

Seventh Joint Meeting of K–J–CaP and CaPSURE: extending the global initiative to improve prostate cancer management

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This report summarizes the presentations and discussions that took place at the Seventh Joint Meeting of the Korea–Japan Study Group of Prostate Cancer (K–J–CaP) and the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) held in Seoul, Korea, in September 2013. The original J–CaP and CaPSURE Joint Initiative has now been established since 2007 and since the initial collaboration between research teams in the United States (US) and Japan, the project has expanded to include several other Asian countries. The objective of the initiative is to analyze and compare data for prostate cancer patients in the participating countries, looking at similarities and differences in patient management and outcomes. Until now the focus has been primarily on data generated within J–CaP and CaPSURE, both large-scale, longitudinal, observational databases of prostate cancer patients in Japan and the US, respectively. This year's meeting was hosted for the first time in Korea which has recently established its own national database–K–CaP–to add to the wealth of data generated by J–CaP and CaPSURE. As a newly-developed database, K–CaP has also provided a valuable 'template' for other countries, such as China and Indonesia, planning to establish their own national databases and this will ultimately allow greater opportunities for international data comparisons. A range of topics was discussed at this Seventh Joint Meeting including comparison of outcomes following androgen deprivation therapy or radical prostatectomy in patients with localized prostate cancer, the use of active surveillance as a treatment option and the triggers for intervention when employing this regimen, patient quality of life during treatment, the impact of comorbidities on outcomes, and a comparison of recent outcomes data between J–CaP and CaPSURE. The participants recognized that prostate cancer was now a global disease and therefore major insights into understanding and improving the management of this condition would arise from global interactions such as this joint initiative.

Keywords: Prostatic neoplasms, Prostatectomy, Drug therapy for prostate cancer, Comorbidity, Quality of life

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INTRODUCTION

The Japan Study Group of Prostate Cancer (J-CaP) and the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) Joint Initiative was established in 2007 and has now held seven annual meetings to review 'real world' data drawn from these two well-established, longitudinal databases. Initially, the objective was to analyze and compare data for prostate cancer patients from Japan (J-CaP) and the United States (US, CaPSURE) to try and identify trends within these different cohorts in terms of patient characteristics, treatment approaches and outcomes, and then to compare them at a national and global level. However, the initiative has since been expanded to include representatives of other Asian countries. Korea has now developed its own national database and both China and Indonesia plan to do the same, which will ultimately generate a large pool of patient data for analysis.

The J-CaP database was established in 2001 and gathers information about hormone therapy administered to Japanese prostate cancer patients and the outcomes of such treatment. The CaPSURE database was founded in 1995 and currently contains data on more than 14,000 prostate cancer patients treated with various forms of therapy within the US. The Korea Study Group of Prostate Cancer (K-CaP) currently holds data for 7,198 patients who have undergone radical prostatectomy (RP), radiotherapy or hormone therapy.

This report summarizes the presentations and discussions that took place at the Seventh Joint Meeting of J-CaP and CaPSURE held in Seoul, Korea, in September 2013.

The meeting was cochaired by Professor Hideyuki Akaza (The University of Tokyo, Japan), Professor Peter Carroll (University of California, San Francisco, CA, USA) and Professor Choung Soo Kim (Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea). The Chairmen noted that the valuable collaboration between research teams in the US and Asian countries was continuing to expand year-on-year with discussions becoming ever more productive, providing guidance for healthcare professionals and their patients when selecting treatment options for prostate cancer at different disease stages. While there were still many important issues to resolve, this forum allowed meeting participants to share the benefit of their experience of prostate cancer management in their countries and to discuss the challenges they face.

MEETING REPORTS

1. Development of the Korean smart prostate cancer database system

Presented by In Young Choi

Both the J-CaP and CaPSURE databases have been estab-

lished and collecting data for many years however when creating a new national database 'from scratch' there are several challenges that need to be overcome to ensure that the database is usable by healthcare professionals in the field and that the data collected are of value. Dr. Choi, a specialist in medical informatics at The Catholic University of Korea, gave an overview of the Smart Prostate Cancer Database (SPC-DB) system that has been developed for K-CaP to collect and manage data from five major hospitals in Korea. The five contributing hospitals use a variety of methods for collecting and entering the patient data into the K-CaP system depending on their available resources. These include Excel spreadsheets (Samsung Medical Center and Seoul National University Bundang Hospital), a web-based electronic data entry system (Severance Hospital and Asan Medical Center) and a Clinical Data Warehouse system (Seoul St. Mary Hospital) which allows direct electronic transmission of specific information on a patient's prostate cancer from their medical records. These different methods are all supported within the K-CaP database but each presents their own challenges in terms of data management. For example, in the case of the Excel system, it can be difficult to trace and correct text and data entry errors. It was noted that an app has also been developed for the K-CaP database to make data entry easier.

Dr. Choi reported that during the database development process they had endeavored to create a common data model so that each hospital could use the same database structure and collect identical information – this would allow for easier data comparison in the future. In addition, certain rules had been established to ensure uniformity of data collection across the participating institutions, notably: the diagnosis of prostate cancer is defined as International Statistical Classification of Diseases (10th revision), code C61; the initial prostate-specific antigen (PSA) value is the first PSA measurement obtained after C61 diagnosis; the preoperative PSA value is the preoperative biopsy PSA measurement; and the patient's height and weight should be taken from the nurse's report for in-patients. Some data, such as magnetic resonance imaging (MRI) or pathology information, undergo verification with the electronic medical records (EMR) data. In addition, programming is also undertaken in some cases to convert unstructured EMR reports into a format suitable for the database. Each patient is given a unique identifier so this can be followed throughout their disease course, for example if they change treatment or move from one treatment centre to another, and the database updated accordingly. Currently, the SPC-DB holds data from 7,198 patients from the five contributing hospitals.

Dr. Choi noted that while there are similarities between the database structures currently in place for K-CaP, J-CaP, and CaPSURE in that all of them collect demographic data (age, gender, race), body measurements (height, weight, body mass index) and clinical history (any comorbidities, medications, surgical history, family history), there are also notable differences (Table 1). Only CaPSURE collects data on the use of complementary and alternative therapies and on health behaviors (nutrition, consumption of alcohol, and smoking). Differences can also be observed between databases in the laboratory, radiology and pathology data captured and in the types of patients/treatments captured – CaPSURE includes all types of treatments whereas K-CaP and J-CaP only include RP, radiotherapy and hormone therapy. To date, only K-CaP has established a tissue bank and collects urodynamic data.

Dr. Choi advised that to allow the best possible collaboration between databases, ideally they should all collect the same information and that this should be borne in mind for any new national databases. In the case of J-CaP, it was noted that at the time the database had been developed (from 2001–2003), computer facilities were limited and this dictated to a certain extent what was possible; now the database is being re-structured and new features added.

In terms of staffing and support to maintain the K-CaP database, in addition to Dr. Choi there are six staff working on the project: two to extract the data, three working on database development and one nurse checking for data anomalies. All participants were impressed with how much progress had been made with the K-CaP database since it had first been discussed at the Sixth J-CaP and CaPSURE Joint Meeting in 2012.

Table 1. Comparison of data collected in the K-CaP, J-CaP, and CaPSURE databases

Measurement	K-CaP	J-CaP	CaPSURE
Patient information			
Demographics: age, gender, race	×	×	×
Body measurement: height, weight, body mass index	×	×	×
Past history: comorbidities, surgical history, family history	×	×	×
CAM/health behaviors: alcohol, nutrition, smoking, CAM treatment, vitamins, herbs, nutritional supplements			×
Laboratory/radiology/pathology			
Hemoglobin	×	×	×
Prostate-specific antigen	×		×
Radiology: bone scan, MRI, CT	×		×(NE)
Pathology			
Biopsy	×	×	×(NE)
Pathology	×		×(NE)
Survey			
International Prostate Symptom Score	×		×
International Index of Erectile Function	×		×
Continence			×
Quality of life according to patients and physicians			×
Treatment			
Radical prostatectomy	×	×	×
Radiotherapy	×	×	×
Hormone therapy	×	×	×
Active surveillance			×
Brachytherapy			×
Cryotherapy			×
Hormone refractory and chemotherapy agents			
Other			
Concomitant medication: cardiovascular, antihypertension, statins, diabetes medication, other			×
Survival	×	×	×
Biobank	×		
Urodynamic data	×		

K-CaP, Korea Study Group of prostate cancer; J-CaP, Japan Study Group of prostate cancer; CaPSURE, cancer of the prostate strategic urologic research endeavor; CAM, complementary and alternative medicine; MRI, magnetic resonance imaging; CT, computed tomography; NE, not exact.

2. Comparison of outcomes among prostate cancer patients treated with PADT or radical prostatectomy at Seoul St. Mary's Hospital

Presented by Ji Youl Lee

Dr. Ji Youl Lee provided an overview of recent data generated from the Seoul St. Mary's Hospital prostate cancer database—one of the contributing institutions to the K-CaP initiative—regarding risk assessment and a comparison of outcomes amongst patients receiving primary androgen deprivation therapy (PADT) and those undergoing RP. He reminded the participants that the K-CaP team had first participated in the Fifth J-CaP and CaPSURE Joint Meeting in 2011 in Tokyo and had started developing the K-CaP database around that time. As discussed by Dr. Choi in her presentation, the K-CaP database currently receives information from five large hospitals in Korea (Severence Hospital, Seoul National University Hospital, Asan Medical Center, Samsung Medical Center, and Seoul St. Mary's Hospital) which together treat around 50% of the prostate cancer patients around the country. Last year saw the inaugural meeting of the K-CaP group in Daegu, Korea, to discuss progress and plan the next steps for the initiative. He advised that there are now plans to extend the database to include other hospitals around the country.

