UvA-DARE (Digital Academic Repository)

Focal therapy
Scheltema, M.J.V.

Link to publication

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)

Download date: 15 Dec 2018
This chapter will discuss the concluding remarks of this thesis, the future perspective of IRE and concludes by positioning focal therapy to the prostate cancer treatment guidelines.

This chapter is based on the following peer-reviewed publications:


**Scheltema MJ, van den Bos W, Wagstaff PG, Postema AW, de Bruin DM, Laguna Pes MP, de la Rosette JJ**


**Scheltema MJ, Hentschel AE, de la Rosette JJ**
DISCUSSION

Concluding remarks and future perspectives

One of the aims of this thesis was to advance the field of focal therapy by improving patient selection and disease detection/localization. An international consensus project was initiated to discuss the current role and position of mpMRI throughout the focal therapy protocol. One of the most important statements was that the quality of mpMRI must be assured to perform focal therapy and before any decision can be taken to dismiss (follow-up) prostate biopsies. So far, heterogeneous outcomes have been reported on the ability to detect prostate cancer with mpMRI, highlighting that standardized reporting, training and protocol performance are necessary before implementing this imaging modality as standard of care.\(^1\) The performance of the entire MRI protocol, including patient preparation and fine-tuning of spine and pelvis phased array coiling is complex and requires expertise. For mpMRI interpretation and lesion targeting it is of paramount importance that continuous imaging and histology feedback is established between radiologists and urologists. The PROMIS trial showed the potential of mpMRI; - to reduce unnecessary biopsies in patients suspected for prostate cancer; - increasing the detection of significant prostate cancer; - reduction of over- and under-treatment.\(^2\) Therefore, it is our duty as clinicians to establish centres of expertise that assure high-quality mpMRI and lesion targeting. Moreover, future studies are initiated to compare the diagnostic accuracy of mpMRI (T2-MRI, diffusion-weighted imaging and T1-dynamic contrast-enhanced imaging) with biparametric MRI (T2-MRI and diffusion-weighted imaging). Biparametric MRI potentially leads to a drastic reduction in costs and time (~10 min. versus 45 min. with mpMRI), enabling the implementation of the prostate MRI for biopsy-naïve or diagnosed patients on a national scale. Also, the addition of 68-Gallium Prostate-Specific Membrane Antigen (PSMA) PET CT to mpMRI was found to increase the diagnostic accuracy of mpMRI remarkably for the detection of intraprostatic Gleason 7 tumours, whilst a low diagnostic accuracy was found in the detection of intraprostatic Gleason 6 tumours (submitted to BJUI, Chang JI, Stricker PD, Scheltema MJ et al). It is known that mpMRI can accurately detect high-grade and high-volume lesions, while most of the missed tumours are low-volume and usually intermediate-grade (Gleason 3+4).\(^2\) Therefore, the addition of PSMA PET CT may be promising and warrants evaluation for prostate cancer diagnosis in biopsy-naïve men or for the detection of upgrading in active surveillance patients. Although PSMA PET CT scanning leads to radiation exposure to patients, only low-dose CT scanning is required for intraprostatic imaging. Moreover, since focal therapy is used in intermediate-risk patients, the additional benefit of PSMA PET CT is the exclusion of M+/N+ disease.
Furthermore, new advancements in CT technologies (e.g. digitization) will reduce the spatial resolution to 2 mm collimated slides, which will improve the diagnostic accuracy of PSMA PET CT even more.

The future in prostate cancer care may be optical diagnosis or liquid-biopsies, but it is important to stress that most evidence for treatment outcomes are significantly associated with and stratified by histopathological grading scores.\(^3\) For focal therapy in prostate cancer it will be crucial to establish and guarantee high-quality radiological imaging, as focal treatment is only feasible when significant prostate cancer can be localized whilst ruling out multi-focal significant disease.

