Title

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Journal

Japanese Journal of Clinical Oncology, 43(7)

ISSN

0368-2811

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Publication Date

2013-07-01

DOI

10.1093/jjco/hyt071

Peer reviewed

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(7)756–766
doi:10.1093/jjco/hyt071
Advance Access Publication 29 May 2013

Meeting Report

Sixth Joint Meeting of J-CaP and CaPSURE—A Multinational Perspective on Prostate Cancer Management and Patient Outcomes

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Received February 26, 2013; accepted April 22, 2013

This report summarizes the presentations and discussions that took place at the Sixth Joint Meeting of J-CaP and CaPSURE held in San Francisco, USA, in August 2012. The J-CaP and CaPSURE Joint Initiative was established in 2007 with the objective of analyzing, reviewing, comparing and contrasting data for prostate cancer patients from Japan and the USA within the two important large-scale, longitudinal, observational databases—J-CaP and CaPSURE. Since this initial collaboration between teams in the USA and Japan, the initiative has now expanded to include representatives of other Asian countries, several of whom have either established or are planning their own national prostate cancer databases. Several key topics were considered at this Sixth Joint Meeting including the current status of the J-CaP and CaPSURE databases and opportunities for collaboration with the more recently developed Asian prostate cancer databases. The latest comparative data from J-CaP and CaPSURE regarding outcomes following androgen deprivation therapy and combined androgen blockade were also reviewed. The possibility of a global chemoprevention trial to investigate the influence of soy isoflavones on prostate cancer incidence was considered. In addition, the ongoing debate regarding the role of screening and the use of active surveillance as a treatment option in the USA was discussed. The collaborators agreed that sharing of data and treatment practices on a global scale would undoubtedly benefit the clinical management of prostate cancer patients worldwide.

Key words: prostate cancer – androgen deprivation therapy – overall survival – risk stratification – chemoprevention – active surveillance

OVERVIEW

The J-CaP and CaPSURE Joint Initiative was established in 2007 with the overall objective of analyzing, reviewing, comparing and contrasting data for prostate cancer patients from Japan and the USA within two large-scale, longitudinal, observational databases—J-CaP and CaPSURE. Over the past 6 years, the initiative has expanded to include representatives of

other Asian countries, including Korea, Indonesia and China. Some of these countries have now either established or are planning their own national prostate cancer databases. The J-CaP database was established in 2001 and gathers information on hormone therapy administered to more than 24 000 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 USA. A third national database has now been established in Korea—K-CaP—which collects data on surgical treatment only (radical prostatectomy, RP); it currently holds data for 3639 patients.

The aim of the multinational collaboration between these groups was to identify trends within these different sets of data in terms of patient characteristics, treatment approaches and outcomes and to compare them at regional, national and global levels. It is hoped that these findings might assist physicians, patients and others when selecting treatment options at different prostate cancer disease stages. This report summarizes the presentations and discussions that took place at the Sixth Joint Meeting of J-CaP and CaPSURE held in San Francisco, USA, in August 2012.

The objectives of the Sixth Joint Meeting were to provide an update on the current status of J-CaP and CaPSURE and to discuss the ongoing Asian prostate cancer databases and the opportunities for collaboration and data sharing. The latest comparative data from the J-CaP and CaPSURE databases regarding outcomes following androgen deprivation therapy (ADT) and combined androgen blockade (CAB) were reviewed, in particular the effects of ADT on localized and/or locally advanced prostate cancer, as well as on advanced/metastatic prostate cancer. Looking to the future, participants also considered other key topics including the possibility of a global chemoprevention trial to answer the question of whether it is possible to reduce prostate cancer incidence by altering the consumption and metabolism of soy isoflavones. In addition, the management of patients with low-risk disease using active surveillance (AS) and the ongoing debate about this treatment approach in the USA was reviewed.

The meeting was co-chaired by Professor Hideyuki Akaza (The University of Tokyo, Japan) and Professor Peter Carroll (University of California, San Francisco, USA).

PRESENTATION 1: UPDATE ON PROSTATE CANCER AND ITS MANAGEMENT IN ASIAN COUNTRIES

Korea

B.-H.C. (Yonsei University College of Medicine, Seoul, Korea) reported that data from the annual report of cancer statistics in Korea in 2008 showed the number of patients diagnosed with prostate cancer had doubled in the country between 2004 and 2008 (1,2). According to the National Cancer Registry, prostate cancer was now the fifth most common cancer in Korean men after stomach, colorectal, lung and liver cancer, and had an incidence rate of 23.1 per 100 000 men (3). The current evolution of prostate cancer in Korea showed an increase in the number of patients with localized disease and an increase in surgical treatment, in particular RP.

There was a need for reliable, long-term data on Korean patients regarding the outcomes of surgical treatment, life expectancy in metastatic disease, and both overall and cause-specific survival. K-CaP, the multicenter Korean Prostate Cancer Database, is a longitudinal, observational database that undertakes prospective studies and research in Korean men with prostate cancer. Its overall aim was to gather basic information on prostate cancer in Korea, to analyze the clinical and oncological outcomes and ultimately to improve patient care. B.-H.C. advised that the database currently held information on about 4200 patients who had undergone RP at five centers in Seoul: Asan Medical Center (1002 patients), Samsung Medical Center (894 patients), Seoul NU Bundang Hospital (453 patients), Seoul St. Mary's Hospital (465 patients) and the Severance Hospital (1362 patients). While participating centers were predominantly based in the capital at present, the future plan was to expand the database to include centers in other areas of the country.

