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Original Article

Report of the Second Asian Prostate Cancer (A-CaP) Study Meeting

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ABSTRACT

The Asian Prostate Cancer (A-CaP) Study is an Asia-wide initiative that has been developed over the course of 2 years. The study was launched in December 2015 in Tokyo, Japan, and the participating countries and regions engaged in preparations for the study during the course of 2016, including patient registration and creation of databases for the purpose of the study. The Second A-CaP Meeting was held on September 8, 2016 in Seoul, Korea, with the participation of members and collaborators from 12 countries and regions. Under the study, each participating country or region will begin registration of newly diagnosed prostate cancer patients and conduct prognostic investigations. From the data gathered, common research themes will be identified, such as comparisons among Asian countries of background factors in newly diagnosed prostate cancer patients. This is the first Asia-wide study of prostate cancer and has developed from single country research efforts in this field, including in Japan and Korea. At the Second Meeting, participating countries and regions discussed the status of preparations and discussed various issues that are being faced. These issues include technical challenges in creating databases, promoting participation in each country or region, clarifying issues relating to data input, addressing institutional issues such as institutional review board requirements, and the need for dedicated data managers. The meeting was positioned as an opportunity to share information and address outstanding issues prior to the initiation of the study. In addition to A-CaP-specific discussions, a series of special lectures was also delivered as a means of providing international perspectives on the latest developments in prostate cancer and the use of databases and registration studies around the world.

1. Introduction

The Second Meeting of the Asian Prostate Cancer (A-CaP) Study, from 12:30 to 18:00 on September 8, 2016, at St. Mary's Hospital, Seoul, Korea was attended by representatives of 12 countries and regions in Asia participating in the study (Hong Kong, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, Turkey, and China) and collaborators from the University of California San Francisco (UCSF), the Peter MacCallum Cancer Centre (Australia), the University of Queensland (Australia), and the South Australia Prostate Cancer Clinical Outcomes Collaborative (SA-PCCOC). Following on from the A-CaP launch symposium in December 2015,[1] members discussed progress dates and addressed various issues. These included technical challenges in creating databases and selecting appropriate database creation software; issues relating to raising awareness at medical institutions to ensure registration of patients; measures to prevent patients dropping out, institutional review board (IRB)-related issues; points of clarification concerning input methods and codes; and the importance of ensuring appropriate data management. Collaborators from the USA and Australia provided information on similar databases in their respective countries [Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), Victorian Prostate Cancer Registry (V-PCR), and SA-PCCOC]. The following is a summary of the proceedings of the symposium.

2. Opening

Choung-Soo Kim (Urology Cancer Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea) thanked Hideyuki Akaza (Graduate School of Interdisciplinary Information Studies, University of Tokyo, Tokyo, Japan) for his preparations for the launch of the A-CaP in December 2015 and noted that now 10 Asian countries are participating, together with involvement by collaborators from the USA and Australia. He noted that the meeting today would signify the start of the A-CaP study. He expressed thanks to Hideyuki Akaza for making arrangements and his efforts to procure budgetary allocation.

3. Special Lecture: Open Source Activities of Open Source Electronic Health Record Alliance—Open Source Information Technology, Collaborative Innovation

Seong Ki Mun (Open Source Electronic Health Record Alliance; OSEHRA, Arlington, VA, USA) noted that the essence of OS is collaboration and making improvements to develop capabilities that can change over time. OS is an innovative process that is based on collaboration. OSEHRA was established in 2011 by the United States (US) Government. It is an independent nonprofit organization and its mission is to build and support an OS community engaged in advanced health information technology for patient care. OSEHRA has a software repository, and facilitates collaborations for both improvements and product management and OS code certification. There is also a national standard that applies to OS software, enabling engineers to work on open source software with confidence.

The original OS software was the Unix operating system which is popular multi-user, multitasking operating system (OS) developed at Bell Labs in the early 1970s. This software has become the core of many commercial products. The preference for OS was a reaction in Europe to US dominance in software. There are many OS interests in Europe in many different sectors. There are > 1,000 OS communities around the world. Many of the cloud computing resources around the world were developed by NASA (US National Aeronautics and Space Administration), and this year, the US Government has issued an OS policy.

Engineers think of OS as free software available online. However, to ensure reliable performance, it is important to have rules of engagement, a business model, and to engage in efforts to develop the community and engineers. OS can be thought of as the future of software, with efforts being led by such organizations as Openstack, Firefox, GENIVI, and Android.

OS has become prominent in recent US administrations and Expresident Barak Obama has advocated open government, which means open data, sources, and science. This is similar to the way in which A-CaP will be seeking to collaborate and strategize about ways to deal with prostate cancer.

OS software has a source code that anyone can inspect, modify, and enhance. It is possible to copyright OS software and license it for others to study, modify, and distribute. There are many OS licenses, but OS is license free. It can be used as is, but can also be made into commercial products.

The US Department of Veterans Affairs provides comprehensive care to > 8.3 million veterans each year through 1,500 hospitals and uses VistA software for electronic records to run these hospitals. VistA installations are situated at 2,500 sites globally. The way the VistA has been implemented differs among facilities and locations in the US, and other countries are in discussions to use VistA. Jordan has adopted VistA across the country and no longer relies on external consultants, and has 140 technicians, 90 engineers, and 50 project management staff members. Jordan is now capable of providing support to other countries, including others in the Middle East. Software constantly needs to be managed and OS life cycles involve code improvements that result in product improvements.

