

MEETING REPORT

The 5th Conference on Asian Trends in Prostate Cancer Hormone Therapy

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Abstract

The Conference on Asian Trends in Prostate Cancer Hormone Therapy is an annual forum for Asian urologists now in its 5th year. The 2006 conference, held in Bali, Indonesia, was attended by 27 leading urologic oncologists from China, Indonesia, Japan, Korea, Singapore, and Taiwan and featured a packed program of presentations and discussions on a wide range of topics such as relationships among clinicians and the newly opened Asia Regional Office for Cancer Control of the International Union Against Cancer (UICC), detection rates of prostate cancer by biopsy in each of the 6 Asian countries, and favored treatment modalities for hormone-refractory prostate cancer (HRPC) in each country.

The first session of the conference kicked off with a keynote lecture entitled "Activities of the UICC ARO". UICC's new office will be the nerve center for its activities in the Asia region. Along with the Asian Pacific Organization for Cancer Prevention (APOCP), UICC aims to shift the focus of attention to cancer control. As such APOCP's long-running publication the APJCP is to be re-launched as the Asian Pacific Journal of Cancer Control. Although UICC is primarily concerned with cancer, several risk factors for cancer are common also to other non-communicable diseases such as diabetes and heart disease, and an important strategy is to implement measures to control these various pathologic conditions as a whole. Apart from contributing to an Asian prostate cancer registry the UICC-ARO will provide training courses, working groups, and assistance in collecting and processing data.

The keynote lecture was followed by a roundtable discussion on possible ways in which clinicians from each Asian country can work with UICC. A number of suggestions were put forth including better registration, epidemiology research, possible implementation of UICC prostate cancer guidelines, early detection and screening, and roles of diet and phytotherapy. The underlying reasons for the large but dwindling difference in incidence rates of prostate cancer in various regions of Asia should be studied while the opportunity lasts.

Session 2 was devoted to 6 presentations on detection rates by biopsy in each country. Although biopsy is the gold standard for detecting prostate cancer in most areas, indications for conducting biopsy are different in each country. For example, in Indonesia doctors may use PSAD 0.15 as the cutoff level. TRUS-guided biopsy is most widely used in Asian countries. Traditional sextant biopsy is often performed, although multiple-core biopsy is commonly available and associated with better detection rates, especially in men with large prostate volume. Positive DRE, high PSA, and older age were identified as factors associated with high biopsy detection rate, although elevated PSA has limited specificity. First biopsy in men with elevated PSA had a positive detection rate of approximately 30% in all countries. Community-based screening in some countries has an overall detection rate of approximately 1%.

The favorable treatment modality for HRPC was the subject of the final session. First priority for doctors in all 6 countries is to maintain serum testosterone at castration level. Many therapeutic options are available, from cytotoxic drugs to traditional herbal medicines. Chemotherapeutic agents such as estramustine, docetaxel, cyclophosphamide, and mitoxantrone are often given to patients with HRPC although not all are available in every country. Prednisone and dexamethasone are used for secondary hormonal therapy. External beam radiotherapy, radioisotopic drugs such as strontium 89, and bisphosphonates are common choices to control bone pain.

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Introduction

The 5th Conference on Asian Trends in Prostate Cancer Hormone Therapy was held at the Sheraton Laguna Nusa Dua, Bali, Indonesia, on Sunday, August 27, 2006. Twenty-seven leading urologic oncologists from 6 Asian countries (China, Indonesia, Japan, Korea, Singapore, and Taiwan) converged at the venue to listen to a keynote lecture titled "Activities of the International Union Against Cancer (UICC) Asian Division" presented by Malcolm Moore and to engage in a program of roundtable discussions on topics of possible future relationships among prostate cancer clinicians and the UICC in Asia, detection rates of prostate cancer by biopsy in each country, and favored treatment modalities for hormone-refractory prostate cancer (HRPC) in each country. The principal themes of the 2006 conference were expressed by conference chair Hideyuki Akaza (Japan) who in his opening remarks stated that the society is ready to take the first steps towards instigating clinical trials in the region. Ethnicity among Asian peoples exhibits more similarity than it does with western peoples, he added. Although in the field of prostate cancer currently 90% of original published research derives from researchers in the USA and Europe, it seems that more effort should be focused on gathering evidence in Asian prostate cancer patients. Professor Akaza welcomed distinguished guest speaker Dr Moore and congratulated him on his efforts in founding the UICC Asia Regional Office, which is due to open in Bangkok, Thailand, in 2006.

Following these opening remarks, Rainy Umbas (Jakarta, Indonesia) delivered a welcome address and expressed his wishes that the day's discussions may prove fruitful and contribute to greater improvements in the management of prostate cancer.

I. Session 1: Activities of the Conference on Asian Trends in Prostate Cancer Hormone Therapy (chaired by Hideyuki Akaza and Malcolm Moore)

1. Keynote Lecture: Activities of the UICC Asian Division, Malcolm Moore

After many years of continuous activity, the UICC Japanese committee decided to support an office for the Asia region as a whole. Over the last 5–6 years, the UICC has been involved with many different researchers and clinicians all over Asia, in particular in connection with its sister organization, the nonprofit concern Asian Pacific Organization for Cancer Prevention (APOCP) and its quarterly publication the Asian Pacific Journal of Cancer Prevention (APJCP).

With the opening of the UICC Asia regional office in 2006, the intention is for the APOCP to expand its activities to include cancer control. To this effect, the journal will be renamed the Journal of Cancer Control. The UICC Asia regional office will be responsible for the journal's publication and for preparing a number of meetings during the year.

