Epidemiological and Clinical Aspects in Diagnosis and Treatment of Renal Cell Carcinoma

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”Man skal ej læse for at sluge,
men for at se, hvad man kan bruge.”

Henrik Ibsen, *Peer Gynt*

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List of publications

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II. Beisland C, Medby PC, Sander S, Beisland HO. Nephrectomy – Indications, complications and postoperative mortality in 646 consecutive patients. *Eur Urol 2000; 37: 58-64.*

III. Beisland C, Medby PC, Beisland HO. Renal Cell Carcinoma – A retrospective study of 368 patients. *Tidsskr Nor Lægefor (The Journal of the Norwegian Medical Association) 2002; 122: 2431-5.*

IV. Beisland C, Medby PC, Beisland HO. Presumed radically treated renal cell carcinoma: recurrence of the disease and prognostic factors for survival. *Scand J Urol Nephrol 2004; 38: 299-305.*

V. Beisland C, Talleraas O, Bakke A, Norstein J. Multiple primary malignancies in patients with Renal Cell Carcinoma. - A national population-based cohort study. BJU Int 2006; *In press.*

Abbreviations

BS:	Bone Scan
COD:	Cause of Death
CRN:	The Cancer Registry of Norway
CSS:	Cancer specific survival
CT:	Computer tomography
DFI:	Disease free interval
ESR:	Erytrocyte Sedimention Rate
IRCC:	Incidentally detected Renal Cell Carcinoma
LND:	Lymph node dissection
LRN:	Laparoscopic Radical Nephrectomy
MRCC:	Metastatic Renal Cell Carcinoma
MRI:	Magnetic Resonance Imaging
NSS:	Nephron Sparing Surgery
PS:	Performance status
RN:	Radical Nephrectomy
RCC:	Renal Cell Carcinoma
RV:	Renal vein
SIR:	Standardised Incidence Ratio
SRCC:	Symptomatic Renal Cell Carcinoma
SSB:	Statistics Norway
TNM:	Tumour – Node - Metastasis
US:	Ultrasound
VCI:	Inferior Vena Cava

1. INTRODUCTION

1.1 General Introduction

The Renal Cell Carcinoma (RCC) comprises approximately 80-90 % of all malignant renal tumours. Due to the work of Paul Grawitz (1850-1932), published in 1883(1) and claiming that this type of tumour originated from intrarenal adrenal remnants, Renal Cell Carcinoma (RCC) for many decades was known as hypernephroma or Grawitz tumour. It was not until the beginning of the second half of the twentieth century, and the introduction of the electron microscope, that it was established that these tumours originated from renal tissue (2). Today, RCC is known to originate from mature tubular structures. Most of the tumours, including conventional (clear cell) RCC, arises from the proximal tubule (3).

1.2 Incidence and epidemiology

RCC accounts for approximately 2 per cent of reported new cancers in Norway (4). Of a total population of ≈ 4 600,000 (5), annually 450-500 persons are diagnosed with RCC. In 2003, 244 persons died of cancer of the renal parenchyma in Norway, which is 2.3 % of all cancer deaths in Norway (6). Most reports on incidence conclude that there is an increase in incidence of RCC (7;8). The rise in incidence over the last half century is also demonstrated in the reports from CRN (Figure 1).

1.2.1. Geographic distribution

The occurrence of RCC varies around the world. The highest incidence rates are found in Western Europe and North America. The lowest are found in Asia and Africa (Table 1). Differences in cancer registration, cancer detection tools and autopsy rates may be part of the explanation for this variation. Different dietary and environmental factors in the industrialised and developing parts of the world may also play a role. These latter may be the explanation to the fact that Afro-Americans in the

United States, have higher incidence rates than the white population and much higher than their genetic relatives in Africa (7;9).

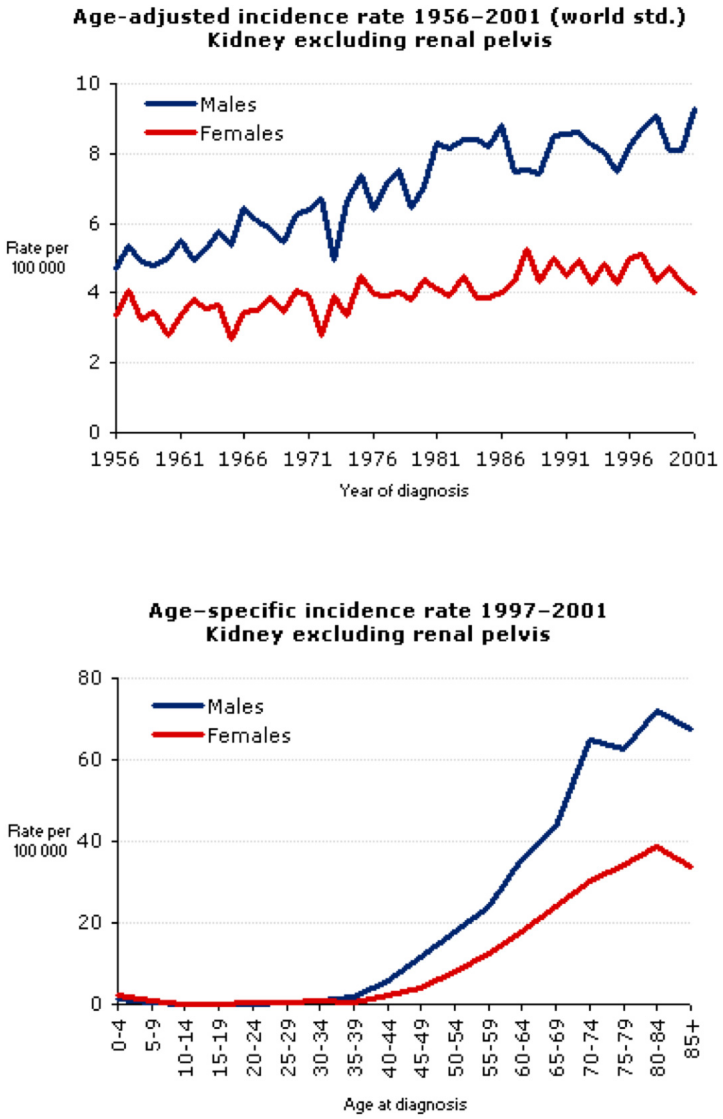
Table 1. Adapted from Beisland & Beisland (10)

Country/ Area	Incidence/100.000 (world standard)
Norway	10,55
Sweden	8,78
Denmark	8,78
Finland	12,03
Iceland	12,52
USA	11,15
Swaziland	0,23
More developed countries	9,77
Less developed countries	2,11

1.2.2. Age and Sex

The diagnosis of RCC peaks in the 6th through 8th decade (11-15), and the male: female ratio are reported between 1,4:1 and 2,5:1 (13;14;16). In Figure 1, these reported findings also are demonstrated on the Norwegian national level.

Figure 1. (From the Cancer Registry of Norway) (15)



1.3 Aetiology and Risk Factors

Most of RCC are sporadic, but the small fraction of cancers caused by familial genetic alterations has increased our knowledge of the mechanisms leading to RCC. Many risk factors for RCC have been proposed, but few remain undisputed.

1.3.1. Inheritance

Von Hippel-Lindau disease (VHL) is an autosomal-dominant disorder, which result in clear cell RCC. It is caused by a defect in the short arm of chromosome 3, and

occurs in 1 of 40,000 live births. 70 % with the disease will have developed RCC by the 7-decade (17). These patients have high risk for multiple new tumours, and they need lifelong surveillance (18). Nephron-sparing surgery, and minimally invasive techniques (i.e radiofrequency ablation or cryotherapy) are the preferred treatment modalities for these patients (19). Eventually most VHL patients die of metastatic RCC.

Inherited forms of papillary RCC (20) and chromofobe RCC (21) also exists, but are less common than clear cell RCC/VHL.

1.3.2. Tobacco

There are many studies that demonstrates the connection between cigarette smoking and RCC (22-26). The increase in relative risk is reported to be moderate, but there seems to be a well-documented dose-response effect. If smoking is stopped, the risk seems to decrease (24). Most of the various chemicals in cigarette smoke are excreted trough the kidneys, but the exact cause of RCC is not known. The main suspect, however is nitrous compounds, which have caused kidney tumours in animal models (27).

1.3.3. Obesity

There is a strong and documented relationship between obesity and RCC (28-31). The risk seems to be higher among women and in those with severe obesity. The reasons for this connection are still not fully known, and several explanations are possible. Obesity increases the levels of endogenous estrogens, which in animal models have resulted in kidney tumours (32). Furthermore, obesity may increase levels of insulin-like growth factor (IGF-I), which may contribute in carcinogenesis. This also may reflect the fact that patients with diabetes mellitus have increased risk of RCC (33).

1.3.4. Other factors

Physical activity, dietary factors, occupation, antihypertensive medication, alcohol, radiation, analgesic medication and kidney stones have all been proposed to increase the risk of RCC. However, all these remain controversial and are in need of further investigation (34).

