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Opinion paper

Phase I study of cancer lesion-targeted microwave coagulation therapy for localized prostate cancer: A pilot clinical study protocol

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ABSTRACT

Background: Whole-gland therapy for prostate cancer, which might cause more harm than no therapy (observation or active surveillance), might be a overtreatment. In order to avoid overtreatment as well as undertreatment of localize prostate cancer, novel strategy of organ-preserving therapies have been developed to achieve both cancer control and functional preservation. For the therapeutic techniques, microwave ablation would be an option for lesion-targeted focal therapy to eradicate biopsy-proven cancer lesion with its safety margin. Following our recent pilot clinical study of lesion-targeted focal cryotherapy, prospective clinical trial was designed to investigate the safety and therapeutic effects of lesion-targeted microwave therapy for localized prostate cancer.

Methods: This is a single-center, phase I, clinical study to evaluate primarily the safety of lesion-targeted focal microwave treatment for prostate cancer. Patients with a magnetic resonance imaging (MRI)-visible, MR-ultrasound image-fusion targeted biopsy-proven clinically significant cancer will be enrolled. The target sample size is 5. Transrectal ultrasound-guided focal microwave ablation will be performed under general anesthesia. The primary endpoint is adverse events after microwave focal therapy. Secondary endpoint includes to assess both cancer control and quality of life (functional preservation).

Discussion: This single-center, phase I, clinical study aims to evaluate the safety and efficacy of lesion-targeted focal microwave treatment for prostate cancer. The importance of this clinical trial is that it may establish new treatment for prostate cancer.

Trial registration: This study was registered with Japan Registry of Clinical Trials (jRCTs052190026).

1. Introduction

The incidence of prostate cancer has recently been increasing due to the expansion of screening tests for prostate-specific antigen (PSA) in Japan as well as US or Europe. The current standard treatments for prostate cancer, such as prostatectomy and external radiotherapy, target the whole-gland prostate, likely resulting in damage to the surrounding tissues (external sphincter and cavernous nerves) and a reduction in quality-of-life (QOL). The associated comorbidities by such whole-gland therapy remain a great concern to patients with low-to-intermediate-risk small-volume prostate cancer as potential overtreatment. In the era of minimally invasive surgery to maintain QOL, focal therapy has offered to target the clinically significant cancer (CSCa) as prostate-preservation strategy. Focal therapy aims controlling or curing CSCa while minimizing adverse events. Although focal therapy has not yet become a standard treatment option for localized prostate cancer, the techniques used for multiparametric magnetic resonance imaging (MRI) and targeted biopsies aimed at identifying regions of CSCa have recently evolved. In a previous study, we showed that targeted biopsies allow the accurate identification of "index cancer", which is characterized as the lesion with the highest Gleason score or the largest volume or that exhibits the greatest amount of extra-prostatic extension or origin of metastasis [1]. Thus, targeted ablation of MR-visible, targeted biopsy-proven index cancer is now possible.

As one of the minimally invasive techniques, microwaves have been used to treat solid tumors, such as kidney, liver, or lung tumors [2–6]. To our knowledge, there are few reports about the microwave ablation of prostate cancer. The high temperatures induced by microwaves cause cell death by denaturing and coagulating structural proteins and abrogating the local blood supply. Compared with RFA, microwave ablation

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has unique advantages, e.g., it involves larger ablation volumes, shorter ablation times, and higher intra-tumoral temperatures. Following our recent pilot clinical study of lesion-targeted focal cryotherapy [7], prospective clinical trial was designed to investigate the safety or adverse events by cancer lesion-targeted microwave coagulation therapy in localized prostate cancer.

2. Material and methods

2.1. Study design

This is a single-center, phase I, clinical study to evaluate whether focal microwave treatment for prostate cancer is safe and feasible. This study will obtain data relating to various QOL parameters, particularly those related to urinary, rectal, and sexual side effects. The patients will be evaluated prospectively after legion-targeted microwave treatment. This study was registered with Japan Registry of Clinical Trials (jRCTs052190026). Written informed consent will be obtained from all patients before registration according to the Declaration of Helsinki. Independent monitoring will be planned according to the Japanese clinical trial guideline. The flowchart of study shown in Fig. 1. The total in-hospital treatment costs (including treatment, examination, and in-hospital expenses) in this study are entirely borne by the pre-advanced medical promotion project cost of Kyoto Prefectural University of Medicine, University Hospital.

