Focal therapy
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This chapter focuses on the background of prostate cancer and focal therapy

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WHY THIS THESIS?

Prostate Cancer (PCa) is among the leading causes of cancer-related death in men.\textsuperscript{1} Recommended therapies by guideline for localized PCa are radical prostatectomy (RP), radiotherapy using either brachytherapy or external beam radiotherapy (EBRT) or active surveillance. Radical treatment is associated with side effects that have a detrimental impact on the quality of life of PCa patients.\textsuperscript{2,3} This sparked the interest to improve current techniques and to develop new PCa treatments.

In focal therapy only the tumor lesion is targeted, while sparing adjacent anatomical structures that are of importance for urinary, bowel and sexual function. At present focal therapy is been evaluated in patients that harbor low- to intermediate-risk PCa, a population in which the equilibrium of quality of life versus the oncological benefit of treatments is delicate.\textsuperscript{4} Accurate PCa diagnosis and lesion localization is required to allow focal treatment.

The main aim of this thesis was to evaluate the current standard of focal therapy and to advance this treatment paradigm by improving patient selection, treatment planning and follow-up and to identify risk factors for impaired outcomes.

In order to understand the main aims of this thesis (the delicacy of the beneficial equilibrium behind PCa treatments and the rationale behind focal therapy) a profound understanding is required on the:

1. Epidemiology and screening of prostate cancer
2. Biology of prostate cancer
3. Prostate cancer diagnostics
4. Outcomes of current prostate cancer treatments
5. Introduction of focal therapy
6. Introduction of irreversible electroporation (IRE)

1. EPIDEMIOLOGY AND SCREENING

A significant proportion of men are at risk to develop PCa in their life due to longer life expectancy, however, the incidence is decreasing as a result of the recommendations against population-based screening. In the 2017 update of the American Cancer Society cancer incidence report the incidence of newly diagnosed PCa in the United States (US) of America was estimated to be 161,360 men that year.\textsuperscript{1} In the Netherlands 11,064 men were diagnosed in 2016 (ref: Integraal kankercentrum Nederland). The US preventive
services task force, Dutch and European Association of Urology (EAU) PCa guidelines recommend against population-based screening to prevent men from being “over-diagnosed” and over-treated. This recommendation is mainly based on the results of the European Randomized Study of Screening for Prostate Cancer (ERSPC) study, showing that in order to prevent 1 PCa-specific death the number needed to screen and treat are 781 and 27, respectively. In the United States of America the estimated number of men who will die from PCa in 2017 is 26,730, whereas in the Netherlands 2,641 men died in 2015 from PCa (ref: Integraal kankercentrum Nederland). This reflects the main challenge we face in PCa care; a lot of men are diagnosed in their life with PCa, a significant part of those men will eventually die from PCa, however, we are currently not able to accurately differentiate those patients that require treatment from those that should not be treated. New insights in the biology of the disease and improvements in PCa diagnosis might help to identify patients that need (focal) treatment.

2. BIOLOGY OF PROSTATE CANCER

The following paragraphs on the biology of the disease and clinical outcomes of different PCa treatments will focus on low- to intermediate-risk PCa (Table 1), since focal therapy is only recommended for this subset of disease. PCa is usually slow growing, with a long preclinical phase before progressing to clinical significant disease (if at all). The SPCG-4 study and PIVOT trial showed important information on the likelihood of clinical progression in patients that did not receive any treatment. Between 1989 and 1999, prior to the prostate specific antigen (PSA) period, the SPCG-4 study randomly assigned 695 men with localized PCa to either watchful waiting or RP. Mean follow up was 13.4 years (range 3 weeks to 23.2 years). For low-risk PCa, the SPCG-4 study showed a significant decrease in all-cause mortality and distant metastasis at 18 years for the RP group. Yet, this was not the case for PCa-specific mortality. The PIVOT trial randomly assigned 731 men with localized (PSA detected) PCa to watchful waiting or RP between 1994 and 2002 and mean follow up was 10.0 years (range 7.3 to 12.6 years). For low-risk PCa, the PIVOT trial showed comparable results on PCa-specific mortality at 10 years for both arms and found no significant decrease in all-cause mortality following RP.

In intermediate-risk PCa the SPCG-4 study found a significant decrease in all-cause mortality, PCa-specific mortality and distant metastases only at 18 years following RP. The PIVOT trial did not show a significant decrease in PCa-specific mortality for the RP group at 10 years follow-up. This may teach us that for low-risk disease the majority of the patients should not be treated, whereas for intermediate-risk PCa there is a long window of opportunity to treat before clinical progression or PCa-specific mortality
occurs. At this point the internationally used risk stratification (Table 1) is not able to sub-stratify for the need of treatment within the low- or intermediate-risk group, respectively.

### Table 1. Defined d'Amico Risk Groups in Prostate Cancer

<table>
<thead>
<tr>
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<th>Low-Risk</th>
<th>Intermediate-Risk</th>
<th>High-Risk</th>
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<tbody>
<tr>
<td>Gleason Score</td>
<td>GS 6</td>
<td>GS 7</td>
<td>GS &gt;7</td>
</tr>
<tr>
<td>PSA</td>
<td>PSA ≤10 ng/mL</td>
<td>PSA 10-20 ng/mL</td>
<td>PSA ≥20 ng/mL</td>
</tr>
<tr>
<td>TNM</td>
<td>cT1-2a</td>
<td>cT2b-2c</td>
<td>&gt;cT3a</td>
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Defined risk groups according to the D'Amico classification. If any of the three determinants (Gleason Score, PSA, TNM) are positive, patients are upgraded to the corresponding risk group. Abbreviations: GS; Gleason score, PSA; prostate-specific antigen

Using the Surveillance, Epidemiology, and End Results (SEER) database, it is estimated that about 8% of all men will develop clinically significant PCa in their life. Pathological examination of cystoprostatectomy specimens in 139 patients with bladder cancer revealed that 40% (55/139) harboured PCa (Gleason sum score ≥6). When the percentage of men that will develop clinically significant PCa cancer was applied to this cohort (8% according to the SEER database) 11 men (7.9%) would be likely to develop clinically significant PCa. The authors measured the volumes of the largest tumour lesion in all 55 men with PCa in their cystoprostatectomy specimen, and determined that lesions of >0.5 mL corresponded with these 11 men (20%, 11/55). This led to the hypothesis that tumour lesions of >0.5 mL are associated with the likelihood to develop clinically significant PCa. The <0.5 mL cut-off for the lesion volume of insignificant disease has been confirmed (<0.5 mL) in patients that received RP in the ERSPC study (n=325), but it was shown that for Gleason 3+3=6 the lesion volume of significant disease is >1.3 mL in pT2 tumours. Recently, the correlation between lesion volume and tumour grade has been described. High-volume lesions are more likely to bear Gleason 7 or higher, whereas the likelihood to harbour Gleason ≥7 was only 10% for lesions <0.5 mL and 5% for lesions <0.2 mL (predominantly Gleason 3+4=7). Other known pathological risk factors to develop clinically significant disease are tumour stage, pre-treatment PSA, Gleason score, seminal vesicle invasion and surgical margin status.