1.4 Classification of RCC

1.4.1. Subtypes of RCC

Today, the Heidelberg classification of RCC (35) is the most widely used system for subtyping of RCC. This classification uses the genetic abnormalities in the different tumours as basis for each subcategory. RCC is subdivided into (with frequencies)

- Conventional (Clear Cell) RCC (≈ 59-83%) (36-39)
- Papillary RCC (≈ 10-27%) (36-39)
- Chromophobe RCC (≈ 4 - 11%)(36-39)
- Collecting Duct RCC (≤ 1%) (36-39)
- RCC, Unclassified (≈ 0,7- 5%)(36-39)

1.4.3. TNM-Classification

The term stage describes the anatomical extension of the tumour and also the general involvement of the disease. The first staging system for RCC was introduced in 1958 by Flocks and Kadesky (40). Robson et al modified this staging system in 1969, also to include venous involvement of the tumor (41). This modified classification system still remains in use today. However, the correlation between the different stages and survival is not as good as between the stages in the TNM-system and survival. The TNM – system, which initially was considered to be too complicated in daily use, have been modified several times. The major

advantage of the TNM – staging system is the integration of different characteristics like tumor size, vascular involvement, lymph node metastasis and distant spread. The TNM-system came into use during the 1980`s, but especially after the 1997 revision by UICC (Union Internationale Contre le Cancer) (42), where the main change was the expansion of the T1 category from 2,5 cm to 7 cm in diameter, the staging system have consolidated its position as a significant prognostic marker both for time to progression and for survival (43-45). In 2002 the most recent update of the TNM- system was published (46). The confirmation of the 1997-edition optional subdivision of the T1 – stage was the only change. At present, there is an ongoing debate on how to classify adrenal involvement. Most authors, based on their materials, seems to support a separate category within the TNM-system for adrenal involvement (39;47;48). Both T4a and M1a have been proposed as term for the new category.

Based on the TNM-classification, every tumour can be assigned to one of the four stages (I-IV), which are widely used for prognostication.

An overview of the TNM system in renal cancer is showed in the Appendix, table 1 and 2. Stage is the single most valuable prognostic factor for predicting outcome of RCC (49).

1.4.3. Classification of nuclear grade

In spite of problems regarding both definitions of each grade and interobserver/intraobserver reproducibility (50), the four-grade system published by Fuhrman et al. (51), still are the most commonly used grading system for RCC. Better reproducibility seems to be achieved if the Fuhrman system is turned into a two-grade system (50).

1.5 Diagnosis and Pre-treatment evaluation

1.5.1. Symptoms

Traditionally, the classic triad of renal cancer have been flank pain, gross hematuria and a palpable tumour. This full combination is today seldom seen in the everyday clinical practice (52). In the last decade there has been a steady increase in the number of incidentally detected tumours (IRCC). In 1971 Skinner et al reported 7 % IRCC (53), today there are reports demonstrating a increase from 10 to approximately 50 % IRCC (16;54). Some authors have even reported over 60 % IRCC (52;55). As a group, patients with IRCC have better prognosis than those with symptomatic RCC (SRCC)(14;16;54). Patients with local symptoms (hematuria, flank pain) have been reported to have a better prognosis compared to patients with general symptoms (fever, weight loss, fatigue) (56).

1.5.2. Imaging

Due to the increasing number of IRCC, renal tumours have been nicknamed “the radiologist’s tumour”. Over the last 2 decades the imaging techniques and possibilities have changed enormously. From RCC detection by using I.V. urography and final diagnosis made by selective renal angiography in the 1970`s to US, CT and MRI today.

1.5.2.1.CT

CT is the single most important tool in diagnosis and pre-treatment planning of RCC. Today the standard procedure for diagnosis of RCC is a triphasic acquisition by a helical CT-scanner (57). The three phases are plain pre-contrast, the corticomedullary phase and the excretory phase. Until recently, there have been problems in staging correctly by means of CT. The ability to show perinephric fat invasion has not been good enough. By use of modern high-resolution Multidetector CT (MDCT), this ability has improved (58). This technique also has increased the diagnostic ability to detect enlarged lymph nodes.

By using reformations of the voxels obtained by MDCT, the anatomy of the patient can be shown in any plane or in 3-D (59;60). Due to this technology, CT now gives excellent information of venous involvement of the tumour. Furthermore, 3-D MDCT arteriograms are used in the planning of tumour resections (61;62).

1.5.2.2.MRI

MRI is not used as the primary tool in diagnosis of RCC. The modality has many of the same possibilities as MDCT. It is mainly used in cases of allergy to contrast necessary to CT. For high caval and/or intrahepatic tumour thrombus MRI might be the investigative tool of choice (63).

1.5.2.3.Ultrasound

The main role for US is for the initial diagnosis of a renal tumour. In order to detect kidney tumours < 3 cm, US has a sensitivity of 80 %. However, usually 1.5 cm is the smallest to be detected in ordinary investigations (64). After a positive US, further triphasic investigation by a helical CT scanner is the rule.

In NSS, there is an intraoperative role for US. US is helpful both in the planning of the tumour resection and to make certain that small additional tumours is not present (65).

1.5.2.4.Other radiological imaging techniques

Intravenous urography has been abolished as a tool for detection of RCC. The sensitivity of this method is reported to approximately 67 % (64). Selective renal angiography is no longer in routine use, but remains as a tool for embolization in order to reduce bleeding and pain from RCC in patients not suitable to surgery (66).

1.5.3. Pre-treatment evaluation

In addition to symptoms and the results of the radiological investigations, pre-treatment evaluation also includes a carefully review of the patients past medical history (including other primary cancers) and a physical examination. From this,

ASA-Status and Performance Status (PS) (Karnofsky, ECOG (Eastern Collaborative Oncology Group)(67)) should be assessed in all patients. PS have been shown to be an independent prognostic factor in RCC (44;68). If cytoreductive surgery in MRCC is planned, this is especially important as short-term mortality rates are closely connected to these parameters.

Blood tests like ESR, CRP, Serum-calcium, haemoglobin and alkaline phosphatases are prognostic. The latter three, however, are connected to metastatic disease (68-70).

The lungs are the most common sites (68) of metastasis a preoperative chest X-ray seems indicated. Some centers, however, uses chest-CT in their preoperative evaluation (71).

Routine bone scan in RCC patients is not necessary when no symptoms of skeletal metastasis are present (72-75).

Tumour biopsy is not a routine part of the pre-treatment investigations. Biopsy, however, should be performed in cases where surgery seems to be impossible. This is in order to make the diagnosis certain, and also not to miss the diagnosis of a lymphoma.

1.6 Treatment of RCC

Surgery is the only known cure for RCC. Since the work of Robson (41), the radical nephrectomy has been the standard treatment for RCC. In the later years, NSS and mini-invasive treatment modalities have gained increasing popularity.

1.6.1. Localised RCC (T1-T3a)

1.6.1.1.Radical Nephrectomy

1.6.1.1.1 Operative technique

Traditionally open radical nephrectomy (RN) included early vascular control, removing the kidney with intact Gerotas fascia (including ipsilateral adrenal gland) and lymph node dissection (LND).

The combination of the size and location of the tumour and the patients' body characteristics determine the surgical approach to the kidney. The transperitoneal approach is mainly done via a midline or an anterior subcostal incision (76). The postoperative ileus and possible later intraabdominal adhesions are the disadvantages of the transabdominal approach. Thoracoabdominal approach is seldom used, and only if there is a large upper pole tumour. In the Nordic countries, with the exception for Finland, transabdominal approach is the most frequently used (77).

In the later years, several reports have questioned the necessity of the ipsilateral adrenalectomy. The reported frequency of adrenal involvement is 2,8-7,1 % (39;47;78;79). The current opinion today is only to perform adrenalectomy if preoperative CT and intraoperative findings by the surgeon cannot rule out the possibility of adrenal involvement (39;47;79).

The cost-benefit of LND also has been questioned. If no pre- or intraoperative suspicion of metastasis are present, only 2-3,3 % of the extensive LND will reveal metastatic disease (80;81). Today, LND in patient with no clinical evidence of enlarged lymph nodes, is not standard procedure (82). It does not improve overall survival (83). Enlarged lymph nodes should be removed completely. A large

proportion of these will show only inflammatory enlargement (84). Patients with lymph node enlargement on CT should therefore not be considered inoperable.

Extensive LND, however, might have justification in a subset of young patients with lymph node metastases only and are planned for immunotherapy, and there have also been proposed protocols for when to perform this procedure (85).

1.6.1.1.2 Intraoperative complications

The two most common intraoperative complications are splenic injury and haemorrhage. Reports on intraoperative blood loss vary. Most of the bleeding occurs because of damage to the veins. Bleeding from the suprarenal vein, collateral pathologic tumour veins or lumbar veins are most common, in addition to the VCI and the main renal vein. Transfusion rates vary in different reports. Overall transfusion rates are reported in 16-77 % of the operations (76;86-88). However, for low stage tumors (T1-T3a), this frequency is considerably lower (87). High ASA-status patients more often need transfusions (89).

Splenic injuries are not uncommon in connection with left RN, and reports estimate this to occur in 1,3-24 % (76;90-94).

1.6.1.1.3 Postoperative complications

Postoperative complications occur in 15-30 % after RN (76;88). These may be divided into those requiring surgery and those that do not.

1.6.1.1.3.1. Reoperations

Few updated reports on reoperations after RN have been found. Reoperations seem to occur in 0-3 % (76;88;95). Most of the reports are single institutional series. Bleeding, gastrointestinal complications and wound infections are the most common causes for reoperations.

1.6.1.1.3.2. Non-surgical complications

Pulmonary infections are the most common non-surgical complications (76). Paralysis of the intestines due to the transabdominal approach, and surgery in close

connection with the diaphragm, probably are the main reasons for decreased ventilation of the lungs. Acute myocardial infarction and other vascular incidents are complications seen at regular intervals (88).

1.6.1.1.4. Perioperative mortality (30-days mortality)

Perioperative mortality has decreased over the last decades. Skinner reported an 5 % overall mortality in nephrectomy for RCC in 1971(53). In the later years, single-institution series often publishes smaller series with no or very low mortality rates (0,2 – 0,6 %) (76;88). In contemporary studies from Iceland, USA and England, taking closer look at perioperative mortality on a national level, the overall mortality rates are 2,1 – 3,0 % (96-98). There are also studies showing that a higher surgical volume decreases intrahospital mortality (99).

In regard to cytoreductive nephrectomies before immunotherapy, careful considerations should be done before surgery, due to higher mortality rates in this group (see Ch 1.6.3.1.). For special subgroups like tumours with vein invasion see Ch. 1.6.2.1.1.