Precision medicine has become a buzz word in recent years and big data and analytics involves medical, genomic, lifestyle, and behavioral data to compile personalized therapy that is best for the patient. For this to work effectively, it is essential to ensure that data sharing, standards, and analytics are all OS and open collaboration. The best science and services will result in the best care and it is to be hoped that the A-CaP study will have such outcomes.

3.1. Discussion

Matthew Cooperberg (UCSF) noted that he had been using VistA for 16 years, but now it lags behind other electronic medical records framework systems. He asked how to engage with patients and citizens in order to drive change in the right direction. Seong Ki Mun responded that OSEHRA is in the process of revamping the VistA software. It organizes work groups that look at particular issues and ensures that the outcomes of these work groups are linked to better overall products. It is important to be responsive to needs and use the feedback from work groups.

Shiro Hinotsu (Okayama University Hospital, Okayama, Japan) noted that new drug application companies must send Clinical Data Interchange Standards Consortium (CDISC) standard datasets to government, which are also OS. He asked about system applications of OSEHRA for CDISC. Seong Ki Mun responded that the power of OS is that users can look at the computer code themselves and competent end users have control over what they use. The problem with OS is that there are too many unregulated changes because sometimes end users want to do their own thing. OSEHRA seeks to maintain a certain degree of standardization.

4. Report of Korea Prostate Cancer Study and Japan Prostate Cancer Study and presentation of status of registration for A-CaP

4.1. Japan Prostate Cancer Study

Shiro Hinotsu noted that the Japan Prostate Cancer Study (J-CaP) aims to evaluate the trends and outcomes of hormone therapy for establishing an adequate guideline for hormone therapy for patients who had newly started hormonal therapy between 2001 and 2003. In 2016, the follow-up period was terminated. J-CaP provides a secure database and eligible institutions can connect to the server using an issued identification number and password.

The original J-CaP study consisted of background, treatment, adverse events, survival data, and laboratory data. The majority of patients were registered in general hospitals, with a smaller proportion registered in university and private hospitals. The most-used initial hormone therapy is luteinizing hormone releasing hormone + antiandrogen and combined with surgical castration (SC) + antiandrogen. These two account for ~60% of all therapy for prostate cancer in Japan. The percentage of patients receiving combined androgen blockade increases depending on the staging.

The Japan Cancer of the Prostate Risk Assessment (J-CAPRA) score was developed as a tool for discussion, based on data from J-CaP and the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE). In terms of survival analysis, progression-free survival is 4.93 years after primary androgen deprivation therapy, over 13 years of follow-up. Overall survival has a median of 12.2 years after PADT. In terms of progression-free survival by J-CAPRA score, a high-risk score is ≥ 8 and patients with a lower risk score have been shown to survive longer.

The J-CaP database is large and provides a wealth of data. For example, it has been used to study cause of death and the number of cardiovascular events. An Innovative Study-I was implemented in which patients were able to select between hormone therapy or prostatectomy, and the study has engaged in follow-up of these patients. The J-CaP study data have supported the compilation of many academic papers.

In summary, the J-CaP study comprises long-term follow-up data and has a large number of registered patients. It provides a data source as a novel risk assessment tool. The J-CAPRA score has been developed, which is useful for international comparisons. However, the data structure definition is important because only collected factors can be used for the tool. The J-CaP database can also be used for subgroup analysis.

4.1.1. Discussion

Tadaichi Kitamura (Faculty of Medicine, University of Tokyo, Tokyo, Japan) asked about how many papers have been published based on the J-CaP study. Shiro Hinotsu responded that ~20 papers have been published. Jasmine Lim (Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia) asked whether net survival analysis or relative survival analysis had been performed. Shiro Hinotsu responded that there are data on prostate cancer deaths, other cancer deaths, or other deaths. It is possible to find cancer-specific survival, but what the study focused on was the three kinds of survival data that had been presented.

4.2. Background factors and health-related quality of life in radical prostatectomy or ADT for localized prostate cancer

Yasuhide Kitagawa (Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan) reported on a retrospective study in which the outcomes of radical prostatectomy or primary hormone therapy were compared. The disease-specific survival for patients was surprisingly similar after 10 years, but disease-specific survival according to histological grade differed.

J-CaP Innovative Study-I was implemented for localized prostate cancer [T1c T2N0M0, 67—76 years, prostate-specific antigen (PSA) < 20 ng/ml]. A total of 1,240 patients were initially registered and analysis was finally conducted on 859 patients who underwent prostatectomy and 381 patients who underwent hormonal therapy. In general in Japan, the proportion of patients undergoing PADT is ~10%, but in this study the proportion was 30%. The mean age of both the groups was 71.0 years and 73.0 years, respectively, and that of the hormonal therapy group was higher than that of the prostatectomy group. The PSA level was higher in the PADT group. In both groups, patients with stage T1c cancer were the most common, constituting ~65% in each group. In addition, patients with stage T2a cancer accounted for 30.6% in the prostatectomy group and 21.6% in the hormonal therapy group.

Considering that most patients in the study were elderly, it is natural that many patients had some coexisting diseases. It was

considered that patients in the PADT group were treated with this therapy because the risk of operation was high owing to the risk of cardiovascular or respiratory disease.

The reasons for the selection of the treatment regimen and who made the decision regarding the treatment were investigated. In both groups, the patients' choice of treatment was a major factor. It may be that younger age is a factor in the decision regarding the operation, and comorbidity is the reason why the patients choose PADT.

The results of quality of life (QOL) according to Short Form (SF)-8 were shown in the prostatectomy group. SF-8 contains eight scales that generate physical and mental component summary scores. The scores of each domain, except for mental health, for the radical prostatectomy group decreased at 3 months following surgery. However, their scores returned to pretreatment levels 1 year following surgery. The mental component summary score increased over time. By contrast, the scores of some domains for the PADT group decreased, including physical function. However, the scores for mental health increased during 1 year of treatment.

