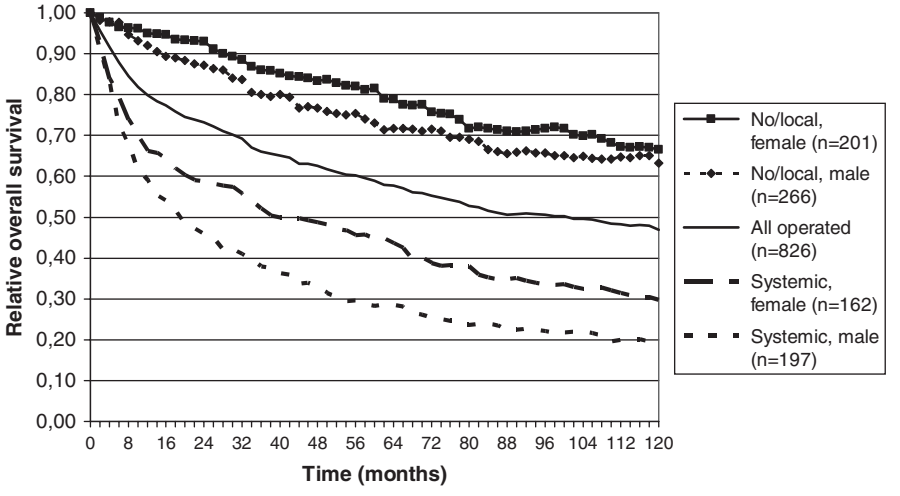

Figure 1. Relative and absolute overall survival according to gender.

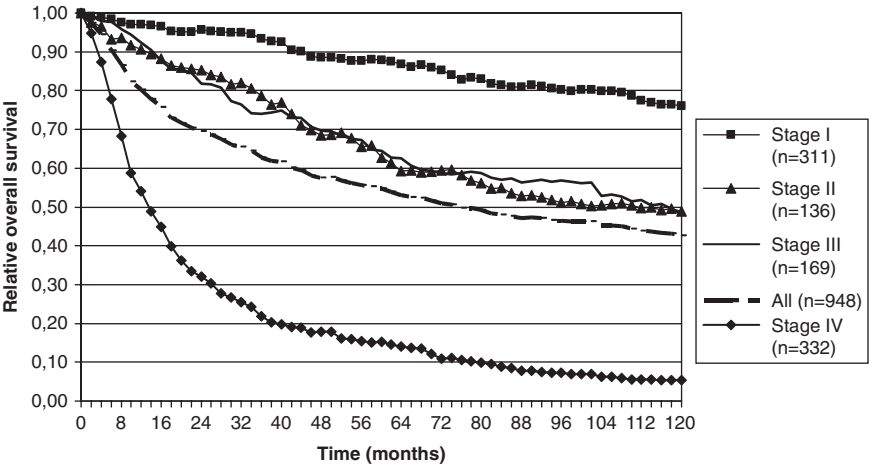

Figure 2. Relative overall survival according to tumour stage.

45% in grade 1–2, grade 3 and grade 4 tumours, respectively. The 10-year OS rates were 75%, 60% and 38%, respectively, and the 20-year OS rates 64%, 47% and 26%. The median survival was 11.4 years, 8.6 years and 3.0 years in these grades ($p < 0.001$). Relapse developed in 13%, 40% and 55% of respective grades ($p < 0.001$). High-grade tumours had more node metastases ($p < 0.001$), and more severe T class ($p < 0.001$) and stage ($p < 0.0001$). They were less often asymptomatic ($p < 0.01$) and had more symptoms associated with poorer prognosis, namely abdominal mass, weight loss and high ESR.

As the histology of tumours was analysed according to heterogeneous classifications during the long study period, survival in different histologies in the whole population was not analysed. In the re-evaluated group there were 90.7% of ccRCCs, 4.9% papillary, 1.8% chromophobic and 0.9% each of sarcomatoid tumours, collecting duct carcinomas and unclassified tumours when classified with the most recent World Health Organization classification. There was no survival difference when ccRCCs were compared with other histologies.

Stage I tumours were found in 60% of asymptomatic patients, in 43% of patients with local and in 17% of patients with systemic symptoms; primarily metastatic disease was found in 14%, 9% and 44% of these groups. The mean (SD) tumour size was 5.9 (3.4) cm, 7.5 (3.7) cm and 8.6 (3.9) cm, respectively ($p < 0.001$). The relative 5-year OS among operated patients with no or local symptoms was 82% in females and 73% in males; the respective rates with systemic symptoms were 45% and 28% (Figure 4). The median survival in asymptomatic patients was 8.1 years, with local symptoms 9.1 years and with systemic symptoms 1.7 years (HSS). Altogether 26.3% of asymptomatic, but 37.2% of patients with local and 70.4% of those with systemic symptoms died of RCC (HSS). The LRS was lower in patients with high ESR, abdominal mass or metastatic symptoms, and better with flank pain (Table III).

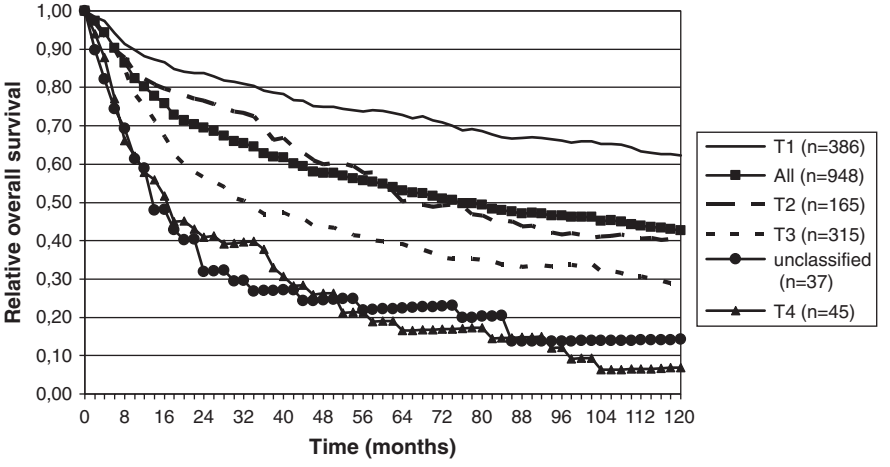

Figure 3. Relative overall survival according to T classification.

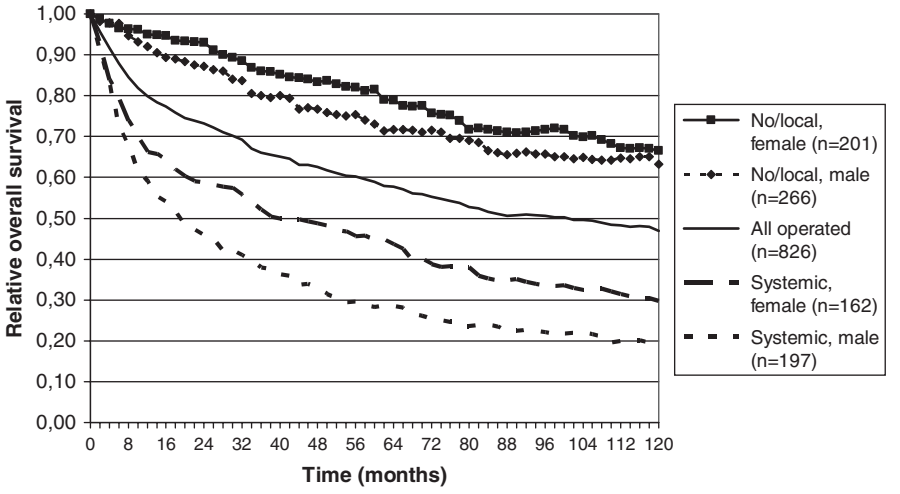

Figure 4. Relative overall survival in operated patients according to symptom classification and gender.

Discussion

This study investigated a large centrally treated RCC population who were operated with the same method throughout the study period. Radical nephrectomy without formal lymphadenectomy has been the standard operation. Broad and reliable data about cancer diagnoses made in the period were collected from the Finnish Cancer Registry. All the other information was collected directly from the original medical records. The follow-up was extensively long, up to 35 years, which is rare in the literature after the 1980s. No other long-term survival data were found for patients treated in the era of immunotherapy.

Interferon was first administered in this hospital district in 1988. It was the first line choice in metastatic disease until 2007. No tyrosine kinase inhibitors (TKIs) were used in this population; these became more common in Finland in 2008. In this population 56.5% of patients relapsed (Table I). Primarily, metastases were present in 20% of operated and in 62% of non-operated patients. Almost half of relapsed patients did not receive any treatment because of high age or lowered general condition or because no effective methods were available. The therapies administered are shown in Table I. Half of the relapses were noted in the era of immunotherapy; 34.3% of these patients were treated with interferon.

RCC involves clearly increased mortality and patients demonstrate diminishing OS with no plateau. The 25-year relative OS was only 26%, demonstrating the devastating effects of RCC. In women diagnosed before 63 years of age excessive mortality was 36%. Women survived longer than men in this study, whereas in other studies no difference between the genders was noted [2,15]. Metastases were found even after a DFI of 21 years. In an older study with follow-up up to 37 years, the OS was only 15% at 20 years and was affected by late recurrences: 11% of patients relapsed after 10 years [19]. Although the present material was collected from a long period, the year of diagnosis was not relevant to prognosis.

Stage II and III tumours had very similar survival, but the difference between stages I and IV was clear. T classification did not give any extra information, but it correlated to nodal and distant metastases and cancer-related death. Fuhrman's grade was a significant prognostic indicator with more aggressive and symptomatic tumours. Age emerged as a significant factor. Asymptomatic patients survived better than symptomatic ones. Symptoms correlated with stage, tumour size and OS. Asymptomatic tumours were found equally frequently in both genders, but women had less aggressive tumours and fewer cancer-related deaths even when all the patients were treated according to similar diagnostic, surgical and follow-up guidelines. The most important prognostic factors in this study were symptomatic disease, age and stage, with 80% sensitivity, 78% specificity and mean error of 21%.

Up to 2001, symptomatic disease had been found to be an independent prognostic factor in only one series [20]. Primarily, metastases are found almost two times more often in symptomatic malignancies than in asymptomatic [21], this difference being seen here especially with systemic symptoms. In this study low grade and stage and small tumour size were more common in incidental than in symptomatic tumours, as also shown elsewhere [12,22]. The LRS of patients with systemic symptoms was worse than in other groups. However, patients with systemic symptoms are included by others in incidental diagnosis and still better prognosis is found than in patients with classic symptoms such as haematuria [23]. In contrast to that and supporting the present results, it is reported

that even a small elevation in ESR worsens the prognosis [16]. This may be related to increased levels of MMP-2 and MMP-9, reflecting the invasive potential of the cancer [11].