Cancer prevention and cancer control have a long and

Table 1. Historic Findings in Cancer Causality

Year	Scientist(s)	Findings
1700	B Ramazzini	Occupation, breast cancer in nuns
1761	J Hill	Snuff tobacco and nasal polyps
1775	P Pott	Chimney sweeps and scrotal cancer
1851	T H Bilharz	Parasites and cancer
1871	R Virchow	Irritation theory
1879	F H Harting/W Hess	Lung cancer among miners
1895	L Rehn	Aniline dyes and bladder cancer
1915	K Yamagiwa/ K Ichikawa	Tar-induced skin cancer
1920	R Sasaki	Azodyes and liver cancer
1995	T Sugimura	Heterocyclic amines and cancer

international history that can be traced back to Ramazzini's observations of breast cancer occurring in Italian nuns in 1700 through to Sugimura's recent work on heterocyclic amines and cancer in Japan (Table 1). This historic cooperative effort is certainly set to feature increasingly more Asian contributions in future. There have also been a significant number of national cancer associations starting with the Anti-cancer League in France in 1893 to the present situation wherein almost all Asian countries have their own anticancer association or cancer societies, many of which are members of UICC or the Asian Pacific Federation of Organizations for Cancer Control (APFOCC). Hence there is a proliferation of national organizations brought together under the aegis of larger international organizations, not only UICC (established in 1933) but also the World Health Organization (WHO; founded 1948), International Agency for Research on Cancer (IARC; 1965), and so on, each with its own calendar of regular meetings and events. Last but not least, there is the International Association of Cancer Registries.

Although the UICC World Cancer Congress is presented as a global platform for cancer research, statistics show that Asia is severely underrepresented in terms of speakers at the conference: recently of 39 plenary speakers 18 were North American, 10 European, and only 2 were from Asia (one each from Mainland China and Hong Kong). To put this in perspective, there were 250 times as many Australians as there were Asians in terms of their relative populations (4 speakers from a total population of 24 million versus 2 representing 4040 million, respectively). Therefore the utmost should be done to increase Asian presence in the fight against cancer. To this effect it has been proposed that international organizations such as UICC, WHO, and IARC will focus more attention on Asia Pacific by bringing together APOCP (and APJCP), APFOCC, and WHO's Regional Offices for South East Asia (SEARO) and Western Pacific (WPRO) so as to work more closely together in Asia. Although the UICC is primarily concerned with cancer, several risk factors for cancer especially adenocarcinoma are common also to diabetes and heart disease; therefore it is reasonable for cancer control organizations to think in terms of overall noncommunicable disease (NCD) control. In Japan for example cancer-related mortality is highly prevalent in males and females at approximately 30% of all deaths, with cerebrovascular disease the second-most common cause of death from NCD. Regarding prostate cancer, the incidence rate is very high in Australia and New

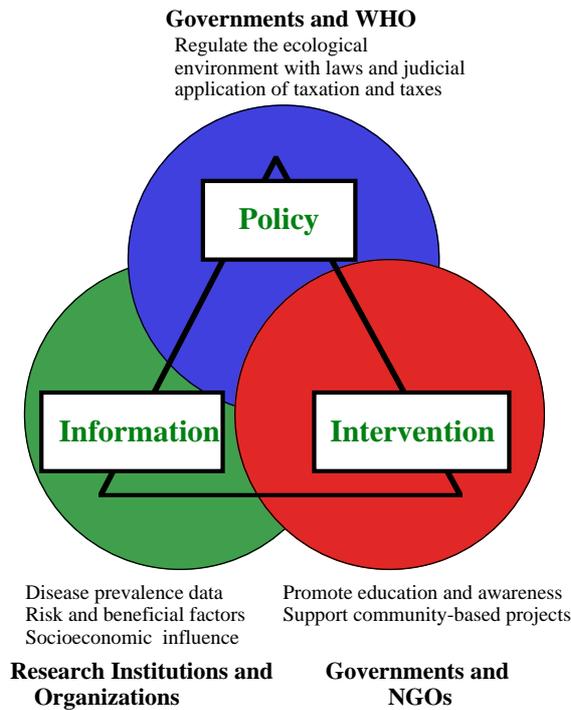


Figure 1. Health Determinant Triad

Zealand and quite high in the Philippines, Japan, and Malaysia and the problem is expected to increase in the future. Focusing on other etiologically linked diseases, cerebrovascular and ischemic heart diseases are following a similar pattern of increased prevalence, as is the pattern of diabetes prevalence, with Japan having the worst problem, although up-to-date data are insufficient in many countries in the Asian region. Better registration of disease epidemiology is required. In any case, over the next 20 years an explosion in the number of Asian people who are obese with diabetes, with a concomitant increase in breast cancer and possibly prostate cancer along with many of the other adenocarcinomas, is foreseen. Therefore agencies such as UICC will be trying to bring together researchers and clinicians operating in different disease areas so as to reduce risk factors and promote beneficial factors for cancer, cardiovascular diseases, and diabetes, which considerably overlap.

Figure 1 shows a triad for determinants of our health

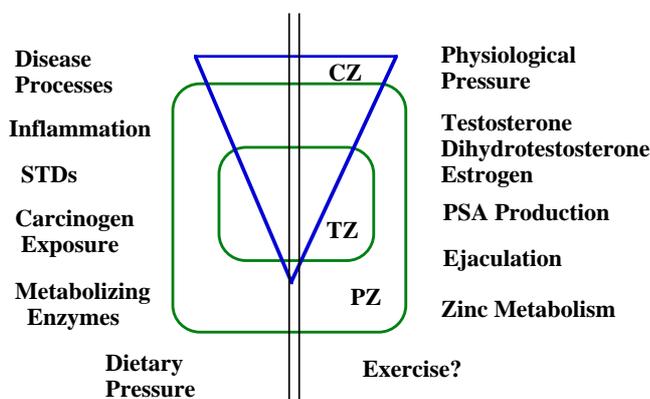


Figure 2. Prostate Cancer Pathophysiology and Risk Factors

and illustrates a schema for input required from various health and environmental professionals and organizations for the promotion of NCD control. Basically, it is envisaged that the pharmaceutical industry, government policymakers, health professionals such as surgeons and clinicians, cancer registries, epidemiologists, toxicological pathologists, and screening centers will work together under the auspices of organizations such as APOCP to fight cancer and other NCDs. The four main areas of activity within the UICC Asia regional office will be disease diagnosis and registration, risk factor and protective factor identification, practical primary and secondary prevention, and clinical treatment and palliative medicine. Our approach to the first of these aims, diagnosis and registration, will be to set up an Asian network for cancer registration similar to the European and North American models (European Network of Cancer Registries and North American Association of Central Cancer Registries, respectively) to collate up-to-date information on cancer incidence, prevalence, and mortality so as to enable us to devise plans to tackle the disease. Although there are several extant cancer registries at the local level in Asia, these only cover small sections of the population and there are many countries for which registries are not established. Therefore another of the aims of the UICC Asian network will be to provide training courses, working groups, and assistance in collecting and processing data.