B.-H.C. considered that there were several key success factors for the K-CaP database. First, it would be important to develop a uniform format between participating Institutions and initially it was intended that K-CaP would focus on surgical treatment only (RP) at each center, although in the future, patients treated with hormone therapy would be included. Baseline characteristics already collected for the 3639 patients currently in the database are shown in Fig. 1; it had been found that 320 (36.3%) could be categorized as high risk, 1203 (33.1%) as intermediate risk and 1116 (30.6%) as low risk. Some risk migration had been observed since the database had been established in 2006 with low-risk patients becoming more prevalent.

Another important factor was continuing and convenient management. The K-CaP system was web-based, making data input and extraction simple. Although the interface was currently in English, the K-CaP group was considering the use of a multilingual system in the future.

Finding ways to collaborate with other databases such as J-CaP and CaPSURE would facilitate the exploration of national and regional differences in the disease and its treatment. To achieve this, it was anticipated that there would be close cooperation between staff working on the K-CaP database with other groups and regular exchange of opinions at scientific congresses, such as the Asian Pacific Prostate Society. Ideally, the system would be opened to participation from other national groups in Asia.

B.-H.C. presented some initial data comparing oncological outcomes between K-CaP and CaPSURE patients. K-CAP data stratified according to the low, intermediate or high CAPRA-S score—a tool developed to improve predication of outcomes after RP—showed a similar pattern to that

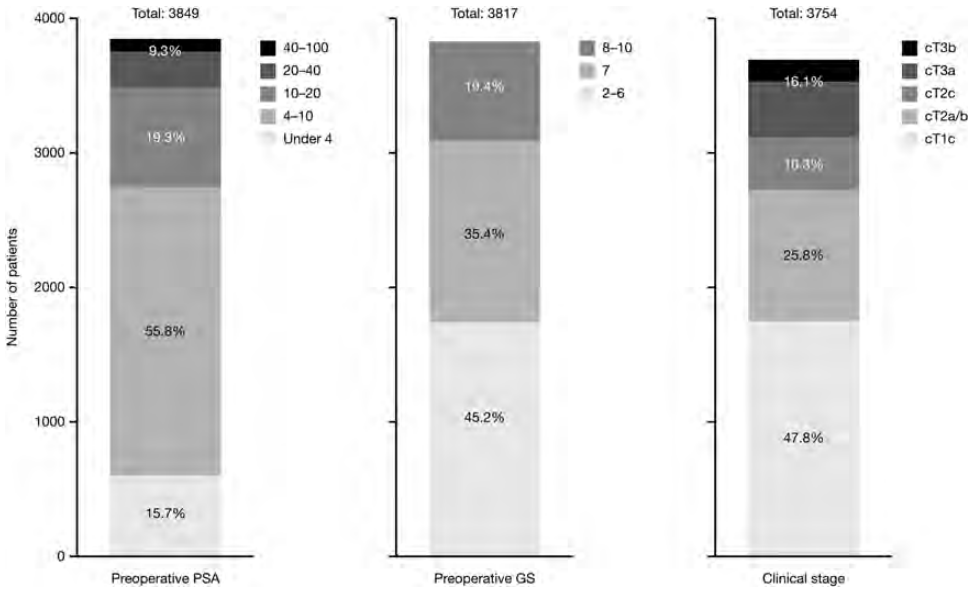

Figure 1. Baseline characteristics of patients in the K-CaP database. GS, Gleason score; PSA, prostate-specific antigen.

reported for CaPSURE patients in terms of the proportion of patients who remained event-free over time (4). It was noted that K-CaP was planning to have a tissue bank system which might be valuable in the future for the assessment of biomarkers.

Indonesia

R.U. (University of Indonesia, Depok, Indonesia) reported that prostate cancer was now Indonesia's third most common male cancer after lung and colorectal cancers (5). He gave an overview of the patient characteristics and treatment patterns observed in his country. A survey of 940 patients treated at two tertiary-care hospitals in Jakarta between 1995 and 2011 had found a median age of 68 years (range: 23–92 years), and a median PSA value of 60.9 (range: 0.08–17750). Of these, 4% were Stage I, 27% Stage II, 5% Stage III and 64% Stage IV, with 11.6% having castration-resistant prostate cancer. R.U. advised that the Indonesian Urological Association had published treatment guidelines in 2011 that doctors could refer to when selecting therapy (6). PSA testing was not undertaken routinely in Indonesia but would be performed in men >50 years of age if they attended hospital.

Data collected for the period 2006–2010 from three cities in Indonesia (Jakarta, Bandung and Yogyakarta; $n = 781$ cases) found that 58.8% had advanced Stage IV disease (Safriadi F et al., unpublished data). About 60% of these patients with localized or locally advanced disease were treated with primary ADT (PADT), in addition to those with advanced (N + M+) disease. He said that in his experience most patients preferred hormonal therapy to orchiectomy as they often felt ashamed to undergo orchiectomy.

The majority (around 60%) of Stage I–III prostate cancer in Indonesia is treated with radical therapy—RP (37.6%) or radiotherapy (RT; 62.4%) (7). PADT is generally reserved for patients aged >70 years with T3 or T4 disease that is organ-confined. No significant difference has been found in the overall survival at 5 years of patients aged >70 years with organ-confined disease treated with either PADT, external beam RT (EBRT) or EBRT plus hormonal therapy (8).