The prevalence of cancers among Korean men is rapidly changing, with prostate cancer now being the third most prevalent (8.9%) after stomach and colon cancer [1]. However, Dr. Lee noted that survival for patients with prostate cancer has increased over the last decade and that treatment decisions are also changing.

For advanced prostate cancer patients in Korea, PADT is a standard treatment modality resulting in the best outcomes for survival and quality of life (QoL). In localized prostate cancer however, RP is the standard treatment modality as it can achieve a complete cure for localized disease and the use of PADT is still controversial in this setting. However, an analysis of the database shows that patients receiving PADT tend to be older, less educated, and on a lower income, and that their survival and disease control appear to be affected by their socio-economic status. Dr. Lee considered that the potential benefits of PADT in clinically localized prostate cancer need to be re-evaluated in a large patient population and went on to present data on the use of PADT at Seoul St. Mary's Hospital.

Demographic data for prostate cancer patients who were treated with PADT or RP showed differences in age distribution (<60, 60–70 or >70 years), PSA level, clinical stage and Gleason score (GS). A comparison of patients who had received PADT at St. Mary's Hospital with J-CaP and CaPSURE data showed a similar data pattern to J-CaP in terms of age

distribution, GS, clinical stage and risk group. In contrast, the type of primary therapy for low-risk prostate cancer patients at St. Mary's Hospital was very similar to that seen in CaPSURE, being predominantly RP. A comparison of risk stratification using the D'Amico classification found a similarity in the distribution pattern between St. Mary's Hospital and J-CaP data with both being quite different to that pattern seen in CaPSURE. In general, CaPSURE data showed a larger proportion of low risk patients and a smaller proportion of high risk patients across all age ranges compared with the other two cohorts.

Focusing on data from St. Mary's Hospital, Dr. Lee showed an analysis of disease recurrence and survival comparing patients who had received PADT with those who had received RP. Follow-up in both cohorts of patients was five years. This showed that in localized prostate cancer patients, there is no difference in recurrence between those treated with PADT or RP but noted that when making a choice of treatment the potential adverse effects of each therapy needed to be taken into consideration. However, in terms of survival, differences can be observed between PADT and RP for the treatment of both localized and advanced disease. Dr. Lee noted that these results were similar to those reported for 10-year survival in another study of Japanese patients comparing luteinizing hormone releasing hormone (LHRH) agonist monotherapy and RP [2]. In that study, patients who received either PADT or RP had a similar life-expectancy to that of the normal population.

Multivariate logistic regression analysis of the Seoul St. Mary's Hospital data showed that the risk factors for recurrence in advanced prostate cancer patients receiving PADT are Gleason grade, T stage and PSA level. The risk factors for survival in localized and advanced prostate cancer patients receiving PADT or RP is the treatment modality itself. He considered that these interesting results warranted further evaluation in a larger patient population, including an analysis of the whole K-CaP database.

Dr. Lee concluded his presentation by giving an introduction to the Asian Pacific Prostate Society (APPS; <http://ap-prostate.org/>). The APPS was established by a gathering of renowned urologists on prostate health and disease factors from 11 countries worldwide, not only from Asia but also from the rest of the world including Australia, the United States, and Canada. Participating Asian countries included Korea, China, Japan, Taiwan, Singapore, the Philippines, Malaysia, Indonesia, and Hong Kong. The aim of the APPS is to provide a forum for urologists to exchange their ideas regarding basic and clinical research studies on prostate health and disease. In addition, APPS leads the way in multinational and

multicentered clinical research studies in the Asia-Pacific region, and holds an annual meeting to develop treatment guidelines for this region. It also has its own official journal: Prostate International which publishes clinical research articles, basic research articles, and clinical trials reporting the latest data on prostate cancer, benign prostatic hypertrophy and prostatitis. APPS is now developing a combined Asian database system and has a Korean prostate biobank that collects samples from several hospitals. Around 200 urologists attended the recent APPS 2013 meeting in Melbourne, Australia. The APPS 2014 meeting will be held in Okinawa, Japan in March 2014 and will be hosted by Shigeo Horie, Professor of Urology at Juntendo University School of Medicine, Tokyo, Japan.

3. Determining the triggers for intervention among men undergoing active surveillance for prostate cancer

Presented by Byung Ha Chung

Professor Chung, current President of the APPS, discussed which factors determined the triggers for intervention amongst men undergoing active surveillance (AS) for prostate cancer. A recent publication from his institution had analyzed the trends in prostate cancer management and patient characteristics over five years due to the significant increase in prostate cancer incidence and the introduction of robotic equipment in Korea [3]. They found that as the incidence increased, the proportion of localized and locally advanced cancer had also increased. In addition, the most commonly used treatment modality had changed from nonsurgical treatment to RP.

Professor Chung also noted that the establishment of the K-CaP database was announced in another recent publication to provide urologists with details of its methodology and anticipated future development [4]. K-CaP is the first database of comprehensive, observational, longitudinal data about prostate cancer patients in Korea and includes information covering a range of treatments, both surgical and nonsurgical. Professor Chung reported that in Korea, the concept of 'active surveillance' as a treatment option has only been accepted in the past few years. He described a study undertaken at his institution to compare contemporary AS protocols based on pathological outcomes in 1,662 patients who had undergone RP [5]. Experimental cohorts were identified from prostate cancer patients who had undergone RP between 2001 and 2011, and who met the inclusion criteria of five published AS protocols, namely: Johns Hopkins Medical Institution, University of California at San Francisco, Memorial Sloan-

Kettering Cancer Center, University of Miami and Prostate Cancer Research International: Active Surveillance. A total of 376 patients met the criteria for AS according to these protocols. According to the investigators these protocols showed similar pathological characteristics in patients who had undergone RP, however they concluded that the Prostate Cancer Research International: AS protocol was likely to be the most suitable for the Korean population when selecting candidates for AS considering the balance between sensitivity and specificity, and the accuracy of diagnosis. A comparison of the Korean data with that of a similar study of 391 Western AS candidates found more adverse prostate cancer features (GS, 8-10 and/or extracapsular extension and/or seminal vesicle involvement) among Korean patients than their western counterparts [6]. Professor Chung said that this highlighted the importance of carefully selecting candidates for intervention among patients undergoing AS.

Professor Chung went on to review the various strategies for deciding whether to intervene during AS, including PSA kinetics, a confirmatory repeat biopsy, novel biomarkers, or diffusion-weighted multiparametric MRI. He reminded participants that the debate continues as to the most appropriate eligibility criteria for AS and what triggers for intervention should be considered [7]. Studies assessing the association between various clinical characteristics and unfavorable repeat biopsy results show that there is currently no general consensus regarding PSA kinetic parameters (PSA density, PSA doubling time and PSA velocity) or cutoff values for predicting disease progression. Professor Chung advised that in fact, several reports suggest that PSA kinetics should not be used to assist decision making during AS [8-11].

Confirmatory repeat biopsy is a method commonly used to assess the need for intervention. However, in around 28% of cases there is pathological upgrading following the biopsy, reflecting a reclassification rather than disease progression. It has been shown that low-risk tumors that are later reclassified as high-risk have a worse prognosis so the recommendation is to perform a confirmatory biopsy early, within one year of initial diagnosis [12]. However, there is still a lack of consensus and limited follow-up data regarding the size of the tumor and the GS that should trigger intervention. A recent review concluded that AS is a well-tolerated treatment option in carefully-selected groups of patients. However, the authors recognized that there are no over-arching criteria for patient selection or triggers for intervention and that decisions need to be guided by individual patient histology, PSA kinetics and imaging information [7].

Various biomarkers have also been investigated as poten-

tial triggers for intervention. PCA3, a prostate specific non-coding mRNA that is significantly over expressed in prostate cancer tissue, is not significantly associated with short-term biopsy progression in men with low-risk prostate cancer undergoing AS [13]. Another study has shown a significant correlation between serum and tissue levels of another biomarker, pro-PSA, at diagnosis and the need for subsequent treatment. The study also suggested that the increase in the ratio of serum pro-PSA: percentage free PSA might be driven by increased pro-PSA production from 'pre-malignant' cells in the prostate benign-adjacent areas [14].

Professor Chung advised that recent data suggest that intra-prostatic imaging using MRI can help improve the selection of candidates for AS [15]. Two studies from Professor Chung's own research group also supported these findings [16,17]. The first study showed that a simple measurement of the diameter of suspicious tumor lesions on diffusion-weighted MRI could improve the prediction of insignificant prostate cancer in patients who are candidates for AS [16]. The second study found that tumor visibility on multiparametric MRI was a predictor of favorable disease for those prostate cancer patients who did not meet the criteria for AS (Table 2) [17]. A retrospective analysis was undertaken of 464 prostate cancer patients with clinically localized disease who had undergone multiparametric MRI before RP. Of these, 238 were eligible for AS (group 1) and 226 were not. These 226 patients were divided into two groups according to the result of multiparametric MRI: 59 patients (26.1%) with no visible tumor (group 2) and 167 patients (73.9%) with visible tumor (group 3).