The relationship between lesion volume and metastatic disease or death may be explained by the potential monoclonal origin of metastatic PCa. Men with metastatic PCa were invited to donate their body in event of death. Thirty patients with 94 metastatic lesions were analysed using high-resolution genome-wide single nucleotide
polymorphism and copy numbering. It was found that the origin of separate metastatic lesions in these men derived from the same single genomically aberrant PCa cell.\textsuperscript{15,16} This opened the door to lesion-based treatment, with the rationale that high-volume lesions (>0.5 mL or >0.2 mL) may be the cause for metastatic disease derived from a monoclonal origin, whilst smaller ‘satellite’ lesions would not exhibit the metastatic potential. By treating the so-called ‘index lesion’ (high-volume and high-grade lesion) the risk for developing clinically significant PCa might be reduced.\textsuperscript{16} Critics of such approach argue that the multifocality of the disease jeopardizes a targeted approach. Histopathological analysis of 100 RP specimens showed indeed multifocal disease in 78%. When all lesions were analysed it was shown that, apart from the index lesion, 99.4% of the remaining lesions were Gleason 6 or less and 87% had a volume of <0.5 mL.\textsuperscript{17} Long-term oncological data following focal treatment of the index lesion will establish or nullify the theory behind this paradigm. However, as mentioned before, accurate PCa diagnosis and ‘index lesion’ localization is required to allow focal treatment.

### 3. PROSTATE CANCER DIAGNOSTICS

The high number of patients needed to treat in the ERSPC study highlights the necessity for improved PCa diagnostics, since still a significant number of patients will die from PCa whilst the majority will not develop clinically significant PCa and do not need treatment.\textsuperscript{1,7} Family history, increased awareness or symptoms may result into the need to test for PCa. Suspicion for PCa is based on elevated serum PSA levels and/or abnormal digital rectal examination (DRE).

#### 3.1 Prostate biopsies

Elevated PSA levels and/or abnormal DRE is an indication to perform prostate biopsies and standard of care is to obtain 10 to 12 core transrectal prostate biopsies.\textsuperscript{5} These random biopsies are taken following a standardized template using transrectal ultrasound. However, such an approach has been shown to under-grade and –stage patients with PCa. In 44% ($n=10.287$) of the patients receiving a RP (SEER database) for low-grade (Gleason 6) PCa, the tumour grade was upgraded to Gleason 7 or higher upon pathological evaluation of the resected specimen and 9.7% were upstaged.\textsuperscript{18} This highlights the need for improved PCa diagnosis, as these non-targeted random biopsies are nowadays the basis for treatment selection. Transperineal template-mapping biopsies (TTMB) have shown to detect PCa in 51.6% (138/294) of men that had (multiple) previous negative transrectal biopsies, and 53.6% (74/138) of these men had Gleason ≥7 PCa on TTMB.\textsuperscript{19} Another advantage of transperineal biopsies is the reduced risk for post-biopsy infection.\textsuperscript{20} However, TTMB also carry additional burden for both
the patient and healthcare system, including the need for (general) anaesthesia, higher costs, additional equipment and a longer learning curve. For TTMB it was calculated what biopsy cancer core length correlated with 95% sensitivity to predict lesions of >0.5 mL or >0.2 mL. Using 107 RP specimens a total of 665 tumour lesions were reconstructed. This formed the basis for computer-simulated TTMB that incorporated varying needle targeting errors. In each individual case 500 simulations were performed. It was found that a maximum cancer core length of 6 mm or 4 mm corresponded in 95% with tumour lesions of >0.5 mL or 0.2 mL, respectively. These biopsy characteristics were combined with tumour grade to provide the two common definitions of clinical significant disease on transperineal prostate biopsy:

1) ≥Gleason 4+3=7 with any cancer core length OR ≥Gleason 3+3=6 with a cancer core length of ≥6 mm.
2) ≥Gleason 3+4=7 with any cancer core length OR ≥Gleason 3+3=6 with a cancer core length of ≥4 mm.

Altogether, although prostate biopsies provide essential information regarding tumour grade and thereby aid risk stratification, standard transrectal prostate biopsies systematically under-diagnose and under-grade patients. New whole-gland imaging modalities must be developed to indicate the need for prostate biopsies and to guide needle placement to prevent under-grading and -staging.

3.2 Multiparametric Magnetic Resonance Imaging (mpMRI)

At present the main whole-gland imaging modality in PCa care is mpMRI. With mpMRI T1- and T2-weighted imaging is combined with dynamic contrast-enhancement (DCE) and diffusion-weighted imaging (DWI). Due to increasing use, research and technological advancements the ability to detect and rule out PCa with mpMRI has improved. The recommendations of the Prostate Imaging and Reporting and Data System (PI-RADS) steering committee aided in uniform execution and reading of mpMRI. The ability to detect significant PCa ranged from 44% to 87% in a systematic review, whereas the presence of existing significant PCa was ruled out in 63% to 98%. These heterogeneous outcomes may be the result from different trial designs (histological verification with biopsy versus prostatectomy) and mpMRI quality. Furthermore, verification with whole-mount prostatectomy specimen is complicated by the loss of the imaging orientation when compared with histology. This was solved when whole-mount sections were performed following the mpMRI planes by use of a three-dimensional customized molt that was printed for each individual patient. Recently, the multicenter PROMIS trial has been reported. This study compared the diagnostic accuracy of mpMRI with
transrectal biopsies in biopsy-naïve men with elevated PSA (<15 ng/mL), using TTMB as reference standard. MpMRI was found to be more sensitive (93%, 95%CI 88–96%) compared to transrectal biopsies (48%, 42–55%; p<0.0001) with a higher negative predictive value (NPV) to rule out existing significant PCa (NPV of 89% for mpMRI versus 74% for transrectal biopsies). MpMRI missed significant PCa (all Gleason 3+4=7 with 6-12 mm cancer core length) in only 17 men out of the 576 men that had a negative scan. Transrectal biopsies missed significant PCa in 119 men (13 men with Gleason 4+3=7, 99 men with Gleason 3+4=7 and 7 men with high-volume Gleason 3+3=6). These data suggest that mpMRI may improve PCa diagnostics and reduce the need for unnecessary prostate biopsies. However, as the systematic review by Futterer et al. highlighted, heterogeneous mpMRI results are published and still significant PCa is being missed. Before this imaging modality can be implemented as standard of care in terms of screening, high-quality mpMRI should be assured without unbearable financial burden for healthcare systems. The development of new MRI parameters may help to increase the diagnostic accuracy of mpMRI (e.g. luminal water imaging) and reduce the costs.

