Renal tumor ablation: beyond limitations of biopsy and follow-up
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Citation for published version (APA):
Barwari, K. (2012). Renal tumor ablation: beyond limitations of biopsy and follow-up

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Download date: 13 Dec 2018
General introduction

Outline of this thesis
Introduction
In the olden days, availability of radiological diagnostic imaging studies was scarce. As a result, a renal tumor was most frequently diagnosed through clinical symptoms like hematuria, abdominal pain a palpable abdominal mass or paraneoplastic symptoms, resulting in the nickname the ‘internist’s tumor’. At discovery those renal tumors were likely to be relatively large and often in an advanced stage, leaving no option except surgical removal of the complete affected kidney. This procedure was first described by Robson in 1963[1] and current clinical guidelines still suggest that the only curative treatment modality for renal cancer is surgery[2;3]. Nevertheless other aspects of the current medical practice regarding renal cancer have changed tremendously.

1 THE SMALL RENAL MASS
In the current medical practice there is a vast increase of availability and use of radiological imaging modalities compared to the olden days[4]. Due to the increased use of radiological imaging studies, renal tumors are nowadays more likely to be discovered incidentally being asymptomatic and still relatively small. A recent study based on data from the United States cancer registry SEER (Surveillance, Epidemiology and End Results) showed that from 1991 to 2006 39% of all registered renal tumors were less than 4 cm in diameter compared to 28% in the period between 1975 and 1990[5]. In the current TNM-criteria this 4 cm cutoff is the upper limit of classified T1a tumors[6] and this category of tumors is currently widely regarded as ‘small renal mass’ (SRM). This alteration has several consequences. First, the decreased average tumor size does not necessarily require removal of the complete kidney and more tumors are potentially eligible for nephron sparing surgery. This enables preservation of healthy nephrons that are unaffected by tumor and are still contributing to the renal function. Since a lower renal function (expressed as estimated glomerular filtration rate or eGFR) is an independent risk factor for several negative aspects including death[7], there is an absolute necessity to perform nephron sparing surgery in cases where this is feasible. The guidelines of the European Association of Urology (EAU) and the American Urological Association (AUA) recommend performing a partial nephrectomy (when feasible) in case of a T1 renal tumor (< 7 cm)[2;3]. Removing a part of the kidney implies in most cases that the renal artery or its segmentary branches of the affected kidney need to be clamped in order to establish a blood-free surgical environment.
This temporary ischemia causes to a certain extent inevitable damage to the remaining kidney tissue leading to a decline of renal function\[8;9\]. Therefore a partial nephrectomy is not the best treatment option for those patients who already suffer from a mild or severely impaired renal function\[10\]. Furthermore a partial nephrectomy is considered as a technically difficult urological surgical procedure and certainly performing a laparoscopic partial nephrectomy is reserved for skilled urological surgeons with an advanced laparoscopic expertise. As a result still the majority of T1 and even T1a renal tumors is treated with a radical nephrectomy despite the recommendation in the guidelines\[11;12\]. Robot-assisted laparoscopic partial nephrectomy seems to ease the technical procedure but availability is subjected to social and budgetary factors.

Second, it has been demonstrated that with a decreasing renal tumor size, the chance of a benign tumor or low-aggressive carcinoma increases\[13;14\]. When looking at the pathology of excised small renal mass (SRM, < 4 cm) it becomes clear that 23% of surgically treated SRM appears to be benign\[3;13\]. Therefore, while for the larger and more aggressive tumors surgery is the only curative option, a large part of smaller tumors is actually overtreated. Furthermore, since the majority of renal tumors is discovered as an incidental finding on diagnostic imaging focused on other organs, there are relatively more tumors discovered in patients with comorbidities, and frequently of older age\[15;16\]. This has huge implications for the treatment strategy, since patients might be unfit for surgery and there is a high chance of death from competing causes\[17\].

Ergo, the field of renal tumor treatment has changed dramatically compared to the olden days and this requires other measurements in terms of both tumor diagnostics and treatment.