The proportions of organ-confined, Gleason ≤ 6 disease and unfavorable disease were 63.9 and 11.3% in group 1, 59.3 and 10.2% in group 2, and 38.9 and 22.8% in group 3. Comparing groups 1 and 2, these proportions were not statistically different ($P=0.549$ and $P=1.000$, respectively). However, comparing groups 1 and 3, they were significantly different

Table 2. Comparison of pathologic outcomes between active surveillance candidates (group 1) and nonactive surveillance candidates without visible tumor on multiparametric magnetic resonance imaging (group 2)

Variable	Group 1	Group 2	P-value
Tumor volume (cm ³)	0.81 \pm 0.78	0.93 \pm 0.85	0.959
Organ-confined, Gleason score ≤ 6 disease	152 (63.9)	35 (59.3)	0.549
Insignificant prostate cancer	81 (34.0)	16 (27.1)	0.354
Unfavorable disease	27 (11.3)	6 (10.2)	0.999

Values are presented as mean \pm standard deviation or number (%). Adapted from Lee DH, et al. *Jpn J Clin Oncol* 2013;43:553-8, with permission of Oxford University Press [17].

($P<0.001$ and $P=0.002$, respectively). In multivariate logistic regression analysis, no visible tumor on multiparametric MRI was an independent predictor of organ-confined GS 6 disease (odds ratio, 0.426; $P=0.007$) but there was no statistically independent predictor for unfavorable disease. It was concluded that this imaging technique might help to determine the most appropriate treatment modality for low-risk prostate cancer patients who consider AS as an option even if they do not meet standard criteria.

Within the CaPSURE database, it was noted that the number of patients undergoing AS was quite low compared to the number of low-risk patients who were candidates for this treatment option. Participants considered that there were probably multiple reasons for the low uptake of AS—patients often did not understand the concept of not treating cancer while physicians were trained to treat it. It was commented that each of these prostate cancer databases should not only be used as tools for research but also for quality improvement and should be able to feed back to the participating institutions about how they are performing and how they could improve their treatment practices.

4. J-CaP prospective observational study: background factors of patients who underwent PADT or radical prostatectomy for localized prostate cancer

Presented by Satoru Ueno

Dr. Ueno discussed the findings of a J-CaP prospective observational study undertaken at his institution to investigate the background characteristics of patients who had undergone RP or PADT for localized prostate cancer.

To introduce his presentation, he highlighted the results of two similar studies in this setting. The first was a retrospective study comparing the outcomes of patients treated with PADT with those treated with RP [18]. The results showed that disease-specific survival rates of relatively younger patients with performance status 0–1, who were generally good candidates for RP, were surprisingly similar between the two groups, even after 10 years of follow-up. While PADT, as expected, did not provide long-term efficacy in cases of poorly-differentiated adenocarcinoma, it was found that none of the patients with well-differentiated adenocarcinoma who had been treated with PADT died from prostate cancer during the 10-year observation period.

In light of these results, the investigators had decided to evaluate which types of prostate cancer were potential candidates for PADT and had conducted another retrospective study [19]. A total of 628 patients with T1c–T3 prostate cancer without metastasis were analyzed. A comparison of

combined androgen blockade (CAB) treatment with castration monotherapy, found that disease-specific survival in the CAB group was significantly higher than that of the castration monotherapy group: 92.8% versus 78.5% survival at 10 years, respectively ($P=0.037$).

According to D'Amico risk grouping, the outcomes of patients in the low- and intermediate-risk groups, a total of 331 patients, were satisfactory. These 331 patients were divided into two groups based on the time to nadir PSA levels after the commencement of hormonal therapy, with a PSA level of <0.2 ng/mL being defined as the nadir. PSA levels decreased to the nadir level within 6 months in 192 patients; these patients were designated as group G (good response group). The remaining 139 patients whose PSA did not decrease to 0.2 within 6 months were designated as group P (poor response group). The 10-year disease-specific survival rate of group G was excellent (98.9%) and notably no cancer-related deaths were observed during this period among group G patients receiving CAB treatment. In addition, the progression-free survival rate of patients treated with CAB in group G was 87.2% at 10 years compared with 79.4% in the monotherapy group ($P=0.45$). Therefore, a long-term survival rate of more than 10 years can be expected with CAB treatment.

Dr. Ueno noted that while these initial studies suggested PADT was effective in some patients in the early stage of prostate cancer it was recognized that more comparative studies were needed to elucidate the usefulness of this approach. To address this issue, his research team had initiated a new clinical study, the J-CaP Innovative Study-1. Although this study is an observational trial, this type of prospective, comparative study has never been undertaken before. Patients aged 67–76 years with localized prostate cancer and clinical stage T1c or T2 disease, a PSA of <20 ng/mL, and a GS of ≤ 7 were enrolled in the study. The mean age was 71.0 and 73.0 years for the RP and PADT groups, respectively. In both the groups, more than 90% of patients had a good general status (performance status=0). Patients with the PSA level <10 ng/mL accounted for 70.4% of the RP group and 59.5% of the PADT group. The proportion of the patients with high PSA levels (15–20 ng/mL) was greater in the PADT group. Around 50% of patients in each group had a total GS of <7 . Similarly, patients with the GS of 7 accounted for 50.4% of the RP group and 47.8% of the PADT group.

Patients with stage T1c cancer were the most common, constituting approximately 65% in each group (Fig. 1). In addition, patients with stage T2a cancer accounted for 30.6% in the RP group and 21.6% in the PADT group. Dr. Ueno noted that considering that most participants were elderly patients,

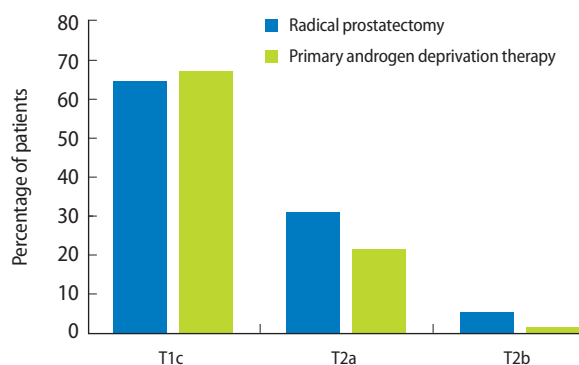


Fig. 1. T-category distribution amongst patients with localized prostate cancer treated with primary androgen deprivation therapy or radical prostatectomy in the J-CaP Innovative Study-1. J-CaP, Japan Study Group of prostate cancer.

it was to be expected that many had coexisting diseases. He considered that many patients in the PADT group might have been treated with this therapy due to the potential risk of surgery in patients with established cardiovascular or lung disease. The reason for the selection of treatment regimen and who made the decision regarding the treatment were therefore investigated. In both the groups, the patient's choice of treatment was a major factor in deciding therapy. It may be that younger age is a factor in the decision to select RP while comorbidities are the reason why the patients choose PADT.

5. QoL surveillance data for patients who underwent PADT or radical prostatectomy (J-CaP study data)

Presented by Satoru Ueno

In his second presentation, Dr. Ueno reviewed the QoL survey results of the J-CaP study comparing PADT and RP treatments which had been estimated using the 8-item, short-form generic health-related QoL questionnaire (SF-8) and expanded prostate cancer index composite (EPIC) instruments. These questionnaires were prospectively administered before treatment and during follow-up at 3 and 12 months.

The SF-8 instrument contains eight scales (physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health) that generate physical and mental component summary scores. The completion rates for SF-8 at each time point were considerably high, even 12 months after the initiation of treatment. At 12 months, the completion rates were 76.8% in the RP group and 75.6% in the PADT group. In the RP group, scores for each SF-8 domain, except for mental health, decreased at 3 months following surgery. However, their scores returned to pretreatment levels one year following the surgery. The mental component summary score increased over time. In

contrast, for the PADT group the scores for some domains, including physical function, decreased slightly. However, the scores for mental health increased over the one year of treatment. No significant differences were observed between the two groups at 12 months for the scores of individual domains.

The EPIC instrument contains 50 items from five scales (urinary incontinence, urinary irritative-obstructive, bowel, sexual and hormonal), with scores ranging from 0-100. Participants queried which QoL instrument was the best to use for studies of patients with prostate cancer. It was noted that the CaPSURE team generally used the EPIC-26 instrument, a shorter version of the EPIC-50, in clinical practice at University of California, San Francisco (UCSF) and were moving to this for CaPSURE.