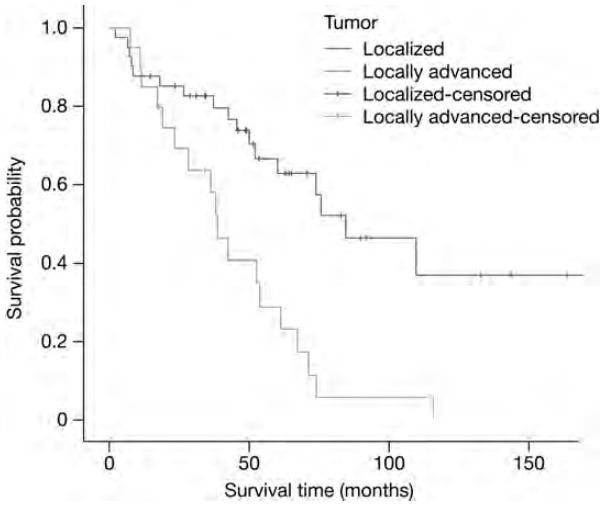

Figure 2. Survival among prostate cancer patients with localized or locally advanced disease treated with primary ADT (9). [Reproduced with permission of the *Indonesian Journal of Internal Medicine*].

R.U. also reported a study that showed no significant differences between mean survival and 5-year survival rate, between localized and locally advanced prostate cancer patients who had received PADT (Fig. 2) (9). It was noted that M1 patients generally underwent orchiectomy (47%) with 20% receiving an LHRH analog continuously and 28% receiving intermittent hormonal therapy. There was no significant difference in survival observed between these treatment groups.

Japan

M.N. (Kanazawa University Graduate School of Medical Science, Ishikawa, Japan) gave an overview of a recent study undertaken in Japan to validate the Japan Cancer of the Prostate Risk Assessment (J-CAPRA) scoring system (10) using data from patients treated with CAB in the Department of Urology, Kanazawa University Hospital.

Within this study, data for a total of 319 patients treated with an LHRH agonist plus bicalutamide in the Department of Urology were reviewed retrospectively. Progression-free survival (PFS) periods of patients treated with PADT were compared among patients stratified according to their J-CAPRA score. Patients included in the analysis were aged 46–91 years (mean: 75 years), and the mean follow-up period was 3.67 years. The results showed that the PFS of patients treated with CAB could be stratified by the J-CAPRA score even for a relatively short-term follow-up period, providing good external validation of the J-CAPRA scoring system (Fig. 3) (11).

He concluded that J-CAPRA was a useful risk assessment tool for prostate cancer patients treated with CAB, and noted that the results also suggested that patients with low-risk disease achieve better outcomes with PADT than those with higher-risk disease.

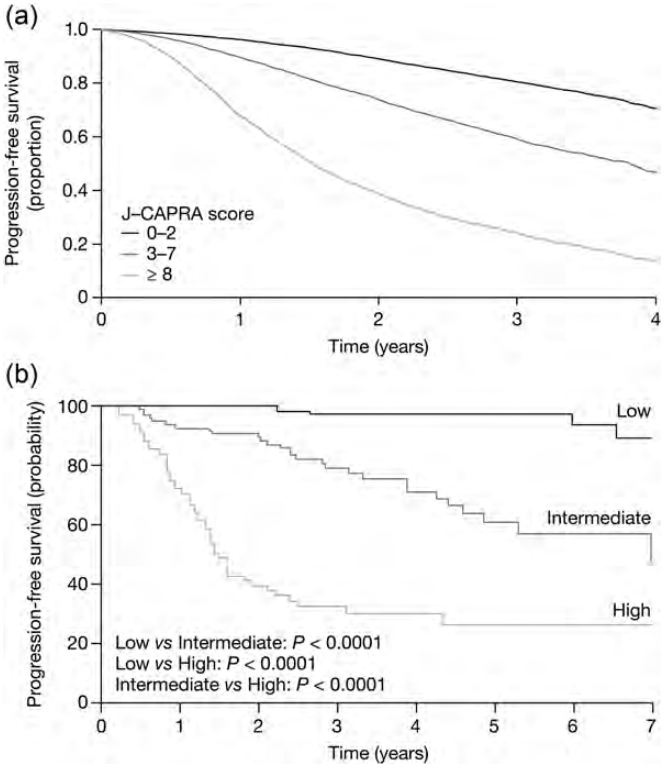

Figure 3. Comparison of progression-free survival (PFS) according to the J-CAPRA score for patients (a) in the CaPSURE database (10) and (b) those treated at Kanazawa University Hospital (11). [Fig. 3a: Reproduced with permission of the *American Society for Clinical Oncology/Journal of Clinical Oncology*; Fig. 3b: Reproduced with permission of *John Wiley & Sons/International Journal of Urology*].

PRESENTATION 2: OBSERVATIONAL STUDY OF LOCALIZED PROSTATE CANCER: PRIMARY HORMONAL THERAPY VERSUS RADICAL PROSTATECTOMY

M.N. (Kanazawa University Graduate School of Medical Science, Ishikawa, Japan) reported the preliminary results of an observational study of patients with localized prostate cancer which compared the outcomes of treatment with primary hormonal therapy or with RP. He noted that various national guidelines do not recommend hormonal therapy as a first-line treatment in low-risk disease in patients with a life-expectancy of ≥10 years. However, surveys of actual clinical practice in Japan suggest that while many urologists recommend RP for of T1c–T2 disease, even for patients >70 years of age, hormonal therapy is often preferred as a first-line therapy by patients (12). The reason for this is probably because hormonal therapy is more tolerable to Japanese patients than invasive treatments, such as surgery. In addition, urologists are familiar with the efficacy of hormonal therapy in this setting and therefore accede to their patients wishes.