Although it is known that the majority of prostate cancers arise in the peripheral zone with high-grade prostate intraepithelial neoplasia (PIN) or atypical small acinar proliferation (ASAP), there are many aspects of this disease that are less clear. For example, what is the involvement of benign prostate hyperplasia? What are the differences between cancers that arise in different zones of the prostate gland? These are examples of areas within the pathology field that still require a great deal of exploration, especially since most of the data that are available derive from the USA and Europe. Comparative Asian data are severely lacking. For this reason one of the aims of UICC Asian division is to introduce a hospital-based registration system to collect urgently needed data.

The second major aim of the UICC in Asia is to identify risk factors and beneficial factors as determined by tissue physiology (Figure 2). In the peripheral, transitional, and central zones of the prostate for example several factors have differing effects on carcinogenesis, including inflammation, sexually transmitted diseases, exposure to carcinogens, metabolizing enzymes, and dietary pressure, physiological pressure, and hormonal milieu must be taken into consideration. PSA production and entry into the bloodstream need better understanding, as do the influences of ejaculation and zinc metabolism and the role of exercise.

Primary and secondary prevention of prostate cancer refers to prevention strategies in men who do not have any evidence of the disease and in those who have screened positively for precancerous lesions, respectively. There are many different modalities that can be explored in primary and secondary prevention, but the most effective means of prostate cancer prevention are not well understood.

Finally, the UICC Asian office aims to become involved in the area of cancer clinical intervention. This includes

screening and diagnostics, hormone therapy, surgery, radiotherapy and chemotherapy, and palliative care. It has been proposed that introducing a hospital-based clinical registration system across Asia using a standardized protocol could be a very useful tool with which to conduct investigations of clinical interventions by enabling us to obtain easily comparable data. With this tool researchers can look at screening, biopsy, treatment, and outcomes. Furthermore, a comprehensive explanatory document published in English, Chinese, Japanese, Korean, Indonesian, Malaysian, and so on could enable us to standardize and very quickly produce a large database of information on risk factors such as diet, exercise, supplement intake, body size, hormone level, and morphology of the prostate. For screening, many PSA parameters and complicating factors are vitally needed data, as is evidence for biopsy methodology, the number of cores required, and pathological diagnosis of lesions observed. Treatment strategies must be determined by decision making at the individual patient level, including quality of life, watchful waiting, and the various different treatment modalities including hormonal, surgical, and radiation therapy, chemotherapy alone and in combination, and so on, which are all questions that require answers in the Asian context since to date there have been very few papers published from this part of the world (see Cheng et al., 2006).

The role of UICC in Asia can be summarized as to form a “cooperation triad” of policy, information, and intervention in the region. Policy is dictated by governments and to a certain extent by WHO; the ecological environment is regulated by laws and the application of taxation, and the environment in turn impacts on what diseases the people develop. Hence policy is very important. Information is dependent on our understanding of incidence, prevalence, and mortality rates of diseases such as prostate cancer. This helps us to identify risk and beneficial factors, and with this knowledge we can assess at the local environmental level socioeconomic influences. Gathering this information is the role of research institutions and organizations such as national cancer centers, local hospitals, universities, and research groups. Finally, evidence-based information can be used for the purpose of intervention among local populations by promoting education and awareness, supporting community-based projects, and encouraging hospital-based clinical cooperation.

The UICC Asia regional office at first will be a small office in Bangkok. It will have a library open to visitors, but most importantly the office will form a physical base for UICC operations. The office will run a web site for free communication and downloads such as guidebooks and other cancer information in several languages. The APJCP journal is available on PubMed and likewise all PDF files are available as free downloads. The UICC Asia regional office will provide several training courses and books including an Asian handbook for cancer prevention probably within 2007. The office will also act as a research collaboration center. A number of meetings are also planned, or have been held, for example a breast cancer meeting in November 2006; the UICC strongly promotes the idea of having more cancer congresses and specialist meetings in the Asia region.

2. Roundtable Discussion: The Possible Future Relationship with the UICC in the Field of Prostate Cancer

The first session concluded with a roundtable discussion in which the chairpersons were joined by Shujie Xia (China), Rainy Umbas (Indonesia), Masaru Murai (Japan), Choung-Soo Kim (Korea), Han Yong Choi (Korea), Christopher Cheng (Singapore), and Chi-Rei Yang (Taiwan), who each presented brief comments on possible ways in which their countries might benefit from working with the UICC in Asia.

Doctor Xia began the proceedings by stating that in China the Chinese Urological Association (CUA) has a number of different specialty groups such as uro-oncology, endourology, urinary stone, urodynamics, andrology, and transplantation. Many guidelines have been issued by CUA including guidelines for prostate cancer, BPH, urinary stone, overactive bladder, and prostatitis. However, the incidence of prostate cancer especially is fast increasing in China, so there is much room for cooperation with UICC, especially in the immediate areas of epidemiological research, differences in therapeutic approaches in each region such as pharmacologic or surgical castration, and possible implementation of a UICC prostate cancer guideline. Furthermore, the presence of UICC in Asia brings promise of the exciting possibility of conducting prospective multi-country clinical trials in the region.

Following this, Dr Umbas made a short presentation focusing on the clinical situation of prostate cancer in Indonesia. According to the government, prostate cancer is included among the 10 most common malignancies in men, although whether this is accurate is obscure because the last survey was conducted a decade ago in 1996. In fact, the incidence rate of prostate cancer in Indonesia is unknown. At the University of Indonesia Cipto Mangunkusumo Hospital most (75%) prostate cancer patients present with stage III–IV disease. Over the last 10 years, the number of patients referred to the hospital for prostate cancer treatment has trebled. Hence the most urgent need in Indonesia is to get information on prostate cancer prevalence. It is hoped that with the aid of UICC a national cancer registry can be developed in Indonesia similar to those of Japan and Korea. In addition, in cooperation with the Indonesian Cancer Foundation and Indonesian Urological Association, there is a need for a national program of early detection and screening because currently this varies widely depending on the geographical area and at each hospital. An epidemiological study especially in rural areas could provide valuable data since in western countries where there is a very high incidence of prostate cancer it is difficult to discover factors that could prevent the disease, whereas if in some parts of Indonesia the prevalence is very low this would be of interest. This approach has already been started in China in collaboration with some European countries and research centers that are looking into why prostate cancer is so uncommon in China. Lastly, Indonesian researchers are very interested in conducting or collaborating in research on the roles of diet and phytotherapy, especially the latter which is very popular in Asian countries on the whole: the first medication that many Asian patients will take is a herb even before going to see a doctor.