The pathological staging was not re-evaluated, which may affect the survival analysis. Unrecognized tumour invasion outside the kidney may explain the similarity of stage II and III survival curves. However, this similarity was not seen in survival according to T classification. Although the grade and histology were not re-evaluated in all tumours, they were re-evaluated in all tumours diagnosed between 1985 and 1995 without selection, hence giving reliable results for survival according to these factors.

The present study provides information on long-term survival of RCC patients with a follow-up time up to 35 years. These findings support those of previous studies of prognostic factors [4,5,8,10–17]. The results showed that RCC may relapse after a very long DFI. The survival did not change significantly in the study period, even after immunotherapy became available. In this material 26.8% of diagnoses were incidental, these patients having no symptoms or only abdominal pain. The percentage of incidental diagnoses can nowadays be up to 80% of cases [10], chancing the nature of RCC. TKIs are the first choice nowadays for metastatic disease and adjuvant treatments are being studied. It is hoped that these positive developments will improve the prognosis in the future.

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BJUI BJU INTERNATIONAL

Changes in symptoms of renal cell carcinoma over four decades

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Study Type – Symptom prevalence (case series)
Level of Evidence 4

OBJECTIVE

To determine whether there has been a change in typical symptoms of renal cell carcinoma (RCC), by evaluating the symptoms of patients diagnosed during four decades, as although the increasing incidence of a diagnosis of incidental RCC has been widely reported, the change in other symptoms has not.

PATIENTS AND METHODS

The study included RCC cases diagnosed in the Pirkanmaa Hospital District between 1964 and 1997. The original medical records of 970 patients with 982 RCC tumours were analysed. Primary symptoms were recorded and changes were analysed in three groups, i.e. diagnoses made before 1980, in the 1980s and in the 1990s. Symptoms were also analysed according to stage, tumour class, gender and age.

RESULTS

The incidence of haematuria ($P < 0.01$) and an increased erythrocyte sedimentation rate ($P < 0.001$) decreased, but there was no change in other symptoms. Incidental diagnoses increased from 12% to 19% ($P < 0.01$). Less chronic or systemic symptoms were noted more recently. Stage and tumour class were highly correlated with symptoms: systemic symptoms increased (24% in stage I to 72% in stage IV, a highly statistically significant increase) and asymptomatic tumours became rarer (27% in stage I to 8% in stage IV, again a highly significant increase) with increasing stage. Haematuria was more common in male patients, anaemia and flank pain in women. Elderly patients were more often asymptomatic than younger patients, with 70–79-year-olds being the least symptomatic.

CONCLUSIONS

Incidental cases of RCC have recently become more common. Haematuria, hypersedimentation, chronic and systemic symptoms have decreased. Stage, tumour class, gender and age are correlated with symptoms.

KEYWORDS

incidental findings, RCC, symptoms, change

INTRODUCTION

RCC is notorious for its presentation with various symptoms; paraneoplastic manifestations are present in up to 30% of patients [1]. The classic triad of Virchow (haematuria, palpable mass and abdominal pain) was present in 9% of patients in a report by Skinner *et al.* [2], but it has since become rarer, with a 3.8–5.5% incidence now reported [3,4].

In the era before CT and ultrasonography (US), 7% of RCCs were detected incidentally [2]; currently incidental diagnoses can constitute up to 80% of cases [5]. There are differences between countries in the numbers of incidental diagnoses, but in many studies the proportion of asymptomatic cases has increased. In Iceland the incidence of incidental diagnoses increased from 11% to 37% between 1971 and 2000 [6], and in a French study from 14% to 48% between 1980 and 1991 [7]; in Italy the incidence increased from 13% to 59% between 1982 and 1997 [8].

In many cases the first symptoms are caused by metastases, but 22% of metastatic diseases are asymptomatic [9]. RCC can by nature metastasize to any site in the body and equally by both blood-borne and lymphatic routes; reports describe ≈50 different sites of metastases [10,11]. The most frequently involved sites are the lungs (29–54%), bone (16–27%), brain (2–10%) and liver (1–7%) [12]. Impairment of blood flow due to the presence of a tumour thrombus in the renal vein and vena cava might be responsible for a higher rate of atypical metastatic sites [13].

Few modern series assessing the symptoms of RCC have been reported. In a Chinese study, 26% of patients were asymptomatic, 56% had local and 19% had paraneoplastic symptoms [14]. In another study, haematuria was the most common symptom, with flank pain, and paraneoplastic syndromes being next in order of frequency [15]. In an older Finnish study of patients diagnosed between 1968 and 1972, haematuria was seen in 25% of patients, 24% had pain, 4% a palpable tumour, <1% fever, 14% lowered general condition, and only 6% were asymptomatic [16].

The increase in the incidence of incidental tumours is reported widely, but the change in other symptoms is not. We analysed the change in symptoms during four decades, together with the relatedness of symptoms to their duration, to gender, stage and tumour class, in a centrally treated large population of patients with RCC.

TABLE 1 Patient and tumour demographics

Variable	*n* (%), or as indicated
Patients (970)	
Men	532 (54.8)
Women	438 (45.2)
von Hippel-Lindau syndrome	3
Tuberous sclerosis	1
Operated	826 (85)
Nephrectomy	806 (96.6)
Kidney resection	28 (3.4)
Relapsed	548 (56.5)
Diagnosis in	
1964–69	29 (3.0)
1970–74	73 (7.5)
1975–79	90 (9.3)
1980–84	143 (14.7)
1985–89	225 (23.2)
1990–94	227 (23.4)
1995–97	183 (18.9)
Age, years	
Mean (SD)	64.1 (12.1)
Median (range)	62.7 (6–93)
Tumours (982)	
Right	49.6%
Left	50.4%
Synchronous bilateral	2 (0.2)
Asynchronous bilateral	10 (1.0)
Size range, cm	0.4–30
Tumour classification	
T1A	179 (18.2)
T1B	229 (23.2)
T2	169 (17.2)
T3A	170 (17.3)
T3B	146 (14.9)
T3C	3 (0.3)
T4	45 (4.6)
Unclassified	41 (4.2)
N1	24 (2.5)
N2	101 (10.4)
M1	259 (26.4)
Sites of metastases among patients with M1	
Single	167 (64.5)
Multiple	92 (35.5)
Pulmonary	151 (58.3)
Bone	81 (31.3)
Liver	41 (15.8)
Stage	
I	330 (33.6)
II	142 (14.5)
III	172 (17.5)
IV	338 (34.4)

TABLE 2 Incidental and symptomatic patients according to age groups

Age, years	Incidental	Symptoms, *n* (%)		
		Local	Systemic	Together
<20	1 (20)	4 (80)	0	5 (0.5)
21–29	2 (7)	11 (41)	14 (52)	27 (3)
30–39	8 (9)	44 (49)	38 (42)	90 (9)
40–49	27 (13)	82 (38)	105 (49)	214 (22)
50–59	41 (14)	127 (42)	133 (44)	301 (31)
60–69	47 (19)	79 (31)	125 (13)	251 (26)
70–79	16 (20)	26 (33)	37 (47)	79 (8)
≥80	1 (33)	1 (33)	1 (33)	3 (0.3)
Total	143 (15)	374 (39)	453 (47)	970 (100)

PATIENTS AND METHODS

RCC cases from the Pirkanmaa Hospital District (Tampere University Hospital and four secondary centres) diagnosed between the years 1964 and 1997 were collected from the Finnish Cancer registry; Wilms', uroepithelial and benign tumours and lymphomas were excluded. Patients whose treatment was conducted only partly in our hospital district or whose medical records had already been destroyed 20 years after death were excluded (204 from the first study years were excluded for this reason, some of them uroepithelial cancers, as we had no information on their exact diagnoses).

Information as it was recorded in the original medical records was collected on symptoms at the point of diagnosis and on the length of the symptomatic period. Symptoms were classified as local (haematuria, flank pain, palpable mass, varicocele) and systemic (anaemia, erythrocytosis, weight loss, fever, hypercalcaemia, a high erythrocyte sedimentation rate, ESR, and metastatic symptoms). If patients had both, they were placed in the latter group. This classification is validated multi-institutionally [17]. According to the duration of symptoms before the first visit to the doctor, patients were divided into groups of asymptomatic, acute (<1 week), subchronic (<1 month) and chronic (>1 month) symptoms. The change in symptoms was analysed in three groups according to the year of diagnosis. Symptoms were also analysed according to tumour class and stage, and patient gender and age. Tumours were re-staged according to the 2002 TNM classification, re-staging being a combination of clinical (surgeon's estimate), pathological and/or radiological measurements: the pathological measurement was the first choice, if available, then radiological and finally clinical measurement. The Pirkanmaa Hospital District ethical committee gave permission to collect information.

Statistical dependencies within the groups were analysed by the chi-squared or Wilcoxon rank test using two-tailed interpretation. Other statistical differences were analysed by Fisher's exact test or Kruskal–Wallis test. Statistical significance was indicated at $P < 0.05$. The rating 'highly statistically significant' (HSS) was given at a $P < 0.001$.

RESULTS

In all, 970 patients with 982 tumours were recorded for this study; the demographics are shown in Tables 1 and 2. Of all tumours, half were assessed by pathological, 84% by radiological and 75% by clinical size measurement. Flank pain was the most common symptom, others being recorded in Table 3. Only 0.7% of patients presented with the whole classic triad. Other symptoms were fatigue (2.2%), UTIs such as recurrent pyelonephritis and urosepticaemia (1.6%), hypertension (1.0%), pathological fracture (0.6%), increase in serum creatinine level (0.6%), oedema in the legs (0.6%) and in the hands (0.1%), thromboembolic events (0.2%), pruritus (0.1%), hypercalcaemia (0.1%) and pollakisuria (0.1%).