In Dr. Ueno's study, the completion rates for EPIC at each time point were considerably high, similar to SF-8. Even after 12 months, the completion rates were 75.9% in the RP group and 72.9% in the PADT group. The mean urinary scores for surgical patients decreased at 3 months posttreatment 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, as expected the scores in this section for patients

receiving PADT gradually decreased over time compared with those of RP patients. The mean score of the sexual domain in both the groups was already low at baseline and exhibited a decline at 3 months after treatment which did not return to baseline. The differences in urinary and sexual QoL scores between RP patients receiving nerve-sparing and non-nerve-sparing procedures were not clinically significant. A comparison of the subscale scores between the two patient populations showed that baseline QoL was almost the same in both the groups (Fig. 2). However, the subscale scores of urinary and sexual function at 3 months for RP patients were significantly lower than those for patients who received PADT. While these scores improved at 12 months, they did not return to baseline. Dr. Ueno considered it was notable that in patients treated with PADT, sexual bother did not decrease despite a considerable decrease in sexual function after the initiation of PADT. He proposed that this is reason why many Japanese patients are happy to receive PADT.

In terms of overall satisfaction scores, the numbers of patients with increased and decreased satisfaction were almost equal in the RP group. In contrast, in the PADT group, the average satisfaction tended to increase over the one-year treatment period.

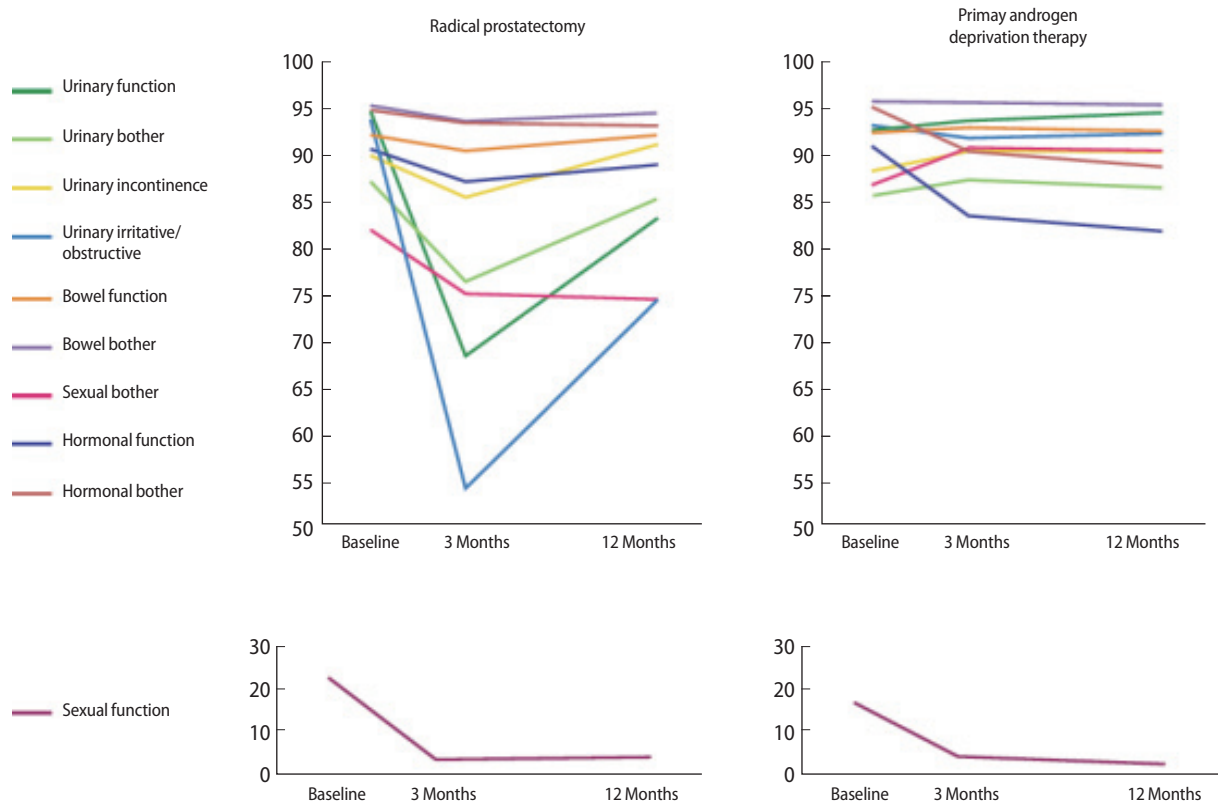


Fig. 2. Subscale score of the expanded prostate cancer index composite instrument in patients with localized prostate cancer treated with primary androgen deprivation therapy or radical prostatectomy.

Dr. Ueno concluded by noting that various considerations were involved when choosing a treatment for prostate cancer patients. Urologists tended to emphasize the outcome and QoL. However, many patients may favor a less invasive treatment, and they will ultimately choose a treatment based on their personal preferences. Although few clinical practice guidelines recommend PADT as an option for the treatment of localized prostate cancer, many patients, particularly in Japan, prefer to receive PADT rather than surgery.

6. Recent trends in initial therapy for newly-diagnosed prostate cancer (J-CaP surveillance data)

Presented by Mizuki Onozawa

Dr. Onozawa provided an update on a J-CaP surveillance study undertaken to evaluate initial therapy for newly-diagnosed prostate cancer. Firstly, he reviewed the background, objectives and protocol for the study noting that over the previous decade in Japan, the value of PSA screening had been the subject of much discussion and had become widely recognized by both physicians and amongst the general population. New treatment technologies, such as intensity modulated radiotherapy (IMRT) and robotic surgery, had been introduced and their usage had increased. Overall, the clinical practice pattern of prostate cancer had changed considerably.

The objective of the J-CaP surveillance study 2010 was to investigate the trends over time in patient characteristics at the point of diagnosis of prostate cancer and in the choice of initial treatment. Inclusion criteria for the study were patients with histologically-proven, newly-diagnosed prostate cancer whose treatment started between 1st January 2010 and 31st December 2010. Each patient's background characteristics and initial treatment for prostate cancer were recorded in a multi-institution, cross-sectional, retrospective, observational study undertaken nationwide across Japan. Registration of patients started in 2011 and closed on 30th September 2012.

A total of 9,011 patients were registered and data for 8,326 of these patients from 140 institutions (37 university hospitals, 52 public hospitals, 51 private hospitals) was analyzed. The following patient characteristics were recorded: age, any comorbidity, TNM and clinical stage, PSA, GS, and risk score (D'Amico, Cancer of the Prostate Risk Assessment [CAPRA], Japan-CAPRA [J-CAPRA]). Initial treatments were also recorded (RP, radiation therapy, PADT). These data were descriptively analyzed and compared with those from other studies undertaken in Japan (Japanese Urological Association [JUA] 2000 [20], JUA 2004 [21], J-CaP 2001–2003 [22]) and the US (CaPSURE [23,24]; National Prostate Cancer Registry [NPCR], and Surveillance, Epidemiology, and End Results

[SEER] Program 2001–2007 [25]).

The median age at the diagnosis in the J-CaP surveillance study 2010 (J-CaP 2010) was 71 years. The proportion of younger patients (<70 years.) in JUA 2000 [20], JUA 2004 [21] and J-CaP 2010 was 33%, 37% and 43%, respectively.

The proportion of patients with T1 disease was 42% in J-CaP 2010 compared with 26% in JUA 2000 [20] and 39.7% in JUA 2004 [21]. T3 and T4 disease were observed in 18% and in 4% of the patients, respectively. The proportion of T3–4 disease was much higher in J-CaP 2010 than reported in CaPSURE (4%–5%) [24,26]. The proportion of patients with M1 disease was 11% in J-CaP 2010 compared with 23% in JUA 2000 [20], 12% in JUA 2004 [21], and 3% in NPCR and SEER 2001–2007 [25]. The proportion of patients with Stage I–II disease was 74% and 81% in J-CaP 2010 and in NPCR and SEER 2001–2007 [25], respectively. The reason for the increase in the proportion of patients diagnosed with localized disease was queried in light of the fact that PSA screening is not undertaken routinely in Japan. It was suggested that in clinical practice both physicians and patients were now more aware of the availability of screening and wanted to be tested.

The proportion of patients with PSA <10 ng/mL in J-CaP 2010 was 49% compared with 30% in JUA 2000 [20] and 39% in JUA 2004 [21]. The proportion of patients with PSA ≥100 ng/mL in J-CaP 2010 was 9% compared with 12% in JUA 2004 [21]. When GS was categorized into three groups, they were almost equally distributed. The proportion of GS <7 was 39% and 64% in JUA 2004 [21] and CaPSURE, respectively [24]. Risk assessment showed that J-CaP 2010 included a greater number of higher risk patients compared with CaPSURE [24].

When treatment choices were analyzed, the most frequently selected initial treatment was PADT, followed by RP, radiation therapy and surveillance. Although this order was the same as found in JUA 2000 [20] and JUA 2004 [21], it was different from that seen in CaPSURE data. PADT was less frequently used in J-CaP 2010 than in JUA 2004 [21]. In CaPSURE data, the use of PADT has increased gradually [23].