A study undertaken to investigate the impact of race on the effectiveness of hormonal therapy in patients with prostate cancer had found marked racial differences in clinical outcomes after hormonal therapy between Japanese–American men and Caucasian men treated with hormonal therapy at a single institution (13). As both overall and cause-specific survival rates of Japanese–Americans proved to be higher than those of Caucasians, it is likely that not only sensitivity of prostate cancer to hormone therapy but also side effects of hormone therapy differ among ethnic groups.

The particular efficacy of primary hormonal therapy in Japanese patients with localized disease has been further supported by other clinical studies. Akaza et al. found that the progression of prostate cancer was inhibited by primary hormone therapy in Japanese men with localized or locally advanced disease. Following treatment with primary hormone therapy or prostatectomy, the men had a life-expectancy similar to that of the normal population (14).

To assess the benefits of hormone therapy in localized disease, J-CaP has undertaken a prospective, observational study in patients with localized prostate cancer (T1c or T2N0M0) treated with either PADT or RP according to their own choice. From 2007 to 2011, a total of 830 patients treated with RP and 339 treated with PADT were registered; the study is currently ongoing and survival outcomes and health-related quality of life (HRQoL) will be assessed. M.N. went on to present the preliminary HRQoL data which had been assessed using the SF-8 and EPIC questionnaires pre-treatment, then after 3 months and 12 months.

In the PADT group, after 12 months of treatment, physical function scores showed a slight decrease but mental health scores were significantly increased. In the RP group, scores for several SF-8 domains decreased significantly 3 months after surgery although some had returned to pre-treatment levels at 12 months. When assessed using the EPIC

questionnaire, subscale scores for urinary and bowel domains were unchanged over the study period for those treated with PADT but scores for sexual function, hormonal function and hormonal bother decreased over time; sexual bother remained unchanged.

In contrast, in the RP group, both sexual function and bother decreased over time while hormonal function and bother were unaffected. Summary scores for EPIC domains for patients in the PADT group showed that urinary and bowel domains scores were unaffected while both sexual and hormonal domain scores decreased significantly compared with pre-treatment levels. In RP-treated patients, scores for all four domains were significantly decreased compared with pre-treatment levels at 3 months and this decrease was maintained at 12 months other than for the bowel domain scores which had returned to pre-treatment levels. In terms of overall satisfaction with treatment, in the PADT group, scores increased significantly after 3 months and then again after 12 months compared with pre-treatment levels; in contrast to the RP group, scores did not change over the study period. M.N. concluded by noting that when choosing therapy, urologists generally focused on outcomes, whereas patients made their selection based on their own individual philosophy—a balance between optimal clinical outcomes on one hand and the QoL and the invasiveness of the treatment on the other.

PRESENTATION 3: HOW SHOULD THE RESULTS OF THE SWOG 9346 (INT-0162) STUDY BE INTERPRETED?

M.C. [University of California, San Francisco (UCSF), USA] discussed recent data comparing outcomes following treatment with continuous versus intermittent hormonal therapy for locally advanced and metastatic prostate cancer. He outlined the findings of the Cochrane Review published in 2007, which included five studies comparing continuous androgen deprivation (CAD) and intermittent androgen deprivation (IAD) in a total of 1382 patients with advanced (T3 or T4) prostate cancer. Based on this analysis, the overall conclusion at that time was that more research was needed (15). He noted that data from randomized, controlled trials comparing IAD with CAD were limited by small sample size and short duration. In particular, no data were available for the relative effectiveness of IAD versus CAD on overall survival, prostate cancer-specific survival, disease progression or QoL. Limited information suggested that IAD may have a slightly reduced incidence of adverse events. One study suggested that IAS was more favorable than CAD in controlling impotence. Overall, IAD appeared to be as effective as CAD on potency, but was superior during the interval between cycles.

M.C. then reviewed some of the more recent studies comparing IAD and CAD. A study of 766 patients with locally advanced or metastatic PC undertaken by Calais De Silva et al. had concluded that IAD should be considered for use in routine practice as, compared with CAD, it is not associated with any reduction in survival, there is no clinically meaningful impairment in QoL, better sexual activity and considerable economic benefit to the individual and the community (16). Another study by Langenhuijsen et al. reported that metastatic prostate cancer patients with high baseline PSA levels, pain and high PSA nadir have a poor prognosis with ADT. The results of the study suggested that patients with low PSA nadir do significantly worse with IAD compared with CAD, suggesting that IAD is not a good treatment option for many metastatic PC patients (17). The FinnProstate Group had undertaken a randomized trial to compare IAD and CAD in 852 patients with advanced prostate cancer. The group reported that IAD appeared to be a feasible, efficient and safe method to treat advanced prostate cancer compared with CAD (18).

In the light of these findings, M.C. went on to review the results of the SWOG 9346 (INT-0162) Phase III trial comparing IAD and CAD in hormone-sensitive metastatic PC that were reported at ASCO 2012 (19). This was an intergroup study and 3040 patients were recruited by the different participating groups—SWOG, CALGB, ECOG, NCIC and EORTC—between May 1995 and September 1998 (20,21). The study included metastatic prostate cancer patients with baseline PSA of $\geq$5 ng/ml who received 7 months induction ADT. Those achieving PSA levels of $\leq$4.0 ng/ml at Months 6 and 7 were randomly assigned to receive CAD versus IAD at Month 8. Data for the first 1395 patients show that after controlling for prognostic factors, those with a PSA of 0.2 to $\leq$4 ng/ml had less than one-third the risk of death compared with those with a PSA of $>$4 ng/ml ($P < 0.001$). The median survival was 13 months for patients with a PSA of $>$4 ng/ml, 44 months for patients with a PSA of $>$0.2 to $\leq$4 ng/ml and 75 months for patients with a PSA of $\leq$0.2 ng/ml (20).