Haematuria and an elevated ESR became less common (HSS) during the study period (Table 3). The percentage of other symptoms did not change, but more recent cases had fewer symptoms than earlier groups. There were more systemic symptoms in the earlier

TABLE 3 The percentage of different symptoms in all tumours, and change according to study decades

Symptoms	All	Before 1980	1980s	1990s	*P*
Haematuria	30	39	30	26	<0.01
Flank pain	35	36	35	34	ns
Abdominal mass	8	10	9	7	ns
Fever	8	9	8	8	ns
Weight loss	14	14	15	12	ns
Anaemia	15	14	15	16	ns
High ESR	26	28	33	20	HSS
Erythrocytosis	1	1	1	2	ns
Varicocele	1	2	1	1	ns
Metastatic symptoms	13	10	15	12	ns
None	15	12	11	19	<0.01
Local	39	42	35	41	HSS
Systemic	46	46	54	40	HSS
Acute	40	28	35	49	HSS
Subchronic	14	25	12	10	HSS
Chronic	31	33	40	21	HSS

ns, not significant.

groups and more incidental diagnoses were made more recently (HSS); local symptoms decreased correspondingly. Before 1980, operated patients presented with a mean of 1.7 symptoms, in the 1980s 1.6, and in the 1990s 1.5 symptoms. The respective median symptom count was two, one and one ($P <$ 0.01). Symptoms also became more acute over the study period and correspondingly the proportion of subchronic and chronic symptoms decreased (HSS).

Of asymptomatic patients, 39% were women in the 1980s, and in other decades 46%. The percentage of women among patients with acute symptoms decreased in the study period: before 1980, 49% of patients with acute symptoms were women, in the 1980s 46%, and thereafter 41%. Of patients with subchronic symptoms the corresponding percentages were 43%, 53% and 49%, and of patients with chronic symptoms 46%, 48% and 42%. These differences were HSS, but the percentages fluctuated and no clear trend was apparent.

Haematuria was more common in men (36% vs 23%, HSS), and flank pain more common in women (41% vs 30%, HSS). Anaemia was also more frequent in women (19% vs 12%, $P <$ 0.01). In the case of other symptoms there was no difference between the sexes, but varicocele obviously only occurred in men. There was no difference in symptom groups (asymptomatic/local/systemic) or the number of symptoms between the genders: women had a mean of 1.7 different symptoms and men a mean of 1.6. Of asymptomatic tumours, 56% were found in men and 44% in women. Acute symptoms were present in 40% of patients (56% men, 44% women), subchronic symptoms in 14% (52% men, 48% women) and chronic symptoms in 31% (54% men, 46% women), with no difference between the sexes. The greater proportion of men is caused by male dominance among patients with RCC; there was no change in the percentage of men in the study period.

More asymptomatic tumours or tumours with local symptoms only were present on the right side (53% vs 47%); systemic symptoms were more common in left-sided tumours (54% vs 46%; $P < 0.05$). Non-operated tumours presented more commonly with systemic symptoms such as elevated ESR (40% vs 25%), weight loss (23% vs 13%), anaemia (31% vs 13%), metastatic symptoms (35% vs 10%), or with abdominal mass (15% vs 8%). Only 3.2% of non-operated tumours were asymptomatic, vs 14.5% of operated tumours.

Tumours with local symptoms presented with fewer symptoms than tumours with systemic symptoms, the respective mean symptom count being 1.3 and 2.4 (HSS). In patients with local symptoms, haematuria was the most common symptom (53%); in patients with systemic symptoms, 21% also had haematuria. Of patients with haematuria, 53% had these symptoms only acutely, but 29% already for >1 month before contacting healthcare services. In the group of acute symptoms, haematuria and flank pain were the most common manifestations (41% of patients). In the subchronic group the most common symptoms were flank pain (43%) and fever (16%), in the chronic symptoms group flank pain (41%), a high ESR (39%), weight loss (30%), anaemia (21%), metastatic symptoms (21%) and abdominal mass (12%). There was no statistical difference in these symptoms between the groups. If there were acute-onset symptoms, 46% of patients had systemic symptoms. In the group of subchronic symptoms, 50% presented with systemic symptoms, and among those with chronic symptoms, 68% (not significant).

Tumour classification and stage were strongly correlated with symptom groups (Table 4). Patients with T1 tumours were more often asymptomatic than those with other tumour classes. However, as many as 33% of T1 tumours presented with systemic symptoms or signs. The same was apparent between stages; systemic symptoms increased with increasing stage (HSS). In stage IV, local symptoms were seen in 20% of patients, systemic symptoms being the most common presentation. Of different symptoms, only acute varicocele and fever showed no difference according to stage. When analysed according to tumour class, flank pain and erythrocytosis likewise did not correlate with it. Analysing symptomatic disease according to patient's age (Table 2), those aged <60 years were more commonly symptomatic (89%) than older patients, and patients aged 70–79 years were least symptomatic ($P <$ 0.01). The median age among asymptomatic patients was 69 years, in those with local symptoms 62 years, and in those with systemic symptoms 66 years (HSS). The median age of patients with acute and subchronic symptoms was 64 years, and of those with chronic symptoms 63 years. Compared with asymptomatic patients this was statistically significant ($P < 0.01$).

DISCUSSION

The most common symptom of RCC was flank pain, with no change during the study period. Although 26% of patients had primarily

metastatic disease, only 38% of them had symptoms caused by these metastases. However, only 8% of metastatic diseases were totally asymptomatic, in contrast to the 22% reported in a previous study [9]. Haematuria and an elevated ESR became less common; otherwise the single symptoms of RCC remained stable. Systemic symptoms were seen in 46% of cases, but this value decreased during the study period. This change might be even greater, as the medical records of patients from the earliest cohort with the shortest survival (i.e. with most systemic symptoms) were destroyed 20 years after death, before this study was initiated. In the more recent decade, symptoms were often prevalent for <1 week, when the patient contacted healthcare services. Incidental tumours were found in 15% of cases, but when studied in 5-year groups, incidental cases were apparent in only 7% of patients in the 1960s and already in 21% after 1995. CT became a more common imaging method in the early 1990s in our hospital district, this explaining the change. US had already become more common between 1985 and 1989, and in this 5-year group asymptomatic RCC was diagnosed in 14% of patients. This increase in incidental tumours has also been reported in other countries [5–8].

TABLE 4 The percentage of different symptoms according to stage and tumour class in 982 tumours

Symptom/stage	I	II	III	IV	*P*	T1	T2	T3	T4	*P*
Haematuria	27	44	40	23	HSS	24	39	34	33	<0.01
Flank pain	38	35	41	29	<0.05	37	31	36	40	ns
Abdominal mass	3	10	9	13	HSS	3	11	12	24	HSS
Fever	7	7	8	9	ns	7	7	9	9	ns
Weight loss	6	9	16	22	HSS	7	10	23	20	HSS
Anaemia	8	15	14	23	HSS	10	18	19	27	HSS
High ESR	15	29	36	32	HSS	18	28	36	29	HSS
Erythrocytosis	1	4	1	0	<0.05	1	4	1	0	ns
Varicocele	1	1	1	2	ns	1	1	1	4	ns
Metastatic symptoms	–	–	–	38	na	9	12	16	13	HSS
None	27	11	9	8	HSS	24	8	7	11	HSS
Only local	49	50	45	20	HSS	43	46	32	36	HSS
Systemic	24	39	46	72	HSS	33	46	61	53	HSS
Acute	54	50	49	40	<0.05	52	51	40	49	<0.05
Subchronic	16	16	18	16	<0.05	17	12	17	23	<0.05
Chronic	30	34	33	44	<0.05	31	37	43	28	<0.05

na, not available; ns, not significant.

Haematuria was more common in men, anaemia and flank pain in women. There was no difference between the genders in the number or the duration of symptoms. In the present study we found no predominance of women in the incidental group. In another study the male : female ratio in the incidentally detected group was 50.5 : 49.5, and in the symptomatic group 63.2 : 36.8, possibly because women use health services more [18]. More incidental tumours were found on the right side, as also shown by other investigators. This might be because US is frequently requested for hepatobiliary disease and US is easier in the right kidney than in the left [19]. Elderly patients were more often asymptomatic, possibly because of imaging studies done for other medical conditions. In another study, the clinical presentation of RCC did not differ between young and elderly (>70 years) patients [20].

In previous studies, hypercalcaemia had been detected in 3–8% of patients [2,21,22], in contrast to the present 0.1%. In this unselected retrospective study only clinically relevant hypercalcaemia was mentioned in the medical records. Hypercalcaemia is caused mostly by parathyroid hormone-related protein secreted from a primary tumour, more rarely by local osteolytic metastases or prostaglandin-mediated factors [21]. Also, an elevated ESR was noted in 26% of the present patients, but if systematically recorded can be found in 70% of patients with RCC [23]. The ESR has been shown to increase significantly for up to ≥6 years before the diagnosis, and the increase is marked during the last year before the malignancy becomes apparent. The mean ESR is 47 mm/h in men and 52 mm/h in women, but 20% of the patients in the cited study had an ESR of >100 mm/h [23]. Varicocele is often a late sign of RCC, carrying a very poor prognosis. In previous studies it was the presenting symptom in 2.3–3.3% of cases [2,24]. In the present study varicocele was found in only 1% of cases, with no correlation with stage or tumour class.

With increasing stage and tumour class, systemic symptoms such as weight loss, anaemia and elevated ESR, and chronic symptoms increased, and tumours with no or local symptoms became rarer. Patients with systemic symptoms had more symptoms than the other patient groups. Fever was present in 8% of patients, with no correlation to stage or tumour class. As previously shown, the presence of these symptoms is not absolutely a sign of metastatic disease, as paraneoplastic symptoms are also caused by tumour-secreted hormones such as parathyroid hormone, prostaglandins, erythropoietin, prolactin, renin, insulin, glucagons, gonadotrophins and glucocorticoids [1]. However, paraneoplastic syndromes have been shown to be stage-dependent, i.e. in 5% of stage-I patients, in 9.3% in stage II, 17.9% in stage III and 38.5% in stage IV [14]. The clinical presentations can be various, e.g. metabolic, hepatic, neuromuscular, haematological, renal or cutaneous syndromes [25]. Reports have also suggested the possible role of interleukin-6 overexpression by the primary tumour [26], which has proved to be associated with anaemia, thrombocytosis, increase in C-reactive protein and haptoglobin, neutrophilia, monocytosis and decreased albumin [26,27]. Also, elevated ferritin in the tumour is associated with RCC-related anaemia [28]. Paraneoplastic symptoms are partly different from our systemic symptoms, but we also showed that systemic symptoms can be present in low-stage disease, although the incidence is greater in higher stages.