3.3 Other whole-gland imaging modalities

Several other whole-gland imaging modalities are currently under evaluation, aiming to improve PCa diagnosis and localization. Multiparametric ultrasound, which may include grey-scale ultrasound, contrast-enhanced ultrasound, shear wave elastography and doppler, has the potential to add extra parameters to mpMRI using MRI/TRUS fusion or could be proven superior to mpMRI as a stand-alone modality. However, the present EAU guidelines state that these new ultrasound modalities (e.g. elastography or contrast-enhanced ultrasound) are still investigational methods to diagnose PCa. Another recent development in prostate imaging is (68-gallium) prostate-specific membrane antigen (PSMA) Positron Emission Tomography - Computed Tomography (PET CT) scanning. With PSMA PET CT a specific membrane antigen is administered that can be visualized with PET CT scanning. This has proven to be very specific in detecting lymph node, high-risk and bone metastatic disease, but the detection of low-to intermediate-risk intraprostatic tumors has not yet been evaluated.

Conclusion on the biology and diagnosis of prostate cancer

The current risk group classification is unable to stratify patients for the need for treatment. New insights in the biology of PCa have formulated definitions of significant lesions that need treatment. The assumed monoclonal origin of metastatic disease, derived from high-volume and/or high-grade index lesions, may allow focal treatment but warrants long-term follow-up. Present PCa diagnostics under-grade and under-stage
patients and a considerable number of patients will undergo prostate biopsies that do not harbour PCa. MpMRI has been shown to increase the detection of significant PCa and also decreases the need for prostate biopsies. However, significant PCa is still being missed and heterogeneous outcomes have been published. New biopsy and imaging techniques are being developed to improve PCa diagnostics, as it is our obligation to optimize the foundation on which our treatment selection is based.

4. OUTCOMES OF CURRENT TREATMENT OPTIONS

Current curative treatments by guidelines for low- to intermediate-risk PCa are RP, EBRT (plus or minus androgen deprivation therapy) and brachytherapy, all proven to be effective and safe treatment options for localized PCa. The other ‘treatment option’ is active surveillance, postponing and selecting definitive treatment only for patients that are in need of curative treatment whilst preventing a significant proportion of patient from being (over)treated at all. The following paragraphs will summarize the outcomes and evidence behind these treatments for localized for low- to intermediate-risk PCa.

4.1 Active surveillance

Since the majority of PSA detected PCa remains biologically indolent, active surveillance with serial PSA testing and biopsies is an attractive option for low-risk or favourable intermediate-risk tumours and takes advantage of the slow-growing nature of PCa. By standardized PSA testing and follow-up prostate biopsies, the aim is to identify patients that are at risk for disease progression and who are candidates for treatment with curative intent, whilst sparing patients with insignificant PCa from being treated and experiencing side effects. Different protocol entry and follow-up criteria exist, all including serial PSA measurements and repeat biopsies at set time points following diagnosis.

A prospective cohort study (n=993) showed that in patients with low- to intermediate-risk PCa (84% Gleason ≤6 and 13% Gleason 3+4=7), active surveillance spared 55% of patients from radical treatment at 15 years whilst in only 5.7% prostate-specific mortality occurred. Patients were offered radical treatment for PSA doubling time of <3 years, Gleason score upgrading or unequivocal clinical progression. In another analysis it was shown that in 213 patients with intermediate-risk PCa (60% Gleason 7) the metastasis-free survival at 15 years was 94% for patients with Gleason 6 (PSA 10 to 20 ng/mL), 84% for Gleason 3+4=7 with PSA <20 ng/mL and 63% for Gleason 4+3 with PSA <20 ng/mL. Since patients on active surveillance did not receive treatment,
their functional outcomes are superior to either radiotherapy or RP, with lower rates of urinary incontinence, erectile dysfunction and bowel complaints. The most frequent complications are related to repeat biopsies and include prostatitis, bleeding and urinary retention. Overall health-related quality of life was similar for active surveillance and radical treatments.

Likewise, the recently published ProtecT trial showed no differences on the SF-12 mental summary score compared to surgery and EBRT, suggesting no extra anxiety or stress for patients on active surveillance. A major pitfall for active surveillance is the inherent under-staging and under-grading of current PCa diagnostics. A total of 197 patients diagnosed with low-grade PCa by 10 or 15 systematic TRUS-guided prostate biopsies were treated with RP. These patients were eligible for active surveillance (according to the EAU guidelines for PCa). Whole-mount pathology showed upgrading in 41.1% (40.1% Gleason sum score 7 and 1% Gleason sum score 8). Sub-analysis showed that the number of prostate biopsies taken did not influence under-grading. This is in line with the aforementioned trial with 44% upgrading Gleason sum score 7 or higher. It has been shown that mpMRI is able to increase the detection of significant PCa in patients on active surveillance, improving the risk stratification in this subset of patients. This underlines the EAU statement to perform mpMRI before repeat biopsies in active surveillance to reduce PCa under-staging or under-grading.

Active surveillance is able to spare about half of the patients from radical treatment, however, some patients actively choose to discontinue. Moreover, clinical progression or metastasis does occur, especially in the intermediate-risk group. Therefore, the PCa guidelines state that for intermediate-risk patients, and some low-risk patients that do not accept active surveillance, active treatment is warranted.

### 4.2 Radical prostatectomy

RP can be performed through open suprapubic, transperineal, laparoscopic or robot-assisted approach. At present none of these approaches has been shown superior in terms of oncological control. Among intra- and peri-operative complications of RP are: anastomotic leakage, damage to adjacent structures/organs, ileus, bleeding and infection. Extended lymph node dissection needs to be discussed in cases at risk of lymph node metastasis, e.g. >5% chance according to the Briganti nomogram.

As mentioned before, benefit on PCa-specific, overall- and metastasis-free survival was only demonstrated for intermediate-risk patients in the SPCG-4 study, whilst this was not shown in the low-risk group. At 10 years of follow-up neither the PIVOT (low- to high-risk) nor the ProtecT (low- to intermediate-risk) trial showed a significant impact on PCa-specific mortality compared to watchful waiting and active monitoring, respectively. In a prospective, non-comparative longitudinal trial, Mendhiratta et al. included 1864
men with low (55.5%)-, intermediate (35.3%)- and high (9.2%)-risk localized PCa treated with RP between 2000 and 2013 to investigate the effect of RP on PCa-specific mortality (mean follow up 9.1 years, range 9 months – 13.2 years). These authors found a relative risk for PCa-specific mortality at 10 years of 0.9% for low-risk and 1.0% for intermediate-risk PCa.