The distribution of treatment was analyzed by age and T-category. When J-CaP 2010 was compared with JUA 2004 [21], the proportion of RP was not increased even in young and low T-staged patients. In young and low T-staged patients, radiation therapy use was increased and PADT use was decreased. PSA surveillance was selected nearly equally across all age groups. When analyzed according to CAPRA score, the proportion of patients undergoing RP was lower in those with a low score. PSA surveillance was selected by about 20% of patients with low CAPRA score. In CaPSURE, the proportion of patients opting for PSA surveillance was much lower, even

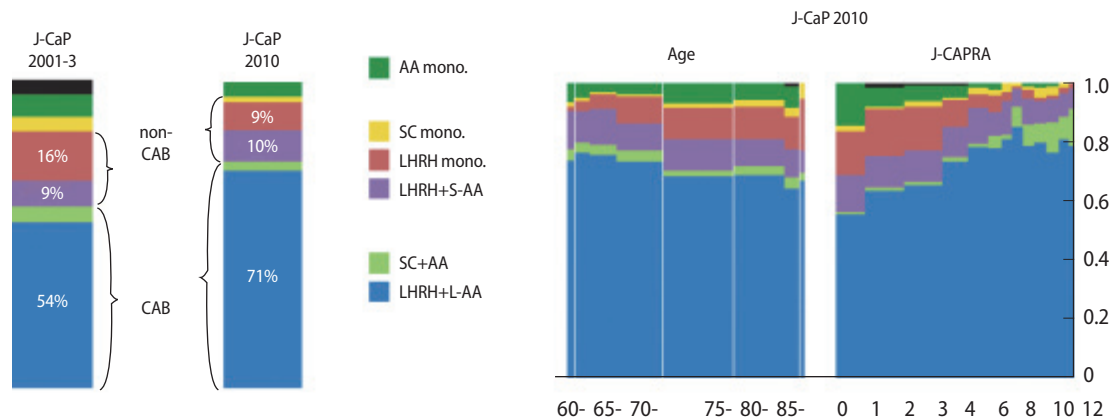


Fig. 3. Comparison of primary androgen deprivation therapy use in J-CaP 2001–3 and J-CaP 2010 studies. J-Cap, Japan Study Group of prostate cancer; J-CAPRA, Japan cancer of the prostate risk assessment; AA, antiandrogen CAB, combined androgen blockade; LHRH, luteinizing hormone releasing hormone agonist; mono., monotherapy; SC, surgical castration; L, long-term; S, short-term. Adapted from Hinotsu S, et al. *Jpn J Clin Oncol* 2007;37:775-81 [22].

in those with CAPRA 0–2.

Looking at individual treatments, in JUA 2004, 89% of patients had undergone RP with an open procedure [21]. Laparoscopic RP had increased from 7% in JUA 2004 [21] to 12% in J-CaP 2010. In Japan, robotic prostatectomy was approved in 2009 but only 16 institutions had these facilities in 2010. Nowadays they are installed in 130 institutions. The percentage of brachytherapy use in J-CaP 2010 was 46% compared with 17% in JUA 2004 [21] and 50% in CaPSURE [24,27]. Brachytherapy use tended to be lower in older patients, which is supported by findings from the CaPSURE database [27]. In the SEER–Medicare database, the proportion of IMRT was six times higher than external beam radiation therapy (EBRT) [28].

In term of PADT, the CAB/non-CAB ratio in J-CaP 2010 was 3.5 (2.3 for Stage I–II disease, 4.8 for Stage III, and 7.1 for Stage IV); this ratio was 2.0 in J-CaP 2001–2003 [22] (Fig. 3). Notably, this increase in the use of CAB was observed at both Stage III and Stage IV disease. LHRH plus an antiandrogen was used in a substantial proportion of patients, even those with very low-risk disease. Surgical castration was performed in 5% of patients with J-CaP 2010 compared with 10% in JUA 2000 [20], 10% in J-CaP 2001–2003 [22], and 6% in JUA 2004 [21].

7. Comparative analysis of comorbidity and other confounding factors in patients who underwent PADT or radical prostatectomy for localized prostate cancer

Presented by Matthew R. Cooperberg (CaPSURE) & Shiro Hinotsu (J-CaP)

Dr. Cooperberg presented the latest data from the CaPSURE database on patient comorbidities. He suggested that one of

the possible reasons for the differences observed between the CaPSURE and J-CaP cohorts was the underlying diseases burdening prostate cancer patients. The comorbid conditions that CaPSURE tracks are as follows: arthritis, blood disease, cancer (nonprostate), diabetes, endocrine (other), ENT disease, eye disease, heart disease, hypertension, infection, kidney disease, liver disease, lung disease, mental health conditions, stomach/intestinal disease, stroke/other neurological condition and urinary conditions. This information is primarily collected by patient report whereby they are asked to complete a survey once or twice a year to collect data on QoL, comorbidities etc., and are required to give simple yes/no answers. He acknowledged that this system did have limitations as no detailed information is collected, for example on glycated haemoglobin levels or severity of CHF. As it is self-report, it also means that the patient could have an asymptomatic condition that they are unaware of.

Dr. Cooperberg reported that the overall prevalence of comorbidities in CaPSURE appears to reflect that of the general US population with the most common comorbidities being hypertension (~45%), arthritis (~38%) and heart disease (~23%) (Fig. 4). Also notable are other cancers, diabetes and gastrointestinal disease. In terms of comorbidity count (the total number of comorbid conditions the patient has) the modal number is one, which again reflects the general population.

When the comorbidity count was analyzed according to the type of primary treatment, some striking differences were observed between those patients undergoing surgery and those receiving other treatments (radiation therapy, PADT or watchful waiting/AS). Patients undergoing surgery tended to be healthier and had fewer comorbidities. There were no

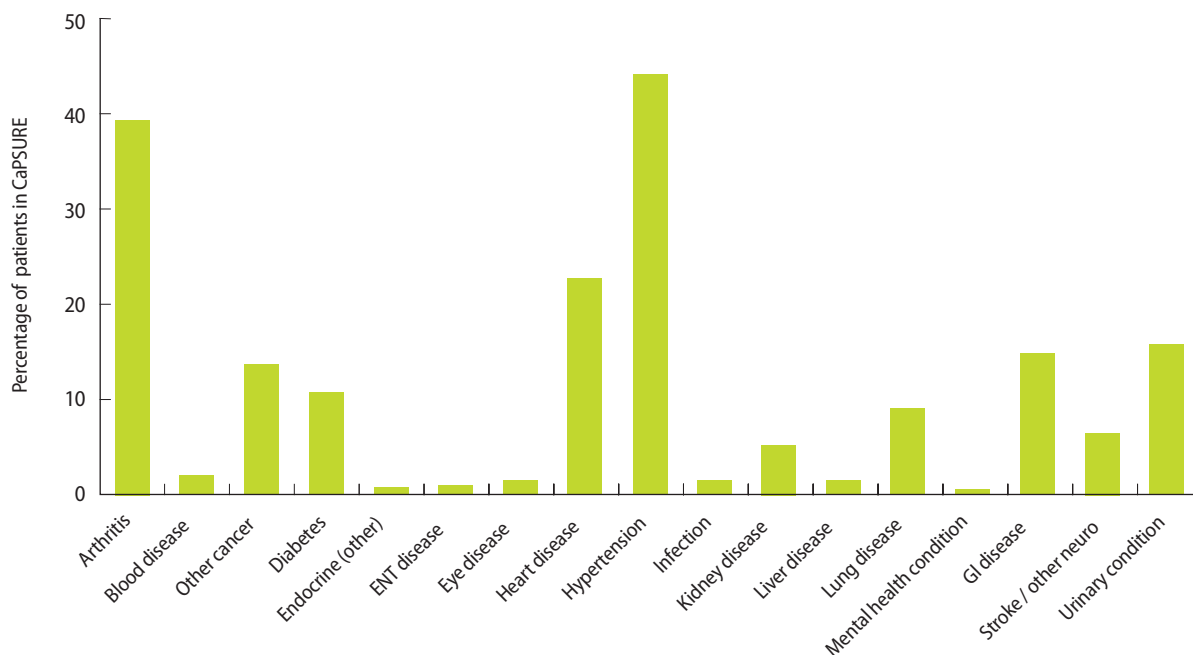


Fig. 4. Overall prevalence of comorbid diseases amongst patients in the CaPSURE database. CaPSURE, cancer of the prostate strategic urologic research endeavor; ENT, ear, nose, and throat; GI, gastrointestinal.

significant differences between the other treatment groups in terms of comorbidity count.

Dr. Cooperberg then went on to show data for some of the major comorbidities analyzed over time and according to the primary therapy the patient received. Around 8% of men undergoing RP self-reported with diabetes and surprisingly this did not change significantly over time (since around 1990) despite the recognized increase in obesity, metabolic syndrome etc. in the US. This figure was around 12% for those who underwent radiation therapy, 14% for those treated with PADT and 14% for those who underwent watchful waiting/AS. No significant trends over time were observed for any of the treatment groups.

A similar pattern was observed for hypertension: around 48% of patients in all treatment groups with minimal trends over time. Differences were observed however for heart disease: Only 15% of men undergoing RP reported having heart disease whereas these figures were much higher for other treatments: radiation, 31%; PADT, 31% and watchful waiting/AS, 34%. Again, there were limited trends over time in each group. Another notable difference for patients undergoing surgery were a higher reporting of genito-urinary disease compared with those undergoing other treatments. Dr. Cooperberg considered that all of these observed trends probably just reflected the patient's age as patients in CaPSURE undergoing surgery tended to be younger than those receiving other therapies.