1.6.1.2.Laparoscopic Radical Nephrectomy

Laparoscopic RN (LRN) introduced in 1991, either by the transabdominal or the retroperitoneal route, has gained popularity over the last decade. In many centres, it has replaced open RN for T1-2 tumours < 10 cm. The indications are similar for open RN and LRN. LRN in very large tumours and tumours with known vascular involvement still are considered experimental (100;101).

The oncological principles in LRN regarding vessels, Gerotas fascia, adrenals and lymphadenectomy are similar to those applied in open RN. The main benefit of LRN is a more rapid recovery after these operations. Shorter hospital stay, less postoperative pain and a shorter time to convalescence for the patients, have all been demonstrated in published studies (102-104). The operative time and the learning curve are longer in LRN (104). By use of the hand-assisted method, the results regarding these parameters may be improved. Generally, LRN are reported to have

less postoperative complications than open RN. The definition of complications vary between studies, but 13 – 38 % are reported (103-106). Some studies also claim that LRN is especially well suited for patients with high ASA-scores (107) or obesity (108).

A long term result in regard to survival is however, the most important measure of the treatment of RCC. These data are not yet fully available for LRN. So far, however, all indications seem to support the current opinion that LRN and open RN are equal in regard to cancer control (104;109-111).

1.6.1.3.Nephron-sparing Surgery (NSS)

1.6.1.3.1 Indications

The indication for NSS may be split into imperative, relative and elective (table 2). In the imperative group, where RN would lead to renal failure and dialysis, NSS is the procedure of choice. In patients with a normal contralateral kidney, however, and preservation of the total renal function is the aim, the role of NSS vs. RN is still disputed.

The occurrence of metachronous tumour in the contralateral kidney and the aim of decreasing the risk of renal insufficiency after the operation are the most often used arguments for NSS. Both these are debatable. Metachronous contralateral RCC occurs only in 1-2 % and most of them can be treated with NSS when they are diagnosed. Ljungberg et al. demonstrated that during a 10-year follow-up period, patients treated with RN and normal preoperative serum creatinine, only rose slightly in serum creatinine levels and did not deteriorate further in renal function over the years (95). However, in opposition to this study, several others have documented less risk of renal insufficiency after NSS compared to RN (112-114).

Among other arguments, supportive of NSS, is a study claiming better quality of life among patients with more renal tissue (115). Further, the increased risk of later other malignant tumors in RCC patients, which might need treatment requiring good renal function, is supportive of NSS (116-118).

The drawbacks of NSS are the risk of not being radical at the operation as well as the risk of local recurrences. Preoperatively, patients may be understaged. Small tumour

Table 2

Imperative indications
Tumour in solitary kidney
Bilateral tumours
Multifocal tumours in patients with hereditary RCC
Relative indications
Contralateral kidney with impaired function
Factors predisposing for renal insufficiency (Diabetes mellitus, nephrosclerosis), especially in younger patients
Elective indications
Incidentally discovered tumor ≤ 4 cm, with a normal contralateral kidney

thrombus in the renal vein is often not seen on CT-scans. Further, small tumours < 3 cm grow invasive in 18 % of the cases (119). A careful preoperative planning is therefore necessary in NSS. 3-7 per cent local recurrences are reported after NSS (120-123). This is probably mostly due to multifocal tumours (124), and not to inferior surgical techniques.

Despite the local recurrences, overall and cancer specific survival after NSS is comparable to RN (112;125).

1.6.1.3.2 Surgery and Complications

This procedure is usually performed via an extraperitoneal flank incision. The kidney is mobilised within the Gerotas fascia, but with leaving the fat over the tumour in place. Early vascular control should be achieved, the kidney cooled and then the tumour should be excised with free margins. Intraoperative US and frozen sections

are helpful in securing the tumour excision. Haemostasis and closing of the collecting system should be carefully done (125;126).

Complication rates have been reported higher in NSS than in RN (119). Especially bleeding and postoperative urinary leakage, have been reported as relatively common (125).

1.6.1.4.Laparoscopic Nephron-sparing Surgery

Laparoscopic NSS (LNSS) is increasing in popularity. Many published reports have demonstrated the efficacy of the technique (127;128). In order to achieve these results, an operative technique as similar to open procedure as possible should be used (129).

So far, the laparoscopic approach is associated with longer warm renal ischemia time, more major intraoperative complications, and more postoperative urological complications (130). Therefore, open NSS remains as the gold standard at this point of time, and LNSS should be performed only in selected patients.

1.6.1.5.Mini invasive techniques

The aim of these modalities is to destroy the tumour, and at the same time preserve as much renal parenchyma as possible. They are still to be considered as experimental and the results have to be compared with the standard care. They might, however, be an option in selected groups of patients like elderly or patients with decreased renal function and high surgical risks.

1.6.1.5.1 Radiofrequency ablation (RFA)

This procedure might be done percutanously. The RFA-needle is placed in the tumour under image control. The procedure is quick and simple to perform. A few and small series are published. From 79-100 % complete destruction is reported (131-134). However, in one report persistent viable tumour was found in 7/11 tumours after treatment (135). Procedure related complications are few and the treatment was generally well tolerated (131;132).

1.6.1.5.2 Cryoablation

This procedure may be performed laparoscopically or percutanously. The tumour is frozen by use of a cryoprobe. Few long-term results are available. Gill reported 98 % cancer specific survival after 3 years 56 patients (136). Complication rates are low (11 %), and most were minor (137).

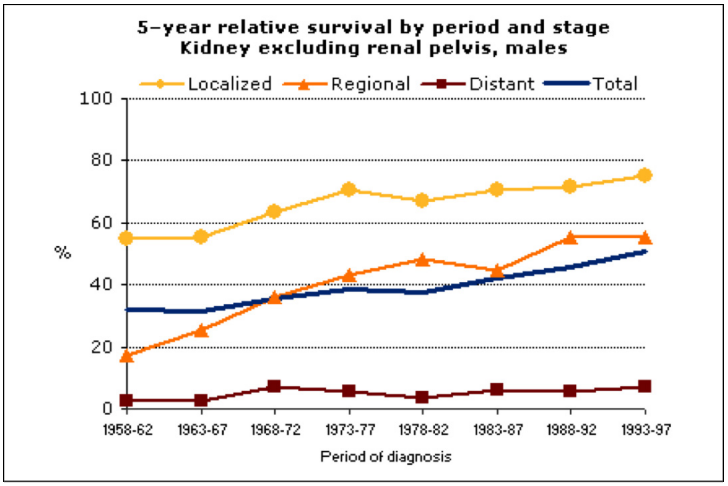
1.6.1.5.3. Other

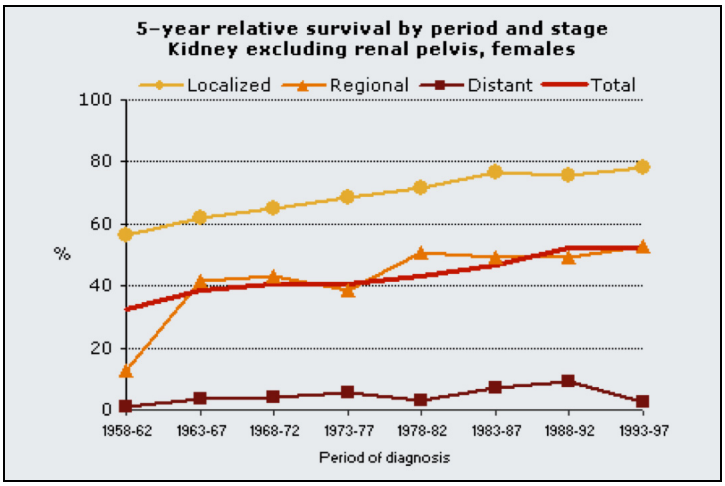
High-intensity focused ultrasound (HiFU), microwave thermotherapy, laser interstitial thermal therapy and intracavitary photon radiation are all modalities, on which there are experimental studies.

1.6.1.6.Survival

Five-year CSS in localised RCC in Norway is ≈ 80 % (Fig. 2). The survival has increased over the last decades.

Figure 2. (From the Cancer Registry of Norway) (15)





Internationally reported CSS for RCC in regard to the TNM-system demonstrates for Stage I tumours 5-year CSS is between 90-95 % (43;44;49;138;139). For Stage II it is lower and has been reported to be 71-89 % (43;44;49;138-141). For stage III, the figures are 37-67 % (43;44;49;138).

1.6.2. Locally advanced Tumours (T3b – T4)

The locally advanced tumours include those with invasion beyond Gerotas fascia and those with tumour thrombus formation. They generally have poorer prognosis, and special care should be taken during the treatment planning.

1.6.2.1.Tumour thrombus into the Renal Vein, VCI and Right Atria (T3b-c)

The tumour thrombus (TT) is one of the special characteristics of RCC. A TT is present in 4-10 % of the cases. The classification of TT in Renal Cell Carcinoma is given in table II, appendix 1.

Of patients with TT, in ≈ 90 %, the TT has the highest level below the diaphragm. Thus, ≈ 10 % reaches above the diaphragm, and of these, 2/3 reaches into the right atria.

Of the TT patients, 25-63 % have either lymph node (N+) or distant metastases (M+) (142-146). Further, of the N0M0 patients with TT, 22-60 % have tumour invasion into perinephric fat or the renal hilum (142-146). The remaining ≈ 25 % have a good prognosis and can be treated with curative intention.

Patients with TT generally have a poorer PS than patients without (146).

1.6.2.1.1 Surgery for TT in RCC

The basis for the operation is the radical nephrectomy, often in co-operation with other specialists. Different approaches in order to gain access to the highest level of the thrombus have been described (147). Further description of these methods is beyond the scope of this introduction.