Erectile dysfunction, urinary toxicity and bowel dysfunction are common side effects following RP, all progressing over time. In a long-term follow up study following RP, urinary incontinence (no control or frequent leakage) was seen in 18.3% of all men at 15 years following their RP (n=1164) and urinary dripping was seen in 17.3%. The rates of erections insufficient for intercourse increased from 78.8% to 87% at 2 and 15 years post RP, respectively. Of all men, 21.9% reported rectal toxicity (bowel urgency, pain, frequent bowel movements) 15 years after RP. Understandably, these side effects have a detrimental impact on a patient’s quality of life. The functional outcomes following robot-assisted RP range from 54% to 90% in terms of preserved erectile function sufficient for intercourse at 12 months and urinary incontinence at 12 months (requiring ≥1 pads) occurred in 4% to 31% (mean 16%). In this single-surgeon analysis, who had performed >3.000 prior open RPs, it was shown that after a steep learning curve, superior functional and oncological results were achievable with robot-assisted procedures compared to open RP. However, the benefit of robot-assisted RP compared to open RP is still under debate and the (long-term) results of three randomized trials are awaited.

4.3 External Beam Radiation Therapy

EBRT is one of the treatment options for localized PCa and is performed nowadays by using Intensity-modulated radiotherapy (IMRT) alone or a combination with image-guided radiotherapy (IGRT). IMRT enables the distribution of radiation doses around complex and irregular target volumes. IGRT visualizes organ movement, aiming to improve tumour control and reduce treatment toxicity.

The 10-year outcomes of the ProtecT trial illustrated that for low- to intermediate-risk PCa comparable results were found for EBRT (n=545) compared to RP (n=553) or active monitoring (n=545) in terms of PCa-specific mortality (0.4 – 1.2%). No differences in the rates of metastases and disease progression were found between EBRT and surgery. Randomizing patients for radiation therapy with conventional dose (60-70Gy) versus dose escalation (range 74-80Gy), has shown a significant superiority in 5-year biochemical disease-free survival rates for the dose escalation cohort. From 1994 to 2001, 1979 patients with T1b-cT2b PCa and PSA ≤20 ng/mL were included (36% low-risk, 53% intermediate-risk and 11% high-risk) and randomly assigned to radiotherapy
plus short-term ADT (987 patients) or radiotherapy alone (992 patients) with a mean follow up of 9.1 years. The PCa-specific mortality was 8% in the radiotherapy alone group, while this was 4% in the radiotherapy plus short-term ADT group. The 10-year overall survival rate was more favourable in the radiotherapy plus short-term ADT group (62% vs. 57%). However, the reductions in overall- and disease-specific mortality were only significant in intermediate-risk patients.\textsuperscript{57} It has also been shown that in high-risk localized PCa long-term ADT is required for optimal disease control.\textsuperscript{58} Therefore the EAU guidelines state that the addition of ADT is recommended for patients with intermediate- and high-risk disease and not for patients with low-risk disease.\textsuperscript{5} Recently, the randomized CHHip trial demonstrated that hypo-fractionated IMRT (60 Gy, 20x 3 Gy, n=1074) was non-inferior to standard fractionated treatment (74 Gy, 37x 2 Gy, n=1065) in terms of recurrence-free survival and side-effects at 5 years.\textsuperscript{59}

Fatigue is the most commonly reported complaint following EBRT with a peak level at the end of treatment. Zelefsky et al. included 561 patients between 1996 and 2000 with localized PCa (36% low-risk, 46% intermediate-risk and 18% high-risk) who were receiving IMRT with a dose of 81 Gy (mean follow-up 7 years, range 5-9 years) and 53% of patients received neoadjuvant short-term ADT. The National Cancer Institute Common Terminology Criteria for Adverse Events toxicity scale was used to score late toxicity. The 8-year actuarial likelihood of late grade \geq 2 urinary toxicities was 15% and for rectal toxicities this was 1.6%. Erectile dysfunction developed in 49% of the men that had erections sufficient for intercourse before IMRT (72%)\textsuperscript{60}, although others have reported rates up to 60.8% 2 years following EBRT.\textsuperscript{3} Another series by the same authors on the incidence of late rectal and urinary toxicities following conformal radiation therapy and IMRT for localized PCa found that the occurrence of acute symptoms was a significant risk factor for experiencing late toxicity. Late rectal and urinary toxicity was seen in 42% of the patients with previous acute symptoms (10-year incidence) versus 9% in patients without previous acute symptoms\textsuperscript{61}. The prospective longitudinal study of Sanda et al. showed that EBRT significantly affects health-related quality of life. From 2003 to 2006 they included 202 patients receiving EBRT alone and 90 patients receiving a combination of EBRT and ADT. At 1 year following EBRT, 11% of patients had moderate or severe distress due to urinary toxicity whereas for rectal toxicity this percentage was 9%\textsuperscript{2}. Furthermore, ADT is associated with negative effects on multiple quality of life domains.\textsuperscript{2} The patient-reported quality of life outcomes from the ProtecT trial suggested that EBRT was superior to RP in preserving urinary continence and erectile function. More bowel complaints were documented for EBRT compared to RP or active surveillance.\textsuperscript{42} However, at present it is unknown whether these results will be the same with current new technologies (e.g. robot-assisted RP, image-guided EBRT).
4.4 Brachytherapy

In brachytherapy radioactive sources are implanted into the prostate using a transperineal approach and ultrasound guidance. Brachytherapy can be divided in low dose rate (LDR) and high dose rate (HDR) brachytherapy. With LDR radioactive seeds are permanently placed in the prostate (e.g. 125-Iodine or 103-Palladium), whereas with HDR cannulas are placed in the prostate through which a high energy radioactive source (e.g. 192-Iridium or 60-Cobalt) is temporary implanted. This allows real-time adaptation and dosimetry. Patients with low- and favourable intermediate-risk localized PCa are most qualified for LDR monotherapy. In patients with intermediate- or high-risk localized PCa HDR brachytherapy is preferred.46

