1st APPS Seoul., 2011.3.3-5

Satellite Symposium II

Consensus Meeting for Asian Pacific Prostate Cancer Guideline

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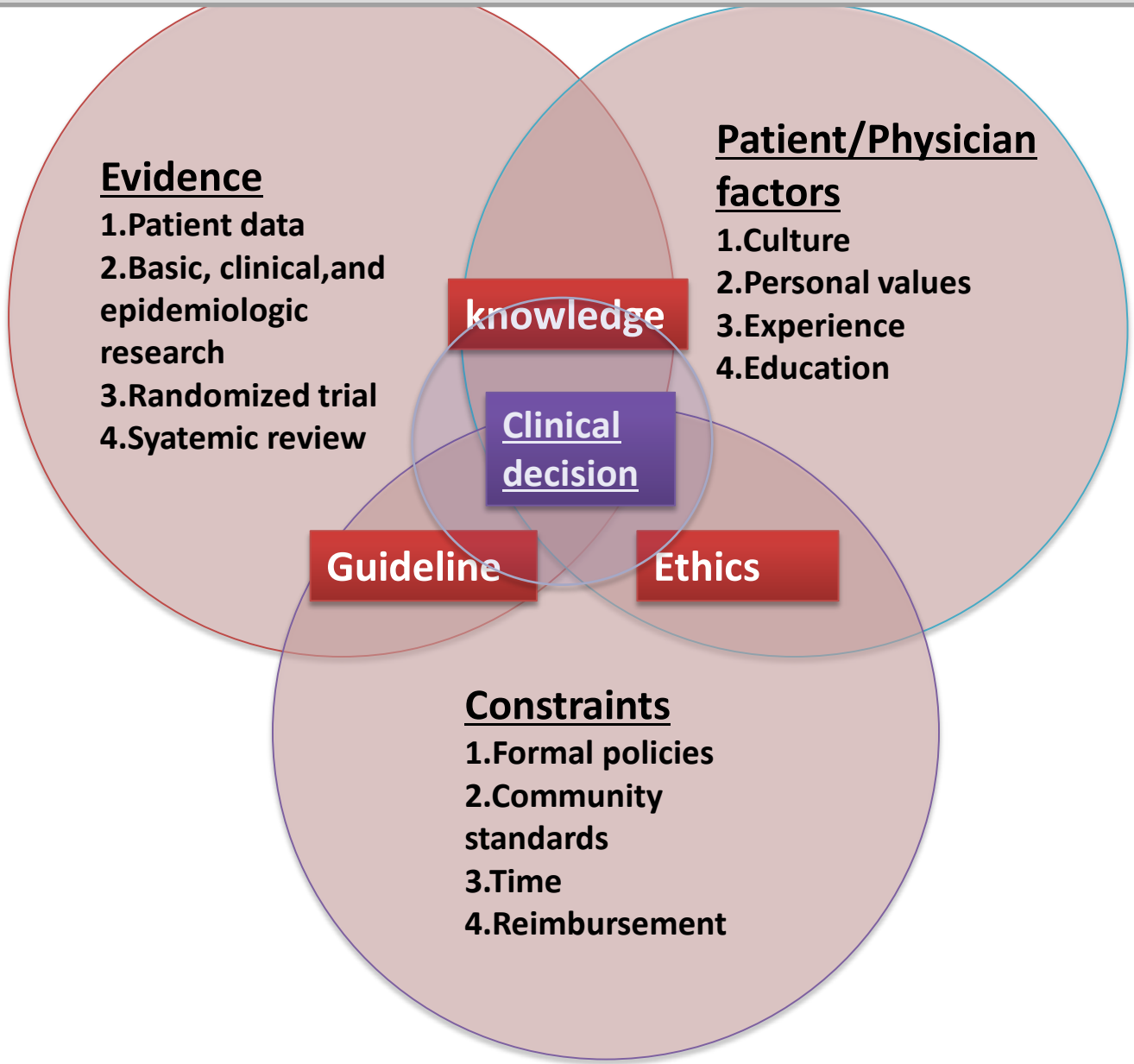
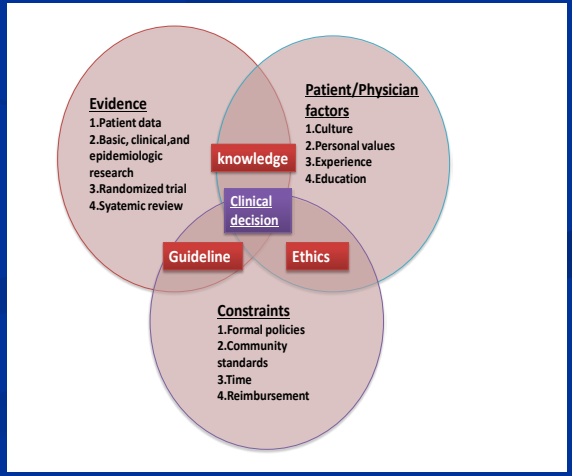
How to make a treatment decision?