The morbidity and mortality rates in these operations are higher, and reflect the more complex surgery performed. Complication rates of 20-30 % and perioperative mortality rates of 3-8 % are reported in contemporary reports (142;145;148).

1.6.2.1.2 Survival

T3b-cN0M0 5-years survival after operation is 39 – 68 % (142-146). Without invasion of perinephric fat or the renal hilum, the survival increases (146). If the patient is N0M0, the level of the TT is of little significance to survival rates. After operation for TT in the right atria, 5-year survival has been reported to reach 56 % (149).

For T3b-cN+ with or without M1 the 5-year survival rates are 14 – 27% (146).

1.6.2.2.Tumour invasion of adjacent organs (T4)

Few and very small series (7-15 patients) are reported, mostly from Japan (and in Japanese) (150-152). In most cases patients with T4-tumours also have lymph node and /or distant metastases (50-75 %). The colon, the spleen and the pancreas are the most frequently involved other organs. Prognosis is poor both in regard to short and long term survival (92). This is major surgery, and should be offered only in highly selected patients.

1.6.3 Primary metastatic RCC

Historically, approximately 1/3 of patients with RCC has been diagnosed with metastases (13). In the years to come, this fraction is supposed to decrease due to the stage migration. However, the absolute figures seem to increase also for this group. As shown by Ljungberg (68), this group in general has a poor prognosis. Median cancer specific survival for this group is 7 months. The 5-year survival rates are reported to be 0-20 % (13;68;153). In selected materials, after treatment with immunotherapy, 3-year survival rates have reached 30 % (153). PS, number of metastases and localisation of metastases influences on the patient selection for this type of treatment. Eighty per cent of RCC metastases are multifocal and 40-50 % limited to one organ (68). The lungs are the most common metastatic sites, and together with bone the most frequent location of solitary metastases.

1.6.3.1 Immunotherapy

Immunotherapy, like Interferon-α (IF-α) and Interleukin-2 (IL-2) has been used in MRCC over the last 20 years. IF-α has been shown to give overall response rates of approximately 8 - 26 %, with a complete response in 2-7 %. The long-term response, however, is poor with a median time to progression of 10 months (154). For IL-2 the response rates are 7-23 %, of which 1/3 is complete, and the duration of the response is 12-19 months. Combination of IF-α and IL-2 does not give higher response rates (154). The primary tumour when the patient is diagnosed with MRCC, shows little response to immunotherapy. An overall response rate of 6-12 % is reported (155;156).

In earlier years, cytoreductive nephrectomy was performed to relief patients of symptoms from the tumour. Recently, it has been shown that cytoreductive nephrectomy prior to immunotherapy significantly prolongs the survival of patients eligible for this treatment. Two randomised studies have confirmed this (157;158). The overall survival benefit was 3-10 months.

However, great care should be taken when selecting patients for this combined treatment. Bennett et al. (159) reported in 1995 their experience with cytoreductive nephrectomy before immunotherapy. They reported a 50 % complication rate, a 30-days mortality rate of 17 % and 77 % of the patients could not receive the immunotherapy. This paper highlights the necessity of strict patient selection criteria.

The well known spontaneous regression of metastases after nephrectomy in MRCC, have been documented to occur in 4,4% % of the cases in a study from National Cancer Institute (160). It occurred only if the metastases were located in the lungs, and the mean duration of the regression was 24 months. This rare phenomenon does not justify cytoreductive nephrectomy if later immunotherapy is not planned. Laparoscopic cytoreductive RN may evolve as the treatment of choice in selected patients due to the shorter time to convalescence (161).

1.6.3.2 Metastasectomy

RN and metastasectomy should be considered when a solitary metastasis is present at the primary diagnosis of RCC. 5-year survival rates of 20-35 % can be achieved (162). The survival rates after treatment for synchronous solitary metastasis is lower than for later solitary recurrence (162).

1.6.3.3 Palliation

In cases of primary MRCC, a good palliative care is fundamental. Interventions like radiation of painful bone metastases, orthopaedic treatment of pathological fractures and intra-arterial embolization (66) belong to this group. Further, good co-operation with anaesthesiologists and palliative care units are essential to urological departments treating MRCC patients.

1.6.4 Recurrence after primary radically treated RCC

Between 25-40 % of radically treated RCC will recur. Fifty per cent recurs within 2 years, and 75-85 % within 5 years (49;163;164). There is, however, a 10 percent risk of recurrence after a disease free interval of 10 years (165). The lungs are also the most common sites of recurrent disease, and the majority of recurrences are multifocal. The median survival is less than 1 year in most reports. For patient with good prognostic factors, substantial survival can be expected. The stage migration hopefully will lead to a drop in recurrences.

1.6.4.1 Surgery for recurrent metastases

In cases of solitary recurrences, higher 5-year survival rates are reported than for synchronous metastases. Survival rates after 5 years are 39 and 22 %, respectively (162). Whether or not the lesion is completely resected is important. Kavolius demonstrated this with a 52 % survival in the totally resected group and 29 % in the rest (166). Best results are seen after removal of pulmonary metastases (162;166). The surgical treatment of solitary metastases is today recognised as a part of the treatment, surgery in cases of multiple metastases has a more limited role. In the majority of reports multiple metastases have poorer survival than

solitary ones. However, some reports have stated that there is no real difference in the outcome of these two groups (167). Some authors have stated that immunotherapy in combination with or prior to surgery might improve the outcomes further (168). There are, however, few controlled trials on this subject.

1.7 Follow-up

The reason for follow-up protocols is to detect the metastases as soon as possible, in order to offer additional treatment.

Different types of follow-up protocols are known (49;163;164;169). They usually are based on pathological stage (pTNM), and are most intense during the first years after primary treatment. The usual investigations performed at follow-up visits are, physical examination, blood tests (serum creatinine, ESR, alkaline phosphatases etc.) and chest X-ray. For locally invasive tumours CT scan are done at regular intervals. This is also done after NSS due to the risk of local recurrences.

During the last five years there have been several attempts to stratify the risk of recurrences based on more factors than just pTNM (170;171). Belldegrun and co-workers at UCLA presented their UISS (University of California Los Angeles Integrated Staging System)-system in 2001 (172). In this system they combine TNM Stage, Fuhrman nuclear grade and ECOG PS (67). From these variables they stratify the risk of recurrence into high risk, intermediate risk and low risk. This system has been internationally validated and seems to be a good predictor for survival in localised RCC (71). Lam et al. have used UISS to publish a follow-up protocol for the individual risk groups (173).

2. Aims of the thesis

The major aim of this thesis has been to explore the field of diagnosis, treatment and outcome of RCC in the Norwegian community. No larger Norwegian study has investigated these parameters. Further, when this study started in the second half of the 1990`s minimal invasive treatment modalities were new and possible complications partly unknown. In addition, new imaging techniques were introduced during the last decade. With this background the aims of this study were:

- To look for the international trend named "stage migration" and the shift from symptomatic tumours to incidentally detected tumours in the Norwegian community. Further, to investigate any gender differences in detection and survival.

- To gain information about the indications for, complications to and outcome of open nephrectomy in a Norwegian community. Thus creating standards for future evaluation of minimal invasive techniques in the same environment.

- To investigate prognostic factors for and survival after recurrence of primary radically treated RCC. Further to use the information to create a follow-up regimen.

During the work with the material, we observed that many of the patients had or died from another primary cancer than RCC. Therefore during the study a new aim was added:

- To establish the frequency and types of second primary malignancies associated with RCC. In addition, to estimate the risk of developing and mortality of a second primary tumour after the diagnosis of RCC.

3 Patients and methods

3.1 Patients

The background material consists of 764 surgical interventions on kidneys at Oppland Central Hospital - Lillehammer[1] (n = 261) and Aker University Hospital (n = 503), Oslo between January 1, 1978 and December 31, 1997. A total of 646 nephrectomies were performed **(Paper II)**, 72 were kidney resections (174) and 46 were miscellaneous. 325 of the 646 had a RCC **(Paper II)**.

In **paper I, III and IV,** the last inclusion date for RCC at Lillehammer was December 31, 2000. The RCC material therefore consists of 368 consecutive patients treated for RCC with open radical nephrectomy at Oppland Central Hospital - Lillehammer (n = 177) and Aker University Hospital, Oslo (n = 191). There were 219 males and 149 females. The average age at nephrectomy was 64 years (median 66 years, range 15 – 90 years).

The present material represents approximately 5 % of the total number of RCC patients in Norway in the twenty year period 1978-97.

In **paper V** all new cases in Norway diagnosed with the ICD-7 four-digit code 180.0 – cancer of the renal parenchyma – in the years 1987 – 1993 was primarily included. These patients were retrieved from the main database at CRN. The completeness of the cancer registration in Norway is estimated to be close to 100 % (4). This is due to national law, which requires both clinicians and pathologists independently to report all new cases of cancer to the registry without patient consent. A total of 3.119 patients was identified and became subject to further investigation.

3.2 Data Collection

Papers I – IV: The data was obtained in a retrospective manner. All hospital records were manually searched for information of symptoms, preoperative evaluation, intra- and postoperative complications, perioperative mortality, histopathology reports, later recurrence and cause of death. Permission to create a database of these patients was granted from The Norwegian Data Inspectorate. If the cause of death (COD) was not found in the hospital records, it was retrieved from the Norwegian COD Registry at Statistics Norway (SSB). Permission to access these data was given from The Norwegian Board of Health.

At the time of initiation of the project, application to the regional ethics committee was not necessary.

The hospital records for patients alive have been searched several times during the study period and the data in regard to follow-up has been updated continuously with the final update April 1, 2003 (**paper IV**)

Paper V: The necessary data was retrieved from the Main Database at CRN. In order to avoid inclusion of nefroblastomas (Wilms tumour) and to secure an estimated life expectancy of 10-15 years, we excluded patients < 15 years of age and patients > 70 years of age. Patients with no histology verification of the tumour were also excluded. 1.425 patients were matched against the main database at CRN to find the patients with multiple primary cancers. In all cases of more than one primary tumour, manual check of original reports and histology reports were done to secure the diagnoses.

