CT Guided Ablation of T1 Renal Tumors

VANESSA ACOSTA RUIZ
Abstract

The widespread use of medical imaging contributes to the increased detection of incidentally detected small renal tumors, a majority which are often indolent masses found in elderly patients with preexisting chronic kidney disease. In Sweden, partial nephrectomy with minimal invasive surgical approach is the current standard for removing these tumors, although another option is percutaneous image-guided tumor ablation that allows treatment of elderly patients with comorbidities for whom surgery is a risk. Due to the lack of long-term follow-up studies and prospective randomized trials, ablation is still considered an alternative option to surgery in Sweden. The aim of this thesis was to evaluate treatment of T1 renal tumors with CT guided radiofrequency (RFA) and microwave ablation (MWA).

Factors affecting the efficacy rate of complete tumor ablation with RFA after a single session were evaluated (Paper I). Optimal electrode placement and a long tumor distance to the collecting system were associated with an increased primary efficacy. Renal tumor RFA was compared with laparoscopic partial nephrectomy (LPN: Papers II-III): both methods had comparable secondary efficacy rates, but RFA involved several treatment sessions. Total session times and hospitalization times were shorter and complications less frequent for RFA than for LPN (Paper II). After treatment, renal function impact was assessed by evaluation of both renal function quantity and quality through determination of the split renal function (SRF: Paper III). Standard renal function measurements were assessed and both RFA and LPN were nephron sparing when treating small renal tumors and did not affect creatinine or GFR. However, LPN involved greater SRF reduction in the affected kidney than RFA. Initial experience with microwave ablation was evaluated and this new ablation technique demonstrated high efficacy rates with fewer complications, and was comparable with the mid-term results of now established ablation techniques (Paper IV).

In conclusion, CT guided RFA and MWA are safe and effective treatments for the removal of T1 renal tumors. This thesis provides further insights into the field of thermal ablation of small renal masses, which can aid future treatment selection and patient management.

Keywords: Renal tumor, Ablation, Radiofrequency ablation, Microwave ablation

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ISSN 1651-6206
urn:nbn:se:uu:diva-392318 (http://urn.kb.se/resolve?urn=nbn:se:uu:diva-392318)
To my parents Rafael and Maria Esther
This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

Predictive factors for complete renal tumor ablation using RFA.
*Acta Radiologica, 57*(7):886-93

Periprocedural outcome after laparoscopic partial nephrectomy versus radiofrequency ablation for T1 renal tumors: a modified R.E.N.A.L nephrometry score adjusted comparison.
*Acta Radiologica, 60*(2):260-8

Split renal function after treatment of small renal masses: comparison between Radiofrequency ablation and Laparoscopic partial nephrectomy.
*In manuscript*

IV. Acosta Ruiz, V., Dahlman, P., Brekkan, E., Lönnemark, M., Magnusson, A.
Percutaneous CT guided microwave ablation of 105 T1a-T1b renal tumors: technique efficacy with a mean 2-year follow-up.
*In manuscript*

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# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AML</td>
<td>Angiomyolipoma</td>
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<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
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<td>AUA</td>
<td>American Urological Association</td>
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<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<td>EAU</td>
<td>European Association of Urology</td>
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<tr>
<td>(e)GFR</td>
<td>(estimated) Glomerular Filtration Rate</td>
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<tr>
<td>GEE</td>
<td>Generalized Estimating Equations</td>
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<td>HU</td>
<td>Hounsfield Units</td>
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<td>ICC</td>
<td>Intra Class Coefficient</td>
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<tr>
<td>LPN</td>
<td>Laparoscopic Partial Nephrectomy</td>
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<td>m-RNS</td>
<td>Modified R.E.N.A.L Nephrometry Score</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>MWA</td>
<td>Microwave Ablation</td>
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<td>NSS</td>
<td>Nephron Sparing Surgery</td>
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<tr>
<td>PN</td>
<td>Partial Nephrectomy</td>
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<td>RALPN</td>
<td>Robot Assisted Partial Nephrectomy</td>
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<td>RCC</td>
<td>Renal Cell Carcinoma</td>
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<td>RFA</td>
<td>Radiofrequency Ablation</td>
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<td>RMB</td>
<td>Renal Mass Biopsy</td>
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<td>ROI</td>
<td>Region of Interest</td>
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<td>RRF</td>
<td>Relative Renal Function</td>
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<td>SRF</td>
<td>Split Renal Function</td>
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<td>SRM(s)</td>
<td>Small Renal Mass(es)</td>
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<td>TA</td>
<td>Thermal Ablation</td>
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<tr>
<td>TNM</td>
<td>Tumor, Nodes, Metastasis, Classification System</td>
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1. Introduction

Kidney cancer is the fourteenth most common type of cancer worldwide and in adults it includes malignant tumors developing from the renal parenchyma or renal pelvis (1). Renal cell carcinoma (RCC) (i.e. adenocarcinoma arising from the renal parenchyma) accounts for 90% of kidney cancers. Cancer in the renal pelvis arising from transitional cells represent 10% of kidney cancers (2). The latter malignancy is not a focus in this thesis.

1.1 Renal Cell Carcinoma

1.1.1 Epidemiology and Etiology

The highest incidence of RCC occurs in Europe and North America, representing 2-3% of all cancers (2, 3). In Sweden, RCC is the tenth most common cancer diagnosis affecting approximately 1000 people per year (4). The majority of patients diagnosed with RCC are between 60-80 years (25% are <60 years), with a male predominance (incidence: 61% men, 39% women) (4). Established risk factors for RCC are obesity, hypertension and cigarette smoking. Familial or inherited predisposition to renal neoplasms accounts for <4% of renal tumors (5). Hereditary forms of RCC are caused by Von Hippel Lindau syndrome, hereditary papillary renal cell carcinoma, hereditary leiomyomatosis and RCC, and Birt-Hogg-Dubé syndromes (3) and tend to be bilateral and multiple, and occur at an earlier age than sporadic renal tumors (5).

1.1.2 RCC Subtypes and Benign Tumors

Renal tumors are subdivided according to their cell of origin and morphologic appearance (6). The World Health Organization’s (WHO) classification of adult renal epithelial neoplasms differentiates RCC types based on pathology, cytogenetic and genetic analyses (5). The differentiation of RCC from benign tumors makes it possible to avoid overtreatment of benign tumors. Therapeutic strategies and prognosis differ between RCC subtypes, as different subtypes have their specific pathological and imaging features.

The most common malignant subtype is clear cell carcinoma, which represented 77% of RCC diagnosed in Sweden during 2010-2014 (4). On CT im-
ages, it appears as a highly heterogeneously hypervascular tumor in the cortico-medullary phase and presents some washout of contrast in the nephrographic and excretory phases (7). Five-year survival of between 43-89% is reported (7).

The second most common malignant subtype is papillary RCC, and represents 13% of reported RCC in Sweden (4, 7). On CT, papillary RCC is more homogenously low-enhancing than the adjacent cortex and demonstrates a homogeneous gradual enhancement when assessed in the corticomedullary- and nephrographic phase. The low attenuation and homogeneous enhancement patterns make papillary RCC distinguishable from clear cell RCC. Five-year survival is reported between 57-85% (7). There are two types of papillary RCC (8): Type 1 (low-grade neoplasm with better prognosis) and Type 2 (high-grade neoplasm with worse prognosis).

Chromophobe RCC represents approximately 6% of RCC. The degree of enhancement on CT imaging is intermediate between clear cell RCC and is hypovascular compared to the renal cortex (7). Five-year survival ranges between 76-100% (9). Other unusual malignancies include carcinoma of the collecting ducts of Bellini (<1% of RCC) (9, 10).

Benign renal tumors account for 7-33% of all kidney masses (3, 11) and can appear similar to RCC on imaging and are thus challenging to differentiate from malignant tumors under pathological assessment (11-13).

Oncocytoma, a benign tumor, accounts for 8% of all renal cell neoplasms (14). On CT images, oncocytoma present similar enhancement to clear cell RCC and chromophobe RCC; therefore, CT cannot be solely used for diagnosis. Histopathological assessment is used for diagnosing oncocytoma, but not all oncocytomas can be differentiated from malignant tumors with this method (7, 11, 15).

Angiomyolipoma (AML) represent 3% of all renal tumors (14). The majority of angiomyolipoma are benign, except those with epithelioid features, which can have malignant potential. Large size AML (>4 cm) may cause hemorrhage and local invasion. The presence of macroscopic fat (<10 HU) is sufficient for diagnosing AML on imaging. However, 10% of AML are fat-poor, containing <25% adipose tissue, making AML difficult to differentiate from RCC on CT images (7, 9). Normally, the presence of macroscopic fat in a renal mass is characteristic of an AML, but some rare cases of fat-containing RCC may be secondary to cholesterol necrosis or engulfment of adjacent fat (16). However, the presence of calcifications can increase the suspicion of RCC as calcifications are not present in AML (17). Other renal masses that can be differentiated are renal adenoma, urothelial carcinoma, metastatic tumor, infarct, abscess, pseudotumor or vascular malformation.
1.1.3 RCC Diagnostic Assessment

According to the 2019 European Association of Urology (EAU) guidelines (18), the work-up for RCC assessment includes the following recommendations:

- Contrast-enhanced multi-phasic abdominal CT or MRI should be used for renal tumor characterization.
- For determining staging, lungs and mediastinum should be evaluated with a chest CT.
- When in need to avoid ionizing modalities, contrast enhanced ultrasound can be used for further characterization of small renal masses, evaluation of tumor thrombus or unclear renal masses.
- Renal tumor biopsy with a coaxial technique is suggested before ablative treatment, systemic therapy and for selected patients considered for active surveillance.
- Percutaneous renal tumor biopsy is preferred over fine needle aspiration for characterizing of solid renal tumors.

The TNM classification system (19) is used to classify and stage RCC (3, 6). Tumor size, venous invasion, renal capsular invasion, adrenal or lymph node involvement and the presence of distant metastasis are evaluated for TNM classification. Survival rates are strongly correlated to TNM-stages; the 5-year cancer specific survival rates in patients with T1 tumors is 91% for grade 1, 83% for grade 2, 60% for grade 3, and 0% for grade 4 (3, 20). In this thesis, only T1N0M0 (≤7 cm tumors limited to the kidney) tumors will be discussed. T1a includes tumors 4 cm or less in the greatest dimension, whereas, T1b include tumors more than 4 cm but not more than 7 cm in the greatest dimension.

1.2 Small Renal Mass Management

1.2.1 The Clinical Dilemma of Small Renal Mass Management

Although there are varying size limits exists in the literature for a small renal mass (SRM), in this thesis the SRM is defined as ‘an incidentally detected ≤4 cm in diameter contrast-enhancing renal tumor’, as used in the American Society of Clinical Oncology (ASCO) guidelines (21).

Tumor characteristics of patients diagnosed with RCC have changed over time. Between 1986 and 2010, a Swedish study (22) reported a decrease in median tumor size from 70 mm to 50 mm. This is partially explained by the widespread use of medical imaging, which has contributed to the increased detection of asymptomatic incidentally found renal masses (23). In Sweden, the proportion of incidentally found renal cancer has increased from 43% in 2005 to 60% in 2014 (4). The incidence of T1a renal tumors has also increased, now representing up to 66% of all diagnosed renal tumors (24). Even
though kidney cancer is treated aggressively, mortality from RCC has not declined. Possible explanations are that a large proportion of small renal masses (SRMs) may be clinically benign or indolent and that their removal represents over diagnosis and overtreatment, suggesting that the current practice is insufficient (11, 25).

SRMs are often found in elderly patients with preexisting chronic kidney disease. However, in this patient group, the high incidence of co-morbidity means patients are more likely to die with their renal tumor rather than because of it (23, 26).

The likelihood of malignancy in a solid renal lesion increases with size each 1 cm increase in tumor size is associated with a 17% increase in the odds of malignancy (27). Approximately 80% of SRMs are malignant, with 20% being benign (27), and an average growth rate of <3 mm per year for SRMs is reported (28). As the growth rate of SRMs is slow (29, 30), it raises the questions of whether treatment can be delayed or if older patients need to be treated at all. Nevertheless, prediction of growth rate is not possible and there is no established growth trajectory for intervention.