Why consensus?
How consensus?

- To widely use global knowledge
- To customize international guideline
- To improve clinical outcome

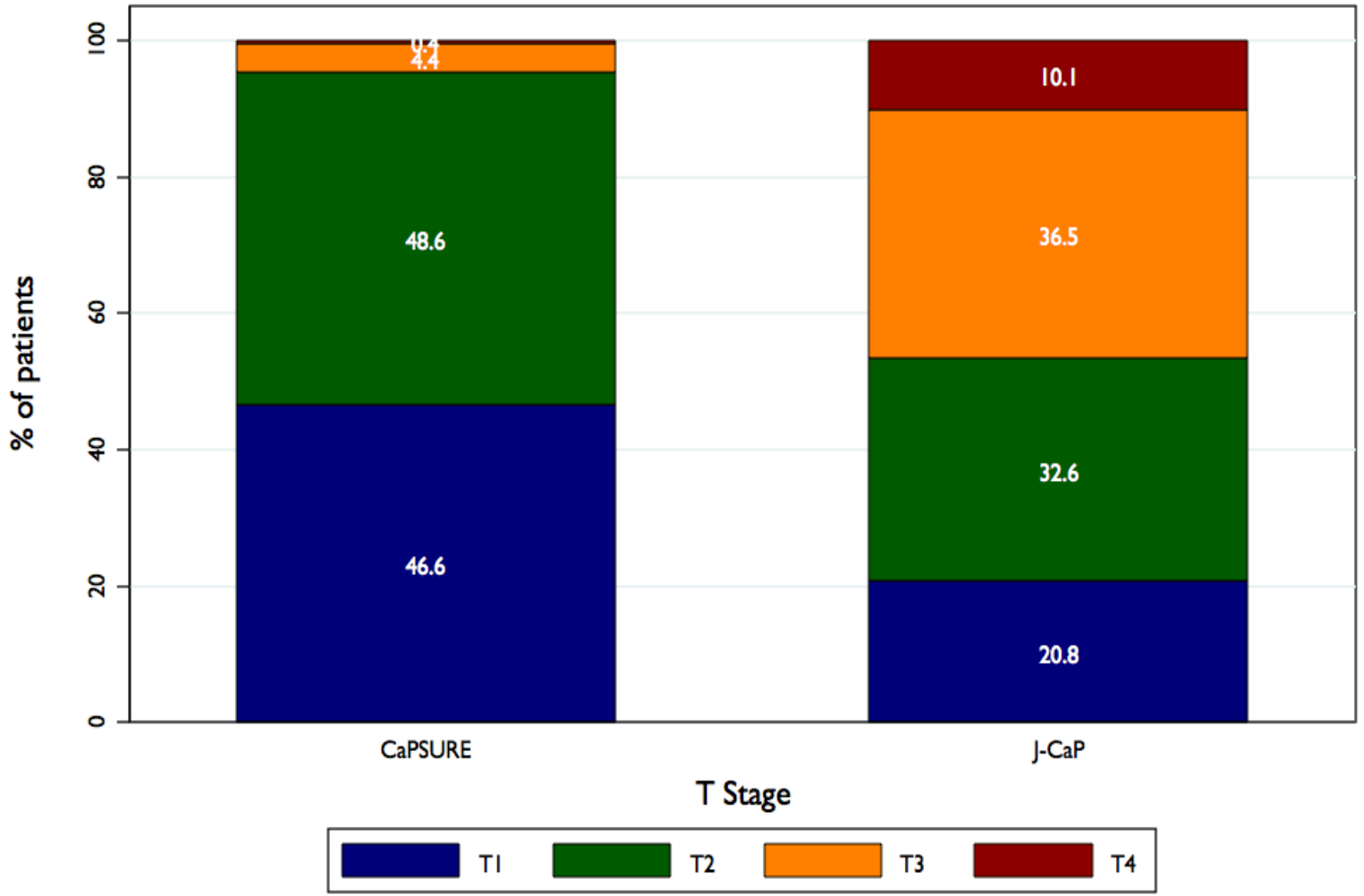
1. Compare knowledge globally
2. Consensus panel meeting