A multinomial regression analysis (adjusting for practice site) was undertaken to look at possible predictors of treatment. This showed that if adjusting for individual comorbidities rather than comorbidity count, then hypertension, stroke, diabetes, heart disease, and blood disease were predictors of nonsurgical therapy. Income remains a predictor of surgical therapy, while education and race are less significant.

In terms of overall survival, the main comorbidities (heart disease, stroke, diabetes, and lung disease) and treatment with PADT are all predictors of a shorter survival while undergoing surgery predicts longer survival. In a competing risks survival analysis model, none of the comorbidities appeared to be a predictor of mortality while a high CAPRA score was predictor of shorter survival. Compared to radiation therapy, treatment with PADT predicts shorter survival while surgery improves survival, after adjusting for competing risks.

Professor Hinotsu then presented data from J-CaP on a comparative analysis of comorbidity and other confounding factors for patients who have undergone RP and PADT for the localized prostate cancer. The most common comorbidity in J-CaP was hypertension (~30% of patients) followed by heart disease (~15%); other comorbidities tended to be $\leq 10\%$. When comparing with CaPSURE, it was apparent that CaPSURE patients appeared to have a higher burden of comorbidity than those in J-CaP in particular for hypertension, heart disease, and diabetes.

He noted that one of the limitations of the web reporting

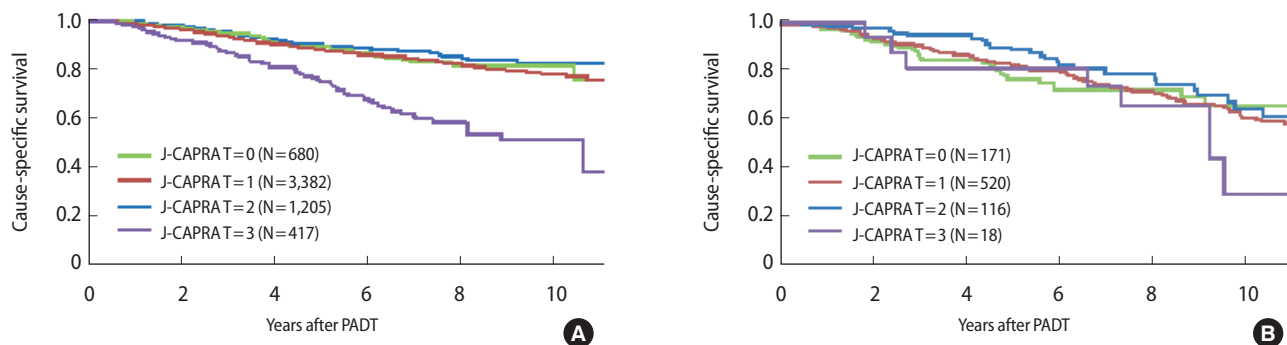


Fig. 5. Kaplan–Meier curves for cause-specific survival according to T stage in J-CaP (A) and CaPSURE (B) for intermediate risk patients (J-CAPRA score, 3–7). J-CaP, Japan Study Group of prostate cancer; CaPSURE, cancer of the prostate strategic urologic research endeavor; J-CAPRA, Japan cancer of the prostate risk assessment; PADT, primary androgen deprivation therapy.

system was that it was not possible to distinguish between the answer ‘no’ and missing data. In addition, in many cases it is not possible to obtain detailed medical records data from the hospital to verify any missing information as in Japan they are only required to keep the records for five years.

As a result, Professor Hinotsu advised that they had focused on other possible confounding factors, including T stage. It was noted that J-CaP used the 1997 T-stage classification system while CaPSURE used the 2002 version, so slight adjustments had been made for comparative purposes (T2a in the 1997 system = T2a+T2b in 2002/2009 system, while T2b in the 1997 system = T2c in 2002/2009 system). A comparison of T-stage distribution for J-CaP and CaPSURE showed that in the J-CaP cohort had a much higher proportion of stage T2c, T3a, and T3b patients than CaPSURE. He considered that one of the possible reasons for this was that the diagnosis of T stage might be different between J-CaP and CaPSURE. He noted that clinical practice guidelines issued by the JUA [29] recommended MRI for identification of the stage of locally advanced disease so this had become routine practice in Japan. According to the National Comprehensive Cancer Network (NCCN) guidelines published in the US, MRI is not mandatory [30].

Professor Hinotsu went on to present Kaplan–Meier curves for cause-specific survival according to T stage in J-CaP and CaPSURE for intermediate risk patients (J-CAPRA score, 3–7) (Fig. 5). Patients categorized at T stage 3 in J-CaP appeared to have a worse prognosis than similarly staged patients in CaPSURE. These results suggest that the difference between T-stage categorization of the two databases equates to a 1 or 2 point difference J-CAPRA score. While this is not a major confounding factor, it contributes to the overall clinical picture. Professor Hinotsu summarized by recommending that further analysis is needed to uncover other confounding factors between J-CaP database and CaPSURE database.

The importance of collecting comorbidity data within

the databases was highlighted, since they were not part of a randomized trial. This would allow examination of any confounding factors that might influence patient survival.

8. Consideration of the reasons underlying the trans-Pacific variation in outcomes for men treated with PADT for localized prostate cancer

Presented by Matthew R. Cooperberg (CaPSURE) & Shiro Hinotsu (J-CaP)

Dr. Cooperberg and Professor Hinotsu presented an update on the manuscript that was about to be submitted for publication which reported J-CaP and CaPSURE data on outcomes of patients treated with PADT for localized prostate cancer. The data had been presented by Professor Hinotsu at this year’s annual meeting of the American Urological Association (AUA) and had been reviewed at the Sixth Joint Meeting of J-CaP and CaPSURE in San Francisco, US.

As background to this, Dr. Cooperberg reminded everyone that there was a significant discrepancy between US and Asian guidelines on recommendations for the use of PADT in localized disease. The NCCN Asia Consensus statement says that androgen deprivation monotherapy is an option for all men except those with very low-risk disease and he noted that there is a much greater published experience in Asia with the use of PADT this setting [31]. The goal of this publication therefore was to analyze the two databases to try and determine any differences in outcomes of patients undergoing PADT for localized disease. Risk adjustment had been undertaken using the J-CAPRA scoring system.

In terms of age at diagnosis, those in J-CaP tended to be older than those in CaPSURE. There was more comorbidity in the CaPSURE cohort compared with J-CaP, recognizing that there are differences in data collection between the two databases. Regarding the type of PADT, orchiectomy was relatively uncommon in both cohorts. Notably, 67% of patients in J-

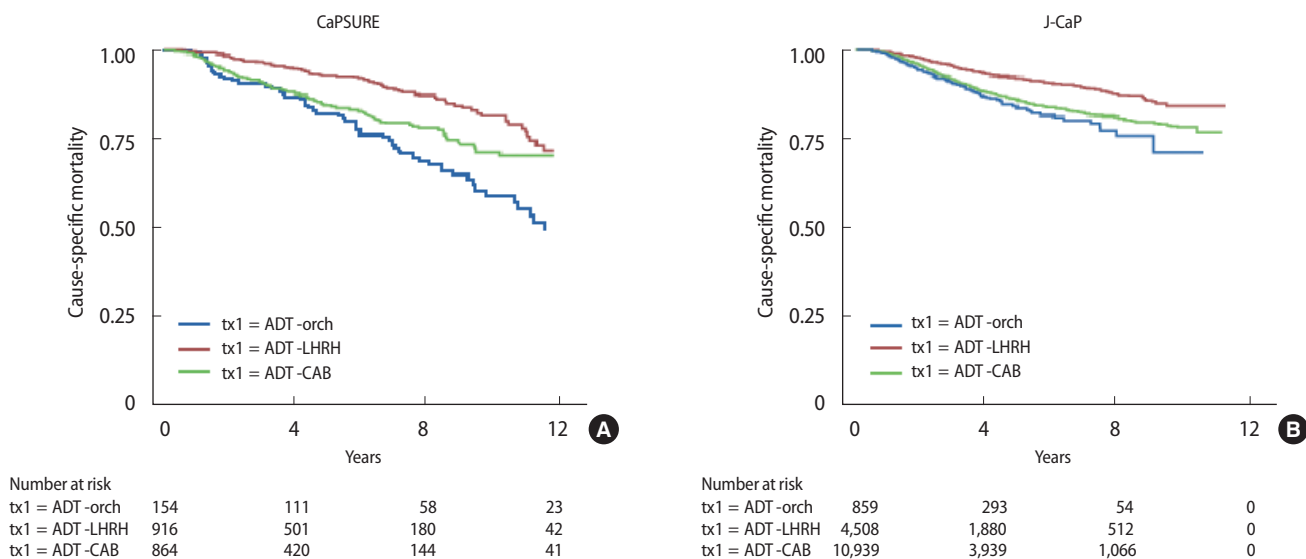


Fig. 6. A comparison of prostate cancer-specific mortality in patients undergoing combined androgen blockade in CaPSURE (A) and J-CaP (B). CaPSURE, cancer of the prostate strategic urologic research endeavor; J-Cap, Japan Study Group of prostate cancer; ADT, androgen deprivation therapy; LHRH, luteinizing hormone releasing hormone; CAB, combined androgen blockade.