Next, Professor Murai made some comments on the

natural history and epidemiology of prostate cancer. Although in Asia the incidence of prostate cancer is still low, it is rising sharply. In Japan, there is still no complete national database set up as yet but several registration systems exist and also some clinical studies have been conducted. From 2001, the Japanese Urological Association (JUS) started a computer-based registry of prostate cancer patients and the first report, which appeared in the December 2005 issue of *IJUA*, presented data on a total of 4,529 patients at 173 institutions. In addition, the ongoing JCAP Study of endocrine therapy with or without adjuvant treatment has so far accrued approximately 9000 prostate cancer patients annually. Another study of brachytherapy started in 2005 and has enrolled 3000 patients. There are 1200 educational hospitals in Japan and most surgical procedures were conducted therein: the number of radical prostatectomy performed in 2003 was 15,000 with figures for radical nephrectomy and radical cystectomy 9000 and 4000, respectively.

The report from Korea was made by Dr Kim, who began by pointing out that prostate cancer is the sixth most common cancer in Korean males with a prevalence rate of 7/100,000 population. Prostate cancer incidence increased by 211% between 1995 and 2002. Surgery is the mainstay of treatment for prostate cancer, especially radical prostatectomy and open or laparoscopic and even robotic surgery, and many patients receive radiotherapy. However, although many treatment modalities are available for patients currently there is no patient registration program specific for prostate cancer. Therefore the UICC office in Asia represents a good chance to begin international epidemiologic and prevention studies in the region. There are two important ways in which Korean researchers can collaborate with the UICC: first would be a hospital-based clinical study or West Asian study. The second is to capitalize on UICC's expertise to design a large nationwide study.

Following this, Dr Cheng speculated that the involvement of UICC in Asia promises to bring the mission and purpose of such groups as the Asian Trends in Prostate Cancer Hormone Therapy society into much sharper focus, especially as regards formulating an effective strategy to lessen the burden of urologic cancer. UICC brings a recognizable branding to the group, lending it a certain legitimacy that everybody can acknowledge and perhaps that will lead to better fundraising and more activities. The main obstacles to the society's vision and mission include technical dimensions such as mailing protocols, networking, e-mail, and so on, but probably the biggest problem is that Asian countries are at various different stages of socioeconomic development and that makes it difficult to collaborate. However, these obstacles are not insurmountable. Researchers in each country need to make a list of potential collaborations chiefly depending on what is the purpose. It seems that a parallel effort to network all cancer registries for all cancers by personal contact with national registries is a good place to start. In particular, there is at present a great window of opportunity for Asian urologists that is fast closing: there is a large difference in incidence rates of prostate cancer in various regions of Asia, which provides us with an opportunity to study why that is so before the difference diminishes altogether.

The session ended with Dr Yang's presentation on the situation in Taiwan, where the incidence and death rates of prostate cancer have also increased rapidly in recent years. Since 1982, all-site cancer has been the leading cause of death in Taiwan. The National Health Department has been working on a nationwide cancer registry and has built a database of data on each cancer patient at every hospital since 1979. The capital area, Taipei, has the highest incidence rate of the disease with the Taichung area close behind. Surprisingly, the area with the highest mortality does not have the highest incidence, suggesting that treatment may not be adequate in that region. Taiwan has its own prostate cancer treatment guidelines but much of the data used to prepare the guidelines were gathered in the USA and Europe. Therefore if Asian countries could unite together and share homegrown data it might be very useful for disease control. Finally, the leading cancers in Taiwan are hepatoma, stomach cancer, and breast cancer, so it is always difficult to obtain funding for prostate cancer research; international collaborations made possible by the presence of UICC could improve that situation for Taiwanese urologists.

II. Session 2: Detection Rate of Prostate Cancer by Biopsy in Each Country chaired by Wun-Jae Kim and Kesavan Esuvaranathan

1. Report from China presented by Dr Shujie Xie

Prostate cancer morbidity in China is growing fast. In Beijing, the morbidity rate rose from 2.1 to 3.5/100,000 population between 1987 and 1995. In Shanghai over the same period standard morbidity rose from 1.7 to 3.7/1000/000 and reached 7.7/100,000 in 2000. Biopsy is the gold standard for detecting prostate cancer. Indications for biopsy are positive DRE and any PSA, elevated PSA level >10 ng/mL with any free-to-total PSA ratio (f/t PSA) and PSA density (PSAD), and PSA 4–10 ng/mL and abnormal f/t PSA or PSAD. Furthermore, suspicious transrectal ultrasonography or MRI is an indication for biopsy irrespective of normal PSA parameters. Common strategies for biopsy include rectal route and transperineal and transrectal ultrasound-guided methods. Usually traditional sextant biopsy is performed; also sextant biopsy plus suspicious nodule and multiple (13) cores biopsy as applicable.

Factors well correlated with high tumor detection rate include positive DRE, high PSA, older age, and high PSAD. Gangzhi (2006) performed a study of the impact of different prostate biopsy strategies on tumor detection rate, and found that 8- and 10-core biopsy was associated with an overall sensitivity of 94.8% and 97.4%, respectively, with no significant difference observed versus 13 cores ($P=1.25$ and 0.5 , respectively). However, sextant biopsy (apex/mid/base or apex/mid/lateral base) was significantly ($P<0.001$) inferior to multiple-core biopsy with a sensitivity of 85.7%. On the other hand, sextant biopsy at apex/lateral mid region was associated with a fairly high sensitivity of 90.9% ($P=0.008$ vs 13 cores). In comparison with sextant biopsy, >10-core prostate biopsy was not associated with more complications such as hematuria, hemoproctia, fever,

hemospermia, and dysuria although it caused more pain. Indications for >10-cores biopsies include comparatively large prostatic volume >40 mL, elevated PSA, negative initial biopsy, and suspicious delitescence of prostate cancer. Indications for repeated biopsy include PSA >10 ng/mL and any f/t PSA or PSAD; for PSA 4–10 ng/mL if f/t PSA/PSAD and DRE are normal but CT/MRI is positive or two consecutive increases of PSA are observed over 3 months, repeat biopsy is also performed.