J-CaP Study Group established since 2003
24,000 cases' data base

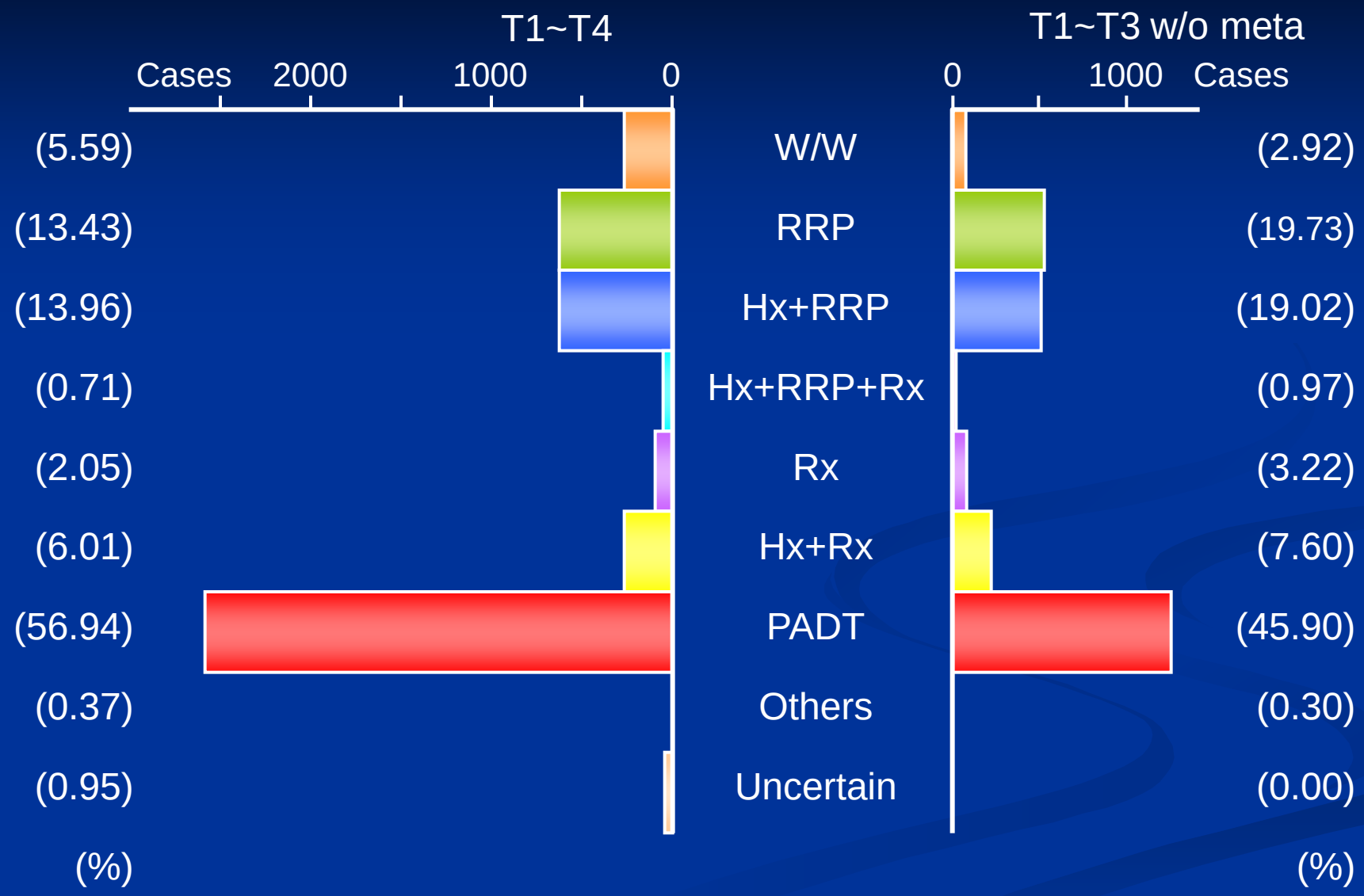
J-CaP Home Page;
www.j-cap.jp/

T stage distribution (U.S. and Japan)