2 CURRENT STATUS OF RENAL MASS DIAGNOSTICS

2.1 Radiological evaluation

Ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) are currently available imaging modalities to detect and evaluate renal masses. Ultrasonography is widely available and harmless to patients making it a useful diagnostic modality. However the sensitivity of US for detection of renal masses is
lower compared to CT and decreases with smaller tumor size[18], with the detection rate between US and CT not being equal until the lesion measures 3.5 cm. Therefore, a contrast-enhanced CT-scan is the reference standard for assessment of (small) renal mass in the current clinical guidelines[2;3]. A small renal mass is suspect for solid tumor in the presence of contrast enhancement as a sign of vascularization, with contrast enhancement being defined as an increase of >10 Hounsfield units between unenhanced and contrast-enhanced images[19]. However since normal renal parenchyma is vividly enhanced physiologically, pseudo-enhancement of small renal masses can occur simulating an enhancing tumor, and therefore there are some pitfalls when assessing small renal masses by CT[20]. MRI has long been the alternative when CT-imaging is contraindicated or in case of inconclusive findings on CT[20]. Due to good sensitivity and specificity for detecting renal masses combined with the lack of ionizing radiation and a nephrotoxic contrast agent, MRI is a good imaging modality for renal tumor detection although drawbacks as availability and costs hamper it from being the modality of first choice. After detecting a renal mass suspect for solid tumor, there is a challenge to differentiate benign masses from those that are malignant given the fact that almost 25% of renal masses < 4 cm appears to be benign[13]. Although different renal tumors types bear different radiological features, histological characterization of renal masses by radiological means is proven to be very difficult, with only macroscopically seen fat being pathognomonic for angiomyolipoma[20] and as a result current practice does not include histological differentiation of (small) renal masses by radiological means[21].

2.2 Renal tumor biopsies

In most visceral tumors other than renal tumors, performing a biopsy of the tumor to obtain a tissue sample for pathological confirmation of the tumor biology forms one of the main components of the diagnostic process, but historically this was not the case for renal tumors. The fear of tract seeding of malignant cells, the risk of complications such as hemorrhage and the high a-priori likelihood of a malignant tumor led to an abstentious policy towards performing a renal mass biopsy (RMB). However technical developments and increased knowledge resulted in a renewed interest in RMB[22].
First of all, performing tumor biopsies using a coaxial needle minimizes the risk of tract seeding and as a result there have not been reports of tract seeding incidents since 1994[22;23]. Furthermore complication rates are very low in recent reports with a minor complication rate of less than 5% and major complications being almost anecdotal[22;23].

In general, those who perform RMB use a histological (core) biopsy rather than a cytological puncture (or fine needle aspiration, FNA) since most reports show advantageous results for the former[23]. In recent studies, the diagnostic accuracy of a histological core biopsy of renal tumors is considered good with 90% accuracy to detect a malignancy reported in most series[22;23]. Although the number of false-negative results is low, there is discussion on the value of a benign biopsy result. Overlapping morphological characteristics and hybrid tumors exist such as overlap between benign oncocytoma and chromophobe RCC[24] and the co-existence of benign oncocytoma with RCC[25] in one tumor.

Apart from histological subtype, given its prognostic significance the nuclear grade of a renal tumor is important when evaluating the biological potential of a renal tumor[26]. Performance of RMB to determine the nuclear grade (in terms of Fuhrman grade I-IV) is reported to be less accurate with a reported accuracy ranging from 76-94% which does increase to 76-100% in some series when the Fuhrman grades are dichotomized into low-grade and high-grade[23]. In an effort to eliminate both issues, recent advances in the field of molecular analysis, gene expression, and fluorescence in situ hybridization have led to the development of an ‘enhanced RMB’ showing promising results in terms of determination of the nuclear grade and differentiation between overlapping features of oncocytic tumors[22].

Apart from the aforementioned issues, currently one major drawback of performing RMB is the number of non-diagnostic results. A non-diagnostic biopsy result implies that the result of a biopsy contains insufficient material for analysis, or contains only normal renal parenchyma, only fat or fibro-fatty connective tissue, only necrotic tissue or a blood clot or only inflammatory or fibrotic tissue[27]. A recent report shows a non-diagnostic rate of 20% in the RMB-studies performed in SRM’s from 2000 onwards and this is reproduced in their own patient population[28]. When the non-diagnostic cases were re-biopsied, 66% showed a malignancy while again approximately 20% of cases
resulted in a non-diagnostic biopsy indicating that with current techniques this rate of non-diagnostic results is apparently inevitable. Furthermore this study confirms that a non-diagnostic biopsy result should not be regarded as a proof of no cancer, which was already demonstrated in earlier surgical series with the majority of non-diagnostic tumors being malignant tumors upon surgical extirpation\[27;28\].

