A population based study on Kidney Cancer in Norway (2008 - 2013)

Aspects of biopsy use, surgical treatment and outcome.

Karin Margrethe Hjelle

Thesis for the Degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2018

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Scientific environment

The work in this thesis is carried out at the Department of Urology, Haukeland University Hospital and through the PhD-program at the Department of Clinical Medicine (K1), University of Bergen and in collaboration with the Cancer Registry of Norway, Oslo.

Acquisition of data has been conducted at the Cancer Registry of Norway.

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Bergen, June 2018 Karin Margrethe Hjelle

Abstract

Aims:

The aim of this study was to explore whole nation data, reveal trends and obtain updated numbers on kidney cancer (KC) treatment in the six-year period from 2008-2013. The field of KC management has undergone substantial changes over the last few decades regarding surgical approaches, the use of pretreatment biopsies, surveillance and management of metastatic disease. We wanted to evaluate patient outcomes, and to see if new guidelines were implemented.

Material and methods:

Data on 4,449 patients diagnosed with KC (ICD10 code 64) was extracted from the Cancer Registry of Norway for all three articles. In Paper I, an analysis is performed on patients with data on biopsies (n=4,051). For Paper II, the data subset constitutes all patients with a surgically treated localized kidney cancer ≤7cm (n=2,420). Paper III includes all surgically treated Norwegian patients (n=3,273), both with localized and advanced disease, operated on in hospitals performing more than 4 KC surgeries/year.

Results:

Paper I: A renal mass biopsy (RMB) was performed in 20.2% of all patients. From the first to the second half of the study period, the use of RMB increased from 9.1 to 11.5 % for localized disease, and was doubled among patients for observation. Predictors of RMB were older patients, tumor < 4 cm, multiple tumors and second primary cancer. Fewer patients with metastatic disease were without histopathology verification in the second period. Those without RMB had poorer survival. The majority of biopsies were performed in patients who had a cytoreductive nephrectomy (CN), and CN was performed in 35% of all patients.

Paper II: There was a 28% increase in surgically treated patients, with tumors ≤ 7 cm and the rates of partial nephrectomy (PN) increased, while the rate of radical nephrectomy (RN) decreased. PN was performed for 58% of tumors ≤ 4cm and for

14% of tumors 4.1-7cm. There was also an increase for minimally invasive (MIM) approaches. The regional differences in the distribution of PN and RN were less pronounced at the end of the study period. Furthermore, our results indicate a possible survival benefit for a patient undergoing PN vs. RN.

Paper III: RN was performed in 69% of the patients and PN in 31%. Overall, the 30-day mortality (TDM) was 0.89%, whereas the rate for localized and metastatic disease was 0.73% and 2.6%, respectively. TDM was higher in older patients and lower for PN and MIM procedures. The odds ratio for TDM in a low-volume- compared to a high-volume hospital was 3.35 and 4.98 for patients with localized and metastatic disease, respectively

Conclusion:

These studies demonstrate that trends in KC diagnostics and treatment are in line with international recommendations, and that Norwegian urologists seem to adapt to changes in guidelines. Lastly, patient outcomes in regard to TDM are in line with previous reports.

List of Publications

I. Hjelle KM, Johannesen TB, Beisland C. (2018). Real-life use if diagnostic biopsies before treatment of kidney Cancer: Results from a Norwegian population-based study. Scandinavian Journal of Urology 2018; 52: 1, 38-44

II. Hjelle K, Johannesen TB, Bostad L, Reisæter LAR, Beisland C. (2018): National Norwegian practice patterns for surgical treatment of Kidney Cancer ≤ 7 cm: Adherence to changes in guidelines may improve overall survival. European Urology Oncology, published online may 1st, 2018. doi.org/10.1016/j.euo.2018.04.001

III. Hjelle KM, Johannesen TB, Beisland C. (2017): Postoperative 30-day mortality rates for kidney cancer are dependent on hospital surgical Volume: Results from a Norwegian Population based study. European Urology focus 2017; 3: 301-307

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Abbreviations

AS	- Active Surveillance
AT	- Ablative Therapy
ccRCC	- Clear Cell Renal Cell Carcinoma
CHA	- Central Health Authority
CN	- Cytoreductive Nephrectomy
chRCC	- Chromophobe Renal Cell Carcinoma
CRN	- Cancer Registry of Norway
CSS	- Cancer Specific Survival
IMDC	- International Metastatic Renal-Cell Carcinoma Database Consortium
HVH	- High-volume Hospital
ISUP	- International Society of Urologic Pathologists
KC	- Kidney Cancer
LPN	- Laparoscopic Partial Nephrectomy
LRN	- Laparoscopic Radical Nephrectomy
LVH	- Low-volume Hospital
MIM	- Minimal Invasive Method
MSKCC	- Memorian Sloan Kettering Cancer Center
mRCC	- Metastatic Renal Cell Carcinoma
NHA	- Northern Health Authority
OS	- Overall Survival
PN	- Partial Nephrectomy
pRCC	- Papillary Renal Cell Carcinoma
PS	- Performance Status
RALPN	- Robot Assisted Laparoscopic Partial Nephrectomy
RCC	- Renal Cell Carcinoma
RN	- Radical Nephrectomy
SHA	- South Eastern Health Authority
UICC	- The Union for International Cancer Control
WHA	- Western Health Authority
WHO	- World Health Organization

1. Introduction

1.1 Historical considerations for Renal Surgery

Renal Cell Carcinoma (RCC) constitutes approximately 90% of Kidney Cancer (KC), and originates from mature renal tubular structures. In 1883, Grawitz published a yellowish tumor that probably arose from intrarenal adrenal remnants [1], further supported by Birch-Hirschfeld in 1894, which was named hypernephroma [2]. Its origins were discussed by surgeons, pathologists and radiologists from the early 1900s [3, 4], until Oberling documented the renal origin of the tumor in 1960 using an electron microscope [5]. The "Heidelberg classification of renal tumors", a consensus presented in 1997, still applies, but is regularly updated with new genetic knowledge and histopathology [6].

In 1869, Simon cured a woman with a persistent ureteral fistula doing the first planned nephrectomy [7]. Eight years later, Langenbuch did the first nephrectomy for neoplastic disease [8]. Renal surgery expanded steadily in subsequent years. Furthermore the interest in organ-preserving and reconstructive surgery was highlighted in 1879 by Harrison's tumor-decapsulation and Czerny's partial kidney resection of a tumor in 1887 [7-9].

After Robson's work in the 1960s, open radical nephrectomy (ORN) became the standard treatment for localized KC [10]. The key surgical steps described by Robson still serve as basic principles for urologic surgeons today, and he was also the first to correlate the survival to tumor stage (known as the Robson staging system).
At this time, a partial nephrectomy (PN) was only done for imperative reasons by very few urologists. When Wickham presented a 5-year survival of 72% in a review in 1975, the scene opened for elective PN. However, the topic was discussed during the next decades. In 1993, Licht and Novick presented patients followed for three years with a normal contralateral kidney demonstrating 95% survival and rare local recurrences. Around the millennium when these successful results were further supported by 10-year follow-ups, elective PN become widely accepted [8].

Minimallyinvasive methods (MIM) in renal surgery were introduced when Clayman performed the first laparoscopic RN (LRN) in 1991, while the first retroperitoneal LRN for neoplastic disease was performed in 1994. During the next decade, the development of instruments and operative techniques continued, culminating with the introduction of the robotic system around the millennium. Robotic-assisted techniques facilitated PN with the advantages of three-dimensional magnification and endowrist features of the instruments, thereby simplifying resection and suturing compared to pure laparoscopic PN (LPN).

Surgically treatment for RCC is still the mainstay in curative treatment for kidney cancer. Even so, the landscape has changed dramatically, from having only one treatment (ORN) that should fit all patients to the present management, which includes several surgical methods, ablative treatments and surveillance.

1.2 Epidemiology

1.2.1 Incidence and prevalence

KC comprises 2.4% of cancer incidence worldwide [11, 12]. It is the 9th most frequent cancer in men and the 14th in women [13]. In 2016, the incidence in Norway was 2.7%, whereas between 2007 and 2016, the incidence increased by 52%, from 574 to 872 patients. Furthermore, the prevalence increased by 77%, from 3,853 to 6,816 patients [14]. Incidence rates vary considerably, both within Europe and worldwide [13]. The Czech Republic and neighboring countries have the highest incidence in Europe. The lowest incidence is found in southern Europe (figure 1 and 2).

Population growth, changes in age structure and increasing incidence rates account for 35%, 35% and 37%, respectively, of the two-fold KC increase seen between 1990-2013 [15].

Approximately 34% of all KC was diagnosed in developed countries, and 42% in developing countries [15]. The difference may be biased because of cancer registration, detection tools, imaging and autopsy rates. The lifetime risk of developing KC approaches 3% in the Czech Republic and 1-2% elsewhere in Europe [11].

1.2.2 Mortality and Survival

Of all cancer deaths worldwide, KC accounts for 1.7%, and is the 16th most common cause of cancer-specific death [13]. The numbers of deaths have increased for both genders and all ages [11], but mortality rates are stable and have declined in high-resource settings since the 1990s [13]. Interestingly, an 11% decrease in mortality rate among women balanced the 15% increase in mortality in men [15], while five-year relative survival is increasing [12, 13] (figure1-3). The age standardized mortality rate in Norway (2016) is 6.4 for men and 2.5 for women [14].

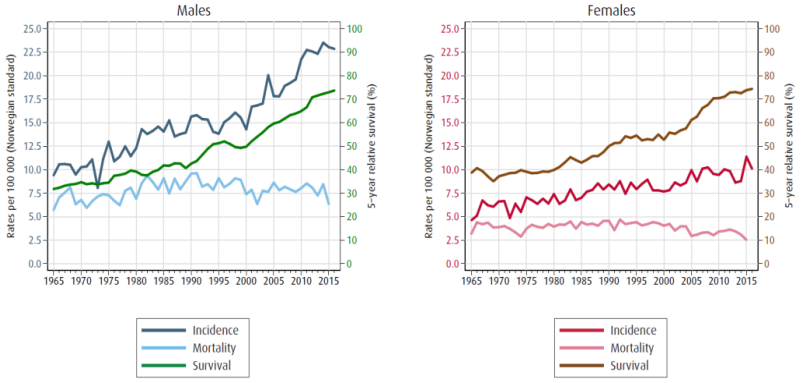

Figure1: Trends in incidence, mortality and five-year relative survival for Norwegian men and women with Kidney Cancer (ICD-10 C64) [14]

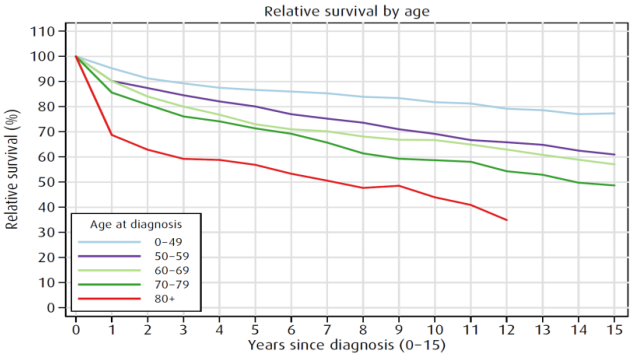

Figure 2: Relative survival up to 15 years after KC diagnosis by age, 2012-2016[14]

Country	Incidence 2003-2007 Age standardized/100 000				Mortality 2003-2007 Age standardized/100 000			
	Male	Change/10 yr	Female	Change/ 10 yr	Male	Change/ 10 yr	Female	Change/10 yr
Iceland	13.5	0.7 %	8.3	0.1	6.1	0.0	2.8	-2.2
Norway	10.1	2.5 %	5.3	1.1	3.7	-0.8	1.6	-2.7
Finland	9.4	0.8%	5.8	-0.3	4.1	-2.7	2.0	-1.2
Denmark	8.4	3.6%	4.1	1.6	3.9	-1.5	2.0	-2.7
Sweden	7.1	1.2%	4.4	0.2	3.7	-2.0	2.1	-2.3
Czech Rep.	22.1	0.8%	9.9	-0.5	9.1	-2.8	3.6	-2.7
Estonia	16.0	0.4%	6.9	-1.6	7.9	-1.0	2.3	1.6
Slovakia	15.0	3.1%	7.5	3.5	6.1	-0.2	2.4	-1.0
Bulgaria	6.7	5.7%	3.0	3.6	3.5		1.2	
France	12.2	1.5%	5.4	1.0	3.6	-0.8	1.3	-3.3
Austria	11.3	-1.6%	6.1	-2.1	3.3	-3.0	1.7	-3.0
Netherlands	8.8	1.8%	4.9	1.7	4.0	-1.0	2.0	-1.3
Australia	10.4	1.0%	5.1	1.2	3.4	-0.5	1.6	-2.0
New Zealand	9.2	1.7%	4.5	1.5	3.3	-0.1	1.6	-0.2
Canada	10.2	1.8%	5.7	2.4	3.5	-0.8	1.6	-0.9
US black	15.2	2.7%	7.3	2.7	3.7	-0.9	1.6	-1.3
US white	12.5	1.3%	6.7	1.1	3.6	-1.0	1.6	-1.3
Brazil	7.9	6.8%	5.0	6.4	1.5	2.5	0.8	1.1
Costa Rica	4.1	3.0%	2.4	2.5	1.6	1.1	0.9	-0.4

Figure 3: Age standardized incidence and mortality for Kidney Cancer [13]

1.2.3 Age and gender

The incidence of KC increases with age [15], and is highest in the 6th and 7th decade [16]. More KC is diagnosed today among patients older than 70 years: 30% vs. 37% (1990-2013) [15]. The incidence is higher in men than women at a ratio of 1.5-2.5:1 [14, 17, 18], with the incidence increasing more in men than women. Lastly, the mortality rate for women is half that of men [12-14].

1.3 Renal Cell Carcinoma Etiology and Risk factors

1.3.1 Inherited RCCs

Most RCCs are sporadic and only 3-5% present with a hereditary cause [19]. The hereditary renal cancer syndromes (HRCS) have a defined genetic mutation, while familial non-syndromic renal cancers (FNSRC) have a multi-genetic inheritance caused by a combination of genes. Hereditary RCC should be suspected, and genetic counseling offered in patients with early-onset RCC (<40 years), a familial history of RCC, bilateral or multiple tumors. Knowledge of non-renal manifestation of HRCS is important. Currently, 10 HRCS, all with autosomal dominant inheritance, are described. Von Hippel Lindau (vHL) is the most common HRCS. Approximately 70% present with ccRCC before the age of 70, with multiple and bilateral tumors, in addition to non-renal manifestations [19, 20]. FNSRC present with a single RCC in more than one first- or second-degree relative and they can skip a generation [21]. They typically have an early onset (<50 years), and are often multiple or bilateral [22].

1.3.2 Tobacco

Smoking increases the risk of RCC dose-dependent, and more so in men than women. Cessation reduces the risk substantially [23, 24]. Smokers present with more aggressive phenotypes and at higher stage [24], and smoking has a negative impact on survival [25]. Among men and women, 21-30% and 9-24% of RCC is attributed to smoking [15, 17]. Most of the constituents in cigarette smoke are metabolized or excreted through the urinary tract. RCC predisposition is comprised of nitrous-compounds, the formation of oxygen-free radicals [24], smoking-related chronic tissue hypoxia [26] and to be a slow-acetylator genotype [17].

1.3.3 Body Weight

Obesity increases the risk of RCC. In Europe and in the US 30-40% of RCC is attributed to overweight [26, 27]. A Norwegian study confirms the correlation between body mass index (BMI) and RCC, and the risk is dose-dependent [13, 28, 29]. Paradoxically, obese patients present with lower grade and stage RCC, and have better cancer specific survival (CSS) and overall survival (OS) [30, 31]. The complex interplay between obesity and RCC involve inflammation, tissue hypoxia, lipid peroxidation, VHL mutation, increased production of insulin-like- and other growth factors [32]. The adipose tissue-derived hormones, adiponectin and leptin, are linked to more aggressive RCC in low and high levels, respectively [32].

1.3.4 Kidney Disease and Hypertension

Patients with acquired cystic kidney disease (ACKD) present more than six-fold higher incidence of RCC[16] compared to the general population. After renal transplantation, native kidneys also have a higher incidence of RCC [17, 33]. Hypertension and antihypertensive drugs as risk factors for RCC are hampered by the fact that it is difficult to separate the effects of each [16, 17]. However, the EPIC study documented a positive relationship between RCC and systolic and diastolic blood pressure [34].

1.3.5 Other risk factors

Occupational high exposure to asbestos, trichloroethylene, cadmium and lead in the metals industry [35-38] are linked to increased risk, as is chronic exposure to arsenic in drinking water [17]. A high protein diet and fatty food are linked to an increased RCC risk[16] whereas an intake of fruit and vegetables is protectable [17, 39].

1.4 Classification of Kidney Cancer

1.4.1 From Renal mass to Kidney Cancer and Renal Cell Carcinoma

A practical approach and the everyday challenge for clinical urologists, radiologists and pathologists is to differentiate between malign, benign and inflammatory renal masses (figure.4). Renal masses might be classified by either histopathology or by imaging. The latter uses the radiographic appearance to denominate a renal mass as simple cystic, complex cystic, fatty tumors and other solid lesions [40].

1.4.2 Histopathological Classification of RCC

There has been a significant development from the first morphology based (Heidelberg) classification in 1997 [6] to the latest update on renal neoplasia by ISUP/Vancouver 2012 and WHO 2016 [33, 41, 42]. Several new entities have emerged, and existing tumors have been refined during the last decades [43]. Today, 17 morphological types of renal malignancy are characterized. Classification is based on predominant cytoplasmic-, staining- and architectural features, cell type, anatomic location, genetics or a combination of all these features [6, 33, 41].

Clear cell renal carcinoma (ccRCC), arising from the proximale tubule constitutes 75-80%, papillary renal cell carcinoma (pRCC) 10-18%, chromophobe renal cell carcinoma (chRCC) 5%, collecting duct carcinoma 1%, whereas 3-5% remains unclassified [44].

Furthermore, pRCC is subdivided into type 1 and 2, representing low and high-grade, respectively, and is related to prognosis. The molecular heterogeneity of type 2 is not fully characterized, but several subtypes emerge [42, 45]. Since 2016, the term papillary adenoma, with a low malignancy potential, is used for low grade papillary tumors ≤15 millimeters[41].

1.4.3 Cystic Renal Lesions

Renal cysts are common, with most benign and asymptomatic. The Bosniak classification (BC) introduced in 1986 simplified the differentiation between simple (BC type I) cysts and more

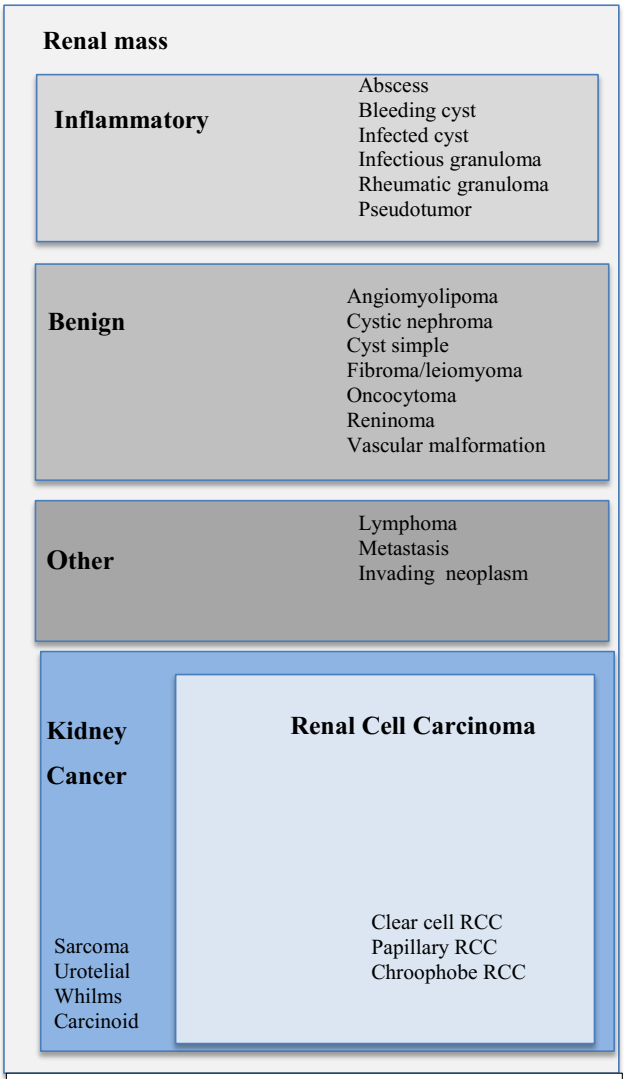

Figure 4: From Renal Mass to Renal Cell Carcinoma

complex (BC type II-IV) cysts, which could harbor carcinoma. The classification is based on morphology and enhancement characteristics on contrast-enhanced CT. The system was quickly adapted by radiologists and urologists [46, 47].

BC type I–II cysts are invariably benign. The BC type IIF represents a subgroup, in which approximately 5-7% will develop RCC. Regular follow-up(FU) is needed, during which 12% will be upgraded to BC type III [46]. Resected BC III and IV cysts turn out to be RCC on final histopathology in 51% and 89%, respectively. However, they tend to be of a low stage and low grade, and thus a low potential to metastasize. Hence, these tumors carry a good prognosis [48, 49].

1.4.4 Non-renal malignancies in the kidney

Lymphomas may present hypovascular multiple renal masses on CT, either as a solitary mass or a diffuse renal infiltration [50]. Patients with atypical or massive lymphadenopathy, splenomegaly, immunosuppression, autoimmune disease or B-symptoms should undergo a renal mass biopsy in order to avoid unnecessary surgery [51].

Sarcomas account for 1% of KC, and should be suspected when there is a rapidly growing mass with the presence of fat or bone. The prognosis is generally poor, even when the wide-margin RN and en bloc excision of adjacent organs are performed and combined with adjuvant chemotherapy.

Only 3% of Wilms tumors are in adults, and should ideally be treated after protocols, as for pediatric Wilms tumors. However, an adult Wilms tumor is often an unexpected finding at final histopathology [51]. Other rare renal tumors include carcinoid, small-cell carcinoma and primitive neuroectodermal tumors, of which the latter two require multimodal therapy [51].

Renal metastases predominately have a pulmonary or colorectal origin [50, 52]. They typically present asymptomatic, with two-thirds as a solitary nodule and the rest being multiple or bilateral. The interval between the primary cancer diagnosis/treatment and metastases can be substantial [53].

1.4.5 TNM-classification

The TNM classification describes the anatomic extent of malignant tumors. This staging based on tumor, nodes and metastases was launched as a cooperation between the Union for International Cancer Control (UICC) and the American Joint Committee for Cancer Staging and End Results Reporting (AJCC) [54]. Today, this has replaced older staging systems for KC [55].

There have been several revisions over the last few decades. Such revisions are based upon new knowledge for the ability to predict progression and survival. Among the present candidates for upcoming revisions, there are the questions of whether T1 and T2 should be further sub-classified, as well as whether sinus fat invasion may exhibit a worse prognosis than perinephric fat invasion. Presently, both are classified as T3a.

Finally, there is an ongoing discussion if microscopic (in addition to macroscopic) vein-, hilar sinus and pelvicalyceal system invasion should be classified as T3a. This latter discussion has caused discrepancies between the last TNM revisions from UICC and AJCC [42, 56, 57].

1.4.6 Histopathological Grading of Renal Cell Carcinoma

1.4.6.1 *Nuclear Grading*

Fuhrman et al. published their nuclear grading system in 1982. They based their system on tumor aggressiveness (nuclear size and prominence, in addition to nucleolar prominence). The system is evaluated according to survival and prognosis[58]. Validation, interpretation and reproducibility of this system have been problematic, although the system is still widely used. WHO and ISUP/ Vancouver (2016/2012) have proposed a new four-tier grading system based only on nuclear prominence. The highest grade should be reported [41, 42]. It has been validated as a prognostic marker for ccRCC and pRCC, and its use has also been accepted to describe other morphotypes of RCC. However, for chRCC, an improved grading system is needed [41, 59].

1.4.6.2 *Presence of Necrosis*

The microscopic appearance of coagulative necrosis predicts a worse prognosis for ccRCC and chRCC [42]. Outcome in pRCC is not related to necrosis, as the tumors likely are predisposed to undergo spontaneous necrosis [59]. Necrosis is also incorporated in various prognostic models [60, 61].

1.4.6.3 *Sarcomatoid features*

Sarcomatoid features can be identified in all RCC subtypes, and is not a separate entity. Any presence of such features offsets an ISUP grade four score. Moreover, the greater the proportion is, the worse the prognosis [42, 62].

1.5 Diagnostic Work–Up in KC Management

Among others, mode of presentation, symptoms, the patient's medical history, performance status, laboratory findings, image-defined clinical tumor stage and burden are all important features for the evaluation of a KC patient during the pretreatment work-up. As 80% of patients present with localized disease, and are thus candidates for curative management, stratification according to patient risk of recurrence or metastasis helps the surgeon in decision-making, and in counseling the patient regarding treatment.

1.5.1 Clinical presentation and Symptoms

Today, incidentally detected tumors represent the majority, increasing from 7% to 60-70% over the last 50 years [63-65]. A more widespread use of imaging is among the reasons for this. It is not only imaging for newly arisen back-, flank- or abdominal pain, but also imaging for FU for both cancers and chronic diseases, which has led to this increased discovery. Because most of these tumors are small, there has been a "stage migration" in KC over this period of time.

The classic triad of flank pain, hematuria and a palpable tumor is infrequently seen today, though one or two of the symptoms is not unusual[66]. Moreover, obstructing venous thrombus can cause varicocele or lower extremity lymphedema.

Patients may present with symptoms from local tumor growth, tumor bleeding (with gross hematuria), paraneoplastic manifestations or metastatic disease.

A tumor can produce hormones, peptides, cytokines and inflammatory mediators, hence causing paraneoplastic syndromes in up to 20% of the patients [67]. These substances may induce weight loss, cachexia, fever, anemia, hypertension, neuromyopathy, amyloidosis, hepatic dysfunction and polycythemia, plus lowered albumin, elevated ESR and CRP [68, 69].