In terms of the results of the Expanded Prostate Cancer Index Composite (EPIC), the completion rate of EPIC was similar to SF-8. The mean urinary scores for surgical patients decreased at 3 months post-treatment and improved at 12 months, but remained lower than those at baseline. The section of hormonal function in the EPIC questionnaire includes hot flashes and breast tenderness, therefore, the scores of patients receiving PADT gradually decreased over time, compared with those of surgical patients. The mean score of the sexual domain was already low at baseline, declined after 3 months of treatment, and did not return. The difference in urinary and sexual QOL scores between surgical patients and patients receiving nerve-sparing and non-nerve sparing procedures was not clinically significant.

In terms of the overall satisfaction scores of each group, the numbers of patients with increased and decreased satisfaction were almost equal in the prostatectomy group. By contrast, in the PADT group, the average satisfaction tended to increase during the 1-year treatment period. Patient selection was higher in the PADT group and patient hope may therefore reflect patient satisfaction. Many patients may prefer noninvasive treatment and this is why many patients in Japan select PADT.

4.2.1. Discussion

Levent N. Türkeri (Turkish Urooncology Association, Turkey) noted that it seems that there is a discrepancy between Western countries and Japan in terms of treatment. Yasuhide Kitagawa responded that the result is from clinical studies and < 10% of localized prostate cancer cases received PADT in Japan, which is similar to other Asian countries. However, the adverse effect of cardiovascular disease is lower in Japan than in other countries. Hideyuki Akaza added that Shiro Hinotsu had shown a graph showing cardiovascular events with people who had undergone treatment and those who had not. There was no significant difference and therefore concerns of cardiovascular risk are not as great as in Japan.

Robert A. Gardiner (University of Queensland Centre for Clinical Research at Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia) noted that as Western men age they tend to become hypogonadal and asked if this is also the case for Japanese men. Mikio Namiki (Graduate School of Medical Science, Kanazawa University, Japan) noted that the average testosterone level is lower in Japanese than Western men.

Matthew Cooperberg noted that, even in the West, the impact of ADT on cardiovascular endpoints is controversial. There has been a large meta-analysis that showed no impact. There may be a selection bias in that the sickest patients are put on ADT. Cancer survival was much better in Japan in comparisons between J-CaP and CaPSURE. This is interesting and there is still no definitive answer.

4.3. Smart care for prostate cancer using the Internet of Things and artificial intelligence (Korea Prostate Cancer Study)

Ji Youl Lee (St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea) noted that the trend in medicine is moving towards precision medicine, big data, smart medicine, and artificial intelligence (AI). IBM Watson is famous for AI for Medicine and now Watson Genomic Analysis. The future direction for prostate cancer is precision medicine using AI and the Internet of Things because prostate cancer is heterogeneous. It may be possible to use AI for prostate cancer in order to detect Gleason scores more accurately, among other uses. The major issues for precision medicine are medical informatics (big data), bio-banking, genomic profiling (nanodata), and the integration of big and nanodata.

To create a clinical decision supporting system, it is important to create a smart clinical database (phenotype), engage in bio-banking and create genomic databases. The Catholic Prostate Institute has created an Electronic Genomic Medical Record system, comprising imaging and prostate bio-banking. The Korea Prostate Bank has been used to publish many papers.

In terms of smart databases, the Korea Prostate Cancer Study (K-CaP) database was created in 2012 and is now supported in multiple languages, and many papers have been published based on the K-CaP database. Work is still ongoing to integrate database systems. St. Mary's Hospital is famous in Arab countries and many patients from the United Arab Emirates, Russia, and China come to Seoul for treatment. Telemedicine is therefore important for these patients and a smartphone application has been developed to respond to their needs, including an Arabic language version. Memorandum of understanding (MOUs) have been concluded with many institutions on the use of the application.

4.3.1. Discussion

Yoshihiko Hirao (Osaka Gyoumeikan Hospital, Osaka, Japan) noted that AI is important for decision-making, but asked whether it is readily accepted by patients. Ji Youl Lee responded that, for prostate cancer, it is difficult to determine the appropriate treatment. If AI could provide a clinical decision-supporting system, combining genomic and research data, it could give a recommendation about which treatment option is best for the patient. The Gleason score is important for active surveillance, but perhaps it would be possible to rely more on AI. AI is a decision-making-supporting system.

Shigeo Horie (Juntendo University Graduate School of Medicine, Tokyo, Japan) noted that in statistical analysis it is normal to eliminate confounding factors and asked how AI could deal with such confounding factors in decision-making. Ji Youl Lee responded that for clinical applications it is imperative to consider many options. There is no remarkable genomic marker in prostate cancer and so it is necessary to use multiple genomic factors, from which a decision can be made on which decision would be best.

5. Present status of the registration for A-CaP in each country

5.1. Hong Kong

Ng Chi Fai (Division of Urology, The Chinese University of Hong Kong, Hong Kong) noted that Hong Kong has already applied for approval and three out of nine hospitals with coverage of > 40% of the population has been achieved for registration in the A-CaP study. The REDCap (Research Electronic Data Capture) system is being used to collect data and this system provides a good basis to collect data and has inbuilt measures to eliminate duplication.

In terms of future progress, efforts will be made to invite more centers to participate, although this will depend on funding and manpower.

5.1.1. Discussion

Shiro Hinotsu noted that REDCap is a cloud server and asked how it is utilized. Ng Chi Fai responded that once the software is downloaded the information is stored on the hospital server. Teng Aik Ong (Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia) noted that in Malaysia REDCap is also used and the information is stored on hospital servers.