The latest results found that median survival of all patients (from accrual, not randomization) was 3.6 years (17% at 10 years) (19). For CAD-treated patients, the median survival was 5.8 years (29% at 10 years) and for IAD-treated patients it was 5.1 years (23% at 10 years). The hazard ratio for IAD versus CAD was 1.09 (095−1.24). Prostate cancer was found to be the cause of death in 56% of CAD and 64% of IAD patients. Overall, IAD was not proven to be non-inferior to CAD; however, a *post-hoc*, unplanned subset analysis found that IAD was statistically inferior in patients with minimal disease, suggesting that CAD might be preferred in this group.

QoL analyses were also performed at randomization and after 3, 9 and 15 months of follow-up. Compared with IAD, CAD was associated with a greater incidence of impotence, lower libido and lower emotional function ($P < 0.01$ for each); these differences persisted to 9 months.

M.C. noted some of the caveats to be borne in mind when interpreting these results: IAD was not proven to be non-inferior in this study, except in patients with minimal disease, and this was an unplanned subset analysis. Median survival in both the groups had been found to be longer than expected, subgroup definitions were non-standard, and these analyses had not been pre-specified. He added that the results did not

apply to M0 prostate cancer. He added that for the oncologist, survival is often the most important end point of treatment, but for patients, the QoL may be more important, particularly when the difference in survival between IAD and CAD is only about 6 months, as shown in this study.

PRESENTATION 4: UPDATE ON THE CAPSURE–J-CAP ANDROGEN DEPRIVATION THERAPY ANALYSIS

M.C. [University of California, San Francisco (UCSF), USA] reminded participants that the NCCN guideline 2011 specified that: 'Primary therapy with ADT should be considered only for patients who are not candidates for definitive therapy'(22). It was also an option for selected patients with 'very high risk'/T3b–T4 locally advanced disease. The AUA guideline 2007 specified that: 'Primary ADT may be employed with the goal of providing symptomatic control of prostate cancer for patients in whom definitive treatment with surgery or radiation is not possible or acceptable'(23). In contrast, the NCCN Asia Consensus Statement 2011 advises that ADT monotherapy is an option for all men, except those with very low-risk disease (24).

Data from CaPSURE for risk-adjusted mortality outcomes after primary surgery, RT or ADT for localized PC had shown that prostatectomy was associated with a significant and substantial reduction in mortality relative to radiation therapy, and both local treatments relative to ADT monotherapy in high-risk patients (25). However, a survey of practice patterns in the USA showed that ADT is commonly used in the USA as primary therapy, particularly for higher-risk patients (26). He noted that practice patterns in CaPSURE showed that men with low-risk disease tend to be treated with surgery and as their risk score increased, the likelihood of receiving ADT also increased substantially, which is essentially the opposite of what the data suggest should be used.

M.C. also showed the results from other datasets—Medicare (government financing for patients >65 years of age) and i3 (private health insurance) which showed similar patterns. He noted that treatment patterns in CaPSURE varied markedly across clinical sites, and this variation is not explained by case-mix variability or known patient factors (26). Results of a study into what drives selection of ADT for prostate cancer treatment have suggested that in fact which urologist a patient sees might be more important in determining whether they will receive ADT than tumor or patient characteristics (27).

Of the patients in CaPSURE treated with PADT, ~40% receive LHRH monotherapy and another 40% CAB, and this proportion has remained consistent over time. Preliminary results comparing data from J-CaP and CaPSURE for patients treated with PADT found that overall they showed very large differences in cancer-specific mortality for PADT patients in the USA compared with Japan, even after adjusting for risk. M.C. advised that from these results it could be concluded that the guidelines in both the regions—the USA and Japan—are appropriate for the particular populations in those regions. He noted that the underlying cause of these variations was currently unknown but various factors had been proposed including genetics, diet/lifestyle/environment, selection bias, era of treatment and treatment variations.

PRESENTATION 5: DIFFERENCES IN OUTCOMES FOLLOWING CAB TREATMENT BETWEEN CAPSURE AND J-CAP PATIENTS

S.H. (Kyoto University, Kyoto, Japan) provided an update on the Japanese Urological Association (JUA) prostate cancer registry and on comparisons with CaPSURE for patients treated with ADT. Between 2000 and 2004 data collected by the JUA had revealed a change in the type of primary therapy used over that time, with an increase in watchful waiting and radiation therapy and a decrease in RP and ADT (28,29).

A recent analysis of practice type for participating institutions in J-CaP had shown that the vast majority were general hospitals with a smaller proportion of University and private hospitals. Regardless of institution, treatment choice (CAB or not CAB) showed a similar pattern; the proportion of patients receiving CAB increased with increasing J-CAPRA risk score. Similarly, there was no difference in PFS or overall survival between practice type at any J-CAPRA risk category (low; 0–2; intermediate, 3–7; high ≥8) or when stratified according to age. An analysis of survival in the J-CaP database found that about half of events were due to prostate cancer death. He noted that in Japan, many end-stage patients move to terminal care hospital or a terminal care unit in a general hospital; therefore, survival data for University hospitals tended to be an underestimate.