Despite a small size, 20-30% of renal masses <4 cm are reported as aggressive with high metastatic potential (31). Simultaneously, the amount of accumulating evidence supporting the indolent nature of SRMs has questioned whether these lesions should be treated at all (23). This raises the question as to whether the exceptionally good 95% five-year survival (11) of surgically resected SRMs is explained by a high presence of benign and indolent tumors rather than treatment effect. Not all small renal masses can be fully characterized with a method. Imaging with CT has limitations and renal mass biopsies of these small lesions can lead to non-conclusive results, further questioning the type of disease is being handled.

Given this setting, less aggressive treatment alternatives have been developed. Lesions, traditionally managed with an aggressive surgical approach, are now managed with nephron sparing surgical procedures, percutaneous ablative treatments or by active surveillance. The continuous development of treatment alternatives raises several clinical dilemmas, such as which SRM should be treated, how it should be treated, and when it should be treated.

1.2.2 Imaging Modalities for Small Renal Mass Evaluation

Several imaging modalities are used to assess SRMs, but there is no absolute reference method. CT is the main imaging modality able to detect SRMs. MRI is sensitive, but rarely used as a first step imaging alternative, except for high-risk patients (32).

1.2.2.1 Computed Tomography (CT)

CT is used for characterization, aiding diagnosis and staging of renal cancer and aids pre-operative planning. CT examination both prior and after contrast
medium injection should be included, as long as renal function allows contrast administration. Image findings help to divide renal masses into solid or cystic lesions by evaluating lesions based on, for example, density measurements, demonstration of fat or calcifications, and enhancement patterns (6, 9). The majority of solid malignant lesions have characteristic contrast enhancement, with a change of more than 15 HU between images before and after contrast administration (33). Four-phase CT-scans (unenhanced, corticomedullary-, nephrographic- and excretory phase) maximize the potential for differential diagnosis. CT has a median sensitivity of 88% and specificity of 75% in diagnosing adult RCC (34), and is more easily available and quicker than MRI. Disadvantages include radiation and risk of contrast-induced nephropathy (3, 9).

The characterization of SRMs can be challenging. In very small tumors (i.e. ≤1.5 cm), the presence of enhancement can be difficult to determine due to volume-averaging (16). Renal masses ≤5 mm are too small to be characterized on CT reconstructions with 3 mm slices and thinner slices entail image-noise inhibiting analysis. As these “too-small to characterize” masses are likely to be benign, additional imaging is usually not recommended (23).

A minority of small RCC, especially papillary RCC, have a low level of enhancement, and near to significant enhancement, and hence can be mistaken as hyperdense cysts (16). Furthermore, CT and MRI cannot reliably differentiate oncocytoma and fat-poor AML from malignant neoplasms (18). Approximately 20% of small, solid renal masses suspected as RCC (enhancing on CT images) have been found to be benign oncocytoma or fat-poor AML after surgical resection (6).

1.2.2.2 Magnetic Resonance Imaging (MRI)

MRI is preferentially used for patients who are pregnant, have an allergy to intravenous contrast, possible venous involvement or locally advanced malignancy (6). Patients with hereditary forms of renal malignancy can use MRI as an option to minimize radiation exposure from CT scans.

1.2.2.3 Other Imaging Modalities

Ultrasound may be sufficient for distinguishing a simple cyst that requires no follow-up. However, the use of ultrasound for characterizing SRM (beyond simple cysts) has yet to be evaluated (23). Other modalities e.g. Positron emission tomography and angiography are also reported as an aid to RCC characterization (35, 36).

1.2.3 Renal Mass Biopsy

Renal mass biopsy (RMB) aims to obtain material for renal tumor histopathological diagnosis (18). The four-tiered WHO/ISUP (World Health Organization/International Society of Urological Pathology) grading system based on
nucleolar features is used for histological assessment as the grading system correlates to tumor aggressiveness and prognosis (18).

Although RMB has an high sensitivity (97.5%) and specificity (96.2%) and positive predictive value (99.8%), it has a non-diagnostic rate of 14% (12). The accuracy of tumor grade (Fuhrman grading) diagnosis with RMB ranges between 52-76%, entailing a variability that potentially affects patient management and prognosis (12). Histologic heterogenic tumors present a challenge (i.e. hybrid oncocytic tumors with chromophobe RCC) as RMB may not include all cell types (12). Differentiation between oncocytoma and chromophobe RCC may also present a challenge and a non-malignant biopsy result does not imply the presence of a benign lesion. Among patients undergoing extirpation despite a negative biopsy, 37% had malignant disease on final surgery pathology (13).

The role of RMB in characterizing SRMs has been discussed and international guidelines differ in their recommendations. Small tumor size is predictive for biopsy failure, however, repeat biopsy has a high (80%) diagnostic success rate (37). The EAU 2019 guidelines recommend RMB before ablative treatment, and active surveillance for selected patients, in order to avoid unnecessary surgery in the event of a benign tumor (18). Conversely, the AUA does not require RMB for older patients who will be managed independently of RMB findings, but do recommend RMB prior to ablation (12). Considering the indolent nature of SRMs and the competing risks of mortality from other diseases in patients presenting with incidental SRMs, the ASCO guidelines recommend RMB when results may alter management (21).

1.2.4 Anatomic Scoring Systems

Several anatomical classification systems have been proposed that objectively describe renal tumor complexity in a quantitative manner (38). Initially developed to aid choice of surgical approach for treatment, these classification systems serve to predict treatment outcome, risk of complications and renal tumor malignancy grade (39-44). The standardized reporting of tumor characteristics facilitates comparison between tumor populations and reduces selection bias.

In this thesis, the modified R.E.N.A.L nephrometry scoring system (m-RNS) was used, as it is one of the most reported systems and it has a greater predictive performance of ablation success with radiofrequency than the original scoring system (45).

1.2.4.1 Modified R.E.N.A.L Nephrometry Score (m-RNS)

Gahan et al. (45) proposed a modified scoring system adapted to the smaller renal masses treated with ablation. Four of the five included parameters are given 1-3 points depending on different criteria (Table 1). A suffix is assigned to the total sum (ranging between 4-12 points) to describe the tumors’ anterior (“a”), posterior (“p”), neither a/p (“x”) and/or hilar (“h”) location (Figure 1).
A limitation of the scoring system is that several parameters influence each other. Growth in tumor size increases the tumor’s possibility of expanding into the renal pelvis, acquiring a central location. Similarly, exophytic tumors will often be further away from the collecting system. In addition, the m-RNS does not consider other factors that may affect the ablation approach, e.g. the tumor’s relationship to bowel and ureter affect the ablation approach, e.g. the tumor’s relationship to bowel and ureter (46, 47).

Table 1. Points given according to criteria for each parameter of the modified R.E.N.A.L nephrometry score (45).

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<th>1 point</th>
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<tr>
<td>Radius (maximal diameter</td>
<td>&lt;3</td>
<td>3-4</td>
<td>&gt;4</td>
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<td>in cm)</td>
<td></td>
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<td>Exophytic/endophytic pro-</td>
<td>≥50%</td>
<td>&lt;50%</td>
<td>Entirely endophytic</td>
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<td>perties</td>
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<td>Nearness of the tumor to</td>
<td>≥7</td>
<td>&gt;4 but &lt;7</td>
<td>≤4</td>
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<td>the collecting system or</td>
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<td>sinus (mm)</td>
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<td>Location relative to the</td>
<td>Entirely above</td>
<td>Lesion</td>
<td>&gt;50% of mass is</td>
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<td>polar lines</td>
<td>the upper or be-</td>
<td>crosses polar</td>
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<td>low the lower</td>
<td>line</td>
<td>mass crosses the axial</td>
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<td>renal midline; or mass</td>
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Figure 1: Example of a SRM categorized with the modified R.E.N.A.L nephrometry score. Evaluation of parameters Radius (a), Exophytic/endophytic properties (b), Nearness of the tumor to the collecting system or sinus (c), Anterior or Posterior location (suffix) (d) and Location relative to polar lines (tumor within the dashed circle) (e). Total RNS score: 8a.
1.3 Treatment Options for T1a Renal Tumors

Several aspects need to be considered when choosing treatment alternatives. Patient factors (age, co-morbidities, life expectancy, renal function, personal preference), tumor characteristics (size, location) and technical considerations for each treatment method must be assessed.

Since the 1990s, treatment of localized RCC has evolved. There are three main management alternatives for patients with T1 renal tumors: surgery, ablation or active surveillance. Depending on the individual setting, these alternatives can aim to cure the patient from disease, minimize the tumor burden, or actively follow the patient to discuss possible future intervention, if necessary.

1.3.1 Surgical Approaches

Nephron-sparing surgery (NSS) implies the enucleation of the tumor (without concomitant adrenalectomy) by partial nephrectomy (PN). In the 1970’s, PN was introduced for high-risk patients where the alternative was total nephrectomy followed by renal replacement therapy (48). As studies began to report equivalent tumor-free survival rates after both PN and total nephrectomy, PN gained increased interest (49-51). In the 1980s, survival rates were improved and the development of NSS continued from imperative to elective treatment, parallel to the increase of incidentally found SRM (52). Later, further advantages including renal function preservation, reduced patient morbidity and risk for chronic kidney disease development made partial nephrectomy (PN) standard in treating T1a tumors with a curative intent. The EAU includes T1b tumors for NSS treatment, whenever technically feasible (4).

An open, laparoscopic or robot-assisted approach can be used depending on the surgeon’s knowledge and skills (3). Small, peripheral exophytic lesions are less complicated to remove and make good candidates to start with. Complex tumors e.g. invading the collecting system, totally endophytic, tumor in a solitary kidney, are be feasible with increased surgical expertise (53). Surgeons may choose a transperitoneal (for anterior or upper pole tumors) or a retroperitoneal approach (for posterior tumors). CT imaging is important for identifying renal tumor location for pre-operative planning (18).

After port placement, renal hilar dissection and mobilization of kidney fat, renal vessels are prepared for cross-clamping. To improve visualization of the kidney tumor and minimize blood loss, renal hilar clamping can be used; this minimizes or shuts down renal blood flow allowing work in a bloodless field, i.e. obtaining renal ischemia. For large, intra-renal or hilar tumors, temporary hilar cross-clamping is used (to reduce bleeding and facilitate dissection) i.e. warm ischemia can be induced. Renal hypothermia, i.e. cold ischemia, may be induced to lower ischemic damage to the kidney e.g. by retrograde cold perfusion or with intracorporeal ice slush. The tumor is then resected followed...
by pelvicalyceal repair (if necessary). The renal defect is then reconstructed over a hemostatic agent, e.g. oxidized cellulose (48, 54). Other hemostatic techniques may be used to aid hemostasis (e.g. fibrin glue, gelatin sponges, argon beam coagulator, electrocautery, laser) (48).

Current advantages of laparoscopic partial nephrectomy (LPN) over open partial nephrectomy include shorter hospital stay, reduced blood loss and analgesic requirement (55). Difficulties in ensuring renal hypothermia, parenchymal hemostasis, pelvicalyceal reconstruction and renorrhaphy make LPN a more technically challenging procedure than open partial nephrectomy. This may result in longer warm ischemia time (entailing subsequent renal dysfunction) and higher per operative complication rates (55, 56). Even so, the benefits of reducing morbidity of the flank incision are substantial, encouraging the use of less invasive laparoscopic or robot assisted techniques (56-62). Contraindications for LPN are multiple renal tumors, locally advanced disease, morbid obesity, renal vein/inferior vena cava thrombus, bleeding diathesis or other general contraindications to laparoscopic surgery (48, 54).

Robot-assisted laparoscopic partial nephrectomy (RALPN) is a further development for NSS. A camera, controlled by the primary surgeon, adds a three-dimensional view and the instruments allow greater range of motion, facilitating tumor excision and suturing. RALPN and LPN have comparable oncological outcomes and postoperative morbidity, but shorter hospital stay and reduced blood loss are reported after RALPN. The increased costs of this approach are a disadvantage (61) and as with all new methods, further evaluation of RALPN is needed.

1.3.2 Thermal Ablation (TA)

For this thesis, the terminology suggested by the Society of Interventional Radiology guidelines (63) are used for reporting ablation techniques and results.