In conclusion, ultrasound-guided biopsy is common in China; 13-cores biopsy is more accurate than other methods but the detection rate in Chinese patients is similar to that seen in other countries.

2. Report from Indonesia presented by Dr Rainy Umbas

Doctor Umbas presented data on first biopsy only collected at Cipto Mangunkusumo Hospital over the last 11 years from 1995 to 2005 inclusively. At first, a 6–10-cores biopsy is usually performed if the prostate volume is <60 mL, but >10 cores might be considered if the volume is greater. Almost all biopsies are done on an outpatient basis. Patients are given antibiotics such as ciprofloxacin for 3 days; all anticoagulants are stopped for ≥1 week, and suppository painkiller might be used approximately 1 hour before the procedure especially in the case of multiple-core biopsy. Indications for biopsy are fairly standard: abnormal DRE, PSA >10 ng/mL, or PSAD >0.15 if PSA level is 4–10 ng/mL. This latter indication is slightly different to the preference in western countries wherein biopsy is usually done when PSA is >4 ng/mL; Indonesian doctors still use PSAD 0.15 as cutoff level to do a biopsy.

In the last 11 years, 455 patients were diagnosed with prostate cancer at Dr Umbas' hospital; diagnosis was made by biopsy in 68% of cases, TURP in 28.8%, and open surgery in 3.3%. A total of 975 patients underwent first biopsy, and the results were positive in 284 cases. Median PSA was 63.9 ng/mL in patients with positive biopsy and 15.5 ng/mL in negative cases. Interestingly, 3.5% of positive cases had PSA <4 ng/mL. Furthermore, among 691 patients with a negative biopsy 515 (74.5%) had PSA >10 ng/mL, underlining the notion that high PSA does not always guarantee the presence of cancer. The sensitivity of PSA is quite good but physical examination has superior specificity: if one can feel the tumor, we can be almost sure to find it. Indeed, the positive predictor value (PPV) for DRE is 92% whereas that for PSA using a cutoff of >10 ng/mL is only 25.5%.

Next, Dr Umbas looked at patients with normal DRE (n=703) and observed that <10%, 63 patients, gave a positive biopsy. Median PSA in these patients was slightly higher than that in the negative biopsy group (21.6 vs 16.3 ng/mL, respectively). These results suggest that the specificity is very low and the PPV of PSA >10 ng/mL in normal DRE patients is <10%. In patients with abnormal DRE, on the other hand, of a total of 272 cases 221 went on to give a positive biopsy. Nearly all of the patients with abnormal DRE had PSA >10 ng/mL, and the specificity and PPV of PSA >10 ng/mL was calculated as 100%.

In conclusion, positive biopsy rate in patients with normal DRE findings is quite low but in those with abnormal DRE the rate increases to 80%. The overall average positive

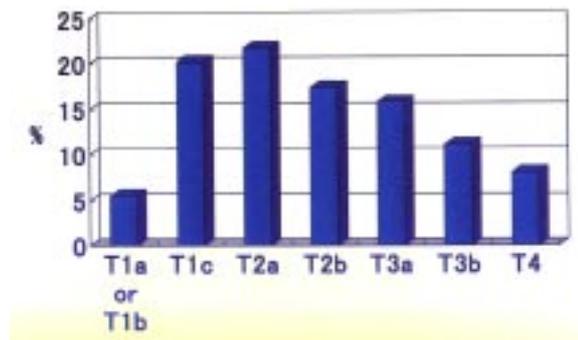


Figure 3. Tumor Stage for 4,529 Japanese Patients Diagnosed with Prostate Cancer in 173 Institutes in 2000 According to the JUA Registry

biopsy rate is approximately 29–30%, and two thirds of prostate cancer patients are diagnosed by TRUS biopsy. Individuals with abnormal DRE and PSA >10 ng/mL are by far the most likely to be biopsy positive.

3. Report from Japan presented by Dr Shiro Hinotsu

Doctor Hinotsu presented the results of the first survey of JUA registration system data published in 2005 (JUA 2005). This database includes 4529 prostate cancer patients from 173 institutes who were diagnosed in 2000. Tumor stage of the patients and imaging methodology used are shown in Figure 3. TRUS was used in approximately 80% of cases, with two thirds of patients undergoing CT and >40% MRI and almost three-quarters a bone scan. Just over half of the patients had a 6-core biopsy; the proportion of Japanese patients undergoing >6-core biopsy has probably grown since the time these data were obtained. Among patients who underwent biopsy at University of Tsukuba between 1997 and 2004 <18% of those with <4 ng/mL were positive whereas a positive diagnosis of prostate cancer was obtained in 32% and 55% of those with PSA 4–10 and >10 ng/mL, respectively. Therefore higher PSA was associated with higher detection rate in biopsy. These results are similar to data obtained in the USA in 1993 (Haas et al, 1993). Recently in Japan, however, it has been shown at one hospital that the positive rate of biopsy in patients with PSA 2–4 and 4–10 ng/mL was the same (both 23.6%); hence it might be advisable to lower the cutoff value for indication to perform biopsy in future.

Mass screening data on 197,682 Japanese men in Gunma prefecture during the period 1989–99 show an overall detection rate of 0.86%. Biopsy detection rate increased according to age with about 10% positive rate in men aged 50–54 years rising to >45% in the 75–79- and >80-year age groups; total biopsy positive rate was 34.0%. Similar results were obtained in Ibaraki prefecture (Ito et al, 2000). The first JUA treatment guideline for prostate cancer was published in May 2006. Biopsy should be performed when prostate cancer is suspected because of abnormal DRE, PSA, or imaging. PSA cutoff level is 4.0 ng/mL; there seems not sufficient evidence to lower this value at present. Age-adapted cutoff level is also controversial. Recommended number of biopsy cores is standard 6 + 2 or 4.

In summary, most Japanese physicians currently accept PSA cutoff level to perform biopsy as 4.0 ng/mL; biopsy is usually performed by TRUS-guided method, and the

Table 2. Detection Rates According to Serum PSA in 3,555 Korean Men*

PSA level (ng/mL)	Detection rate, n (%)
<2.5	16/154 (10.4)
2.5–3.9	51/266 (19.2)
4.0–9.9	354/1892 (18.7)
10–19.9	213/645 (33.0)
>20	463/598 (77.4)
Total	1097/3555 (30.9)

*Patients enrolled at 26 Korean hospitals evaluated by TRUS-guided biopsy

detection rate according to PSA <4, 4–10, and >10 ng/mL is 20–25%, 25–30%, and >50%, respectively. The detection rate increases according to age in mass screening.