In the present study the incidence of incidental cases increased between 1964 and 1997. Of single symptoms, the incidence of haematuria and elevated ESR decreased, and of symptom groups, systemic and chronic symptoms decreased. Elderly patients were more often asymptomatic. The clinical presentation differed between the sexes, as there were differences in the incidence of

haematuria, flank pain and anaemia. Tumour class and stage correlated with most of the symptoms.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **US**, ultrasonography; **ESR**, erythrocyte sedimentation rate; **HSS**, highly statistically significant.

Original Study

Influence of Body Mass Index and Smoking on the Long-Term Survival of Patients With Renal Cell Cancer

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Abstract

Obese patients with renal cell carcinoma (RCC) have a better prognosis than that of normal or underweight subjects. In this retrospective study of 948 patients with RCC, we determined the relationship of clinical prognostic factors. Symptoms are a stronger prognostic factor than body mass index (BMI). Smokers have more relapses and shorter disease-free survival than do nonsmokers.

Background: Smoking and obesity are known risk factors for renal cell carcinoma (RCC). We determined the influence of smoking, body mass index (BMI), and symptoms on the survival of patients with RCC. **Patients and Methods:** In this retrospective study, the relative overall survival (OS) up to 25 years was calculated among 948 Finnish patients with RCC diagnosed between 1964 and 1997 using a Bayesian univariate analysis and the life-table method. **Results:** Obese patients had better OS than did normal or underweight patients (median, 5.9 years, 3.4 years, and 12 months, respectively), with lower stage and more asymptomatic tumors at diagnosis and fewer relapses during surveillance. Clinical presentation of the tumor was a stronger prognostic factor than BMI; however, asymptomatic patients with a low BMI had poorer survival compared with normal or overweight patients. There was no difference in tumor stage or presentation at diagnosis between the nonsmokers and smokers; however, the smokers had more relapses with shorter disease-free intervals (DFIs) than did the nonsmokers. The OS was poorer in the smokers (4.2 years compared with 6.6 years in nonsmokers), but no difference was observed in cancer-specific survival (CSS). **Conclusion:** Overweight patients have better survival, with more asymptomatic or local tumors. The clinical presentation was a stronger prognostic factor than BMI. Additionally, survival is poorer in smokers, even if there is no difference in tumor stage or symptoms.

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Introduction

Obesity, smoking, and hypertension are the most prominent risk factors for renal cell carcinoma (RCC), accounting for approximately half of cases.[1] The rising incidence of RCC might be associated with obesity, because the risk of RCC increases by 7% for each unit increase in body mass index (BMI).[2] Additionally, an increase in the incidence of hypertension can explain, in part, the rising incidence.[3] Although the prevalence of smoking was shown to have decreased in a recent study, smoking increases the risk of RCC, even after smoking cessation. Former and current smokers have a risk of 1.3-fold and 1.6-fold, respectively, when compared with individuals who have never smoked.[4] Although a correlated decrease in the risk may be observed for 10 to 20 years after smoking cessation, it is only after 30 years of cessation that the risk is reduced to the level of someone who has never smoked.[5]

The explanations offered for the observed increased RCC risk in smokers include renal damage caused by several mechanisms. These include increased lipid peroxidation,[6] tubular toxicity, hemodynamic changes, endothelial cell dysfunction, and oxidative stress. All these increase cell turnover and induce DNA damage.[7] Smoking is also associated with genetic and epigenetic abnormalities such as gene mutations (eg, in the p53 gene), gene deletions, and DNA methylation.[7] Smoking also has a suppressive effect on the immune system, which might limit its ability to suppress the growth and

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progression of metastases.[8] Nicotine is associated with an alteration of vascular endothelial growth factor.[7]

The explanations offered for the observed increased RCC risk in obese individuals are increased lipid peroxidation and chronic inflammation. Also, cytokines, interleukins, and adipokines secreted by adipose tissue increase angiogenesis caused by high leptin levels and epigenetic silencing of the RASSF1A tumor suppressor gene, and high levels of insulin-like growth factor-1 (IGF1) increase the risk of RCC in obese individuals. IGF1 has both mitogenic and antiapoptotic effects. Overexpression of insulin and IGF1 receptors is found in RCC cells. Obesity also increases the level of estrogen, but there are no convincing results in relation to the risk of RCC.[9] Additionally, obesity results in the abnormal metabolism of cholesterol in tumors.[10] Furthermore, obesity is related to an increased risk of hypertension and diabetes, both of which are risk factors for RCC.[4,11]

In addition, smoking is associated with advanced RCC: current and former smokers have a 1.6- and 1.5-fold risk of nonlocalized disease, respectively. This association increases with a longer smoking history, higher smoking intensity, and greater cumulative exposure to firsthand smoke. Although cessation reverses the risk of advanced disease, the reversal rate is small: only a 9% decrease in risk has been documented for every smoke-free decade.[7] Thus, the progressive effect of smoking is not only linked to carcinogenesis but also to disease progression. Likewise, in additional studies, current but not former smokers were at an increased risk of death compared with nonsmokers because of the more advanced stage of disease at the time of diagnosis.[12,13] Smokers have higher levels of mutated p53, which can be related to more aggressive disease.[14] Smokers with nonmetastasized disease have a significantly poorer overall survival (OS) than do nonsmokers, but no difference in recurrence-free survival was noted.[15] Smokers may also behave differently when seeking health care, but no reports have been published regarding this hypothesis.

Paradoxically, obesity does not worsen the prognosis of RCC. In retrospective studies, a significant advantage with respect to OS has been found for patients with a BMI > 25 compared with normal-weight patients.[16] In a recent study, this positive association between an overweight BMI and survival was found in organ-confined RCC only, not in patients with advanced disease.[17] In the first, albeit small, retrospective study, the hazard ratio (HR) for recurrence between obese and nonobese patients was 0.43 and the HR for death was 0.68. Patients who lost weight before diagnosis had a death HR 1.43 times greater than that of patients with no weight change.[18] Obese patients have a greater proportion of clear cell RCCs (ccRCCs), comorbidities, and surgical morbidity; however, their greater BMIs do not adversely affect their OS or progression-free survival, and the increased presence of ccRCCs does not translate to a more advanced stage of cancer.[19,20] Overweight patients are more likely to have less aggressive tumors, such as those with decreased lymph node involvement and/or number of distant metastases, as well as a decreased presence of high-grade tumor or tumor necrosis.[21] However, not every study supports this finding.[22] In the only prospective study, underweight patients had a poorer survival when compared with other BMI groups.[23] Weight loss as a primary symptom further worsens the prognosis,[24] but only in patients with a BMI < 30.[25]

Thus, the aim of the present study was to evaluate the effect of smoking and BMI on long-term survival in a large centrally treated RCC population and to find the factors that explain the differences in survival.

Patients and Methods

Between 1964 and 1997, kidney cancer cases from the Pirkanmaa hospital region (Tampere University Hospital and 4 secondary centers) were collected from the Finnish Cancer Registry. Tumors were restaged according to the 2002 TNM classification. The grades of 226 tumors diagnosed between 1985 and 1995 were reevaluated according to the Fuhrman grading system. Symptoms were classified as local (hematuria, flank pain, palpable mass, varicocele) and systemic (anemia, erythrocytosis, weight loss, fever, hypercalcemia, high erythrocyte sedimentation rate, metastatic symptoms). If patients presented with both types of symptoms, they were placed in the latter group. Patients were divided into 3 classes according to their BMIs: < 18.5, 18.5-25 and > 25 (ie, underweight, normal weight, and overweight patients), and into groups of ever-smokers, never-smokers, or patients with missing information regarding smoking status. Those patients with insufficient information (73 cases) to constitute BMI were excluded from the calculations concerning this factor. Patients were followed until death or August 2007, when data collection ended.

Survival was calculated for 948 patients because 22 patients whose tumors had been diagnosed post mortem were excluded. Survival was analyzed using both the Bayesian multivariate analysis and the life-table method. The univariate analysis included 7 variables: age, sex, stage, BMI, smoking status, symptoms, and year of diagnosis. The likelihood ratio (LR) of 5-year survival was calculated for each variable, and statistical dependencies within the groups were analyzed by χ^2 or Wilcoxon rank tests. Other significant differences were analyzed by the Fisher F or Kruskal-Wallis test. The multivariate analysis was performed using an optimizing stepwise procedure based on the Bayesian approach, which is designed mainly for categorized variables and does not need a perfect variable matrix. This method selects the combination of variables that best explain the selected outcome variable. In the life-table method, the observed survival rates were compared with the rates based on the sex- and age-specific life tables for the whole Finnish population of the same age. The calculations are based on the individual life expectancies of the target population for the target years.[26] Thus, the relative survival of the reference population would be 1.0. If the survival curve remains less than this, there is excess mortality. The odds ratio (OR) curves for 5-year survival according to BMI were calculated using 5-unit windows for each BMI value. The resulting curves were then smoothed with a 3-point moving average. The result is not relative to the Finnish population, and the expected OR value for all 3 curves together is 1.00. Statistical significance was noted at a P value $< .05$. The rating of high statistical significance (HSS) was given at a P value $< .000001$. The Pirkanmaa Hospital District ethical committee gave permission to collect information and the National Authority for Medicolegal Affairs gave permission to reevaluate the tissue samples.

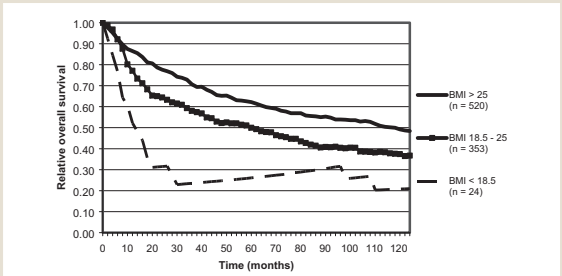
Results

A total of 970 patients were included in the study (demographics in Table 1). The mean follow-up time was 76.9 months (range,

Table 1 Background Factors

Patients (N = 970)	532 men (54.8%)
	438 women (45.2%)
Diagnosis	
1964-1974	102 (10.5%)
1975-1984	233 (24.0%)
1985-1994	452 (46.6%)
1995-1997	183 (18.9%)
Age (years)	
≤49	122 (12.7%)
50-59	214 (22.0%)
60-69	301 (31.3%)
70-79	251 (25.7%)
≥80	79 (8.3%)
	Median 62.7 years (range 6-93 years)
TNM classification	
T1	408 (41.4%)
T2	169 (17.2%)
T3	319 (32.5%)
T4	45 (4.6%)
Unclassified	41 (4.2%)
N+	125 (12.7%)
M1	259 (26.4%)
Stage	
I	330 (33.6%)
II	142 (14.5%)
III	172 (17.5%)
IV	338 (34.4%)
Smoking (Information available for 283 men and 140 women)	74% of men and 26% of women smoked 56.1% of patients with stage I disease smoked 60.4% of patients with stage II disease smoked 45.7% of patients with stage III disease smoked 57.9% of patients with stage IV disease smoked

Figure 1 Relative Overall Survival According to Body Mass Index (BMI)



0 days-35.4 years). At the time of analysis, 83% of the patients had died; 61% of these patients died of RCC and 10% of the surviving patients had recurrent disease. Operative removal of the primary tumor was performed in 85% of patients. The most common surgical procedure was radical nephrectomy without routine lymphadenectomy (96, 4%); only 3.6% of operations were kidney resections. In primary metastatic disease, palliative nephrectomy was conducted in 64% of patients. In the group with the reevaluated tumor grades, there was only 1 grade 1 tumor, and of the other tumors 9.7% were grade 2, 50.4% were grade 3, and 39.4% were grade 4. Most of the tumors were primarily classified as adenocarcinomas or ccRCCs. In the reevaluated group, there were 91.5% ccRCCs, 5.3% papillary RCCs, and 1.8% chromophobic RCCs; the rest (2.7%) were sarcomatoid, collecting duct carcinomas, and unclassified tumors.