Coughing or dyspnea are symptoms of lung metastases. Cerebral metastases may present as confusion, dizziness or epileptic seizures, while bone metastasis most often debuts with pain or a pathological fracture (e.g. femur, humerus or vertebra). Since RCC has a diverse metastatic pattern, metastases may appear in almost all organs or regions of the body (i.e. a vaginal, parotid or pancreatic tumor, a skin nodule or supraclavicular nodes) [41].

1.5.2 Physical examination and Laboratory findings

A complete medical history, including an evaluation of the severity of comorbidity, previous surgery, family history and medication, is crucial during a diagnostic work-up. The physical examination, including a consideration of patient age, compliance, cognitive function and wishes, is also of imperative importance.

It is essential to question whether the patient will actually benefit from surgery, and consequently to assess the risk in conjunction with the surgical procedure.

Based on the information gathered from medical history and a physical examination, preoperative expanded investigations or necessary medical treatment must be scheduled if needed to help optimize patients before surgery.

A blood test should always be evaluated preoperatively, and blood for standard surgical blood assays should be drawn. In addition, blood tests such as ESR, CRP, hemoglobin (Hb), complete blood cell count, alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and S-calcium carries prognostic information. Proteinuria, S-creatinine and estimated GFR all aid predicting postoperative renal function [70].

1.5.3 Quality of Life

The patient's non-oncological Quality of Life (QoL) should be considered in conjunction with oncological outcomes in decisions for treatment [71]. QoL is influenced of sociodemography, comorbidity, psychological factors and the extent of

the cancer disease. In the short term, it is related to pre-, intra- and postoperative factors, including patient counselling, plan of management, experience of support, lack of complications and adequate follow up (FU).

1.5.4 Performance status, Comorbidity and Risk of complications

Patient performance status is most commonly scored by the Karnofsky Performance Scale (100-0) or the Eastern Cooperative Oncology Group Index (ECOG 0-5)[72]. The American Society of Anesthesiologists created the ASA score (I-VI) to communicate the physical status of a patient in order to roughly predict the anesthetic risk and outcome. The Charlson Comorbidity Index preoperatively evaluates and integrates system-affecting comorbid illnesses in such a way that the scoring predicts outcome after treatment [73].

1.5.5 Kidney function

Efforts should be made to preserve kidney function. This is especially important in patients with ongoing impaired kidney function, diabetes mellitus or hypertension. The Glomerular Filtration Rate (eGFR) should be calculated from the CKD-EPI equation, and not only with s-creatinine, since 30% of patients with normal s-creatinine have pre-existing Chronic Kidney Disease (CKD) [74]. CKD represents a dose-dependent risk factor for cardiovascular events, hospitalization and mortality of any cause. Furthermore, this is independent of earlier known cardiovascular disease or proteinuria, with the rate of adverse events abruptly rising when the GFR<45ml/min/1.73m^2 [75]. Surgically induced CKD may worsen existing medical CKD. New-onset CKD is more likely to occur, and pre-existing CKD may progress faster in patients undergoing RN than PN [74, 76]. The only randomized study (EORTC) could not document a survival benefit for PN compared to RN[77]. Other presented data show improved assumed to partly be attributable to the preservation of renal function [78, 79] by reducing cardiovascular events [80].

1.5.6 Imaging

Imaging is essential in KC diagnostics, staging and FU. The quality of various imaging modalities has continuously improved over the past few decades. Contrast-

enhanced imaging with CT and MRI constitutes the basic modalities today, although intravenous urography, venography and angiography are seldom used in modern practice.

1.5.6.1 *Computed tomography*

High sensitivity and specificity in detection earned the helical multi-slice computed tomography (CT), which has been the gold standard for RCC-imaging from the 1990s onward [70, 81]. Today, the more precise multidetector CT (MDCT) has replaced helical scanners, with a short acquisition time, reduced motion artefacts and ultrathin sections, preferably 1.5-3 mm. The vascular- and collecting system is better demonstrated by reformatted images. MDCT is also regularly used for staging, surgical planning, treatment-evaluation and FU. Newer techniques such as dual-energy CT (DECT), using virtual non-contrast (VNC) imaging and iodine quantification maps can reduce the radiation dose by 35-47% [82]. Functional imaging such as perfusion CT (pCT) is relevant in response evaluation and looks at tumor angiogenesis by describing blood flow/volume, transit time and permeability [83]. However, more studies are warranted before both these recent modalities can be routinely used.

For modern primary diagnostics, an MDCT with four phases is preferred [70].
The non-contrast phase establishes the baseline (solid lesion: >20HU, fat as in angiomyolipoma (AML) : < -10HU, cysts: -10-20 HU, high density cysts: > 40 HU).
The arterial phase (20-40s after contrast injection) maps renal artery anatomy, aiding in preoperative planning. Enhancement is related to vascularity. An increase of >15-20 HU in the arterial or nephrographic phase may indicate malignancy in both solid tumors and complex cysts.
Detection is more sensitive, more specific and more accurate in the nephrographic phase (70-100s after contrast injection) [84].
The excretory phase (seven min after contrast injection) illustrates the collecting system, and thus an eventual intrusion of this.

Today, the radiology report is supposed to describe size, necrosis, calcifications, enhancements and location of the tumor. Though accurate, CT has interpretative and technical pitfalls [84]. Small and fat-poor AML is difficult to diagnose with CT and MRI, thereby making biopsy necessary [85, 86]. The spill-in effect from nearby renal tissue and a small region of interest (ROI) makes it more difficult to characterize small renal lesions. Kidney function, cardiac output and volume and rate of contrast administration may affect contrast enhancement. Contrast enhancement is suggestive, but not diagnostic for the type of solid lesion.

For RCC staging, axial imaging depicts adrenals, lymph nodes, involvement of organs, lumbar vertebras, veins (renal, gonadal, lumbals, vena cava inferior, hepatic veins), thrombus level and visible collateral veins. An evaluation of the extension of a bland thrombus is difficult on CT. Signs of locally advanced disease includes the thickening of Gerotas fascia, the presence of collateral vessels in the peri- and paranephric fat [87]. To determine the eventual perinephric fat invasion is challenging with CT, and may be better visualized by MRI. The chest CT is routinely performed in primary staging, looking for pulmonary, pleural or mediastinal metastases.

To avoid a worsening in patients with kidney failure, an iodine contrast should be used with caution. One solution to this is a non-enhanced CT or MRI and US combined with a renal mass biopsy. The dose of irradiation with repeated imaging remains a concern, especially in young patients.

1.5.6.2 *Magnetic Resonance Imaging (MRI)*

MRI is rendered equal to CT in order to characterize renal masses [70]. MRI may be offered to pregnant women and patients with iodine-contrast allergies. Furthermore, the use is indicated if CT is indeterminate, as with some small lesions, cysts and low-enhancing renal masses [81, 88]. For staging, MRI may be better for the detection of perirenal fat invasion, and for the determination of the extension of a venous thrombus[70]. MRI is the preferred modality for the detection of metastases to bone [89] and also for the FU of patients with von Hippel-Lindau disease [70, 81].

Hopefully the non-contrast enhanced diffusion weighted imaging (DWI) can expand its role[90]. In particular, DWI could offer advantages in patients with severe CKD and ACKD, differentiating pseudotumors and solid lesions among multiple cysts [91, 92].

1.5.6.3 *Renal ultrasound*

Renal ultrasound complements other imaging methods. A renal lesion detected with ultrasound, grey scale modus (US) should always be investigated with an up-to-date CT scan.

US may serve as an option for surveillance, the evaluation of tumor growth, image-guided biopsy and therapy, and to define whether a lesion is cystic or solid. It could complement non-contrast CT when contrast agents are contraindicated. US is inferior to CT to detect small renal lesions, although sensitivity increases with tumor size. The sensitivity for lesions 15-20 mm and 25-30 mm was 58% and 100% for US vs. 100% and 100%, for CT, respectively [93].

Contrast-enhanced ultrasound (CEUS) has a high sensitivity and specificity for renal lesions [70], and illustrates the vascularity of the lesions. CEUS can better than US in differentiating solid components in cystic lesions, but is inferior to MRI.

Color Doppler US may aid in the verification of thrombus-extension into the inferior vena cava [81].

To identify the level of supradiaphragmatic caval thrombus (level III/VI), transesophageal ultrasound (TEUS) is a commonly used modality. TEUS has a diagnostic accuracy of 85% vs. MRI 90% [94]. The result of TEUS can affect surgical management concerning the use of cardio-pulmonary bypass and level of clamping [95].

Both in open and laparoscopic renal surgery, intra-operative ultrasound (IOUS) is of great importance to locate intrarenal tumors, depict tumor margins, and reveal additional renal lesions. Thus, it influences and may alter surgery [81, 96].

Finally, US is highly operator- and patient-dependent, so the results must therefore always be interpreted with this in mind [93].

1.5.6.4 *Targeted imaging*

To stage sarcomas and lung carcinomas, ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) combined with low-dose CT, is the standard method [97, 98]. However, there is no such recommendation for primary RCC staging. This is due to a low sensitivity (47%-60%) that limits the diagnostic performance [70, 97]. In locally advanced metastatic or recurrent disease, PET may supplement CT [97]**.** Noteworthy is that a negative PET does not exclude advanced disease, though a positive scan has a strong positive predictive value. Recent publications support a role for FDG–PET in restaging, but it does not necessarily detect all metastatic lesions. False positive results can be benign tumors, inflammatory disease or postoperative scarring [98, 99].

The potential of other tracers not excreted by the urinary system, such as ^{124}I-girentuximab and ^{11}C-acetat are still under consideration for regular use [81, 100].

1.5.6.5 *Other available imaging modalities*

RCC bone metastases are predominantly osteolytic with a poor osteoblastic response. The bone scintigraphy with Technetium-99m methylene diphosphonate (^{99m}Tc-MDP) has a specificity of 94%, but is not recommended in staging because of a sensitivity of only 60% [70, 89]. To assess split renal function, and to predict the glomerular filtration rate after surgery, a MAG3 scan can be performed[70] .

1.5.7 Anatomical scoring systems

To determine the feasibility of PN vs. RN, urologic surgeons need detailed information about tumor size, multifocality, depth, nearness to hilar structures and collecting system, renal vascular anatomy and location (anterior/posterior/ upper/lower/middle). Anatomical scoring systems (ASS) provide a common language for standardizing tumor assessment. A high score indicates a more complex location, and PN is performed with a higher risk of complications. The cut-off values for PN can differ according to the surgeon's experience and surgical technique. Several ASS

(figure 5) have been suggested over the last decade, and several have been compared and tested (inter-observer reliability). For all, a higher score was associated with a longer warm ischemia time, a higher postoperative creatinine level, a larger tumor size and an increased risk of perioperative complications [101].

Anatomical Scoring System	Description	Author
Renal Nephrometry Score	Radius, Exophytic/endophytic, Nearness, Anterior/posterior Location)	Kutikov 2009 [102]
PADUA	Preoperative Aspects and Dimensions Used for Anatomical location	Ficarra 2009 [103]
C-Index	Centrality index (continuous)	Simmons 2010 [104]
RTII	Renal tumor invasion index	Nisen 2015 [105]
Contact Surface Area	Contact area between tumor and surrounding tissue	Leslie 2014 [106]
Zonal Nephro Scoring System	Nearness, physical location, radius,organization	Hakky 2014 [107]
ABC Scoring System	Arterial Based Complexity	Spaliviero 2016 [108]

Figure 5: Different Anatomical scoring Systems

In daily practice, ASS combined with a patient's feature and surgeon's experience can optimize surgery [109]; however, the implantation in routine use is questioned [101, 110]. To make ASSes usable, the scoring system must be easy to use in a preoperative setting and not too time-consuming. As most studies that have used ASS have done so retrospectively, one might question the actual real-world use of the systems. Today, most are used as a tool to improve the communication of surgical results and patient selection.

1.5.8 Other related factors that influence the complexity of surgery

A thick layer of or adherent perinephric fat represents a challenge to surgeons in regard to mobilizing the kidney, and identifying the renal vessels and the tumor. All these factors are related to increased blood loss and an increased operative time [111].

Renal vascular variants as accessory arteries, early branching and existence parallel branches that could lead to an incomplete clamping and excessive bleeding, thereby compromising the operative field. Common venous variants, such as multiple renal

veins, late venous confluence, circum-aortic or retro-aortic veins, may cause operative problems if they are not identified preoperatively [112, 113].

1.5.9 Prognostic factors and nomograms

Prognostic factors can either independently predict CSS and RFS, or they can be combined in a nomogram. The factors must discriminate between favorable and unfavorable RCC phenotypes, and be applicable to clinicians and for all patients . Incidentally detected tumors have a better prognosis than symptomatic RCC [65], while patients with local symptoms do better than patients with systemic manifestations [63]. Symptoms like weight loss, anorexia, malaise and reduced overall health all negatively impact survival.

The TNM staging system provides prognostic information based on anatomical characterization. CSS is shorter with higher stage, nodal and metastatic disease [54, 70]. Measurements of systemic inflammation independently predict survival for both localized and metastatic RCC. These are thrombocytosis, neutrophil/lymphocyte-, monocyte/lymphocyte- or platelet/lymphocyte ratio, hypercalcemia, elevated ESR, CRP, ALP, LDH, lowered Hb and Glasgow prognostic score. Several of these are implemented in predictive models, and those not implemented may provide complementary information to clinicians.

1.5.9.1 *Pretreatment prognostic nomogram for non-metastatic RCC*

Different preoperative nomograms for prognostication have been developed. The model suggested by Karakiewicz et al. included age, gender, symptoms, size, CT stage and metastasis in regard to CSS [114].
Raj et al. incorporated gender, mode of presentation, nodes, necrosis and size at imaging to predict recurrence free survival or metastatis free survival (MFS) [115]. The prognostic model proposed by Hutterer predicts the presence of lymph nodes metastasis, in order to identify patients who profited from a lymphadenectomy [116]. Kutikov and Hollingsworth included preoperative comorbidity in their models, and focused on other-cause and other-cancer mortality in addition to CSS [117, 118].

To aid selection for major surgery in patients with supra-hepatic tumor-thrombus, Haddad et al. developed a model to predict survival and major complications [119].

1.5.9.2 *Pretreatment Prognostic models for mRCC*

Models from the Memorian Sloan Kettering Cancer Centre (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) are the two most widely used prognostic models in conjunction with mRCC. The MSKCC model was originally developed in the cytokine era. RCC patients were stratified based on Karnofsky <80%, low Hb, high LDH, high corrected S-calcium and no prior nephrectomy , into good (0 factors), intermediate (1-2 factors) and poor–risk (≥3 factors) [120]. Later, in the targeted therapy era, the IMDC model was created by adding elevated neutrophils and thrombocytosis to the stratification, and changed no prior nephrectomy to >1 year between diagnosis and targeted therapy treatment. However, the same risk-grouping model was used [121]. The IMDC model predicts an OS in the favorable-, intermediate- and poor-risk group of 43, 23 and 8 months, respectively [121].

Other models exist but are less used [122-124]. Furthermore studies have demonstrated that patients with metastasis to bone, liver or the brain have a worse prognosis [125]. Even if the models are established for ccRCC, at the current time the same prognostic criteria apply for all subtypes of mRCC [126].

1.5.10 Pretreatment Biopsy and FNAC

Renal mass biopsies (RMB) were initially indicated in patients with other primary malignancies, solitary kidneys, older age and multiple comorbid conditions [127]. The rising interest and importance in RMB is due to an increased detection rate of small renal masses (SRM), the introduction of active surveillance (AS) [128], ablative treatments (AT) and novel targeted therapies in metastatic disease [70]. Since a significant number of SRM are benign [129, 130], a RMB with a benign histopathology can spare patients from unnecessary surgery [128, 131, 132].

RMB is not indicated for patients with a limited life expectancy, severe comorbidity and low performance when surgical-, ablative- or targeted systemic treatment is not an option, or for patients with advanced disease in a palliative setting [70, 133].

RMB are usually performed image-guided; two cores biopsies (CB) with a co-axial technique and 18-Gauge needle. To ensure an adequate tissue core, quality can be assessed immediately [133-135], as CB seems to have a better diagnostic yield than Fine Needle Aspiration Cytology [136]. Complications are mostly minor and limited, resolving without any intervention [131, 132, 134, 136]. The co-axial technique has reduced the worry of seeding [136]

The distribution of diagnostic (DCB) and non-diagnostic biopsy (NCB) is typically 80% vs. 20% [134]. Because the rate of malignancy in non-diagnostic CB may reach 80%, a re-biopsy is reasonable in most cases [132]. However, it should be kept in mind that the result of re-biopsies may be indeterminate [137]. The diagnostic yield is lowest in small and endophytic lesions [131]. Additionally, anterior-, upper-, medial- and perihilar-located lesions may demonstrate higher rates of non-diagnostic CB [133]. In cystic lesions, the use of CB should be limited to definite enhancing areas as in BC type IV cysts [70, 133], while in large tumors peripheral necrotic areas should be avoided. The overall ability to differentiate malignant from benign lesions, and to determine subtype is good: 81-97% and 86-98%, respectively, but accuracy for tumor grading is lower [133, 136], as is the estimate of sarcomatoid elements [138].

1.6 Management of RCC

Surgical treatment for RCC has been a subject for changes since the late 1980s, and from having only open RN on the surgical repertoire, the treatment options in 2018 include several alternatives. Since the first laparoscopic nephrectomy in 1991, refinement of surgical techniques and the further development of minimally invasive methods have revolutionized patient care. Hand-assisted laparoscopic techniques, laparoscopic endoscopic single-site surgery (LESS), natural orifice transluminal endoscopic surgery (NOTES) and hybrid techniques have evolved [139-142], but

have not gained the same popularity and become as widespread as robot-assisted laparoscopy [143].

During the last few decades nephron-sparing treatment has developed as an alternative to RN for localized disease. The increasing incidence of RCC [14], unsuspected benign histopathology [129], surgically induced impairment of renal function [74], an increased prevalence of medical CKD, and its relation to metabolic- and cardiovascular disorders and events [75], constitute the background for this. Ablative treatment and surveillance may also be used to preserve renal function and limit morbidity.

1.6.1 Management of Localized RCC (cT1-2)

1.6.1.1 Nephron-sparing surgery

From the initially imperative indications for PN, current European guidelines recommend nephron-sparing treatment whenever feasible for tumors ≤ 7 cm, as long as the trifecta of PN with negative margins, functional preservation and minimal complications can be maintained [70, 127, 144]. Former absolute and relative indications still apply for single kidney, bilateral tumors and multifocal tumors, impaired function in contralateral kidney or renal compromising diseases, such as diabetes and hypertension. PN is demonstrated to be oncological equivalent to RN for tumors ≤ 7 cm [145, 146].

Earlier open surgical access was the gold standard for PN, and performed through a flank, subcostal or midline approach. Laparoscopic PN was introduced in 1994, and from the beginning was associated with longer ischemia time and a higher rate of complications. Around 2003, the first robot-assisted laparoscopic PNs (RALPN) were performed, and RALPN soon became popular among surgeons because of a shorter learning curve and greater instrument flexibility [147, 148]. OPN, LPN and RALPN are now equitable procedures, with the two latter mostly performed with intra-abdominal access, although an extraperitoneal approach can be convenient for posterior tumors

The Key Surgical steps are the same for all PN-methods [40, 149]:

1 - **Mobilization of the kidney** within the Gerotas fascia to permit adequate resection.

2 - **Sufficient access** to the hilum **for vascular control**, and to identify arteries, veins and ureter.

3 - Location of the tumor and preservation of perirenal fat overlying tumor(s).

4 - Arterial clamping: The quality of the remaining parenchyma is better preserved with a short ischemia time [150]. An accepted cut-off for a warm ischemia-time is 20-25 minutes [151]. If a longer time is needed, the use of cold ischemia can increase it to 35-44 minutes [40, 152]. Cooling with ice slush is easily obtained for OPN. Clamping of the renal artery during resection reduces blood loss and visualizes tumor margins to help safely complete the resection and renoraphy [40]

To reduce global ischemia, additional concepts, such as early unclamping [153], zero ischemia with segmental clamping [154], parenchymal clamping [40] and off-clamp procedures [155] have evolved. The preferred method depends on surgeon preference. The renal preventive role of intravenous mannitol infusion before clamping is debated and controversial [156].

5 - **Tumor excision** with free margins: Large, complex or endophytic tumors lead to more devascularized parenchyma than small, simple and peripheral tumors [157, 158].

Negative margins are oncological adequate, with no need for an additional parenchymal rim. Tumor enucleation, including the tumor pseudocapsule, reduces excised normal parenchyma, bleeding and ischemia time [159].

Biopsies of resections surface to ensure that free margins are seldom used [160].

6 - **Renoraphy and reconstruction** of the collecting system: Closing of the collecting system with an absorbable suture to avoid urinary leakage. Renoraphy is most often performed with a running inner suture for hemostasis and an outer parenchyma-closing suture. Hemostatic agents may also be applied at the resection surface.

1.6.1.1 *Radical nephrectomy*

RN can be performed when PN is not feasible, i.e., a non-functioning kidney, an insufficient renal remnant, renal vein or caval thrombosis, complex tumor location and when comorbid with a need for anticoagulants [70].

Depending on tumor size, patient habitus and the surgeon's skills a surgical approach is determined, but if possible MIM-RN is preferred for T2a, though for a large tumor like T2b an open approach is often preferred.

ORN and LRN share the same operative principles with early vascular control, the removal of the kidney with an intact Gerotas fascia and the avoidance of specimen

traumatizing as the key steps. They are found to be equivalent concerning long-term oncological results [161]. The advantages of LRN were soon recognized by both surgeons and patients, and included shorter hospital stays, faster convalescence, less use of analgesia, less bowel symptoms and improved cosmetics [71]. Regarding perioperative outcomes, LRN could be a good alternative in elderly patients or overweight, though also more challenging in the obese patients [162].

An intact specimen is extracted in an impermeable bag through a Pfannenstiel incision, or a muscle-splitting extension in conjunction with one of the ports. Robot-assisted LRN is not as widespread as RALPN, partly due to the expenses.

Open RN is usually performed with an intra-abdominal approach (subcostal or midline incision). A retroperitoneal approach maybe preferred in patients when the intra-abdominal is complicated or inaccessible (i.e. severe adhesions).

1.6.1.2 *Ablative treatment*

Ablative treatment (AT) destroys tumors and saves renal parenchyma. Radiofrequency ablation (RFA) and Cryoablation (CA) are mostly used, but high-intensity focused ultrasound (HIFU) and microwave therapy also exist. Guidelines recommend AT for tumors < 3 cm [70, 163], but is also tried on larger ones [164]. AT is an option in patients not suitable for surgery, and currently RFA and CA show comparable MFS and CSS [164-166]. In a recent meta-analysis, renal function after AT and PN is reported to be similar [167]. A biopsy should be obtained before or during ablation, since there is no final histopathology specimen. Recurrences are slightly more frequent than PN; however, while retreatment after AT is a viable option [165, 166, 168], whereas surgical salvage after PN is surgical challenging [169].

1.6.1.3 *Active Surveillance*

Active surveillance (AS) comprises the combination of initial observation with repeated imaging, with a delayed intervention performed if rapid growth or clinical progression occurs in small renal masses (SRM) [170].

Most SRM grow slowly: 0.2 – 0.6 cm/year, few are high grade (5% of <3cm) and the metastatic potential is low [171-174]. Recommendations call for risk stratification based on age and competing causes of mortality, as well as renal mass biopsy for AS candidates to help prevent unnecessary overtreatment [70, 170, 175]. Delayed intervention does not limit or complicate eventual treatment [176]. Delayed treatment is usually considered when the doubling time is <1yr, the growth rate is 1 cm/year or the tumor reaches 3-4 cm in diameter [170] .

Non-RCC related mortality after surgery for SRM is significant in older patients.[117]. For patients > 70 yrs with surgically treated RCC < 4 cm, 40% died of non-RCC causes during the first five years [118]. AS is regarded as a safe management for old and comorbid patients [70]. For patients with larger tumors and severe competing risks, AS might be considered as an option, though the risk of metastases increases [177].

If comorbidity and compliance render active treatment contraindicated, the patient is not a candidate for AS. In such cases, watchful waiting with symptomatic and palliative treatment when needed is a better strategy [70, 178].

1.6.2 Management of Locally Advanced RCC (cT3a-c)

RN is the recommended treatment for T3a with perinephric fat invasion. The management of T3a with venous extension is more complex, with the procedure ranging from almost a standard RN for a small renal vein thrombus to cardiopulmonary bypass (CPB) for right atrial thrombus [179]. Both the thrombus level and degree of occlusion impact the choice of surgical approach (figure 6). Grouping systems are made for venous tumor thrombi (0-IV) and for blend thrombi (A-D), to aid management [180, 181]. In older series, the incidence of thrombus in vena cava inferior (IVC) is reported to 4-10% [40, 181, 182]. Prognostic factors for survival after surgery are PS, TNM, level of thrombus [119], invasion of the renal vein wall, diameter and rounded vs. fragile appearance of the thrombus [183].

Level of RCC Tumor Thrombus (TT) after Blute [181]				
TT-Level	Incidence	% of TT	Cranial extent of TT	Management of TT
0	12%	65%	Renal vein	Minimal modification of standard approach
I	2%	10%	Within < 2cm over renal vein ostium	Milking of TT, clamping of IVC, contralateral renal vein, lumbals
II	3%	15%	Below hepatic veins	Clamping of IVC below and above, contralateral renal vein and lumbals
III	1%	5%	Between hepatic veins and diapragm	Clamping depends on complete or partial occlusion, liver mobilization, VVP, CPB, DCA
IV	1%	5%	Above diaphragm	CPB, VVP, DCA

Figure 6: CPB – cardiopulmonal bypass, VVP - venovenous bypass, DCA – deep cardiac arrest

Patients with M0 and good PS should be offered radical surgery, since five-year CSS is 18-68% with complete resection [184, 185]. Unfortunately, in patients with VTT synchronous M1 is frequent (25-63%). Complications and mortality is 30% and 3-8%, respectively. Thus, preoperative patient counselling is important [181]. Furthermore, these procedures need careful preoperative planning, often with the involvement of an experienced anesthesiologist, vascular-, thoracic- and liver/transplant surgeons [184]. Preoperative renal artery embolization or an IVC filter is not recommended [70, 181, 184].