2.2. Intervention

MRI will be performed with a 3T MRI unit (Achieva 3T, Philips Medical System, Best, The Netherlands) using a 16-channel phased array coil. The patients will undergo an MRI-transrectal ultrasound (TRUS) image-fusion targeted biopsy, and at least 2 biopsy cores will be obtained from each suspected lesion detected on MRI. After a targeted biopsy has been performed, a systematic biopsy will be conducted in the same session. The MRI-TRUS image-fusion targeted biopsies will be performed using the Urostation® or Trinity® (Koelis, Meylan, France) three-dimensional (3D) US-based organ-tracking system. These systems can be used to display virtual biopsy trajectories on 3D MRI-TRUS image-fusion images, which makes it possible to ensure that the correct biopsy trajectory is employed. No clear patient selection criteria for focal therapy have been established yet. In this study, patient selection will be performed based on the locations of the cancer-containing biopsy cores according to MRI.

Cross-sectional images of the prostate, including 3D cancer maps, will be prepared from 5-mm slices using the Urostation®. On the day of treatment, patients will receive general anesthesia. With the patient in the lithotomy position, Koelis system will be used to register the biopsy-proven tumor using 3D-TRUS. Under TRUS guidance, one guide needle will be inserted into the target lesion via the transperineal approach using free-hand technique. The physician will understand the 3D cancer maps and insert the needle into target lesion that will be confirmed by MR/US image fusion technology. The targeted lesion will be defined as MR-visible, targeted biopsy-proven CSCa. The Koelis system will be replaced by the biplanar 2-dimensional TRUS system (PVT-770RT; Canon Medical Systems, Tochigi, Japan). The needle will be used to monitor the microwave-treated region and will cover the target and a margin of approximately 5 mm. The microwave output level will be set at 30 W or 60 W, and microwave irradiation will be carried out for 30 s each. US images (APLIO 500 TUS-A500; Canon Medical Systems, Tochigi, Japan) will be recorded during treatment, and the ablated area will be measured by hyperechoic lesion due to heat-generated water vapor. Superb micro-vascular imaging (SMI) which provides a more sensitive method in detecting low-velocity blood flow than color Doppler without contrast agents will be performed before and after treatment to determine the completeness of the ablation lesion by confirming the blood flow disappearance [8].

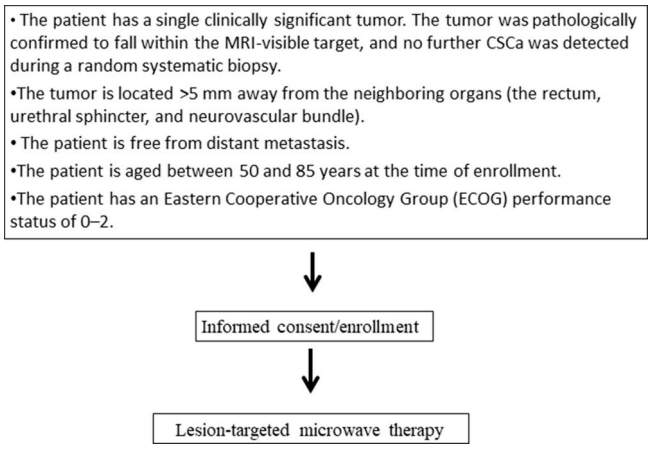

Fig. 1. Flowchart of study. CSCA = clinically significant cancer.

Foley catheter will be inserted immediately after ablation and removed between 12 and 20 h after ablation. The assessment schedule is shown in Table 1. The planned follow-up procedure consists of hospital visits at 1 week, 1 month, 3 months, and 6 months, during which the patients' PSA levels will be measured and any adverse events will be reported according to Common Terminology Criteria for Adverse Events (CTCAE, version 5). The patients will be asked to fill in Expanded Prostate Cancer Index (EPIC, Japanese version) questionnaires at each hospital visit. Multiparametric MRI will be scheduled for the 6-month follow-up examination. If signs of local disease are seen on MRI, a follow-up targeted biopsy will be performed.