[1] Renamed Innlandet Hospital – Lillehammer in 2001

3.3 Data preparation

3.3.1 Tumour Staging

All patients were restaged according to the 1997 revision of TNM-system (175). **(Paper I, II, IV)**

The T-staging was performed by use of the histopathology reports, so all tumours have been assigned a pT – stage.

The N-status was also established in accordance with the histopathology report. However, in only a minority of the cases, a sufficient number (4-8) of negative nodes to establish pN0 were reported. Hence, > 90 % of the patients are pNx. The clinical N-status was obtained by combination of preoperative CT images of the abdomen and the peroperative findings. However, before the CT became available, clinical N-status was determined by the peroperative findings alone. During the whole study period, only enlarged regional lymph nodes have been removed, any type of extensive systematic lymph node dissection has not been performed.

The M-status at the time of operation was made of evaluation of preoperative CT-scans, chest X-ray and intraoperative findings. Chest-CT, BS, MRI and cavagraphy was only performed when indicated.

3.3.2. Incidental vs. symptomatic RCC

Renal cancer related symptoms include palpable tumour, haematuria (both macroscopic and microscopic), flank pain and signs of cachexia related to the disease. Incidentally diagnosed cancers were considered to be tumours discovered by investigations performed for other reasons than the symptoms mentioned above. Tumours discovered by investigation due to elevated ESR, without any other symptoms were also classified as incidental **(paper I)**. The symptomatic group was divided into those having classic urological symptoms (i.e. hematuria (gross and microscopic), flank pain and a palpable tumour) and those with general non-urological symptoms (i.e. cachexia, weight loss, skeletal pain etc.) **(paper III)**.

3.3.3 Performance Status Evaluation

Performance status (PS) at time of metastases detection **(paper IV)** has been established retrospectively. This was possible due to specific information in the records (i.e. "the patient is fully bedridden", "the patient is not physical capable of self-care" and "the patient is still working full hours without any symptoms of the disease"). However, classification was limited to good and poor PS. In **paper IV**, good PS corresponds to ECOG (67) groups 0 and 1, and ECOG 2-4 were classified as poor PS. For nine of the 89 patients with recurrence of the disease, PS could not be established**.**

3.3.4. Databases

Papers I – IV: All the collected data/ parameters were entered into a database. The database software Microsoft Access 97 was used for this purpose.

Paper V: For handling of the data from the database at CRN, the database software Corel Paradox was used.

3.4 Statistics

For comparison between groups of patients in regard to categorical data, *the Chi-square test* was used (**paper I, II, III, IV**). For comparison between groups of patients in regard to continuous data, *the t- test* (**paper I, III**) and the non-parametric *Mann-Whitney U-test* (**paper IV**) (176) was applied. For the use of t-test on continuous variables in **paper I and III**, the distribution of the material was tested for distribution, and was found to be close to normally distributed.

In the survival analyses the method of estimating survival described by *Kaplan and Meier* (177) was used. For comparison between groups in regard to survival, *the Log Rank test* has been used (176) (**paper I, III, IV, V**). Multivariate analysis was performed by the *Cox proportional hazard method* (176) (**paper II, IV**).

Standardized incidence ratios (SIRs) were used to estimate the risk of later primary cancers. SIRs were calculated as the ratio of observed number (ONo) and expected number (ENo) of cases. The expected numbers of cases were estimated by assuming that the patients in the cohort experienced the same cancer incidence as prevailed in the general population of Norway. By use of the Main Database of the Cancer Registry of Norway, tumour site-, gender-, time period- and age-specific rates were combined with the person-years at risk. Person-years at risk was accumulated for each person starting with date of diagnosis of RCC and ending with date of death, date of emigration or December 31, 2002, whichever came first. Statistical significance and confidence intervals (CI) were calculated under the assumption that the observed number of second primary malignancies follows a Poisson distribution (**paper V**).

A p-value ≤ 0.05 has been considered statistical significant

For the statistical analyses, the statistical software package SPSS (Statistical Package of Social Studies) versions 9.0 – 11.0 have been used.

4 Results

4.1 Paper I: *"Renal Cell Carcinoma: Gender difference in incidental detection and in cancer specific survival"*

The frequency of incidentally detected RCC increased from 21.1 % to 34.7 % between the first and second decade of the study. IRCC had significant more low-stage (I-II) tumours ($p=0.002$) and smaller tumour size ($p<0.0001$) at operation. Cancer specific survival was significantly better in the IRCC group ($p<0,01$).

The frequency of women were significantly higher in the IRCC group than in the SRCC group ($p=0.02$). Females had significantly more low-stage (I-II) tumours ($p=0.02$) and better cancer specific survival ($p=0.05$) than males.

4.2 Paper II: "*Nephrectomy – Indications, complications and postoperative mortality in 646 consecutive patients.*"

The results mentioned here are only those regarding the 325 RCC patients included in this paper.

Postoperative complications occurred in 60 of 325 RCC-patients (18.5 %), 1.5 % developed AMI and 5.5 % developed pneumonia postoperatively.

Reoperation was carried out in 3.1 % (10/325) of the RCC cases. Seven of 10 reoperations were due to bleeding.

Overall mortality rate (<30 days) was 3.4 % in the RCC- group. Of these, 1.5 % died of disseminated RCC and 1.8 % due to complications.

If metastases were known at the time of operation the mortality rate was 9.1 %, which was in contrast to 2.5 %, when the patient was presumed to be without metastases.

4.3 Paper III: *"Renal Cell Carcinoma – A retrospective study of 368 patients."*

IRCC constituted 29 %, 52 % had urological symptoms and 19 % had general symptoms.

2 % of the nephrectomies (4/201) on the left side were complicated with splenectomy.

The patients dying of complications were in median 13 years older than median of the total material (79 years vs. 66 years). Most of the deaths occurred in the early part of the study period.

Five years cancer specific survival rates for the four TNM-stages were: 92 % for stage I, 83 % for stage II, 67 % for stage III and 16 % for stage IV.

Within stage I, and if tumour size was smaller than 3,5 cm, no cancer related deaths occurred. No difference between transabdominal and retroperitoneal surgical approach in regard to cancer specific survival was encountered.

4.4 Paper IV: *"Presumed radically treated renal cell carcinoma: recurrence of the disease and prognostic factors for survival."*

Of the patients presumed to be radically treated, 29 % developed metastases, with a median time to recurrence of 25 months.

Within 5 years, 80 % of the metastases were detected with the lungs as the most common site. 35 % of the recurrences were diagnosed as a result of routine follow-up.

Median CSS after recurrence was 10 months. For patients with a DFI ≥ 24 months the median CSS was 35 months.

In a univariate analysis PS, DFI ≥ 24 months, metastases in a single organ, primary tumour size ≤ 70 millimetre, primary tumour stage = pT1-2 and age < 65 years were all associated with a better survival.

In multivariate analysis PS, DFI ≥ 24 months and number of organs affected by metastases were independent predictors for survival.

4.5 Paper V: *"Multiple primary malignancies in patients with Renal Cell Carcinoma. - A national population-based cohort study."*

Of the 1,425 patients, 16.0 % had one, 1.6 % had two, 0.2 % had three and 0.07 % had four other primary malignancies.

34.8 % of the other tumours were diagnosed antecedent, 18.7 % synchronous and 46.7 % were diagnosed subsequent to the RCC.

Cancer in the prostate, bladder, lung, breast, colon and rectum, malignant melanomas (MM) and Non-Hodgkin lymphomas (NHL) were the most commonly encountered other malignancies.

The observed overall number of subsequent other malignant tumours was 22 % higher than the expected number. The observed number of subsequent tumours was significantly higher for bladder cancer, NHL and MM.

The estimated 15-year cumulative risk for RCC patients with no previous or synchronous other malignancy for developing a later second cancer was 26.6% in men, and 15.5% in women. This difference was statistically significant (p=0.04).

Patients with antecedent or synchronous other cancer had significantly poorer overall survival than those without.

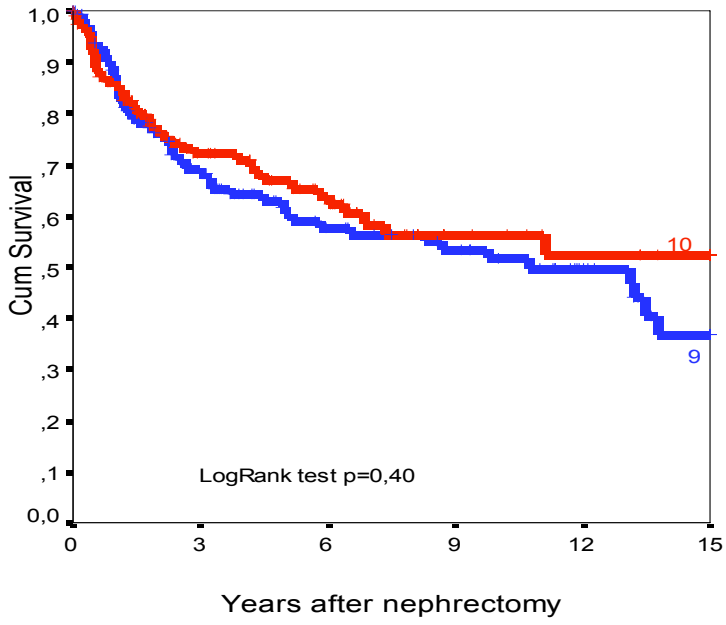
4.6 Previously unpublished data

In the following section we are reporting unpublished data that will deepen some aspects of the material.

