Original Article

Prostate cancer in Asia: design of a patient registry to inform real-world treatments, outcomes, and quality of life

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ABSTRACT

Background: The incidence of prostate cancer (PC) in Asian countries is increasing for reasons that are not clear. Data describing how PC is diagnosed and treated are fragmented across Asia, with marked intercountry and intracountry differences in outcome and knowledge gaps in clinical diagnostic and treatment practices. To address these knowledge gaps, we have established a PC disease registry with the aim of providing a comprehensive picture of PC diagnosis, prognosis, treatment and outcome, population characteristics, and comorbidities in real-world clinical practice in Asia.

Methods: This is a multinational, multicenter, longitudinal, and observational registry of PC patients presenting to participating tertiary-care hospitals in eight Asian countries (www.clinicaltrials.gov NCT02546908. Registry Identifier: NOPRODPCR4001). Approximately 3500-4000 eligible patients with existing or newly diagnosed high-risk localized PC (cohort 1), nonmetastatic biochemically recurrent PC (cohort 2), or metastatic PC (cohort 3) will be consecutively enrolled and followed-up for 5 years. An enrollment cap of 600 patients each will be applied to cohorts 1 and 2. Disease status is collected at enrollment, and outcome variables captured at 3-monthly intervals include diagnostic/staging, treatments including reason for change, laboratory results, comorbidities, and concomitant medications. Treatments and survival outcomes will be captured real time until study end. Patient-reported quality-of-life will be measured every 6 months, and medical resource utilization summarized at study end. Data analysis will include exploratory analyses of potential associations between multiple risk factors and socioeconomic variables with disease progression and evaluation of various treatments for PC including novel therapies on clinical outcome and health-related quality-of-life outcomes.

Results: 3636 men with PC were enrolled until July 2018; 416 in cohort 1, 399 in cohort 2 and 2821 in cohort 3.

Discussion: A total of 3636 patients were enrolled until July 2018. The prospective disease registry will provide comprehensive and wide-ranging real-world information on how PC is diagnosed and treated in Asia. Such information can be used to inform policy development for best practice and direct clinical study design evaluating new treatments.

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1. Background

Prostate cancer (PC) is one of the most common cancers in Asian men, causing approximately 25,000 deaths annually in South-East Asia (2012 data).[1] Marked regional differences exist in PC incidence and survival rates (Table 1). The different disease epidemiology across Asia may be related to differences in the frequency of screening, decisions underlying choice of treatment, and access to screening and healthcare facilities related to economic setting (Table 1). Countries within Asia are economically diverse, with resulting diversity in healthcare and health insurance systems, facilities for diagnosis and treatment, and access to new treatments. Countries also differ in their recommended treatment algorithms and guidelines. Patients living in countries or rural areas where screening for prostate-specific antigen (PSA) is lacking (such as Malaysia and rural areas of China) tend to present with more advanced disease than countries/regions where PSA-screening occurs (such as Japan).[2-4]

Although the incidence of PC in Asian countries is up to 20-times lower than in Western countries, data from national cancer registries indicate that PC incidence and mortality is rising in Asia for reasons that are not clear.[2, 4, 5] Changing diagnostic practices such as increased PSA testing and increased capacity for transrectal ultrasound and biopsy are likely to be contributing to this rise, as well as changes in risk factors such as increased exposure to Western diets and reduced physical activity.[2, 4, 5] Data describing how PC is screened, diagnosed, best treatment practices, and the outcome of treatment in Asian countries are fragmented and incomplete. PC screening and treatment activities in Asia are guided by information from studies conducted in Western populations, even though the epidemiology of PC in Eastern and Western populations is heterogeneous.[6, 7] National cancer databases exist in some but not all countries in Asia (for example, Japan and Korea).[8] These databases vary in size and in the type and quality of the data collected. Treatments administered, the decision-making process guiding treatment selection of individual patients, medical resource utilization, and patient-reported outcomes such as quality of life (QoL) are not routinely collected in healthcare databases or in clinical trial settings.[9] Such data are scarce in Asia and represent key knowledge gaps. By contrast, these data collected from prospective registries of patients with PC in the United States and Australia have been used in numerous clinically relevant studies to compare treatments, expand knowledge, and inform guidelines on PC management.[10-13]