2.3. Ethics approval and consent to participate

The trial received ethical approval from the Ethics Committee of Kyoto Prefectural University of Medicine, Kyoto, Japan (number: CRB5180001, the last edition ver.6, April 28, 2019). The trial is subject to the supervision and management of the Ethics Committee. Written informed consent will be obtained from all patients before registration according to the Declaration of Helsinki. Independent monitoring will be planned according to the Japanese clinical trial guideline.

2.4. Subjects (patient eligibility)

The inclusion criteria are as follows:

[1] The patient has a single clinically significant tumor. The tumor was pathologically confirmed to fall within the MRI-visible target (suggesting that the extent of the cancer was not underestimated by MRI), and no further CSCa was detected during a random systematic biopsy.
[2] The tumor is located >5 mm away from the neighboring organs (the rectum, urethral sphincter, and neurovascular bundle).

Table 1
Assessment schedule.

	Pre-treatment	Treatment	One week post-treatment	1 m	3 m	6 m
Informed consent	○					
EPIC	○		○	○	○	○
PSA	○				○	○
MRI	○					○
CTCAE		○	○	○	○	○
Biopsy	○					○ (if necessary)

[3] The patient is free from distant metastasis. (The patients will undergo computed tomography and bone scans as primary examinations to confirm the absence of lymph node and distant metastases.)
[4] The patient is aged between 50 and 85 years at the time of enrollment.
[5] The patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.
[6] The patient has provided written informed consent to participate in the study.

CSCa is defined as a maximum cancer core length (MCCL) of ≥5 mm in cases involving a Gleason score of 6, or any MCCL in cases involving a Gleason score of ≥7, according to the standards for reporting for MRI-targeted biopsy studies (START) criteria.

The exclusion criteria are as follows:

[1] Patients with active double cancer (synchronous double cancer and metachronous double cancer with disease-free survival of 5 years or less, but excluding carcinoma in situ that is judged to be cured by local treatment)
[2] Patients with Gleason score 9–10.
[3] Patients with uncontrollable diabetes mellitus
[4] Patients who have undergone rectal surgery
[5] Patients in whom a cardioverter defibrillator or pacemaker has been implanted
[6] Any other patients who are regarded as being unsuitable for this study by the investigators

2.5. Primary endpoints

The Common Terminology Criteria for Adverse Events (CTCAE, version 5) will be used to assess the acute and late rectal, urinary, and sexual toxicities that occur after microwave treatment. The CTCAE are widely used throughout the oncology community as the standard classification and grading scale for adverse events in cancer therapy clinical trials and other oncological settings.

2.6. Secondary endpoints

1. The EPIC will be used to evaluate the changes from the baseline in various QOL indicators. The EPIC is designed to evaluate patients' functional abilities and symptoms after prostate cancer treatment.
2. Serum PSA levels will be measured in every visit, before and post-treatment 1 week, 1 month, 3 months, and 6 months.
3. MRI-based evaluations of local cancer control will be performed at 6 months after the microwave treatment. If a suspected cancer focus is seen on MRI based on the criteria of Prostate Imaging Reporting and Data System version2 [9], PIRADS-3 or greater, then an MRI-TRUS image fusion biopsy will be performed.

2.7. Sample size

The target sample size is 5. The safety, adverse events, and feasibility of the legion-targeted microwave treatment for the 5 cases in our institution will be evaluated prospectively. Although the sample size of this pilot study is small, the clinical assessment in this pilot study mimic the evaluation in the study design for main trial. This sample size is calculated in order to be able to answer the feasibility of this treatment under investigation to anticipate what may be observed in the main trial.

2.8. Statistical methods

QOL: EPIC questionnaires score will be measured in every visit, before and post-treatment 1 week, 1 month, 3 months, and 6 months. Wilcoxon rank sum tests will be used to compare.

PSA: disease control rate and its 2-sided 95% CI (Wilson method).

2.9. Date collections

The datasets used during the current study will be available from the corresponding author on reasonable request. Storage of research-related files will be in a locked cabinet in the Kyoto Prefectural University of Medicine.