In addition to the RN`s in the period 1978-97, 5 RCC patients were treated with partial nephrectomy. The tumours were 20-40 mm. Two were T3A and three were T1. One patient with T3A-tumour was M+ (solitary) at diagnosis. The four N0M0-patients were all alive more than 9 years after their operation. Furthermore, 5 patients with RCC were surgically explored, but not nephrectomized. This was due to local invasion. These patients were all dead at median 4.5 months (range 1-9 months) postoperatively. These tumours were from 9-20 cm in diameter.

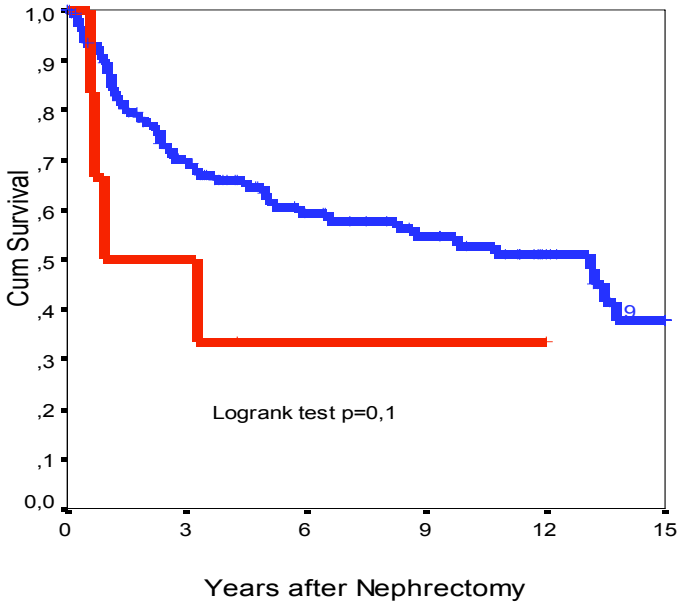
In 254 patients there is information about adrenalectomy, and in 114 patients there are not. Adrenalectomy was performed in 134 patients and was not in 120. There was no significant difference between these two groups in regard to the distribution of stages, tumour size or surgical approach. There is no difference in survival between these two groups **(Figure 3)**.

Figure 3. CSS for RN-patients with adrenalectomy (Blue) and without (Red)



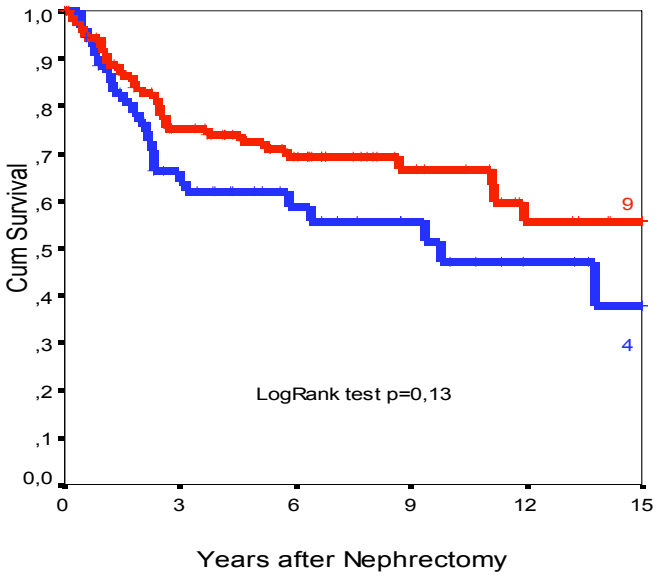
Involvement of the adrenal gland was found in 6 of the 134 patients (4.5 %). Three of these were dead within the first year after RN.

Figure 4. CSS for patients with adrenal involvement (Red, n=6) and without (Blue, n=128)



In **paper III**, we reported that T3A tends to have better survival than T3B. The figure was not printed. 5, 10 and 15 years CSS was 72 %, 66 %, 56 % and 62 %, 51 %, 38 % for the two stages, respectively. Figure 5 shows the Kaplan-Meier estimates.

Figure 5. CSS for pT3A (red, n=94) and pT3B (Blue, n=54)



5 Discussion

5.1 Patients and methods

This study **(papers I-IV)** consists of 368 consecutive patients. There have been almost no selection of patients and due to the health care system in Norway in the years of this study there is only limited referral bias. The study therefore gives a true picture of the variety of RCC within the local areas of these hospitals.

The nature of the study **(papers I-IV)** is retrospective. This form of study clearly has limitations. Especially in regard to the kind of data possible to extract from hospital files. However, the advantage of the study form is the possibilities of a long observation period and to use an open mind and discover new and unknown relations and by this create hypotheses for new studies.

Paper V utilizes a national 7-year cohort in order to avoid selection and bias.

5.1.1. Tumour Classification

The most obvious criticisms of this study are the lack of information regarding tumour subtype and tumour grading **(Paper I, III, IV and V)**.

Regarding subtypes, these came first into practical use in the late 1990`s, and therefore it is not included. In a review article, Ljungberg states that RCC subtype is not an independent prognostic factor in regard to survival (178). This has been confirmed by Patard (179). Furthermore, most of the studies we compare with in regard to long-term survival do not split their materials into these categories (43;49;138;139). New follow-up studies should include the use of subtyping.

Tumour grade is an important prognostic variable in regard to survival. The problems connected to inter- and intraobserver reproducibility make it somewhat difficult to take this classification into use. Some studies identifies grade to be an independent prognostic factor (180;181).

5.1.2. N- and M-Staging

A retrospective study might have several disadvantages, and in this study the accuracy of the N and M-staging used in **Paper I, III and IV** might be questioned. However, as discussed in Ch. 1.6.1.1.1, the probability for finding lymph node metastasis when there is no pre- or peroperative suspicion is very low (2-3,3 %), even if extensive lymph node dissection is carried out (80;81). Removal of only enlarged or suspicious nodes, as was done, seems to be in line with recommendations (82).

Preoperative investigation in order to find asymptomatic metastases differs from one institution to another. Some centres use chest-CT preoperatively in all patients, and BS and brain CT on all patients with MRCC. Others use Chest X-Ray, and BS and brain imaging only when the patients are symptomatic (71). Routine BS in patients without symptoms from the skeletal system is probably not worthwhile (72-75), and has not been performed in asymptomatic patients at the hospitals in this study. Chest X-ray has been used throughout the whole study period and CT of the kidney and the surrounding areas since its introduction in the early 1980`s. These investigations will in our opinion identify pulmonary and liver metastases, which together with the skeleton are the most common metastatic sites (49;68;163;164;182).

Hence, according to arguments above, the accuracy of our primary N- and M-staging in this study seems trustworthy.

5.1.3. What is an incidentally detected tumour

The major problem when discussing IRCC and SRCC **(Paper I and III)** is to define real and uniform criteria's for classifying the RCC as incidentally discovered. The varying definition of IRCC from one report to another, make comparison between different materials difficult. Lee and co-workers (16) defined incidental presentation as *" ...renal tumor detected during evaluation or surveillance of an unrelated medical condition"* and Patard and co-workers (54) used *"...those totally asymptomatic and discovered by US, CT or any other radiological imaging examinations that were requested after the patient reported complaints not associated with the usual renal tumour signs or symptoms"* as their definition. Another example

by Luciani and co-workers (183): *"... when identified during investigation for unrelated diseases or routine examinations in otherwise healthy people"* further expands the range of the different definitions. In most cases these definitions cover the same patients, but there are some areas where there are problems in regard to whether the detection is incidental or not. Elevated ESR in a totally asymptomatic patient at a routine health examination is an example. Gudbjartsson et al. (13) defined it as an incidental finding, and also according to the definition above by Luciani et al. (183), it should be regarded as incidental. On the other side, Homma see this as a marker of symptomatic disease (55). Microscopic haematuria at urinalysis at a routine health examination is another example.

In order to compare different materials, it is therefore necessary to first see if the definitions of IRCC go well together. There is a need for a common international consensus about which tumours that is to be categorised as incidental.

Our definition of IRCC is shared by some authors and is different from that of others. In regard to IRCC, the strength of this study is the long inclusion period. This has provided the possibility of demonstrating differences in detection of IRCC over time.

5.1.4. Population based study vs. hospital based study

In **paper V**, we had the possibility to use our material from the two hospitals, and explore if there really was an overrepresentation of second primary malignancies within. After discussion, we decided to use a national cohort, because population-based studies have the advantages of larger groups of unselected patients and longer follow-up.

This allows for more stable estimates of SIR's, and the same population may be used for calculation of expected number of cancers. Biases with regard to geographical factors, local environmental factors or referral patterns are not likely to affect the results.

A national registry like the Cancer Registry of Norway also has the advantage of a uniform practice regarding reporting and coding. Some authors have pointed out that

hospital series may have advantages over population-based series. They are claimed to be more accurate in regard to tumour stage and pathology reports as well as having better follow-up data, thus potential sources of bias may be discovered (118). However, by manually checking all clinical and histopathology report forms, we have tried to eliminate registration errors, and ensure the quality of the data set so that it resembles the data available at the hospitals. Few registration errors were encountered during this procedure. Data derived from a national cancer registry has the advantage of including all reports on malignancies from all treatment facilities in the country, thus eliminating loss to follow-up or ascertainment of other tumours. In conclusion, we are of the opinion that the method used in this study gives the so far best estimate of the occurrence of multiple primary tumours in patients with RCC.

Regarding the SIR`s established in this study, it should be kept in mind that these are low estimates. The observed figures (ONo) are checked thoroughly as described in previous sections (biopsy verified, manually checked forms etc.). However, the expected figures (ENo) are estimates based on all the reported cancer cases to the main database at the Registry. The observed figures would have been relatively higher compared to the expected ones if the same criteria had been applied to this latter group.