The mean BMI was 26.1 (SD, 4.4) and the median was 26 (range, 11-51). No change was found in the percentages of different BMI groups over the study period or between sexes within the BMI groups. The overweight patients had better survival and median absolute survival time than the normal-weight patients; underweight patients had the lowest survival (Figure 1, Tables 2 and 3).

Additionally, there was a trend that overweight patients died less often of RCC (Table 3). There was only 1 long-term survivor among underweight male patients; the survival time was 8.9 years, and all others had a survival time of < 18 months. In all BMI groups, women had better OS than men (Tables 2 and 3). In patients with missing information, the median survival time was 11 months (male patients, 13 months; female patients, 9 months). The ORs of both 5- and 10-year survival was < 1.0 in patients with a BMI < 24 (data not shown). In the Bayesian analysis, patients with a BMI < 20 had the lowest 5-year survival LR, whereas heavily overweight patients (BMI > 35) had the highest ratio (Table 4).

There was no difference in tumor size between the BMI groups. However, overweight patients generally had fewer involved lymph nodes or distant metastases, fewer high-stage tumors, and a trend toward fewer relapses during the follow-up period (Table 3). When we studied, stage by stage, the effect of BMI in cancer-specific survival (CSS), more underweight patients died as a result of RCC. Only in stage I and stage II disease did obese patients die less often of RCC than normal-weight patients: 12% vs. 13% and 44% vs. 53%, respectively ($P < .01$).

Obese patients less often had systemic symptoms and were more often asymptomatic; weight loss was a common primary symptom among underweight patients (Table 3). However, only 5% of those with systemic symptoms were underweight, whereas 53% of these patients were overweight and 42% had normal BMIs. Obese patients more often had acute symptoms, whereas symptoms of underweight patients more often lasted > 1 month (Table 3). The median patient-dependent delay was significantly longer in underweight patients: 44 days vs. 14 days in normal-weight patients and 7 days in overweight patients ($P < .05$). Doctor-dependent delays were 6, 7, and 7 days, respectively (not significant).

When we studied the effect of BMI and clinical presentation on 5-year survival (Figure 2), we found that patients with local symptoms had good survival rates (OR > 1.0), regardless of BMI. In underweight asymptomatic patients, the OR was < 1.0; in other asymptomatic BMI groups it was higher. In patients with systemic symptoms, the OR was < 1.0 regardless of BMI. When we studied all symptom groups separately, a BMI of 24 was always a cutoff value regarding the OR for survival inside each group: with a lower BMI, the OR for OS was < 1.0, and with a higher BMI the OR was > 1.0 (data not shown).

Table 2 Relative 5- and 10-Year Overall and Cancer-Specific Survival Rates (%) With 95% Confidence Interval by Binomial Distribution According to Body Mass Index, Smoking Status, and Sex

	5 Years				10 Years			
	OS	CI	CSS	CI	OS	CI	CSS	CI
Underweight								
Women (n = 13)	36	8-62	36	8-62	34	7-61	45	15-69
Men (n = 11)	0	NA	9	3-27	0	NA	0	NA
Normal weight								
Women (n = 159)	55	47-62	69	62-75	37	29-44	63	55-70
Men (n = 194)	46	39-52	56	49-63	38	31-45	57	50-64
Overweight								
Women (n = 228)	65	59-71	72	66-78	51	44-57	69	63-75
Men (n = 292)	60	54-65	69	63-74	48	42-54	68	62-73
BMI missing								
Women (n = 26)	34	15-51	56	35-73	31	12-48	51	30-69
Men (n = 25)	14	1-27	28	9-44	10	1-22	20	4-34
Smokers								
Women (n = 36)	63	46-77	74	58-86	49	31-64	69	52-82
Men (n = 209)	50	43-57	59	52-66	35	28-41	54	47-61
Nonsmokers								
Women (n = 104)	63	53-72	67	58-75	49	39-58	61	51-70
Men (n = 74)	73	62-82	78	68-86	65	53-75	86	77-93
No information								
Women (n = 286)	56	50-62	69	63-74	41	35-46	66	60-71
Men (n = 239)	47	41-53	60	54-66	41	35-47	61	55-67

Abbreviations: BMI = body mass index; CI = confidence interval; CSS = cancer-specific survival; NA = not available; OS = overall survival.

Table 3 Tumor Status and Clinical Presentation According to Body Mass Index Group

	Overweight	Normal Weight	Underweight	Statistical Significance; *P* Value
Median absolute survival time (F/M)	5.9 years (F: 7.2 years; M: 5.3 years)	3.4 years (F: 4.8 years; M: 2.7 years)	12 mo (F: 19 mo; M: 6 mo)	HSS
Lymph node metastases	9.1%	17.8%	34.6%	HSS
Primary distant metastases	20.3%	31.5%	42.3%	<.001
Metastases during surveillance	49.1%	54.6%	61.5%	NS
Death from renal cell cancer	48.7 %	53.8%	70.8%	NS
Stage I tumors	37.9%	31.0%	23.1%	<.001
Stage IV tumors	27.8%	40.8%	53.8%	<.001
Systemic symptoms	41.6%	49.6%	80.8%	<.001
Asymptomatic tumors	15.3%	12.7%	11.5%	<.001
Weight loss	8.0%	18.9%	46.2%	HSS
Symptoms <1 wk	41.6%	38.0%	25.0%	<.05
Symptoms <1 mo	13.5%	14.0%	12.4%	<.05
Symptoms >1 mo	28.8%	35.3%	50.5%	<.05

Abbreviations: HSS = high statistical significance; NS = not significant.

Smoking status of the patients is shown in Table 1. Nonsmokers had better OS than did smokers (Figure 3, Table 2). The median absolute survival was 4.2 years among smokers, 6.6 years among nonsmokers, and 3.8 years in the missing information group ($P < .05$). Studying the effect of smoking stage by stage, we noted that nonsmokers with stage I and stage II disease had better OS than did smokers or patients with missing information; in the patients with stage III and stage IV disease, there was no difference (Table 5). In the Bayesian analysis, nonsmokers had a significantly better 5-year survival LR (Table 4). At the time of analysis, nonsmokers were more often alive and smokers had more often died of RCC (Table 5). However, a stage-by-stage analysis of CSS revealed no difference in survival even though the smokers had more recurrences with distant metastases (Table 5). Among patients with relapsing

Table 4 Bayesian Likelihood Ratio With 95% Confidence Interval of 5-Year Survival

Table	Likelihood Ratio	Confidence Interval	*P* Value (χ^2)
Body mass index			
<20	0.25	0.12-0.51	<.00001
20-24	0.76	0.58-0.99	
25-29	1.2	0.98-1.6	
30-34	1.1	0.79-1.6	
>35	2.2	1.1-4.2	
Smoking			
Yes	0.91	0.69-1.2	<.05
No	1.5	1.09-2.1	
Missing information	0.91	0.73-1.1	

Figure 2 Odds Ratio Curves for Survival According to Body Mass Index (BMI)

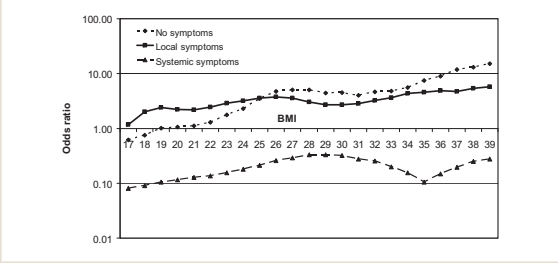
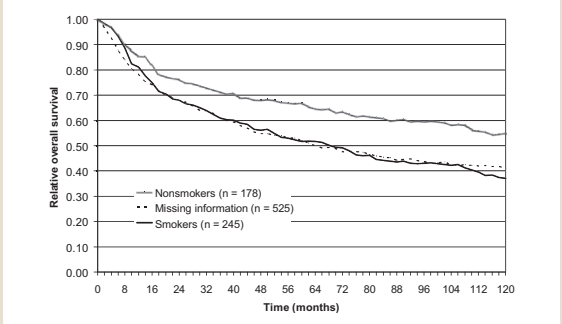


Figure 3 Relative Overall Survival According to Smoking Status



disease, the smokers had a shorter disease-free interval (DFI) in stage I and II disease, but a longer DFI in stage III (Table 5).

Between the smoking status groups, there was no difference in stage, T class, nodal or distant metastases, tumor size, symptoms, or duration of symptoms. The median delay to primary health care contact was 7 days among smokers and nonsmokers, and 13 days in patients with missing information (not significant). The median doctor-dependent delay was 7 days in every group.