Treatment options for patients with advanced PC have expanded in the last few years.[14] In addition to chemotherapy, enzalutamide, an androgen receptor blocker, and abiraterone, which inhibits androgen synthesis, improve overall survival (OS) of men with metastatic castration-resistant PC and may be used in patients unable to tolerate chemotherapy.[15-17] Bone-seeking radionuclides (radium-223) and new chemotherapeutic agents give clinicians a range of options and imply that several treatment options may be available for the same disease stage.[14] However, the optimal timing and sequence of treatments remain undefined.[14, 18] Within Asia, the use of these newer agents is not consistent within the region, and long-term real-world data concerning their use and impact outside controlled studies are not yet available. Because diverse treatments exist for PC, identification of the physical and psychosocial consequences of the disease and its treatment rather than only OS become critical for treatment decision-making.

Such knowledge gaps are unable to be filled just by information gained from clinical trials conducted in homogenous settings that do not reflect real-world practice nor by retrospective observational studies that are limited by the type and integrity of the available data. Therefore, to compile high-quality, real-world data to inform on country-specific patterns of PC in Asia, we elected to use a disease registry design, allowing long-term prospective follow-up of a large number of patients with advanced PC.

We have established a prospective, longitudinal PC registry in eight countries in Asia—China, India, Japan, Malaysia, Singapore, South Korea, Taiwan, and Thailand. The registry will generate real-world data on PC screening, diagnosis, disease status, treatment patterns, the underlying clinical decisions that determine treatment choice, and response to treatment. With the recent introduction of new agents for the treatment of PC into Asia, the registry data will allow comparisons to be made between the benefits and risks associated with new versus conventional treatments. The registry provides the opportunity to identify best practice in PC treatment, and the evolution of clinical practice over time as more treatment options are introduced. Survival and disease progression outcomes, health-related QoL, and medical resource use of patients with PC will be captured. Here, we describe the key features of the prospective, longitudinal registry of patients with PC in Asia and the challenges in its implementation.

2. Registry objectives

The global aim of the registry is to document PC management and outcome including diagnosis, prognosis, treatment, and care in real-world practice. The clinical progression and outcomes of patients with PC will be observed (including OS, PC-related mortality, metastasis-free survival, progression-free survival, time to PSA progression, and health-related QoL) and assessed in relation to different treatments and disease phases at diagnosis. Uniquely, as well as duration and adherence to PC treatments, considerations guiding treatment selection and medical resource utilization will be recorded. Associations between risk factors and disease progression will be explored.

3. Study design

This is a multicenter, longitudinal, observational cohort study of PC patients presenting to participating tertiary-care hospitals in eight Asian countries.

Table 1
Epidemiology of prostate cancer in Asian countries: age-standardized rates (per 100,000 population)

Country/region	2008[4]			2012[1,27]			Income level[28]
	Incidence	Mortality	Mortality/incidence ratio	Incidence	Mortality	Mortality/incidence ratio	
China	4.3	1.8	0.42	5.3	2.5	0.47	Upper middle
Taiwan	20.8	5.2	0.25	29.7	6.6	0.22	High
Japan	22.7	5.0	0.22	30.4	5.0	0.16	High
India	-	-	-	4.2	2.7	0.64	Low middle
South Korea	22.4	4.1	0.18	30.3	4.6	0.15	High
Thailand	6.5	2.0	0.31	7.2	3.7	0.51	Upper middle
Malaysia	9.2	5.8	0.63	10.8	4.6	0.43	Upper middle
Singapore	20.0	3.9	0.20	33.1[a]	4.5	0.14	High

a) The 5-year age-standardized incidence of prostate cancer in Singapore 2011-2015 is 29.7 per 100,000 person-years[29].

Patients are eligible if, at the time of enrollment, they are at least 21 years of age with high-risk localized PC (cohort 1), non-metastatic, biochemically recurrent PC (cohort 2), or metastatic PC (cohort 3). Enrolled patients will be followed-up for a maximum of 5 years during the observational period or until the registry is closed, whichever occurs first. The close of the registry will be approximately 5 years after the first patient is enrolled. In view of the long-term survival typical of patients diagnosed during the early stages of PC, we elected to focus on advanced stages requiring more intensive treatment. This will allow us to collect meaningful information on disease treatment and progression over the 5-year study period. To ensure a patient population representative of clinical practice and to reduce selection bias, all patients meeting the eligibility criteria at an investigative site will be consecutively enrolled in the registry. A total of 3,500–4,500 patients are planned to be enrolled. Eligible patients will be offered the opportunity to enroll in the study when they come to the investigative site for a clinic visit. A screening log will be maintained by each site to record the enrollment disposition of patients potentially eligible for study participation, to better assess the representativeness of the enrolled population. Patient age group, disease stage, and reason for refusal will be recorded for individuals who meet the eligibility criteria but who choose not to participate in the study.