In conclusion, currently one of the major issues regarding RMB is the number of non-diagnostic biopsy results and in the frame of a diagnostic setting with AS or for follow-up purposes after renal tumor ablation. This number should be minimized in order to integrate RMB in the diagnostic workup of newly discovered SRM’s in general and given their new treatment options in particular.

3 CURRENT STATUS OF RENAL MASS TREATMENT

As mentioned earlier, partial nephrectomy accounts for a substantial number of renal tumor surgeries\[29\]. However currently there are several less invasive treatment options available which are potential suitable options when a SRM is newly discovered, with active surveillance and ablation therapies being the most important ones.

3.1 Active surveillance

As mentioned earlier, the chance that older patients will die from a newly discovered SRM or suffer from its symptoms is relatively low\[17\]. Therefore more urologists opt (in close deliberation with the patient) for an active surveillance (AS) management in which regular follow-up of the tumor is performed. In case of tumor growth, improvement of the patient’s medical condition or because of the choice of physician or patient prompts a delayed intervention \[30\]. Nevertheless there is clear evidence that there are SRM’s that do progress locally or even metastasize\[31;32\]. This demonstrates that although AS might be a good management option in selected cases, the real challenge is to determine which tumor is a candidate for this strategy and for which tumors it is contra-indicated. With current imaging techniques it is impossible to predict the biological potential of renal tumors. Both growing and non-growing tumors on surveillance appeared to be a malignant tumor in more than 80% of cases\[33\]. Therefore, in order to obtain information on the biology of a renal tumor histological information is needed and as a result performing a renal mass biopsy might be of
additional value before opting for an AS-management.

3.2 Tumor ablation

Recently, thermal ablation therapies are included in the armamentarium of treatment modalities for localized, small renal tumors. While radio frequency ablation (RFA) converts radio frequent waves into heat resulting in tissue destruction, cryoablation uses cold to achieve the same goal. The beneficial effects of cold on tumors are known for a long time and in several fields of medicine freezing malignant cells is common practice such as treatment for cervical dysplasia or skin tumors. With the development of cryoablation-needles and intra-abdominal ultrasonography, cryosurgery became an interesting treatment modality for visceral tumors resulting in an initial clinical series of renal tumor cryoablation being described in 1998[34;35]. The mechanism to reach the freezing temperatures necessary for cryotherapy is based on the Joule-Thompson effect, which is a physical effect describing the temperature change of pressurized gas or liquid when it is forced through an insulated valve resulting in expansion. At room temperature, all gases except hydrogen, helium and neon cool upon expansion by the Joule–Thomson process[36].

Currently, the major guidelines recommend ablation therapy of renal tumors to treat patients with small tumors and/or significant comorbidity who are unfit for conventional surgery[2;3]. A recent report demonstrates that the contribution of ablative therapies is rising, with 4% of renal tumors in the size range of 2-4 cm being treated by ablation in 2004 compared to 9% in 2008[29]. However there are some drawbacks of the therapy that prevent thermal ablation from being adopted as a treatment option of first choice. Given the relatively short time since implementation of the therapy, long-term follow-up data are still lacking making firm comparison of treatment efficacy with other forms of NSS difficult. Current data suggests that renal tumor ablation is effective in terms of oncological efficacy with cancer specific survival rates being equal to those of PN[12], despite the higher local recurrence rate[37]. This higher recurrence rate is most likely explained by the fact that the tumor is eliminated in situ rather than extirpated, enabling possible residual malignant cells to develop into a recurrent malignant tumor over time. This implies that a stringent follow-up policy is imperative following renal tumor ablation with at least a contrast-enhanced CT
or MRI performed annually in order to trace a recurrence as early as possible. In the undesired case of a recurrence, given its minimal invasive nature a re-ablation is both feasible and effective and therefore the effectiveness of thermal ablation should be assessed after all treatments when assessing its efficacy[12].