Discussion

Weight loss is strongly related to the pathophysiology of RCC. The effect of symptoms and BMI on the prognosis of RCC has not been previously reported. We demonstrated that within each symptom group, a BMI of 24 was a cutoff value regarding surival. Adipose tissue has some clinically significant protective features that are still unknown. In accord with other investigators, we found overweight patients to have a better survival rate,[16-18,21] and in our study female patients had a better survival rate than male patients in every BMI group. The higher survival rate and fewer recurrences among obese patients could be attributed to several factors: obese patients had fewer nodal or distant metastases, which was also shown by others[18,21]; they also had fewer systemic symptoms and more asymptomatic tumors, which had been shown to be a significant prognostic factor.[27] In patients with systemic symptoms, the survival rate was poor regardless of BMI. Thus, obesity did not offer protection for this major clinical prognostic factor. BMI had no effect in patients with local symptoms. An underweight BMI was a clear indicator of a poorer prognosis, as shown previously,[25,26] and it remained an indicator of poor survival even in asymptomatic patients. We confirmed this previous result showing that obesity has a positive association with survival only in organ-confined disease.[17]

We studied 423 patients for whom information on smoking status was available. We found no difference in primary stage, in contrast to other studies.[7,12,13] Smokers nonetheless had poorer OS than nonsmokers, especially when the tumors were localized, as was shown previously.[15] In current smokers, poorer survival has also been shown by other authors.[12,13] However, in CSS, we found no difference between the smoking status groups, even though smokers had more relapses and a shorter DFI. This might be a result of comorbidity, because smokers have other smoking-related diseases that might be the actual cause of death, even if metastatic disease has already been diagnosed. This is shown in Table 2: CSS did not decrease to the degree of the decrease in OS. In stage III, the DFI was longer in smokers than in nonsmokers. There were fewer smokers among the patients with stage III disease who provided smoking information than in the other stages. There may also be a positive bias regarding getting information more frequently in patients with advanced-stage disease. We found no difference in patient-dependent delay or systemic symptoms; smoking itself is thus a factor of recurrent disease.

In this retrospective study, we did not separate current from former smokers and did not collect data on smoking intensity and

Table 5 Prognosis and Disease-Free Interval According to Smoking Status and Stage

	Smokers	Nonsmokers	Missing Information	Statistical Significance; *P* Value
Died	84.5%	75.3%	83.8%	<.05
Died of renal cell cancer	57.0%	51.0%	50.0%	<.05
Relapse with distant metastases	60.0%	55.6%	48.1%	<.01
Mean disease-free interval (SD), stage I (years)	8.7 (5.4)	10.0 (5.7)	11.7 (8.1)	
Mean disease-free interval (SD), stage II (years)	5.8 (4.7)	9.0 (7.8)	7.6 (8.2)	<.01
Mean disease-free interval (SD), stage III (years)	7.9 (7.9)	6.7 (7.3)	6.0 (6.8)	
5-year OS, stage I	71%	89%	74%	
5-year OS, stage II	59%	71%	48%	
5-year OS, stage III	62%	59%	51%	<.01
5-year OS, stage IV	13%	13%	13%	

Abbreviations: OS = overall survival; SD = standard deviation.

duration or cessation after diagnosis of malignancy. Information on smoking status was missing for 56% of our patients. Nonetheless, this study shows the prognostic value of smoking status. In this study population, poorer prognosis was not an effect of a more advanced stage, symptomatic tumor, or patient-dependent delay; thus, smoking has a biological effect on tumor growth.

Conclusion

Overweight patients had better survival rates, especially in localized disease. There was no difference in tumor size between BMI groups, but overweight patients had fewer involved lymph nodes and distant metastases and lower stage tumors. Overweight patients had fewer systemic, and shorter, symptoms as well as shorter patient-dependent delay. A BMI of 24 was the limit value for survival, but clinical presentation of tumor was a stronger prognostic factor than BMI. Smokers had worse OS and a shorter DFI, especially if tumors were localized. However, even if there were more recurrences among smokers, no differences in CSS were observed. At the time of diagnosis, there were no differences in stage, symptoms, or patient-dependent delay between smoking groups; thus, smoking has a prognostic value of its own.

Clinical Practice Points

- Obese patients with RCC have better survival rates in localized disease, but there is no difference in the metastatic situation.
- The limit value for a better survival is a BMI of 24.
- Symptoms are a stronger prognostic factor than obesity. Systemic symptoms predict a poor survival despite obesity.
- Smokers have more recurrences of RCC and worse OS. We found no explanatory factors other than smoking.

Acknowledgments

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Disclosure

The authors have stated that they have no conflicts of interest.

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Development of renal cell carcinoma (RCC) diagnostics and impact on prognosis

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Objective

- To evaluate imaging methods and prognoses between small renal cell carcinomas (RCCs) and larger tumours according to the era of diagnostics.

Patients and Methods

- In all, 784 consecutive patients diagnosed with RCC between 1964 and 1997 at the Pirkanmaa Hospital District in Finland were included.
- Patients were divided into two groups: tumours of ≤3.0 and >3.0 cm in diameter.
- Prognosis was analysed according to the era of diagnostics: (i) pre-computed tomography (CT) and pre-ultrasound (US), (ii) US era and (iii) CT era.

Results

- Small tumours became more common: in the pre-CT and pre-US era, only 4.4% of tumours were small; however, in the CT era 16% were small tumours.
- More diagnostic methods were used in studying small tumours.
- CT proved to be the most reliable method, although it was actually better at diagnosing large tumours.
- Relapses occurred less frequently among patients with small tumours; more than half of the tumours that developed distant metastases (16.0%) already evinced them at the time of diagnosis. There were no relapses after 14 years of follow-up among small tumours, whereas large tumours relapsed within that time. RCC was the cause of death in 14.9% of patients with small tumours vs 50.7% with large tumours.
- The best prognosis was among patients with small tumours diagnosed with CT.

Conclusion

- Among patients with small tumours, prognosis has improved along with better diagnostics, although some showed relapse during a surveillance period of up to 14 years.

Keywords

carcinoma, renal cell, diagnostics, prognosis

Introduction

In RCC, a threshold size of 3 cm has long been considered significant [1]. Beyond this size, there is a sharp increase in the incidence of high stage and grade, multifocality, primary metastases and relapses [2,3]. While small tumours represented only 5.3% of findings in the pre-CT and pre-ultrasound (US) era, this percentage increased almost five-fold after their general adoption [4]. Today, 17.3% of all RCCs and 43.4% of all stage I tumours are discovered at sizes of <3 cm [5,6].

In IVU, a finding of parenchymal, especially central calcification is suggestive of a malignancy [7]. In angiography, a typical pattern involves a hypervascular mass with irregular vessels [8]. With US, most small RCCs are hyperechoic and present as homogeneous solid masses, although isoechoic, hypoechoic and cystic lesions are seen as well. The hypoechoic rim of the capsule is a characteristic feature; protrusion from the kidney is seen in 71% of all cases [9,10]. A common presentation of small RCC in CT is a noncalcified homogeneous lesion with a baseline attenuation of >20 Hounsfield units (HU), enhancing by at least 10 HU after i.v. contrast [11,12].

Occult RCC is identified in 0.3% of patients referred for abdominal CT [13] and in 0.04% referred for US [14]. Anywhere from 10–70% of small tumours are symptomatic: dorsolumbar pain, haematuria, flank mass, hypertension, weight loss, leukocytosis and even paraneoplastic cachexia can be observed. However, in tumours of >5 cm, symptoms are more likely [15–19]. Among incidental tumours, 27.5% are small; of symptomatic tumours, only 2–9.5% are small [18,20].

In most studies, new imaging methods have changed the presentation of RCC. Between 1973 and 1999 the proportion of patients with tumours of >10 cm decreased from 55% to 26% whereas those with tumours of <5 cm increased from 0% to 29% [21]. Likewise, the proportion of small tumours increased from 10.2% to 62.7% between 1981 and 2006 [22]. However, this change has not been confirmed in all reports [23].

In the context of increasing diagnoses of small tumours, we evaluated changes and trends associated with their diagnostic methods and prognoses according to the imaging-method era and symptoms, in comparison to larger tumours.

Patients and Methods

RCC cases from the Pirkanmaa Hospital District (Tampere University Hospital and four secondary hospitals) diagnosed between 1964 and 1997 were collected from the Finnish Cancer registry. Wilms, uroepithelial and benign tumours were excluded, as well as lymphomas. Similarly, patients were excluded if their treatment was conducted only partially in our hospital district or if their medical records were destroyed 20 years after death. In addition, those patients without any imaging studies and patients without pathological or surgical confirmation of tumour sizes were excluded. Originally, 970 patients were identified; of which 784 were eventually included (demographics are presented in Table 1). Patients were divided into three subgroups according to the era of diagnostics. The threshold point was the year when at least 25% of patients were imaged with US and again with CT: pre-CT and pre-US era (1964–1979), US era (1980–1988) and CT era (1989–1997).

Information on symptoms, diagnostic delays, radiological investigations, surgeries, histology, tumour size, TNM stage and grade, recurrence, last date of surveillance or death and cause of death, were collected from the original medical records. The indication for the imaging studies was recorded depending on the question formulated by the clinician. Tumours were stratified according to pathological or operative measurements. Of all tumours, 50% were assessed pathologically, 84% radiologically and 75% by operative size measurement. Tumour grades diagnosed between 1985 and 1995 were re-evaluated by one uropathologist (P.M.K.) according to Fuhrman's grading. The Pirkanmaa Hospital District Ethical Committee and the National Authority for Medicolegal Affairs gave permission to collect information and to re-evaluate the tissue samples, respectively. Follow-up continued until death or August 2007.

Overall survival was analysed using the life-table method: the observed survival rates were compared with rates based on year, gender- and age-specific survival tables for the entire Finnish population. Calculations were based on the individual life expectancies of the target population for the target years. The relative survival of the reference population would be 1.0. If the survival curve remains below this, there is excess mortality. The 95% CIs of relative survival are calculated using Hakulinen's standard error formula [24,25]. For survival rates statistical differences were analysed by *t*-test, other statistical differences were analysed by chi-squared or Wilcoxon rank test using a two-tailed interpretation. A $P < 0.05$ was considered to indicate statistical significance. The rating highly statistically significant (HSS) is given with a $P < 0.000001$.

Table 1 Patient and tumour demographics according to study group.