The term tumor ablation implies the local application of chemical or thermal therapies to a specific focal tumor(s) in an attempt to achieve partial or total tumor destruction (64). The local application of thermal therapies will be discussed in the thesis. Several thermal energy sources destroy a tumor through heat (e.g. RFA, laser) or cold (cryoablation). Common for these techniques is they constitute an energy source connected to an antenna/probe that can be placed intra-operatively (through an open or laparoscopic approach) or percutaneously (under imaging guidance with CT, MR or ultrasound) into the renal tumor.

Some of the benefits of thermal ablation (TA) include the possibility of treating patients who are unfit for surgery, as the procedures can be performed under conscious sedation by a percutaneous approach. One of the main disadvantages is that the tumor is treated in-situ, so tumor characterization is dependent on CT and renal mass biopsy alone. This contrasts to tumor enucleation after surgery that gives the entire tumor for evaluation after treatment.
1.3.3 Radiofrequency Ablation (RFA)

The effects of alternating current causing thermal damage in a tissue was first described in 1891 (65). The first report of RFA for cancer treatment was in the early 1990’s for treatment of hepatic carcinoma (66). Zlotta et al (67) reported the first RFA renal tumor treatments in 1997.

RFA transmits a high-frequency (300-500 kHz) alternating electrical current into the targeted tissue via an electrode. The alternating current induces ionic agitation within the tissue, leading to frictional heat. In other words, the RF electrode itself is not the source of heat – it is the vibrating molecules that are the source of heat. Direct heating caused by the RF electrode occurs only within <1 cm proximity to the electrode tip, the rest of the ablation zone is created by thermal conduction (68). Reliable tissue destruction at temperatures above 55°C (for at least 15 seconds) leads to local tissue destruction and coagulation necrosis (69). Immediate cell death occurs at 60°C, but at temperatures above 100°C tissue vaporization, gas formation, tissue carbonization and eschar form around the electrode and act as an insulator, thereby, reducing the efficiency of the treatment. Thus, the goal is to achieve temperatures between 55-100°C in the targeted tissue (69).

Several RFA systems are available, but they do not all perform the same; therefore, effectiveness rates in different studies need to be interpreted appropriately. The size of the ablation zone may differ due to the length, diameter, surface area and temperature of the electrode. RFA generators vary in how they deliver energy. In the monopolar systems, the electrical circuit is formed between the RF generator, electrode and dispersing pads (placed on the patient’s thigh) (70). In bipolar systems, the current flows from the generator to the active electrode, through the targeted tissue to the second electrode and back to the generator. The generator in impedance-based systems has a feedback system that adapts power delivery in order to avoid quick temperature increases that can char the tissue (70). Temperature-based systems are designed to reach a pre-set target temperature in the tissue around the electrode for a predetermined duration. Internally cooled electrodes (with continuous internal saline perfusion) can create larger ablation zones by minimizing tissue charring. Perfusion electrodes infuse saline into the tissue through the electrode tip to achieve larger ablation zones. Although there are variations in techniques, the different RFA systems are equally effective in achieving cell death (69).

With increasing distance from the tip of the RF electrode, the temperature drops exponentially. Hence, radiofrequency waves can cause thermal ablation within a defined volume of tissue. The RF electrode can be positioned within the kidney through ultrasound guidance and/or CT fluoroscopy. CT fluoroscopy allows visualization of organs adjacent to the renal tumor and an additional temperature probe may be used to control the temperature at the border.
of the ablation zone (71). Contrast medium may be used to visualize the direct effect after ablation (Figure 2).

Figure 2: Example of transverse sections of CT images during an RFA procedure: (a) Renal tumor before ablation (indicated by the yellow dotted line) (b) Tumor targeting during ablation and positioning of the RF electrode (blue arrow) and temperature probe (red arrow) with CT fluoroscopy (c) CT image directly after ablation showing no contrast enhancement within the ablated zone (yellow arrow, i.e. tumor successfully treated).

RFA, together with cryoablation, is one of the most widely used ablation systems, therefore, more data are available on this system. However, RFA is cheaper and treatment durations are considerably shorter than with cryoablation (72). Disadvantages of RFA include the occasional need for repeat treatment (3, 73-75), it is less effective in tumors larger than 3 cm and in tumors with central location in the kidney (73), and, the RF current flow may be redirected to the high electrolyte content in urine causing unwanted ablation (70).

1.3.4 Microwave Ablation (MWA)

Microwave ablation (MWA) is a heat-based system. By applying an oscillating electromagnetic field (at 900-2500 MHz), polar molecules in a tissue (primarily water molecules) are forced to rotate billions of times per second, leading to heat generation. Tumors (and solid organs) have a high water content, making them conducive to microwave heating (76). Irreversible tissue destruction occurs at >55°C, and when tissue is heated to 100°C water starts to boil and escapes as gas, resulting in tissue dehydration (68).

The ablation system is composed of a generator, a power distribution system and an interstitial antenna that radiates the electromagnetic field, directly heating a volume around the antenna. Microwaves have the capacity to propagate through charred tissue, water vapor, dehydrated tissues and other high impedance tissues, allowing larger active zones of heating. This differs from RFA, which is dependent on good tissue electrical conductivity to heat the tissue immediately adjacent to the electrode. MWA can reach temperatures
over 100°C, as the microwaves can continue heating regions of low electrical conductivity. Chilled saline solution can be administered to circulate within the antenna, chilling the antenna shaft, to enable the delivery of higher powers for longer times and for producing larger ablation zones (68, 76, 77). Unlike RFA, MWA is less affected by the “heat sink effect” and does not require grounding pads (68, 76, 77). Although there are several manufacturers of MWA-systems, each with its’ positive and negative properties, the efficacy of MWA on renal tumors has not been fully evaluated and is the reason this ablation system is still considered as experimental for treating renal tumors (18).

1.3.5 Cryoablation

Cryoablation implies tissue destruction by freezing and thawing. Cryoprobes are inserted in the tumor and rapid cooling of the cryoprobe (by rapid expansion of argon gas) causes cellular necrosis and changes to the cellular microenvironment. Ice crystals are formed in the extracellular space, creating an osmotic tension that draws free intracellular water from the cells, which dehydrates them (78). The increase in intracellular solute concentration results in protein denaturation and damages enzymes. Active thawing with helium gas or passive thawing results in endothelial damage, microvascular thrombosis and ischemic cell. The rapid temperature changes to below -40°C cause immediate cell death in the majority of tissues (79).

Cryoablation is advantageous in that the limits of the expanding ice ball are visualized in direct real time with ultrasound, CT or magnetic resonance (MR) and multiple cryoprobes can be used simultaneously, which enables adaption of the ablation zone to the shape of the tumor (79).

However, there is an increased risk of bleeding, as cryoablation does not coagulate the needle path, which can be performed with RFA, and storage of the gases for cryoablation is expensive (79). With cryoablation, complication rates are low (between 6-10.4% in experienced centers) and the most common complications are minor hemorrhages (80, 81). Single-session complete tumor treatment rate (i.e. primary efficacy rate) is high in experienced centers (up to 92.4%; median follow-up 20.1 months (80)) and long-term efficacy is high (5-year efficacy, 97%; overall survival 97.8% for median 2.8 cm tumors (81)).

1.3.6 Planning a Thermal Ablation Treatment

To maximize chances of obtaining complete renal tumor ablation in a single session and avoiding complications, several factors need to be considered.

Preprocedural imaging is essential for procedure planning. On imaging, the feasibility of the procedure, site of access, number of probes needed, nearness of the tumor to adjacent structures, and the need for any ancillary procedures can be determined (82). CT is usually the modality of choice for procedural
planning and probe guidance (82); MR can be used but is not often as available. Ultrasound can be used to enable direct monitoring during probe placement without exposing the operator (and patient) to ionizing radiation. However, as the visualization of adjacent structures is limited, ultrasound in combination with CT is preferred (83).

The effects of ablation on renal tissue are dependent on several factors. Small tumor size, exophytic location and far distance from the collecting system are examples of tumor properties that make ablation more likely to result in complete tumor ablation (70, 79, 84-87). Tumor biology and histopathology may also have an effect (70, 79, 88). The thermal effect of TA is affected by vascularity in a tissue. High blood flow may lead to heat loss for the RFA/MWA zone i.e. the “heat sink effect” and heating for cryoablation). Perirenal- and hilar fat have insulating properties that can lead to ablation failure and probe properties, such as the use of single/multiple probes, internally cooled, mono-/bipolar probes, affect the size of the ablation zone (46, 70, 89).

The few complications reported (between 7.4-11%) include hemorrhage, uretral strictures, obstruction of the ureteropelvic junction, renocolic fistula and neuromuscular complications with paresthesia secondary to ablation in the proximity of the psoas muscle, where the genitofemoral nerve is situated (74, 90). Many of these complications are related to the tumor’s proximity to other structures or its’ central position in the kidney. Therefore, tumor location relative to the bowel, ureter, psoas muscle or other adjacent organs and structures needs to be considered in pre-operative planning. Hydrodissection and/or changing patient positioning may be used to increase the distance between e.g. colon and tumor to avoid colon perforation (Figure 3) (46). Selected renal pre-embolization may increase the ablation zone and minimize hemorrhage (46, 91) and placement of a ureter stent and pyelo-perfusion protects the ureter from thermal injury when ablating centrally located tumors (46).
1.3.7 Active Surveillance

Active surveillance implies continuous imaging to follow potential tumor growth that would require tumor removal. This management is based on data showing that incidentally detected SRMs have a low RCC-specific mortality and low (0.13 – 0.31 cm/year) growth rate (29, 30, 92, 93). This has been supported by data showing that metastatic disease is rare (1-2%) and 20% of SRMs are benign (29, 92, 93). However, these findings are based on small sample studies that do not include young patients without co-morbidities (92), have short follow-up periods (92, 93) or fail to report histopathology (93). Currently, there are no means of truly predicting whether a tumor will be indolent or potentially aggressive (30, 94). Even tumors with zero growth have been proven to be malignant (29). There is always the potential risk of losing the alternative of undergoing NSS or ablation therapy if the tumor progresses to higher TNM stages during active surveillance.

The main challenge is to effectively inform patients of the risk-benefit of this method. There are a wide range of surveillance protocols, making it difficult to establish an optimal. The EAU and AUA guidelines recommend active surveillance for elderly patients with severe comorbidities (making them high
risk for intervention) and limited life expectancy (<5 years), as they are more likely to die with their tumor (than because of it) due to competing death causes (3, 6).

1.4 Follow-up after T1a Tumor Management

Post treatment surveillance aims to assess complications, renal function, local tumor recurrence and metastasis. There is no consensus on an optimal interval between follow-up assessment. Surveillance schemes should be adapted to the patient’s risk profile and current evidence of recurrence risk for each treatment method (3).

1.4.1 Follow-up with Imaging

For PN and ablation therapies, imaging should be annually during the initial 5 years post treatment. As surgery has low recurrence risk and high 5-year cancer specific survival (3, 48), surveillance can be discharged (for patients with a low risk profile) (3). For ablative therapies, there is a lack of long-term randomized prospective studies evaluating recurrence risk, therefore, CT imaging is recommended every 2 years after the initial 5-year follow-up period (3).

On CT, a complete tumor treatment is expected to lack enhancement after contrast injection, indicating coagulative necrosis. If the first follow-up CT presents nodular enhancement of >15-20 HU, residual disease should be considered. If enhancement is seen on the treated site, after at least one follow-up study showing absence of viable tissue, then local tumor progression should be considered (63, 82).

1.4.2 Renal Function Assessment during T1a Renal Tumor Treatment

Current guidelines do not specify a treatment strategy based on renal function. Besides recommending PN as a nephron sparing procedure, the EAU guidelines make no further recommendation on how renal function should, or could, affect management (18). The AUA guidelines recommend evaluation of routine blood tests including the glomerular filtration rate (GFR), urinalysis, complete blood count and complete metabolic panel to assess renal function (12). Nevertheless, renal function preservation is paramount in patients treated for SRMs. Not only should renal function recovery after treatment be assessed, but also the risk of progression to chronic kidney disease (CKD). The potential need of renal replacement therapy and long-term overall survival implications need to be reviewed prior to treatment. The term “renal function” will be used henceforward to denote the kidney’s filtration properties.
1.4.2.1 Evaluation of GFR, Creatinine and Cystatin C

For routine clinical purposes, renal function is evaluated through the glomerular filtration rate (GFR), creatinine and cystatin C. The GFR represents the filtering capacity of the kidneys, showing at which rate substances are filtered from the blood at the nephrons. Creatinine is formed as a degradation product of muscle cells and most of it is cleared by glomerular filtration. A low renal function (i.e. low GFR) will imply a low filtration and therefore an accumulation of creatinine in the blood, resulting in high plasma creatinine values. This test is a cheap and quick way of measuring renal function. However, it is affected by the individual’s muscle mass, which varies with age, gender and diet amongst others. Cystatin C, a protein produced in almost all cells in the body, and is not affected by muscle mass, can be assessed by blood tests and used for GFR calculations, but is affected by medication with corticosteroids (95).