5.2 Results

5.2.1. Incidentally detected tumours

The results **(Paper I and III)** demonstrate the increase in IRCC between the two decades of the study. This increase is in line with most reports, and they all refer this increase to the more widespread use of new an better imaging techniques (11;12;16;56). In contradiction to our expectations we discovered increase in IRCC between the two studied periods within the three higher stages, but not in stage I. No complete explanation can be given for this, but we find our percentage of stage I IRCC in the 1978-87 material remarkably high.

One of the results that need comment is the finding of higher average age in the IRCC group than in the SRCC group (67 years vs. 63 years) **(paper I)**. Since IRCC tumours in general are smaller and of lower stage, demonstrated by **paper I** and others, the natural thought would be that the tumours were detected earlier and, hence, the average age should decrease.

If tumour detection was the result of population screening and the incidence was stable, the average age probably would go down. However, our study is not a population study and older people in general have more health problems. In this Norwegian material, where patients had to be referred to investigation by their general practitioners (GP) due to some kind of health problem, the result is a higher average age in the IRCC group. The finding of higher age in the IRCC group is confirmed by other reports (14;16;183).

In the discussion of **paper I**, we ascribed the increase in mean age to the fact that we now detected tumours that before the introduction of US and CT never were detected. This suggestion was based on previous reported autopsy series. Hellsten and co-workers (184) in their 1958-69 autopsy series showed that only one third of RCC present at autopsy, had been detected before death. Of the 2/3 unrecognised RCC, 80 per cent died with the disease rather than of the disease. We assumed that detection of tumours from this pool of patients explained the increase in IRCC among the elderly. A recent publication by Mindrup and co-workers, however, found only a minor and not significant decrease in number of previous unsuspected RCC found per 100 autopsy in the 1990`s compared to the 1950`s (0.72 vs. 0.91) (185). This report implies that there has to be a real increase the incidence of RCC also among older people beside the increased use of US and CT.

IRCC-tumours are well documented to be smaller and of less malignant potential than SRCC, this gives rise to the question of over-treatment of small tumours in the elderly patients.

This question also arises when authors report that in tumours < 3 cm metastatic disease very seldom occur. In 40 patients with observation time of median 3.5 years,

no metastatic disease has been seen (186). This is somewhat in contradiction to the fact that a relatively large portion of these small tumours have an invasive growth pattern (119).

Still surgery is the recommended treatment, but the minimal invasive treatment modalities (Ch. 1.6.1.5.) may prove to become a real improvement and decrease treatment morbidity for these patients.

As the numbers of incidentally detected renal tumours increases, more and more of the removed tumours turn out to be benign. In our material **(Paper I)** only 2.9 % (10 of 349) renal tumours were benign. In studies, 22 - 33 % of smaller renal masses (< 4-5 cm) suspicious of RCC have turned out to be benign (187;188). NSS should therefore be considered in smaller renal tumours, and especially in those which deviate from the usual picture of RCC.

The higher survival rates among IRCC patients **(Paper I, III)**, is by most authors ascribed to the smaller size of tumours and lower stages/grades among these patients (14;54;183). The significant difference found in our study between IRCC and SRCC (5-year CSS 81 vs. 62 %) is line with other reports (14;16). A difference between the individual stages of the two groups was observed, but was not significant **(Paper I)**. The observed benefit in survival seems to be a result of the stage migration.

5.2.2. Gender difference in detection and survival in RCC

From different official reports we know that women use the health care system more often than males (189;190). In 2002, 78 % of women in Norway had seen their GP, for males the figure was 71 % (191). This gender difference is internationally verified and described in a review article by Malterud & Okkes (192). From investigations of Norwegian general practice in the 1980`s, we know that women fear cancer more often (193), that cancer is more often suspected by the GP in women (194) and that cancer is only diagnosed in less than 1 of 10 suspected cases (195).

These latter studies are performed before US and CT became so easily available. The probable cause of the higher frequency of women among the patients with IRCC

(Paper I) is that due to their demonstrated more frequent use of the health care system, they are investigated more and resulting in a higher detection rate of IRCC. Significant higher proportions of women in the IRCC group are also demonstrated in other reports (14;16).

Of interest is that the same overrepresentation of women is present in clinical detection of adrenal incidentalomas (196;197). No such gender overrepresentation has been encountered in previous autopsy studies. Hence, it is supposed to be result of the more widespread use of imaging in women (196).

In **paper I**, a better CSS for women than for men was found. This is probably due to more low-stage tumours and the higher proportion of IRCC among women. In their studies from 2002, both Onishi and Lee demonstrated a similar trend in regard to better survival for women (16;198).

5.2.3. Complications

The overall complication rate (18.5%)**(Paper II, III)** in this study is in line with other reports (Ch. 1.6.1.1.3.). **Paper I** shows a trend towards lower reoperation rates in the IRCC group, and this is probably due to smaller tumours and therefore less surgical demanding procedures. In regard to other complications, no difference was noted. Stephenson reports in 2004 on complications after 688 RN between 1995 and 2002 (88). They had an overall reintervention (reintervention and reexploration) rate of 1.2 %. In their report there were ≈ 64 % pT1-2 tumours. In our study, pT1-2 represents only 41 %, and we report 2.7 % reoperations **(Paper III)**. This is in comparison with Ljungberg, who reported 2.2 % reoperations for bleeding in pT1-2 patients (95). We had 1.5 % reoperations for bleeding in the same group **(Paper II)**. The study from Mejean and co-workers, on 656 consecutive RCC patients, reported an overall reoperation rate of 2.3 % (76).

Paper II demonstrates the complication and reoperation rates for the different surgical approaches. No statistical differences could be demonstrated, except for pneumonia after transabdominal or thoracoabdominal approach **(paper II, III).** The probable explanation is poor pulmonary ventilation due to pain or abdominal

meteorism. The, in general, similar complication rates between the different types of surgical approach is in line with Nurmi et al. (92).

The splenectomy rate in this in this material is 2 % in left sided RN, **(Paper II, III)**, which is comparable to most other reports (see Ch. 1.6.1.1.2.).

5.2.4. 30-days mortality

In chapter 1.6.1.1.4. the figures on contemporary 30-days mortality are described. In the present study 11 patients died within 30 days, giving a mortality rate of 3 %. Five patients died due to metastatic RCC and 6 died due to complications **(Paper II, III)**. Between the first and second period of the study, the mortality rates went down from 4 % to 2 %. Although not statistically significant, this trend might be a result of both better pre-treatment evaluation and post-operative care.

Of the patients with known MRCC at the time of operation 4 died within 30 days. The mortality rate is significantly higher than among those without known metastases **(paper II, III).** Looking retrospectively, it seems as if there has been a tendency to operate patients with primary MRCC at these two hospitals. Probably, some of the MRCC patients should not have been operated. In 2001, reports on cytoreductive RN before immunotherapy were published (157;158). The implication of these studies is that, with only few exceptions, cytoreductive RN only is indicated in highly selected patients before planned immunotherapy.

This is a consecutive material with little selection or referral bias. The mortality rates in this 20 year study should therefore be compared to population studies. The results are close to those reported in larger contemporary population studies. Hence, in conclusion, the mortality rates in this study are in line with acceptable standards of care.

5.2.5. Adrenalectomy

Why adrenalectomy is not performed in so many cases in this material is not clear retrospectively. The almost identical long-term CSS between the two groups, however, underscores the fact that obligate ipsilateral adrenalectomy is unnecessary

over-treatment. These survival rates support the recommendation based on the literature regarding adrenalectomy discussed in Ch. 1.6.1.1.1. (39;47;79).

Our percentage of adrenal involvement (4.5 %) is within the range that is reported earlier. In our material, the tumour location within the kidney is not specified. However, the tumour location within the kidney appear not to be an important factor in regard to adrenal involvement (39;47;78). Our figures, although the numbers are very small, support the current opinion that adrenal involvement carries an in general poor prognosis. Based on the current available reports, a revision of the TNM-system seems to be in order.

5.2.6. Survival and Recurrence

In **paper III**, the survival figures for the material are presented. With five years CSS rates of 92 % for stage I, 83 % for stage II, 67 % for stage III and 16 % for stage IV, it seems as if the figures compare well to those presented in chapter 1.6.1.5.

The fact that we in the material did not no observe any cancer related deaths in patients of stage I, and tumour size smaller than 3,5 cm **(paper III)**, is in line with the new reports of the 2002 TNM- system indicating that T1a have a 5-year CSS of 97 % (140;141) and T1b has 87-93 % (140;141).

The fact that the survival rates continue to drop after 10 year has to be addressed. In our study this is most pronounced in stage II, but happens in all stages. This trend is also present in most of the other published materials. In a study from 1981 (165), McNichols demonstrated that 11 % of patients surviving for ten years after nephrectomy, would later be diagnosed with a recurrence. In **paper IV**, we found this frequency to be 9.1 %. Especially in the T2-category the risk was high, as 3 of 12 (25 %) patients at risk developed a late recurrence. McNichols had graded his late recurrences, and 16 of 18 were low grade tumours (165). There are few larger series looking at this subject. Most reports are anecdotic. It seems as if large slow-growing tumours, with a low histological grade, are responsible for a large proportion of the very late recurrences. Recurrences have been reported as late as 45 years post nephrectomy (199).

Recurrence occurred in 29 % of the presumed radically treated patients **(Paper IV)**. This is in line with other reports. Median time to recurrence was longer than reported by other authors, and is probably due to the longer observation period in this material.

After 5 year approximately 80 % of the recurrences were identified **(Paper IV)**. This is somewhat lower than reported by Ljungberg (49) and Sandock (164), and also probably reflects the longer observation period.

The number of patients (34,8 %) diagnosed with recurrence as a result of regular follow-up, is within the range of earlier reported frequencies (28-68 %) (49;163;164;200). Most recurrences were found in the lungs and chest X-ray was the most valuable tool in finding these metastases, as also described by others. Lam proposes that chest-CT should to be the standard follow-up procedure (173). If this really is cost – beneficial remains unproven. In addition it will increase the total amount of radiation to the RCC group, and maybe contribute to an even higher risk of secondary primary tumours (See Ch. 5.2.6.)