5.2. Taiwan

Tong-lin Wu (Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan) noted that, after the previous A-CaP meeting, the Ethics Committee of his hospital had agreed to waive consent. To date, 83 patients have data completed, but half of them are from 2015. He raised the issue of finding a coding method. There are also other questions that need to be considered, which include the following. How to define lethal prostate cancer? With regard to the number of positive biopsy cores, how about diagnosis with transurethral resection of the prostate? With regard to T stage, should this be done using the American Joint Committee on Cancer staging alone, or also with magnetic resonance imaging?

5.3. Indonesia

Lukman Hakim (Department of Urology, Airlangga University/ Soetomo General Hospital, Surabaya, Indonesia) noted that, until recently, there was no national cancer registry in Indonesia. On April 24, 2016 a meeting in Jakarta involving eight teaching hospitals was implemented. Representatives were appointed as primary investigators and local scientific benefits were explained. A board of advisors (3 urologists from the 3 largest urology centers) was appointed and a simple web-based application system was announced. The enrollment period started on April 1, 2016.The study has started with six hospitals on Java Island, including the three largest cancer centers in Indonesia. Fifty-one patients have been registered from these six teaching hospitals.

In terms of the study algorithm, data collection is implemented by a study coordinator, who also enters data into the system, following data verification by principal investigators and country coordinators. The application is currently under reconstruction as it has limitations. It would be good if Indonesia could use either J-CaP or K-CaP software. The aim is to enable coordinators to update or input new data from wherever they are. In terms of patient background, 64.7% of patients have no history of prostate cancer or lethal prostate cancer, although, similar to Taiwan, it will be important to consider how to define lethal prostate cancer.

The mean PSA at diagnosis is 361.91 ng/ml and the mean T category is T2c. In general, among the 51 cases, ADT (without chemotherapy) was used as the main treatment. Of the 14% who underwent prostatectomy, all undertook it as first-line curative treatment. ADT was performed mainly as primary treatment and luteinizing hormone releasing hormone + antiandrogen + long-term antiandrogen was the preferred method used by doctors in Indonesia. The antiandrogen of preference was bicalutamide, which was used in 91.4% of cases.

In terms of constraints, there is a risk of loss to follow-up and solutions are being sought by obtaining mobile phone numbers of the patients and their families. In addition, the limited features of the current application software are under reconstruction and it would be appreciated if J-CaP or K-CaP software could be used. In Indonesia the hardcopy of medical documents is still a legal document and hospitals are required to store them for 5 years.

In terms of next steps, the plan is to involve more satellite hospitals, implement regular annual meetings, and look into the potential for using J-CaP or K-CaP software.

5.3.1. Discussion

Kim Moretti (SA-PCCOC, Australia) asked what the median PSA was. Lukman Hakim responded it was somewhere in the region of 150, which is still high. Jason Letran (Cardinal Santos Medical Center, Manila, Philippines) asked who engages in follow-up and whether it is the physicians themselves. Lukman Hakim responded that it is the coordinator who contacts patients or their families by telephone.

5.4. Singapore

Edmund Chiong (National University Health System, Singapore) reported that there are seven hospitals in Singapore looking after prostate cancer patients; of which three have individual prostate cancer databases. There are also a number of observational studies underway. Three of the academic hospitals have agreed to participate in A-CaP. Each has its own existing prostate cancer database. Prospective data are already available for 100−300 patients. The proposed platform is REDCap and attempts are being made to harmonize data fields and centralize subject identification, and methods developed to eliminate duplication. There are still IRB issues, but a single multi-institution IRB application for all hospitals for prospective patients is in progress, and informed consent will be required. Each hospital will retain its own database autonomy and data sharing will require some kind of contractual agreement.

In Phase 2, once the above has been arranged, the aim is to combine anonymized data from major hospitals, which have already been collected in other studies. Modifications and changes will be made and there will be some degree of data governance and oversight. Data sharing with A-CaP will also require some kind of contractual agreement. The target for Phase 1 to Phase 2 implementation is 2017 and the aim is to recruit 500−1,000 patients over the course of 3 years.

In Phase 3 the aim is to combine anonymized data from all participating hospitals, implement modifications and changes, and create a long-term standing database for Singapore. Coordination with societies, such as the Singapore Urological Association, will be required. The target for implementation is from 2018.

The Human Biomedical Research Act, passed by the Singapore Parliament, is a complex piece of legislation that will have a significant impact on the way human biomedical research is conducted. The law includes new, criminally enforceable requirements for consent, documentation, IRB organization and administration, as well as responsibilities of researchers and research institutions. Specific issues are the requirement for individual informed consent from patients, even in databases. There are difficulties with obtaining “waiver of consent due to impracticability” and there are issues with recommendations on the “key-holder” for re-identification of patients. This will have implications for data-sharing agreements and efforts are being made to seek clarification from the government.

5.4.1. Discussion

In terms of the large foreign community in Singapore, a question was asked about follow-up of patients in any given study. In response it was noted that people who are deemed to be unlikely to be available for follow-up are not registered for the study.

5.5. Philippines

Jason Letran noted that following the First A-CaP Meeting 2016 a brain-storming meeting was held in the Philippines and there were 11 training institutions and 20–30 private institutions invited to attend. In the Philippines most patients with localized prostate cancer patients are from the private sector. The Philippines does not have a database of its own and immediately upon receiving an e-mail from Japan, preliminary activities were implemented and used to identify potential problems. One of the problems was the technical limitations of institutions in terms of interest and Wi-Fi access. A decision was made to create a booklet and provide training on how to fill it out. A decision was also made to input data using Excel (Microsoft Corporation, Redmond, WA, USA) and a research assistant is dedicated to this study.