Several mathematical models have been developed to calculate GFR based on creatinine and cystatin C levels and demographic and anthropometric data. Creatinine-based formulas provide an estimation of renal function in adults that is sufficient for clinical practice. The estimated (also called the relative) GFR (eGFR) is correlated to a standard body surface area and height (corresponding to an individual of 170 cm and 63 kg). As GFR is reported relative to an area of 1.73 m², GFR-values between groups of individuals based on reference intervals for normal GFR values can be compared and are therefore applicable for research purposes. The absolute GFR is based on an individual’s height and weight, therefore, preferably used prior to contrast medium administration (96).

A normal GFR for young healthy individuals is 100-130 mL/min/1.73 m². GFR decreases with age; a 10 ml/min/1.73 m² decrease is expected per 10-year period between 40-50 years of age (96). Chronic kidney disease (CKD) implies decreased renal function with permanent albuminuria and/or hematuria and a GFR <60mL/min/1.73 m². Common reasons leading to CKD are age, general atherosclerosis, diabetes and chronic renal inflammatory disease. Decreased GFR increases the risk for complications after surgery, use of medication and intravenous contrast administration. Decreased renal function increases the risk of developing and aggravating cardiovascular disease (96) and is also associated with increased risk of hospitalization, cardiovascular events and mortality from any cause (97).

1.4.2.2 Measuring Renal Function with Imaging

As GFR represents the combined renal function of both kidneys, this limits assessment of the individual kidney’s contribution to the total renal function. Prior to nephrectomy in patients with unilateral renal cancer, the individual kidney function needs to be assessed to predict post-operative renal function. The internal function ratio between the two kidneys, the split renal function (SRF), expresses the contribution of each kidney (in percent) to the total renal
function. Renal scintigraphy with radioactive tracers has long been the routine for this. The uptake of radioactive tracers in each kidney are visualized and quantified with a gamma camera. However, nuclear renography is a time-consuming procedure and implies exposure to radioisotopes.

The intravenous contrast medium used in CT examinations is freely filtered through the glomeruli, is not bound by plasma proteins and is not reabsorbed or secreted in the tubuli. Therefore, the amount of contrast medium accumulating in the kidney is directly proportional to the GFR of that kidney. Measuring the mean attenuation of each kidney on contrast enhanced CT reflects the kidney’s uptake of contrast medium via renal perfusion (98). The calculated result can be related to the volume of renal parenchyma to be able to assess GFR per volume unit of renal parenchyma. Björkman (99) calculates the SRF by multiplying the kidney’s volume with the mean contrast attenuation of the renal parenchyma, which provides sufficient accuracy for clinical routine purposes. As the RCC patient already undergoes a contrast enhanced CT for pre-treatment planning, the SRF can be assessed without adding any extra imaging.

However, the SRF is limited to an internal comparison of the two kidneys of an individual, presented in percentages (e.g. 45% right kidney; 55% left kidney) and will not reflect absolute measurements of renal function. A change in SRF will reflect a change in the internal ratio of function between the kidneys.

1.4.3 Evaluation of Post-treatment Renal Function

Non-modifiable factors in patient (baseline renal function, co-morbidities, age) and tumor characteristics (location, size) affect renal function after renal tumor surgical resection and thermal ablation (100).

Small renal masses are more commonly found in patients of high age and with several co-morbidities. The risk for developing CKD is higher in this patient category. The average age at RCC diagnosis is 64 years old and the incidence of CKD in the group ≥60 years is roughly 26% (101). Some of these patients (26%) already have pre-existing CKD (102). CKD is associated with risk of renal failure, cardiovascular events, hospitalization and premature death (97). This emphasizes how the sparing of nephrons is paramount in these patients in order for minimizing development of end-stage renal disease (3, 102).

1.4.3.1 Renal Function after Partial Nephrectomy (PN):

Long term GFR after PN depends on the amount of remaining renal parenchyma (kidney quantity) and the preoperative function of the kidney (kidney quality) (21). There are non-modifiable factors that predict worse long-term GFR after surgery: higher body mass index, male sex, hypertension, diabetes
mellitus, increasing tumor size, age, higher Charlson comorbidity index, and lower baseline GFR.

Several groups have discussed modifiable procedure-related factors. Surgically induced CKD is associated with a lower risk of progressive renal functional decline than pharmacologically induced CKD: thus, the impact of surgery on postoperative renal function is dependent on pre-existing renal disease and function (103).

A warm ischemia time should be less than <30 min, as longer times result in diminished post-operative GFR and/or irreversible renal damage (21). Cold ischemia allows longer durations of ischemia and is related with improved renal functional results. However, ischemia times vary with tumor size and complexity and a safe lower limit has not been established (104).

Renal parenchymal volume preservation is one of the most important determinants of renal function, with limited ischemia time playing a secondary role (105, 106). Factors associated with increased renal parenchymal loss are large tumor size and central location (i.e. tumors of greater complexity) (107, 108). In summary, the factors affecting post-operative renal function after PN are complex and inter-related.

1.4.3.2 Renal Function after Thermal Ablation (TA):
TA can be performed with zero ischemia time, as it is in-situ and percutaneous. However, the evaluations of renal function after TA present contradictory results for ablation in older patients with more co-morbidities and lower pre-operative GFR (109-111). A meta-analysis (112) reports similar changes in eGFR, incidence of CKD and rates of acute kidney injury for PN and TA, but data on how the affected kidney responds to treatment is limited. Further studies assessing renal functional preservation after TA are needed, where both GFR change is considered and the quality and quantity of the remaining renal parenchyma is assessed.

1.5 Guidelines on T1 Renal Tumor Management over Time
Initially only small renal tumors were treated by RFA with single electrodes. Early studies report a high efficacy rate after treating <3 cm tumors and a greater risk for residual tumor after treating >3 cm tumors (73, 85). Later, RFA techniques evolved introducing the possibility of treating larger tumors with saline perfused electrodes or multiple electrodes (73, 113, 114). Parallel to this, CA grew as a treatment alternative and development of thinner cryoprobes reduced the risk of hemorrhage (115). Even though ablation has been performed on T1b tumors (80, 114, 116, 117), the role of ablation for these tumors is not well defined. As RFA and CA are the most studied ablation
techniques, they are considered in current guidelines, but MWA is still considered as experimental.

In 2009, the AUA were the first to include ablation as a treatment alternative reserved for elderly, comorbid patients who are unfit for surgery (6). With more emerging data, TA now figures in several urology-, radiology- and oncology guidelines, but recommendations among them differ.

The 2016 AUA and 2019 EAU guidelines restrict RFA and CA as alternatives to PN for T1a tumors due to the higher reported recurrence rates after TA (i.e. low primary efficacy rate) (118) and the scarce data on long-term oncological efficacy (12, 119). Conversely, the 2017 ASCO guidelines favor TA as an equivalent alternative to PN in cases where ablation can be reliably achieved, i.e. preferably tumors <3 cm, which are reported with the most available data (21). The CIRSE (Cardiovascular and Interventional Radiology Society of Europe) 2017 guidelines present TA as a valid treatment of T1a tumors with excellent long-term (>5 years) outcomes (82). In the oncology community, the ESMO (European Society for Medical Oncology) 2019 guidelines recommend RFA, MWA, and CA as treatment options for ≤3 cm tumors, highlighting the comparable oncological outcome between PN and TA, however, reserving any definitive conclusions due to the quality of available data (120).

The reservation for recommending TA as an equivalent treatment alternative to PN is often due to the selection bias in patient and tumor selection in TA studies and the lack of prospective randomized control studies comparing PN and TA (121). For partial nephrectomy of T1a tumors, the 5-year recurrence-free survival is higher than 97% (122). For RFA and CA, there are several long-term ≥5-year follow-up studies, reporting comparable oncological outcome for PN, although TA may include several treatment sessions (74, 81, 116, 118, 123). Hence, future studies must be heavily powered to determine significant differences in cancer survival when treating this relatively indolent disease.

There are current ongoing attempts to recruit patients for prospective randomized trials aimed at comparing TA with surgery (124, 125). Even though a direct randomization of percutaneous ablation with partial nephrectomy would be highly desirable, it is not always feasible to recruit sufficient numbers of patients for randomization (126). One group (126) attempted to compare active surveillance and TA in a randomized control trial, and screening of eight centers over 11 months found 154 patients, of whom only 36 patients were eligible for inclusion. Of these 36 patients, 7 patients agreed to participate in the study, one patient was ineligible after biopsy results; thus, only 6 patients were available for randomization, demonstrating that the full trial was not feasible. Patient and clinician preferences, availability of different treatment alternatives and organizational factors affect the possibility of performing these trials. Alternatives to randomized trials are raised by CIRSE (Cardiovascular and Interventional Society of Europe), which would consider robust
evidence from a multi-center registry with >1000 patients with biopsy-proven sporadic T1a RCC treated with TA and followed for a minimum of five years (82). Ongoing registries and databases will hopefully prove promising in aiding future treatment decisions.

1.6 Treatment of T1 Renal Tumors in Uppsala since 2007

In Sweden during 2014, the majority (60%) of T1 tumors (≤7 cm) were found in the Uppsala-Örebro region (4). In Sweden, there was an increase in the performance of NSS for T1a tumors (≤4 cm) from 43% in 2010 to 56% in 2014 (4). Centralization of surgical treatment centers has allowed specialization and increased learning experience with these methods.

At the Uppsala University Hospital, Uppsala, Sweden, both LPN and RFA were introduced in the autumn of 2007. The use of LPN has been stable from 2007 to 2015 (approximately 9 patients per year), in comparison to the use of ablative therapies, which increased exponentially during this period (Figure 4).

![Figure 4: Number of thermal ablation sessions performed per year at Uppsala University Hospital, Uppsala, Sweden.](image-url)

This increase is partially explained by the fact that Uppsala University Hospital has for a long time been the only center in the Uppsala-Örebro region performing ablative therapies on renal tumors. Patients from the entire region (with a population of approximately 2 million people (127)) could be referred if there was a necessity for ablative treatments. Approximately 75% of patients
treated with ablative therapies have been referral patients from outside Uppsala County. In comparison, surgical tumor extirpation is performed at other hospitals in the same region. Since 2016, there has been a stable number of TA treatments of approximately 90 treatments per year.

At the beginning of the study, RFA was still considered as an alternative method for treating renal tumors due to the absence of long-term studies. Patients chosen for ablation were high-risk patients where laparoscopic intervention was considered a high risk. As the RFA technique developed over time, larger tumors (>3 cm) were treated. In May 2014, MWA was introduced as a new technique that could potentially reduce ablation times and provide a safer and more predictable ablation zone. In 2017, the first cryoablations were performed on patients with centrally located tumors that were not technically feasible for surgery. In 2014, LPN was replaced by RALPN and since then, approximately 100 patients have been treated with this technique.

Ablations are performed through a percutaneous approach under CT guidance. In Uppsala, both PN and TA patients are followed with contrast enhanced CT images. Initially, RFA patients were followed at 3 months after treatment. With more data supporting comparative oncological results with PN being available, both TA and PN patients were later followed with the same follow-up CT protocol at 6 months and yearly after treatment (for up to 5 years for low risk patients).
2. Aim of the Thesis

2.1 General Aim
The general aim of this thesis was to evaluate treatment of T1 renal tumors with CT guided radiofrequency (RFA) and microwave ablation (MWA).