Since the tumor is not extirpated, there is no specimen for histopathological assessment revealing the tumor biology unless a biopsy is taken. Given the considerable number of benign and low-aggressive tumors associated with SRM’s, information on the tumor biology is essential to tailor the follow-up policy.

With the rising trend of AS and ablation to treat renal tumors the necessity of performing renal tumor biopsy is rising at the same time. This asks for new developments to further improve the performance of renal tumor biopsies and eliminate negative aspects and drawbacks of performing renal tumor biopsy on a regular basis.

4 OBJECTIVES OF THIS THESIS

In current medical practice there is a vast increase of discovered renal tumors with the majority being small, asymptomatic and low-aggressive or even benign. As a result new less invasive treatment strategies have emerged such as active surveillance and tumor ablation. Histological information revealing the biology of the tumor is essential for diagnostic and prognostic purposes, and the renal mass biopsy, previously regarded as obsolete, is currently the instrument to obtain such information. Although the accuracy of RMB is acceptable, the high rate of non-diagnostic biopsy results is hindering routine use of RMB in the diagnostic process. Therefore the current biopsy technique should be optimized and reinforced by new technological aids in order to allow RMB to be used as a standard diagnostic method. Furthermore the mandatory long-term follow-up after renal tumor ablation using CT/MRI-scans is one of the drawbacks of the therapy. An alternative imaging modality such as contrast-enhanced ultrasound (CEUS) for this application would be highly desirable.

In this thesis we try to optimize the diagnostic performance of RMB and assess the efficacy of thermal ablation of renal tumors together with the initial efforts to optimize the follow-up methodology after ablation treatment.
5. OUTLINE OF THIS THESIS

The altered presentation of renal tumors has changed the attitude towards a renal tumor dramatically. As a result new treatment modalities have been introduced into the armamentarium of the urologist. One of the upcoming modalities is thermal ablation which is currently recommended for treatment of small renal tumors in patients that are unfit for conventional surgery. The lack of long-term follow-up data is one of the reasons preventing thermal ablation from being a first choice treatment modality. Therefore we assessed in chapter 2 the mid-term oncologic and functional outcomes of 100 cryoablations performed in our centre. Since the majority of earlier studies reporting the efficacy of thermal ablation are based on short- and intermediate-term results and are heterogeneous with respect to ablation modality and surgical approach, we sought to summarize in chapter 3 the evidence of the efficacy of renal tumor ablation therapy in terms of oncologic outcome and complication/re-treatment rate based on mid/long-term results and categorized for ablation modality and surgical approach in order to make a fair comparison among the studies.

Since renal mass biopsies gained renewed interest, we provided an overview of the most important aspects of renal mass biopsy in chapter 4, including accuracy results, nomenclature, biopsy technique and complications.

As far as clinical implementation of RMB is concerned, the diagnostic yield and the non-diagnostic biopsy rate is a major issue. As most commonly histological core biopsies are performed for renal tumor sampling, we assessed in chapter 5 the added value in terms of diagnostic yield when core biopsies are combined by cytological punctures in optimized conditions performing the biopsies in bench and using five different pathologists to evaluate the inter-observer variability. In chapter 6 we assessed whether there were any conditions related to a non-diagnostic biopsy result in our own practice where we performed biopsies preceding a laparoscopic renal cryoablation.

Moreover, as it was striking us that there was a clear increase of publications in the recent years on renal mass biopsies, we have assessed the actual penetration of renal mass biopsy in the general urologist’s practice with an electronic survey, as reported in chapter 7.

Optical diagnostic techniques use the interaction of light and tissue to provide real-time histological information of tissues in different organs, however the potential of
such technique has only been explored briefly in the field of renal tumors. Therefore we initially performed an ex-vivo pilot study to assess the potential of Optical Coherence Tomography (OCT) to differentiate renal tumors from normal renal tissue, as reported in chapter 8. Driven by the positive results of this study we continued the investigations resulting in the in-vivo study reported in chapter 9. Finally, in chapter 10 we assessed the potential of the radiation-free and non-nephrotoxic contrast agent imaging technique CEUS (contrast enhanced ultrasonography) to depict enhancement of a cryolesion following laparoscopic cryoablation of renal tumors.
REFERENCES

Part 1