As of August 30, 2016 1,000 booklets have been printed and 600 distributed. The total number of booklets received was 57; all of which have been encoded. The rate of return is only 9.5% at present. Another problem is the low motivation among practitioners and residents to fill out the registry. For the study to be sustainable it will require continuous funding, the training of new practitioners and residents, additional research assistants as follow-up expands, and issues with the IRBs and ethics committees require attention.

Strategies to respond to these challenges are close coordination with the head of the institutions/hospitals on survey conduct, and provision of incentives for every 10 booklets handed over to the Philippine Society of Urologic-Oncologists. It will also be important to make people realize that the data collected will be useful for their own studies or future research.

5.5.1. Discussion

Lukman Hakim asked how updating of the data is monitored. Jason Letran responded that once the hard copy of the booklet is collected and encoded it is returned to the practitioner and is collected again every few months for updates.

5.6. Malaysia

Teng Aik Ong reported that prostate cancer is the fourth most common cancer in Malaysian men. Most of the patients were Chinese, followed by Malays. The urological service in Malaysia is divided into government and private services and 70% of the population will use government services, provided by the Ministry of Health or Ministry of Higher Education. A-CaP Registry will be built based on prostate cancer patients attending for treatment in all government hospitals in Malaysia. There are 12 centers in Malaysia that offer urology services. The challenge is to get everyone involved in A-CaP, including urologists at the Ministry of Health. A letter was received on March 22, 2016 indicating that the Ministry had approved the initiation of the A-CaP study. Each institution has provided an annual estimate of the number of prostate cancer patients. REDCap is the system that is being used. Visits to hospitals to promote the concept of A-CaP to staff and provide information are also being implemented.

In terms of the current status, six institutions have already started and major centers in the Klang Valley are due to begin the study in the near future. The strategy for 2016 is to receive specific approval and seek international and local funding to ensure the sustainability of the study.

5.7. Thailand

Bannakij Lojanapiwat (Faculty of Medicine, Chiang Mai University, Thailand) reported that from January to July 2016 there were 212 new cases of prostate cancer, including 39 in Chiang Mai University Hospital. These are government health-system-covered cases and private cases are not included. Although these patients have been registered, they have not yet been input into a system for A-CaP, but once information has been received from Malaysia about REDCap, the input of data will begin.

In terms of staging, most cases are T3 and T4 and there is more localized prostate cancer to be found in Bangkok. The challenges that need to be overcome are to manage the workload that is faced with other diseases. There are only 350 urologists in Thailand for a population of 67 million. It is hoped that the A-CaP study will gain greater support and awareness and a budget can be procured to ensure the sustainable implementation of the study.

5.7.1. Discussion

Hideyuki Akaza noted that there seems to be differences among institutions on the type of castration provided. Bannakij Lojanapiwat responded that there is a decreasing amount of surgical castration, but it is still used in some institutions due to costs and availability of medical castration. It is recently the case that medical castration was covered under the national health system.

5.8. Korea

Kim Wun-Jae (Chungbuk National Medical University Hospital, South Korea) reported that registration for the A-CaP study had already started in Korea. Prostate cancer incidence was 8.2% in Korea in 2012, which is lower than in Western countries, but the percentage continues to increase. In terms of the changing patterns of primary treatment in Korea, there has been an increase in surgery from 22.4% to 45.4%, a reduction in ADT from 60.3% to 45.4%, and a significant increase in radiation therapy from 7.2% to 18.4%. In multinomial logistic regression analysis, older patients showed a significant association with ADT or radiation therapy compared to surgery. Patients with higher incomes showed significant association with surgery.

Treatment patterns in Korean prostate cancer patients have changed remarkably over the past 10 years. Sociodemographic factors do affect the primary treatment choice and it is likely that they will be important tools for reviewing changing patterns of primary treatment in Korean prostate cancer patients and planning future health policy.

From 2007 to 2013 the incidence of prostate cancer doubled in Korea but mortality decreased. At present, a total of 2,861 cases have been collected from January 2016 for the A-CaP study. Approximately 35% of all K-CaP cases are expected to be included. Of the already registered patients, the most used therapies are radical prostatectomy (62%) and hormonal therapy (28%). The proportion of radical prostatectomy cases registered for A-CaP is larger than the nationwide average and the proportion of hormonal therapy cases under A-CaP is smaller than the nationwide average.

In terms of future steps, it will be necessary to consider who will participate in the A-CaP Scientific Committee, which is the most important part of A-CaP. It should also be recognized that data input for the purposes of A-CaP can be time consuming and ways should be considered to decrease time burden of input.

5.8.1. Discussion

Mikio Namiki noted significant differences among the patients included in the A-CaP study and the nationwide average and asked whether it would be possible to include hospitals other than the major institutions in Seoul. Kim Wun-Jae responded that other hospitals are included in K-CaP and it could be expected that these hospitals would be included in A-CaP if a format similar to K-CaP were used. Hideyuki Akaza noted that for the A-CaP study ~140

institutions around Japan are participating and it is expected that ~20,000 cases will be registered in Japan.

5.9. Turkey

Levent N. Türkeri reported that an epidemiological study was implemented to investigate the incidence of prostate cancer in Turkey. It was designed and executed by the Uro-Oncology Association of Turkey, supported by the Ministry of Health. All cases of prostate cancer in selected areas of the country have been registered, with 6,693 cases registered, and 12 cities participating. The age-adjusted incidence rate is ~36 per 100,000, which is similar to that in Northern Mediterranean countries. Most patients are > 55 years of age and are concentrated around 65–69 years.