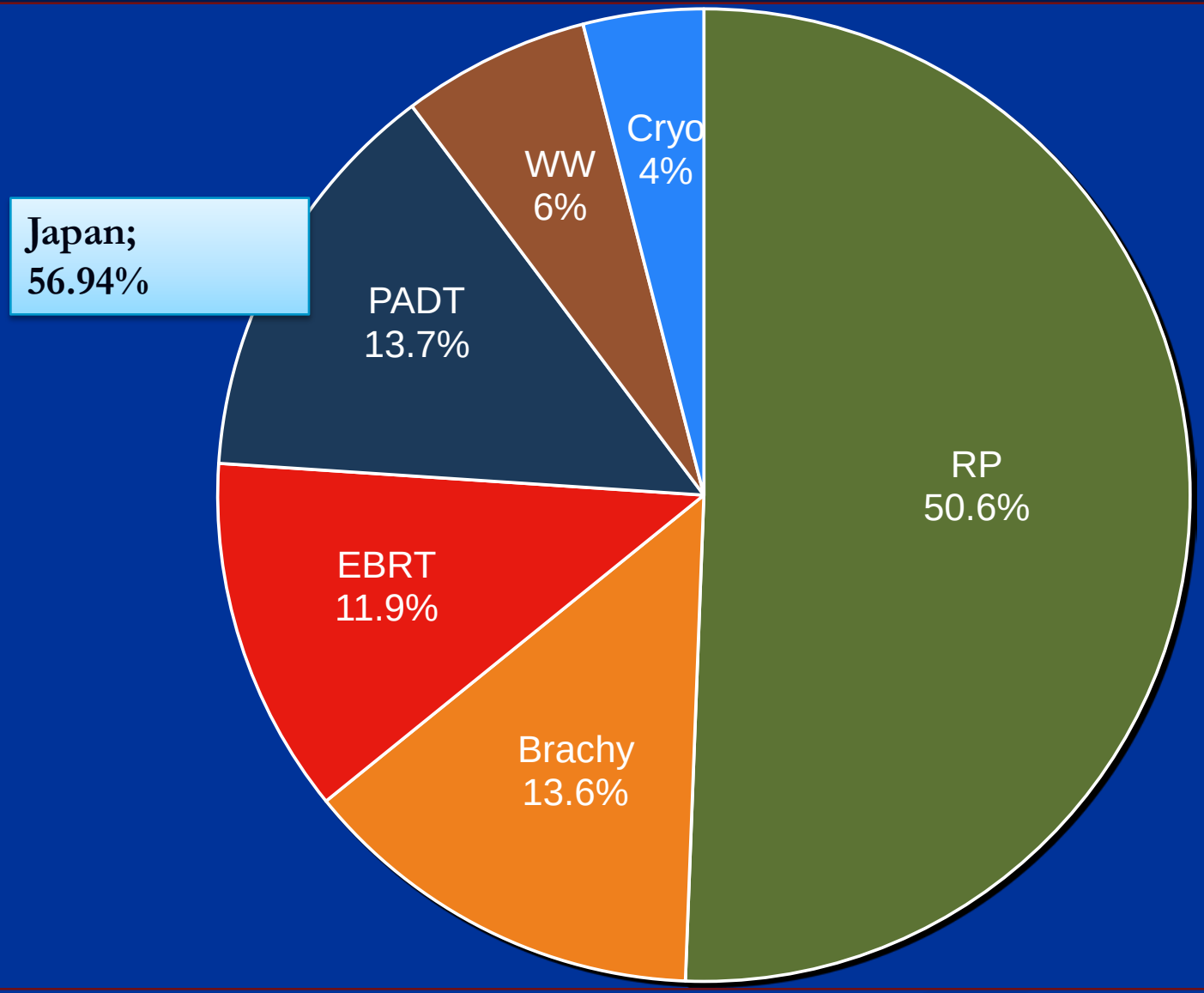
JUA PC Registration 2005

Initial Treatment

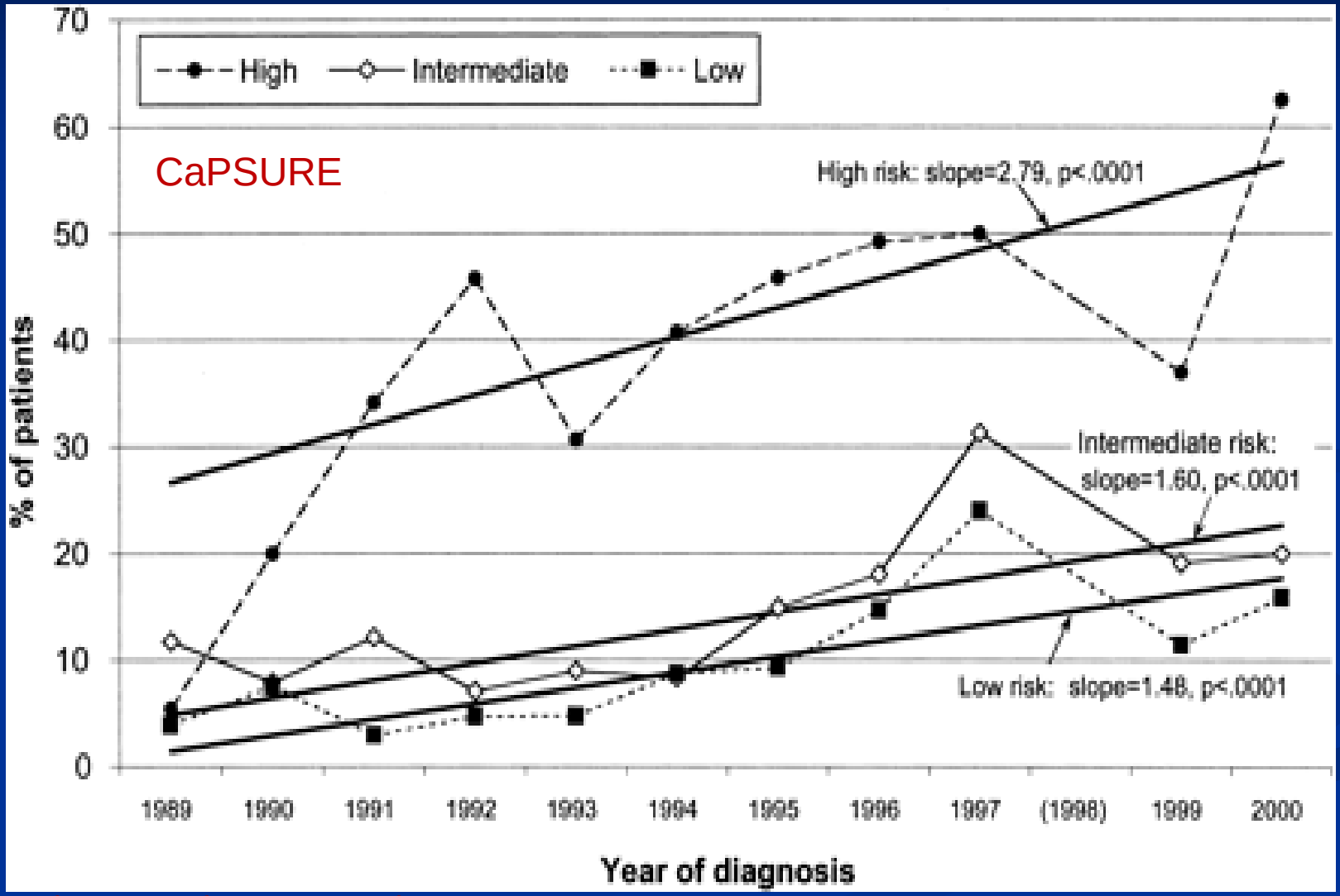


(Int JU, 2005)

Patterns of Treatment in the U.S.



Trend of PADT for localized prostate cancer in U.S.A.



(Cooperberg, et al. JNCI 2003)

Dataset of J-CaP database

- Patients treated by PADT
- Sufficient pathological and clinical data including follow-up update.