At present, it is not possible to predict the extent of the treatment zone before or during IRE. The first steps towards a predictive model for primary irreversible electroporation (IRE) in the prostate were taken by comparing whole-mount pathology with the simulated electrical field strength and distribution (to be published, not included in this thesis). The minimal threshold to ablate prostate tissue was determined, which may be used for future treatment planning and dosimetry models. Although the initial phase 1-2 trials on focal IRE for the treatment of localized prostate cancer showed promising results, none of these trials were able to plan the extent of the treatment zone. Adequate treatment planning and dosimetry models must be developed to improve the outcomes of IRE, as some patients still develop erectile dysfunction or recurrent disease following treatment. Most focal procedures are performed using ultrasound guidance, real-time imaging with multiparametric ultrasound (e.g. three-dimensional contrast-enhanced ultrasound) may provide perioperative feedback on the ablation zone volume. In the absence of such pre-treatment or perioperative models, follow-up imaging (e.g. mpMRI or contrast-enhanced ultrasound) is the only feedback on the treatment planning. Follow-up mpMRI seemed able to detect most high-grade and high-volume residual prostate cancer with negative predictive values of 90% for significant PCa. These findings need to be confirmed in a large enough dataset due to the low incidence of residual prostate cancer and since the sensitivity and positive predictive value were poor. Potentially, the addition of PSMA PET CT scanning in this follow-up setting could increase the diagnostic accuracy of detecting residual disease, as most of these lesions will most likely be low-volume and/or intermediate-grade (Gleason 3+4) prostate cancer.

Primary IRE is able to obtain good oncological control within the ablated zone whilst preserving genito-urinary function and quality of life. Important findings were the increased risk for infield oncological failure when a narrow safety margin was applied or when a system failure occurred. Studies have shown that mpMRI underestimates
the volume of tumour lesions non-linearly, and it has been suggested that a 9 mm safety margin should be respected.\(^4\) In line with this, early evidence suggests that tumour lesions express an epigenetic halo surrounding that lesion, which is already being used in commercially available tests.\(^5\) At present it is unknown whether focal treatments should target that (epigenetic) halo (segmental ablation) or that it could be left untreated (focal ablation). Until these data become available, it is important to respect this safety margin and halo, since any residual disease will have a detrimental impact on the acceptance of this new treatment paradigm. The first randomized trial for IRE is currently enrolling (NCT01835977), randomizing patients between two treatment protocols (focal versus extended ablation). This study should provide new insights in the required size of the ablation zone and the subsequent effect on the oncological control and quality of life. Our results showed that tumour lesion detection and localization need to be optimized in order to improve the oncological outcomes, since most failures occurred in the outfield. Studies are initiated that evaluate the addition of new imaging modalities to mpMRI (PSMA PET CT) or biomarkers to prostate biopsies, both aiming to improve patient selection. The first data on salvage IRE for localized radio-recurrent PCa showed the safety and feasibility of this technique with acceptable morbidity, no high-grade adverse events and promising intraprostatic oncological control. However, these preliminary data also showed the difficulty to rule out metastatic disease at baseline. Based on these results an international prospective multicenter trial has been initiated to evaluate the performance of IRE in the salvage setting for localized radio-recurrent PCa (ACTRN12617000806369).

Despite the focal nature of the procedure, erectile dysfunction occurred following treatment. Older patients and those with poor baseline functioning were at increased risk to develop erectile dysfunction following IRE. It is known that with the current treatment protocols significant Joule-heating is generated, which may be the cause for IRE-induced erectile dysfunction.\(^6\) Preclinical studies are being conducted with the aim to (actively) reduce Joule-heating, while maintaining the ablative effectiveness of IRE. Only then the tissue-selectiveness of IRE may result in superior outcomes compared to thermal ablations.\(^7\) Our early results suggest that IRE can be performed in all prostate segments, but future comparative studies with other ablative modalities are required to establish the position of IRE in the spectrum of ablative energies. Especially, since it is very difficult to compare the outcomes of the available phase 1-2 trials since heterogeneous results are published as a result of different patient selection methods, imaging quality and follow-up protocols. The consensus statements on selection methods, patient criteria and follow-up should be adhered to in clinical trials to ensure translatability of the outcomes.\(^8,9\) The systematic review by Valerio et al. showed comparable results among the available ablative modalities in terms of functional preservation and oncological
control, however, it is not possible to make any firm conclusions or recommendations based on these data as it included different trial designs and patient characteristics.\textsuperscript{10} Furthermore, focal radiation therapy (e.g. Cyberknife\textsuperscript{®} or proton beam) might eventually take away the need for any invasive treatment.