The Uro-Oncology Association has engaged in efforts to create a registry, and a committee was established for that purpose, comprising five expert urologists, one statistician, and two software experts. This committee made an official start on registering patient records in September 2015. A web-based system has been developed for registering patient data and it is similar to the format for A-CaP registration. The registration form includes a general information page, medical history page, diagnosis page, biopsy page, staging page, treatment page, radical prostatectomy page, QOL page, and follow-up and status at last follow-up pages.

The prostate cancer database has a total of 188 main data points; most of which are accessed from drop-down lists. Six hundred and fifty patients have been recorded and one of the major problems is the absence of dedicated data managers. Efforts are being made to recruit data managers through the Uro-Oncology Association, which imposes a financial burden on the Association. Turkey can participate in A-CaP given that there is a functional registration system in Turkey and it is anticipated that it will be a fruitful collaboration.

5.9.1. Discussion

Yoshihiko Hirao asked if PSA screening is implemented in Turkey. Levent N. Türkeri responded that there is a high degree of awareness of PSA in Turkey, which has been driven by media efforts. This is perhaps the reason why many cases are identified earlier.

Frank Gardiner asked about the maintenance of QOL data; to which the response was that the data mangers that have been employed are doing their best to keep data up to date. Dedicated data managers are being trained by a private company with the specific aim of maintaining the database.

6. Special Lectures II

6.1. Report from CaPSURE

Matthew Cooperberg noted that approximately one-third of all CaPSURE patients (~5,000 in total) are still being followed. There are now > 190 publications arising from CaPSURE, and various risk instruments have been developed and validated. There has been a sea change in therapy in the USA, including more watchful waiting and less ADT. In terms of QOL it has been found that differences among treatments tend to attenuate over time.

CaPSURE was the original source of data for CAPRA and the first source of validation statistics for the J-CAPRA score, and has resulted in a number of validation studies. The CAPRA score is moving towards national standards of care and it is hoped that it will provide an alternative as a risk stratification tool.

In terms of the future for CaPSURE, tracking real-world use of medication for castration-resistant prostate cancer is a major challenge. Data input is time consuming and there is little appetite to do this among practitioners. It is anticipated that once current funding runs out that the registration of cases for CaPSURE will end and migrate to the American Urological Association Quality Registry (AQUA), but the monitoring of existing CaPSURE patients will continue, including cases of advanced prostate cancer. Thousands of data points have been collected on imaging, treatment, and outcomes.

Another effort is a retrospective effort to acquire biomarkers. Through a 2012 Transformative Impact Award from the Department of Defense collections of formalin-fixed paraffin-embedded biopsy and prostatectomy tissue specimens has started, along with saliva for germline DNA from CaPSURE participants. The Department of Defense project focuses on low-risk disease and it is hoped that this will be followed up with higher-risk disease in the near future. This will be one of the only biomarker projects including men treated with different modalities, and with long-term follow-up including QOL.

Efforts are also being made to analyze the genomic landscape of prostate cancer and this is an area that will be of increasing importance in the future, with a view to molecular subtyping of prostate cancer, as has been the case for breast cancer for many years.

AQUA collects detailed national processes and outcomes data for patients with urological diseases. The primary goal is quality assessment and improvement through local feedback to practices. Secondary goals are to fuel next-generation health services research and clinical/outcomes research, and inform urology policy efforts. There are 380 urology sites and 2,154 providers that have joined AQUA. Data are available from ~50 sites and the country is well covered, and discussions are underway with the University of Toronto, Toronto, Ontario, Canada with a view to expanding the database beyond the USA. It is possible to pull structured code from the AQUA database. There are also methods to find Gleason scores that are embedded in the text, as well as initiatives to collect patient-reported outcomes (PROs) at the national level.

In parallel with AQUA, UCSF has been leading dictionary development efforts and is on the EPIC, an electronic medical records system. EPIC was not written originally for data collection, but it has the capabilities to create data from notes. The UCSF data model is gradually working its way into the national system through AQUA.

AQUA has successfully registered 15,682 newly diagnosed patients over 2 years, which is faster than the time taken for CaPSURE. Although the data dictionary is not as comprehensive as CaPSURE, it is likely that 100,000 cases will be recorded. The latest (preliminary) data suggest that trends are changing and there is a move towards active surveillance and watchful waiting.

In summary, it is hopeful that prostate cancer studies based on Medicare will disappear, with data based on coding/billing data being replaced by prospective registries working from the point of care and integrating PROs. CaPSURE will continue as a gold standard disease registry with unparalleled depth and follow-up as the AQUA score and size will expand rapidly. Internationally constituted studies like A-CaP will provide unique insights into prostate cancer epidemiology. It is hoped that in the future it will also be able to routinely integrate genomics with registries.

6.1.1. Discussion

Levent N. Türkeri asked whether there is any difference between radical prostatectomy samples and biopsy samples in terms of representativeness. Mathew Cooperberg responded that the aim is to seek whatever materials are available. The representativeness of the biopsy depends on how well the biopsy is done. It is not possible to know until specimens are actually collected. The other source of biomarkers is the use of saliva samples and these are

being collected from recent patients for whom there is no long-term follow-up.

Frank Gardiner noted that one of the problems is that more is not necessarily better. There is heterogeneity and it may be better to focus on those cases that could be guaranteed as being quality information. Matthew Cooperberg responded that for questions of tracking practice patterns and doing real-world comparative effectiveness studies, it will be important to reach the national level. CapSURE focuses on major centers rather than smaller institutions and AQUA is also a similar exercise, therefore, these provide an optimistic picture compared to what is happening across the country. This is why it is important to expand registration to the national level.