- Last update of follow-up : 30 Apr. 2010
- Follow-up periods : 0-9.2 years
- Total events 3399
  - Cancer death 1691
  - Other cause of death 1708

www.j-cap.jp/

Risk Assessment: J-CAPRA*

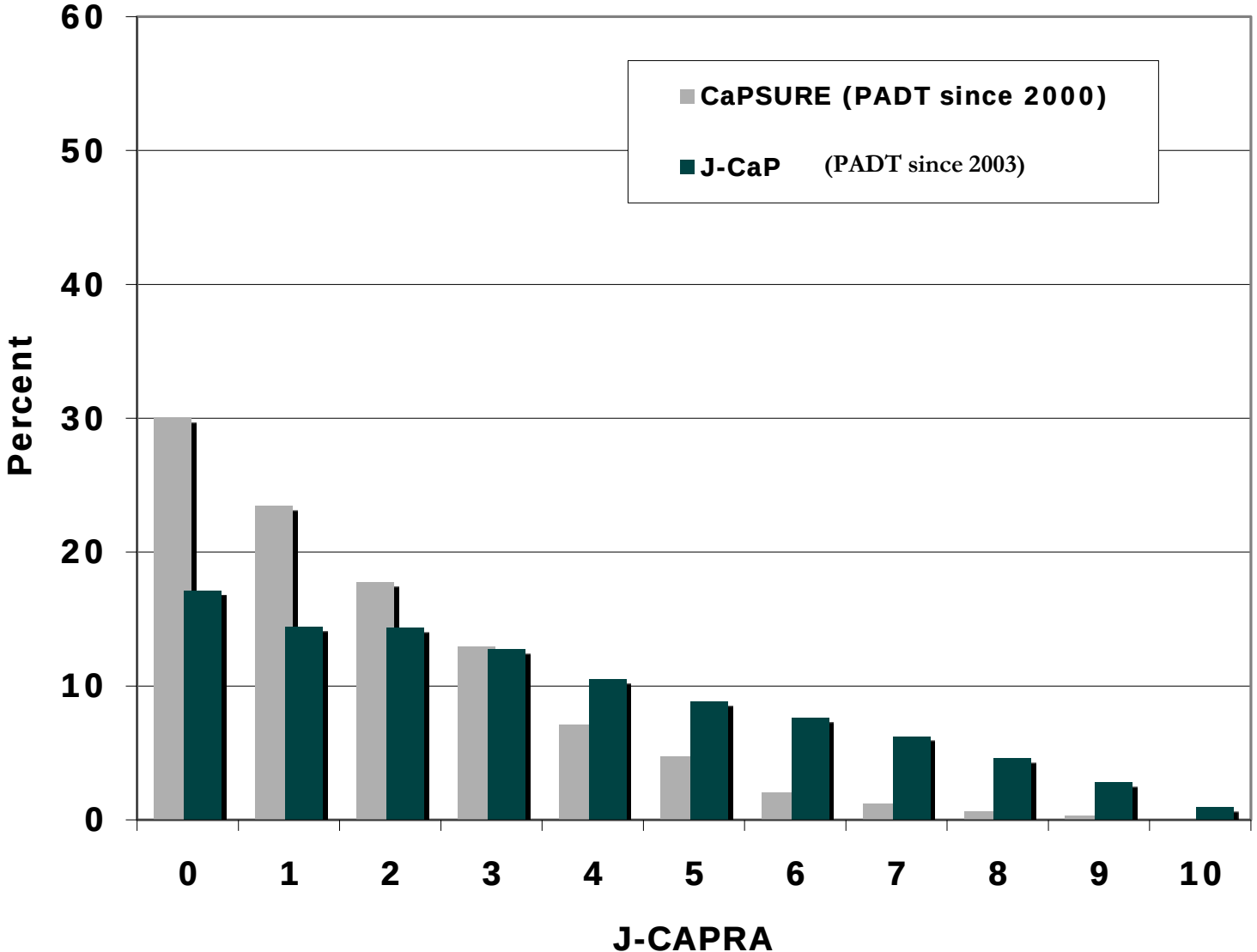
Variable	Level	Points	Variable	Level	Points
PSA	0-20	0	T-stage	T1a-2a	0
	20-100	1		T2b-3a	1
	100-500	2		T3b	2
	>500	3		T4	3
Gleason	2-6	0	N-stage	N1	1
	7	1	M-stage	M1	3
	8-10	2			