Comparing data for J-CaP and CaPSURE, it has previously been shown that CaPSURE patients treated with ADT have relatively lower survival in each J-CAPRA risk category compared with J-CaP patients. Low- and intermediate-risk CaPSURE patients were found to have lower survival estimates when treated with CAB than when not treated with CAB. In high-risk patients, better survival was observed with CAB treatment than those not treated with CAB (30).

To investigate this further, a multivariate analysis was undertaken of a high-risk patient subset from J-CaP (age >75 years; $n = 4689$) looking at the effect of different comorbidities (stroke, heart disease, chronic obstructive pulmonary disease, diabetes, other cancer) on overall survival. In patients with low J-CAPRA scores, stroke, COPD and other cancer significantly increased the risk of mortality. In the case of patients with intermediate J-CAPRA scores, heart disease and other cancer significantly increased the risk and for those with high J-CAPRA scores, stroke and diabetes marginally increased the risk. In this analysis, overall and cause-specific survival were significantly better with CAB treatment in those with high J-CAPRA scores, but there was no difference between treatments in those with intermediate or low

J-CAPRA scores (Fig. 4). Further head-to-head comparisons of the data subgroups from J-CaP and CaPSURE were warranted to investigate these differences.

PRESENTATION 6: CHEMOPREVENTION STUDY IN JAPAN

H.A. (Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan) outlined the results of a chemoprevention study undertaken in Japan to investigate the influence soy isoflavones on the development and progression of prostate cancer. The background of his study stemmed from the observation that prostate cancer incidence and mortality were higher in the West and lower in Asia, whereas soy consumption was lower in the West and higher in Asia, raising the question of whether it was possible to reduce prostate cancer incidence in the West by changing soy consumption.

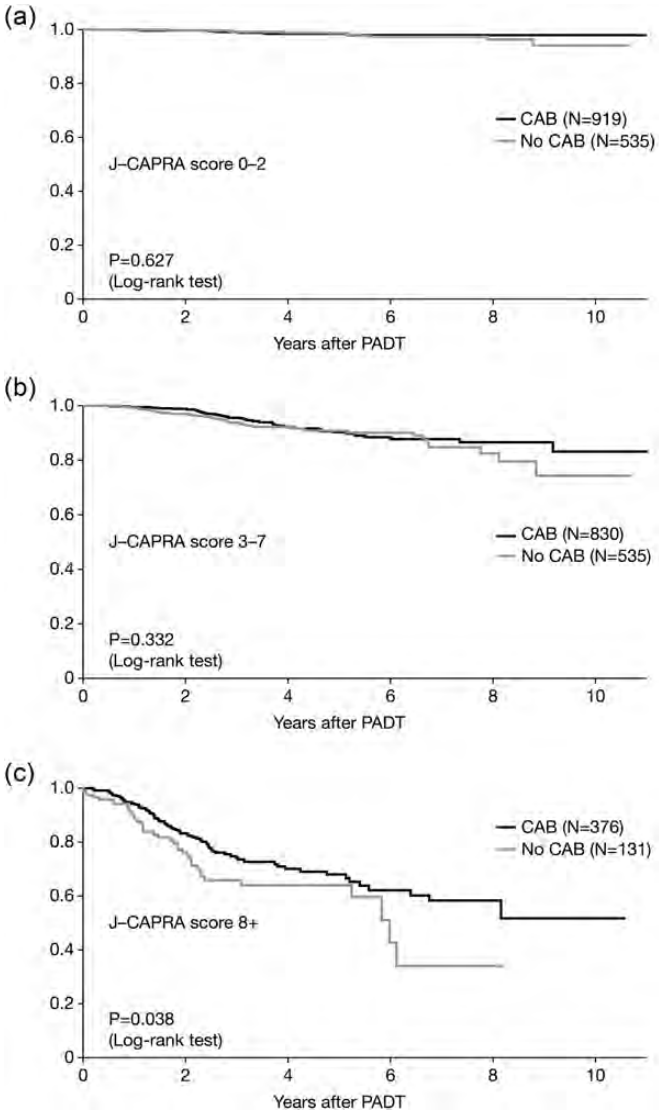

Figure 4. Cause-specific survival according to (a) low, (b) intermediate and (c) high J-CAPRA score in J-CaP patients treated with hormone therapy (unpublished data).

A meta-analysis has been undertaken to evaluate the available epidemiologic studies that relate soy consumption to the risk of prostate cancer in men (31). Overall, these studies showed that consumption of soy food is associated with a lower risk of prostate cancer in men with an overall risk estimate of 0.70 (95% CI 0.59–0.83; $P < 0.001$). Soy isoflavones include genistein, diadzein and it major metabolite, equol. Preclinical studies have shown that equol acts like an antiandrogen by binding with dihydrotestosterone and has been shown to reduce prostate volume in rats (32). He noted that while equol has the most potent bioactivity, not all men can metabolize daidzein into equol and equol producers may possess the equol-producing bacteria in their intestinal tracts. Studies have shown that men who are unable to produce equol are at a higher risk of prostate cancer (33).

Asian countries, such as Japan and Korea, appear to have a high proportion of equol producers, whereas Westerns countries, such as the USA and Germany, have a very low proportion (33). Notably, the proportion of equol producers in Japan and Korea is significantly lower ($P < 0.05$) in patients with prostate cancer than in the general population and the authors suggested that a diet based on soybean isoflavones might therefore be useful in preventing the disease. He advised that equol non-producers had no traces at all in the serum.