Written informed consent was obtained from each patient or their legally acceptable representative allowing source data collection and verification in accordance with local laws. The decision of patients to participate in this study will not in any way impact upon the standard of care they are receiving or any benefits to which they are otherwise entitled. Patients may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a patient is withdrawn prior to completing the study follow-up period, any

known reason for withdrawal should be documented. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the withdrawn patient.

Information from enrolled patients will be collected retrospectively from the initial diagnosis of PC. Newly diagnosed eligible patients will also enter the registry. All patients will be prospectively followed throughout their course of treatment (Table 2). Patients will be given a subject number to ensure anonymity. Routine clinical practice data will be extracted and entered into an electronic data capture system by study staff at a minimum frequency of once every 3 months during the observational period.

The protocol was reviewed and approved by the Institutional Review Boards/Independent Ethics Committees in each of the participating countries.

3.1. Staging definitions

To overcome differences in prostate staging used by individual institutions, disease stage definitions are standardized for registry enrollment (Fig. 1). High-risk localized PC is defined as in this registry as clinical T stage cT3a or higher, with one of the following high-risk features: Gleason score 8-10, PSA level above 20 ng/mL, or N1. This definition was adopted from the National Comprehensive Cancer Network Guidelines in Oncology.[19] Patients whose pathologic stage is reclassified to below T3 at any time during the study will be withdrawn from the study (with the exception of those patients who initially met the criteria for high-risk localized PC or whose stage changed because of therapy).

The definition of nonmetastatic biochemically recurrent PC follows guidelines from the European Association of Urology for patients post-radical prostatectomy (confirmed PSA value of >0.2 ng/

Table 2
Data collection schedule

Registry data collection	Enrollment	Observation period		End of registry
		Every 3 months	Every 6 months	
Screening/consent				
Participation agreement/informed consent	X			
Inclusion criteria	X			
Demographic information	X			
Socioeconomic status	X			
Family medical history[a]	X			
Healthcare reimbursement status	X			
PC characteristics at first diagnosis[b]	X			
PC treatment history	X			
Current prostate cancer status and treatment				
Patient lifestyle (exercise, smoking, alcohol intake)	X			
Comorbidities	X	X		
Concomitant medications	X	X		
Current PC characteristics[b]	X	X		
Current PC treatment	X	X		
Skeletal-related events	X	X		
Biologic parameters	X	X		
Patient-reported outcomes				
EQ-5D-5 L & FACT-P	X		X	
Safety assessment				
Adverse events	X	X		X
Other assessments				
Medical resource utilization				X
Radiologic assessment	X	X		
Vital Status		X		X
ECOG performance status	X			
Study completion/withdrawal				
End of registry form				X

PC, prostate cancer, ECOG, Eastern Clinical Oncology Group; EQ-5D-5 L, European Quality of Life-5 Dimensions, 5 Levels; FACT-P, Functional Assessment of Cancer Therapy for Prostate Cancer (FACT-P); PSA, prostate-specific antigen.
  a) Including PC in male family members and breast cancer in female family members.
  b) Including dates of initial diagnosis, digital rectal exam, PSA level, TNM Stage, and Gleason score.

Cohort 1: High-risk localized prostate cancer

- Clinical T stage ≥cT3a and one of the following high risk features:
  - Gleason score 8-10,
  - PSA level >20 ng/mL,
  - N1.

Cohort 2: Non-metastatic, biochemically recurrent prostate cancer

- Post-radical prostatectomy (European Association of Urology guidelines)
  - confirmed PSA >0.2 ng/ml.
- Post-radiotherapy (American Society for Radiation Oncology guidelines)
  - PSA ≥2 ng/ml above the nadir.
- Castrate-resistant prostate cancer (Prostate Cancer Working Group)
  - PSA rise ≥2 ng/mL above the nadir; the rise ≥25% over nadir,
  - confirmed by a second PSA ≥3 weeks later,
  - Testosterone <50 ng/dL (castration criterion) or post-orchiectomy.

Cohort 3: Metastatic prostate cancer

- Includes metastatic hormone-sensitive prostate cancer and metastatic castrate-resistant prostate cancer.