Variable	Group A, *n* (%)	Group B, *n* (%)
Gender:		
Female	41 (43.6)	
Male	53 (56.4)	385 (55.8)
Age, years:		
<20	0	2 (0.3)
20–29	1 (1.1)	2 (0.3)
30–39	4 (4.2)	24 (3.5)
40–49	8 (8.5)	69 (10.0)
50–59	19 (20.2)	166 (24.0)
60–69	29 (30.9)	228 (33.1)
70–79	28 (29.8)	164 (23.2)
≥80	5 (5.3)	35 (5.1)
Decade of diagnosis:		
1960s	1 (1.1)	17 (2.5)
1970s	6 (6.4)	134 (19.4)
1980s	26 (27.7)	253 (36.7)
1990s	61 (64.9)	286 (41.4)
Era of diagnostics:		
Pre-CT and pre-US	7 (7.4)	151 (21.9)
US	24 (25.5)	222 (32.2)
CT	63 (67.0)	317 (45.9)
Operation:		
Nephrectomy	76 (80.9)	661 (95.8)
Partial resection	15 (15.9)	10 (1.4)
Not done	3 (3.2)	19 (2.8)
Stage:		
I	78 (83.0)	219 (31.7)
II	0	104 (15.1)
III	6 (6.4)	150 (21.7)
IV	10 (10.6)	217 (31.4)
Primary metastases:		
Lymph node	3 (3.2)	104 (15.1)
Distant metastases	8 (8.5)	153 (22.2)
Re-evaluated grade ($n = 25$ and 184):		
I	0	1 (0.5)
II	3 (24.0)	13 (7.1)
III	13 (52.0)	94 (51.1)
IV	6 (24.0)	76 (41.3)

Group A, tumours ≤3.0 cm in diameter; Group B, tumours >3.0 cm in diameter.

Results

In this study population, 94 (12.0%) tumours were ≤3.0 cm in diameter (group A) and 690 (88.0%) were larger (group B), with no differences in gender or age. Small tumours had

Table 2 Indication, diagnostic studies needed and symptoms in the study groups.

	Group A, *n* (%)	Group B, *n* (%)	*P*
Indication for imaging studies:			<0.001
Suspicion of RCC	16 (17.0)	246 (35.7)	
Abdominal complaint	27 (28.7)	162 (23.5)	
General health examination	7 (7.4)	15 (2.2)	
Other	44 (46.8)	267 (38.7)	
Diagnostic studies:			<0.05 < 0.01
1	2 (2.1)	14 (2.0)	
2	20 (21.3)	204 (29.6)	
3	38 (40.4)	316 (45.8)	
4	29 (30.9)	135 (19.6)	
5	4 (4.3)	20 (2.9)	
≥6	1 (1.1)	1 (0.1)	
Kidney biopsy	9 (9.6)	22 (3.2)	
Symptom number:			HSS
0	33 (35.1)	80 (11.6)	
1	40 (42.6)	299 (43.3)	
2	15 (16.0)	158 (22.9)	
3	5 (5.3)	106 (14.2)	
4	0	37 (5.4)	
5	1 (1.0)	8 (1.2)	
≥6	0	2 (0.3)	
Symptoms:			
Haematuria	16 (17.0)	241 (34.9)	<0.001
Abdominal mass	1 (1.1)	64 (9.3)	<0.05
Elevated ESR	11 (11.7)	179 (25.9)	<0.01

Group A, tumours ≤3.0 cm in diameter; Group B, tumours >3.0 cm in diameter; ESR: erythrocyte sedimentation rate.

been diagnosed more recently (Table 1). Asymptomatic tumours were found more often in group A (Table 2). Of all symptomatic cases small tumours were found in 9.1%, of all asymptomatic in 29.2%. Group A had fewer symptoms; differences in the incidence of haematuria, abdominal mass and elevated erythrocyte sedimentation rate were seen (Table 2). Symptomatic patients in group B contacted health care later than symptomatic patients in group A: the median time was 12.5 days vs 1 day ($P < 0.05$).

The indication for imaging studies was suspicion of RCC more often in small tumours than in large ones (Table 2). The median time to the first imaging study after contact with health care was 1 day in group A and 7 days in group B ($P < 0.01$). In group A more diagnostic studies and kidney biopsies were needed (Table 2) and in more recent years more imaging studies have been performed (HSS) resulting in longer operation delays. The median time from the first diagnostic imaging study to operation was 57 days for small tumours vs 27 days for large tumours (HSS). Preoperative angioembolisation was done in 10.0% of cases in group B. There was no difference in the percentage of operated patients, but partial nephrectomy was conducted more often in group A (Table 1; HSS).

The imaging studies undertaken are shown in Fig. 1a,b; results are shown in Table 3. CT came in to general use earlier for studying small tumours than large ones; IVU became rarer along with this change. CT, US and IVU proved superior in large tumours when compared with the study results of small tumours. Altogether 37.5% of IVUs missed malignancy in small tumours. Altogether, a preoperative malignant imaging result was obtained in 93.6% of patients in group A and in 96.7% in group B.

A re-evaluated grade was defined in 26.6% in both groups. Large tumours were higher grade ($P < 0.05$, Table 1) and higher stage (HSS). They evinced also more often primary lymph node involvement ($P < 0.05$) and distant metastases ($P < 0.01$, Table 1). Small tumours had better prognosis than large ones (Fig. 2, Table 4); differences were seen in the amount of relapses (18.1% vs 55.7%), local relapses (2.1% vs 3.2%) and distant metastases (16.0% vs 52.5%, HSS). Again, RCC was the cause of death more often in patients with large tumours (50.7% vs 14.9%, HSS).

According to imaging-method era there were survival differences: the best prognosis was seen in patients diagnosed with small tumours in the CT era (Fig. 3, Table 4). No differences were seen between group A patients diagnosed in the first two eras; in group B this difference was statistically significant ($P < 0.001$) after 5 years, but not after 10 years. When comparing the US era with the CT era, there were marked differences in survival among both study groups ($P < 0.001$). Between the two study groups there was no difference in the first era, while in the US era group A survived better after 5 years, but the situation was the opposite after 10 years. In the last era

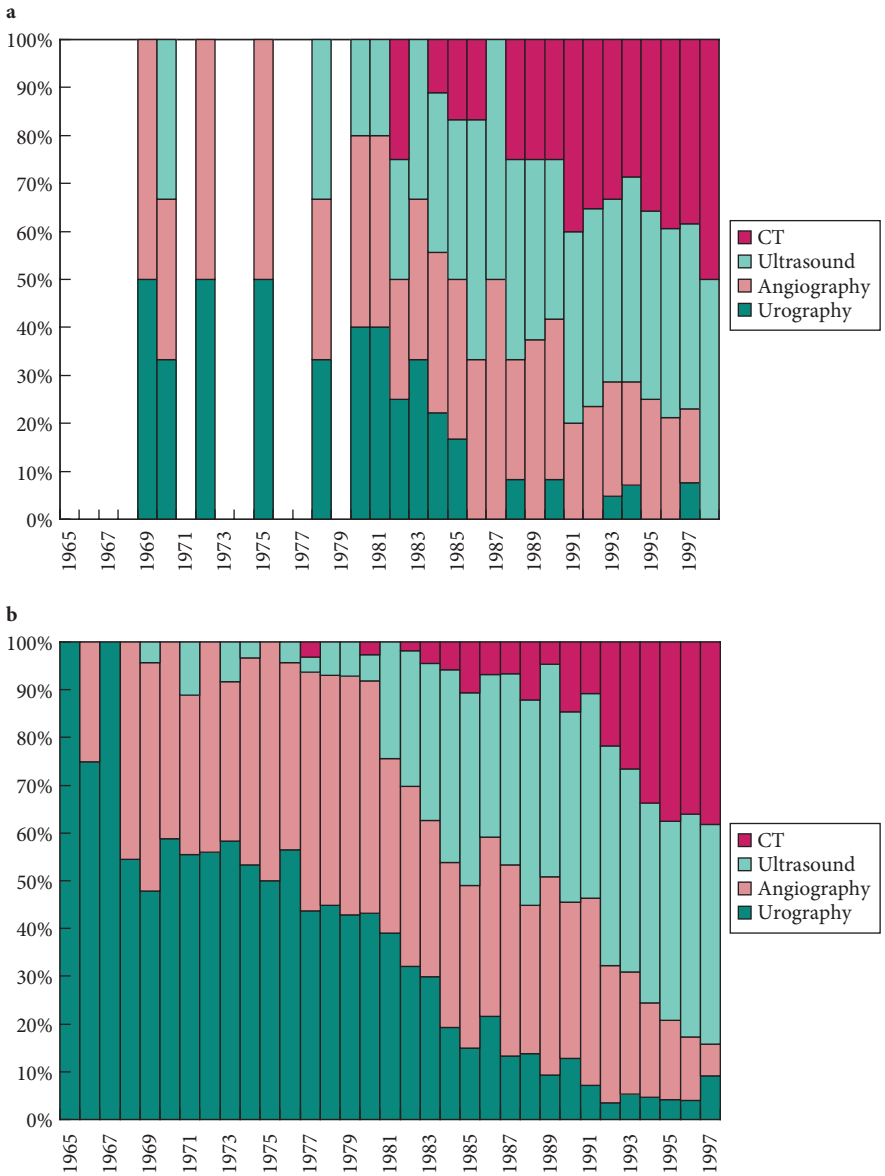


Fig. 1 Percentages of different imaging studies according to study year in groups A (**a**) and B (**b**).

Table 3 Results with different imaging methods in the study groups.

Imaging method	Study group	Done		Normal		Abnormal		Indefinite malignant		Definite malignant		*P*
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	
IVU	A	24	25.5	3	12.5	6	25.0	9	37.5	6	25.0	<0.001
	B	315	45.7	12	3.8	35	11.1	79	25.1	189	60.0	
Angiography	A	65	69.1	2	3.1	3	4.6	5	7.7	55	48.6	n.s.
	B	489	70.9	6	1.2	9	1.8	13	2.7	461	94.3	
Cavography	A	0	0	0	0	0	0	0	0	0	0	n.a.
	B	11	1.6	4	36.4	1	9.1	2	18.2	4	36.4	
US	A	84	89.4	5	6.0	5	6.0	31	36.9	43	51.2	<0.001
	B	199	72.3	4	0.8	19	3.8	79	15.8	397	79.6	
CT	A	61	64.9	1	2.3	2	3.3	26	42.6	32	52.5	<0.001
	B	218	31.6	2	0.9	2	0.9	21	9.6	193	88.5	
MRI	A	3	3.2	0	0	0	0	1	33.3	2	66.7	n.a.
	B	12	1.7	0	0	0	0	1	8.3	11	91.7	

Group A, tumours ≤3.0 cm in diameter; Group B, tumours >3.0 cm in diameter; n.s., non-significant; n.a., not available.

Fig. 2 Overall survival according to study groups.