4. Report from Korea presented by Dr Jae Mann Song

Korean data are slightly different to those obtained in other countries. For example, in Korean men aged >65 years prostate cancer is the fifth most common neoplasm and sixth in all age groups. In Korea onset of prostate cancer most commonly occurs in men aged in their 60s (41% of cases) followed by 70s (37%). Prostate cancer is also the most steeply increasing tumor observed in male patients, with a 211% increase over the period 1995–2002 followed by colon cancer with a 184% increase. By comparison, incidence rates of cancers of the lung, urinary bladder, liver, and stomach have remained relatively stable over the same period.

Detection rates according to PSA level in a cohort of 3555 Korean men with abnormal DRE who were enrolled in a multicenter prospective study from October 2004 to January 2006 are shown in Table 2. All patients underwent TRUS-guided biopsy and data on clinical parameters and pathologic features were evaluated at the Korean National Cancer Institute. In men with PSA <2.5 ng/mL the detection rate was 10%. Interestingly in those with PSA 4–9.9 ng/mL the rate was only 18.7%, which was slightly lower than that observed in men whose PSA was 2.5–3.9 ng/mL (19.2%). In men who had a PSA value PSA >20 ng/mL cancer was detected 77%. Total detection rate was 30%. Percent free PSA was found a very useful parameter when considering whether to do biopsy especially in elderly patients aged >65 years. In these individuals, free PSA <10% was associated with a detection rate of 48%; however, in younger patients aged <65 years the percent free PSA was not so useful.

Detection rates according to laterally deviated, directed sextant biopsy, 10-core biopsy, and 12-core biopsy were very similar across the range of PSA levels; total detection rates in each biopsy group were 35.4%, 26.6%, and 32.2%, respectively. Comparing sextant versus 12-core biopsy, a significant ($P<0.05$) difference of detection rate was noted only in the PSA range 2.5–3.9 mg/mL. Similar detection rates using sextant or 12-core biopsy were also noted when patients were subdivided according to prostate volume, with both biopsy numbers giving lower detection rates as volume increased (overall detection rate with prostate volumes <30, 30–49, and >50 mL: 35.3, 34.4, and 22.7%, respectively).

Detection rates steadily increased with age: in men aged <50, 50–59, 60–69, 70–79, and >80 years the rates were

8.3%, 19.4%, 32.7%, 38.7%, and 56%, respectively. Detection rate was also higher if cancer was suspected by DRE: in those with cancer suspicious and normal DRE findings the rates were 584/1126 (51.9%) and 422/2123 (19.9%), respectively.

In conclusion, the detection rate of first cancer in Korean men with PSA 2.5–3.9 ng/mL is quite similar to that for men with PSA 4–10 ng/mL (approximately 20% in both groups). The detection rate of first cancer in Korean men with PSA 4–9.9 ng/mL is lower than that observed in western patients, in whom the rate is reported as 25–30%. Percentage free PSA can be used as guide for biopsy especially in elderly men (aged >65 years) with PSA 2.5–9.9 ng/mL. There is no significant improvement of prostate cancer detection rate using extended biopsy compared with sextant biopsy in Korean men.

5. Report from Singapore presented by Dr Christopher Cheng

Since there has been no recent autopsy series using modern Epstein criteria of the Gleason score conducted in Asia the actual prevalence of prostate cancer is unknown. However, ever-increasing numbers of papers by Asian urologists and the data presented from each country at this meeting suggest that we are all talking the same language. Eventually, it is assumed that detection rates will be the same among the various countries. Nevertheless, in Asia we are seeing a dramatic rise in the incidence of prostate cancer. However, this rise has not been seen in every country possibly because of the way it is reported, differences of population demographics, number of urologists, and so on. Although mass population screening is not recommended, the population needs to know what is our stance with regard to prostate cancer detection.

In light of this, Professor Cheng presented data on Prostate Awareness Week (PAW) 2004 Singapore. PAW is a voluntary effort, not screening, and reaches a different population to that encountered in the urology office. The first analysis of 3,651 Singaporean males with median age 62 years showed that PSA steadily increased by age range; the mean for men aged 50–60 years was 1.2 ng/mL rising to 2.05 ng/mL in men aged 60–70 years and 2.66 ng/mL in men aged 70–80 years. In PAW 2004, 252 men (7.4%) had elevated PSA (>4.0 ng/mL). Of these, 84% had PSA 4–10 ng/mL and 12% 10–20 ng/mL. The entire cohort with elevated PSA was invited to undergo biopsy, and 168 (60%) underwent the procedure. A total of 43 were revealed to have cancer. Of the cancers detected, the majority were Gleason 6, a few Gleason 7, and very few Gleason ≤5. Most had clinical stage T1 disease. Overall, the cancer detection rate during PAW 2004 was 1.2%.

Professor Cheng also analyzed the repeat biopsy audit. Based on the first biopsy histology on a consensus basis men were asked to undergo second, third, and fourth biopsy over 6–12 months. In the first biopsy the detection rate was 27.6%, second biopsy 18%, and third 33%. A few patients eventually had TURP that revealed incidental low-grade cancer. Of the 95 repeat biopsies cancer was detected in 13.7%, mostly on the second biopsy and very few on the third and fourth.

6. Report from Taiwan presented by Dr Chi-Rei Yang

Widespread screening is not conducted in Taiwan. However, although hospital-based health check-ups are not available, community-based screening of asymptomatic patients such as PSA testing in men aged >60 years does occur. In community-based screening conducted at various locations in Taiwan, people with abnormal PSA (>4 ng/mL) ranged from 4.4% to 16.1%; the average was 11% in that setting. In hospitals abnormal PSA is observed in 6%. Of 306 men with abnormal PSA as detected by community-based screening, finally only 91 received biopsy and this was positive in 26%. Therefore the overall detection rate of community-based screening in Taiwan was 26/2716 (1%).

In a study of 785 Taiwanese men who underwent TRUS-guided sextant biopsies the prostate cancer detection rate in those with PSA 4–10 and 10.01–25 was 63/533 (11.8%) and 79/252 (31.3%), respectively; overall detection rate was 17.9%.