1.6.3 Management of Locally Invasive RCC (cT4)

A total of 5-15% of patients present with RCC in stage T4. This stage reflects a tumour invasion beyond Gerotas fascia or the involvement of neighboring organs such as the colon, spleen, duodenum, pancreas or liver [186]. These tumors are often aggressive, with high-grade or sarcomatoid features. Two-thirds have N+ and/or M+ disease. Surgery for this is associated with a higher morbidity and mortality, and even unresectable disease. Unfortunately, it is often difficult to identify the invasiveness preoperatively [186, 187].

Hence, a T4 tumor necessitates a multidisciplinary assessment before treatment.

CSS for T4 is 37 months and 8 months for non-metastatic and metastatic tumors, respectively. The disease often recurs despite negative surgical margins. An incomplete resection or debulking (kidney with adjacent organs) is also rarely indicated, with a positive surgical margin predicting a worse prognosis [188]. Some report a positive effect of renal bed radiotherapy postoperatively [189], but trials are needed to evaluate its usefulness [190].

1.6.4 Adrenalectomy

Ipsilateral adrenalectomy does not improve survival, Thus, today it is not routinely recommended for RN or PN [70, 191], but should be done concomitantly if preoperative imaging reveals pathology or is suspected intraoperatively [192, 193]. The incidence of ipsilateral synchronous adrenal metastases is low (1-2%). It occurs usually with large, high-grade tumors with venous involvement. The primary tumor location is not predictive[70].

1.6.5 Lymphadenectomy

Lymphadenectomy (LND) for RCC remains controversial, and is not recommended when there is no suspicion of lymph node disease. A study from EORTC showed 4% positive lymph nodes in cN0M0 patients, though with no survival benefit for extended LND (eLND). LND was therefore considered a staging procedure for lymph node metastases [194], influencing the current trend towards less use of LND [195].

In high-risk patients with large tumors and adverse features, there are retrospective studies that suggest a benefit of eLND [70, 196, 197]. The eLND includes a resection of the interaortocaval nodes, of which 35-40% could be involved without involvement of the hilar nodes [196].

Except for a slightly higher risk of surgical bleeding, no increase in complications by doing LND is documented. Nevertheless, this acceptable morbidity is based on limited LND. One study indicates that the rate of lymphoceles, bleeding from major vessel and lesions to adjacent organs may increase with eLND [197]. Consequently, the benefits of LND must be carefully balanced against the total complexity of surgery, tumor stage and patient comorbidity.

Current preoperative image staging (CT/MRI) is used to detect pathological nodes. However, solitary enlarged lymph nodes assessed pre- or intraoperatively can often be inflammatory. Such a finding should not rule out a radical surgery, but a LND should be performed [198].

The fraction of lymph node-positive incidence varies from 13-30 % in older studies [194] to 6% in more recent ones and is higher with increasing stage [196]. Lymph node metastases harbor a poor prognosis and survival is comparable to systemic metastasis, as five-year survival worsens for all stages when combined with pN+ disease. Prognosis worsens with more positive nodes and extra nodal growth [197]. The lymphatic spread in RCC is often multifocal [199], and do not follow a strict template. Sentinel node is not yet an option for RCC [200].

1.6.6 Additional surgical considerations

1.6.6.1 *Surgical Approach to multifocal and bilateral tumors: hereditary and sporadic*

More than one renal tumor increases the surgical complexity. The surgeon must be aware of AS strategies, “the 3cm–rule”, tumor enucleation, multiple PN, re-do surgery and complex renal reconstruction. All these are done with the goal of preventing cancer dissemination and retaining maximal renal function with as few interventions and as low morbidity as possible.

Biopsies, genetic testing and MAG3 renogram must be considered as helpful tools. In case of bilateral tumors, surgery could be done concomitant trough a midline incision, knowing that the risk of complications is greater than with staged procedures. A staged PN reduces the risk of acute renal failure, but requires a second surgery. With hereditary RCC and the possible need of repeated resections in the same kidney, the preservation of Gerotas fascia, minimizing hilar skeletonizing and avoiding unnecessary suturing at the tumor base is emphasized [201, 202].

1.6.6.2 *Conversions from minimally invasive to open procedures*

In a British publication, the conversion rate is 4% for PN. Conversions were caused by bowel perforation (5.9%), hemorrhage (11.8%), failure of progress (17.7%), difficult dissection (23.5%) and other reasons (23.5%). The reasons for the 5.5%

conversions for RN were adhesions (9.4%), size of tumor (12.0%), difficult dissection (18.8%) and hemorrhage (28.2%). The conversion rates for simple nephrectomy are higher (6.6%), and mainly due to (51%) difficult dissection or failure to progress [203].

1.6.6.3 *Concomitant surgery*

The increased detection of RCC is paralleled by the detection of other intra-abdominal pathology. RN combined with benign GI surgery, does not worsen the perioperative outcome, but acute renal failure was more frequent when combined with aortic surgery [204]. Synchronous GI surgery for malignant conditions had more complications, however not significant. Long-term survival was mostly related to GI malignancy. If feasible, with a moderate comorbidity, good PS and young age, surgery should be considered to be performed in a single setting. Alternatively, lesions could be treated in sequence, with the most aggressive cancer first. The ideal approach must be individualized [204].

1.6.7 Complications

1.6.7.1 *Intraoperative complications*

Intraoperative complications must be handled the moment they occur. The most frequent complication is bleeding due to a vascular injury (2%) during hilar dissection. It is usually avulsion or tears in veins, and more seldom from the inferior vena cava. Malfunction of the endovascular stapler is a feared complication with potentially serious consequences.

Injury to the spleen is the second most frequent reason for bleeding (1.4-8%), with bleeding from liver or the pancreas occurring more infrequently.

Bowel injuries (0.8%) are usually thermal (50%) or traumatic during access (32%). They cause little morbidity if they are recognized and sutured intraoperatively. Diaphragmatic injuries (0.6%) during dissection around the upper pol should be sutured and drained [40, 205].The rate of intraoperative transfusion is seldom reported, but transfusion during stay is reported to be 8.5-9.7%[206].

1.6.7.2 *Postoperative complications*

Postoperative complications are deviations from the normal postoperative course, and ranked by Clavien-Dindo with a severity from 1-5 assessing the need for intervention (pharmacological treatment, transfusions and surgical intervention) [207].
Comorbidity is related to complications and length of stay. Patient at a high age, high ASA score and esCKD are more susceptible to complications [208]. Patients treated at high-volume hospital (HVH) experienced a lower rate of complication than patients treated at a low-volume hospital (LVH) [206, 209].
Complications rates after PN and RN are reported to be 16-26% [210-212]. Major complications (defined as Clavien-Dindo ≥3) are reported to be 5.4% for PN and 3.1% for RN [203]. In part, urinary leakage after PN constituted the difference.

The specter of complications is similar for RN and PN: respiratory, infection, posthemorhagic anemia, bleeding, cardiac problems and bowel problems.

Rates of complications do not differ significantly between ORN, hand-assisted or pure LN [213]. Gill previously reported the need for an extra procedure (re-do) for LPN vs. OPN of 6.9% vs. 3.5 %, respectively [214].

Complications rates after PN and RN are reported to be 16-26% [210-212]. Major complications (defined as Clavien-Dindo ≥3) are reported to be 5.4% for PN and 3.1% for RN [203]. In part, urinary leakage after PN constituted the difference.

A total of 80% of major complications occur in-hospital, whereas 70% of minor complications occur post-discharge [211]. The re-admission rate is 5.9%, highest for OPN and lowest for LPN [215]. Early identification of complications is essential to help reduce morbidity.

Reoperations most often occurred because of bleeding bowel perforation or infection at the surgical site. Embolization is also an option for arterial bleeding.

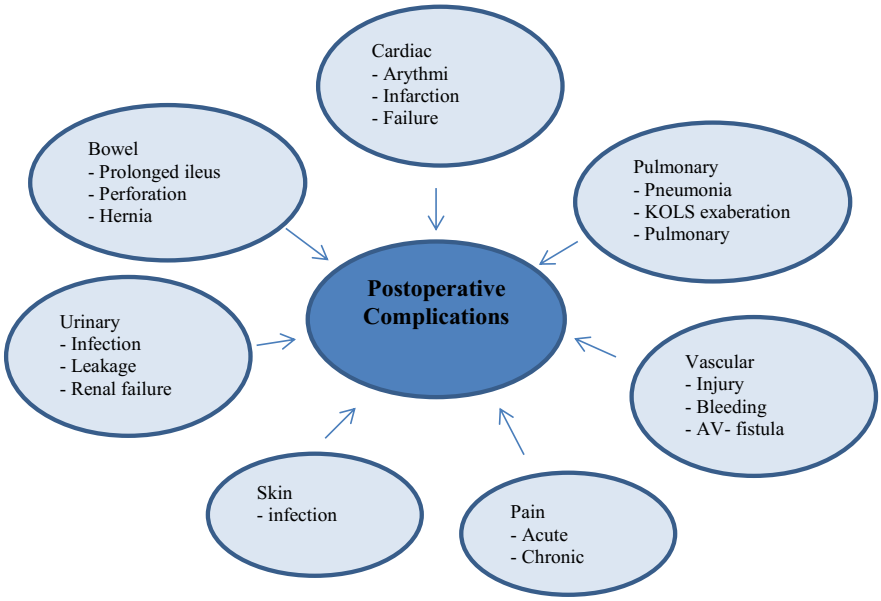

Figure 7: Complications that can occur after renal surgery

1.6.7.3*Mortality*

Perioperative mortality is regarded a quality measure of patient selection and treatment. It was reduced from 5% in the 1970s to an in-hospital mortality (IHM) of 0.7-1.4% [64, 206, 210] and 30-day mortality (TDM) of 0.9-2.8% [216, 217] in contemporary materials. Modern figures for mortality after cytoreductive nephrectomy are still higher (3.2-4.2%) [216, 217].

IHM and TDM increase with an increasing comorbidity and complications [203, 210, 211]. Causes of death differ, but cardiac disease, infectious diseases, embolisms and bleeding are typically related [212, 217]. Gastrointestinal and urologic complications were associated with IHM [210]. As described by Cloutier, tumor stage is determinant of TDM. Furthermore, patients aged 70 -79 doubled, and those >80 tripled their mortality risk compared to those younger [216].

For thrombus above the hepatic veins, Abel reported a TDM of 5.6%, and 90-day mortality of 10.5% (8.7% for level 3 and 11.8% for level 4), thereby illustrating the complexity of this major surgery [218].

In data from the UK, TDM is lower for PN than for RN (0.10 and 0.52% for PN and RN, respectively) [203]. Patients treated at a HVH had less risk of dying during the perioperative period, compared to a LVH [219]. To improve outcomes, it is important to avoid the "failure to rescue". Therefore, a department must postoperatively prevent complications, and organize the postoperative surveillance so that complications are caught early and treated by a competent specialist as soon as possible [203, 210, 212, 220].

1.6.8 Surgical margins

Negative surgical margins (NSM) are among the goals of oncological surgery. However, positive surgical margins (PSM) are reported to occur in 0-7% with OPN, 1-4% with LPN and 4-6% with RALPN [221, 222].

PSM occurs more often with smaller, endophytic, complex and centrally located tumors, but also when multifocal, there is a lack of a tumor pseudocapsule and in PN performed for imperative reasons [221-223]. Adherent (toxic) perinephric fat could create difficulties in defining the right plan of resection.

Contradictory results are published regarding the prognostic value of PSM. Some report an increased recurrence of both localized and metastatic disease [224]. However, Kang et al. found no significant difference between PSM and NSM according to recurrence after PN for T1 ccRCC [221]. Shah et al. found a higher recurrence in patients with high-risk and high-stage RCC with PSM [225]. Even so, the PSM and recurrence do not appear to influence CSS, so careful surveillance may be sufficient for first-line management and re-resection, and nephrectomy should probably remain a second option [223].

1.7 Management of mRCC

1.7.1 Metastatic pattern in RCC

Synchronous RCC metastasis occurs in 20-30% with a falling incidence [226]. Another 20-30% with primarily localized RCC will develop metastasis, of these, 50% will recur within two years and 75-80% within five years [227]. After 10 years of a disease-free interval approximately 10% of those still at risk will experience

metastases. Metastasis most frequently occurs in the lungs, and are mostly multiple. The route of pulmonary metastatic RCC is hematogenous through the renal sinus, renal veins and vena cava, leading to pulmonary metastases.

Drainage through the lumbar veins facilitates the spread to the low-pressure superior and inferior paravertebral venous plexus and to lumbar and pelvic veins, generating metastasis in the CNS, the head and in the central- and peripheral bone.

Nodal involvement could be located in the hilar, aortic, caval, thoracic duct and thoracic nodes, with these different pathways resulting in a spreading to unusual sites. The primary renal tumor and their metastases can differ in biological characteristics, and changes in gene-expression influence RCC aggressiveness. Early metastasis, i.e. < 9 months after nephrectomy, have a worse outcome than late metastasis (> 5 years) [228].

1.7.2 Nephrectomy in patients with mRCC

Historically, two randomized studies [229, 230] showed an improved OS for cytoreductive nephrectomy and interferon over interferon alone. Combined, these two studies showed an improved OS of 6 months, 13.6 vs. 7.8 months for CN, followed by IFN vs. IFN alone [231]; favorable patients experienced the best results from this combination.

With the introduction of targeted therapy (TT) for mRCC, most patients in the early studies were nephrectomized. Several retrospective studies have shown a survival benefit of the combination of CN and TT over TT alone [232, 233].

Two prospective randomized studies have investigated the effect of CN in conjunction with TT. The CARMENA study was recently published, and revealed no difference in OS for CN+Sunitinib and Sunitinib alone [234]. However, the study has been criticized due to patient selection, and thus general validity. Nonetheless, the study demonstrates that for patients with intermediate and poor-risk disease, and a high metastatic tumor burden, upfront CN does not seem indicated. The other study, the SURTIME-study [235] showed an improved OS after deferred CN over

immediate CN. Unfortunately, the SURTIME study is severely underpowered, so conclusions are therefore difficult to draw.

After these studies, CN is still a valid treatment option for carefully selected mRCC patients. For patients with a low metastatic burden and time point, the start of systemic therapy might be awaited. It is reasonable to presume that international guidelines will be updated within a short period of, hence reflecting the results from CARMENA and SURTIME.

Morbidity and mortality rates after CN are not negligible, and a thorough preoperative risk evaluation is essential to help reduce this. Perioperative mortality is higher for CN than RN, 2.4% vs. 0.6-0.9% [203, 209, 216]. A failure to rescue occurs more frequently in patients aged > 75 with postoperative infections, cardiac-, pulmonary or vascular problems [236]. Predictors of postoperative morbidity are also pathological lymph nodes, liver metastasis and the need of intra-operative blood transfusions.

Unaffected by the newer studies, CN is still an option to palliate symptoms (bleeding, pain, paraneoplastic manifestations, etc.). Even so, the number of such patients are limited, and is infrequently done because the symptoms can be treated without surgery and hematuria managed by angio-embolization.

Reports on nephrectomy, combined with a complete resection of metastasis (single or oligometastastic RCC), that could be curative are few, but do exist. Removal of the primary tumor may restore immune competence in the mRCC, and the temporary regression of metastasis after CN is also observed [237].

1.7.3 Management of RCC metastases

Studies on metastasectomy are retrospective and comparative, and no randomized studies exist. It is difficult to demonstrate a favorable outcome since reports on metastases to various organs are very heterogeneous. Surgery is often mixed with systemic and/or radiotherapy.

An OS of 41 months is reported for a complete resection of limited metastasis, and the OS is longer for complete than incomplete resections[70]. If a complete resection is possible and patient in good performance status (i.e. single or oligometastases to the lungs), a resection or lobectomy are the most used options, but ablative techniques are also reported[238].

Surgical resection should be considered if possible for bony metastasis causing pain. Surgery is important to stabilize pathological fractures (i.e. the femur or humerus) or treat medullary- or root compression by metastases in vertebrae. The latter is often combined with adjuvant radiotherapy; otherwise, stereotactic radiotherapy is an alternative [70]. Patients with brain metastasis will benefit from stereotactic radiotherapy, and especially if solitary. It could also be combined with surgery or whole brain radiation [70].

1.7.4 Management of locoregional recurrence

Locoregional recurrences after PN, AT and RN include intrarenal and perirenal relapse. The most effective salvage procedure is not yet defined, but repeated AT or new surgery is advocated for intrarenal recurrence if possible. Most common are locoregional recurrences in the renal vein or fossa, or in lymph nodes and adrenals. A short time to relapse, a large size, sarcomatoid features and positive margins after re-surgery negatively influence the prognosis. If feasible, surgical removal can impact local control and survival [70, 239]. Systemic therapy or stereotactic irradiation should also be considered when surgery is impossible.

1.7.5 Systemic treatment in mRCC

Systemic therapy works through various mechanisms of actions to hamper tumor growth. Many new agents are introduced at a high speed and the field is rapidly changing. Current challenges are when to initiate, switch and discontinue, and how to sequence treatment. These decisions are affected by patient performance status and tolerance, symptoms from the disease, imaging and drug availability. The guidelines differentiate between preferred drugs recommended for first-line and subsequent treatment lines, stratified for prognostic groups (IMDC or MSKCC). Systemic

therapy is not a primary focus of this thesis. So in the following, the different treatment options are briefly discussed with the recommendations mentioned reflecting the standard of care as of June 2018.

1.7.5.1 *Immunotherapy*

The spontaneous regression of metastases after nephrectomy was the earliest evidence that the immune-system was involved in RCC. The response was infrequent (1%) and often transient mediated by T- and B-lymphocytes [40] but stimulated to the development of immunotherapeutic approaches.

The cytokines interferon-α (IF-α) and interleukin-2 (IL-2) are immune-modulating proteins [240]. IF-α had response rates of 16-26%, and OS 8.5 months, this would be 2.5 months longer than for medroxy-progesterone [241]. The associated toxicity was severe for high-dose *IL-2*. The response rate was 15-20% and 7% of responders exhibited a complete response, of which 60% were without recurrence at FU [242].

Allogenic Hematopoietic Stem Cell Transplantation and vaccine therapy are considered experimental [40].

The newest set-up for immunotherapy is the immune checkpoint inhibitors and show promising results in regard to progression free survival (PFS), OS and side-effects. They are human monoclonal antibodies towards receptor involved in tumor suppression, and intend to upregulate the immune response. Nivolumab inhibits the programmed death ligand 1(PD-L1) receptor expressed on macrophages, T- and B-cells. Ipilimumab is an inhibitor of antigen 4-receptor (CTLA-4) expressed on cytotoxic T-cell[40, 70].

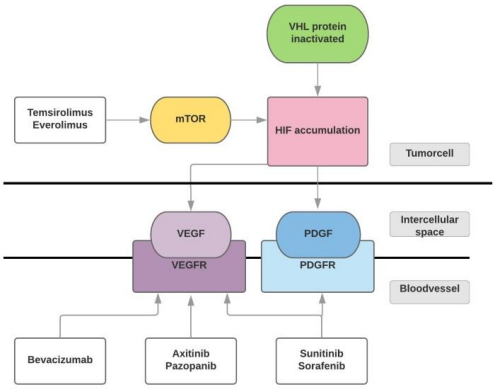

Figure 8: Inactivated VHL protein results in HIF accumulation and up-regulation of growth factors. When secreted they bind to tyrosin-kinase receptors on the surface of endothelial cells and vascular pericytes, resulting in cell migration and proliferation (after WHO 2016)

1.7.5.1 *Targeted therapy*

In ccRCC, hypoxia-inducible factor (HIF) accumulates due to VHL inactivation, and results in an overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which in turn promotes angiogenesis. The function of VHL protein has identified targets for therapy. Targeted therapy (TT) includes the tyrosine-kinase inhibitors (TKI), monoclonal VEGF antibodies and the mammalian target of rapamycin (mTOR).

TKIs inhibit principally the VEGF receptor (VEGFR) and the PDGF receptor (PDGFR) with both anti-tumor and anti-angiogenic activity. Sunitinib was used as treatment from 2006/2009 and demonstrated a partial response rate of 30-40% with PFS and OS of 5-6 mo longer than cytokines [243, 244]. It is the most widely used oral TKI in mRCC. Other established TKIs are sorafenib, axitinib, pazopanib and cabozantibib, the two latter demonstrating less side-effects [40]. Newer TKIs include levantinib and tivozantinib are still under evaluation.

Bevacizumab is a monoclonal VEGF antibody used for patients who have failed with

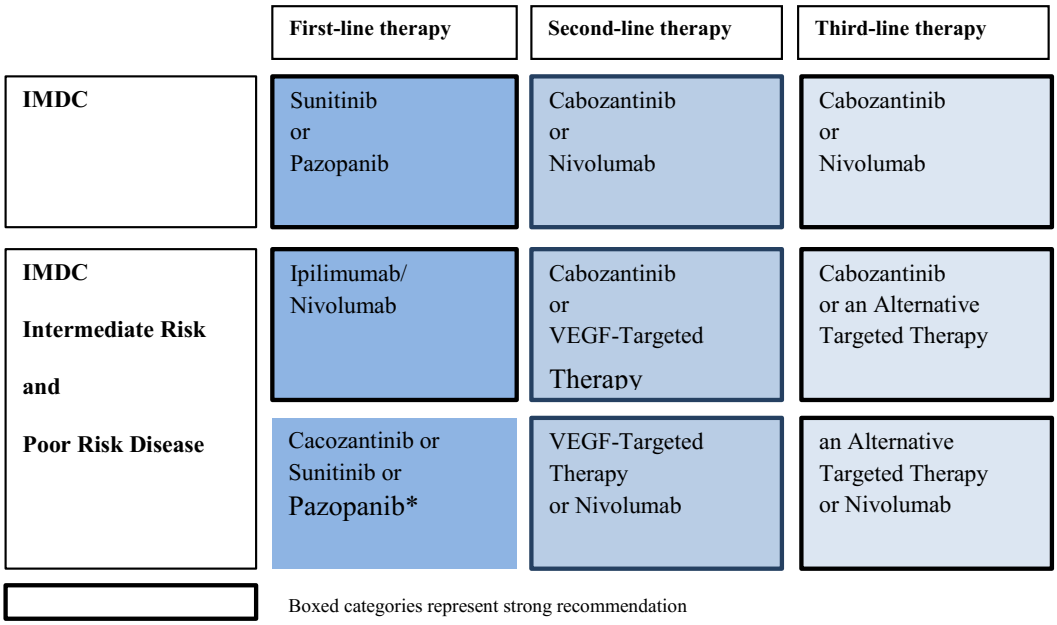

Figure 9: EAU guidelines 2018 for the systemic treatment of metastatic clear-cell renal cell carcinoma.
*pazopanib for intermediate risk only

first-line TKI alone or combined with IF-α[70]. mTOR is an intracellular protein important in signal cascades for growth factors, and blocks HIF translation. The mTOR inhibitors temsirolimus and everolimus is recommended for second-line therapy [245].

1.7.5.2 *Chemotherapy*

RCC is considered chemo-resistant, and approaches with 5-FU, platinum compounds and vinblastine have been disappointing. The combination of gemcitabine with doxorubicin or TKIs could be an option for sarcomatoid RCC [40, 70, 246].

1.7.5.3 *Aspects of metastatic non-CCRCC*

The recommendation applies for mccRCC, and for the time being there is no standard approach or proven efficacy metastatic non-ccRCC [126]. There is a lower response rate in pRCC to TKIs probably because they do not harbor the VHL-mutation. Collecting duct carcinoma is treated with gemcitabine and carboplatin with modest effect.

1.8 Survival

Figure 10 illustrates updated Norwegians numbers on relative survival. For localized disease, there is a 5-year RS approaching 90% compared to the mid-1990s, when it was just below 80%. In comparison with the older Robson publication from 1969, the 5-year survival for localized disease (Robson stage I = T1 and T2) was 66%.For advanced and metastatic disease, the numbers also show improvement over the last few decades [14].

5–year Relative Survival by stage, gender and period of KC-diagnosis in Norway [14]

Stage	**1982-86**		**1992-96**		**2002-06**		**2007-11**		**2012-16**	
Total	44.8	41.7	52.9	52.0	63.1	60.3	71.6	66.6	74.8	73.7
Localized	70.0	71.4	76.6	76.9	86.7	85.0	89.0	86.8	90.0	89.6
Regional	49.3	44.2	51.6	53.0	48.9	54.3	47.7	58.6	51.3	63.7
Distant	7.2	6.8	2.8	6.2	11.1	8.8	16.4	9.3	11.4	10.5
Unknown		-	41.3	33.4	63.6	68.8	80.6	70.0	51.6	43.7

Figure 10: RS presented in % by stage and period of diagnosis. Females in black and men in blue.

CSS is illustrated in figure 11. For pT3a tumors CSS differs according to the type of perirenal invasion. Only renal vein invasion, only perirenal fat invasion and a combination shows a 75%, 66.9% and 32.4% 5-year CSS, respectively. Similarly, for pT3b tumors the CSS was 36% with concomitant perirenal invasion, but reached 65.9% without. To have nodal disease double the CSM, and for patients with metastatic disease, the CSM was four times higher than without metastasis [247].

ccRCC presents with advanced disease (T3-4, N+, M+) at 28% compared to 17% in pRCC and chRCC, with the latter two demonstrating a better long-term survival [248].

Renal Cell Carcinoma 5-year Cancer Specific Survival								
Stage	T1a	T1b	T2a	T2b	T3a	T3b	T3c	T4
5-yr CSS	94.9	92.6	85.4	70	64.7	54.7	17.9	27.1

Figure 11: Cancer specific survival for RCC in % , adapted from Novara 2009 [247]

1.9 Follow-up(FU) for RCC

The focus of the present thesis is on treatment, so therefore FU is only summarized. Follow up programs (FUP) after PN or RN should identify surgery-related complications, follow renal function and detect recurrence or metastasis. Different FUP exists [70, 249, 250], but there is no consensus or high-level evidence on the optimal FUP or its duration. In general, there is very little high-level evidence for recommendations given for follow-up in RCC.