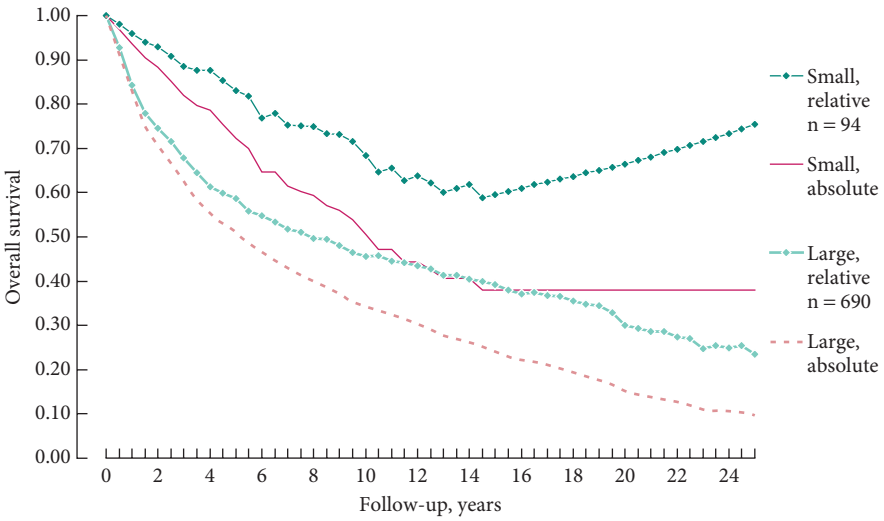
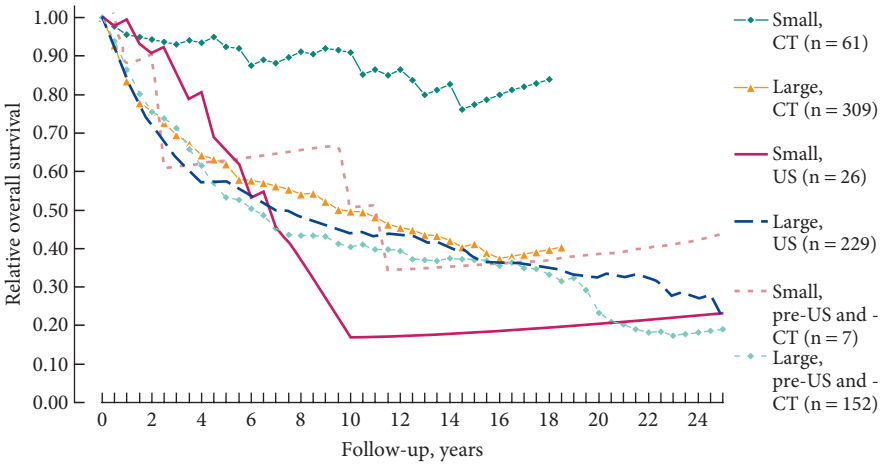


Table 4 Relative overall survival (OS) with 95% CI among all patients and according to study group and diagnostic era.

	Group A		Group B		*P*
	OS, %	95% CI	OS, %	95% CI	
All, 5-year	83	82–85	59	58–59	HSS
All, 10-year	68	66–71	45	44–46	HSS
All, 20-year	67	48–85	30	27–33	<0.001
Before US and CT, 5-year	63	21–95	53	51–55	n.s.
Before US and CT, 10-year	51	10–92	40	37–44	n.s.
US, 5-year	65	55–75	57	56–59	<0.01
US, 10-year	17	3–70	44	42–46	<0.001
CT, 5-year	92	91–94	62	61–63	HSS
CT, 10-year	91	88–94	50	48–51	<0.001

Group A, tumours ≤3.0 cm in diameter; Group B, tumours >3.0 cm in diameter.

Fig. 3 Overall survival according to diagnostic era and study group.



small tumours had better survival. When the background factors concerning this survival improvement were considered, we found that the proportion of patients with primarily metastatic disease stayed the same in group B, but decreased among group A being 29%, 19% and 2% in the respective diagnostic eras ($P < 0.01$). Cancer-specific survival showed a trend of improvement, but it did not reach statistical significance because of the few cases: the

cause of death was RCC in 43%, 30% and 15%, respectively. There was no difference in disease-free survival between the diagnostic eras. The proportion of asymptomatic patients increased (28.9%, 26.9% and 39.3%, respectively), but this did not reach statistical significance.

Discussion

The diagnostics of renal masses have undergone a marked change since the introduction of CT and US. During the study period, the use of IVU and angiography was diminishing while the use of US and CT became more common (Fig. 1a,b), these were also the most common combination of imaging methods. Among British urologists in 1983 only 16% used CT and 93% recommended US [26]. In Finland in 1998 IVU, renography and cytology/biopsy examinations were no longer used while these were still in common use in other Scandinavian countries [27]. After the introduction of helical CT in 1989, more reliable measurements were achieved and the method came in to general use. In 1998, CT machines were equipped with multiple row detector arrays increasing dramatically volume coverage speed. Nowadays, the diagnostic algorithm is to perform abdominal US and then 2/3 phase helical CT with 5 mm collimation to minimise partial-volume artefacts [28]. Kidneys are scanned early during the corticomedullary and the tubular nephrogram phase [29]. Staging is recommended to be done by abdominal and chest CT and bone scintigraphy; cerebral CT is performed only when there is suspicion of brain metastases. If tumour is local, but there is a suspicion of a thrombus after primary imaging, MRI is recommended [28]. The performance of ^{18}F-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG PET) CT in the detection of primary disease is limited because of renal excretion of FDG, resulting in high frequency of false-negative results. However, this method has a good performance in staging and the diagnosis of metastases; the major advantage is the detection of occult lymph node or bone metastases and differential diagnosis of tumour and coagulative thrombus [30].

The indication for imaging studies was often other than a suspicion of RCC. However, almost two thirds of small tumours were symptomatic, even if in 83% of cases, RCC was not suspected. RCC is notorious for variable and unspecific symptoms and even in two thirds of large tumour this malignancy was not primarily suspected. Both local and systemic symptoms were recorded up to five symptoms per patient reflecting the long study period; in more recent studies most tumours are incidental [20]. Only one patient with a small tumour and 14 with large tumours were studied by one method. Over 70% of group A were studied with three of four methods, while large tumours needed one method less. The diagnosis remained indefinite despite all methods in 6.4% of small tumours and in 3.3% of large, this mainly due to cystic tumours. The diagnosis of small tumours was more difficult than that of large tumours; more imaging studies and preoperative biopsies were required, this resulting in longer delays to surgery than for large tumours. The number of studies needed may also reflect the increasing number of methods available. While CT was the most reliable method (Table 3), 4.9% of small tumours were nonetheless missed. Usually, most tumours that are not detected by US can be identified by CT [31], but also CT is known to fail in tumours measuring <1 cm in diameter [32]. CT should detect all surgically verified tumours of >15 mm [33]. MRI has been shown to be slightly superior to CT: sensitivity is the same, but MRI is better in differential diagnosis [34]. As MRI offers no clear advantage, it is most useful in patients with iodine allergy or renal failure [35].

Here angiography yielded better accuracy than US due to its use in 'road mapping' for the surgeon. Currently, angiography is indicated only for interventions and in the cure of complications of nephron-sparing surgery [8]. US missed 12.0% of small tumours and <5.0% of large ones. The main limitations of US are known to emerge in cases of small isoechoic intraparenchymal tumours causing no deformity, and polar tumours with extrarenal growth that may be obscured by bowel gas [36,37]. When comparing US with CT, it detects only 26% of CT-confirmed renal masses of <1 cm, but 85% of lesions of >3 cm [38]. US should detect all surgically verified tumours of >25 mm [33]. IVU failed in as many as 37.5% of small tumours, as unless the tumour is large enough to effect a change in renal contour or distortion of the collecting system, it can be missed [39]. IVU detects only 10% of CT-confirmed renal masses of <1 cm in diameter, but 85% of masses of >3 cm [38]. In another study sensitivity in detecting small RCCs was very similar: 67% for IVU, 74% for angiography and 94% for CT, but only 79% for US [40].

The use of fine-needle aspiration was not frequent. Only 40% of aspirations are reported to yield diagnostic malignant cells [41]. For this reason in 2005, 43% of urologists in the UK never used biopsy and 23% used it only for selected patients [42]. However, there is growing literature after 2001 that currently the success rate is >90% and insufficient material is noted only in 5% [43]. This is achieved by using helical CT-fluoroscopy guided core biopsy [44].

Small tumours became more common during the study period. These were of lower stage and grade evincing fewer nodal and distant metastases yielding better prognosis than large tumours, as also reported elsewhere [2,3]. Most small tumours with metastases were already primarily disseminated, while few patients developed metastases

during the follow-up up to 14 years after diagnosis, but not after that. Larger tumours did not achieve plateau (Fig. 2). In another series, 7.0% of small tumours were primarily metastasised; 7.0% developed recurrence at ≤5 years and 16% at ≤10 years [45], but as long a follow-up as ours has not been previously reported. The prevalence of concurrent metastases was in one large collected series 2.5% [46]. Even 6 mm primary tumours have been reported to have metastasised [45], but the risk of synchronous metastases increases by 22% for each 1 cm increase in tumour size [47]. These few disseminated small RCCs are very aggressive from the outset, but most tumours will grow slowly without relapse [46]. Cancer-related death was noted in 14.9% of patients with small tumours vs 50.7% of patients with larger tumours. Even if the difference in cancer-related deaths between diagnostic eras did not reach statistical significance, it is of clinical relevance that in the first diagnostic era patients died almost three times more often because of RCC than patients in the CT era. Incidental tumours found most often by CT have a good prognosis as these are usually operable.

During the present study period there was not an effective systemic oncological therapy for metastatic RCC [48]. In the study population there were no major perioperative complications to explain differences in survival (data not shown). Along with the change in diagnostics resulting in increasing numbers of incidental findings, patients with small tumours diagnosed in the CT era had the best survival. This is explained by the small proportion of primarily metastatic disease, as we did not find any statistically significant differences in the percentage of asymptomatic tumours or in disease-free and cancer-specific survival. Also, among large tumours, those diagnosed in the most recent era had a better prognosis than tumours diagnosed earlier. Small tumours achieved a plateau in survival after 14 years of follow-up, which was not seen among larger tumours. With multiple imaging methods there was no difference in the reliability of achieving preoperative diagnosis of RCC of any size. As more small tumours have been diagnosed incidentally with developed imaging methods, the overall prognosis of RCC has improved along with this change; clearly some of this is due to improvements in the diagnostics.

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Conflict of Interest

None declared.

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Abbreviations: FDG, fluorodeoxyglucose; HSS, highly statistically significant; US, ultrasonography/ultrasound.

