Renal tumor ablation: beyond limitations of biopsy and follow-up
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Summary,
General Discussion and
Future perspectives
The present thesis discusses a number of topics that are intimately imbricated. The common denominator among them is the changing scenario of renal tumor presentation compared to the 1990s\[1\]. This well documented phenomenon is characterized by an increasing detection of small renal masses (SRM) which calls for more accurate pre-operative diagnostics on account of the high number of benign tumors and low-aggressive malignancies in this size range\[2\]. Together with the introduction and widespread use of ablation in SRMs it makes the subject the ideal field for implementation.

The research in this thesis is organized in three parts. In part II we sought to explore the oncological and functional efficacy of renal tumor ablation both in our own experience and by reviewing the available literature. In part III we focused on different aspects of the renal mass biopsy (RMB), including a recapitulation of the available literature on RMB-performance, assessment of the penetration of RMB in the global urological practice and exploration of the potential to improve RMB-accuracy with conventional pathology methods. Part IV of this thesis focuses on experimental research with novel diagnostic techniques to improve the diagnostic rate of RMB and a novel follow-up modality for post-renal cryoablation follow-up.

**Part II: renal tumor ablation**

In chapter 1 we demonstrated that laparoscopic renal cryoablation (LRC) is a safe and effective treatment modality for small renal masses (SRMs) in selected cases albeit based on intermediate-term results with a mean follow-up (FU) of 30 months. The oncologic efficacy of renal tumor ablation was further confirmed by an up-to-date overview of the available long-term (> 36 months FU) series in the literature in chapter 2. By only including cases with biopsy proven renal cell carcinoma (RCC) and by stratifying results per ablation type and surgical approach, limitations of earlier reviews such as the heterogeneity of analyzed data are overcome. Cryoablation and RFA showed good oncological results, a low complication rate and excellent renal function preservation, although still randomized studies are lacking and all available data is limited to observational studies of low quality. In a recent comprehensive overview published in 2012, Cadeddu et al. confirm that long-term results of renal tumor ablation are still scarce hindering firm conclusions on the efficacy of the therapy\[3\].
However, despite a higher recurrence rate for ablative therapies, the cancer-specific survival (in the end the most important patient outcome) seems comparable to that of partial nephrectomy, although it remains unclear if the effects of the indolent nature of SRMs and the lack of long-term results could change this favorable outcome.

A critical look on renal ablative therapy studies reveals two major issues: the number of RMBs with a non-diagnostic result and the need for a strict post-ablation follow-up schedule using contrast-enhanced CT- and/or MRI-scans. The non-diagnostic rate of RMB is a striking problem in today’s urological practice[4]. While in earlier days a pre- or peroperative RMB was considered both obsolete and useless since all renal tumors were treated by radical or partial nephrectomy (when feasible), the current alteration in both clinical presentation and treatment options for renal tumors calls for a re-definition of the role of RMB in the context of renal tumors.

**Part III: Improving current biopsy techniques**

The basic principles and the state-of-art results of RMB performance are summarized in chapter 3. In general the accuracy of RMB is high when the surgical specimen is taken as reference standard and recent reviews show mean accuracy figures of 96% in all tumor sizes[5] and 93% in SRM[6]. However the varying definition of ‘accuracy’ among authors as well as the definition of the standard reference is hindering a straightforward comparison of studies as was concluded by other authors[4]. In addition, chapter 3 demonstrates the aforementioned high non-diagnostic rate, with almost 20% of RMB resulting in a non-diagnostic result both in SRM and in larger tumors.

When looking at the type of biopsy used in those series, it becomes clear that core biopsies (CB) are preferred over fine needle aspirations (FNA), although both types might result in similar accuracy depending on local expertise[7]. Following our previous ex-vivo studies[8;9] we sought to demonstrate the potential benefit in improved diagnostic yield and accuracy of renal mass biopsy by combining CB with a FNA as described in chapter 4. By using in-bench RMB the biopsy circumstances were optimized and by using five individual pathologists for biopsy assessment the earlier demonstrated inter-observer variability for biopsy results was overcome[8]. Given the fact that both biopsy techniques use different technical and pathological principles
we hypothesized that they might be complimentary. In addition to the fact that even with optimized circumstances and in relatively large tumors (median 5.4 cm) the five pathologists had a non-diagnostic rate ranging from 3.5% to 17.5%, we demonstrated that CB and FNA had comparable accuracy numbers independently. When both techniques were combined, the diagnostic yield and accuracy was higher for all pathologists suggesting that performing both techniques is beneficial and results in less non-diagnostic results. A similar message was published by Parks et al. suggesting that FNA and CB are indeed complimentary, with FNA being more likely to obtain a diagnosis as such, while the information on histological architecture provided by the CB enables subclassification of tumors to a greater extent[7]. Thus, ideally CB and FNA should be combined to achieve maximal diagnostic rate and accuracy. Nevertheless we recognize that in order for this combination to be implemented in the clinical practice other factors such as infrastructure or budgetary aspects play a considerable role.