Fig. 1. Disease eligibility criteria for registry enrollment. PSA, prostate-specific antigen.

mL following prostatectomy)[20] and the American Society for Radiation Oncology guidelines for patients post-radiotherapy (PSA value of 2 ng/mL or more above the nadir following radiation therapy).[21] Prostate Cancer Working Group 2 guidelines for patients with castrate-resistant PC (PSA increase of ≥25% and ≥2 ng/mL above the nadir with confirmation by a second PSA ≥3 weeks later).[22] In addition, the patient is required to have castrate levels of testosterone (<50 ng/dL). Metastatic disease includes metastatic hormone-sensitive PC and metastatic castration-resistant PC.

To increase the proportion of patients with metastatic disease in this study (Cohort 3 which has the largest unmet need), an enrollment cap of 600 per cohort will to be applied to Cohorts 1 and 2. There is no enrollment cap for Cohort 3.

3.2. Outcome variables

Baseline data include demographic and lifestyle characteristics, family medical history, and detailed features of PC at diagnosis such as detection method, laboratory values, staging, Gleason score, and treatment history (Table 2). For patients with longer standing PC, these data will be collected retrospectively from the medical records. Every 3 months during the observation period, information about lifestyle, comorbidities, concomitant medications, PC treatments and characteristics, and relevant biologic parameters (PSA and testosterone levels) will be collected. All assessments are intended to be performed as part of routine clinical practice at the time of a routine clinical encounter, except for health-related QoL data. Clinical visits, medical interventions, treatments, laboratory tests, and procedures are neither mandated nor recommended as part of this study.

Health-related QoL will be captured at routine clinic visits using the European Quality of Life-5 Dimensions, 5 Levels (EQ-5D-5 L) and Functional Assessment of Cancer Therapy for Prostate Cancer (FACT-P) tools.[23, 24] The EQ-5D-5 L measures QoL across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Within each item, there are five response options (no problems, slight problems, moderate problems, severe problems, or extreme problems). Data captured by EQ-5D-5 L relates to the patient's status at the time of completion and takes approximately 5 minutes to complete.

FACT-P consists of the FACT-General and a PC-specific subscale. The FACT-General (version 4) is a 27-item questionnaire composed of four dimensions (physical well-being, social/family well-being, emotional well-being, and functional well-being).[24] The PC-specific subscale comprises 12 items spanning the dimensions of sexual function, bowel/bladder function, and pain. The FACT-P questionnaire has a 7-day recall and takes approximately 15 minutes to complete.

Patient Eastern Clinical Oncology Group score will also be recorded (if performed) potentially allowing evaluation of correlations between Eastern Clinical Oncology Group and FACT-P or EQ-5D-5 L. Previous experience indicates that changes to QoL scores occur over a period of several months.[15, 25, 26] Therefore, the EQ-5D-5 L and FACT-P will be administered no earlier than once every 6 months (Table 2).

Medical resource usage (inpatient and outpatient clinical visits relating to the treatment of the patient's PC) will be summarized at study end. No attempt will be made to collect information on use of other healthcare resources (such as home visits, nursing home, or respite visits) because of the lack of access to source data and inability to validate the information.

3.3. Statistical analysis plan

Descriptive analyses will be performed on all variables including baseline demographic and disease characteristics, radiological information, and treatment patterns.

Quantitative analyses will include incidence rates of events, discontinuation and start of new treatments, time-to-event profiles, comparisons of clinical outcomes between different treatments, and identification of the most effective treatment approaches for each disease stage.

4. Feasibility assessment and identification of study sites

To be successful, the registry requires that the patient population be representative of men with PC in Asia, that data of sufficient detail and quality are electronically available in medical records, that the medical records capture PC treatments across disciplines (including urology and oncology), and that the participating sites provide complete, long-term care of patients with PC to avoid loss to follow-up to other centers. Investigative sites are therefore genitourinary oncology centers within tertiary-care hospitals routinely involved in the diagnosis and treatment of patients with PC. Study feasibility at individual sites was evaluated via questionnaire and meetings with staff. Site selection criteria included proportional representation of a geographical region, projected availability of eligible patients currently receiving care, availability of electronic medical records, previous clinical research experience, and expressed interest in registry participation.