6.2. Prostate cancer registries: Perspective from Australia

Declan Murphy (Peter MacCallum Cancer Centre, Melbourne, VIC, Australia) reported that although mortality rates from 1982 to 2014 have gone down, there is still a high incidence of prostate cancer in Australia. The paper titled "Prostate cancer registries: current status and future directions" concluded that the strengths and limitations of prostate cancer registries should be carefully considered when planning studies using these databases. Although randomized controlled trials still provide the highest level of evidence, large registries play an important and growing role in advancing prostate cancer research and care.

The Victorian Prostate Cancer Registry (V-PCR) was established in 2008 and has accumulated ~19,000 patients (~90% of all patients in Victoria). The goals were to provide information patterns of care following diagnosis of prostate cancer; to monitor quality of care for men diagnosed with prostate cancer; and to provide a platform for further research of prostate cancer. The hospital sends notification to the Victorian Cancer Registry, after which the hospital sends an explanatory statement and letter of invitation to participate. The Victorian Cancer Registry then sends the patients' biopsy results to the V-PCR. V-PCR staff collect patients' results from the hospital and phone patients at 12 months and 24 months to engage in a follow-up questionnaire.

There has been successful recruitment to the V-PCR and there are now 35 sites engaged in recruitment, with 100% clinician opt-in and 98% patient opt-in. In terms of PROs, urinary dysfunction is not reported as much as sexual dysfunction.

One reason that there is good participation in the registry is that the registry sends out reports to clinicians and hospitals on their performance. These reports include such items as mortality rate, positive margins, documentation of *c*T stage in medical records, biochemical recurrence at 24 months, and QOL. Clinicians can see their own standing on a graph that shows positive surgical margins and can take steps to reduce these margins. The V-PCR also helps to measure changes in quality by monitoring changes in three process quality indicators. Monitoring the quality of care is also a key aspect, and since 2010, a 21% reduction in the rate of low-risk patients undergoing active treatment has been achieved.

In summary, V-PCR serves as an excellent disease-specific registry with almost population-level data capture. Quality indicators available to clinicians and hospitals and good publications are now emerging. Improvements in quality in a number of domains have been achieved and moves are being made to expand the initiative nationally and also binationally to include New Zealand.

A future development is the Prostate Cancer Outcomes Registry (PCOR), which is funded by Movember. It may be useful for A-CaP to align with the Movember Foundation and perhaps seek funding for similar registries.

6.2.1. Discussion

Frank Gardiner asked about stumbling blocks to alignment between V-PCR and A-CaP. Declan Murphy responded that the major stumbling block is standardizing datasets. This would be a good thing to aspire towards but will take time. In Australia and New Zealand the indigenous populations have poor outcomes and it will be interesting to see what disparity there is among ethnic populations across Asia as a whole.

6.3. Report from SA-PCCOC data (Australia)

Kim Moretti reported that SA-PCCOC was established in 1998 and its mission is to improve understanding of prostate cancer in SA by monitoring the clinical profile of patients and their treatment and clinical outcomes, and thus improve care of prostate cancer patients through the provision of appropriate reports and analyses to clinicians and health planning bodies that are responsible for their care at the State level.

The SA-PCCOC Registry is a prospective disease-specific registry and longitudinal observational study comprising consenting men diagnosed with pathologically proven prostate cancer in SA. Patients are followed to death or withdrawal. Patients want to know certain things and therefore PROs have been collected from inception of the Registry, including a baseline. The Registry is also compliant with the Australian Commission on Safety and Quality in Health Care Clinical Quality Registries Framework.

The registry has 11,400 patients for a population of 1.45 million and there are good collection systems. It is long running, with 18 years of follow-up and there is a lot of data completeness and data quality. Three party-collected patient reported outcome (PROs) are 12-item short form health survey (SF12), expanded prostate cancer index composite 32 (EPIC32) and international prostate symptom score (IPSS).

The Registry started in 1998 with one surgeon, and as of 2016, it has achieved population coverage of 95%. Governance is critical and it is a requirement to have consumer representatives on SA-PCCOC and other bodies, because the two major funding bodes will not provide funding unless there is a public representative on it.

SA-PCCOC is multidisciplinary, which is important and is also something that is mentioned in the protocol of A-CaP. Ensuring and maintaining growth are important and there has been a move from an opt-in to an opt-out system.

In terms of the changing profile of prostate cancer in SA, radical prostatectomy and radiotherapy have decreased in recent years, with an increase in surveillance and watchful waiting. PROs are important and they have been collected since the start of SA-PCCOC. PROs include urinary and sexual functions. Data show substantial changes in prostate cancer presentation and management over the past 16 years and improvements in prostate cancer survival.

Collaborative research is important for maintaining a database. Publications and presentations have been increasing in recent years, including 13 presentations at international conferences. There are currently 29 projects underway and eight publications have been issued in 2016, a number of them about registries.

It is important to be visible and engage in marketing in order to ensure the continuation of registries and study groups. Engagement is also important and this can be achieved from various symposia and conferences. It is also important to be innovative, and at SA-PCCOC there has been substantial progress made in the development of new methods and tools for e-collection of data.

In Australia it is mandatory for any diagnosis to be notified to pathology laboratories. Therefore, an automated link has been created whereby SA-PCCOC receives notification directly from pathology laboratories. However, SA-PCCOC can only import from the

mailbox of consenting sites, contributors, and patients. Current coverage is ~95% and Electronic LAB (eLAB) has 111,600 PSA values that are provided automatically.