Our results are supported, as described in chapter 6, by a global survey. The potential of FNA is clearly acknowledged by urologists given the high number of responders that indicated to perform both CB and FNA (31%). The increasing trend to use FNA is obvious when this figure is compared to the minority of responders using FNA in a comparable survey conducted in 2005 (10%)[10]. Another major finding of our survey was the low number of urologists that perform RMB in general. From the responders, 73% reported “never” or “rarely” to take an RMB, which suggests that RMB has not yet penetrated the daily urological practice, especially in the non-academic setting (with 20-30% vs. 6% of academic urologists taking a biopsy “never”). Main reasons to refrain from taking RMB were the assumed lack of influence on the clinical management and the potential of false negative results, although false negative biopsy results are sporadic according to modern clinical studies[5;11;12]. A drawback of this survey was the response rate of 10% (190 individuals). However when looking at all available other electronic surveys distributed among all members of the Endourological society in 2011, our response rate is exceeding that of the other surveys (127 – 160) individuals[13;14]. This repeatedly low response rate is most likely explained by the inaccuracy of e-mail reachability and the survey being focused on a particular sub-group within a large population, resulting in a majority being not interested in the survey who therefore refrained from responding. In chapter 5, characteristics of renal
tumors biopsied during laparoscopic pre-ablation and the biopsy procedure were collected in order to assess whether certain factors influence the likelihood of a nondiagnostic biopsy result in this particular setting. While the nondiagnostic rate of 22% is comparable to figures recently published[4], no factors were found to be related to the occurrence of a nondiagnostic result. This suggests that a nondiagnostic result is a matter of technical sampling error rather than a drawback of certain tumor or procedural characteristics[4]. Apparently there is nothing intrinsic to the tumors that leads to a nondiagnostic result and this further strengthens the concept that in order to reduce the number of nondiagnostic biopsies, the aim for improvement lies in the actual sampling of tissue.

**Part IV: Novel diagnostic techniques**

Optical diagnostic techniques provide histological information based on the interaction of light with the tissue under study. The various types of optical diagnostic techniques use different principals leading to different output configurations[15]. Optical Coherence Tomography (OCT) is unique in the fact that it provides an image of the studied tissue, based on the backscattered light intensity in a couple of millimeters depth of the tissue. OCT was developed for ophthalmologic use and is currently standard-of-care in ophthalmologic imaging[16]. The technique is rapidly becoming the standard intravascular imaging method in interventional cardiology[17]. In short, different tissue structures result in a different degree of ineffective scattering. This leads to a different attenuation of light as it goes deeper into the tissue, resulting in a distinct OCT signal per tissue type. This enables identification of different tissue types, such as malignant and non-malignant tissue[18].

We hypothesized that the larger and irregularly shaped cellular structures in malignant tissue (such as nuclei and mitochondria) cause a higher degree of ineffective scattering, leading to a higher attenuation of light per millimeter tissue depth compared to normal renal tissue. By this, OCT can hypothetically differentiate malignant from non-malignant renal tissue. In our institution a model was developed to quantify the light intensity in an OCT-image resulting in an attenuation coefficient or $\mu_{OCT}$ enabling quantitative comparison of different tissue types using OCT[19].

To assess the proof of principle an *ex-vivo* study was performed initially comparing
renal tumor samples with normal renal tissue samples both harvested after surgical extirpation of a renal tumor. The results described in chapter 7 show a higher attenuation-coefficient for malignant renal tissue compared to normal renal tissue. Although these results supported our hypothesis, potential “in-vivo” influencing factors such as blood flow and presence of hemoglobin were obviously missed. Therefore an “in vivo” study was conducted to assess the ability to differentiate normal renal tissue from renal tumors by performing intra-operative OCT imaging before tumor excision. As described in chapter 8, a significantly higher attenuation-coefficient was found for renal tumors compared to normal renal tissue. Being a pilot study, the small size of our cohort precluded a possible difference in attenuation coefficient between malignant and benign tumors. Furthermore to overcome the low depth of penetration of OCT, images acquired from the tissue surface where compared to images from the core of the tumor in the laboratory. Attenuation coefficients were comparable in this last experiment, suggesting that despite the limited penetration depth of the OCT signal superficial tissue imaging is representative for centrally located tumor tissue. These results show that real-time histological information can be obtained from renal tissue without the need for tissue perforation. It appears to be a possible to distinguish between malignant and normal renal tissue, both in-vitro and in-vivo, albeit in a pilot study setting.

Our report was the first publication on in-vivo OCT for renal tumor differentiation. To our best knowledge other publications on the subject are scarce and limited to ex-vivo experiments. Linehan et al. assessed the potential of qualitative OCT to differentiate subtypes of renal tumors in an ex-vivo setting[20]. They were able to distinguish normal renal tissue from angiomyolipoma and urothelial carcinoma, but the heterogeneous appearance precluded identification of different RCC subtypes. The authors suggested an ultra-high resolution OCT might be necessary to accomplish this. This was done by Lee et al. who integrated OCT with Optical Coherence Microscopy (OCM) to obtain the ultra-high resolution images of ex-vivo renal tissue, by which they could indeed differentiate RCC from normal renal tissue with a sensitivity and specificity of 88% and 100% respectively[21].