5. Preliminary results

Between 3636 men with PC who were enrolled into the registry until July 2018: 863 from China, 247 from India, 887 from Japan, 370 from Malaysia, 176 from Singapore, 310 from South Korea, 421 from Taiwan, and 362 from Thailand. There were 416 men with high-risk localized PC, 399 with nonmetastatic, biochemically recurrent PC, and 2821 with metastatic PC. The mean age at enrollment was 71 years [standard deviation (SD) 7.4 years] in patients with high-risk localized PC, 72 years (SD 7.6) in patients with nonmetastatic, biochemically recurrent PC, and 71 years (SD 8.5) in patients with metastatic disease.

6. Discussion

A combination of increased testing resulting in earlier diagnosis and changes in lifestyle that potentially alter risk exposures has seen the emergence of PC as an increasing health burden in Asia. Large differences in disease epidemiology exist between countries in the region; the reasons for which are not fully understood. Approaches to diagnosis and management vary substantially between Asian countries, and knowledge gaps exist in understanding routine management practices and patient outcomes. Good-quality, real-world data are needed to inform current practices and patient outcomes.

By establishing a disease registry, we aim to collect prospective, longitudinal, comprehensive, and structured data covering a wide range of variables in a large number of patients. Unlike drug registries that may not encompass an extensive range of disease stages and that lack comparators to valuate outcomes or randomized controlled trials that usually focus on a single exposure in an homogenous setting, disease registries give a broader picture of real-world exposures and outcomes across numerous heterogeneous investigative sites. The registry allows humanistic and economic outcomes to be captured, such as patient-reported outcomes, compliance, tolerability, and satisfaction with treatment. Collection of data at the hospital level provides broad representation of the population of patients with advanced PC. The registry provides opportunity to identify best practice and patient outcomes in Asian countries.

New agents for treating advanced PC have shown efficacy in prolonging OS, and this registry may allow to assess performance of these therapies in a real-world setting.[14] In parallel, there is a shift in expectations for patients undergoing treatment for cancer, with QoL becoming of more value and potentially being used to differentiate between treatment options. The PC disease registry will collect patient-reported outcomes to quantify the benefits and disadvantages of individual therapies in terms of their impact on QoL outside the context of an interventional clinical study.

Observational studies may be subject to methodological limitations that can result in selection bias and case ascertainment bias. To prevent selection bias, patient enrollment to the registry will be consecutive. Other causes of enrollment bias include but are not limited to patients' inability to comply with the study procedures due to dementia, hearing impairment, speech difficulty, and refusal of any involvement with clinical studies. Enrollment based on standardized disease stage definitions reduces the risk of ascertainment bias. Careful site selection and monitoring reduces the risk of reporting errors. Potential confounding because of country/region and ethnic socioeconomic and health insurance status will be explored. Wide-ranging comprehensive data collection will allow adjustment of confounding factors during analyses.

6.1. Operational challenges in implementation

Implementation of the registry faces challenges at several levels. The case report form is long and detailed allowing collection of comprehensive data from the time of diagnosis and to track changes and progress for up to 5 years. Within each institution, it will be a challenge for site staff to complete and to continue data collection for 5 years. Additionally, in institutions where patient care moves between urologist and oncologist (such as Japan, Taiwan, and Singapore), collaboration between departments is required to ensure collection of the full data set pertaining to individual patients.

At the level of the patient, achieving consecutive enrollment is critical in preventing selection bias. Patient loss-to-follow-up could have a marked impact on data completeness and interpretation of progression/survival outcomes if large numbers of patients leave the study.

Changes to the standard of care may occur as a result of study participation as physicians are aware of third-party scrutiny of their practices. However, any potential impact is likely to be positive in terms of patient care.

7. Conclusion

The prospective patient registry will provide comprehensive and wide-ranging real-world information on how PC is diagnosed and treated in Asia. Such information can be used to inform clinicians, guide policy development for best practice and patient outcome, and direct clinical study design evaluating new treatments. The study is registered at www.clinicaltrials.gov NCT02546908, Registry Identifier: NOPRODPCR4001.

Conflicts of interest

Authors' contributions

D.Y., J.Y.L., E.C., Y.S.P., A.H.A.R., C.P., S.R., Y.L., H.Q., and M.V.K.L. conceived and designed the registry from the beginning, with many rounds discussions about study design, setting, patient populations, and clinical outcomes in 2013 and 2014. G.L., J.C., and W.H. substantially contributed to development of protocol amendment 2. All authors critically reviewed the manuscript. Each author gave final approval of the version to be published.

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