There are no randomized controlled trials available comparing brachytherapy as monotherapy for localized PCa with other treatment options. Taira et al. included 1656 men with low- (34.7%), intermediate- (36.7%), and high- (28.6%) risk localized PCa who underwent LDR brachytherapy monotherapy, combined brachytherapy with ADT (37.6%) or EBRT (49.8%) from 1995 to 2006. Mean follow-up was 7 years. Cause-specific survival (CSS) at 12 years was 99.8% for low-risk, 99.3% for intermediate-risk and 95.2% for high-risk PCa. Tumour grade appeared to be the strongest predictor of CSS.62 Two smaller trials combining HDR brachytherapy with EBRT for the treatment of localized PCa found a CSS of 98% (n=309, 67 patients low-risk, 109 intermediate-risk, 133 high-risk) after a mean follow up of 5 years63 and a CSS of 97% (209 patients, 33.5% low-risk, 44% intermediate-risk and 22.5% high-risk) after a mean follow up of 7.25 years64, however, follow-up in both trials was short. A systematic review on HDR brachytherapy as monotherapy for localized PCa demonstrated good biochemical control for both low-(66 – 100%) and intermediate-risk (63 – 98%) PCa with low grade 3 genito-urinary (0 – 16%) and gastrointestinal (0 – 2%) toxicity.65 However, the inclusion criteria, treatment protocols and the duration of follow-up differed enormously, which complicated the meta-analysis.65

Kittel et al. included 1989 men with low-risk (61.3%), favourable intermediate-risk (29.8%), unfavourable intermediate-risk (4.5%) and high-risk (4.4%) PCa treated with LDR brachytherapy as monotherapy between 1996 and 2007 with a mean follow-up of 6.8 years. Severe late genitourinary toxicities were present in 7.6% of patients, while gastrointestinal toxicities were present in 0.8%.66 Sanda et al. performed a prospective multicenter analysis of 1201 localized PCa survivors, included between 2003 and 2006 (median follow-up 30 months).2 A total of 306 patients were treated with LDR brachytherapy, of whom 59% had low-risk, 39% intermediate-risk and 1% high-risk localized PCa. Rates of poor sexual function were 47% at 2 months and remained high at 2 years (46%). Thirty percent of patients reported sexual functioning as a moderate
to big problem. Urinary toxicity caused moderate to worse distress in 18% of patients at 1 year following LDR brachytherapy. Moderate to worse distress rates for rectal toxicity were 9% at 1 year following treatment.\textsuperscript{2} Functional outcomes following LDR and HDR brachytherapy have been shown to be comparable.\textsuperscript{67} A small trial randomized 200 patients to either LDR brachytherapy or RP.\textsuperscript{68} Brachytherapy patients reported significantly less urinary complaints or erectile dysfunction compared to RP at 6 months and 1 year follow-up, but at 5 years there were no differences in functional outcome. Biochemical control was similar for LDR brachytherapy (91.7%) and RP (91.0%) at 5 years.\textsuperscript{68}

**Conclusion on the established prostate cancer treatments**

Using active surveillance protocols in low-risk patients it is feasible to spare 55% of the patients from radical treatment and treatment-related side-effects.\textsuperscript{38} However, a considerable amount of patients are undertreated due to the inherent errors in current PCa diagnostics. The use of new biopsy techniques, mpMRI or biomarkers may be required to identify this subset of patients. Surgical treatment of intermediate-risk PCa has been shown to reduce PCa-specific mortality at 18 years follow-up. For low-risk disease and medium-term follow-up the oncological benefits are marginal whilst exposing patients to significant morbidity. Better patient selection and advancements in surgical techniques may improve the equilibrium of oncological benefit versus patient morbidity. EBRT is an established treatment option for men with PCa. Future research must focus on the reduction of treatment-related morbidity and on stratifying for the need of ADT within the intermediate-risk group. The results of brachytherapy are promising, nonetheless side-effects are reported and comparative oncological data is warranted.\textsuperscript{2} Comparative trials need to be initiated on patient-morbidity and oncological control following hypofractionated image-guided RT versus high-quality (robot-assisted) RP versus brachytherapy for intermediate- to high-risk PCa. However, as mentioned earlier, radical treatment is associated with a high incidence of side effects that have a detrimental impact on the quality of life of PCa patients.\textsuperscript{2,3} This sparked the interest to develop new PCa treatments.

**5. INTRODUCTION OF FOCAL THERAPY**

In response to this whole-gland approach, focal therapy (FT) as alternative minimal invasive treatment has been developed with the aim to reduce patient-morbidity while achieving oncological control. With FT individual cancer areas are targeted while sparing important functional and anatomical urological structures (e.g. neurovascular bundle, urinary sphincter and rectal wall). FT can be performed on either a targeted
or segmental basis (quadrant, hemi- or hockey-stick ablation). International consensus statements on patient criteria and trial design defined the following eligibility criteria for FT: patients with low- or intermediate-risk (Gleason ≤4+3), unifocal (i.e. dominant index lesion), organ-confined (≤cT2b) PCa with a life expectancy of 10 years or longer.69 One important aspect of patient selection and treatment planning is preoperative determination of the topography of PCa foci. It is recommended that mpMRI should be combined with systematic prostate biopsies (either transrectal or transperineal) for patient selection.69 Tran et al. showed that the combination of TTMB with mpMRI is able to accurately detect locations within the prostate containing significant (low-to intermediate-risk) PCa.70 This highlights that it is feasible to identify the majority of significant PCa lesions, but as lesions are still missed, further improvement of significant PCa diagnosis and localization is of utmost importance to advance the field of focal therapy.70

Techniques used for focal therapy in PCa include cryoablation, radiofrequency ablation (RFA), laser ablation, photodynamic therapy (PDT), high intensity focused ultrasound (HIFU), microwave ablation (MWA), interstitial laser thermotherapy and irreversible electroporation (IRE).71 The actual procedure is different for the respective ablative modalities, which have been described in detail and standardized elsewhere.72–75 Total procedure time generally lasts about 1 hour and is usually performed during a 1-2 day admittance.

In a systematic review on focal therapy (n=2350) in localized PCa it has been shown that FT is a safe treatment option, with the most frequent reported complications being urinary retention (0-17%), urethral stricture (0-5%) and urinary tract infection (0-17%). Functional outcomes were promising, with pad-free continence rates of 95-100%, leak-free continence of 83-100%, preserved erectile function (sufficient for penetration) in 54-100% and almost no bowel symptoms (0-1%).71 In a combined analysis of three prospective trials (n=118) on FT with HIFU for localized PCa (cT1c-T2, low- to intermediate-risk PCa) erectile function was assessed by the International Index of Erectile Function (IIEF-5) score. Although a significant decrease in erectile function was seen at 1 and 3 months following FT, this improved at 6, 9 and 12 months following FT, so no significant changes in individual sexual domain scores were found compared to baseline.76 The overall quality of life following FT showed no significant difference at 12 months when compared to baseline.77

No long term data exists on PCa-specific survival despite one trial treating low- to high-risk PCa with cryoablation, indicating 87% PCa-specific survival after 10 years.78 In the aforementioned systematic review, standardized follow-up biopsies were performed in
9 series and showed an absence of clinically significant PCa in 83-100% and of any PCa in 50-96% of patients. The COLD registry (1997 to 2007) included 1160 patients that were treated with partial cryoablation. Prostate biopsies were performed in case of clinical suspicion and in 43/164 (26.3%) patients recurrent or residual disease was found, but this only comprised a small portion (43/1160, 3.7%) of focally treated patients.