A binational prostate cancer outcome registry combining Australia and New Zealand (PCOR-ANZ) was only recently completed. Initial discussions were on the registry model, including how to approach governance and defining the purpose of the database at the national level. The easiest model to create is a disseminated extraction model, which is what A-CaP will be. A centralized clearing house model is one that is the same as CaPSURE. The PCOR-ANZ model is a federated model. In this system the states own the data and there is an agreement with the central data custodian. In the case of PCOR-ANZ, Movember required the database to include relevant goals identified by patients.

Another important factor to bear in mind in terms of core data sets is to concentrate on minimum not minimal datasets. The PCOR-ANZ registry identified 347 data points and through a Delphi process the 80 most common data elements were identified as Tier 1 for minimum data collection, Tier 2 for anticipated data collection, and Tier 3 is the value-added platinum standard for data collection.

6.3.1. Discussion

Shigeo Horie asked if SA-PCCOC is funded by the state or other sources. Kim Moretti responded that funding is from grants and from the Movember organization. It was also noted that consumer representatives are important in Australia. In terms of feedback, the consumer representative works on marketing and awareness-raising activities.

Frank Gardiner asked about the three tiers for data collection, noting that the classification for TNM is a Tier 1 item in PCOR-ANZ and SA-PCCOC but it is listed as mandatory for A-CaP. He asked whether this could be a barrier to integrating Australian and New Zealand registries with A-CaP. Kim Moretti responded that the Australian and New Zealand databases are heavily aligned with International Consortium for Health Outcomes Measurement datasets, but it is likely that there would not be major hurdles to be overcome in aligning data registries.

6.4. Special report from USA/United HealthCare (UHC) on prostate cancer treatment in the USA

Peter Carroll (UCSF) reiterated Shiro Hinotsu's comments about the richness of collaboration, as evidenced by CaPSURE and J-CaP. In terms of prostate cancer in the USA, there has been a big uptake in the use of radical prostatectomy, and the risk profile of men undergoing this operation is increasingly those with high-risk disease.

In terms of predictions for prostate cancer now and in the future in the USA, the negative public pressure on PSA early detection may be tempered, but it will not go away. There is increased use of novel technology to decrease biopsy rates, and an increasing sense that prostate cancer is a spectrum of disease influenced by host and tumor environment. In addition, active surveillance, although increasingly recognized as a relatively safe option, will be challenged by focal forms of therapy, and the treatment of high-risk disease will be better personalized due to the use of advanced imaging and molecular medicine. The big disrupters here are the US Preventive Services Task Force, tumor biology, changing treatment paradigms, and payment reform. There has been a decrease in PSA testing in the USA over time.

In terms of what will save early detection, the key point is that it has the best impact on quality-adjusted life years saved. In the USA in the next decade, there will be selective detection and treatment, rather than full detection and selective treatment. Increasingly in the USA, there are moves toward measures of increased specificity, such as use of percent-free PSA, 4Kscore, or Prostate Health Index. A strategy of sampling only magnetic resonance (MR) regions of interest would result in missed or downgraded Gleason $\geq 3+4$ tumors in 29 patients (14%). The real issue is what to lead with, whether it be Prostate Health Index/4Kscore or multiparametric magnetic resonance imaging/fusion biopsy, etc.

For first-line treatment there is also a changing paradigm. Focal therapy can benefit only a small proportion of men, and this is a source of concern. Molecular testing and imaging are likely to save the day here. Pre-therapy circulating tumor cell (CTC) nuclear expression of AR splice variant 7 (AR-V7) protein in men with metastatic castration-resistant prostate cancer is a treatment-specific biomarker predicting superior overall survival for taxane therapy over androgen receptor signaling (ARS) inhibitors in a clinical practice setting, warranting prospective validation.

Ga-prostate-specific membrane antigen positron emission tomography is now capable of detecting late biochemical failure. Around 42% of the cases with nodal metastases had positive nodes located outside the primary landing zone (perirectal, presacral, and anterior prostate) using this technique.

There is likely to be a confluence of imaging, refined treatment, and molecular medicine in the future. Prostate cancer is a spectrum of disease and it should be assessed and treated as such. It is important to match the treatment to the patient and his cancer. All treatment options required greater scrutiny in terms of outcomes, costs, and appropriateness. It is important to begin collecting and disclosing patient-reported, risk-adjusted outcomes prospectively, across multiple treatment modalities, facilities, and geographies. Furthermore, efforts should be made to develop, validate, and use novel therapy appropriately.

7. Closing remarks

Yoshihiko Hirao expressed appreciation to Hideyuki Akaza for his initiative in setting up A-CaP. When the idea for A-CaP was first proposed, J-CaP and CaPSURE had already been implemented and K-CaP was also underway. However, the issue of an Asia-wide CaP has presented various challenges due to issues of funding and other logistic matters. It is thanks to the efforts of Dr. Akaza and his colleagues that A-CaP has made a successful start. Appreciation was expressed to Korea for hosting the Second A-CaP Meeting, and in conclusion, it was stressed that the work of A-CaP is only just starting and there will be more to do in the future.

Hideyuki Akaza noted that if A-CaP members wish to meet in Chiang Mai at the 7th Congress of the Asian Pacific Prostate Society (APPS) in 2017, it will be important to launch a common investigation study that will provide a basis for discussion among all participants. He thanked A-CaP members and closed the meeting.

Conflicts of interest

No conflicts of interest.

References

1. Akaza H, Hirao Y, Kim CS, Oya M, Ozono S, Ye D, et al. Asia Prostate Cancer Study (A-CaP) launch symposium. Prostate Int 2016;4:88–96.