In another study conducted in 2003 no difference was observed in detection rate according to whether 6–8 biopsy cores or 10–14 cores were analyzed irrespective of PSA. In men whose PSA was 3.5–10 and 10–20 ng/mL the detection rate for 6–8 and 10–14 cores was respectively 32/326 (9.8%) and 36/226 (15.9%) ($P=0.040$), respectively, and 22/122 (18.0%) and 55/302 (18.2%), respectively ($P=0.319$).

When men were stratified according to prostate volume 30, 30–50, and >50 mL, higher detection rates were noted in those undergoing 10–14-core biopsy than 6–8-core biopsy, especially in men whose PSA was 10.1–20 ng/mL. In men with prostate volume 30, 30–50, and >50 mL detection rates for 6–8 and 10–14 cores were respectively 41.9% and 60%, 25% and 31.5%, and 5.3% and 16.2%, respectively. Therefore in patients with large prostatic volume more prostate cores should be done for early diagnosis of prostate cancer.

III. Session 3: HRPC, Favorable Treatment Modality in Each Country (chaired by Rainy Umbas and Shujie Xie)

1. Report from China presented by Dr Shujie Xie

According to treatment guidelines for HRPC in China it is necessary to maintain serum testosterone at castration level. Available therapeutic options include cytotoxic and Chinese traditional herbal medicines, which are widely accepted among doctors and patients alike. Chemotherapy is another popular choice of treatment for these patients. Single-agent estramustine also can be given to Chinese HRPC patients. Some doctors combine chemotherapy to improve response rates, with measurable response observed in 40–50% using this strategy. Prednisone 10 mg/day and mitoxantrone 12 mg/m² every 3 weeks is another available modality but there is not very much evidence for its efficacy. Radioisotopic drugs especially strontium 89 are commonly used as painkiller for patients with bone metastases. According to the guideline recommendations for cytotoxic therapy against HRPC, if the PSA level is above 2 times the previous reference level the increase should be

documented. When chemotherapy is indicated this should be communicated to the patient. In some patients Chinese doctors also use radionuclides, external beam radiotherapy, and analgesics in the setting of bone metastasis. In patients with metastatic disease treatment is challenging and a standard approach is rare.

2. Report from Indonesia presented by Dr Doddy Soebadi

HRPC is very frustrating because often if a patient has metastatic prostate cancer he becomes very dependent on his doctor; such patients visit us every month and ask about their PSA: if it is going down they are very happy, but when the PSA stops going down or increases they become worried—as does the doctor.

In Indonesia there are no reliable nationwide epidemiologic data, but in Surabaya between 1982 and 2002 the number of patients with prostate cancer increased 6 fold. At Dr Soebadi's center among 40 patients with HRPC 70% previously underwent orchiectomy, 15% had received LHRH analog therapy, and the other 15% maximal androgen blockade. Treatment policy at the center is to continue with hormone therapy either with LHRH analog or offer referral for an orchiectomy. The problem is that for LHRH analog patients themselves have to bear the cost and the treatment is very expensive. An alternative is to give the patient chemotherapy; in this setting a lot of encouragement is required for patients and their families because chemotherapy is also costly and possible side effects must be explained in addition to benefits and response rates. In patients who are deteriorating palliative or symptomatic control is needed. For bone metastases, if the patient can afford it we give him zoledronic acid, maybe surgery for pathologic fracture, or symptomatic control of pain with radiotherapy. For anemia transfusions are given as needed. Obstructive uropathy may be an indication for TURP or stenting; steroids are often given for nerve compression, and for other complaints such as nausea and vomiting good nutrition possibly supplemented with megestrol and supportive therapy is counseled to the patient and his family. Chemotherapy is aimed at palliation of symptoms and reducing PSA. Estramustine phosphate is recommended but not available in Surabaya and the patient's family may have to go to Jakarta or Singapore to obtain this agent. Medical oncologists also give docetaxel with prednisone. In addition, it is estimated that >50% of patients take traditional remedies such as herbal preparations and shark's fin cartilage.

In conclusion, in Indonesia guidelines for HRPC and symptom control are needed. Also the role of cultural, complementary, and alternative treatments merits deeper investigation.

3. Report from Japan presented by Dr Michiyuki Usami

In Japan there are many hormonal treatment modalities available for prostate cancer. Many patients receive combined androgen blockade; LHRH agonist and antiandrogen are also used. Orchiectomy alone is performed in 5%. After relapse, for the castrated group antiandrogen is added or LHRH monotherapy. It is important that testosterone levels are monitored. If testosterone is well

suppressed other antiandrogens may be added; if testosterone is not suppressed castration or switching to another agonist plus antiandrogen or antiandrogen plus LHRH agonist may be indicated. At next failure antiandrogen is changed to another antiandrogen.

Second-line treatments for patients who fail androgen ablation therapy include corticosteroids and chemotherapy using estramustine phosphate, cyclophosphamide, or docetaxel. However, the Japanese government does not reimburse docetaxel. A few patients enter clinical trials of experimental new agents. For palliation several drugs are available such as zoledronic acid in patients with bone metastasis.

4. Report from Korea presented by Dr Sung Joon Hong

Doctor Hong's presentation focused on prevailing clinical trends in the management of HRPC in Korea. In 2004, the Korean Urological Oncology Society suggested clinical guidelines on prostate cancer including HRPC (Figure 4); the guideline is similar to internationally suggested guidelines, so Dr Hong restricted his talk to secondary hormone therapy, chemotherapy, and palliative treatment in Korea.

Presented was a case of a 60-year-old man with PSA 25.6 ng/mL who sought treatment in January 2001. He had a Gleason score 7, and MRI, CT, and bone scan revealed clinical stage cT4acN2cM1b. He took LHRH agonist combined with bicalutamide; after 3 months his PSA dropped to zero level and he continued therapy for almost 2 years till a slight increase was observed. Antiandrogen was withdrawn and his PSA stabilized for nearly 6 months then began to rise and at this time newly developed spinal metastases were discovered. Estramustine was at first tried and his PSA dropped. Radiation therapy was given to control the bone pain. Eventually when the PSA became elevated again dexamethasone was additionally given and PSA dropped rapidly; subsequently docetaxel was given 6 times. PSA re-elevated so docetaxel plus prednisolone combination for 6 cycles was tried. PSA dropped immediately but not for long and later became elevated again. This case includes almost all of the up-to-date therapeutic modalities in Korea.