Follow-up usually consists of serial PSA testing and prostate biopsies. PSA following FT remains detectable and it is recommended to perform PSA testing every 3 months for the first year, biannual for the second year and thereafter annually. Although some studies report biochemical recurrence by use of the Stuttgart (nadir PSA + 1.2 ng/mL) or Phoenix (nadir PSA + 2.0 ng/mL) criteria, it must be stressed that this has not yet been validated following FT and insufficient data is available on PSA velocity of untreated prostatic tissue and the risk of residual/recurrent PCa. MpMRI is usually performed 6 months following FT and thereafter annually up to 5 years. Normally residual or recurrent disease will appear as an enhanced lesion within or adjacent to the ablation zone. However, it may be difficult to distinguish post-FT effects on mpMRI with recurrent lesions and likewise non-enhanced recurrent lesions may be missed as well. Since the diagnostic accuracy of mpMRI in the follow-up of FT has not yet been evaluated and validated, follow-up biopsies are required and ideally performed at least once at 6 months or 1 year following the procedure.

6. INTRODUCTION OF IRREVERSIBLE ELECTROPORATION

In this thesis all FT projects were performed with IRE. The following sections will therefore summarize the technique, and both the preclinical and clinical data that are available on this ablative technique for localized PCa.

6.1 Preclinical data

IRE is a new technique based on a process known as electroporation or electropermeabilisation, induced by generating micro- to milliseconds-long, high-voltage electrical pulses between two or more electrodes. The pulsating current affects membrane repolarization and creates ‘nanopores’ (i.e. nanoscale disruptions of the cell membrane allowing molecules to pass into targeted cells). This electroporation process can be temporarily (reversible electroporation) or become definite (irreversible electroporation) depending on pulse frequency and duration, the intensity of the electric field and type of targeted tissue. The enhanced permeabilization with reversible electroporation is elegantly used with gene insertion therapy or during electrochemotherapy, effectuating higher intracellular concentrations of
chemotherapeutic agents and thereby increasing cytotoxicity.\textsuperscript{89,90} Initially, the effect of IRE, leading to loss of cellular homeostasis and consequent cell death in targeted tissue, was considered an unwanted side effect in electrochemotherapy. Nowadays, IRE is available as an ablative therapy modality in the form of the commercially developed Nanoknife\textsuperscript{TM} System (Angiodynamics Inc., Queensbury, New York).\textsuperscript{91} IRE safety and efficacy has been shown in several \textit{in vitro}, animal and human studies involving focal therapy in pancreas, liver, kidney, lung and prostate.\textsuperscript{92}

Based on the principle of electroporation, IRE holds the potential to preserve connective tissue structures and limit damage to adjacent tissue and vital structures (e.g. neurovascular bundle, blood vessels).\textsuperscript{93–95} Tsivian et al. evaluated erectile function, side effects and the preservation of surrounding tissues in a Beagle dog model following bilateral prostate ablation using IRE with a low-energy direct current ablation system. All dogs ($n=12$) were able to accomplish erections, major arteries and veins maintained patency and surrounding tissues showed no damage on histopathological analysis.\textsuperscript{93} Six other Beagle dogs underwent IRE ablation of the prostate and histopathology showed no destruction or luminal thrombosis of affected blood vessels and 2 weeks following treatment the ablated zone consisted primarily of collagenous tissue. The neurovascular bundle also appeared to be unaffected.\textsuperscript{95} It could be reasoned that ablative modalities such as RFA or cryoablation, which solely depend on their non-selective destructive thermal effect, have a more detrimental effect on the surrounding tissue. Indeed perineal tissue sloughing (3%) and erectile dysfunction (80%) are frequent side-effects in patients receiving third-generation cryoablative procedures, indicating damage to the adjacent skin or neurovascular bundle.\textsuperscript{46} Of critical note, the cumulative thermal effect of consecutive electrical pulses in several clinical IRE focal therapy protocols has been calculated and measured, and is thought to be significant which may question the non-thermal aspects of IRE ablation.\textsuperscript{96–99} Mitigation of the occurring Joule heating could be effectuated with conservative protocols using shorter and low-frequent electrical pulses or perioperative cooling as counter-measure.\textsuperscript{97}

Furthermore, thermal ablative modalities have the limitation of heat sink (i.e. loss of thermal intensity and ablation effect) when applied in proximity to major blood vessels, urethra and bile ducts.\textsuperscript{88,91} This ‘heat sink’ effect is defined as the difficulty to control the extension and therapeutic effectiveness of the ablation zone due to the effect of the blood circulation on local temperature development. Consequently, post-ablation histopathology analysis in thermal ablative modalities showed a transition zone between ablated vs. non-ablated tissue due to partially damaged tissue by insufficient temperatures.\textsuperscript{95} The targeted tissue within the electrical field of IRE showed a distinctive sharp demarcation from unaffected prostatic tissue, possibly enabling more precise
procedure planning of the target area (Figure 1). This distinctive sharp demarcation can be assessed and evaluated in humans with mpMRI and/or CEUS. A recent study showed that three-dimensional ablation volume calculations with either mpMRI or CEUS were closely correlated with whole-mount pathology when subsequent radical prostatectomy was performed.

The IRE console comprises two important components, monopolar needle electrodes (maximum of 6) and a low-energy direct current generator controlled by computer-based therapy planning (Figure 2).
The Nanoknife™ system and needle electrodes are approved and cleared for marketing by both the American Food and Drug Administration (FDA) and European regulating authorities (EMA). It carries the CE marking and is indicated for soft tissue ablation. IRE is performed under general anaesthesia because deep muscle relaxation (using rocuronium) is necessary to avoid severe uncontrolled muscle contractions. IRE electrical pulses can be administered synchronized to the cardiac rhythm in order to prevent potential cardiac arrhythmias, this is mainly relevant when tissue is ablated in proximity to the heart. A brachytherapy grid and transrectal ultrasound is used to position and guide the IRE needles in a similar fashion as with the preoperative transperineal biopsy procedure (Figure 3). Guided by ultrasound imaging, 3 or more parallel electrodes are placed in the predefined target area(s) (based on mpMRI and biopsy results), covered by retractable access sheets for adaptation of the operating length of the electrode. After the electrodes are in place, IRE parameters (e.g. pulse frequency and duration, voltage, amount and length of electrodes) are entered into the Planning Software of the Nanoknife™ system that produces a digital image of the estimated ablation zone for the specified IRE parameters (Figure 2). Ablation time varies from 3 to 5 minutes whereas the total procedure time is approximately 1 hour. Mean time of hospital discharge following focal therapy with IRE is 1 day postoperatively, whilst the indwelling catheter can be removed within 2-5 days.