It should be individualized and risk-stratified [70], and patients experience better survival within FUP than without [250]. Most FUP is limited to five years when the risk of recurrence is highest [227, 250]. Guidelines recommend subsequent imaging control biannually for intermediate- and high-risk groups (UISS risk stratification) [70]. Clinical examination, blood samples and chest imaging plus a CT/MRI of the abdomen constitute the usual FUP visit [227, 250].

Postoperative scoring systems and nomograms aim to discriminate risk groups and predict recurrence and survival. They integrate clinical information, in addition to the histopathology. Stratifying patients postoperatively into low-, intermediate- and high-risk groups for recurrence is done with the Leibovich risk model and the UCLA Integrated Staging System (UISS) [61, 251]. Leibovich included pT, pN, tumor size > 10 cm, Fuhrman grade and necrosis, while Zisman restricted it to pT, Fuhrman grade and ECOG-PS. Another validated prognostic algorithm, the SSIGN, predicts survival and defines five risk groups [60]. Nomograms such as Kattan, Sorbellini and Karakiewich sum different weighted factors to predict the probability of 5-y RFS, CSS and OS [252-254]. One is also made for PRCC, while most of the others are constructed for ccRCC [255]. Surgeons can better counsel patients postoperatively by using these and designing follow-up programs FUP suitable to detect treatable recurrences in time. The intermediate- and high-risk groups need a more intensified FUP, with more frequent imaging than the low-risk group. In case of recurrence or metastasis, survival may be improved in suitable candidates for systemic therapy, surgery or radiotherapy [256, 257].

2. Aims of the Thesis

General aims

The major aim of this thesis was to explore whole nation data, reveal trends and obtain updated numbers on KC treatment in the six-year-period from 2008-2013. To the best of our knowledge, this is the first register study on KC in Norway to such an extent. Both in the years before and during the study period, the field of KC management has undergone substantial changes. The new guidelines supported the implementation of nephron sparing and laparoscopic surgery. In addition, active surveillance and ablative treatment were emerging methods. Furthermore, the use of pre-diagnostic biopsies for tailoring treatment was introduced. Since the Norwegian government set hospital volume requirements for hospitals to do KC surgery, we could also investigate hospital volume vs. patient outcomes in our cohort.

Paper I

The purpose was to describe the use of diagnostic biopsies for localized and mRCC in a population-based setting, and to evaluate whether the practice patterns were in line with updated guidelines. We looked for predictors for performance of RMB, and if doing RMB influenced treatment.

Paper II

The aim was to investigate whether Norwegian surgeons implemented MIM and PN according to changes in European guidelines. Analyses of national and regional trends and patterns in KC surgery were performed. Lastly, outcome in terms of survival was studied.

Paper III

Norwegian health authorities introduced new requirements for hospitals to continue to perform KC-surgery, acknowledging that surgical volume was most likely associated with improved patient outcomes. We wanted to establish Norwegian data on outcome, and compare the impact of hospital volume on outcome in regard to TDM following KC surgery

3. Material and Methods

3.1 Permissions and ethical considerations

Since 1953, Norwegian clinicians and pathologists have been requested by law to report all new cases of cancer to the population-based Cancer Registry of Norway (CRN). The CRN is further connected to the Norwegian Population Registry (NPR). Information about all types of patient/doctor contacts is transferred from the national public health-care system to the CRN. Inclusion in the CRN is mandatory, which is in accordance with national regulations; as insofar present study did not need informed consent from the patients when data was gathered at the CRN.

3.2 Data extraction from the Cancer Registry of Norway

At the CRN, datasets from 4,465 KC patients (ICD-10 code C64) diagnosed during the six-year period from 2008-2013 were extracted from the primary database (figure 12). The datasets consist of demographic, tumor-related-, treatment-related- and follow-up-related variables. Different subsets of data were used for the three different articles, as illustrated in the flowchart. At the CRN, all entered data was manually assured from the registry source.

During this process, 16 patients were excluded due to an improper diagnosis, and the datasets for 4,449 patients were transferred to an anonymous database for subsequent analyses. All patients were restaged according to the TNM 2009 edition based on reading histopathology reports, clinical reports, irradiation reports, surgical records and diagnoses and procedures noted at discharge. Data on survival was obtained from the CRN (Paper I, 30 June 2016; Paper II, 31 Dec. 2016; Paper III, 31 Dec. 2014).

3.3 Study population

Paper I: From the anonymous dataset of 4,449 patients, patients <18 year, with a lack of biopsy data and date of diagnosis < 30 days prior to death or autopsy, were excluded and the final study population consisted of 4,051

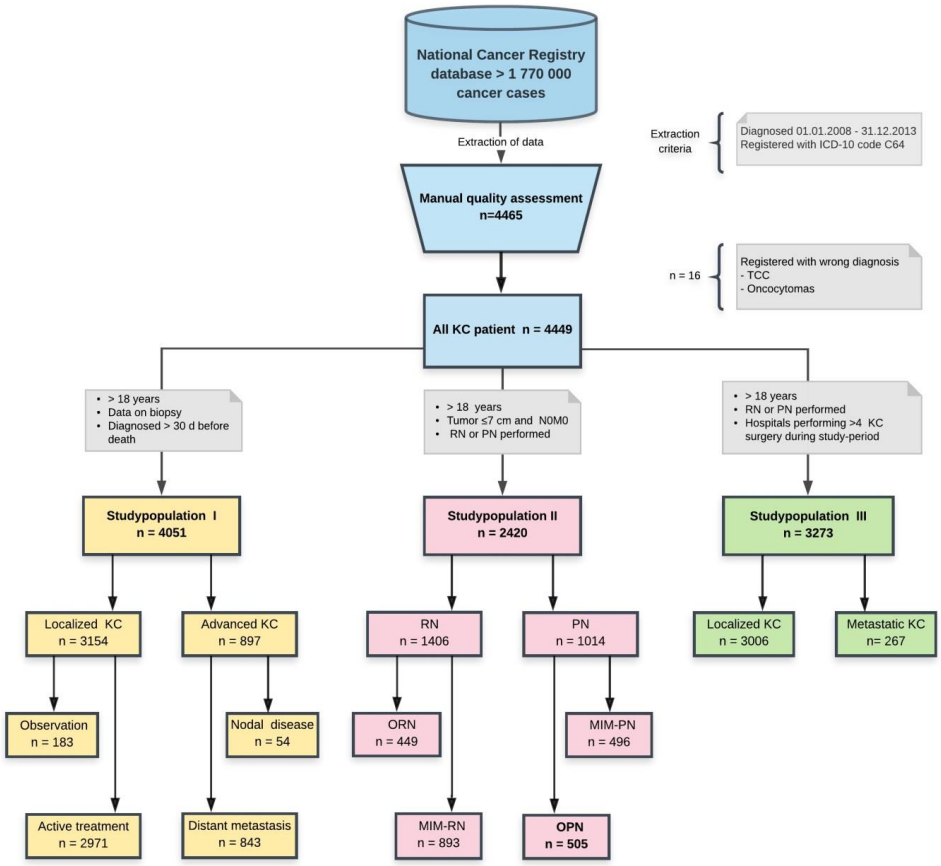

Figure 12: *Flowchart illustrating the different studypopulations*

Paper II: From the anonymous dataset of 4,449 patients, patients ≥18 years, N0 M0, KC≤7 cm and treated with RN or PN were included in the final study population, a total of 2,420 patients remained.

Paper III: A subset of data for hospital stay and surgical conversions was available and consisted of all patients for 2010-2013, but data were missing in part from the two first years. A total of 3,313 patients ≥18 year, treated with PN or RN, remained in the dataset. Hospitals performing less than four KC surgeries during these six years

were excluded (average of ≤0.5/year). The final study population consisted of 3,273 patients.

3.4 Statistical analysis

Standard descriptive statistics: Mean values are presented as Mean ± standard error of means (SEM). Median and interquartile range (IQR) is used for descriptions of variation within groups.

T-test: Comparison of continuous variables, normally distributed.
Mann-Whitney U-test: Comparison of continuous variables, non-normally distributed.

Exact chi–square test (χ 2): To determine the significant level of difference for categorical data. A p–value < 0.05 was considered statistically significant.

Bootstrapping: 1,000 resamples for TDM rates with associated confidence intervals (CIs) are used in Paper III because the proportion of TDM I is low (simulate TDM rates for 1,000 cohorts of 3,273 patients, i.e., 3,273,000 patients).

Cox proportional regression: Multivariate analysis.
Kaplan-Meier method: A survival analysis/survival plot of incomplete observations and Log-Rank test were used to determine statistical significance between groups.

Overall survival (OS): Time from diagnosis or surgery to death irrespective of cause.
Cancer Specific Survival (CSS): Time from diagnosis or surgery to death from cancer.
Relative survival: Calculated by the method of Pohar-Perme [258].

Competing risks assessment: Conditional probability estimates for different groups.

Multiple logistic regression models: Established without pre-selections of variables (Papers II, III).

Joinpoint Regression Analysis: Calculated using Joinpoint Regression Program, Version 4.5.0.1- June 2017, Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute.

Calculations: Performed using IBM SPSS Statistics software (Release 23.0 and 24.0; IBM Corp., Armonk, NY, USA) or R software (R –version 3.3.0; the R foundation for Statistical Computing, http://www.r-project.org/) with the survival packages, rms and cmprsk.

4. Summary of Results

4.1 Paper I

A diagnostic biopsy was performed in 20.2% of the patients, with a small increase between the first and second part of the study period, 19.7% vs. 20.7%.

For patients with localized RCC, we found a significant increase in the use of diagnostic biopsies from 9.1% to 11.5%, which was partly driven by a doubling of RMB among patients for observation. The use of RMB was more frequent in older (> 70 years) than younger patients (< 70 years), in tumors ≤ 4 cm than 4.1 ≤ 7 cm and in patients with a secondary primary cancer (for all; $p < 0.001$). Age, size, multiple tumors and secondary primary cancer were all predictors for RMB in a multivariate logistic regression model. Patient managed by observation were older, with more other primary cancers and more RMB than actively treated patients (for all; $p < 0.001$). There was a tendency towards a lower Fuhrman grade in tumors in the observation group (81% vs. 68%).Of patients with N1M0 disease (54), 72% received active radical treatment, but only eight of the 54 patients underwent RMB. For M1 patients, there was a close to significant increase in RMB. Fewer patients with mRCC were without histopathology verification in the second period, 19% vs. 14%. Those without histopathology had significantly poorer survival than those with RMB. The majority of biopsies were performed in patients who had CN. The use of CN was stable in the study period, performed in 35% of patients with metastatic kidney cancer.

4.2 Paper II

Patients undergoing RN were older (64.8 yr vs. 61.2 yr) with larger tumors (4.3 ± 0.4 vs. 2.7± 0.4) than PN patients.

There was a 28% increase in surgical treated patients with tumors ≤7cm. While the number of RN annually was stable, the use of PN doubled.

Joinpoint analysis illustrates an increased use of PN and a decreased use of RN. In the entire study period, 58% of tumors ≤4cm were treated with PN. A significant increase in PN was registered from 2008 to 2013 (43% vs. 66%).For tumors 4.1 - 7

cm, only 14% underwent PN, but increased from 10% to 18% (2008-13). MIM showed an increase for both RN and PN. MIM-RN rose from 53% to 72% and MIM-PN from 25% to 64%, of which 55% was RALPN in 2013. Distribution of PN and RN, Open- and MIM procedures differed significantly between counties and regions, but throughout the period an increase of both PN and MIM was seen.

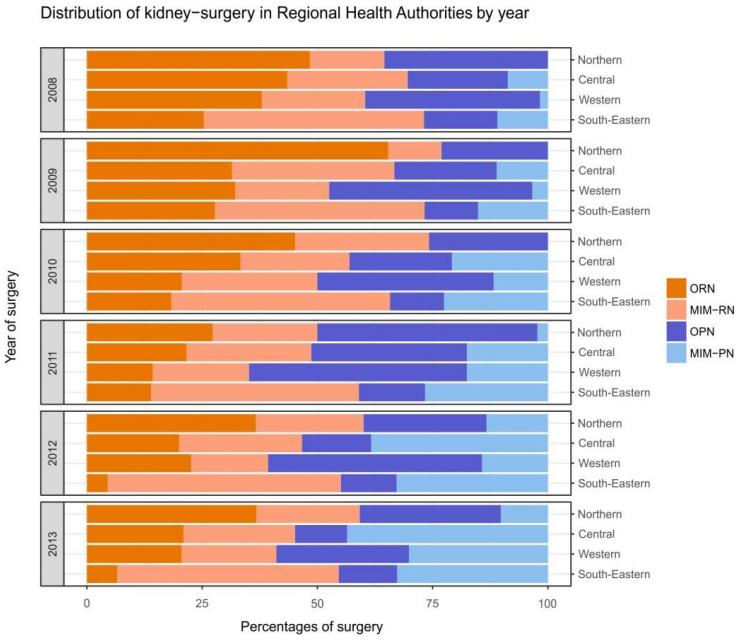

Figure 13: Distribution of treatment in the four Regional Health Authorities for ORN, MIM-RN, OPN and MIM-PN. Minimally Invasive includes pure laparoscopic, hand-assisted and robot-assisted method.

In multivariate logistic regression, younger age, smaller tumor size, HVH, second half of the study period and Western (WHA) and Central Health Authority (CHA) remained independent predictors of PN. Predictors for MIM were female gender, HVH, second half of the study and South-Eastern Health Authority (SHA).

A Kaplan Meier Plot illustrates an overall survival benefit for patients undergoing PN or RN. In a Cox regression analysis, PN, age, Fuhrman grade and stage were predictors of survival, and no difference in CSS was found (p =0.8). A 5-yr relative survival was higher for PN than RN, though not significant for both T1a 98.1 (95%

CI 93.6-99.4) vs. 92.8 (95% CI 88.1-95.7) and for T1b: 98.8 (95%CI 16.3-100.0) vs. 90.0 (95% CI 85.1-93.3).

Competing risk analysis revealed a higher probability of competing risk in the RN group compared to the PN group, with an early separation of the curves. When splitting other causes of death into cancer and non-cancerous conditions, PN and RN had the same probability of death from non-cancerous conditions the first two years before the curves separate and the competing risk increased for RN.

4.3 Paper III

Of the 3,313 who had surgery done for KC from 2008-2013, 69% underwent RN and 31% underwent PN; almost the same proportion did open and MIM procedures. Twenty-nine patients died within 30 days, while the overall mortality rate was 0.89%. TDM for localized and metastatic RCC was 0.73% and 2.6%, respectively.
For all stages, TDM was higher in older age groups, and significantly lower for PN and MIM procedures. On average, low-volume hospitals did 5.2 procedures/year, intermediate-volume hospitals did 27/year and high-volume hospitals did 53/year; the overall TDM for these hospitals was 2.2%, 0.83% and 0.39%, respectively, ($p<0.001$). In the multivariate logistic regression model, hospital volume, tumor stage and age were independent predictors of TDM following KC surgery. The odds ratio (OR) for TDM in the LVH compared to the HVH was 4.98 (CI 1.72-14.4) for patients with distant metastasis ($p =0.003$), and 3.35 (CI 1.32- 8.50) for patients with p T1-2 disease ($p =0.002$).

5. Discussion

5.1 Pretreatment evaluation

In Paper I, we explore how many diagnosed patients who had a biopsy before the choice of treatment was taken. This was possible if the biopsy was confirmed, such as KC/RCC on histopathology. The complete use of RMB was not possible to reveal because benign and non-diagnostic biopsies are not reported to the CRN, but others have reported it to be approximately 26% and 10-20%, respectively[131, 134]. We do not know the numbers of re-biopsies, nor the numbers of cores needed to verify malignancy. Additional RMB showing non-renal malignancy was not accessible for us. The diagnostic yield is reported to be lower with small, endophytic and cystic lesions, and in biopsies of tumors with a complex location [131-133]. In this way, the biopsy rate may be influenced by location, size, as well as patient anatomy, adipositas and radiologist experience. However, this study pictures the magnitude of RMB pre-diagnostic, and how information from malign biopsies is used in a treatment setting.

In the European Association of Urology (EAU) guidelines from 2009, RMB is only mentioned in one line: "There is a limited indication for fine needle biopsy." In 2010, the importance of RMB was more emphasized and given its own chapter. Based on new publications and evidence, it was stated that biopsy always should be done before ablative therapy and systemic therapy (without previous histopathology), and is recommended in surveillance strategies. 2010 was also the first year that surveillance and ablative treatment were noted as alternative treatments. An increased use of RMBs was noted before, but when documented in guidelines surgeons realize both the role of RMB and surveillance as options. The use of biopsies is a part of the modern more tailored and customized treatment.

We found that 20.2% of diagnosed KC patients had RMB, and it was used as a pre-diagnostic tool for surveillance, in active treatment for localized disease and in a metastatic setting, both for those who underwent CN and not. Because the literature is sparse and there is a lack of comparable data on the real-life use of RMB, our rate of use is difficult to interpret. The use of RMB for localized KC increased significantly

from the first to second period, from 9.1-11.5%. Of those treated with surgery, 8.4% had pretreatment RMB with a slight but not significant increase. For localized KC managed with observation, the rate of RMB was doubled from 29% to 61%, which illustrates an increased rate of patients when a verified malign biopsy was scheduled for surveillance. Patients undergoing observation had a tendency towards a low grade, compared to those undergoing active treatment. Hopefully, this illustrates that several more tumors in general were biopsied, and that those found to be benign did not undergo surgery and were spared from unnecessary follow-up.

Only seven patients underwent ablative treatment, and all had pretreatment RMB as is in line with recommendations.

The increase in use of RMB for localized KC reflects the growing awareness of an increasing incidence of SRM in general and in the elderly [15], and probably a more active trend of going for active surveillance. In a study from the Nordic countries, Nisen reported that 11%, 26% and 30% of resected renal tumors ≤ 4 cm were benign in Denmark, Norway and Sweden, respectively [259]. This illustrates that both biopsy and treatment practice may vary in these neighboring countries. The occurrence of 30% benignity in resected SRM is also seen in published materials from the USA [133].

Indication for biopsy is discussed in several papers and as expected, predictors for biopsy for localized cancer in our study were small tumor, secondary primary cancer, multiple tumors, older age and second period. This use of RMB reflects that the urologists can perform a risk-to-benefit analysis to construct a surveillance or surgical plan for the patients. Because age can be used as a proxy for comorbidity [216], this probably illustrates that patients with limited life expectancies could be sorted for surveillance.

Fewer metastatic patients in the second than in the first period were without verified histopathology, 19% vs. 14%, respectively. RMB was not performed for almost half the patients >80 years, compared to 14.5% of patients between 70-79 years and 3.1% < 60 years. This illustrates that many of the oldest were likely not candidates for

either surgical or systemic treatment, unlike the approach in young metastatic patients.

Approximately 80% of the patients with localized disease did not have any biopsy and 90% of these underwent surgery, which could be considered to be in line with current guidelines; patient scheduled for surgery do not need biopsy.

From initially only being indicated in patients with other primary malignancies, solitary kidneys, older age and severe cardiac or pulmonary comorbid conditions [127], RMB is now an important instrument in pre-treatment evaluation, and its importance will probably increase patient candidates for a surveillance strategy [70]. Because of the earlier perception that the biopsy would not change treatment, the fear of false-negative biopsies may be the reason why many urologists do not use pretreatment RMB, as illustrated in two surveys [260, 261]. In a review, RMB is shown to impact management in 24-64%. Benign histopathology is described to avert surgery in 16-26% [131-133]. The diagnostic accuracy of RMB has improved. A recent meta-analysis illustrates the ability to differentiate benign from malign lesions (81-97%), to determine subtype (86-98%) and also that the concordance with the final specimen is good [133, 136]. Based on this, urologists will probably trust RMB more and in the future actively use the results in management decisions. Current Norwegian biopsy patterns seem to be in line with recommendations in the guidelines.

5.2 Treatment

5.2.1 New evidence - changes in guidelines

In Paper II we focus on N0M0 patients, who were surgically treated for tumor size ≤ 7 cm. Today, surgeons choose PN if feasible for tumors of this size, and secondary RN [70]. In 2008, the scenario was quite different. From 2006, the EAU Guidelines implemented PN as care for tumors ≤ 4 cm, and for tumors 4.1-7 cm was the only option for selected patients at experienced centers [262]. Guidelines changed significantly in 2010, when PN became standard care whenever feasible for all tumors ≤ 7cm. Moreover, LRN was recommended for cT1 if PN was not possible

[144]. By using the dataset from the CRN 2008-2013, we wanted to find out how these expanded indications were adapted among Norwegian urologists, and how practice patterns were influenced by guidelines.

5.2.2 Distribution of treatments

In Paper II, we clearly demonstrate that the overall use of PN in Norway increases from 31% to 49%, and the increase is greatest for tumors ≤4 cm from 43% to 66%, but also substantial for tumors 4.1–7 cm from 10% to 18%. This is in line with current evidence-based knowledge for localized KC ≤7 cm, which advocates PN rather than RN whenever feasible. Norwegian data is comparable to Dutch, Swedish and data from other continents [18, 263, 264]. In the Dutch study (2010-2014), Aben found the amount of PN in 2014 was 67% for T1a and 30% for T1b. Ljungberg demonstrated an increase in PN for cT1a from 22% to 53% from 2005-2011, with a higher rate of 9% AT in Sweden vs. 5% AT in The Netherlands. Likewise, he found an increase from 0% to 10% for T1b. USA data from the period just before 2008 also illustrates this gradual increase in the use of PN [265].

Simultaneously, the use of laparoscopic procedures increased, a trend seen both for RN from 52% to 72%, and for PN from 25% to 64%. A clear treatment shift is seen in 2010, reinforced by new guidelines and publications. Surgeons were reassured with the knowledge of the oncological equivalent of PN and RN for tumors ≤ 7 cm, and could be performed if feasible [127, 144, 266]. Secondly MIM-RN and MIM-PN were equitable to the open procedures [127, 144, 214], and LRN should be done if PN was not possible. The rate of complications for both open and MIM surgery were comparable. The documented lower perioperative morbidity, better cosmetics and QoL were advantages that made MIM preferable over open surgery [71], both for surgeons and patients. Referral routines could be influenced when patients demanded a laparoscopic procedure, if his or her primary hospital could not offer this. Additionally Go's publication from 2004 illustrated a dose-dependent risk of death from any cause, cardiovascular disease and events and risk of hospitalization related to CKD [75]. RN was found to be a significant risk factor for developing CKD, compared to PN for small renal cortical tumors [267].The importance of renal

preservation on OS and morbidity was assumed; however, controversies exist and further investigation of this association has been and will be crucial [78, 79].

The pure laparoscopic PN is more challenging than laparoscopic RN. The intracorporal suturing in LPN is perceived by urologists to be technically difficult and time-consuming, which may have limited the implementation. The initial experience with robot-assisted laparoscopic partial nephrectomy (RALPN) was encouraging [143]. The three-dimensional visual field and magnification made the procedure safer and easier. The robotic platform and RALPN is later shown to increase the adoption of PN, probably because of a shorter learning curve than LPN [147], with favorable results concerning complications, conversions and ischemia time [268]. In Norway, the robotic platform was acquired in SHA in 2004, in WHA in 2009, in CHA in 2010 and in Northern Health Autorithy (NHA) in 2012, with the first kidney surgery done in 2006, 2010, 2010 and 2012, respectively, (information from Intuitive). Since then, acquisition of the robotic platform in Norway has continued, and today 15 robotic systems are distributed in Norway. In our cohort, the use of RALPN surpassed pure laparoscopic PN in 2013, which both illustrates the feasibility and increased availability of the robotic platform. Improvements are also done in standard laparoscopy, by offering the 3-D laparoscopy. For RN, this is surely better, and could probably increase the use of PN as well.

Paper III illustrates the distribution of all surgical management for KC during the study period. A total of 74.4% of patients >18 years underwent surgery, and of these 69% underwent RN and 31% PN. LVH performed significantly less PN and MIM procedures than intermediate-volume hospital and HVH, thereby illustrating a slower adherence to guidelines and the implementation of new procedures.

5.2.3 Cytoreductive nephrectomy

In Paper I, we found that 35% of patients diagnosed with metastatic RCC underwent CN, with no difference from the first to second period, which is lower than in Sweden where the number for CN was 58.5% for 2009-2012 [269]. The majority of biopsies

were performed in patients who did not undergo CN, many probably heading for systemic treatment, though this data was not accessible.

5.2.4 Regional differences in treatment

Interestingly, in Paper II we found pronounced discrepancies in treatment between the four HA. We revealed that RN was used more regularly for patients within the SHA and NHA compared to the CHA and WHA: 62% and 63% vs. 55% and 45%, respectively. Furthermore, the most frequent procedure in SHA was LRN, as was OPN in the WHA. Earlier studies have suggested a possible negative impact of LRN on the use of PN, and surgeons were doing urologic laparoscopy on small renal tumors to achieve that experience. In the publication from Australia, when LRN was introduced the rate of PN fell, but rose again after some years [270]. Norwegian data on the distribution of treatment before 2008 is not available, although the Norwegian situation could be similar. It is also shown that the use of the robot facilitates more PN in general and not only RALPN [271].

Another theory is that different surgical traditions and practice settings were decisive. PN was more frequent among younger surgeons in university hospitals, increasing renal case volume and the percentage of PN [18, 272]. Predictors of doing MIM were also younger surgeons and high surgeon volumes [273]. The characterization of surgeon level on the uptake of contemporary treatment is not well understood, and many factors are probably involved. The understanding of feasibility differs and correlates to the surgeon's skill and experiences.

Patients living within one HA experienced a divergent treatment strategy, but trends toward a more equal distributed treatment for the second period. For all counties, an increased use of PN was documented. Corresponding variability is seen in population-based data from Sweden [18]. A different referral practice could also influence this diversity.