To examine the relationship between isoflavone intake and the incidence of prostate cancer in Japan, an age-stratified dietary survey of soybean foods was undertaken in 102 healthy Japanese men and 100 healthy Korean men; serum isoflavones and equol levels were measured (34). It was found that the proportion of equol producers among subjects over 40 years of age was significantly higher than in those under 40 years of age. H.A also reported the results of the Phase II, randomized, double-blind, placebo-controlled trial to examine the effect of oral isoflavone (60 mg/day for 12 months) on the incidence of prostate cancer (35). A total of 158 Japanese men aged 50–75 years, with a serum PSA level of 2.5–10.0 ng/ml, and a single, negative prostate biopsy in the 12 months prior to enrollment were included in the study. The median age of the patients was 66.0 years and the numbers of equol producers and non-producers were 76 (48%) and 82 (52%), respectively. The incidence of biopsy-detectable prostate cancer in the isoflavone-treated and placebo groups showed no significant difference (21.4 versus 34.0%; $P = 0.140$); however, for the 53 patients aged $\geq$65 years of age, the incidence of prostate cancer in the isoflavone-treated group was significantly lower than that in the placebo group (28.0 versus 57.1%; $P = 0.031$) (35) (Table 1).

H.A. reported that the Benziger Winery in California had established a biodynamics program with the aim of improving their vines. He suggested that there were similarities with the intestinal environment, since there is a similar symbiotic relationship between a bacterium and its human host. As such, the concept of biodynamics might be usefully applied in cancer prevention (35). In particular, such research might help improve the intestinal environment to enable equol production

Table 1. Proportion of men with prostate cancer and high-grade prostatic intraepithelial neoplasia (PIN) according to equol-producing ability and treatment (isoflavones or placebo) (35)

	Equol producer			Equol non-producer		
Positive biopsy	Isoflavone ($n = 22$)	Placebo ($n = 22$)	*P* value	Isoflavone ($n = 20$)	Placebo ($n = 25$)	*P* value
Age (years):						
All	5/22 (22.7%)	8/22 (36.4%)	0.255	4/20 (20%)	8/25 (32%)	0.288
<64	1/9 (11.1%)	0/6 (0%)	0.600	1/8 (12.5%)	0/13 (0%)	0.381
≥65	4/13 (30.8%)	8/16 (50.0%	0.293	3/12 (25%)	8/12 (66.7%)	0.049*
Gleason score:						
5–6	2/5 (40.0%)	6/8 (75.0%)	0.25	3/4 (75.0%)	6/8 (75.0%)	0.764
7–9	3/5 (60.0%)	2/8 (25.0%)	(G6 versus 7–9)	1/4 (25.0%)	2/8 (25.0%)	(G6 versus 7–9)
High-grade PIN	1/22 (4.6%)	4/22 (18.2%)	0.172	1/20 (5%)	4 /25 (16%)	0.251

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*$P < 0.05$

in equol non-producers and thus potentially reduce the risk of PC. The research has identified NATTS bacteria from among the intestinal microflora of a normal Japanese man who had ability to metabolite daidzein into equol. H.A. pointed out that successful chemoprevention studies had been undertaken previously with 5α-reductase inhibitors (the PCPT and REDUCE studies) (36), but noted that this approach was not suitable for population-based prevention. The non-production of equol is a possible biomarker for a high-risk prostate cancer and potentially a soy-based diet with the addition of equol-converting bacteria, or the converting enzyme itself, could restore the subject's equol-producing ability. He gave an overview of their ongoing research project that will evaluate the serum levels of genistein, daidzein and equol in 60 Japanese and 60 Caucasian subjects (in each group: 30 prostate cancer patients and 30 cancer-free controls). In addition, it will evaluate the equol-producing ability and the presence of the NATTS equol-producing bacterial strain in Japanese and Caucasian men in Hawaii.

H.A. concluded by saying he hoped that the next step would be a global interventional trial for prostate cancer chemoprevention. The intake of soy foods, the use of an equol supplement and the intake of foods including NATTS bacteria and isoflavones were also possibilities for investigation. He asked participants to consider the possibility of undertaking such interventional trials in the USA, Korea, Indonesia or Japan.

He advised that the intestinal content of equol-producing bacteria did not appear to be influenced by a short-term diet high in soy isoflavones. As equol-producing bacteria were not found in all people, it was suggested that it was inherent in some people but not in others. It was recognized that in other therapy areas, for example bladder cancer, studies have been undertaken to investigate the use of probiotics to prevent disease progression. This means that 'symbiosis' in humans may not only be a phenomenon worth investigating for prostate cancer but also for other diseases.

PRESENTATION 7: PRESENT STATUS OF ACTIVE SURVEILLANCE IN THE USA

M.C. [University of California, San Francisco (UCSF), USA] stated that prostate cancer management in the USA was currently at a crossroads since the US Preventive Services Task Force (USPSTF) has recommended against PSA-based screening for prostate cancer. Despite an increasing aging population, there had been a substantial (40%) drop in age-adjusted prostate cancer mortality since the 1990s (37). However, treatment changes only explained a fraction of this positive decline and mortality trends suggested a clear role for screening (38). He cautioned that if screening was abolished in the USA, the likely outcome would be a steep rise in prostate cancer incidence, in particular metastatic disease.