2.2 Specific Aims
1. To identify factors that may affect primary efficacy of complete renal tumor ablation with radiofrequency after a single session. (Paper I)

2. To compare percutaneous RFA and LPN for treating small-intermediate (≤5 cm) renal tumors through evaluating efficacy rates, periprocedural outcome (technical success, session and hospitalization time and complications), taking tumor complexity into account. (Paper II)

3. To compare the renal function preservative properties of RFA and LPN after SRM treatment, through evaluation of the split renal function, creatinine and eGFR values. (Paper III)

4. To evaluate technique efficacy and complications of our initial experience of percutaneous MWA-treated renal tumors for patients having a minimum follow-up interval of 12 months. (Paper IV)
3. Materials and Methods

3.1 Patients

The overall inclusion criteria for this thesis were patients treated for a renal tumor with RFA (Papers I-III), LPN (Papers II-III) or MWA (Paper IV) and contrast enhanced CT-scans from before and after treatment.

In a retrospective study (Paper I) of subjects undergoing percutaneous RFA ablation between October 2007 and May 2012, a total of 60 renal tumors in 51 patients were treated by percutaneous RFA. Only 44 patients (with 52 index tumors in total) were included for assessment as seven patients did not follow the CT protocol required for inclusion into the study.

A consecutive subset of patients with index renal tumors (≤5 cm diameter) for whom RFA or LPN was chosen as primary treatment methods for treating the tumor with a curative intent were included in the study in Paper II. Both methods were introduced at Uppsala University Hospital in October 2007; between October 2007 to May 2014 a total of 97 RFA (91 patients) and 57 LPN treatments (57 patients) were performed. Retrospective analysis included 84 tumors (in 82 patients) in the RFA group after excluding patients with multiple (n = 4) or large (n = 1) tumors and those not following the CT protocol (n = 4). In the LPN group 49 tumors (in 49 patients) were analyzed after exclusion of patients with multiple (n = 2) or large (n = 4) tumors, those who did not follow the CT protocol (n = 1) or had simultaneous laparoscopic cholecystectomy (n = 1).

The same patients were included in the study for Paper III, with the further addition of patients treated until to December 2016 (total of 166 patients treated with RFA and 92 patients treated with LPN). Only patients with single T1a, non-hereditary, renal tumors originating from the renal parenchyma treated with a curative intent by only percutaneous CT guided RFA or LPN as treatment methods were included. A 100% success rate (i.e. complete tumor treatment/absence of residual tumor or local tumor progression) during the follow-up time of the study (median 3.2 years) was a requirement. In total, 60 patients treated with RFA and 31 treated with LPN (total 91 patients) were included.

Patients treated with MWA were assessed in the study for Paper IV. Between May 2014 and August 2017, a total of 156 patients with 173 tumors were treated with percutaneous CT guided MWA with a curative intent. Only patients with diagnostic biopsies, treated for ≤T1b renal tumors, either renal
cell carcinoma or oncocytoma, and who were only treated with MWA were included. After excluding patients who did not meet the criteria, a total of 93 patients (105 tumors) were followed.
4. Methods

The study was approved by the Uppsala regional ethical review board (Dnr 2012/518).

4.1 Patient Recruitment

Initial treatment decision was based on CT image findings alone (i.e. tumor appearance). Previous tumor biopsy was not a requirement for renal tumor treatment, as this did not alter management. Choice of treatment alternatives (RFA/LPN/MWA) was discussed at a joint meeting between the urologists, radiologists and pathologist. RFA/MWA was preferred for elderly patients with severe co-morbidities, with a solitary kidney, impaired renal function, multiple or bilateral tumors, and/or hereditary predisposition for developing renal tumors. LPN was considered for patients fit for surgery. Neither tumor location nor tumor size (≤5 cm) influenced treatment choice between RFA/LPN/MWA. However, tumors adjacent to the pelvo-ureteric junction were not considered for RFA/MWA treatment. LPN was preferred for patients who were fit for surgery. The final treatment decision was taken during an individual consultation between the urologist and patient.

4.2 Patient and Tumor Analysis

The patients’ medical records were assessed retrospectively. Data collection included patient age, gender, co-morbidity status (with the Charlson comorbidity index), ASA score, weight, height, BMI and associated hospital (if the patient was a referral patient).

The parameters for calculating m-RNS (45) were assessed retrospectively by a medical student in consensus with an experienced radiologist. This was performed on pre-procedural CT images in the corticomedullary phase. The histopathological diagnosis was obtained from the pathology report.
4.3 CT Image Analysis

CT images served for pre-procedural planning, peri-procedural assessment and for post-treatment analysis. The technical development of CT reflects the use of different scanners in different parts of the study. A Somatom Definition scanner was used between October 2007 to January 2012 and Somatom Definition Flash was used February 2012 to June 2015 (Siemens, Forchheim, Germany).

To obtain baseline images for pre-procedural planning, patients had CT scans the day before treatment. This included unenhanced and contrast enhanced corticomedullary-, nephrographic, and excretory phase images with contrast medium (Iomeron 400 mg I/ml iomeprol, 1 ml/kg, maximum 80 ml, Bracco Imaging SpA, Milano, Italy).

4.4 Pre-procedural Analysis

Prior to RFA/MWA treatment the pre-procedural CT was reviewed to measure tumor size, skin-tumor distance, assess the tumor’s position relative to adjacent organs, and possible RFA/MWA electrode/antenna entry points. The need for pyelo-perfusion of hydrodissection was evaluated. For LPN patients, tumor size, tumor location and renal vascular anatomy was assessed before treatment. The m-RNS was evaluated for all renal tumors irrespective of treatment method.

4.5 Anesthesia

Before RFA/MWA, the anesthesiologist, referring urologist and the interventional radiologist discussed the method of anesthesia: age, health, co-morbidities and the patient’s own wishes were considered. Patients were treated preferably under conscious sedation, which allows patient interaction and collaboration during treatment. For conscious sedation, Midazolam 1mg/ml (Midazolam Panpharma, Rotex Medica GmbH, Trittau, Germany) was administered intravenously at intervals of 0.5 mg until the desired effect was reached. In addition, Remifentanil 5 mg (Ultiva, GlaxoSmithKline, Solna, Sweden) was diluted to a concentration of 50 μg/ml and administered to an initial plasma target level of 0.5 ng/ml. If needed, a maximal plasma target level of 3 ng/ml was used. Vital parameters were monitored constantly by the anesthesiologist during the procedure. Full anesthesia was used when patients did not want the treatment under conscious sedation. All LPN patients were treated under general anesthesia.
4.6 Pre-ablation Biopsy

Directly before ablation, between one to three 1.2 mm core biopsies of the tumor were taken under CT fluoroscopy, unless diagnostic biopsy had been achieved before. A non-contrast enhanced CT scan was used to control the position of the tumors(s) in the kidney. The SeeGrid® position marker (Apri-oMed, Uppsala, Sweden) was placed on the patient’s affected kidney side to estimate the biopsy needle’s entry position on an axial image and calculate the needle path. A mark was drawn on the skin with a laser slice indicator to assess the tumor’s projection relative to the skin. The SeeStar™ guiding device (AprioMed, Uppsala, Sweden) was used to visualize and adjust the CT-guided biopsy needle track and the skin and needle track were infiltrated with 8-10 ml local anesthesia, 10 mg/ml Lidocaine with 5 μg/ml Epinephrine (Xylocain adrenalin, Astra Zeneca, Södertälje, Sweden) before a 2-5 mm incision was made. The percutaneous placement of the biopsy needle was done under CT fluoroscopy and biopsy samples were macroscopically evaluated. If the first biopsy yielded sufficient material, further biopsies were not taken.

4.7 RFA Technique

A single tumor was ablated per session. Patients with multiple tumors were treated successively with 1 electrode per tumor in one session, if their health condition permitted; otherwise, two sessions were planned. RFA treatments were performed by three radiologists experienced in CT guided interventions with 30-, 20- and 10-years of experience respectively.

Before tumor targeting, it was ensured that adjacent organs were at least 2.5 cm away from the intended ablation zone. When needed, hydrodissection was used to increase the distance between the structures. Glucose (100 to 500 ml of 50 mg/ml: Glucos, Fresenius Kabi AB, Uppsala Sweden) mixed with contrast agent (20 mL/L Omnipaque 300 mgI/mL) was continuously infused percutaneously under the control of CT fluoroscopy until organs were satisfactorily separated. A ureter catheter with continuous pyelo-perfusion was used to protect the pelvo-ureteric junction before ablating tumors close to the pelvo-ureteric junction or ureter (tumors with 3 points in “Nearness” parameter from the m-RNS and/or less than 1 cm away from the ureter).

The Cool-tip™ RF Ablation system E Series (Covidien, Boulder, Colorado, USA) was used for RFA. Choice of electrode type was based upon the recommendations from the manufacturer. The aim was to cover the tumor with the ablation zone, achieving at least a 5 mm ablation margin beyond the tumor border. If the ablation zone from a single electrode could not achieve this, multiple or cluster electrodes were used. The SeeStar™ was used to position single RFA electrodes of sizes 2 and 3 cm, as this design allows only these electrodes to be positioned.
CT fluoroscopy enabled the procedure to be monitored during percutaneous electrode placement and tumor targeting. If the targeted tumor was challenging (i.e. targeting an entirely endophytic tumors), a series of contrast enhanced CT images were taken (with 60-80 ml of contrast medium Omnipaque 350 mg I/ml) to be able to visualize the tumor borders. All ablations were performed according to manufacturer’s recommendations, except in cases where complications occurred which interrupted treatment. The minimum target temperature for complete ablation was set to 55°C with a total treatment time of 12 min (electrodes with up to 3 cm ablation zones) or 16 min (electrodes with ablation zones >4 cm). Continuous temperature monitoring was with a separate thermocouple (Cool-tip RF Ablation Remote Temperature Probe E series, Covidien, MA, USA) in a co-axial needle (17 Ga co-axial introducer needle, Argon Medical Devices Inc, TX, USA) placed within 5 mm of the ablation zone margin. Tract ablation was used during electrode removal and immediately after a contrast enhanced CT scan was performed. In cases where residual tumor was found, the electrode was repositioned and the residue ablated. After the treatment session, patients were admitted for observation and discharged if no complications were observed within 24 hours.

4.8 LPN Technique

Two urologists with 25 and 15 years of experience in laparoscopic surgery introduced this treatment method in 2007. Patients were in the prone position with the affected side elevated 45 degrees. Four to six trocars (12 mm trochars) were utilized. The renal artery and vein were dissected and secured by vessel-loops. The kidney surface was dissected to identify the tumor. For tumors located at the upper pole or dorsal aspect, the kidney was fully mobilized to allow it to be flipped over to gain access to the tumor. For tumors at the lower pole or ventral aspect only local dissection was performed. Hemostatic material was prepared in advanced with 1-3 compressing sutures around a roll of Surgicel™ (Ethicon, Neuchatel, Switzerland) and introduced into the abdomen so it was readily available for renal suturing. The tumor was then delineated by monopolar diathermy, including a 0.5 cm margin. Ischemia was obtained by pulling and locking the vessel-loops, or in later cases, by applying Bulldog clips (Aesculap AG, Tuttlingen, Germany) around the artery. The tumor was then excised with cold (non-diathermy) scissors. Sutures closed the collecting system, when the resection margin included this part of the kidney, and vessels were suture ligated. The parenchymal defect was sutured over the roll of Surgicel™. At this point, the vessel-loops or Bulldog clamps were removed, thus, restoring renal circulation. For further hemostasis, the area was covered with TISSEEL™ (Baxter Healthcare Corporation, Westlake Village, CA, USA) and the kidney and colon were repositioned and anchored if neces-
sary. Through a slightly widened trochar, the tumor was removed with a retrieval bag; a drainage tube was inserted through one of the trocars. The tumor was sent immediately to pathology. After surgery, patients were admitted for observation and discharged if no complications were observed, usually within 48 hours.

4.9 MWA Technique

The same CT monitoring technique as for RFA was used for MWA treatments. Biopsies were performed by the technique described above. Hydroadissection was used and a ureter catheter was placed with the same criteria. The Emprint™ ablation system with thermosphere technology antennas (Medtronic, Minneapolis, MN, USA) was used with a single antenna at 100 W; ablation time varied depending on tumor size. Manufacturers recommendations were followed to achieve a 5 mm ablation margin and immediate postablation imaging was used to assess any complications. In the case of immediate detection of residual tumor, the antenna was repositioned and an additional ablation was performed during the same session. After the treatment session, patients were admitted for observation and discharged if no complications were observed within 24 hours.