3. Discussion

This clinical phase I trial has been designed to evaluate the safety of lesion-targeted microwave focal therapy to treat MRI-visible targeted-biopsy-proven CSCa lesion. Our clinical phase I trial of legion-targeted focal therapy for localized prostate cancer using Cryoablation technology was completed according to similar design to this protocol reported recently [7]. Prostate cancer presents as multifocal disease on whole-mount pathology in about 80% of cases, especially if a sampling frame of 3 mm is used [10]. Although the multifocal nature of prostate cancer has been considered as a potential limitation of focal therapy, there is increasing evidence that the prognosis of patients with prostate cancer depends on the "index cancer" amongst the multifocal lesions. The "index cancer therapy" is a fundamental concept to support the way for focal therapy, in which only CSCa and its safety margin is ablated [11]. Importantly, concordance between the epigenomic or genomic analysis of so-called index cancer and metastasis sites suggest that the index cancer lesion could be the origin of metastasis [12,13]. In our previous study, we analyzed concordance of the spatial location of the identified possible index cancer between MR/US image-fusion biopsy-proven CSCa and dominant cancer lesion in prostatectomy specimen in 135 consecutive patients. The location of the index cancer identified by MR/US image fusion biopsy corresponded to the location of the RP specimen in 95% of cases (128/135) [14]. In the remaining 5% of patients, the index cancer was not visible on MRI, and all of these tumors were very small. Although not all cancer lesions are detectable on MRI, these findings suggest that MRI-US image-fusion biopsies could be a valuable tool for identifying the locations of CSCa. The targeted ablation of MR-visible, targeted biopsy-proven CSCa seems possible.

The definition of criteria for therapeutic success after focal therapy for prostate cancer are disputed. However, there is some consensus agreement among the experienced expert for prostate focal therapy. At a 2019 consensus meeting, it was proposed that multiparametric MRI should be used for follow-up examinations after focal therapy, and PSA has a definitive role for defining of effective treatment [14]. Immediately after treatment, successful ablation is defined as the loss of enhancement on the dynamic contrast-enhanced sequence [15]. Targeted biopsies should be carried out if a residual tumor is suspected on follow-up MRI [15]. Based on our experiences of hemi-cryoablation, which involved a median follow-up period of 3 years, the follow-up biopsies were negative for CSCa in all patents who met the following criteria: (1) a PSA level of <4 ng/ml, (2) a reduction in the PSA level of >50%, and (3) no local signs on multiparametric MRI [7]. In this study, we will use criteria based on a combination of biochemical and MRI findings to assess the control of CSCa.

Microwave ablation is one of the thermotherapy heating cancer cells within the body. Elevating the temperature results of tumor cells in cell membrane damage, which, in turn, leads to the destruction of cancer cells. Microwave ablation has been proved as a safe and effective treatment for renal cell carcinoma; [316] however, there are few reports about its use to treat prostate cancer. In 1999, Lancaster et al. were the first to report the use of percutaneous microwave ablation to treat a case of primary prostate cancer, without any treatment-related complications.[17] Sherar et al. performed percutaneous microwave ablation in patients in whom external beam radiotherapy failed. They reported that the frequency of negative biopsy findings at 24 weeks was 64%.[18] Since these previous reports were in the era before the evolved

multiparametric MRI for prostate cancer diagnosis, effectiveness of microwave ablation for prostate cancer should be reassess by using recent evolved technology including MRI, PSA, and targeted biopsy if indicated. Similar to the role of microwave therapy for eradication of renal cancer, we hypothesized that technology of microwave could be a suitable "cancer-targeting therapy" for localized prostate cancer. This is a single-center, phase I, clinical study to evaluate the safety of lesion-targeted focal microwave treatment for prostate cancer. The primary endpoint is safety or adverse events, and secondary endpoint include both cancer control and QOL.

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None.

Abbreviations

CSCa	clinically significant cancer
CTCAE	Common Terminology Criteria for Adverse Events
EPIC	Expanded Prostate Cancer Index
MCCL	maximum cancer core length
MRI	magnetic resonance imaging
US	ultrasound
PSA	prostate-specific antigen
RFA	radiofrequency ablation
RP	radical prostatectomy
START	standards for reporting for MRI-targeted biopsy studies
SMI	Superb micro-vascular imaging
TRUS	transrectal ultrasound
QOL	quality-of-life

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The total in-hospital treatment costs (including treatment, examination, and in-hospital expenses) in this study are entirely borne by the pre-advanced medical promotion project cost of Kyoto Prefectural University of Medicine, University Hospital.

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