CaP received CAB compared with 45% of those in CaPSURE. J-CAPRA distribution showed that the CaPSURE cohort includes a greater proportion of lower-risk patients.

Prostate cancer-specific survival curves were very similar for PADT patients in the two databases for at least the first 10 years, despite the fact that the J-CaP cohort includes men with higher risk disease. However, for all-cause mortality, the survival of J-CaP patients was significantly better than that for CaPSURE patients. Prostate cancer-specific mortality (PCSM) was analyzed according to J-CAPRA risk category (low, 0–2; intermediate, 3–6; high, ≥ 7). For each category, lower PCSM was observed for the J-CaP cohort than the CaPSURE cohort.

Dr. Cooperberg then presented a univariate analysis of PCSM according to type of androgen deprivation therapy (orchiectomy, LHRH monotherapy and CAB) and according to J-CAPRA risk score. The data showed that overall within any given risk category there were relatively small differences, if any, between types of PADT. The exception is high-risk disease where men undergoing CAB appear to have a better survival than those receiving LHRH monotherapy (Fig. 6). Using a multivariable competing risks model, if the analysis is restricted to high-risk (J-CAPRA > 6) men, then CAB is associated with better survival than LHRH monotherapy. This phenomenon is seen in the J-CaP cohort but not in the CaPSURE cohort. Adjusting for known confounding variables the analysis also showed that over time, men were 60% less likely to die in the J-CaP cohort than in the CaPSURE cohort (hazard ratio, 0.42; 95% confidence interval, 0.32–0.56; $P < 0.001$). The difference in outcomes with CAB and LHRH monotherapy seen in

the J-CaP cohort appear to be driven by the very high-risk patients however it was noted that there are very few of these in CaPSURE which might explain why differences were not seen in that group.

Dr. Cooperberg considered that these findings in fact validate both sets of guidelines (Japanese and US), since the recommendations they state are correct for that particular population. It was acknowledged that the results show the response sensitivity to CAB is different between US and Japanese patients with localized prostate cancer. In terms of treatment, however, the main difference was in the dose of antiandrogen used (80 mg bicalutamide was used in Japan but 50 mg in the US) however participants agreed that it seemed unlikely that this could be the primary cause of the observed results.

Dr. Cooperberg concluded by noting that very large differences could be observed in PCSM for PADT patients in the US compared with Japan. There are many possible contributors to these variations including genetics, diet/lifestyle/environment, selection bias, era of treatment, or treatment variation, and these warrant further investigation.

9. Biomarker progress in the US

Presented by Matthew R. Cooperberg

Dr. Cooperberg gave an overview of progress with identification and use of biomarkers in prostate cancer. The overall goal of risk assessment in prostate cancer is to improve risk stratification and to inform physician–patient decisions about the optimal initial treatment choice and timing of therapy. While numerous risk stratification instruments are available for the

physician to use, currently there is too much over-treatment of low-risk disease coupled with under-treatment of high-risk disease. This anomaly is something that biomarkers might help address.

Recently, several studies have called into question the usefulness of existing methods in risk stratifying cases of localized prostate cancer. One study has shown that clinical T stage offers no independent information in predicting biochemical recurrence [32]. In addition, Gleason scoring has evolved over the years but there is still a lot of heterogeneity in grading, particularly for smaller volume tumors [33]. For example, if four cores are involved with GS 3+4, one core with GS 4+4, what is the overall GS? It has been found that 81% of Society of Urologic Oncology members will use the highest grade to determine the overall score which is probably one contributor to over-treatment [34]. A quantitative GS has recently been proposed as a modification of the current Gleason grading system and is based on the weighted average of Gleason patterns present in the pathology specimen [35]. It has been suggested that this might improve prostate cancer risk stratification and help prevent the over-treatment of patients with clinically indolent tumors, to help select suitable candidates for AS, and to decide when to intervene in patients undergoing AS.

Dr. Cooperberg commented that the threshold for improving accuracy in predicting cancer-specific mortality after treatment is high as it is possible to do a lot with the patient information and instruments we currently have available. Importantly, any putative biomarker must improve on an existing clinical standard as demonstrated in a study by Shariat et al. [36] which confirmed that the biomarkers transforming growth factor-beta1 and interleukin-6 soluble receptor considerably enhanced the accuracy of the standard preoperative nomogram for the prediction of biochemical recurrence after RP.

Although research methods for biomarker evaluation still lag behind those for evaluating therapeutic treatments, there have been considerable advances over the last decade in biomarker research in particular how methodology should be standardized to ensure accuracy of results – the Prospective-specimen collection, Retrospective Blinded Evaluation (PROBE) and the REporting recommendations for tumor MARKer prognostic studies (REMARK) guidelines are good examples of this [37,38].

There are a huge number of candidate biomarker assays currently under investigation in tissue, blood and urine and also using novel imaging techniques. One of the key challenges deciding treatment is to determine what is an ideal marker to signal the endpoint of AS. Dr. Cooperberg advised

that the tissue repository at UCSF had now been established for 13 years and with the currently available techniques it was now possible to undertake very good validation studies.

UCSF currently works with three companies investigating tissue biomarkers. They are working with Myriad Genetics on their cell cycle progression (CCP) assay which has been investigated in a retrospective study of two cohorts of patients with prostate cancer in which they measured the expression of 31 genes involved in CCP using quantitative reverse transcription-polymerase chain reaction (RT-PCR) on RNA extracted from tumor samples [39]. The results suggested that the CCP score was a robust prognostic marker and might have role in determining the appropriate treatment for patients with prostate cancer. Dr. Cooperberg's group has recently published a study validating the CCP score for predicting RP outcomes [40]. The results also showed that combining the CCP and CAPRA-S scores improved the concordance index for both the overall cohort and patients with low-risk disease. In addition, the combined CAPRA-S+CCP score consistently predicted outcomes across the range of clinical risk (Fig. 7). Overall it was concluded that the CCP score had significant prognostic accuracy after controlling for all available clinical and pathologic data and may improve accuracy of risk stratification for men with clinically localized prostate cancer, including those with low-risk disease, who are undergoing RP. While this use of CCP is currently in the post-operative setting, UCSF are also working with Myriad Genetics to explore its use in the pre-treatment setting to see if it is possible to predict adverse pathologies.

UCSF is also working with genomic health on the Oncotype

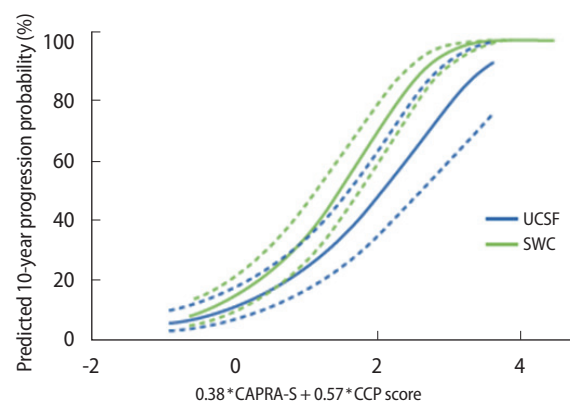


Fig. 7. Prediction model for likelihood of 10-year progression probability for University of California, San Francisco (UCSF) and Scott and White Clinic (SWC) cohorts based on the combined cancer of the prostate risk assessment postsurgical (CAPRA-S) score and cell-cycle progression (CCP) score. Dashed lines represent 95% confidence interval. Adapted from Cooperberg MR, et al. *J Clin Oncol* 2013;31:1428-34, with permission of American Society of Clinical Oncology [40].

DX genomic prostate score (GPS), a quantitative 17-gene RT-PCR assay using manually microdissected tumor tissue from needle biopsies. With the improvements in technology in recent years, both the Oncotype DX GPS assay and the CCP assay are capable of getting good genetic signals from very small amounts of tumor tissue. The Oncotype DX GPS uses genes from four different pathways: androgen signaling, cellular organization, stromal response and proliferation, normalized to a set of five reference genes. Two major challenges have been addressed with this method: (1) biopsy under-sampling and tumor heterogeneity—genes have been identified that predict clinical outcome in both dominant and highest grade regions, and (2) very small biopsy tumor volumes—standardized quantitative methods have been developed for reliable gene expression measurement in prostate needle biopsies. In fact the RNA extraction technique has been optimized to work with as little as 1 mm of tumor.

Dr. Cooperberg reported that initially two large development studies were conducted: firstly to identify genes predictive of clinical recurrence and adverse pathology across multiple tumor foci within patients, and secondly to confirm the predictive value of these genes in prostate biopsies [41]. The 17-gene GPS, developed from these data, was then validated as a predictor of true grade and stage over clinical criteria alone in an independent validation study of biopsies from patients suitable for AS. A total of 732 candidate genes were analyzed in the first development study ($n=441$ patients) and 288 genes were identified that were predictive of clinical recurrence regardless of Gleason patterns in separately-sampled specimens. A total of 81 genes were taken forward into the second needle biopsy study of low/intermediate-risk patients ($n=167$ patients) confirmed strong association of the genes with adverse pathology. Multivariate analysis of both development studies yielded 17 genes across multiple biological pathways and a GPS algorithm. In the subsequent validation study ($n=395$ patients), GPS assessed in biopsies from patients suitable for AS was found to be strongly predictive ($P<0.005$) of high grade and/or pT3 disease after adjusting for CAPRA or other standard pretreatment factors. The addition of GPS to CAPRA also improved risk discrimination. While some of the GPS biomarkers in this study were related to metabolism, Dr. Cooperberg considered that future studies on tumor metabolism were likely to use novel imaging techniques rather than measure circulating metabolites.