4.10 Follow-up Routine

After treatment, follow-up imaging included CT exams in the same phases as the pre-procedural routine at 3 months (RFA group only), 6 months, 12 months and annually thereafter. After January 2012, the 3-month follow-up image was removed for the RFA group due to more accumulating evidence suggesting comparable oncologic outcome between RFA and surgically removed renal tumors. The MWA patients were followed in the same manner. Referral patients were scanned at their referring hospital which meant they could be examined through different CT protocols than those at the Uppsala University Hospital. However, all exams were sent to the University Hospital and reviewed: this included any abdominal CT imaging and kidney-specific protocols.

In the case of residual tumor or local tumor progression, tumors were treated with a second ablation session and followed-up in the same manner. The length of follow-up time was calculated as the time from the first RFA/LPN/MWA treatment until the latest performed CT image that evaluated the kidneys (in unenhanced, corticomedullary- and/or nephrographic- and/or excretory phase). In the study for Paper I, patients were followed for a median of 7 months (range 2 – 45 months). The median follow-up time in the study for Paper II was 20.5 months (range 3 months – 5.9 years) for the RFA group.
41 months (range 6 – 7.3 years) for the LPN group. In the study for Paper III, patients were followed for a median of 3.2 years (range 2.5 – 99 months) and for Paper IV, a mean of 2.1 years (range 1 year – 4.6 years).

4.11 Treatment and Image Analysis

The terminology used to assess and report results were based on the criteria approved by the Society of Interventional Radiology (Table 2) (63).

Table 2: Definitions of procedural outcome

<table>
<thead>
<tr>
<th>Term (unit)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete tumor ablation/resection</td>
<td>Absence of contrast enhancement (&lt;20 HU) where the tumor was previously situated, including the ablation/surgical margin.</td>
</tr>
<tr>
<td>Residual tumor</td>
<td>Contrast enhancement ≥20 HU within the treated tumor site, and/or ablation/surgical margin</td>
</tr>
<tr>
<td>Local tumor progression</td>
<td>Contrast enhancement ≥20 HU at the treated tumor site (including margin) after at least one follow-up study shows absence of viable tumor tissue</td>
</tr>
<tr>
<td>Technical success</td>
<td>Achieved when the tumor is treated according to protocol. In other words, when LPN is performed without conversions to total nephrectomy or without conversion to an open approach. For RFA, this is when total coverage of the tumor by the ablation zone is achieved.</td>
</tr>
<tr>
<td>Technique efficacy</td>
<td>Referrers to treatment results assessed on CT images. Baseline CE-CT images are compared with follow-up images to evaluate technique efficacy. Technique efficacy is achieved when complete tumor removal is achieved during the period of the study.</td>
</tr>
<tr>
<td>Primary technique efficacy rate (%)</td>
<td>Percentage of tumors successfully removed after a single treatment session</td>
</tr>
<tr>
<td>Secondary technique efficacy rate (%)</td>
<td>Percentage of tumors successfully removed after all treatment sessions during the duration of the study*</td>
</tr>
<tr>
<td>Side effects</td>
<td>Often expected, unwanted consequences which do not result in substantial morbidity</td>
</tr>
<tr>
<td>Complication</td>
<td>Event leading to disability and/or morbidity that increases the level of care, lengthens hospital stay, or results in additional hospital admission</td>
</tr>
</tbody>
</table>

(*) In Paper I secondary efficacy rate referred to percentage of tumors successfully ablated after a second ablation session. Tertiary efficacy rate referred to tumors successfully ablated after three ablation sessions.

The position of the RFA electrode was evaluated for its effect on the primary efficacy rate for complete renal tumor ablation (Paper I). A medical student
and an experienced radiologist assessed CT images taken during tumor targeting. The ablation sizes (as reported by the manufacturer) were drawn on CT images to evaluate whether the tumor was fully covered by the ablation zone.

Electrode placement was estimated as “optimal” when the entire tumor was within the ablation zone. When part of the tumor was outside the ablation zone, electrode placement was considered “non-optimal”.

The following treatment related factors were assessed (Paper II):

1. Session time: for the LPN group, session time was defined as "knife-to-skin” to closure time. For the RFA group, session time started from the time of tumor targeting (and included monitoring, intraprocedural modification and ancillary procedures) and finished after assessment of immediate treatment response had been done.

2. Total treatment time: additional time (i.e. multiple session times) for treating local tumor progression (irrespective of treatment method).

3. Hospitalization time: starting at the day of LPN or RFA treatment and ending at the day of hospital discharge.

4. Total hospitalization time: the amount of re-admission days (related to procedural complications or treatment of local tumor progression) plus the hospitalization time.

Side effects and complications were reviewed in all patient’s medical records from the date of procedure to May 2015 and were categorized after the procedure as immediate (within 6-24 h), peri-procedural (within 30 days) or delayed (>30 days). Complications were categorized according to the Clavien-Dindo classification (128). Clavien-Dindo grades I-II were considered as minor and grade III-V as major complications.

Renal function parameters were assessed (Paper III). Creatinine values were collected at either the University Hospital or at the referring hospitals before (median 1 day) and within one year after complete treatment (median 310 days for RFA, 225 days for LPN). The revised Lund-Malmö formula (129) was used to calculate the estimated glomerular filtration rate (eGFR).

Contrast enhanced CT images in the corticomedullary or nephrographic phase were used to calculate split renal function (SRF) before and after treatment. The MultiModality workstation (Siemens, Forchheim, Germany) was used with the program “Volume”. On pre-treatment CT images, multiple regions of interest (ROI) were placed manually throughout the length of the kidney. The renal tumor and any structures which did not contribute to the filtration process (e.g. renal vessels, collecting system) were excluded. The limits of the ROI tool were set between 75 and 250 HU to include contrast enhancing
renal parenchyma. The program automatically computed the volume (cm$^3$) and mean attenuation (HU) from the marked ROI of each kidney and these values were registered. The SRF was obtained with the formulas:

$$Relative \ renal \ function \ (RRF) = \frac{\text{renal volume (cm}^3\text{)} \times \text{mean attenuation(HU)}}{}$$

$$SRF \ affected \ kidney = \frac{RRF \ affected \ kidney}{RRF \ affected \ kidney + RRF \ non \ affected \ kidney}$$

In the same manner, the SRF was calculated on the first follow-up image after completed treatment, excluding any operative material placed after LPN (e.g. hemostatic material or surgical clips). Both a resident in radiology and a medical student performed the SRF measurements blinded from each other. As there was a high inter-rater agreement in SRF measurements between the two observers (ICC average: 0.997 95% CI: 0.997-0.998), the mean value of the two observer’s measurements was used for further calculations. The main goal was to determine the SRF change in the affected kidney (from pre- to post-treatment) in percentage points. Additionally, changes in creatinine and eGFR values were assessed.

MWA treatment outcome was reviewed (Paper IV) and reported according to the Society of Interventional Radiology guidelines (63). The Clavien-Dindo classification (130) was used to classify the severity of complications.

4.12 Statistical Methods

Statistical analyses were performed with SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA). A p-value <0.05 was considered statistically significant in all studies. The electrode placement, m-RNS (including distance between tumor and collecting system/renal sinus, tumor size), method of anesthesia, gender and age were evaluated for their effects on ablation results (Paper I). To estimate the association between these factors and complete ablation generalized estimating equations (GEE) were used for logistic regression analysis. The GEE was used to account for possible correlation between tumors within the same patient. Due to the low number of incompletely ablated tumors, only univariable models were estimated. Calculations were based on the results after the first ablation session to assess what affected primary efficacy rates. The numeric score of the m-RNS for each tumor was used in the statistical analysis; however, the suffixes “a, p, x and h” were excluded
as they were not considered clinically relevant in the study.). Mean ± SD (or median for quantitative variables) were calculated. The odds ratio (OR) was calculated with a 95% confidence interval.

Baseline patient- and tumor characteristics in addition to treatment results were reviewed as frequencies for categorical variables and median (min - max) for continuous variables (Paper II). For tests of differences between the LPN and RFA groups, the Mann Whitney U test was used for continuous and ordinal variables and the Fisher’s exact test for categorical variables. Differences between the groups’ medians were calculated with 95% confidence intervals through the bootstrap percentile method (1000 replications). Differences in proportions with 95% exact confidence intervals were calculated. Due to non-normal data distributions, medians and non-parametric methods were used. To adjust for m-RNS (when comparing treatment groups), the analysis was stratified by m-RNS. The stratified Mantel-Haenszel test (for categorical variables) and the Van Elteren test (stratified Mann-Whitney U test, for continuous and ordinal variables) were used. This allowed estimation of group difference in each stratum and controlled for confounding through combining (pooling) the stratum-specific estimates into one estimate. Further, calculations restricted to tumors of ≤4 cm in diameter and stratified by distance to the collecting system or sinus (<7 mm, ≥7 mm) were performed.

Pre-treatment characteristics between the LPN and RFA groups were compared (Paper III). The Student’s t-test was used for continuous variables and the Fischer’s exact test for categorical variables. The Students t-test and multivariable linear regression models were used to compare treatment effects. Three single regression models were fitted with the change in SRF (post – pre-value), creatinine and eGFR as the response variables. Treatment (LPN/RFA), the pre-value of the response variable and confounders were included in the models as explanatory variables. The confounders were pre-treatment eGFR, BMI, age, tumor size, tumor nearness (distance to the collecting system or sinus) and Charlson comorbidity index. These were selected for adjustment based on previous knowledge regarding their effect on renal function and choice of treatment. All statistical tests were 2-tailed. Intra class coefficient (ICC) estimates (with 95% confident intervals) were calculated to assess interrater reliability for SRF measurements, based on a mean rating (k = 2) absolute agreement and 2-way mixed-effects model.

Baseline characteristics and treatment results with frequencies for categorical variables, median for non-continuous and/or non-normally distributed values were summarized (Paper IV).
5. Results

5.1 Paper I

In total 52 renal tumors were treated. Median patient age was 64 years ± 25.4 (range 40-79 years). Median tumor diameter was 24 mm (range 10 – 46 mm) and median m-RNS score was 6 points (range 4 – 11 points). The most common tumor was clear cell carcinoma (n = 21).

Primary efficacy was 82.7% (43/52 tumors). During follow-up, two patients died of causes other than the renal tumor. Secondary efficacy rate was 94% (48/51) and tertiary (final) efficacy rate was 100% (50/50). General anesthesia was used for 18 patients and 34 were treated under sedation.

Treatments with an optimal electrode placement had sixteen times greater odds in resulting in a complete ablation. The median m-RNS for partially ablated tumors was greater (7 points) than the median m-RNS of completely ablated tumors (6 points). However, the m-RNS was not a predictor for complete ablation. All tumors ≥10 mm away from the collecting system/sinus were completely ablated. More treatments resulted in residual tumor when tumor distance to the collecting system or sinus decreased. For every 1-mm increase in distance, the odds of ablation resulting in complete treatment increased by 18% (Figure 5). All tumors ≤2 cm were completely ablated after a single session. Smaller tumors were more frequently completely ablated, although tumor size did not show a statistically significant correlation. Age was a predictor for complete tumor ablation after a single session, but gender and anesthesia method were not predictors (Figure 5).

Six of nine (67%) tumors incompletely ablated after a single session were clear cell carcinomas. All oncocytomas (n = 6: median size 19 mm (range 16 – 14)) and all papillary RCC (n = 9: median size 30 mm (range 16 – 35 mm)) were completely ablated in a single session.
Figure 5: Association of factors for complete ablation after a single session. OR (95% CI) and p-values from univariable logistic regression of complete ablation through generalized estimating equations.

5.2 Paper II

In total, 84 patients were treated with RFA and 49 with LPN. The RFA group was older and suffered greater co-morbidities (i.e. higher Charlson index) than the LPN group. There was no difference gender distribution. The median m-RNS score did not differ between LPN and RFA. However, the RFA group had smaller tumors (median 26 mm, range 11 – 50 mm) than the LPN group (median 32 mm, range 13 – 49 mm). RFA tumors were more centrally located (distance to collecting system/sinus median 4.2 mm) than LPN tumors (median 8.4 mm). The most common tumor in both groups was clear cell RCC (RFA 46.4%, LPN 61.2%). Oncocytomas were present in 10.7% of RFA and 14.3% of LPN cases. In the RFA group, 8.3% of cases had no-diagnostic biopsy results.