Sum of points from each variable for 0-12 score

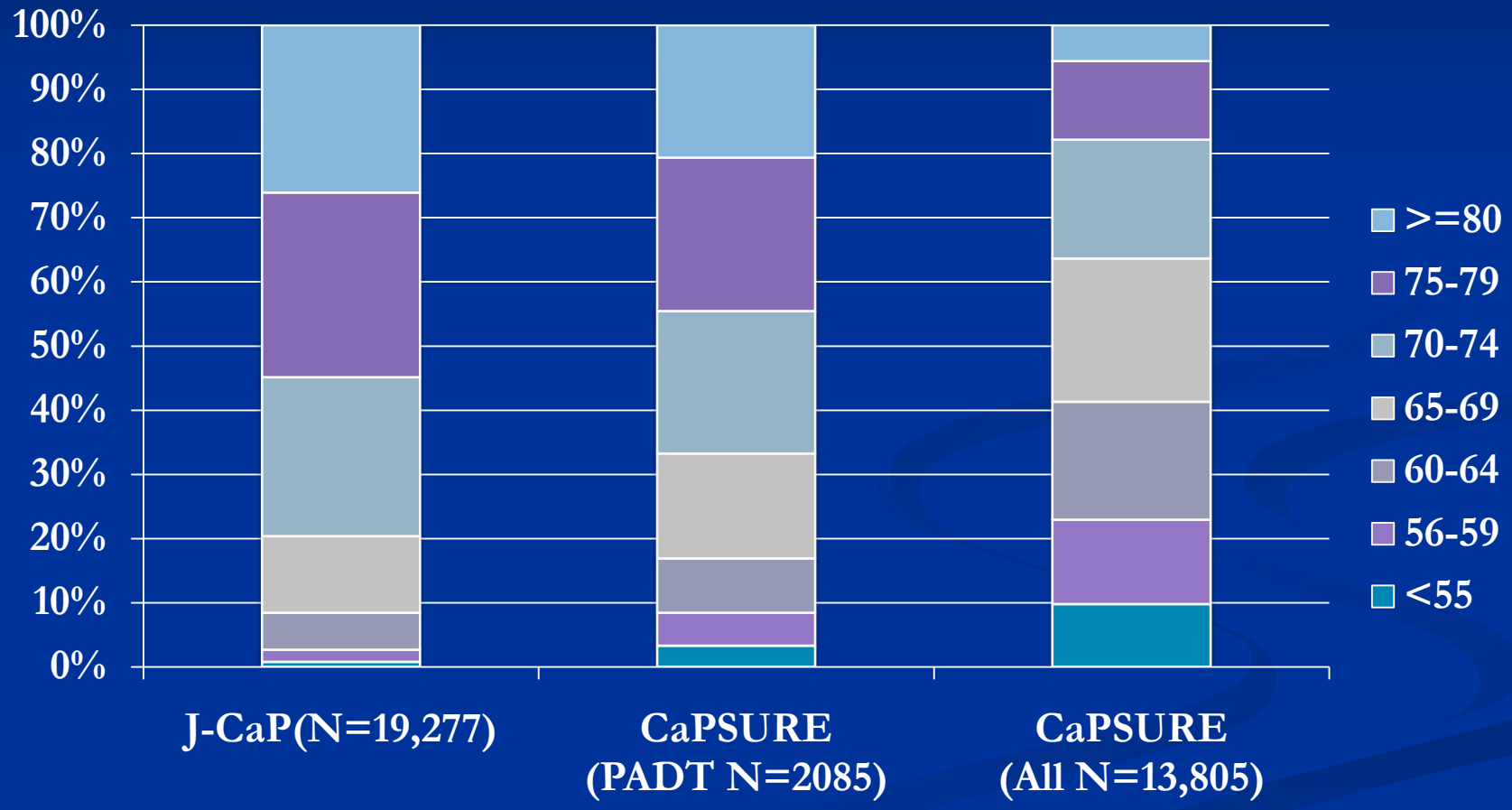
* Risk assessment among prostate cancer patients receiving primary androgen deprivation therapy; JCO 2009