As mentioned earlier there are different types of optical diagnostic techniques and several groups have explored their potential for renal tumor diagnostics.
All aspects and up-to-date results are summarized in a recent review[22] showing that both Optical Reflectance Spectroscopy (ORS) and Raman spectroscopy (RS) have shown good results with respect to renal tumor differentiation, albeit in initial pilot studies and mostly ex-vivo[20;23;24]. Nevertheless it is clear that the results, although preliminary, point in the same direction showing promising results, suggesting that optical diagnostic techniques might play a definitive role as a diagnostic method for renal tumors.

**Post-ablation follow-up**
Apart from establishing a pathological diagnosis through an RMB, a capital issue regarding renal tumor ablation is the long-term follow-up management that ensures the early diagnosis of potential recurrent disease. Despite the reported recurrence rates are low. Suggesting a good oncological efficacy, a strict post-ablation follow-up policy is still considered essential and current schedules include contrast-enhanced cross sectional imaging: CT- and MRI-scans[25]. Associated drawbacks of these modalities are ionizing radiation, nephrotoxicity of the contrast agent and costs. Contrast-enhanced ultrasound (CEUS) is a novel imaging modality expanding its application in several medical fields[26]. The technique employs a conventional ultrasound device fitted with specific software and a harmless contrast-agent consisting of microscopic gas bubbles. The ability to monitor post-cryoablation lesions by CEUS has not been explored earlier, although favorable initial results are shown for monitoring post-RFA lesions by CEUS[27;28]. In a pilot study in post-cryoablation lesions chapter 9 we described a high concordance between CEUS and the standard modalities in terms of post-cryoablation lesion assessment appearance. A major limitation of the study was the absence of radiological recurrences in our cohort of 46 patients, which again confirms the high oncologic efficacy of renal cryoablation although consequently the sensitivity and positive predictive value (PPV) of the index test (CEUS) could not be assessed.

**Future perspectives**
In the oncoming years it is to be expected that urologists will deal with an increasing number of SRM in both the younger and the ageing population. This serendipitous diagnosis will lead to more minimally invasive procedures. Judicious counseling and
the choice between active surveillance and active treatment will be more challenging in the elderly and sick. Two factors will play a decisive role: decreasing morbidity of minimally invasive surgery and avoiding unnecessary treatment in benign renal masses. Almost 15 years after the first clinical series of renal cryoablation[29;30], observational long-term follow-up results are emerging[3]. When considering the fact that patients counseled for ablation are not candidates for radical or partial nephrectomy (mostly because of high surgical risk), the aforementioned results are highly satisfactory and support the full implementation of ablation techniques in the future. Nevertheless the trend to liberalize tumor ablation should be carefully balanced with life expectancy in the elder and with the radiological burden of the follow-up in the younger.

In this thesis, initial steps have been taken to overcome major hindering factors associated with renal tumor ablation: the possibility of reducing the rate of nondiagnostic biopsy results and the assessment of a harmless follow-up modality after cryoablation.

Optical diagnostic techniques such as OCT and Raman spectroscopy developed over the last years from experimental hyper-modern gadgets to commercially available and medically approved devices with disposable probes for use in several organs. Anticipating on validation of the initial results presented in this thesis, implementation of OCT is revolutionary because at present it is impossible to obtain histopathological information in real-time without removal of the tissue. With respect to RMB, by advancing an OCT probe through the coaxial outer needle, the tip of the biopsy needle can be positioned in a location showing renal tumor tissue as determined by real-time feedback of the OCT-image without the need for tumor perforation. This may reduce the likelihood of a nondiagnostic biopsy result. In a best case scenario the conventional biopsy and subsequent pathological analysis might even be replaced by an ‘optical biopsy’ by OCT, saving both the risk of complications, costs and time as the ‘biopsy’ result is available instantly, without the need for a pathological assessment.

CEUS is an imaging modality that has demonstrated potential in several diagnostic purposes. In this thesis the initial experience in the follow-up of cryoablated lesions are described. It is likely that these positive results may be reproduced and validated in a
larger series. If the efficacy is confirmed, CEUS can certainly lessen one of the current disadvantages of performing renal cryoablation. Enabling follow-up using an ultrasound device, without the need for ionizing radiation or a nephrotoxic contrast-agent will decrease the toxicity of follow-up and improve the cost-effectiveness of renal cryoablation.

In conclusion, with the “new” renal tumor profile at presentation, the current and future medical practice regarding renal mass biopsy bears new perspectives. Novel non- or minimal-invasive treatment modalities urge for the need of a diagnostic renal tumor biopsy, which is not sufficiently accurate with current biopsy methods. Optical diagnostic methods may improve this diagnostic biopsy rate in the near future, while an imaging modality usable for the inevitable long-term follow-up after renal tumor ablation without harmful negative aspects such as CEUS might eventually improve the follow up after renal ablation.
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