A major driver of the backlash against screening is common overtreatment of low-risk disease (39) caused in part by the tendency in the USA to treat by age rather than by level of risk. Based on the results of the Prostate Cancer Intervention Versus Observation Trial (PIVOT), which had shown no difference in overall survival rates between surgery and watchful waiting for low-risk prostate cancer (40), a NIH consensus statement had concluded that men with low-risk PC may be better candidates for AS rather than immediate treatment. However, subset analyses of the PIVOT trial, which were not as well publicized, showed that for high-risk disease there is a significant, substantial benefit of treatment. The conclusions that should be drawn from the results of the trial were that low-risk disease does not need to be treated immediately in all cases, but high-risk disease definitely does.

Overall findings from an analysis of seven large AS series showed that this approach offered an opportunity to limit intervention to patients who are likely to benefit the most from radical treatment and confers a low risk of disease-specific mortality in the short to intermediate term (41).

One of the areas identified for future research regarding AS in localized prostate cancer was biomarkers. The use of clinical parameters to risk-stratify prostate cancer to aid treatment decisions was well established; however, novel biomarkers are needed to help predict tumor behavior more accurately. An ongoing research partnership at UCSF was the Canary Prostate Active Surveillance Study, a multicenter study and a biorepository that aims to discover and confirm biomarkers of aggressive disease as defined by histological, PSA or clinical criteria (42). UCSF has also started a collaboration with the University of Washington to investigate upgrading/upstaging from biopsy to surgery and also progression on AS which will look at a number of markers in serum (TGF-β1, IL6-SR), urine (PCA3, TMPRSS:ETS fusion) and tissue (GEMCaP, Prolaris), and also QoL. The Prolaris assay has already been validated by Cuzick et al. who assessed the prognostic value of the RNA expression signature derived from predefined cell-cycle progression (CCP) genes in patients with PC and found it to be a robust prognostic marker (43).

M.C. reported the results of his group's study presented at ASCO 2012 to validate the ability of a previously described 46-gene expression panel consisting of 31 CCP genes and 15 'housekeeping' genes to predict recurrence in a cohort of men undergoing RP (44). Men undergoing RP at UCSF since 1994 who had $\geq$5 years of follow-up were included in the study. The CCP score was found to have significant prognostic accuracy even when controlling for clinical and pathologic data. Adding the CCP score to the CAPRA-S score improved accuracy significantly ($P < 0.0001$). The authors concluded that, based on Kaplan–Meier analysis, the CCP score improved the accuracy of risk stratification in both the overall cohort and for patients with clinically low-risk disease (CAPRA-S score 0–2).

M.C. concluded that AS is an increasingly viable option for men with low-risk (and perhaps intermediate-risk) prostate cancer, and it should be recognized that while AS often delays treatment, it does not avoid it altogether. In clinical practice, adequacy of sampling was a concern, and defining progression remained a significant challenge for clinicians. He recommended that additional QoL and psychooncology research was needed to quantify more precisely the potential benefits of AS. Novel imaging and biomarkers that are currently in development will undoubtedly aid the decision-making process in due course.

DISCUSSION

J.Y.L. asked whether it was possible for groups outside of J-CaP and CaPSURE to contribute ideas. It was agreed that ideas were welcome from other national groups—the aim was to have an international perspective on prostate cancer and its treatment. It was intended that each national database would be kept separate but the data generated from them could be combined in order to answer specific questions.

It was noted that CaPSURE has an ongoing scholars' program which usually took applicants from the USA and Canada who worked with a local mentor; however, applications from other countries would be welcomed. In addition, UCSF was part of nine-center study of AS (CANARY) which aimed to recruit over 1000 patients.

The availability of screening and its likely impact on future prostate cancer incidence were a 'hot topic', particularly in 2012, the US Preventive Services Task Force (USPSTF) had recommended against PSA-based screening for prostate cancer (D recommendation). Added to this were the results of the PIVOT trial which had had shown no difference in overall survival rates between surgery and watchful waiting after 12 years of follow-up (40). Participants considered that the PIVOT trial was not perfect, noting that the results had wide confidence intervals and surgical treatment had been found to be beneficial in patients with high-risk disease.

There were some concerns that these recent recommendations and results might give the impression that prostate cancer in the USA was a disease that does not need treatment. The issue had arisen initially due to public concern about overtreatment of low-risk disease; however, if this resulted in a move to stop screening altogether, there was a danger that high-risk disease would not be detected and incidence of metastatic disease, and also disease-specific mortality, would increase.

CONCLUSION AND NEXT STEPS FOR THE JOINT INITIATIVE

P.C. (University of California, San Francisco, USA) made the initial closing remarks for the meeting by acknowledging the importance of continuing the collaborative work in between the annual joint meetings and to publish the group's findings wherever possible, for example the comparative survival data following hormonal therapy.

H.A. (Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan) commended the rapid progress that had been made by K-CaP and hoped that China would be represented at the next joint meeting.

R.U. (University of Indonesia, Depok, Indonesia) said that his team hoped to follow in the footsteps of K-CaP and develop a similar database for Indonesia. To reflect the increasing representation of other countries and the ongoing development of the K-CaP database, it was proposed that the next joint meeting be held in Korea.

In closing the meeting, the Co-Chairmen thanked all the participants for attending and for their valuable contributions to the discussions, and also acknowledged Takeda

Pharmaceutical Company Ltd for their continued support of these joint meetings.

Conflict of interest statement

None declared.

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APPENDIX

MEETING PARTICIPANTS
Left to right: R.U., M.N., J.Y.L., M.C., P.C., H.A., T.T., B.-H.C., S.H.

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