Risk Distribution by J-CAPRA

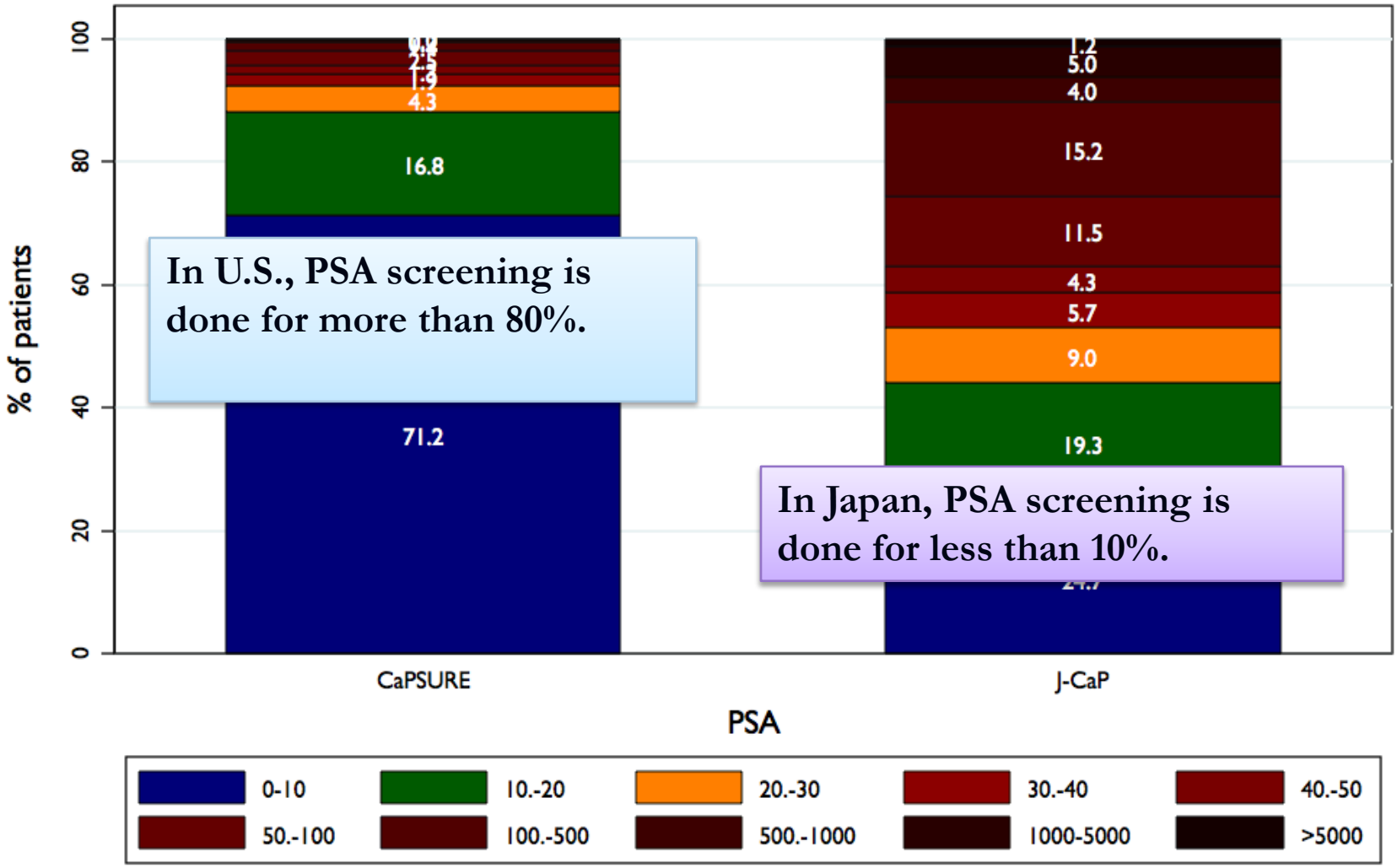
Comparison between Japan and US for the patients who have PADT