**Positioning focal therapy from consensus to guideline**

The main objective of the PCa international guidelines is to provide patients with safe and effective PCa treatment options, based on the best evidence available.\textsuperscript{3,11} The implementation of new therapies should include the recommendations of expert panels based on consensus projects, pooled data from available database registries, randomized level 1 evidence trials and systematic reviews. Focal therapy is proven to be a safe therapeutic option for low- to intermediate-risk PCa. In this thesis, promising functional preservation was found when patients treated with unifocal IRE were matched and compared with patients treated with expert nerve-sparing robot-assisted radical prostatectomy. Nevertheless, randomized trials comparing focal therapy with other PCa treatments are lacking to confirm these preliminary data.

Data from the first phase I/II trials are being pooled into databases (e.g. CROES for IRE NCT02255890, COLD for cryosurgery).\textsuperscript{12} These registry datasets are evolving into large datasets with long-term functional, oncological and quality of life outcomes, including the initial results that are already more than 15 years ago.\textsuperscript{13} However, long-term oncological outcomes on metastasis-free survival, PCa-specific mortality and overall survival are still awaited and are required before this new treatment paradigm can be evaluated for a position in the guidelines. It may be complicated to obtain mature and distinctive oncological control data. As seen in the SPCG-4 trial, surgical intervention only showed oncological benefit (PCa-specific mortality) after 18 years for the intermediate-risk prostate cancer cohort, whereas no significant difference was found in the low-risk group at 18 years.\textsuperscript{14} With the ever-evolving landscape of prostate cancer treatments, (epi)genetic studies and imaging technologies it may be reasoned that prospective head-to-head randomized trials are not the appropriate design anymore. Especially, since the follow-up for low- to intermediate-risk prostate cancer should be more than 15-20 years before any firm statements regarding oncological control can be made. Similar conclusions can be drawn from the recently published 10-year results of the ProtecT trial, randomizing radical prostatectomy versus EBRT versus monitoring for PSA-detected localized low- to intermediate-risk prostate cancer.\textsuperscript{15} In the future, new imaging techniques (e.g. PSMA PET CT) or (epi)genetic biomarkers may possibly be able to provide earlier surrogate outcomes on oncological control.
Recent scientific developments have improved our understanding of prostate cancer behaviour and have revolutionized our approach towards lesion-specific risk assessment. Due to the advancements made in mpMRI technology, lesion characteristics can be assessed on size/volume, topography and morphology, aiding both risk stratification and treatment planning. This may provoke a shift towards the assessment of prostate-specific risk factors that may be compared to the same risk assessment in active surveillance (evaluating patient-specific risk factors). By focally treating the prostate-specific risk factors (e.g. the index lesion or clinical significant lesions), the relative risk of prostate-specific mortality could be reduced. This may result into new treatment algorithms with early treatment of such risk factors, reserving radical treatment for high-risk, significant multi-focal or recurrent disease. The relative low risk of PCa-specific mortality in low- and intermediate-risk PCa serves well the main rationale behind active surveillance, reserving radical treatment only for patients that show upgrading or upstaging. It may be difficult to comprehend that it is acceptable (according to the guidelines) to under-grade 44% of active surveillance candidates due to the inherent errors of current PCa diagnostics, but not accept any residual (satellite) lesions after focal therapy due to these same inherent errors of current PCa diagnostics. Especially, since all radical treatment options are still possible after focal therapy, as well as salvage focal therapy. Long-term oncological data will provide the required answer whether these residual/satellite lesions will be of any clinical significance. If oncological control is proven, focal therapy can be positioned in the guidelines as a mediating treatment option between active surveillance and radical treatments. Patients that require no treatment (low-risk) should be followed with active surveillance and patients that require immediate treatment (high-risk) should be treated radically. However, for a large proportion of patients the future may be to target dominant lesions that harbour prostate-specific risk factors that require treatment. By sparing patient-specific functioning we can, and have to preserve the quality of life following prostate cancer treatments.
REFERENCES


Concluding remarks and future perspectives