Secondary hormonal therapy is usually given as single

drugs, but prednisolone and dexamethasone can be given at first. Recently, Dr Hong uses high-dose bicalutamide monotherapy. The Korean health insurance regulatory agency has grouped chemotherapy into two classes: protocols containing estramustine- and mitoxantrone-based combinations on the one hand and docetaxel-based combination therapy on the other. The first group is not restricted as strictly as the second. After 3 cycles with elevated PSA docetaxel-based combinations must be stopped.

In Korea the armamentarium against prostate cancer-related bone pain includes anti-pain medications, external radiotherapy, radiopharmaceuticals such as strontium 89, and bisphosphonate.

5. Report from Singapore presented by Dr Kesavan Esuvaranathan

In Singapore testosterone-deprivation therapy (TDT) is indicated for the treatment of metastatic prostate cancer in approximately 50% of cases, PSA relapse (>0.2 ng/mL) following radical prostatectomy, and as primary therapy with or without TURP in certain patients with locally advanced disease. Furthermore, TDT is given with radiotherapy in the neoadjuvant setting and as adjuvant therapy with or without radiation against margin-positive prostate cancer with persisting PSA.

Forms of TDT include LHRH agonist (goserelin or leuprolin) in 90% of cases, orchiectomy in 8%, bicalutamide monotherapy (1%), and cyproterone acetate (1%). After bone mineral density evaluation bisphosphonates may be considered for patients with osteoporosis or bone metastases.

The protocol for surveillance in Singaporean patients is usually clinical review every 3 months or every 6 months in elderly or infirm individuals.

For HRPC the treatment algorithm is LHRH agonist with serum testosterone monitoring. If the decision is not to castrate, bicalutamide or flutamide may be added; if the patient is to be castrated trial of antiandrogens should be discussed and the medical oncologist consulted. When antiandrogen is given as monotherapy LHRH agonist may be added. When this treatment fails, antiandrogen is withdrawn; if the patient is on flutamide, he may be switched

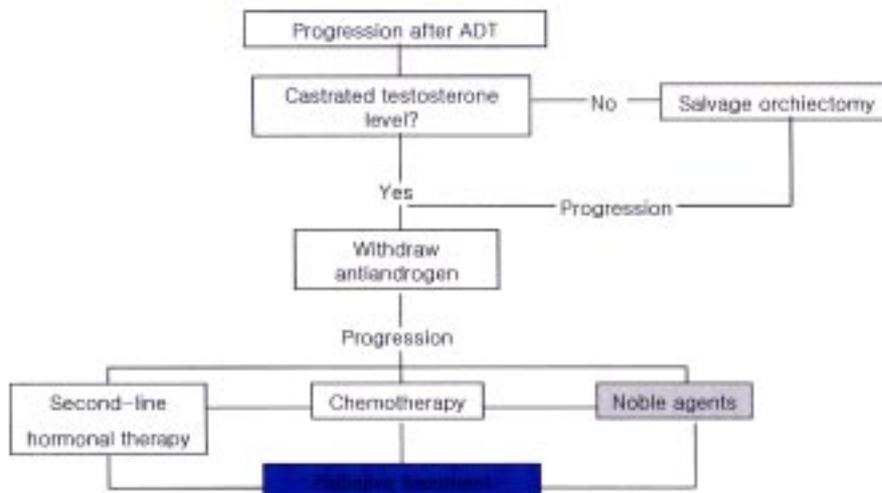


Figure 4. Guidelines for HRPC Management in Korea (published by the Korean Oncological Society, 2004)

to bicalutamide. Finally, chemotherapy containing estramustine or new agents may be considered.

6. Report from Taiwan presented by Dr Shu-Jen Chang

In Taiwan primary hormonal therapeutic options for metastatic prostate cancer include orchiectomy, flutamide or cyproterone (Androcur®), LHRH agonist, and combined androgen blockade.

In patients who progress flutamide or bicalutamide (Casodex®) may be added or orchiectomy or LHRH offered. When these strategies fail flutamide should be withdrawn and diethylstilbestrol (DES) tried as third line of hormonal therapy. DES has cytotoxic effects and if given at 1–3 mg/day can elicit 30–40% response rates including PSA reduction and improvement of physical condition. The effect normally lasts 3–6 months and in some patients ≤ 2 years. DES is cheap and very applicable to oriental patients who experience less cardiovascular accidents on this agent than western patients. About 5% of patients treated with DES have very severe adverse events such as thrombosis and this can be countered by warfarin. After DES there is no more hormone therapeutic option to control the cancer and on progression chemotherapy should be used for HRPC. In Taiwan etoposide, mitoxantrone plus prednisolone, and paclitaxel are available; estramustine has been withdrawn from the Taiwanese market for 1 year. About 30% of patients respond to etoposide. Treatment can be done at home and patients are advised to visit their clinics for follow-up. This is very easy for older patients in particular; prices are good and side effects tolerable on most occasions. Patients who experience difficulty in swallowing the large etoposide capsule can instead take mitoxantrone and prednisolone, which is safe and achieves a similar response rate that lasts approximately 6 months. Recently, docetaxel was approved in Taiwan. Patients who do not respond to the more tolerable chemotherapeutic regimens may be switched to receive docetaxel. This treatment should be given by medical oncologist since docetaxel is more toxic than other chemotherapy agents and side effects such as leukopenia make the patient very sick and weak.

Radiation therapy is given as palliation for bone pain and to keep the patient away from morphine. Patients on morphine need a lot of care and normally there is no person available to look after them round the clock.

IV. Summary and Closing Remarks

At the end of session 3 chairperson Dr Umbas rounded up the proceedings by reminding participants that the first important strategy is to ensure that patients have a castration level of testosterone. Second, for patients who require chemotherapy it is best to sit together with the medical oncologist and radiotherapist and concoct a workable protocol so that each patient with similar clinical features receives the same treatment; then at the end of the day the results can be properly evaluated, which is also important.

Following this, conference co-chair Seiji Naito (Japan) in his closing remarks thanked the participants and sponsor AstraZeneca and looked forward to a bountiful relationship with UICC in Asia Pacific. The schedule for the next

Conference on Asian Trend in Prostate Cancer Hormone Therapy is not yet decided.

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