Hospital volume is also discussed in several publications, and will influence the type of surgery, perioperative complications, morbidity and mortality. In our study, we

demonstrate in both Papers II and III that PN and MIM procedures were done significantly more at HVH.

5.3 Survival

5.3.1 Short-term survival for surgically treated patients

Perioperative mortality is considered a major indicator for the quality of patient outcomes, which is focused on in Paper III. Perioperative mortality summarizes patient selection, surgical treatment and postoperative care. At least two definitions for this are in use, the TDM and IHM. Literature reports this to be approximately 0.-1.5% for localized KC and 2-4% for metastatic KC. Most authors use IHM, but this is often lower than TDM. Unlike IHM, TDM illustrates mortality independently of length of stay, discharge- and readmission routine and geography. Bilimoria et al. demonstrated that 39.7% of postoperative complications and 23.6% of deaths occurred post-discharge [274], and that TDM was a more reasonable measure than IHM. The TDM of 0.89% we found in our study is comparable to other data of the time [216]. Well-known determinants of TDM, such as patient age, stage and metastatic disease, were also found to be predictors of mortality in our cohort [216], the latter illustrated with 0.73% for TDM for localized- and 2.6% for metastatic disease.

A striking finding was the relationship between hospital volume and TDM. In many other malign and benign diseases, HVH are associated with improved patient outcomes. The Norwegian government relied on this data when new volume demands for hospitals doing KC surgery were put on top of the general requirements. The definition of LVH and HVH vary in the literature and hospital volume definition used in our study is based on KC surgery requirements declared from Norwegian government. LVH, IVH and HVH presented significant differences in TDM for all stages of 2.2%, 0.8% and 0.4%, respectively. Regarding metastatic disease and cytoreductive nephrectomy, the difference was greater, 5.0% for LVH and 2.2% for IVH and HVH. Our primary hypothesis was that no difference existed, although this was disproven.

This hospital level variability in outcomes is multifaceted. There is an increasing attention towards measuring and reducing postoperative morbidity. Postoperative mortality is related to postoperative complications, which in turn are more frequent, i.e. patients with a higher comorbidity, additional procedures and more than one metastatic site. Patients in HVH may have undergone a more thorough surveillance before hospitalization and selection for surgery, especially in a metastatic setting, which is more stringent and rigorous[275] . Hospitals with a high number of beds and a high volume of surgeons have fewer complications. For sure, post-operative complications will occur to a certain extent in every hospital performing surgery, so the process of care involved in detection must be addressed. An awareness of early signs of complications and to be able to diagnose them is important in this regard. Care providers must be able to handle complications in a timely manner to avoid serious adverse outcomes. A complex interplay underlies postoperative mortality. General requirements such as multidisciplinary teams and 24-hour intensive care units are of course important, but it is important not to forget is the establishment of adequate counseling and routines at discharge to discover complications that occur post–discharge, in order to reassure that patients are re-admitted when needed.

In this surgical cohort, 29 patients died within 30 days from 2008-2013. Could these "29 failure-to-rescue" have been avoided? We are not able to answer this, but the causes of deaths reported in our study coincide with results from other studies [212]. In our study, five deaths were classified as procedure related, four from intestinal injuries and one from hemorrhage. The rest were related to cardiovascular conditions, infectious diseases or multi-organ failures, and from the KC itself.

LVH did PN and MIM to a lesser extent, and additionally had a higher rate of conversions from MIM-RN to ORN. Generally speaking, the TDM was higher among converted patients, illustrating that more than one procedure adds to the complexity. This observation may indicate the need for an adequate yearly surgical load is > 20/year to introduce and routinely use advanced techniques, such as, e.g., MIM-RN and MIM-PN. In addition, HVH may practice a higher threshold to operate

on patients with a poor performance status, and may be more willing to introduce surveillance as an option for comorbid patients.

5.3.2 Long-term survival

In Paper II, different tests were performed to help analyze survival for surgically treated patients with tumors <7 cm. Kaplan-Meier Plots showed a better OS for patients undergoing PN than RN. In a Cox analysis, PN was an independent predictor for OS in addition to age, stage and grade. No difference in CSS was found when stratified for stage. The five-year RS was higher for PN than RN, though it was not significant. These findings support and amplify PN as a contributor to better survival. However, Schuch et al. question this in a study in which patients undergoing RN and PN were compared with non-cancer controls. RN showed a similar OS as non-cancer controls and PN did better, thus suggestive of a selection bias for the latter group. Nonetheless, the patients were 10 years older than the average KC patient. They propose that the survival advantage of PN is a result of biased observational data. More research is needed to solve this ongoing debate on the OS gain. We performed competing risk analyses to investigate this more closely, and found a higher probability of death after RN from competing risks, but with an early separation of the curves. The most important finding is when dividing other causes of death in non-cancerous and other cancer deaths, the curves starts to diverge at two years, hence reflecting similar a competing risk for PN or RN in the beginning, but increasing for patients with RN thereafter. This demonstrates that even though unmeasured confounders might be present, it looks like a non-cancerous survival effect for PN exists, which can be partly due to a better preserved renal function.

5.3.3 RMB and survival

Survival was also focused on in Paper I. The causes of death were studied among patients who had done RMB or not. Not surprisingly, patients with localized KC who underwent RMB had a higher likelihood of dying of causes other than KC. This illustrates that a pretreatment evaluation was done, and that only if a biopsy uncovered malignity should surgery be rendered as an alternative. RMB is usually

performed in patients who are comorbid and presenting an increased risk of intra- and postoperative complications, in addition to a limited life expectancy [70].

Patients on observation with no active treatment had a higher probability of especially dying from other causes, and secondly from KC, than those undergoing active treatment (surgery). It is likely to be believes that for patients without active treatment, the burden of comorbid diseases prohibited surgery. Surveillance is also recommended when the probability of non-RCC deaths overshadow the risk of RCC progression [276].

To obtain systemic treatment for patients with mRCC, a histopathological verification of ccRCC from the primary tumor or metastasis was needed. Patients with a poor performance status, and with a severe comorbidity and advanced disease who are not candidates for treatment, are not likely candidates for biopsy either [133]. In our material, patients without RMB or CN had the poorest outcome regarding survival, and performed significantly worse than those who had RMB with no CN. Today, RMB is used as an integrated part of an active customized treatment strategy for mRCC. New treatments have shown less side-effects, and in the future even more patients can be candidates for both RMB and systemic therapy.

6. Strength and Limitations

6.1 Strengths

Many studies are based on joint databases, which partly include whole nation data or rely on self-reporting by surgeons. To the contrary, the present study is strengthened by the fact that CRN has more and independent reporting routines, which enhances the completeness of the registry database at CRN, and improves the outcomes of studies. Its completeness is close to 100%, and is considered to be reasonably accurate and timely [277]. The strength of this study is also that all CRN data was manually quality assured from registry sources, including a reevaluation of histology reports, staging and biopsy/surgical procedure. Survival data was also regularly updated.

6.2 Limitations

The CRN does not harbor information about tumor complexity, renal function, clinical data on comorbidity , complications and performance status all of which would have been valuable and deepened the understanding of the results. With such data available, the question of "failure to rescue" rates could have been better addressed in Paper III since the ability to avoid mortality after surgery is associated with both complications and comorbidity [275, 278].

Because hospitals, surgeon experience, practice setting and their annual caseload were all anonymous, their influence on selection and the diffusion of treatment could not be evaluated. Lack of the latter, as well as data on accompanying diseases and history of prior surgery, could be possible confounders.
Data on hospital stay and surgical conversion were incomplete in 2008-2009; therefore, those two years are excluded from any analysis on these years.

The numbers of deaths in Paper III were low; hence, there is a risk of overfitting in the multivariate analysis.

A major limitation of the study population in Paper I is the lack of data on patients with benign renal tumors. Consequently, few conclusions on the pretreatment use of

RMBs and final outcome for this relatively large group can be drawn. Lack of specific information on how the biopsies were taken, the numbers of cores and of earlier non-diagnostic biopsies is missing. Moreover, tumor grading is often not registered, so the results should therefore be interpreted accordingly.

7. Conclusion

- For patients with localized KC, the increased use of RMB is partly driven by a doubling of RMB among patients for observation. RMB is more frequently used in older patients with smaller tumors, with multiple tumors and with a second primary malignancy.
- Fewer patients with advanced KC were treated without a histopathological verification at the end of the study period. The majority of biopsies were performed in patients who had CN.
- RMBs in Norway seem to be in line with the indications in current international guidelines.
- For tumors ≤ 7 cm, the study demonstrated an overall increase of 28% in surgically treated patients, which was a result of increased PN, as the numbers of RN were stable**.**
- The use of PN increased significantly for tumors ≤ 4cm, and slightly for tumors 4.1-7cm. Open surgery decreases and MIM increases for both RN and PN. The treatment shiftt coincides with new guideline recommendations from 2010.
- Patients undergoing PN ≤ 7 cm seem to have an improved OS and RS compared to similar RN patients.
- Among all surgically treated KC patients, TDM after KC surgery was 0.9% overall, which is in line with previous reports.
- For all stages, TDM was higher in older age groups, and significantly lower for PN and MIM procedures.
- Patients treated at LVH have significantly poorer outcome in terms of TDM.
- The study supports the new hospital –volume regulation from the Norwegian health authorities in regarding KC-surgery.

8. Future perspectives

A systematic registration of comorbidity, kidney function, surgery, peri-operative and follow-up data is clearly needed in order to surveil the quality of the KC diagnostics, treatment and outcome. A dedicated kidney tumor registry modelled on, e.g., the National Swedish Kidney Cancer Registry [18] , is warranted.
We believe that a registry represents a unique opportunity to understand Norwegian practice- and referral patterns. It could assist in developing better regional- and national treatment algorithms, thereby assuring a suitable catchment area for the different treatment options. Patients should be offered uniform treatment, irrespective of their region of residence.

The future will probably bring a more active attitude to active surveillance. It could be that renal mass biopsy should be mandatory for all in order to avoid unnecessary surgery and morbidity. In many other malignancies, the cancer diagnosis is verified before surgery, and this is likely what lies ahead for both KC and RCC as well.
The multidisciplinary approach to metastatic RCC challenges the partnership between surgeons and oncologists more than before. Patients deserve the best sequencing of different systemic treatments and surgery, and dedicated urologists and oncologists must join forces to help accomplish this.

9. Appendix

2009 TNM staging classification of renal cell carcinoma

T-primary tumor				
TX		Primary tumor cannot be assessed		
T0		No evidence of primary tumor		
T1		Tumor ≤ 7 cm in greatest dimension, limited to the kidney		
	T1a	Tumor ≤ 4 cm in greatest dimension		
	T1b	Tumor > 4cm but ≤ 7 cm in greatest dimension		
T2		Tumor > 7 cm in greatest dimension, limited to the kidney		
	T2a	Tumor > 7 cm but ≤ 10 cm		
	T2b	Tumor > 10 cm, limited to the kidney		
T3		Tumor extends into major veins or perinephric tissue but not into the ipsilateral adrenal gland or beyond Gerota`s fascia		
	T3a	Tumors grossly extends into renal vein, segmental muscle containing branches or invades perirenal and/or renal sinus fat(peripelvic), but not beyond Gerota`s fascia		
	T3b	Tumor grossly extends into the vena cava(VC) below the diaphragm		
	T3 c	Tumor extends into vena cava above the diaphragm or invades the wall of VC		
T4		Tumor invades beyond Gerota`s fascia (including contiguous extension into the ipsilateral gland)		
N-Regional Lymph nodes				
NX		Regional LNs cannot be assessed		
N0		No regional LN metastasis		
N1		Metastasis in a single regional lymph node		
N2		Metastasis in more than one regional lymph node		
Distant metastasis				
MX		Metastasis cannot be assessed		
M0		No distant metastasis		
M1		Distant metastasis		
TNM stage grouping				
Stage I		T1	N0	M0
Stage II		T2	N0	M0
Stage III		T3	N0	M0
		T1,T2,T3	N1	M0
Stage IV		T4	Any N	M0
		Any T	N2	M0
		Any T	Any N	M1

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National Norwegian Practice Patterns for Surgical Treatment of Kidney Cancer Tumors ≤7 cm: Adherence to Changes in Guidelines May Improve Overall Survival

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Abstract

Background: Guidelines on surgical treatment for kidney cancer (KC) have changed over the last 10 yr. We present population-based data for patients with KC tumors ≤7 cm from 2008 to 2013 to investigate whether surgical practice in Norway has changed according to guidelines.

Objective: To assess the predictors of treatment and survival after KC surgery.

Design, setting, and participants: We identified all surgically treated KC patients with tumors ≤7 cm without metastasis diagnosed during 2008–2013 (2420 patients) from the Cancer Registry of Norway.

Outcome measurements and statistical analysis: Relationships with outcomes were analyzed using joinpoint regression, multivariate logistic regression, Kaplan-Meier survival estimates, Cox regression, relative survival (RS), and competing-risk analyses.

Results and limitations: The mean follow-up was 5.2 yr. There was a 28% increase in the number of patients undergoing surgical treatment over the study period. Joinpoint regression revealed a significant annual increase in partial nephrectomy (PN) and a small reduction in radical nephrectomy (RN). PN increased from 43% to 66% for tumors ≤4 cm and from 10% to 18% for tumors of 4.1–7 cm. Minimally invasive (MI) RN increased from 53% to 72% and MI PN from 25% to 64%, of which 55% of procedures were performed with robotic assistance in 2013. The geographical distribution of treatment approaches differed significantly. Both PN and MI approaches were more frequent in high-volume hospitals. Cox regression analysis revealed that PN, age, and Fuhrman grade and stage were independent predictors of survival. There were no significant differences in cancer-specific survival ($p = 0.8$). The 5-yr RS for T1a disease was higher after PN than after RN.

Conclusions: The rate of PN for tumors ≤7 cm increased in the 6-yr study period. MI approaches increased for both RN and PN. This treatment shift coincides with the new guideline recommendations in 2010. The possible better survival for patients undergoing PN compared to RN indicates the importance of following evidence-based guidelines.

Patient summary: The use of partial nephrectomy and minimally invasive surgery for kidney cancer tumors increased in Norway from 2008 to 2013 according to population-based data, coinciding with guideline changes. The study illustrate that adherence to guidelines may improve patient outcomes.

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1. Introduction

In Norway, the incidence of kidney cancer (KC) increased by 52% over the course of one decade (2007–2016) [1], with similar observations in Europe and worldwide [2]. Surgical treatment is still the mainstay of intervention for localized KC. Partial nephrectomy (PN) has oncological outcomes similar to radical nephrectomy (RN) for tumors ≤7 cm [3]. Furthermore, several retrospective studies have suggested that PN patients may achieve better overall survival (OS) [4–7], most likely attributed to lower impairment of renal function. However, recent publications have challenged this possible OS gain for PN over RN, claiming that it is caused by selection bias [8]. Since the early 1990s, the "pure" laparoscopic and later the robot-assisted laparoscopic approach to kidney surgery evolved to complement the RN and PN open approaches. It has been shown that minimally invasive methods (MIMs) have equivalent oncological outcomes to open surgery [9] and add benefits such as less surgical trauma, lower morbidity, and shorter hospital stays [10].

From 2006, the European Association of Urology (EAU) guidelines recommended PN as the standard of care for tumors ≤4 cm and as an option in experienced centers for selected patients with tumors of 4.1–7 cm [11]. In 2010, the EAU recommendation changed significantly, as PN then became the standard of care for all tumors ≤7 cm. Moreover, a laparoscopic approach was recommended for RN if PN was not indicated [12].

On this basis, we aimed to establish updated population-based Norwegian data on KC surgery for tumors ≤7 cm. Furthermore, we evaluated adherence to changing guidelines and the implementation of MIMs and PN. Finally, predictors for treatment and survival after surgery were assessed.

2. Patients and methods

2.1. Data source, data extraction, exclusions, and quality assurance

Data sets for all 4465 kidney cancer patients in Norway (ICD-10 code C64) diagnosed during the 6-yr period from 2008 to 2013 were extracted from the Cancer Registry of Norway (CRN) database. Information on reporting and the CRN is provided in the Supplementary material. The data sets consist of demographic, tumor-related, treatment-related, and follow-up (FU)-related variables. Information on kidney function, comorbidity, and complication rates was not available. Data quality assurance and removal of erroneously registered patients (n = 16) was performed at the CRN, and has been previously described [13]. Thereafter, data sets for 4449 patients were transferred to an anonymous database for subsequent analyses. Of these, 2420 patients aged >18 yr with N0M0 KC ≤7 cm and surgically treated with PN or RN remained within the data set. Figure 1 shows details for the inclusion and exclusion of patients. In accordance with national regulations, the study did not require informed consent from the patients when performed at the CRN.

2.2. Definitions used for analyses

Patients were classified as N0M0 if they had no nodal or distant metastasis at the time of surgery or within 4 mo thereafter. Details on staging and follow-up are described in the Supplementary material. For tumor staging, the 2009 version of the TNM classification was used [14]. Tumor size was based on the histology report, whereas survival and FU were estimated from data received from the Norwegian Cause of Death Registry dated December 31, 2016. Open operations were classified as those that started as open or were converted from a MIM approach to open surgery. Procedures classified as RN started as RNs or were PNs converted to RN during surgery. MIMs included pure laparoscopy, hand-assisted laparoscopy, and robot-assisted laparoscopy.

Norway is subdivided into 19 counties and the health care system is organized in four regional health authorities (HAs): the Northern (NHA), Central (CHA), Western (WHA), and South-Eastern (SHA) HAs. Hospitals performing KC surgery were divided into two groups on the basis of national volume recommendations according to their mean annual surgical volume: low-volume hospitals (LVH) performed <20 KC operations/yr, while high-volume hospitals (HVH) performed ≥20 KC operations/yr [13,15]. Hospitals performing fewer than four KC surgeries during the study were excluded.

2.3. Statistical analysis

Standard descriptive statistics were used, with results presented as the mean ± standard error of the mean (SEM). The median and interquartile range (IQR) were used for descriptions of variation within groups. We used t tests and χ^2 tests for comparisons of continuous and categorical variables, respectively.

Multiple logistic regression models were established without any preselection of the variables. Survival estimates, OS and cancer-specific survival (CSS) were calculated using the Kaplan-Meier method. Relative survival (RS) was calculated using the Pohar-Perme method [16]. Cox regression was performed to identify predictors of OS, with the hazard ratio (HR) and 95% confidence interval (CI) reported. Conditional probability estimates for death were calculated for different groups with competing risks. Joinpoint regression analysis was carried out using Joinpoint Regression v.4.5.0.1 (https://surveillance.cancer.gov/joinpoint) [17]. Statistical significance was set at $p < 0.05$. Calculations were performed using SPSS v.24.0 (IBM, Armonk, NY, USA) or R software v.3.3.0 (www.r-project.org).

3. Results

3.1. Patient characteristics

The mean observation time from surgery to death or last FU was 5.2 yr (median 5.0, range 3.8–6.6). Patients undergoing RN were older (64.8 vs 61.2 yr; $p < 0.001$) and had larger tumors (4.3 ± 0.04 vs 2.7 ± 0.04 cm; $p < 0.001$) than those undergoing PN.

The male/female ratio was 1.9:1. There was no difference between the RN and PN groups for gender (p = 0.23) or tumor size (p = 0.1). Table 1 lists patient, tumor (including stage, grade, and histopathological subtypes), and treatment characteristics for the whole cohort.

3.2. Treatment status and changes

3.2.1. Nationwide

There was a 28% overall increase in surgical treatment of patients with a KC tumor ≤7 cm. The number of patients who underwent RN yearly was stable, while the number of patients undergoing PN doubled from 2008 to 2013 (Supplementary Table 1). Joinpoint regression analysis

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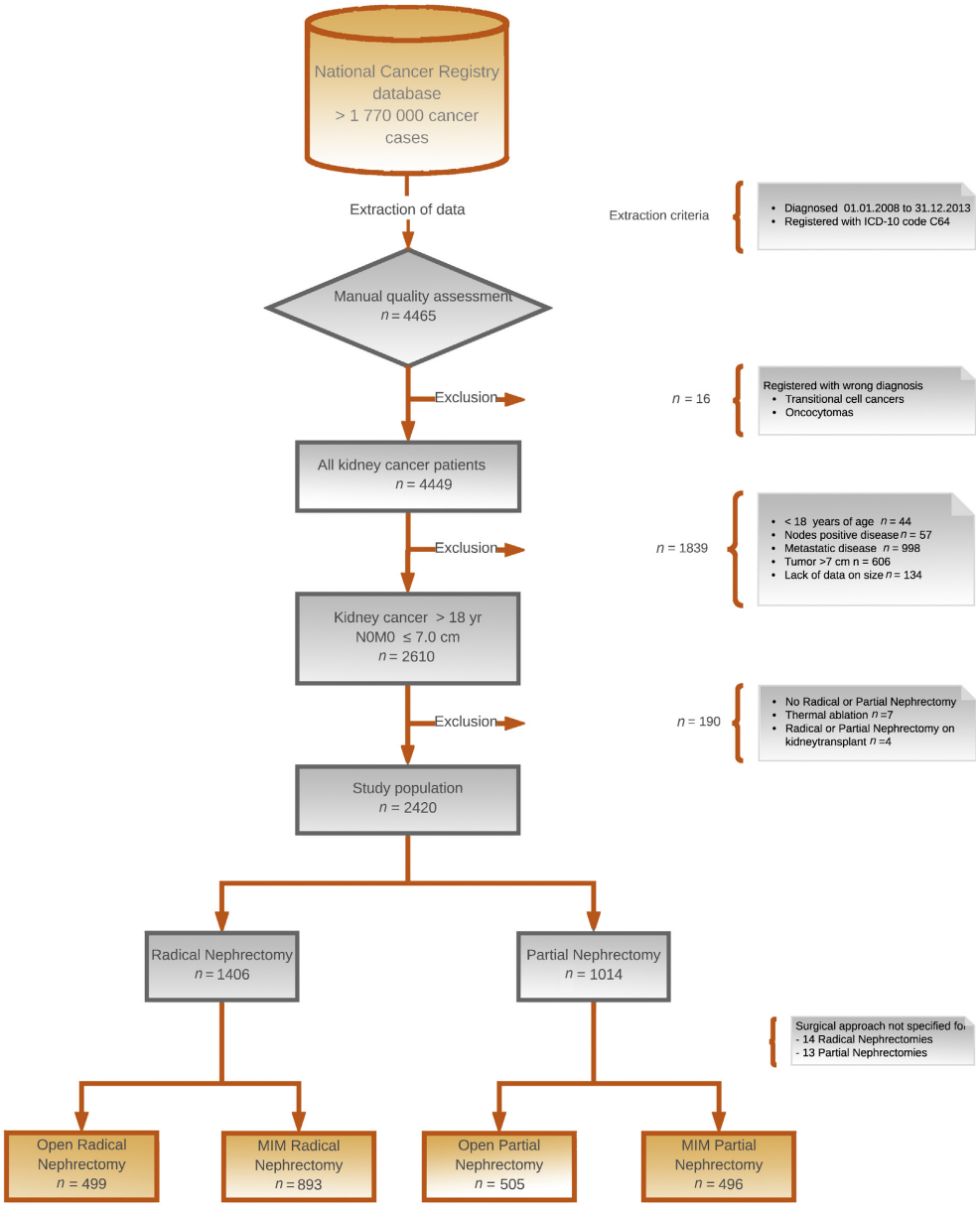

Fig. 1 – Flowchart for data extraction from the main database of the Cancer Registry of Norway according to the inclusion and exclusion criteria. MIM = minimally invasive method.

revealed an increase in the use of PN and a decrease in the use of RN (Fig. 2). Throughout the study period, 58% of tumors ≤4 cm were treated with PN and a significant increase was observed from 2008 to 2013 (43% vs 66%). For tumors of 4.1–7 cm, only 14% were treated with PN, but with an increase from 10% in 2008 to 18% in 2013. The distribution of treatments and time trends are illustrated in Figure 3 and Supplementary Figure 1. In the RN group,

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Table 1 – Characteristics of patients with a kidney cancer tumor ≤7 cm (N0M0) surgically treated during 2008–2013

	Overall	RN	PN	*p* value
Patients, *n* (%)	2420 (100)	1406 (58.1)	1014 (41.9)	
Age (yr)				<0.001 [a]
Mean ± SEM	63.3 ± 0.2	64.8 ± 0.3	61.2 ± 0.4	
Median (range)	65 (18–92)	66 (18–92)	63 (18–89)	
Gender, *n* (%)				0.2 [b]
Female	845 (35)	505 (36)	340 (34)	
Male	1575 (65)	901 (64)	674 (66)	
Side, *n* (%)				0.03 [b]
Right	1225 (51)	706	523	
Left	1178 (49)	697	482	
Bilateral	10 (0)	5	5	
Not specified	7 (0)	2	5	
Tumor size (cm)				
Mean ± SEM (median)	3.6 ± 0.03 (3.5)	4.3 ± 0.04 (4.4)	2.65 ± 0.04 (2.5)	<0.001 [a]
≤4 cm (*n* = 1553)	2.6 ± 0.02 (2.5)	3.0 ± 0.03 (2.2)	2.3 ± 0.03 (3.0)	<0.001 [a]
>4 to ≤7 cm (*n* = 867)	5.5 ± 0.03 (5.3)	5.6 ± 0.03 (5.5)	5.0 ± 0.07 (5.0)	<0.001[a]
Subtype, *n* (%)				<0.001 [b]
Clear cell	1701 (70)	1028 (73)	673 (66)	
Papillary	407 (17)	197 (14)	210 (21)	
Chromophobe	149 (6)	85 (6)	64 (6)	
Multicystic clear cell	76 (3)	35 (2)	41 (4)	
Other kidney cancers	87 (4)	61 (4)	26 (3)	
Fuhrman grade, *n* (%)				<0.001[b]
1	269 (11)	124 (9)	145 (14)	
2	1314 (54)	742 (53)	572 (56)	
3	544 (23)	366 (26)	178 (18)	
4	61 (2)	50 (3)	11 (1)	
Not specified	232 (10)	124 (9)	108 (11)	
T stage, *n* (%)				<0.001 [b]
pT1a	1497 (62)	614 (44)	883 (87)	
pT1b	716 (30)	604 (43)	112 (11)	
pT3a	193 (8)	174 (12)	19 (2)	
pT3b	9 (0)	9 (1)	0 (0)	
pT4	5 (0)	5 (0)	0 (0)	

RN = radical nephrectomy; PN = partial nephrectomy; SEM = standard error of the mean.
[a] According to a *t* test between the RN and PN groups.
[b] Exact ^{2} test for comparison between the RN and PN groups.