There were no differences in primary or secondary efficacy rates between groups. Technical success was achieved in fewer cases in the LPN group than in the RFA group (Table 3). Six LPN cases were converted to an open approach due to technically challenging resections and one case converted to a total nephrectomy due to renal vein hemorrhage.

The RFA group had shorter session time (median time 2 h 10 min) than the LPN group (median time 3 h 35min: Table 3). A single session was needed for treatment of 48/49 tumors (98%) in the LPN group: the one tumor in requiring a second session was managed with a total nephrectomy. In comparison, 88% (74/84) of the tumors treated with RFA were treated in a single session. Ten tumors in the RFA group needed more than one session to achieve
Despite the necessity of several treatment sessions, RFA had a shorter median total session time (2 h 17 min) than with LPN (3 h 35 min; Table 3). LPN patients also had a longer hospitalization and total hospitalization time than the RFA group (Table 3).

Table 4. Comparison of LPN and RFA groups with respect to treatment results and periprocedural outcome.

<table>
<thead>
<tr>
<th></th>
<th>LPN (n = 49)</th>
<th>RFA (n = 84)</th>
<th>LPN vs. RFA (median (95% CI) or % (95% CI))</th>
<th>P value*</th>
<th>P value adjusted(^y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment sessions per tumor (n) (median (range))</td>
<td>1 (1–2)</td>
<td>1 (1–3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technical success (n (%))</td>
<td>42 (85.7)</td>
<td>84 (100)</td>
<td>-14.3 (-27.9 to -4.7)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Primary efficacy rate (n (%))</td>
<td>48 (98)</td>
<td>72 (82.5)</td>
<td>12.2 (0.0 to 22.2)</td>
<td>0.031</td>
<td>0.059</td>
</tr>
<tr>
<td>Secondary efficacy rate (n (%))</td>
<td>46 (93.9)</td>
<td>80 (95.2)</td>
<td>-1.4 (-18.9 to -16.2)</td>
<td>0.71</td>
<td>0.90</td>
</tr>
<tr>
<td>Session time (min) (median (range))</td>
<td>215 (115–435)</td>
<td>130 (65–290)</td>
<td>-85.0 (-110.0 to -59.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total treatment (min) (median (range))</td>
<td>215 (115–448)</td>
<td>137 (65–393)</td>
<td>-78.8 (-105.0 to -50.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization time (days) (median (range))</td>
<td>5.0 (2–15)</td>
<td>2.0 (1–8)</td>
<td>-3.0 (-3.0 to 2.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total hospitalization (days) (median (range))</td>
<td>5.0 (2–23)</td>
<td>2.0 (1–9)</td>
<td>-3.0 (-4.0 to 2.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No post-procedure complication (n (%))</td>
<td>28 (57.1)</td>
<td>75 (89.3)</td>
<td>-39.3 (-47.9 to -16.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P value from Fisher's exact test or Mann-Whitney U test.

\(^y\)Adjusted P value from Mantel-Haenszel test or Van Elteren test. Stratification by modified R.E.N.A.L nephrometry score.
Four cases of side effects presented in the RFA group; abdominal pain during ablation (n = 3) or abdominal tenderness during hydrodissection (n = 1). The only side effect in the LPN group was one case of immediate post-procedure abdominal pain. RFA group had less post-procedure complications (10.7%) than in the LPN group (42.9%). The frequency of complications was continuous over time in the LPN group and the most common complications were Clavien-Dindo grade II. Nine of the twenty-one complications in the LPN group were major complications (≥grade IIIA Clavien-Dindo) (Figure 6).

Figure 6: Frequency of post-procedure complications after RFA and LPN treatments, arranged according to the Clavien-Dindo classification.

5.3 Paper III

The RFA group was older (mean age RFA 65.0 years) than the LPN group (mean 57.8 years; p = 0.003), but there was no difference in mean Charlson comorbidity index, BMI, gender distribution or tumor characteristics between the groups. The most common tumor in both groups was clear cell RCC (RFA 45%, LPN 64.5%). Oncocytomas were present in 10% of the RFA treated tumors and 16.1% of the LPN treated tumors. Non-diagnostic biopsies were only present in the RFA group (13.3%). In the RFA group 56/60 patients were treated in a single session and four patients needed two sessions to achieve complete tumor treatment. All the 31 LPN patients were treated in a single session.

The RFA and LPN groups did not differ in pre-treatment SRF (RFA 50.8%, LPN 49.0%, p = 0.10). SRF was reduced after treatment in both groups, however, the reduction was greater in the LPN group (change post-pre SRF value
RFA -3.5%, LPN -5.7%, difference 2.2%-points, p = 0.013). After adjusted analysis, this difference remained, as the SRF was lower by 3.2%-points (p = 0.001) more in the LPN group than the RFA group. Two LPN patients presented a distinct reduction in SRF (Figure 7): both patients had challenging resections with adhesions from prior surgery and perfusion from several polar arteries reducing visibility during resection. Even when these two outliers were omitted from the analysis, the LPN group still had a greater SRF loss (adjusted difference 2.1% points, 95% CI 0.58 to 3.57, p = 0.007).

The RFA and LPN groups did not differ in pre-treatment mean creatinine or eGFR values. Both treatments affected kidney function, but there was no difference in the change of these values.

Figure 7. Split renal function after RFA or LPN treatment. Hybrid parallel line plot of the patients’ pre- and post-treatment SRF values. RFA n = 60, LPN n = 31.
5.4 Paper IV

Microwave ablation was used to treat 93 patients (58 men and 35 women, median age of 70 years (range 34-87 years) with 105 renal tumors (median size 25 mm, range 10-42 mm). The majority (n = 101) were T1a tumors. Four tumors were T1b tumors. Median tumor m-RNS was 7 points (range 4-11 points), and 41.5% were low complexity tumors (4-6 points), 43.5% medium complexity (7-9 points) and 15% were high complexity tumors (10-12 points). Clear cell carcinoma was the most commonly treated RCC subtype (n = 53), followed by papillary type 1 (n = 22), chromophobe (n = 9), and papillary type 2 (n = 2). Oncocytomas were found in 19 cases.

In total 107 MWA sessions were performed. Hydrodissection was used in 68 of these sessions and a ureter catheter was used for eight patients. Between 1 to 5 antenna positions were used (one position, n = 61; two positions, n = 32; three positions, n = 9; four positions, n = 4; and, five positions, n = 1) and median ablation time per tumor was 5 min (range 2.5-20 min).

After a single ablation session, 100/105 tumors were completely ablated, resulting in a primary efficacy rate of 95.2%. Secondary efficacy rate was 96.2% (101/105).

Few periprocedural complications were present (4.7%, 5/107). Four complications were Clavien-Dindo I (n = 4). A single Clavien-Dindo IIIa was found, which was a pneumothorax occurring after the infiltration of local anesthesia and before percutaneous renal biopsy of the tumor in the upper renal pole. This patient was managed with a chest drain.

Only one post-procedural complication (Clavien-Dindo II) was found, which was a 11 cm limited retroperitoneal hematoma requiring blood transfusion and vasopressor treatment.

In total, three cases of side effects were found. Two patients experienced nausea, low grade fever and vomiting 24 h after the procedure, and one patient experienced pain during ablation.
6. Discussion

Although renal tumor ablation has been performed since the 1990s, it has not been considered as a standard option for renal tumor management. In 2017, ablation was suggested in the ASCO guidelines as an alternative for achieving complete tumor treatment for <3 cm tumors (21). However, several guidelines still recommend thermal ablation together with active surveillance as two competing management options (121). As the patient group in which small renal masses are often found are elderly (with several comorbidities and pre-existing low renal function), the need for a minimally invasive approach is paramount in managing these tumors.

An optimal RF electrode placement increased the frequency of complete tumor ablation (Paper I). As assessment of electrode placement during procedural monitoring varied depending on which RF-system was used, temperature-based systems with deployable curved tines visible on CT could further aid assessment of electrode placement. Theoretically, this could result in more optimal placements than with the impedance bases systems used in the study (131). As this was the evaluation of the first cases with RFA, further experience could have contributed. Longer distances to the collecting system were a predictor for complete tumor ablation. Tumor location is a well-known factor affecting ablation outcome (73, 85, 87). Centrally located tumors are more difficult to ablate due to the “heat-sink” effect, a result of the proximity to large vessels as perfusion limits the ablation effect (87). All the ≤20 mm tumors were completely ablated in a single session and smaller tumors more often resulted in complete tumor ablation. However, several experienced groups confirm small tumor size (<3 cm) is a predictor for complete tumor ablation (73, 85, 132). Even though m-RNS was not a predictor for complete tumor ablation in the study, several of the components in this scoring system are verified as affecting ablation outcome (47, 73, 132). Highly vascularized tumors (e.g. clear cell carcinomas) were potentially more difficult to ablate than less vascularized tumors (e.g. papillary RCC and oncocytomas), and another report confirms our findings (133). However, the limited data available restricts any definitive conclusions. Even though the study was limited by its’ retrospective nature and small sample size, several factors influenced ablation outcome after a single session. These factors need to be assessed for optimization of patient selection for RFA treatment.

Both RFA and LPN treatment achieved comparable secondary efficacy rates (Paper II). Even though RFA treatment could involve several sessions,
session time and hospitalization times were shorter, and complications were less frequent and of less severity than after LPN treatment. Larger tumor size and central tumor location impacted negatively on both RFA and LPN outcome. The larger tumors treated in the LPN group could partially account for the higher complication rate in this group. However, the RFA group had more central tumors and the more peripheral LPN tumors entail less challenging resection and are associated with lower complication rates (134). The analysis was stratified by m-RNS to minimize the effect group differences in tumor characteristics had on periprocedural outcome. The primary experience with both techniques affected periprocedural outcome in both groups. LPN is a technically challenging technique and in experienced hands, hospitalization times are reduced, and complication rates are lowered (135, 136). The more favorable periprocedural outcome in the RFA group could be secondary to our previous experience with percutaneous CT guided biopsies. The use of hydrodissection, ureter catheters and patient repositioning, when needed, optimizes conditions for RFA treatment and complications are rare (73, 74). However, RFA patients were older and suffered from comorbidities, which should disfavor any periprocedural outcome benefit. The study (Paper II) is from a single-center’s primary experience with both treatment methods, therefore, the results need to be validated in other cohorts. The small sample size limited evaluation of other possible confounders (e.g. renal function, previous abdominal surgery, BMI, anesthesia method, patient operability), which could affect outcome. The possibility of performing RFA with a percutaneous approach certainly contributed to the favorable periprocedural outcome in this group, however, this is one of the main benefits of this treatment method.

Both RFA and LPN had high preservation of renal function when treating small renal masses, as neither serum creatinine nor eGFR changed after treatment (Paper III). However, RFA treatment was associated with a more favorable preservation of renal function in the treated kidney, as there was a greater reduction in SRF after LPN. Several factors affect renal function recovery after treatment, e.g. tumor size and location, patient age, baseline renal function, renal volume preservation and ischemia time during surgery (107, 109, 113, 137). Except the difference in age (RFA group was older), LPN and RFA patients did not differ in patient or tumor characteristics. The age difference was unlikely to explain the results as age together with several cofounders affecting renal function were included in the adjusted analysis. RFA can be performed percutaneously under zero ischemia time, thus, avoiding any possible ischemic renal insult. The wedge-shape incision used to remove the tumor and the tension applied on the parenchyma during renorrhaphy in LPN could entail a greater loss of nephrons than removing the tumor with a sphere-shaped ablation zone adapted to tumor shape and size (54). The greater complication rate in the LPN group was a disadvantage for renal function recovery. Serum creatinine tests were not analyzed at a single laboratory, which introduced errors into comparisons between values, and a single post treatment creatinine
value was analyzed without assessment of the long-term effect on renal function. Other comorbidities or medications that might affect renal function were not assessed. The SRF is not an absolute measurement of renal function, so translation of the results to the individual patient were limited. Nevertheless, RFA was associated with a more favorable preservation of renal function than LPN when assessing the effect on the treated kidney’s split renal function. As patients presenting with small renal masses are often elderly with pre-existing chronic kidney disease, renal function preservation is vital for minimizing the development of end-stage renal disease.