Figure 3. Left plane; IRE electrode placement through a transperineal brachygrid. Right plane; the transperineal brachygrid projected on the digital screen of the ultrasound machine to guide electrode placement.
6.2 Clinical data

The first phase I-II trials in humans have shown the safety of IRE for focal ablative therapy of PCa and showed promising results on functional preservation and ablative effectiveness. The group of Neal et al. performed ablations on 2 patients with IRE before their scheduled prostatectomy at 3 or 4 weeks post-IRE procedure, respectively. Both patients had organ-confined PCa (T1c and cT2a), low- and intermediate-grade (Gleason score 6 and 7) and initial PSA levels of 5.4 and 4.3 ng/mL, respectively. The IRE procedures consisted of 90 pulses in total of 70 µsec using 4 electrodes (2 in each prostate lobe). No complications occurred during the procedures. Both patients received a transurethral catheter for 10 days, experienced mild haematuria and recovered without any serious adverse event. There were no vital PCa cells within the IRE ablation zone on histopathological analysis of the prostatectomy specimen. Regional tissue necrosis surrounded the electrodes and inflammatory infiltration was seen with adjacent reactive stromal fibrosis and regenerative changes in the epithelial lining of prostatic ducts. Total ablation volumes were 1.14 and 2.46 cm³, respectively.

The first larger series (n=16) was published in a book chapter by Onik et al, these authors treated 16 patients ranging in age from 40-78 years with organ-confined, low- to high-risk (Gleason 6 to 8) PCa and initial PSA of 3.0 to 7.0 ng/mL. Four electrodes were placed and 90 pulses of 70-100 µsec in length were delivered at 1500 Volts. The resulting electrical field was not mentioned. All patients were reported to be continent immediately after the procedure and remained so at 6 months follow-up. TTMB was performed 3 weeks following IRE and showed no evidence of remaining tumour or viable glandular tissue within the ablated zone (n=15). In 1 patient a small low-grade PCa focus (Gleason score 6) was found outside the ablated zone.

Valerio et al. assessed the safety and clinical feasibility of IRE in 34 patients with a mean age of 65 (SD=6), mean initial PSA of 6.1 ng/mL (IQR 4.3-7.7) and low-, intermediate- or high-risk PCa (n=9, n=24 and n=1, respectively). IRE procedures consisted of 90 pulses of 70 µsec, with 2-6 electrodes depending on lesion size, interelectrode distance of ≤2cm, maximum exposure length of 2 cm, an electrical current range of 20-40 Ampere and a safety margin of 3-5 mm, however, no electric potentials were mentioned. Post-IRE, patients received either a transurethral or suprapubic catheter for 3 to 5 days. No serious adverse events occurred; only mild haematuria (n=5), dysuria (n=6), unsuccessful withdrawal of catheter (n=2) and uncomplicated urinary tract infections (n=5). All patients (24/24) continent at baseline remained so at 6 months follow-up. Potency was preserved in 95% (19/20) of men who were potent prior to the IRE procedure. The mean ablation volume was estimated to be 12 mL (IQR 5.6 – 14.5 mL) on mpMRI. Six patients...
showed residual disease on mpMRI, 2 of which chose active surveillance, 3 patients underwent salvage therapy with HIFU or IRE and 1 patient opted for RP (final pathology showed residual pT2c Gleason score 3+4=7 PCa).\textsuperscript{104}

In another phase I/II trial conducted by Van den Bos et al., 16 patients with a mean age of 60 years (range 44-75), mean initial PSA 9 ng/mL (range 3.6-25) and low- to high-risk (Gleason score 6-8) PCa underwent IRE 4 weeks prior to RP.\textsuperscript{100} The aim of this study was to evaluate the ablative effect of IRE using different treatment protocols. IRE was performed with 3- and ≥4-electrode configurations, active tip length of 1.5 cm, 90 pulses of 90 µsec of pulse intensity, set at 1200-2100 Volt resulting in a current of 15-45 Ampere. Only mild adverse events occurred during short-term follow-up and all resolved within one month following the procedure. Electrode configuration and histopathology correlated with the ablation zone, exceeding the electrode configuration by 2.7 times, probably due to extended electric field generated by multiple electrodes.\textsuperscript{100,107} Microscopic analysis showed fibrosis without glandular ducts and necrotic tissue with sharp demarcation of unaffected prostatic glandular tissue.\textsuperscript{108} No skip lesions were observed within the ablation zone and histopathological assessment showed no differences between tissue close or at a distance from the inserted electrodes. IRE affected the prostate capsule in 12/16 patients, extended in the neurovascular bundle in 13/16 patients and the prostatic urethra in 9/16 patients, whether this would have resulted in long-term impaired functional outcomes remains unknown.\textsuperscript{100}

Ting et al. performed FT with IRE in 32 patients, average age of 67 years (range 60-71 years), with low- to intermediate-risk (Gleason score 6 and 7) organ-confined (T1c to cT2a) PCa and a mean PSA of 6 ng/mL (range 4.3 to 8.6 ng/mL). All patients were treated with IRE using 3 to 6 electrodes, interelectrode range of 1-2 cm and active electrode length of ≤2 cm depending on tumour volume. Ninety pulses of 70 µsec were delivered resulting in an ablative current of 20 to 40 Ampere, no voltages were mentioned. Only 25 patients were included for analysis after the exclusion of patients that had a previous PCa treatment (n=5), Gleason score of 8 or higher (n=1) or no visible lesion on mpMRI (n=1). Eighteen patients completed questionnaires and 100% was pad-free continent and 56% had erections sufficient for penetration at 6 months following IRE. All 21 patients that received TTMB were histologically free of PCa within the ablated zone, whereas 16/21 patients had no significant disease outside the ablation zone. Four patients had residual tumour adjacent to the ablation zone. Of the 5 remaining patients that had significant disease, 3 remained on active surveillance, 1 awaited salvage IRE and 1 decided for active treatment with robot-assisted RP.\textsuperscript{105}
Murray et al. performed focal IRE in 25 patients with low- to intermediate-risk PCa. No high-grade adverse events occurred, except two grade 3 complications (epididymitis and urinary tract infection). Follow-up biopsy at 6 months demonstrated residual PCa within the ablated zone in 4 men (16%). At 12 months one patient reported erectile function insufficient for intercourse, while another 2 patients required pads for urinary incontinence.\textsuperscript{106}