MIM use increased from 52% in 2008 to 72% in 2013. Figure 3 demonstrates the shift in 2010 towards more MIMs. For PN, MIM use increased from 25% to 64% during the study period, and 55% of PNs in 2013 were performed with robotic assistance (vs 7% in 2008). The major shift in the use of PN occurred from 2010 onwards, including a gradual increase in MIM. In 2013, the use of robot-assisted laparoscopic PN (RALPN) surpassed pure laparoscopic PN (Supplementary Table 1). The use of MIM-PN and open partial nephrectomy (OPN) was similar between the age groups (<65 vs ≥65 yr); by contrast, MIM-RN was used significantly more often than open radical nephrectomy (ORN) for patients <65 yr (70% vs 60%; $p = 0.004$).

3.2.2. *Regional and county trends*

The geographic distribution of PN versus RN and open versus MIMs differed significantly between the regions, as illustrated in Supplementary Figure 2 ($p < 0.001$). RN was used more frequently for patients within the SHA (62%) and NHA (63%) compared to the CHA (55%) and WHA (45%). The most frequent procedure was laparoscopic RN (LRN) in the SHA and OPN in the WHA. In each region, PN increased significantly from the first to the second half of the study period, but differences persisted ($p < 0.03$). The distribution of treatment types by HA and year is shown in Supplementary Figure 2. Patients living in the 19 counties experienced divergent treatment strategies, although with a trend towards an increase in PN use for all counties, as shown in Figure 4.

3.2.3. *Hospital trends*

The tumor size distribution did not differ between HVHs and LVHs, although HVHs used PN for KC surgery more often than LVHs (44% vs 33%; $p < 0.001$). This was particularly evident for tumors ≤4 cm ($p < 0.001$) but was less pronounced for tumors of 4.1–7 cm ($p = 0.295$). PN use increased from the first to the second period at both HVHs (from 36% to 51%) and LVHs (from 24% to 38%), despite no change in tumor size.

3.3. *Predictors of treatment*

To identify predictors of PN, several factors were entered into a multivariate logistic regression model (Table 2). Younger age, smaller tumor size, HVH, second half of the study period, and WHA and CHA remained independent predictors. Furthermore, the independent predictors of undergoing MIM surgery were female gender, HVH, second half of the study period, and SHA.

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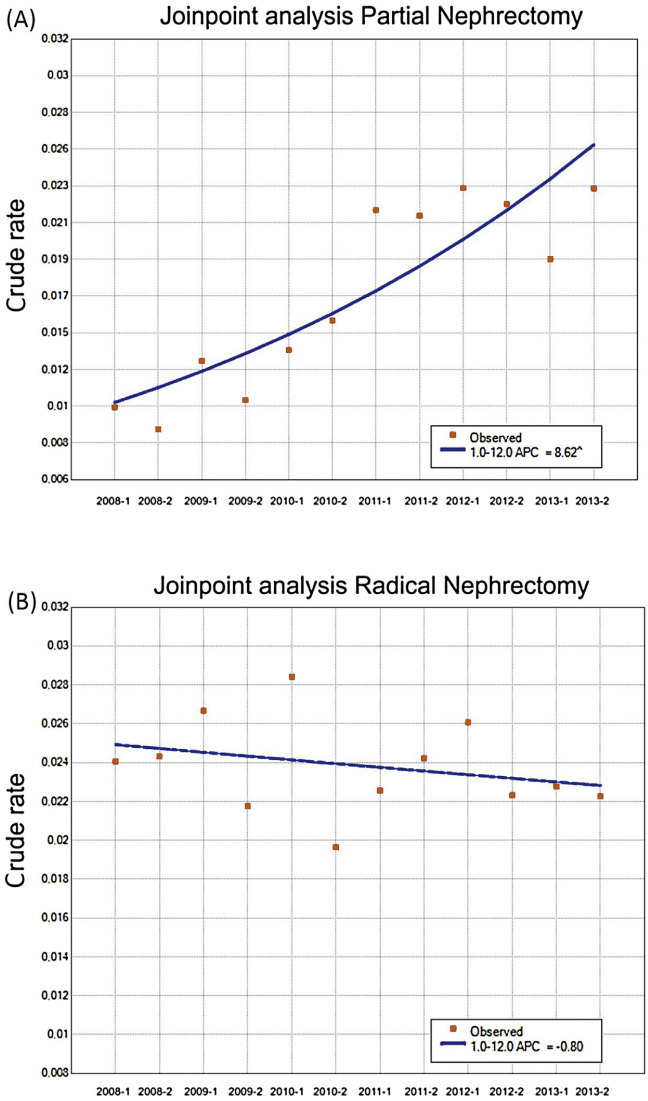

Fig. 2 – Temporal trends in the use of (A) partial nephrectomy and (B) radical nephrectomy for 2420 patients. Data points show the annual frequencies and the trend line demonstrates the joinpoint regression results. The annual percentage change (APC) was significantly different from zero at $\alpha = 0.05$ for partial nephrectomy, indicating a significant increase in this procedure. The small decrease in radical nephrectomy was not statistically significant.

3.4. Survival analyses

Kaplan-Meier plots showed an OS benefit for patients undergoing PN compared to RN (Supplementary Figs. 3 and 4). On Cox regression analysis, PN was an independent predictor of OS, as were age, Fuhrman grade, and T stage (Supplementary Table 2). There was no difference in CSS between PN and RN when stratified for stage ($p = 0.8$). Although the difference is not significant, the 5-yr RS was higher for the PN group (98.1, 95% CI 94.0–99.4) than for the RN group (92.8, 95% CI 88.1–95.7). For T1b tumors the 5-yr RS was 98.8 (95% CI 16.3–100.0) after PN and 90.0 (95% CI 85.1–93.3) after RN. Competing-risks analysis (Fig. 5A) revealed a higher probability of death from competing risks in the RN group, with early separation of the curves for RN and PN. However, after splitting other-cause deaths into other cancers and noncancerous conditions (Fig. 5B), PN and RN patients had a similar probability of death from a

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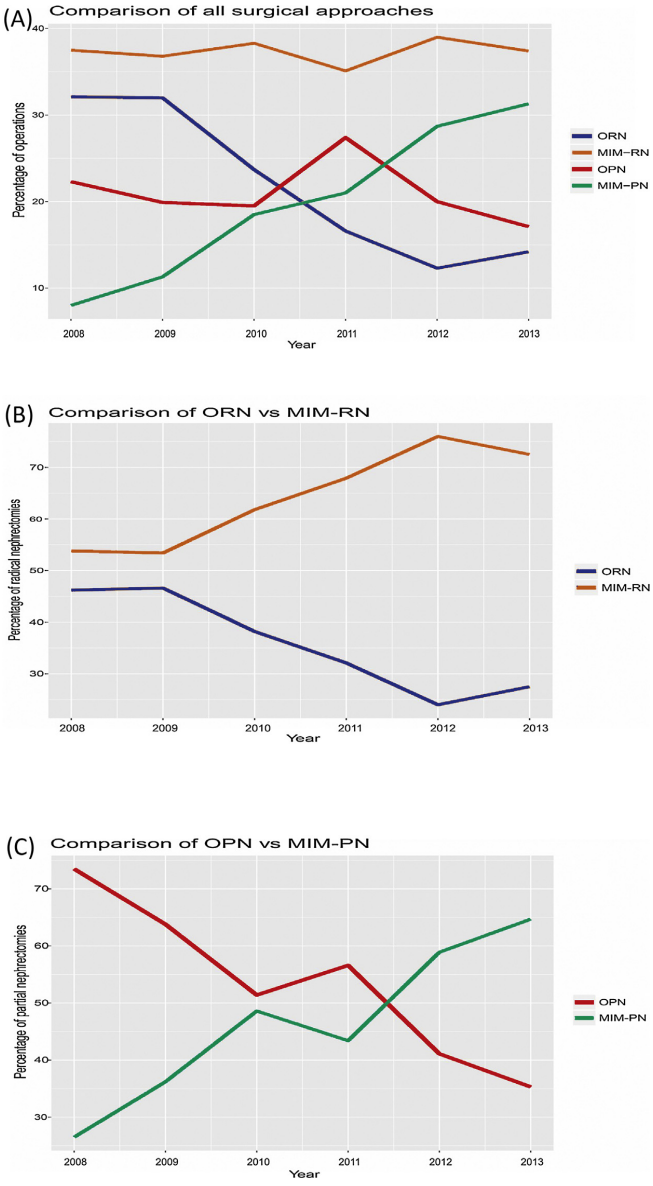

Fig. 3 – Comparison of treatments in terms of percentage of procedures per year. (A) All approaches investigated. (B) Open radical nephrectomy (ORN) versus minimally invasive radical nephrectomy (MIM-RN). (C) Open partial nephrectomy (OPN) versus minimally invasive partial nephrectomy (MIM-PN).

noncancerous condition the first 2 yr before the curves separate, and the competing risks increase for RN patients. Figure 5C shows similar separation of the curves comparing death from all cancers to death for noncancerous conditions.

4. Discussion

The present study clearly demonstrates that the field of KC surgical care and management is rapidly changing. Over the past 20 yr the toolbox for personalized surgical treatment of

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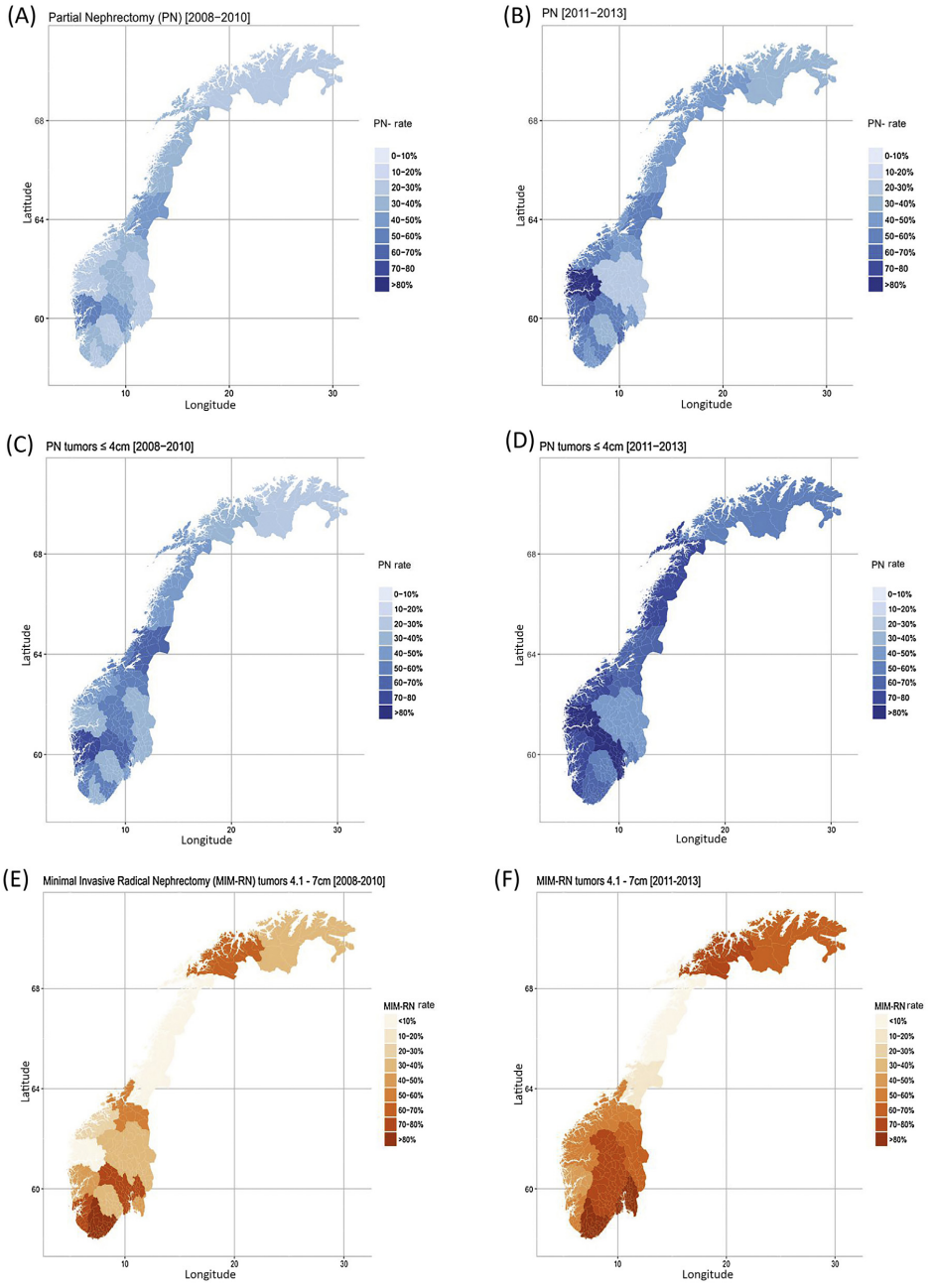

Fig. 4 – Distribution and changes in treatment in the 19 counties in Norway in the first half (2008–2010) and second half (2011–2013) of the study period. PN during (A) 2008–2010 and (B) 2011–2013. (C) PN for tumors ≤4 cm during (C) 2008–2010 and (D) 2011–2013. MIM-RN for tumors of 4.1–7 cm during (E) 2008–2010 and (F) 2011–2013. MIM includes pure laparoscopic, hand-assisted, and robot-assisted laparascopic methods. Overall, the variation in PN among counties ranged from 26% to 59%. The variation in PN rate ranged from 36% to 77% for tumors ≤4 cm and from 2% to 28% for tumors of 4.1–7 cm (data not shown). Counties with a PN rate of <25% PN in 2008 doubled the PN rate in 2013, whereas counties with a PN rate of 25–40% in 2008 increased this to approximately 60% in 2013. Four of the 19 counties generally used PN more often than RN during the study period. From the first to the second half of the study, the use of MIM-RN for tumors of 4.1–7 cm became more widespread. PN = partial nephrectomy; MIM-RN = minimally invasive radical nephrectomy.

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Table 2 – Multiple logistic regression analyses to predict PN and MIM in surgically treated kidney cancer patients

Variable	PN vs RN (n = 2420)		MIM vs open (n = 2396)	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (continuous in years)	0.97 (0.96–0.98)	<0.001	0.99 (0.99–1.00)	0.6
Gender (male vs female)	1.20 (0.97–1.39)	0.20	0.81 (0.67–0.98)	0.03
Tumor size (continuous in cm)	0.42 (0.39–0.45)	<0.001	1.02 (0.96–1.07)	0.6
Year of diagnosis		<0.001		<0.001
2008–2010	1.00 (reference)		1.00 (reference)	
2011–2013	2.17 (1.73–2.58)	<0.001	1.93 (1.61–2.31)	<0.001
Hospital volume		<0.001		<0.001
<20 procedures per year	1.00 (reference)		1.00 (reference)	
≥20 procedures per year	1.87 (1.45–2.46)	<0.001	2.2 (1.78–2.88)	<0.001
Regional Health Authority		<0.001		<0.001
South-Eastern	1.00 (reference)		1.00 (reference)	
Western	3.0 (2.26–3.89)	<0.001	0.20 (0.16–0.25)	<0.001
Central	2.1 (1.55–2.75)	<0.001	0.44 (0.34–0.56)	<0.001
Northern	1.2 (0.84–1.73)	0.3	0.13 (0.09–0.18)	<0.001

PN = partial nephrectomy; RN = radical nephrectomy; MIM = minimally invasive method; OR = odds ratio; CI = confidence interval.

renal tumors has expanded. In the past, most urology surgeons had one standard open surgical procedure for all, but today urologists face multiple choices regarding both the surgical approach (standard, single site, hand-assisted, or robot-assisted laparoscopy) and tumor removal (RN vs PN). Moreover, ablative treatments and surveillance could be appropriate alternatives. In this changing landscape, evidence-based guidelines are important contributors in helping to choose the best treatment for individual KC patients. One of the important changes demonstrated in this study is the marked increase in PN following the major change in the EAU recommendation for PN in 2010. The overall use of PN in Norway increased from 31% to 49% between 2008 and 2013. The implementation was greatest for tumors ≤4 cm (66% in 2013), but was also substantial for tumors of 4.1–7 cm (18% in 2013). This is in line with current evidence-based knowledge on the surgical treatment of localized KC tumors of ≤7 cm, which advocates PN rather than RN whenever feasible [12]. The current data show that use of PN in Norway is comparable to recent Dutch and Swedish population-based data. In the Dutch study, the use of PN was 62% for T1a and 30% for T1b tumors in 2014, while in the Swedish study it was 53% for T1a and 9% T1b tumors in 2011 [18,19]. Similar data are also available from the USA [20,21].

Similar to the more widespread adoption of PN, MIM use has also increased. This trend is evident for both MIM-RN and MIM-PN. MIM is popular among patients because of lower perioperative morbidity and better cosmetic results [22]. In studies on quality of life after KC surgery, laparoscopic procedures performed better than open surgery [23]. Pure laparoscopic PN is a more challenging procedure than LRN. It requires considerable surgical expertise, which may have limited its implementation. The learning curve for RALPN seems shorter than for pure laparascopic PN [24], and RALPN is also favorable in terms of complications, conversions, and ischemia time [25]. Costs for the purchase and maintenance of the robotic platform are considerable, and therefore acquisition is not warranted in every hospital [26,27]. However, when RALPN is available, it increases the adoption of PN [27,28].

The data from the first half of the present study reflect the EAU recommendation of PN as an established treatment, and national guidelines calling for all tumors ≤4 cm to be evaluated for PN before treatment [11,29]. These guidelines offer great latitude for individual surgeons to decide on

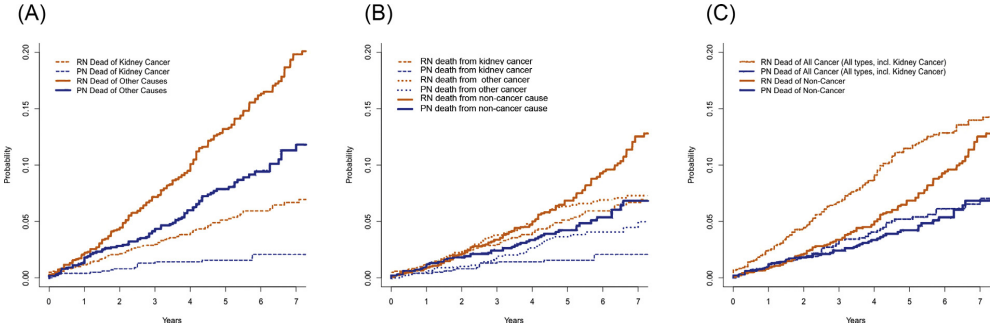

Fig. 5 – Competing-risks analysis for partial nephrectomy (PN) and radical nephrectomy (RN). Probability of death (A) from kidney cancer versus death from all other causes; (B) from kidney cancer versus other cancers and noncancerous conditions; and (C) from all cancers (including kidney cancers) versus noncancerous conditions.

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treatment according to their own preferences. The important change in the 2010 edition of the EAU guidelines was the recommendation of PN "whenever possible" and of whether or not to perform LRN on T1 tumors suitable for PN [12]. This recommendation probably made the decision to continue performing open RN for all tumors more difficult for LVHs. The present study demonstrates that regional discrepancies were less pronounced in 2013 than earlier, and that the regional treatment patterns seem to have equalized. More imperative recommendations might have been a key to this change. It has been demonstrated that surgeons interpret terms such as "if technically feasible" differently. In a survey among American urologists, the willingness to offer PN depended on the surgeon's preferences, skill, experience, practice setting, renal tumor caseload, and percentage PN, rather than just on tumor size and complexity [30]. In a Canadian study, high-volume surgeons predicted MIM and academic status predicted PN [31]. Our study lacks data at the surgeon level, but obviously more imperative guidelines force changes in management. This could occur with uptake of new methods or referral to larger centers. The hospital volume effect has been discussed in several publications, and influences the type of surgery, perioperative complications, morbidity, and mortality [19,30–32]. In our study, we also found that HVHs were independent predictors of PN. Overall, the present study indicates that the Norwegian urology community seems to have adapted relatively quickly to changing guidelines.

In line with other authors [7,19], we found that Norwegian patients treated with PN experienced better OS and RS and that PN independently predicted OS.

Earlier publications have partly related this to better preserved renal function, as chronic renal insufficiency represents a dose-dependent risk factor for cardiovascular diseases and events, risk of hospitalization, and mortality from any cause [4]. However, a meta-analysis by Wang et al [33] did not indicate that PN reduced the rate of cardiovascular events.

Newer findings indicate that only selected groups of patients presenting with preoperative chronic kidney disease (CKD) or concomitant comorbidity benefit from PN [34,35] and that worsening of already existing CKD is faster and more pronounced after RN than after PN, possibly leading to more subsequent deaths among RN patients. The additional contribution of medically induced CKD to outcome when compared to surgically induced CKD is also important [36].

There is an ongoing debate on whether the OS gain after PN is caused by selection bias [37]. Even though our study is population-based, selection bias and unmeasured confounders might be present, and should be kept in mind when considering the degree of survival benefit for PN, as discussed by others [8,37]. However, our competing-risks analysis demonstrates that it takes approximately 2 yr before the noncancer mortality rates for PN and RN separate, indicating a lesser degree of selection bias in this group of patients. On the basis of our data, we cannot rule out that the less steep noncancer mortality rate is partly due to improved renal function, but further research is warranted.

The present study is not without limitations. The CRN register data do not include information about tumor localization and complexity, renal function, or clinical data such as Charlson comorbidity scores and postoperative complications. Since hospitals were anonymous, as was surgeon experience, practice setting, and annual caseload, their influence on selection and diffusion of treatment could not be evaluated.

5. Conclusions

In Norway, the rate of PN for KC tumors $\leq$7 cm increased over the study period. For both RN and PN, the rates of open surgery decreased while the rate of MIM approaches increased. The rise in PN observed coincides with the new guidelines recommendations in 2010.

In general, KC treatment practice in Norway is comparable to that in other countries, but with divergent regional practice patterns. Patients undergoing PN for KC tumors $\leq$7 cm may have better OS and RS compared to similar RN patients, which supports the importance of following evidence-based guidelines.

Author contributions: Karin M. Hjelle had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hjelle, Beisland, Johannesen.
Acquisition of data: Hjelle, Johannesen.
Analysis and interpretation of data: Hjelle, Beisland, Reisæter.
Drafting of the manuscript: Hjelle.
Critical revision of the manuscript for important intellectual content: Hjelle, Beisland, Bostad, Johannesen.
Statistical analysis: Hjelle, Beisland, Johannesen, Reisæter.
Obtaining funding: None.
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Supervision: Beisland, Johannesen.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eururo.2016.04.035.

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Supplementary text

Part 1- Data Source

As described in earlier publications[1] , Norwegian clinicians and pathologists (since 1953) have been requested by law to report all new cases of cancer to the population-based Cancer Registry of Norway (CRN). Data for all clinical or pathological cancer and operation codes used for all types of patient/doctor contacts are transferred to the CRN from the national public health-care data systems, and checked against clinical and pathological report forms. In case of missing report forms, reminders are sent to the various departments. The CRN is connected to the Norwegian Population Registry. The registry database contains information on >1,770,000 cancer cases (2016), and has a completeness of close to 100%[2] . Inclusion in the registry is mandatory.

Part 2 - Staging and Follow-up

This study is based on a national database and does not include data on preoperative evaluation and post-operative follow-up in detail. However, in 2007new national guidelines for RCC were introduced[3] and preoperative M-staging with CT of the chest and abdomen were recommended. These guidelines have been implemented nationally. A Nordic survey from 2015(including 93% of Norwegian KC treating hospitals) was published in 2017[4] , and demonstrated that chest CT was used in > 90% of cases ≤4 cm. Furthermore, as described in a study from our hospital[5] and published in 2015, the overall use of preoperative chest CT was 94.6% during the years 2007-2013. As Norway is a relatively homogenous society, it is reasonable to assume that most patients have been staged for distant metastasis according to generally accepted rules.

N-staging is based on what is reported on histopathology reports and as a result of preoperative imaging.

When it comes to follow-up (FU), details for each hospital are not collected in the registry. The Norwegian standard of FU has been FU visits every six months for 5-years with at least chest X-ray for low-risk RCC and CT-scans for the higher risk groups. In 2007 our department launched a risk stratified FU-program that has been widely accepted and used in Norway. The program and results has been published in 2016[6]. In our opinion, there is no reason to believe that FU in Norway has been of a lesser quality than recommended in international guidelines during the study period. However, as data for FU is not included in the national database, we have not looked disease free/metastasis free survival. We have focused on cancer specific and overall survival, as these data are collected from national death certificates.

Patients were described as N0 M0 if they had no nodal metastasis or distant metastasis at the time of surgery or within four months thereafter, as recommended by the AJCC[7].

Part 3 - Thermal ablation and active surveillance

The scope of the present study was surgical treatment of KC, and therefore patients treated with thermal ablation (TA) and active surveillance (AS) was not included. In Norway utilization of TA has been limited. Only seven patients with kidney cancer ≤ 7cm N0M0 were treated with TA during the study period (2008 – 2013) (figure 1). Regarding AS, our data on this is unfortunately not complete. However, we know that approximately 5-6 % of patients diagnosed with localized KC in Norway did not undergo any kind of active treatment. This is documented in a paper published earlier this year[8].

Part 4 - Acquisition and availability of the robotic platform in Norway

Today 15 robotic systems are distributed in Norway. Norwegian Urologic surgeons started with prostatectomies and secondly partial nephrectomies.