The initial experience with 93 MWA treated patients (Paper IV) revealed high efficacy rates and a low incidence of complications, and confirmed results in another report (138). These results followed the same trend as early RFA studies, which is now an established ablation technique based on studies with longer follow-up (73, 74). The use of an actively cooled MWA probe with a high-power generator and the unique design of the used MWA antenna in our study has contributed to the high efficacy rates. Ablation with first generation MWA technology, low power generators and different antenna designs result in significantly lower efficacy rates (139). The wide variation of MWA systems used, differences in procedural monitoring (CT/ultrasound/MR) and anesthesia method (conscious sedation/full anesthesia) among different studies complicates the comparison between studies. Similar to RFA, MWA efficacy is also affected by tumor size and location, but an upper size limit at which complete ablation should be expected has not yet established (140, 141). In addition, the MWA manufacturers’ promise of predictable and reproducible MWA ablation zones is often based on ex-vivo studies. Even though some provide in-vivo studies, ablations are still performed in healthy porcine or bovine liver and kidney. This does not assess how MWA propagates in different RCC subtypes. There were several limitations to the study (Paper IV). Only immediate post-procedural complications were collected, as the retrospective nature of the study and the wide geographical spread of the referral patients limited further data collection. However, another group report that late complications are rare and of low severity (141). Renal function was not evaluated and comparisons with standard treatment methods need to be further evaluated. Ideally, longer follow-up could assess cancer survival rates, but short follow-up is unavoidable when assessing a new treatment method. Nevertheless, after a mean follow-up of 2 years, the MWA efficacy rates were comparable with other reports (138, 141, 142). The technical benefits of MWA, including decreased ablation time, larger and more predictable ablation zones with less susceptibility to heat-sink effect and higher intra-tumoral temperatures, makes MWA an attractive ablation technique. The favorable oncological outcome and low incidence of complications means MWA can be considered for renal tumor management.
7. Conclusions

7.1 General

CT guided RFA and MWA are safe and effective treatments for the removal of T1 renal tumors.

7.2 Specific

1. Predictors for complete renal tumor ablation are optimal electrode placement and long distance between the tumor and the collecting system. Although tumor size affects RFA efficacy, this could not be demonstrated in this small series. Tumor histopathology may affect RFA outcome, but further studies are needed to assess this.

2. Even though LPN has a higher primary efficacy rate, both LPN and RFA achieve comparable secondary efficacy rates. More treatment sessions are needed in RFA treatment, but session and hospitalization times are shorter and complication rates less frequent than with LPN. The results remain the same after adjustment for tumor complexity.

3. Both RFA and LPN are good preservers of renal function when treating small renal masses. RFA has more preferable preservation of renal function than LPN, when assessing the impact of treatment on the affected kidney’s split renal function. There is no difference in the change in creatinine and eGFR after treatment between RFA and LPN, which can be due to renal compensatory mechanisms.

4. MWA ablation of renal tumors with a mean 2-year follow-up presents similar results to the earlier results reported in now established thermal ablative therapies. Comparable efficacy rates and low incidence of complications suggest MWA has the potential to be included as a standard ablation treatment. Studies with longer follow-up times will be needed to assess this further.
8. Future Perspectives

The ability to treat localized renal cancer with good oncological outcome with few complications and at the same time preserve renal function has been a great advancement in the field of renal cancer. Additionally, the provision of a minimally invasive percutaneous treatment alternative allows treatment of patients who could not be considered for surgery. This present thesis provides insights into renal tumor ablation which will aid future treatment decisions. However, there are still questions regarding the best management in various clinical scenarios.

Small renal masses can be difficult to characterize with current methods, therefore, further development in this area could avoid overtreatment. Although some biomarkers have been correlated to tumor progression, their role in kidney cancer is not fully understood (18). This raises the question of whether biomarkers could help to distinguish between malignant and benign small renal masses in the future. It would be beneficial if biomarkers could predict the risk of disease progression and aid the selection patients for whom treatment could be avoided.

Further developments in methods aiding tumor targeting could increase ablation efficacy and predictability. Procedural imaging with real time CT-ultrasound fusion imaging allows targeting of tumors that are not visible in unenhanced CT images. Semiautomated computer programs and electromagnetic navigation systems have been developed to aid selection of optimal ablation paths and ablation volumes, which potentially standardizes treatment (143). In conjunction, virtual planning models have been developed to aid RALPN, suggesting improved procedural outcomes (144). However, all novel techniques need further assessment.

Follow-up after ablation lacks pathological analysis, relying solely on imaging. In patients who cannot undergo a contrast enhanced CT scan follow-up comparing different imaging modalities can be challenging. Poor correlation between post ablation radiographic imaging and biopsy results of the ablated tumor is reported (145). Therefore, imaging with diffusion-weighted MR or other imaging modalities can provide further information of treatment response. Similarly, post mortem studies of ablation patients could contribute to increased knowledge of how the renal parenchyma reacted to treatment.

With the rapid development in imaging and treatment techniques the past 20 years, the possibilities of future RCC management is exciting to imagine;
however future studies are needed so that the best option for the individual patient can be evaluated based on the clinical scenario.
9. Svensk Sammanfattning (Summary in Swedish)


Metoden lämpar sig väl för riskpatienter som inte kan genomgå kirurgi på ett säkert sätt. Ablation kan nämligen som regel utföras på patienter i vaken sedering och därmed undviker man att söva patienten. Då det har saknats evidens för att behandlingseffekten är likvärdig med kirurgisk tumörresektion har perkutan ablation hittills använts på icke-operabla patienter samt patienter med nedsatt njurfunktion, singelnjure, hereditär njurcancer och multipla tumörer.

Perkutan ablation av njurtumörer har utförts vid Akademiska sjukhuset sedan 2007 och hittills har cirka 550 njurtumörer behandlats. Till en början utfördes alla behandlingar med RFA. Sista 5 åren har nyare ablationsterapier
introducerats och numera görs ablation med mikrovågor (värmeablation) och kryoablation (ablation där man kyler tumören). Mikrovågsablation (MWA) påverkas mindre av vävnadsimpedansen och ger därmed mer förutsägbara ablationszoner. Kryoablation gör att man kan abladera större tumörer och tumörer med central lokalisation i njuren.


9.1 Delarbete I


9.2 Delarbete II

Allt fler retrospektiva studier har visat jämförbara onkologiska resultat mellan RFA och kirurgisk resektion vid behandling av små njurtumörer. Men vid val av behandlingsmetod måste även hänsyn tas till komplikationsrisken, patient morbiditeten och kostnaderna. Målet var att jämföra RFA och laparoskopisk njurresektion (LPN) avseende behandlingseffekt, behandlings- och vårdtid samt komplikationer. Retrospektivt utvärderades 49 LPN- och 84 RFA-behandlade patienter med endast en njurtumör (≤5 cm). Genomgången innebar journal- och DT granskning av samtliga pre-operativa undersökningar samt postoperativa kontroller. Resultaten visade att båda behandlingsme-
toderna uppnådde jämförbara behandlingseffekter. RFA innebar fler behandlingsomgångar, men trots detta var den totala behandlingstiden och vårdtiden betydligt kortare och komplikationsfrekvensen var lägre för dessa jämfört med de LPN-behandlade patienterna.

9.3 Delarbete III
Både RFA och LPN har som mål att vara nefronsparande vid behandling. Men tidigare studier, som utvärderar njurfunktion utifrån blodprover (kreatinin och eGFR), har redovisat motstridiga resultat, utan att utvärdera hur det kvarvarande njurparenkymet påverkas av behandling. På en kontrastmedelsförstärkt DT kan både kvantitet och kvalitet av njurfunktionen utvärderas genom beräkning av ”split renal function” (SRF). Målet var att jämföra njurfunktionspåverkan vid RFA och LPN behandling genom beräkning av SRF och utvärdering av rutinblodprover. Retrospektivt jämfördes 60 RFA och 31 LPN patienter behandlade för en tumör vardera. SRF beräknades före och efter behandling och njurfunktionsvärden (kreatinin och eGFR) samlades in. Resultaten visade att i båda grupperna minskade SRF i den drabbade njuren, men denna minskning var mer påtaglig i LPN-gruppen. Det fanns ingen skillnad i förändringen av njurfuktionsvärden mellan grupperna.

9.4 Delarbete IV

9.5 Konklusion
Perkutan DT-vägledd ablation är en effektiv metod vid behandling av små njurtumörer. Metoden är säker, komplikationsfrekvensen är låg och påverkan
på njurfunktionen är mycket liten. Genom ökad kunskap kring behandlings-
metodens fördelar och begränsningar kan vi förbättra urvalet av de patienter
som kommer att gynnas av behandling.
This thesis is the result of all the dedication, teaching, help, patience, multiple emails, phone calls, meetings, conferences, courses, late-night-working-sessions, helpful reminders, tips, keep-on-going-you-can-do-it-cheering and endless support from people who made me get through this process with a smile at the end. I would like to thank all the awesome people, who still keep on doing amazing things, and are truly endless resources of inspiration.

Anders Magnusson, my fantastic “Super Professor” and main supervisor. I will always be grateful for your trust in me, letting me research from different locations and for always asking for my opinion. Thank you for making me feel included in your research group, as a colleague at work and with your family members. And above all, thank you for making research fun.

Maria Lönnemark, my co-supervisor. Thank you for introducing me to the field of Radiology, for teaching me structure early in my carrier, for your feedback and support and for giving me opportunities to teach others.

Håkan Ahlström, my co-supervisor. Thank you for your valuable input.

To the rest of my co-authors, Pär Dahlman, Einar Brekkan, Michael Häggman, Sam Ladjevardi, Thomas Nilsson, Sarah Båtelsson, and Elina Onkamo. Your contributions made this thesis possible.

Thank you to the rest of our uro-radiology research group. Thank you Malin Helenius, Monica Segelsjö, Pär Dahlman and Klara Sahlén, for your valuable comments and input. Thanks to the students Elinor Wajngot and Carl-Johan Karlsson who chose us as colleagues for their projects.

Lisa Wernroth, my life-saver in statistics. I would be totally lost without your support. Thank you for your explanations, answers and patience.

Håkan Pettersson, solving all my computer issues in a calmly manner. Thank you for making me know that my work is always in good hands.

To my amazing fellow radiology residents at Akademiska Sjukhuset. Thank you for your cheerful messages, pep talks and encouragement. Thank you for
wanting to celebrate this work with me and letting our group know we have each other’s backs. “Vi är bästa ST-gänget!”

To my colleagues at the Department of Radiology at Akademiska Sjukhuset. Thank you for everything you have taught me, keep on teaching, and for the inspiration I receive from you daily.

To the Head of the Radiology Resident program, Allina Dimopoulou Creusen, and the Head of the Radiology Department, Adel Shalabi. Thank you for helping me balance my clinical training with research opportunities.

“AT-ledningen” at Akademiska Sjukhuset. Thank you for believing in me and giving me the opportunity to continue my work through a “forskar-AT block”. Thanks to my AT-colleagues, especially my “forskar-AT”-colleagues, who continue to encourage each other. And to my dear friend and colleague Hanna Andersson who has followed me during this process since medical school.

Special thanks to my proofreaders, Stephan Foy, Sue Pajuluoma, Christina Lundberg and my father. To Mats Magnusson for plotting graphs and helping with statistics. To the Uppsala University administrative staff at the Radiology Department, especially Christl Richter Frohm, Elin Eriksson and Siv Andersson for organizing my research process. To the secretaries at the Urology department for helping me gather patient-lists and to nurse Pernilla Helgesson for getting me in contact with patients.

To my relatives and friends. Thank you for cheering on me always and reminding me to look back on my accomplishments once in a while. Thank you to everybody who keeps in touch from different parts of the world.

The biggest hugs and kisses to my family. “Mami y Papi”, thank you for your unconditional support, phone calls, annual Australia-Sweden trips, love and care. Thank you for our FaceTime rehearsal sessions before every presentation, for your live cheering from the other side of the world in a different time zone, and for letting me become the person I am. Thank you for being my best role models in life. This work is for you.

To my siblings Rafael, Valeria and Sebastian, for reminding me what is important in life, for always making me laugh and keeping me down to earth.

And to my favorite person in the world, my husband Renzo. Thank you for making my dreams come true.
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Acta Universitatis Upsaliensis

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