The median survival in patients with recurrent RCC is low **(Paper IV)**. A median CSS of 9.8 months is in line with other reports (165) and also comparable to the CSS of patients with primary MRCC **(Paper III)** (68).

We found that the easy accessible information regarding DFI, number of organs with metastases and PS at the time of diagnosis all were independent prognostic factors for survival **(Paper IV)**. DFI have also in other reports been linked to improved survival after recurrence (166;201). In this way, long term survivors may be identified very soon and perhaps be treated differently from the rest. Resection of metastases is probably more indicated in these patients, and results as described in Ch. 1.6.4.1. may be achieved.

5.2.7. Multiple primary tumours in patients with RCC

In **Paper V**, we found a rate of multiple primary malignancies of 16.1%. This rate is higher than the earlier reported 4.5-11.9% (116;117), but lower than the 26.9%

reported by Rabbani et al. (118). All these studies, however, were either single institution series or smaller groups of patients.

In **Paper V**, almost 50% of the other malignancies were diagnosed subsequently, while others earlier have reported subsequent malignancies in the range of 15-23% (117;118). The probable cause of this difference is the longer observation time in this study.

In the literature (116-118;202-204), supported by this study, cancer of prostate, breast, colon and rectum, bladder, and lung as well as NHL were the most common other primary cancers in patients with RCC.

The elevated risk of subsequent bladder cancer after RCC is the one most often reported other primary cancer (116;118;203;204).

The overrepresentation of bladder cancer has been ascribed to surveillance bias, because of frequent visits to an urologist during follow-up after treatment for RCC,. This is in our opinion not likely, due to the fact that bladder cancer seems to appear not only in the early years after the RCC diagnosis when follow-up visits are frequent, but also after an interval of more than 10 years (204). In addition, due to the nature of most bladder cancer, during a long follow-up period, all these cancers will turn out to be symptomatic and therefore reveal themselves independently of regular control regimens. Much more intriguing is the possibility of a common environmental or genetic etiological agent like smoking (203). Other carcinogens excreted through the kidneys, probably also will influence on this axis.

It is well known that cancer therapy may result in other primary cancers (205;206), but these usually will appear after 10 years. Since the standard treatment of RCC does not include chemotherapy or radiation, this is probably not a major causal contributor to the increased risk of second primaries. Also, since the usual follow-up regimen in Norway during this follow-up period has consisted of physical examination, blood tests and chest X-ray every six-month, follow–up investigations are unlikely to influence the increased risk.

However, if the RCC treatment results in a patient with deteriorated overall kidney function with the need of dialysis, and a later renal transplantation, then an increase in second cancers may be due to immunosuppressive medications. Non-Hodgkin lymphomas have been reported to occur in a highly increased rate (10-30-fold) (207) after renal transplantation. Other primary cancers also are reported to occur more frequently after renal transplantation. After a nephrectomy for RCC, in the group of patients with preoperatively normal kidney function, more than 20% of the cases may develop chronic renal failure over time (112). End stage renal disease and renal transplantation related to RCC, may thus be a minor factor influencing on the occurrence of other primary tumours, but further investigation is warranted.

The major impact on overall survival by antecedent or synchronous other cancers in this study are earlier discussed by Sato et al. (117). They reported that other primaries at the time of nephrectomy for RCC were an independent prognostic factor for overall survival after the operation. Furthermore, patients with localized RCC (T1-2) and coexistent other cancer had poorer overall survival than the others with localized RCC (T1-2). In our opinion, treatment of RCC in patients with multiple primary tumours should be based on stage and operability of the kidney tumour, but also on an evaluation of the disease status of the other malignant disease.

The cumulative risk of a second primary cancer after a diagnosis of RCC, as shown in this study, has not been found reported in the literature. The study by Czene & Hemminki (204) clearly indicates that RCC patients have a higher risk of other cancers not only in the first year after the primary diagnosis, but also after more than 10 years. For males the cumulative risk of a second cancer reached 26.6% after 15 years. In fact 7.2% died from the second cancer.

5.2.8. Follow-up of RCC

The benefit of follow-up after treatment for RCC may be questioned. There is reported a significant difference between different Nordic countries in regard to the use of follow-up (77). How follow-up is valued, probably depends on different attitudes towards the possible benefits from further treatment.

A follow-up program should be kept simple and focus on those common metastatic sites, where additional surgical or other treatment modalities can be offered to the patient. Further, it should be cost-effective, both in regard to the amount of money spent and the time used for routine follow-up. There are different follow-up protocols published. Most of them are terminated after five years (49;163). However, some have longer follow-up as an option (169) and other very recently published reports advocates longer follow-up (173).

Based on our results and earlier studies, we presented our suggestion for a follow-up protocol in **paper IV**. The overall risk for recurrence after a DFI of 5 years after nephrectomy, was 11.5%. A simple model with our figures of patients, recurrences and percentage of metastasis detection as a result of follow-up was made to calculate how many follow-up visits that was necessary to diagnose one patient with metastases. In **Paper IV** we reported that with one yearly routine follow-up visit between 5 and 10 years post nephrectomy, between 100 and 125 patients had to be examined, in order to diagnose one. In addition, the study showed no survival benefit due to recurrence detection at routine follow-up. Hence, in our opinion routine follow-up after 5 years is not indicated. However, the patients should be informed of their approximately 1/10 chance of developing a later recurrence.

The results of **Paper V**, however, in our opinion may influence on how RCC patients should be followed after the diagnosis. Due to the fact that these patients have an increased risk of secondary primary malignant tumours, it might be discussed if these patients should be followed with more general examinations after the termination of specific RCC follow-up.

Urinalysis, tests for occult blood in the stool and general physical examination including skin inspection, digital rectal examination and lymph node palpation every second year at a general practitioner (GP), seems to be one proper regime for such long time follow-up. In subgroups of RCC patients, Chest X-ray might be included.

To use more invasive screening tools as for instance cystoscopy or colonoscopy, probably would turn out to be less cost-effective, although colonoscopy at 10-year

intervals might be considered, as proposed for the general population by some (208). Such follow-up is probably even more appropriate if the patient is smoking in spite of advice on smoking cessation or having other risk factors for other primary cancers.

6 Conclusions

From this study the following conclusions might be drawn:

- The internationally trend of increasing number of IRCC is present in Norway as well.
- Women seem to benefit from the more widespread use of modern imaging modalities.
- Complication and 30-days mortality rates in RN are in line with those reported internationally.
- Survival rates after treatment for RCC are in line with those reported internationally.
- In about 30 % of presumed radically treated RCC patients, the disease will recur.
- Based on easy accessible information, patients with different prognosis for survival after detection of metastases can be identified.
- After 10 year of DFI, there is still about 10 % risk of recurrence.
- RCC patients have increased risk of developing other primary cancers.
- Based on the information in this study, a follow-up protocol after treatment for RCC is suggested.

7 Further perspectives

RCC is still a highly unpredictable disease with considerable recurrence and mortality, and in order to better the prospects for RCC patients in Norway continuing research is necessary. Based on the work with this material some interesting thoughts about the future in regard to RCC have turned up. Among those are:

- There is a need for improved registration of RCC in Norway. All new cases should be included. Information about symptoms, diagnosis, treatment and follow-up should be gathered.

  Recently we were granted permission to set up a local clinical database combined with a tissue bank. This will allow us performing interesting research in regard to clinical, immunological and genetic questions. With a total number of approximately 500 patients per year in this country, this local database could easily be expanded to a national tissue and databank.

- Today the laparoscopic and mini-invasive treatment modalities are becoming increasingly popular. Follow-up studies of these, to see if they show similar oncologic long-term results as the open procedures, are mandatory. In addition, these techniques have a longer learning curve. A supervising organ should have the possibility to monitor the complication and mortality rates on a national level as the popularity of laparoscopy increases.

8 Appendix

Table 1. 2002 TNM- staging system

TNM	Subcategory	Description
T1		Tumour ≤ 7,0 cm confined to the kidney
	A	Tumour ≤ 4,0 cm confined to the kidney
	B	Tumour > 4,0 cm confined to the kidney
T2		Tumour > 7,0 cm confined to the kidney
T3		Extension beyond renal capsule or venous involvment
	A	Perinephric or adrenal invasion
	B	Invasion of renal vein or VCI below diaphragm
	C	Invasion of VCI above diaphragm
T4		Invasion beyond Gerotas fascia
N0		No lymph node involvement
N1		One positive lymph node
N2		More than one positive lymph node
M0		No distant metastases
M1		Distant metastases

Table 2. The four stages according to TNM 1997 (42)

Stage	TNM-category
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T1-2N1M0, T3A-CN0-1M0
Stage IV	T4N0-1M0, T1-4N2M0, T1-4N0-2M1

Table 3. After Blute et al. 2004 (142)

	Level of top of tumour thrombus
Level 0	Tumor in the Renal Vein
Level I	Tumour in VCI ≤ 2 cm over the Renal Vein
Level II	Tumour in VCI > 2 cm over the Renal Vein, but below the hepatic veins
Level III	Tumour in VCI at the level of or above the hepatic veins, but below the diaphragm
Level IV	Above the diaphragm

9 Errata

In **Paper I**: Table IV, the latter time group should be **1988-2000**, not 1988-2001.

In **Paper III**: page 2432, Middle column, 7th row after the start of the Terminology section: *(f. eks. mikrohematuria)* should be replaced with **(f. eks. forhøyet SR**)

In **Paper IV**: Table III, PS: *> 0,001* should be replaced with **< 0,001**

In **Paper IV**: Table V, Last group (Other), the number in the "total" column should be **10** (not 3). Further, NIA, n = 1 should be added in the last column

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