The first robotic system was installed in the South Eastern Regional Health Authority in 2004, the second and the third in 2007, the fourth in 2012, the fifth in 2015, the sixth in 2016, the seventh in 2017 and the latest bought by a private health care company this year. The first robotic kidney surgery was done in 2006, but as illustrated in supplementary table 2, few such surgeries were performed the first years.

In the Western Regional Health Authority the two first robotic platforms were achieved in 2009, and the first robotic kidney surgery was done autumn 2010.

The Central Regional Health Authority acquired their first robotic system in 2010, and started also with kidney surgery late the same year (they achieved their second robot in 2012).

In the Northern Regional Health Authority one robotic system was installed in 2012 and another one in 2016.

Figure captions

Supplementary figure 1 - Trends in treatment 2008–2013 illustrated in bar diagrams A: Distribution of Radical Nephrectomy (RN) and Partial Nephrectomy (PN) in numbers/year. B: Distribution of RN and PN for tumors ≤4cm and 4.1 ≤ 7cm in numbers/year. C: Distribution of Open Radical Nephrectomy (ORN), Minimal Invasive Radical Nephrectomy (MIM-RN), Open Partial Nephrectomy (OPN) and Minimal Invasive Partial Nephrectomy (MIM-PN) in numbers/year. Minimal Invasive includes both the pure laparoscopic, hand-assisted and robot-assisted method.

Supplementary figure 2 - Distribution of treatment in the four Regional Health Authorities. Open Radical Nephrectomy (ORN), Minimal Invasive Radical Nephrectomy (MIM-RN), Open Partial Nephrectomy (OPN) and Minimal Invasive Partial Nephrectomy (MIM-PN). Minimal Invasive includes both pure laparoscopic, hand-assisted and robot-assisted method.

Supplementary figure 3 - Kaplan-Meier plot demonstrating survival probability for Partial Nephrectomy (PN) and Radical Nephrectomy (RN):
Solid line (blue) – PN (1011 patients at risk initially, 71 still at risk after 8 years)
Dotted line (orange) – RN (1401 patients at risk initially, 152 still at risk after 8 years)

Supplementary figure 4 - Kaplan-Meier plot demonstrating the survival probability for Partial Nephrectomy (PN) and Radical Nephrectomy (RN) stratified for stages T1a, T1b and T3a. Numbers at risk are illustrated in the figure.

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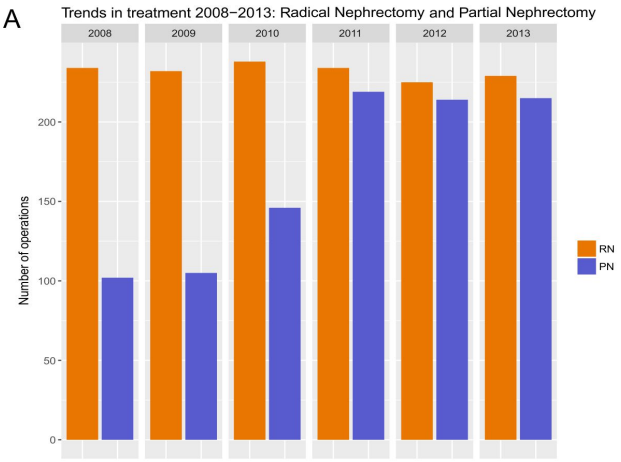
A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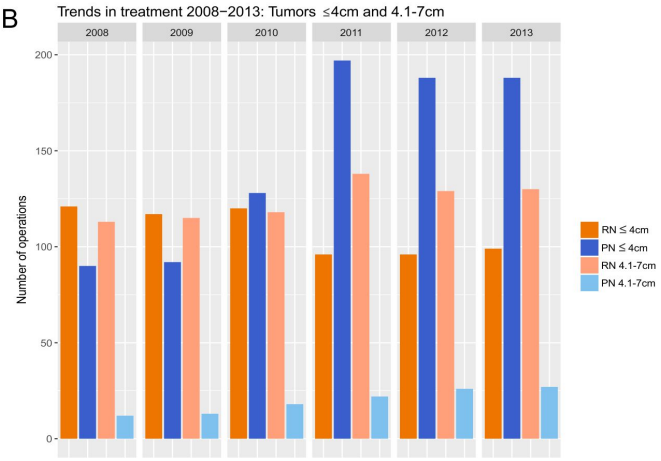
2009
2010
2011
2012
2013
Number of operations
0
50
100
150
200
RN
PN

B


Trends in treatment 2008−2013: Tumors ≤4cm and 4.1-7cm
2008
2009
2010
2011
2012
2013
Number of operations
0
50
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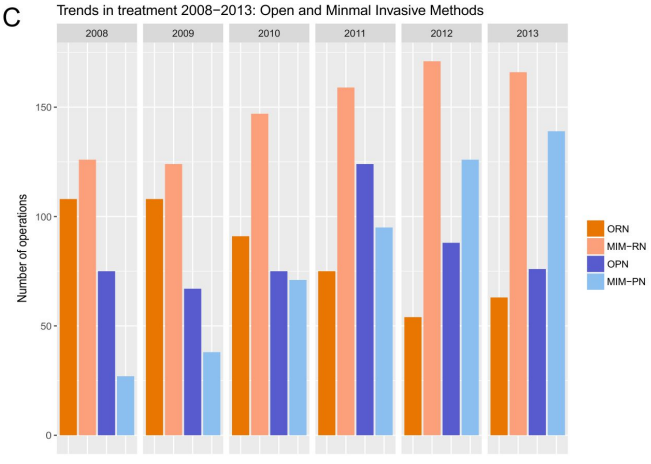
200
RN ≤ 4cm
PN ≤ 4cm
RN 4.1-7cm
PN 4.1-7cm

C


Trends in treatment 2008−2013: Open and Minmal Invasive Methods
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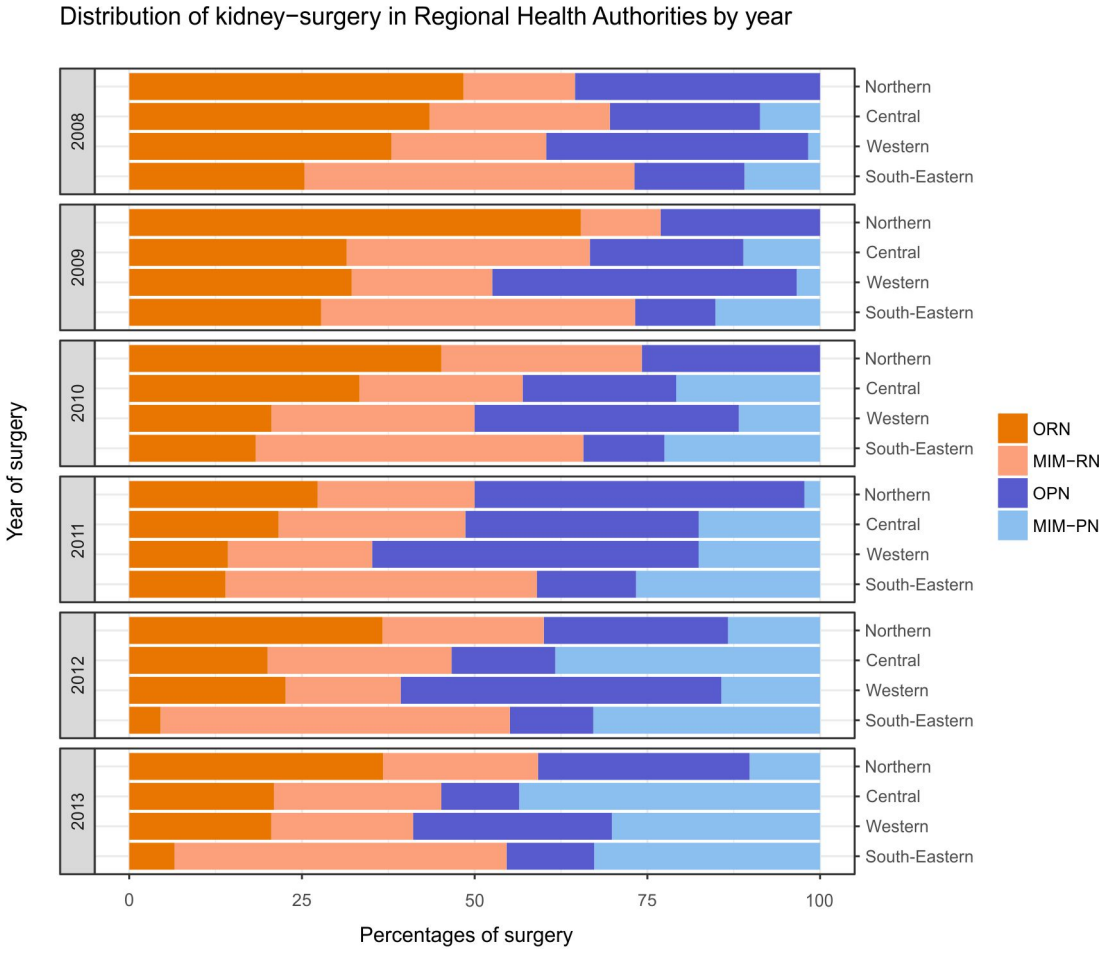
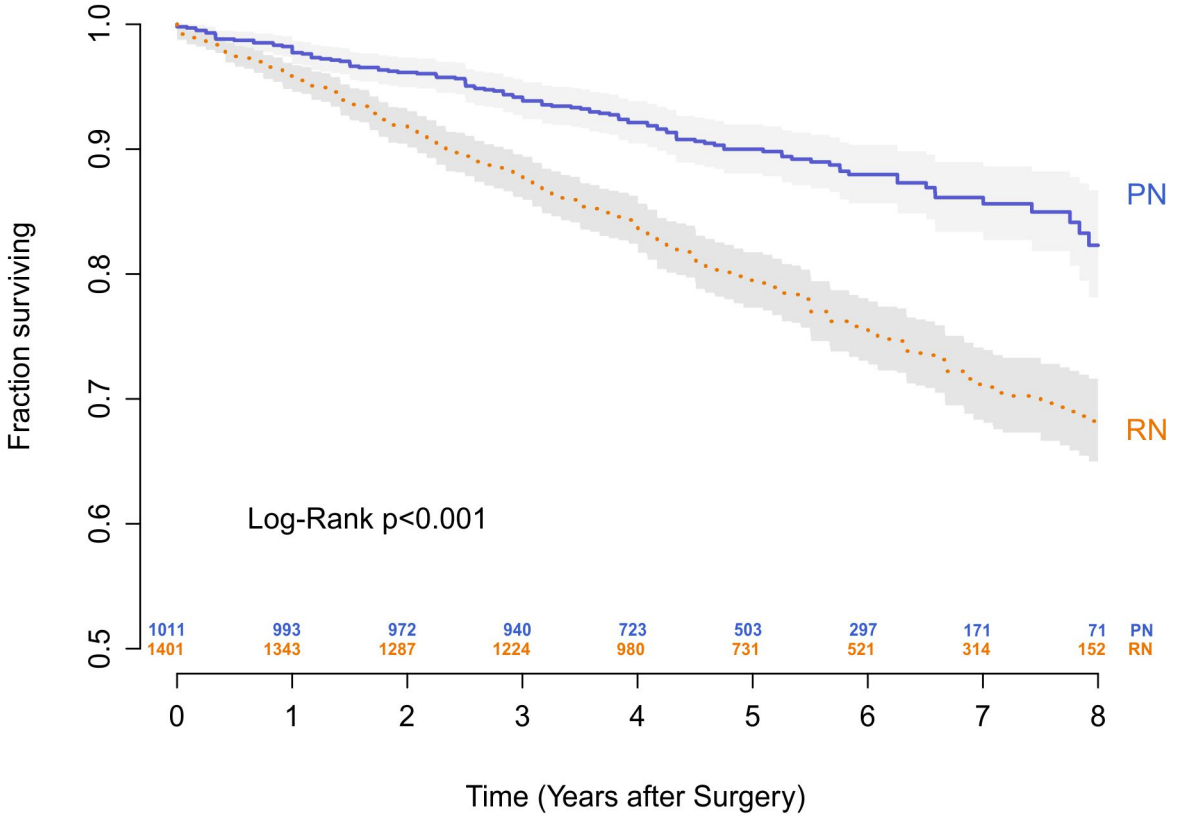
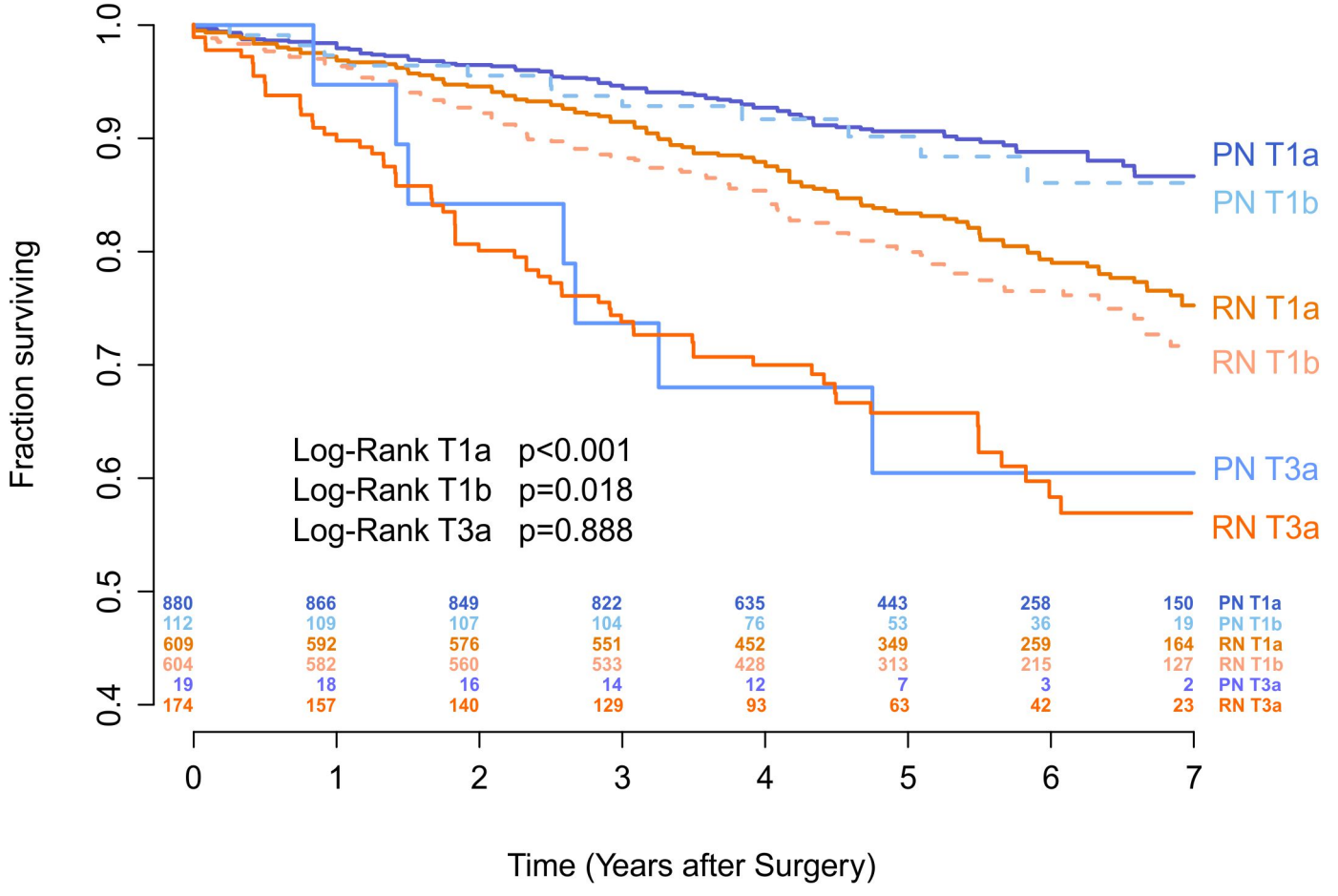
2010
2011
2012
2013
Number of operations
0
50
100
150
ORN
MIM−RN
OPN
MIM−PN


Distribution of kidney−surgery in Regional Health Authorities by year
Year of surgery
2008
2009
2010
2011
2012
2013
Northern
Central
Western
South-Eastern
0
25
50
75
100
Percentages of surgery
ORN
MIM−RN
OPN
MIM−PN


Fraction surviving
1.0
0.9
0.8
0.7
0.6
0.5
PN
RN
Log-Rank p<0.001
1011 993 972 940 723 503 297 171 71 PN
1401 1343 1287 1224 980 731 521 314 152 RN
0 1 2 3 4 5 6 7 8
Time (Years after Surgery)


Fraction surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
PN T1a
PN T1b
RN T1a
RN T1b
PN T3a
RN T3a
Log-Rank T1a p<0.001
Log-Rank T1b p=0.018
Log-Rank T3a p=0.888
880 866 849 822 635 443 258 150 PN T1a
112 109 107 104 76 53 36 19 PN T1b
609 592 576 551 452 349 259 164 RN T1a
604 582 560 533 428 313 215 127 RN T1b
19 18 16 14 12 7 3 2 PN T3a
174 157 140 129 93 63 42 23 RN T3a
0 1 2 3 4 5 6 7
Time (Years after Surgery)

Supplementary table 1: Distribution of surgical treatment for kidney cancers ≤ 7 cm 2008-2013

	Total	Radical Nephrectomy (RN)					Partial Nephrectomy (PN)				
Year		**RN**	**Open**	**Lap***	**Robotic**	**Nos****	**PN**	**Open**	**Lap***	**Robotic**	**Nos****
2008	349	241	108	126	0	7	108	75	20	7	6
2009	345	237	108	124	0	5	108	67	26	12	3
2010	384	238	91	147	0	0	146	75	51	20	0
2011	455	235	75	148	11	1	220	124	55	40	1
2012	441	226	54	155	16	1	215	88	71	55	1
2013	446	229	63	145	21	0	217	76	63	76	2
Total	2420	1406	499	845	48	14	1014	505	286	210	13

* Laparoscopic, not robotic, ** Not specified, numbers – numbers of patients

Suppl. table 2: Time dependent Cox-regression analysis (n=2186) for Surgical treated Kidney Cancer ≤ 7 cm (N0 M0) 2008-13

	Overall survival		
Variables	**HR**	**95% CI**	**p-value**
Surgery (RN vs PN)	1.4	(1.09 - 1.80)	0.008
Age (cont. in years)	1.1	(1.05 - 1.07)	<0.001
Gender (m vs. f)	1.4	(1.14 - 1.74)	0.002
Histopathology			
Fuhrman 1	1.0	ref	
Fuhrman 2	1.5	(1.02 - 2.29)	0.038
Fuhrman 3	1.7	(1.14 - 2.67)	0.010
Fuhrman 4	3.4	(1.96 - 5.95)	<0.001
pT-Stage			
T1a	1.0	ref	
T1b	1.1	(0.90 - 1.44)	0.266
T3a-T4	1.9	(1.37 - 2.49)	<0.001

RN - Radical nephrectomy, PN - partial nephrectomy, cont. – continuous,
m – Male, f – Female, HR - Hazard ratio, CI - Confidence Interval,
ref –Reference value, pT-stage - 2009 TNM

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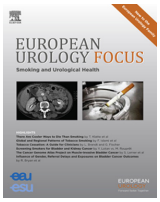

Kidney Cancer

Postoperative 30-day Mortality Rates for Kidney Cancer Are Dependent on Hospital Surgical Volume: Results from a Norwegian Population-based Study

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Abstract

Background: To improve cancer care in Norway, the government introduced surgical volume requirements for hospitals in 2015. To treat kidney cancer (KC) in Norway, the lower limit is 20 surgical procedures per year.
Objectives: To compare the impact of hospital volume on outcome with regard to 30-d mortality (TDM) following KC surgery.
Design, setting, and participants: We identified all KC patients from the Cancer Registry of Norway diagnosed during 2008–2013 whose surgical treatment involved partial or radical nephrectomy. Hospitals were divided into three volume groups: low (LVH), intermediate (IVH), and high (HVH) volume.
Outcome measurements and statistical analysis: Relationships with outcome were analysed using multivariate logistic regression.
Results and limitations: In total, 3273 patients were identified. The TDM rate was 0.89% overall, 0.73% for localised KC, and 2.6% for metastatic KC. The mean (median, interquartile range) numbers of procedures for LVH, IVH and HVH were 5.2 /yr (3, 1.3–8.7), 27 /yr (26, 23–30) and 53 /yr (53, 48–58), with TDM rates of 2.2%, 0.83%, and 0.39%, respectively ($p = 0.001$). In a multivariate logistic regression model, tumour stage, age, and hospital volume remained independent TDM predictors. The odds ratio for TDM was 4.98 (confidence interval 1.72–14.4) for LVH compared to HVH ($p = 0.003$). Study limitations include a lack of data for surgical complications and other possible confounders.
Conclusions: TDM is associated with age, stage, and hospital volume. The study supports the new regulation for hospital volume introduced in Norway.
Patient summary: The risk of dying within 30 d following kidney cancer surgery is low. Advanced disease and older age are risk factors for higher mortality. In this study, we also showed that more patients die within 30 d in hospitals performing fewer operations per year than in hospitals performing many operations.

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1. Introduction

Surgical treatment is still the mainstay of treatment for kidney cancer (KC). Therefore, perioperative mortality is an important quality indicator for patient outcomes [1]. In the literature, contemporary perioperative mortality (both 30-d mortality [TDM] and in-hospital mortality [IHM]) is reported as 0.5–1.5% for localised KC and 2–4% for metastatic (M+) KC [2–7]. For several surgical treatments for other malignancies and for benign conditions, hospital volume is an important factor that significantly affects outcomes [8–10]. However, studies evaluating the impact of hospital volume on outcomes for KC surgery are sparse. Furthermore, there is no generally accepted definition of a low- or high-volume hospital.

Acknowledging that surgical volume is most likely associated with improved patient outcomes, the Norwegian health authorities introduced requirements in 2015 for hospitals that should continue to perform cancer surgery [11]. In addition to general requirements for hospitals to have multidisciplinary teams, 24-h intensive care units, and documented adherence to guidelines, specific volume demands for hospitals and surgeons were established. For KC, hospitals must perform at least 20 surgical procedures per year to remain operative.

Against the background of these new hospital volume requirements, we investigated the relationship between hospital volume and TDM in a national population-based setting. We used other well-recognised (age, stage) [3,12] and potential (surgical procedure, gender) [6,12] prognostic factors as covariates in the study. The study aim was to establish updated Norwegian population-based TDM rates for KC surgery.

2. Patients and methods

2.1. Data source

Since 1953, Norwegian clinicians and pathologists have been required by law to report all new cases of cancer to the population-based Cancer Registry of Norway (CRN). Data for all clinical and pathologic cancers and operation codes used for all types of patient-doctor contact are transferred to the CRN from the national data systems for public health care, and checked against clinical and pathologic report forms. In the case of missing report forms, reminders are sent to the various departments. The CRN is further connected to the Norwegian Population Registry. The registry database contains information on >1 700 000 cancer cases up to 2015, and has completeness of close to 100% [13]. Inclusion in the CRN is mandatory. Thus, in accordance with national regulations, our study did not require informed consent from patients for data extraction from the CRN. The registry does not include data for benign kidney tumours.

2.2. Data extraction, exclusions, and quality assurance

Using the CRN, data sets for all 4465 KC patients (ICD-10 code C64) diagnosed during the 6-yr period from 2008 to 2013 were extracted from the primary database. The data sets consist of demographic, tumour-related, treatment-related, and follow-up variables. A subset of data (~80%) for hospital stay and surgical conversions was available and consisted of all patients for 2010–2013, but data were missing in part for the two first study years.

All CRN data used in the study were manually quality assured from the registry sources by one author (K.M.H.), including re-evaluation of all histopathology reports. During this process, 16 patients (0.36%) were excluded because of a diagnosis other than renal cell carcinoma (RCC). Then data sets for 4449 patients were transferred to an anonymous database for subsequent analyses. Of these, 3313 patients aged ≥18 yr and treated with partial (PN) or radical nephrectomy (RN) remained within the data set.

We excluded patients treated at hospitals performing fewer than four procedures in 6 yr (average of ≤0.5 /yr) on the assumption that these hospitals do not treat KC on a regular basis. In this step, 40 patients were excluded. Hence, the final study population consisted of 3273 patients. Figure 1 shows the details for inclusion and exclusion of patients.

2.3. Definitions used for analyses

Localised KC was defined as disease without distant metastases (M0) at diagnosis or within 4 mo thereafter [14]. Metastatic KC was defined as M+ disease. For tumour staging, the 2009 version of the TNM classification was used.

TDM was defined as death from any cause within 30 d following surgery. IHM was defined as death during the primary hospital stay for surgical treatment.

Open operations were classified as those that started as open procedures and those converted from minimally invasive to open procedures during surgery. Similarly, those classified as RN were operations that started as RN and PN procedures converted to RN during surgery.

Minimally invasive methods (MIMs) included pure laparoscopy, hand-assisted laparoscopy, and robotic-assisted laparoscopy. Ablative treatments involving cryotherapy or radiofrequency treatment were not included in the data.

Hospitals performing KC surgery were divided into three groups according to their mean annual surgical volume: low-volume hospitals (LVH) performed <20 KC operations per year, intermediate-volume hospitals (IVH) performed 20–39 KC operations per year, and high-volume hospitals (HVH) performed ≥40 KC operations per year. The LVH upper limit was defined according to the 2015 Norwegian regulation [11], while the HVH lower limit was arbitrarily based on the presumed volume at the major academic hospitals in Norway.

2.4. Statistical analysis

Standard descriptive statistics were used. Mean values are presented as mean ± standard error of the mean, with median and interquartile range (IQR) used to indicate variation within groups. Because the proportion of TDM is low, we applied bootstrapping with 1000 resamples for TDM rates and associated confidence intervals (CIs). Using this method, we could simulate TDM rates for 1000 cohorts of 3273 patients (ie, 3 273 000 patients).

The specific tests used for comparisons between different groups are indicated. A TDM curve was calculated using the Kaplan-Meier method.