The last published trial on focal IRE for localized PCa was performed by Valerio et al.\textsuperscript{75} In this study patients with mpMRI-visible disease were treated with IRE that was located in the anterior part of the prostate. A total of 19 men were included for final analysis, median PSA was 7.75 ng/mL (IQR 5.5-10.03) and median age was 60 years. At 12 months all patients remained pad-free continent and one patient reported treatment-induced erectile dysfunction. Follow-up biopsies showed significant residual disease in 6 of the 18 patients (33%). The high number of cases with residual disease may be explained by the lesion volume underestimation by mpMRI and because anterior tumours often have large lesion volumes.\textsuperscript{109} Therefore, the needle configuration might not have encircled the entire lesion.

**Conclusion on focal therapy and irreversible electroporation**

The initial phase 1-2 trials on focal therapy for localized PCa illustrated the safety and feasibility of this new treatment paradigm. Promising rates of preserved urinary continence and erectile function were found, however, long-term quality of life and oncological outcomes are awaited. With multiple ablative modalities available, comparative trials are required evaluating modalities on quality of life and oncological control. Furthermore, the use of the mpMRI in the follow-up needs to be validated on the ability to detect of residual PCa following focal therapy. IRE is a new and distinct ablative modality, however, clinical experience is limited and treatment protocols need to be optimized.

**SPECIFIC AIMS OF THIS THESIS**

**What is lacking?**

Due to the recent advancements with mpMRI the role of systematic prostate biopsies is challenged. Before trials omit standardized prostate biopsies for patient selection or treatment follow-up, clear consensus needs to be attained on the validity of such design. Especially, since it has been shown that mpMRI still misses significant PCa.\textsuperscript{22} Although it has been shown that the addition of TTMB can improve PCa detection and localization, not all significant lesions are detected.\textsuperscript{22,70} This may consequently impair the outcomes
following focal therapy and thereby cause a potential risk for the patient (e.g. salvage treatment with added morbidity). Although the follow-up mpMRI following focal therapy is recommended by the consensus guidelines,69 no whole-gland evaluation is published on the diagnostic accuracy to detect residual significant PCa following focal therapy.

The study by Van den Bos et al. showed that the ablation size volume following focal IRE extended the needle configuration by 2.5 to 2.9 times the surface area between the electrodes.100 At present it is neither possible to predict the ablation size volume during treatment, nor is it possible to compare the ablation size volume on follow-up imaging with the treatment planning for therapy feedback.

The first phase 1-2 trials with focal IRE showed promising results in terms of preserved urinary and sexual function, while follow-up biopsies demonstrated good short-term oncological control. However, small patient numbers, the retrospective study designs and lack of standardized follow-up, including sometimes the absence of prostate biopsies, compromise the results of these first trials. A large series with follow-up biopsies on focal IRE for localized PCa is awaited in order to evaluate the ability to obtain oncological control, preserve functional outcomes, and to identify potential risk factors for oncological and functional failure. Moreover, the feasibility of focal IRE for localized radio-recurrent PCa has not yet been evaluated. The first IRE outcomes look promising, however, little is known about the performance of IRE treatment in different segments of the prostate. Likewise, no comparative studies are available comparing IRE to the current accepted PCa treatments.

**Specific aims of this thesis:**

- To advance the field of focal therapy by improving patient selection and disease localization
- To improve focal irreversible electroporation treatment planning, feedback and follow-up
- To evaluate outcomes following primary focal IRE and identify risk factors for impaired outcomes
- To assess the safety, feasibility and outcomes following salvage IRE for localized radio-recurrent PCa
- To position focal IRE towards other ablative modalities and PCa treatments
- To initiate the future steps required to establish this new treatment paradigm in the clinic
Chapter 1

OUTLINE OF THESIS

An international collaborative consensus project was initiated among experts in the field of focal therapy and PCa care to discuss the current use of mpMRI in clinical practice and focal therapy. In Chapter 2 the results of the Delphi process and final meeting are summarized including consensus statements on the use of mpMRI throughout the focal therapy protocol.

Follow-up mpMRI was performed in patients that underwent focal IRE for localized PCa. The diagnostic accuracy of mpMRI to detect residual significant PCa was evaluated using follow-up TTMB. Chapter 3 summarizes the outcomes of this first whole-gland mpMRI evaluation following focal therapy.

In Chapter 4 mpMRI, grey-scale ultrasound and CEUS were performed in the follow-up following IRE. Imaging results were summarized to aid clinicians with an understanding on IRE-specific changes on imaging. Furthermore, the ablation size volumes on mpMRI and CEUS were reconstructed and compared with the intended volume to be ablated to provide treatment feedback with imaging.

In Chapter 5 the world’s largest published series on primary focal IRE for localized PCa was evaluated on oncological and functional outcomes. Patient inclusion followed the consensus guidelines on patient criteria and selection methods. In case of oncological failure (i.e. residual PCa within the treated area) potential risk factors were identified.

It has been suggested that some ablative modalities have unique characteristics that may result in better results depending on the area of the prostate treated. In Chapter 6 the genito-urinary function and quality of life results were evaluated per segment of the prostate treated. In case of functional failure (i.e. urinary incontinence or erectile dysfunction) risk factors were identified.

Although salvage focal therapy has been evaluated with other ablative modalities, no results are available on focal IRE for radio-recurrent PCa. Chapter 7 evaluated the safety and feasibility of focal IRE for patients with localized radio-recurrent PCa.

At present, no comparative trials exist on focal therapy versus an accepted treatment according to the guidelines. In Chapter 8 primary focal IRE treatment was compared with robot-assisted RP using propensity score pair-matching. Patients were evaluated on genito-urinary function and quality of life using an identical follow-up scheme with validated questionnaires.
In **Chapter 9** the protocol is published of the multi-centre prospective randomized trial, evaluating 200 patients with localized low- to intermediate-risk PCa that will be treated with either a focal or extended IRE ablation protocol. This prospective cohort will provide new insights in the short- and long-term oncological and quality of life outcomes of focal versus extended IRE.

Finally, in **Chapter 10** the concluding remarks of this thesis are summarized. Future studies are initiated to improve patient selection and to advance this new treatment paradigm in both the primary and salvage setting. Finally, the position of focal therapy to the PCa guidelines is discussed.
REFERENCES


Chapter 1


General introduction & aims of thesis


Chapter 1