Dr. Cooperberg noted that while these developments in biomarkers were extremely valuable, there was no guarantee that they would change clinical practice. He considered that the picture was in fact much more complex and that treat-

ment decisions required an array of information including genetics, risk scores, lifestyle and comorbidities. However, to actually prove that one treatment is better than another is more complex still.

With this in mind, Dr. Cooperberg informed participants that UCSF had just been awarded a \$6 million 3-year grant from the US Department of Defense, the DOD Transformative Impact Award, to prove that the treatment paradigm for low-risk prostate cancer in the US can be changed. Currently, it is thought that men make treatment decisions about prostate cancer therapy on poor quality information plus they have a limited understanding of that information. This can result in dissatisfaction with treatment and poor outcomes. The aim is to provide better information and assist patients in interpreting it to ultimately improve decision making, achieve better outcomes, higher satisfaction with treatment and less over-treatment. A 'decision support system' is being developed where trained counselors will assist patients through the process.

Dr. Cooperberg also commented that biomarkers could prove to be a valuable tool in helping to uncover the reasons behind national differences in prostate cancer epidemiology and outcomes. He highlighted the fact that the global picture of prostate cancer incidence did not correlate with prostate cancer mortality plus there were also differences between countries in mortality trends over time which probably reflect changes in screening practices, stage migration and risk migration. Interestingly, if you take a single city in the US, such as Los Angeles, there are definite ethnic and racial differences in incidence of prostate cancer in that one city; the reasons for this are currently unknown.

Dr. Cooperberg concluded that emerging biomarkers held great promise to improve prostate cancer risk assessment and reduce overtreatment. However, changing practice will take more than improved accuracy, and for research and clinical practice will require a multidisciplinary approach. Biomarkers may help provide guidance with respect to the timing and intensity of both treatment and surveillance but studies are required to prove this. International studies will yield fascinating and critical insights into the interactions between biology and environment. However, it was recognized that could be difficult to undertake any international collaborations that involve using tissue bank samples due to the restrictions and regulatory issues of transporting them between countries.

10. Plans for the development of C-CaP

Presented by Dingwei Ye, Gang Zhu & Chi-Fai Ng

On behalf of the C-CaP Organizing Committee (Professors Na

Yanqun, Ye Dingwei and Chi-Fai Ng) Professor Zhu gave an overview of the development of the Chinese prostate cancer database, C-CaP. He advised that data from the Chinese National Cancer Registration Center (1998–2009) revealed that prostate cancer had the fifth highest incidence of all male and was ninth in terms of mortality [42]. In common with other countries, China has an increasing ageing population with an average life expectancy of 71.3 years (these figures are 79.1 years in Beijing and 80.18 years in Shanghai). In 2009, the incidence of prostate cancer in China overall was an average of 9.92/100,000; in cities it was 13.13/100,000 and in rural areas was 3.00/100,000.

Professor Zhu noted that prostate cancer was becoming an increasingly important issue for Chinese urologists—at the Chinese Urological Association Annual Meeting the number of clinical and basic research reports on prostate cancer had increased year on year. In addition, there was an increase in the use of minimally-invasive surgery including robotic surgery for RP so this was an important area for them to focus on in order to improve services for patients.

Professor Zhu reminded that attendees that the CaPSURE database had been founded in 1995 in the US and currently contains data on around 14,000 prostate cancer patients. The J-CaP database was established in 2001 and the J-CaP and CaPSURE Joint Initiative was established in 2007. Following discussions between Professor Na Yanqun and Professor Akaza, they had decided to establish C-CaP.

The aims of C-CaP are to gather information about Chinese prostate cancer patients from the top 20 urological departments in China, including Hong Kong. This will then allow analysis, review and comparison of data on Chinese prostate cancer patients and evaluation of the outcomes of treatment in order to develop a better understanding of the disease process in Chinese patients. C-CaP also plans to provide clinical evidence for the development of guidelines regarding optimal prostate cancer treatment regimens. Ultimately, it is also hoped they can contribute to the Joint Meetings between C-CaP, J-CaP, K-CaP, and CaPSURE.

Professor Zhu advised that C-CaP planned to gather the following patient information: hospital information, patient characteristics, PSA, testosterone, biopsy data, cancer characteristics, comorbidity, hormonal therapy, surgical procedures, radiation therapy, chemotherapy, active surveillance, other treatment options, and patient status. Descriptive results of sub-groups categorized by age, cancer characteristics and risks will also be analyzed.

The C-CaP database is currently under construction and is mainly based on translation of the J-CaP database. Once the

C-CaP data base is set up, they plan to undertake an experimental run in 5–10 centers (December 2013) and then formally launch it early in 2014 with the first publication of data by the end of 2014.

Professor Ng gave an overview of the situation in Hong Kong, since although Hong Kong is part of China they have different social and healthcare systems. Data from the Hong Kong Cancer registry in 2010 showed that in this year almost 1,500 new prostate cancer cases were registered and it has an incidence of 10.7% of all male cancers (4.1% in terms of mortality) [43]. The incidence of prostate cancer has been rapidly increasing in Hong Kong over the past 20 years. Mortality from prostate cancer however has remained relatively stable probably due to increasing public awareness of the disease and early detection and treatment.

Hong Kong has a very dense population of around 7.8 million and has a Government-subsided health care system similar to UK National Health Service system. It has a territory-wide electronic database system which includes most electronic consultation notes, operation records, imaging and laboratory results. In terms of prostate cancer care, there is no population screening policy but a recent increase in awareness has prompted health checks and the identification of an increasing number of cases. Professor Ng advised that more than 90% of RP is undertaken using robotic surgery and there are four such systems in public hospital in Hong Kong. In terms of radiation therapy, image guided radiotherapy and IMRT are used but brachytherapy is less common. In the case of hormone therapy, LHRH agonists are widely available but the use of CAB as first-line therapy is not common.

11. Plans for the development of I-CaP

Presented by Rainy Umbas

Professor Umbas gave an update on the plan for an Indonesian national database, the Indonesia Study Group of Prostate Cancer (I-CaP). This had started around three years ago with the intention of collecting data from three large hospitals in Indonesia.

Prostate cancer management in Indonesia currently follows guidelines published by the Indonesian Urological Association in 2011 [44]. Imaging is generally undertaken using transurethral resection of the prostate, MRI, computed tomography, bone scan or plain X-ray. In terms of treatment modalities, AS is not widely used but RP, EBRT, ADT, chemotherapy for castration-resistant prostate cancer and palliative treatment are all available.

The next steps for I-CaP are to expand and promote the program to six urology training centers and their affiliates

(10 hospitals). They will be provided with an Excel database program and asked to complete their last five years' data as comprehensively and accurately as possible.

A meeting of all centers was held in February 2013 to discuss any issues with the database for individual centers, particularly in terms of the equipment they have available, e.g., for the determination of GS, their method of determining bone metastases and lymph node metastases, and possibilities for patient duplication especially if they have moved around the country. Key problems identified were errors in database input, missing data and patient duplication.

The following database items are currently being collected: age, birth date, Karnofsky index, PSA at diagnosis, prostate volume, method of diagnosis, date of diagnosis, GS, TNM classification, number of bone lesions, disease stage, treatment, date of treatment, last follow-up, date of death, and survival. It has been suggested that additional information should be collected on pretreatment body mass index, testosterone levels, QoL and comorbidity.

It was recognized that while individual countries should develop their own national databases to suit their particular situations, it was important to agree on a core data set that would allow comparison between databases in the future.

CONCLUSION

Professor Akaza thanked all the participants for their interesting and valuable contributions to the meeting. He hoped that the expansion of the collaborative effort would continue and include more countries next year. Professor Carroll extended his thanks to all the participants for attending, to the Korean team for hosting the event, and to the organizers. He added that each year he attended the meeting it is larger and more productive and he looked forward to another meeting next year to discuss the latest developments.

Dr. Cooperberg reported that he and Professor Carroll had met with the AUA in 2009 to discuss the adoption of a national database structure for prostate cancer patients. The AUA board would be meeting soon to decide whether they will grant approval for a 3-year pilot study with 10 sites initially expanding to around 100 sites by the end of the 3-year period. It is a complex project as there are over 9,000 urologists in the US with a huge range of practice settings. This project not only offers tremendous research opportunities but can also be a means of improvement in quality of care. He hoped they would be able to report on the progress of this initiative at the next Joint Meeting.

Professor Chung closed the meeting on behalf of the Ko-

rean hosts. He noted that although this was the Seventh Joint Meeting, Korea had only participated for the past two years and he was very pleased to be able to hold the current meeting in Seoul. He thanked Dr. Lee for his tremendous work in organizing this event. Dr. Lee also extended his thanks to the meeting participants, in particular the co-Chairmen Professor Akaza, Professor Carroll and Professor Kim.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Appendix. 1. Participants at the 7th Joint Meeting of K-J-CaP and CaPSURE.