Multiple logistic regression models were established without preselection of the variables. A p value of <0.05 was considered statistically significant. Calculations were performed using SPSS version 23.0.

3. Results

3.1. Patient characteristics

In this surgically treated cohort of patients, 69% underwent RN and 31% PN. In both groups, approximately the same

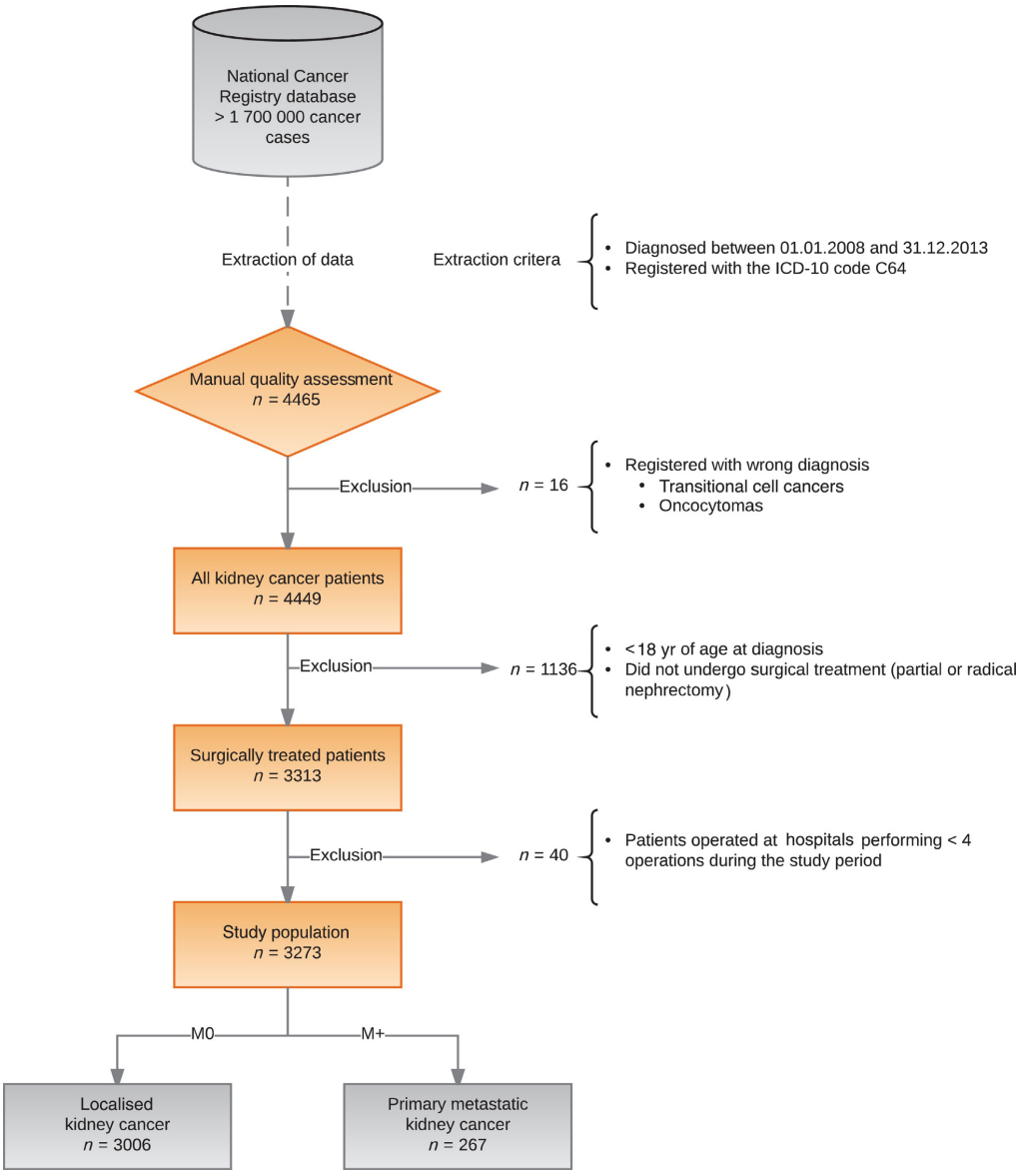

Fig. 1 – Flowchart for data extraction from the main database at the Cancer Registry of Norway according to the inclusion and exclusion criteria.

proportions underwent open and MIM operations. The median age was 64 yr and the male/female ratio was 2:1. Among the tumours, 78% were T1–2Nx–0M0, 14% were T3–4Nx–0M0, and 8.2% were T1–4Nx–0M1. Supplementary Table 1 and Table 1 list patient, tumour, and treatment characteristics for the whole cohort and the hospital volume subgroups, respectively.

3.2. TDM

In the present cohort, 29 patients died within 30 d, resulting in an overall TDM rate of 0.89%. The TDM rate for KC surgery was 0.73% for localised KC and 2.6% for metastatic disease ($p = 0.007$, exact χ^2 test). Table 2 show the TDM rates for different TNM categories. TDM was significantly higher for

Table 1 – Comparison of patient and tumour characteristics for the three hospital volume groups

Variable	Patients	LVH	IVH	HVH	*p* value
Age (yr)	3273	64.5 ± 0.2 (65.0, 58–73)	63.7 ± 0.3 (64.0, 56–72)	62.4 ± 0.3 (64.0, 55–77)	0.012[b]
Male	3273	354 (66)	974 (67)	872 (68)	0.4[c]
Laterality	3264				1.0[c]
Left		268 (50)	729 (50)	630 (49)	
Right		266 (50)	718 (49)	641 (50)	
Bilateral		2 (<1)	6 (<1)	4 (<1)	
Tumour size (cm)	3294	5.6 ± 0.2 (4.5, 3–7.5)	5.5 ± 0.1 (4.5, 2.7–7.2)	5.2 ± 0.1 (4.2, 2.5–7.0)	0.2[b]
Primary tumour status	2959				<0.001[c]
pT1aN0M0		226 (46)	639 (49)	610 (52)	
pT1b–2N0M0		165 (34)	498 (38)	396 (34)	
pT3–4N0M0		99 (20)	164 (13)	162 (14)	
Regional lymph node status	3270				0.3[c]
pNx–0		528 (98)	1416 (97)	1276 (97)	
pN+		11 (2)	39 (3)	39 (3)	
Distant metastases	3273				0.5[c]
No (M0)		499 (93)	1321 (91)	1186 (93)	
Yes (M+)		40 (7)	136 (9)	91 (7)	
Fuhrman grade[a]	2628				0.9[c]
1		40 (9)	103 (9)	83 (8)	
2		233 (55)	642 (55)	566 (54)	
3		126 (30)	337 (29)	323 (31)	
4		24 (6)	81 (7)	70 (7)	
Surgical treatment	3273				<0.001[c]
Radical nephrectomy		407 (76)	1002 (69)	812 (64)	
Open		256 (63)	478 (48)	382 (47)	<0.001[d]
Minimally invasive		151 (37)	524 (52)	430 (53)	
Partial nephrectomy		119 (22)	430 (30)	449 (35)	
Open		91 (76)	204 (47)	208 (46)	<0.001[d]
Minimally invasive		28 (24)	226 (53)	241 (54)	
No data available		13 (2)	25 (2)	16 (1)	
Length of stay (d)	2604	7.8 ± 0.5 (6, 4–8)	6.0 ± 0.1 (5, 3–7)	6.1 ± 0.2 (5, 4–7)	<0.001[b]

LVH = low-volume hospitals; IVH = intermediate-volume hospitals; HVH = high-volume hospitals.
Data are presented as mean ± standard error of the mean (median, interquartile range) for continuous variables and as *n* (%) for categorical variables.
[a] Includes only clear cell and papillary renal cell carcinoma.
[b] According to *t*-test between LVH and IVH/HVH combined.
[c] Exact χ^2 test for trend over all groups.
[d] Exact χ^2 test for trend over all the volume groups within the partial or radical nephrectomy group.

older age groups, and especially among patients >80 yr, consistent for all stages (Table 2). Table 3 show the cause of death for the 29 patients who died within 30 d. Overall TDM rates were significantly lower for PN and MIM procedures.

According to an analysis of data in the subset (n = 2604), overall IHM and TDM rates were 0.69% and 0.81%, respectively.

3.3. *Hospital volume*

A total of 56 hospitals reported surgical procedures for RCC, of which 26 performed fewer than four procedures over the period (40 patients). Consequently, there were 17, nine, and four hospitals in the LVH, IVH, and HVH groups, with mean (median, IQR) numbers of procedures of 5.2 /yr (3, 1.3–8.7), 27 /yr (26, 23–30), and 53 /yr (53, 48–58), respectively.

The overall TDM rate was 2.2% for LVH, 0.83% for IVH and 0.39% for HVH. The difference is statistically significant (Table 2).

Both PN and MIMs were used more extensively in the HVH group (Tables 1 and 4). Subset analyses revealed that the LVH group used MIMs for RN to a significantly lesser degree. In addition, the LVH group had the highest rate of conversion from MIM to open RN and the highest rate of subsequent TDM among patients who experienced such conversion. However, the latter data did not reach statistical significance (Table 4). Figure 2 shows the mortality within each volume group during the first 30 d after surgery.

3.4. *Multivariate analysis*

To identify predictors of TDM following KC surgery, several factors were entered into a multivariate logistic regression model (Table 5). Hospital volume, tumour stage, and age all remained independent TDM predictors. The odds ratio (OR) for TDM was 4.98 (95% CI 1.72-14.4) in the LVH compared to the HVH group (p = 0.003) and 3.35 (95% CI 1.32–8.50) for patients with distant metastases compared to patients with pT1–2 disease (p = 0.02). The model was tested and was stable for OR with regard to these groups.

4. Discussion

This study confirms the predictive ability of older age and more advanced disease stage with regard to higher TDM. Both of these are well-established determinants [12].

Table 2 – TDM rates after kidney cancer surgery for the 6-yr population-based cohort from the Cancer Registry of Norway. To increase the precision of the estimates, the rates and 95% confidence intervals were obtained via bootstrapping with 1000 resamples

	All stages		T1-2N0–1M0		T3–4N0–1M0		M+	
	TDM, % (95% CI) (*n*/*N*)	*p* value	TDM, % (95% CI) (*n*/*N*)	*p* value	TDM, % (95% CI) (*n*/*N*)	*p* value	TDM, % (95% CI) (*n*/*N*)	*p* value[b]
Overall	0.9 (0.6–1.2) (29/3273)	0.007[a]	0.7 (0.4–1.0) (17/2544)		1.1 (0.2–2.2) (5/455)		2.6 (0.7–4.9) (7/267)	
Age		0.001		0.039		0.015		0.028
≤49 yr	0 (0/439)		0 (0/367)		0 (0/38)		0 (0/34)	
50–59 yr	0.6 (0.2–1.2) (4/662)		0.8 (0.2–1.5) (4/530)		0 (0/74)		0 (0/58)	
60–69 yr	0.7 (0.3–1.3) (8/1105)		0.6 (0.1–1.2) (5/853)		1.3 (0–3.1) (2/160)		1.1 (0–3.3) (1/92)	
70–79 yr	1.1 (0.5–1.9) (9/819)		0.6 (0.2–1.3) (4/626)		0 (0/130)		7.9 (1.6–14.3) (5/63)	
≥80 yr	3.2 (1.3–5.8) (8/248)		2.4 (0.6–4.8) (4/168)		5.7 (0–13.2) (3/53)		5.3 (0–15.8) (1/19)	
Gender		0.3		0.4		0.6		0.7
Male	1.0 (0.6–1.4) (22/2200)		0.8 (0.4–1.2) (13/1675)		0.9 (0–2.1) (3/326)		3.1 (1.0–5.6) (6/194)	
Female	0.7 (0.2–1.2) (7/1073)		0.5 (0.1–0.9) (4/868)		1.6 (0–3.8) (2/129)		1.4 (0–4.2) (1/73)	
Period (*n* = 3269)		0.3		0.8		0.4		0.5
1st half	1.1 (0.7–1.6) (18/1641)		0.7 (0.3–1.2) (9/1255)		1.7 (0.4–3.4) (4/233)		3.3 (0.7–6.6) (5/151)	
2nd half	0.7 (0.3–1.0) (11/1628)		0.6 (0.2–1.1) (8/1288)		0.5 (0–1.4) (1/222)		1.7 (0–4.3) (2/115)	
Procedure		0.03		0.08		1.0		1.0
PN	0.3 (0–0.7) (3/1014)		0.3 (0–0.7) (3/983)		0 (0/22)		0 (0/8)	
RN	1.1 (0.7–1.6) (26/2259)		0.9 (0.4–1.4) (14/1561)		1.2 (0.2–2.1) (5/433)		2.7 (1.2–5.0) (7/259)	
Technique (*n* = 3219)		0.002		0.057		0.7		0.2
Open	1.3 (0.8–1.9) (21/1619)		0.9 (0.4–1.5) (10/1113)		1.3 (0.3–2.7) (4/300)		3.4 (1.0–5.9) (7/205)	
MI	0.3 (0.1–0.6) (5/1600)		0.3 (0.1–0.6) (4/1393)		0.7 (0–2.1) (1/146)		0 (0/58)	
Hospital volume		0.001		0.004		0.3		0.8
<20 /yr	2.2 (1.1–3.5) (12/539)		1.8 (0.5–3.3) (7/392)		2.9 (0–6.7) (3/104)		5.0 (0–12.5) (2/40)	
20–39 /yr	0.8 (0.3–1.3) (12/1457)		0.7 (0.3–1.2) (8/1140)		0.6 (0–1.7) (1/178)		2.2 (0–5.1) (3/136)	
≥40 /yr	0.4 (0.1–0.7) (5/1277)		0.2 (0–0.5) (2/1012)		0,6 (0–1.7) (1/173)		2.2 (0–5.5) (2/91)	

TDM = 30-d mortality; PN = partial nephrectomy; RN = radical nephrectomy; MI = minimally invasive; CI = confidence interval.
Unless otherwise indicated *n* = 3273; data for stage were missing for seven patients.
[a] *p* value for χ^2 test across strata.
[b] χ^2 test for comparison of 30-d mortality proportions.

Table 3 – Cause of death for the 29 patients who died within 30 d after kidney cancer surgery

Cause of death	*n*	Procedure-related deaths	Known relevant comorbid conditions
Gastrointestinal conditions			
Complications to GI haemorrhage	1		
Complications to intestinal perforation	2	2 (intestinal injuries)	
Complications to intestinal necrosis	2	2 (intestinal injuries)	
Cardiovascular conditions			
Acute myocardial infarction	3		
Sudden cardiac arrest	2		2 (substantial heart disease)
Pulmonary embolism	2		1 (other cancer)
Acute subarachnoid haemorrhage	1		
Infectious conditions			
Pneumonia	4		1 (renal failure)
Peritonitis	1		
Septicaemia	1		
Organ failure			
Renal failure	2		1 (substantial heart disease)
Multiple organ failure	4	1 (haemorrhage)	
Renal cell carcinoma			
Metastatic kidney cancer	3		
Kidney cancer	1		
Total	29	5	5

Although not perfect, age can be seen as a proxy for comorbid conditions [12]. Furthermore, the threefold to fourfold higher TDM for M+ disease is well recognised [2,3,12].

Therefore, the most intriguing finding is identification of hospital volume as an independent TDM predictor. Older studies have previously reported this association [10,15]. Recent studies identified significant correlation between hospital volume and postoperative complications [7]. Other studies revealed a definitive correlation between perioperative mortality and postoperative complications, but not hospital volume [4,5,16]. The reason for the lack of

Table 4 – Use of minimally invasive (MI) radical nephrectomy (RN) and conversions to open procedures by hospital volume groups

Variable	All hospitals	LVH	IVH	HVH	*p* value
Surgical procedures	2473	407	1108	958	
RN procedures	1674 (68)	314 (77)	763 (68)	597 (62)	<0.001[a]
Tumour size in the RN group (cm)	6.6 ± 0.1 (5.7, 4.0–8.5)	6.3 ± 0.2 (5.0, 3.5–8.5)	6.8 ± 0.1 (5.9, 4.0–8.5)	6.5 ± 0.1 (5.6, 4.0–8.0)	0.12[b]
RN started as MI procedure	914 (55)	141 (45)	423 (56)	350 (59)	<0.001[a]
Conversions from MI to open RN	62 (7)	14 (10)	22 (5)	26 (7)	0.2[a]
Tumour size for converted procedures (cm)	6.8 ± 0.5 (6.4, 4.2–8.0)	6.3 ± 1.3 (5.0, 2.5–6.9)	6.3 ± 0.6 (6.2, 3.9–8.5)	7.5 ± 0.7 (7.4, 4.7–8.5)	0.063[c]
TDM among patients with converted procedure	3 (5)	2 (14.3)	1 (4.5)	0 (0)	0.13[a]

LVH = low-volume hospitals; IVH = intermediate-volume hospitals; HVH = high-volume hospitals; TDM = 30-d mortality.
Data are presented as mean ± standard error of the mean (median, interquartile range for continuous variables and as *n* (%) for categorical variables.
[a] Exact χ^2 test between LVH and IVH/HVH combined.
[b] According to *t*-test between LVH and IVH/HVH combined.
[c] Nonparametric Mann-Whitney *U*-test between LVH and IVH/HVH combined.

correlation between hospital volume and perioperative mortality in contemporary studies is probably multifaceted. Low overall perioperative mortality, a lack of valid and accepted definitions of LVH and HVH, and variable data quality in different databases are all probably contributing factors that need to be discussed.

The overall TDM rate of 0.89% is in line with contemporary data for perioperative mortality (0.7–1.4%) [4–7] but is lower than reports from 15–20 yr ago (2–4%) [10,17–19]. As mortality rates decrease, demands for larger volumes increase, and thus the possibility of timely surveillance of changes in perioperative mortality is impeded [20]. The fact that most authors use IHM instead of TDM further complicates this [4–7,16]. As demonstrated in the present study, the two rates are not necessarily alike, and IHM is often lower (IHM 0.69%, TDM 0.81%). The most obvious objection to the use of IHM is that it is highly dependent on local/regional/national routines for length of stay and discharge, including the handling of patients dying from a terminal disease [21,22]. It is documented that a considerable proportion of perioperative deaths occur after discharge, but within 30 d [23]. For KC surgery, it will be important to look for an anticipated increase in this post-discharge proportion of perioperative deaths as the shorter length of stay associated with MIMs becomes more widespread.

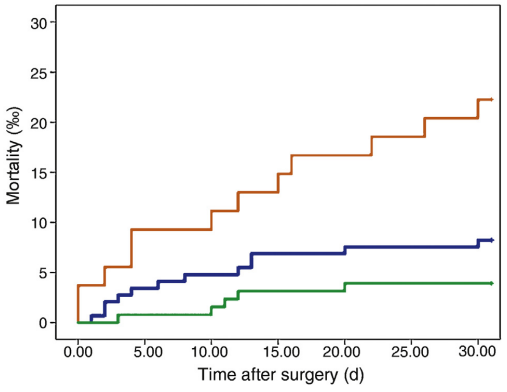

Fig. 2 – Kaplan-Meier plot of cumulative mortality in the different hospital volume groups during the 30-d period following surgery. Red, low-volume hospitals (539 patients at risk initially and 527 still at risk after 30 d), yellow, intermediate-volume hospitals (1457 patients at risk initially and 1445 still at risk after 30 d); green, high-volume hospitals (1277 patients at risk initially and 1272 still at risk after 30 d).

Table 5 – Multiple logistic regression analyses to predict 30-d mortality in patients undergoing surgery for kidney cancer (*n* = 3264)

Variable	OR (95% CI)	*p* value
Age (continuous in yr)	1.10 (1.05–1.15)	<0.001
Gender (male vs female)	2.00 (0.84–4.79)	0.12
Type of nephrectomy (RN vs PN)	2.05 (0.59–7.19)	0.3
pT stage		0.03
T1–2	1.00 (reference)	
T3–4	0.99 (0.35–2.78)	1.0
M+	3.35 (1.32–8.50)	0.01
Hospital volume		0.006
≥40 /yr	1.00 (reference)	
20–39 /yr	1.87 (0.65–5.35)	0.2
<20 /yr	4.98 (1.72–14.4)	0.003

OR = odds ratio; CI = confidence interval; RN = radical nephrectomy; PN = partial nephrectomy.

Second, LVH and HVH definitions are several and diverse. The definition range in terms of KC surgeries is 5–25 yr for LVH and 16–70 /yr for HVH [4,5,7,24]. The issue is complicated by the fact that some authors used separate cutoffs for RN and PN in the same study [16], while others used caseload per surgeon as a stratification tool [2]. The reasons for group allocation in many studies are difficult to grasp. In some studies, allocation seems to be based on post hoc analysis, with simple splitting into parameter tertiles, though the basis is often not disclosed. In the present study, LVH was predefined by a new regulation issued by the Norwegian health authorities. The evidential basis for the new regulations might be questioned, and our hypothesis was that no difference would be found. Nevertheless, the hypothesis was disproved, and in our opinion the data presented indicate that the higher TDM in the LVH group should not be disregarded.

Assessment of volume for KC surgery is further complicated by major changes in treatment introduced

during the last few decades. Open RN used to be the treatment of choice for all KCs, but choices must be made today between RN and PN, and between open surgery and one of several MIMs. Most other studies report lower PN rates than in our case (5–18% vs 31%), which is probably a reflection of older data [4,5,7,12,15], when more active use of PN as advocated by modern guidelines did not apply. Since 2007, the Norwegian national RCC guidelines have recommended that all T1a tumours should be assessed for potential PN. Our study shows that Norwegian LVHs use PN and MIMs to a lesser extent than IVHs and HVHs. This could be an indication that <20 KC surgeries per year is below the threshold for the introduction and routine use of more advanced surgical procedures such as minimally invasive PN. This assumption is further supported by the findings that minimally invasive RN conversion was more frequent in LVHs and that LVH conversions were for smaller tumours with poorer TDM outcomes.

The recent introduction of observation as a modality for the management of smaller KC in older and/or comorbid patients may also have contributed to the higher TDM in the LVH group. Observation and/or active surveillance in an organised approach was first introduced at larger academic centres to avoid overtreatment and unnecessary treatment-related mortality and morbidity [25]. There is a possibility that LVHs with less experience choose to perform surgery on poorer surgical candidates in comparison to larger centres.

Third, current studies on perioperative mortality, such as ours, are based on different registries or joint databases. However, some of these databases only include 10–20% of the actual population [5,12]. Other nationwide databases rely on self-reporting by surgeons, with under-reporting of up to 20% [26]. These limitations might increase difficulties in demonstrating a volume-mortality effect. The present study is strengthened by the fact that CRN has more and independent reporting routines. This enhances the completeness of the registry, which thus improves the outcome of studies.

Our study is not without limitations. In particular, access to data on postoperative complications such as Clavien-Dindo class [27] and Charlson comorbidity scores [28] would have deepened understanding of the results. For example, if such data were available, "failure to rescue" rates could have been addressed. The ability to avoid mortality after major complications is identified as a mechanism underlying the difference between high- and low-mortality hospitals [29,30].

Other limitations include a lack of data regarding possible confounders, such as surgeon experience and individual case load, and incomplete data sets on accompanying surgical procedures and history of prior surgery. Furthermore, as the number of deaths in the present study was low, there is a risk of overfitting in the multivariate analysis. The results should therefore be interpreted accordingly.

Finally, because of the limitations of the present registry, to achieve better understanding and surveillance of the quality of KC treatments and outcomes, a dedicated kidney tumor quality registry modelled on the Swedish KC Registry [31] is warranted for the Norwegian KC environment.

5. Conclusions

This population-based study, encompassing a consecutive 6-yr cohort, shows that TDM after KC surgery was 0.9% overall and in line with previous reports. We also demonstrated that TDM outcome is significantly poorer for LVH (<20 procedures/yr). The study supports the new Norwegian health authority regulation dictating that KC surgery should be discontinued in this group of hospitals.

Author contributions: Christian Beisland had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Beisland, Hjelle, Johannesen.
Acquisition of data: Hjelle, Johannesen.
Analysis and interpretation of data: Beisland, Hjelle.
Drafting of the manuscript: Hjelle, Beisland.
Critical revision of the manuscript for important intellectual content: Beisland, Hjelle, Johannesen.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euf.2016.10.001.

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Supplementary Table 1 Patient and tumor characteristics for the six-year Norwegian cohort of surgically treated kidney cancer patients

Variables	Mean±SE (median, IQR) or n	%
Age (years) (n=3273)	63.3±0.2 (64.0, 56-72)	
Male gender (n=3273)	2200	67.2
Laterality (n=3264)		
Left	1627	49.8
Right	1625	49.8
Bilateral	12	0.4
Tumour size (cm) (n=3294)	5.4±0.1(4.5, 2.6-7.0)	
Primary tumour status (TNM 2009) (n=3255)		
pT1a	1486	45.6
pT1b	741	22.7
pT2a	244	7.5
pT2b	147	4.5
pT3a	530	16.3
pT3b	49	1.5
pT3c	9	0.3
pT4	49	1.5
Regional lymph node status (n=3270)		
pNx-0	3181	97.3
pN+	89	2.7
Distant metastases (n=3273)		
No (M0)	3006	91.8
Yes (M+)	267	8.2
Fuhrman grade[a] (N=2794)		
1	226	8.1
2	1441	51.6
3	786	28.1
4	175	6.3
NDA	166	5.9
Subtype (n=3270)		
Clear cell RCC	2294	70.2
Papillary RCC	500	15.3
Chromophobe RCC	201	6.1
Multicystic clear cell RCC	82	2.5
Other RCC	122	3.7
Unclassifiable	71	2.2
Surgical treatment (n=3273)		
Radical nephrectomy	2259	69.0
Open	1116	49.4
Minimal invasive	1105	48.9
NDA	38	1.7
Partial nephrectomy	1014	31.0
Open	503	49.6
Minimal invasive	495	48.8
NDA	16	1.6
Length of stay (days) (n=2604)	6.3±0.1 (5, 4-7)	

[a]-includes only clear cell and papillary RCC. IQR – inter quartile range, NDA – no data available, p – pathological stage (from histopathology reports), n-number, SE – standard error of the mean, %-percent

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