Age distribution between Japan and US



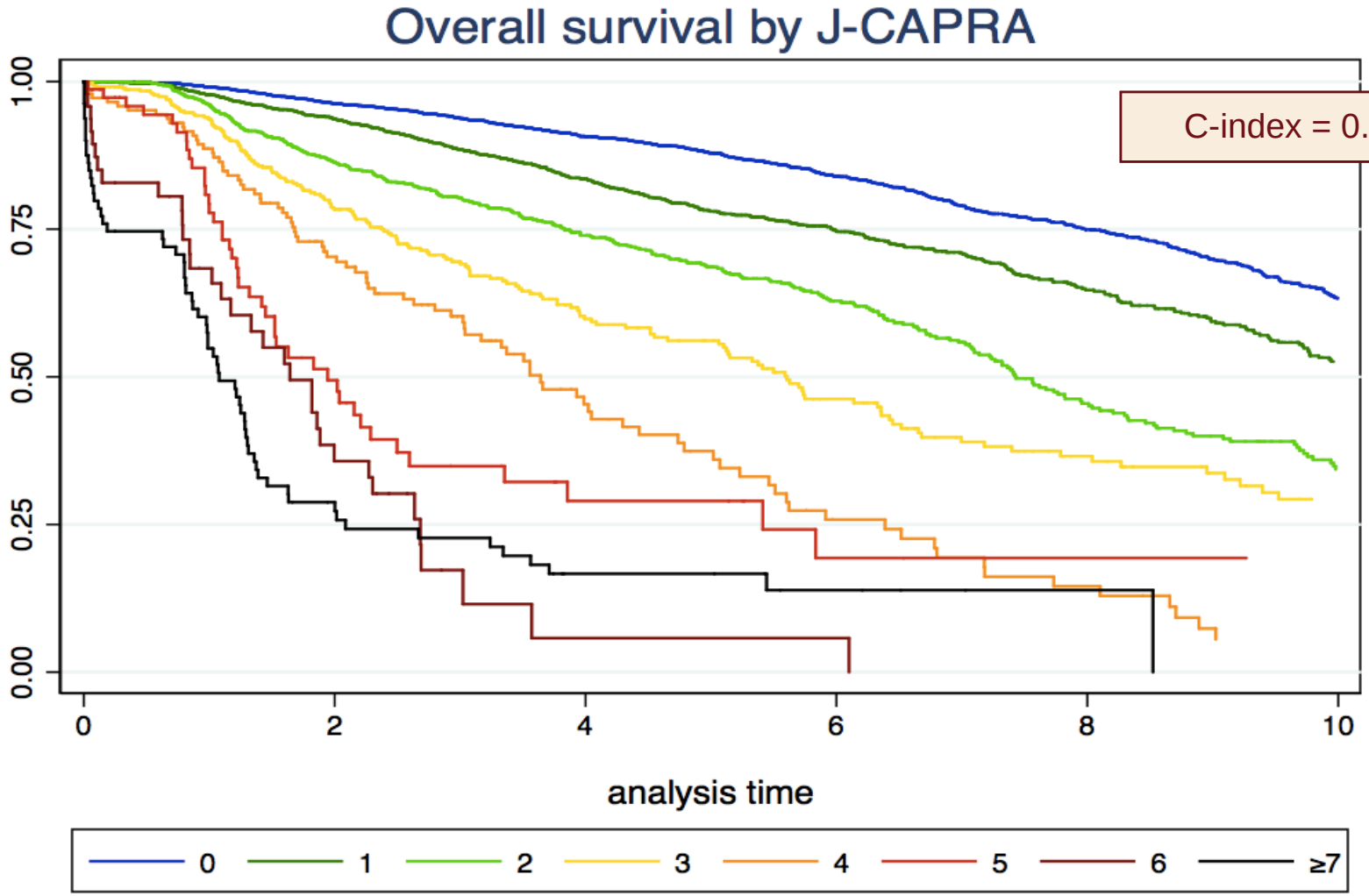
PSA distribution (U.S. and Japan)



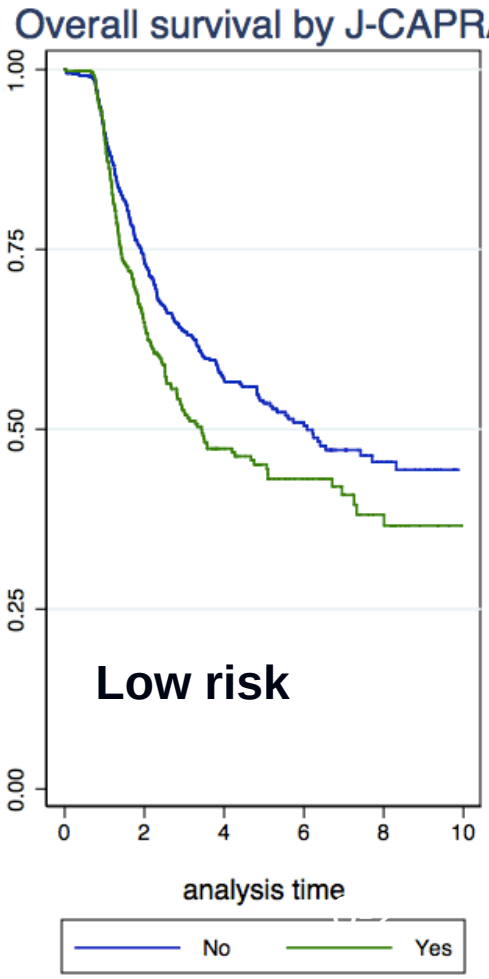
In U.S., PSA screening is done for more than 80%.

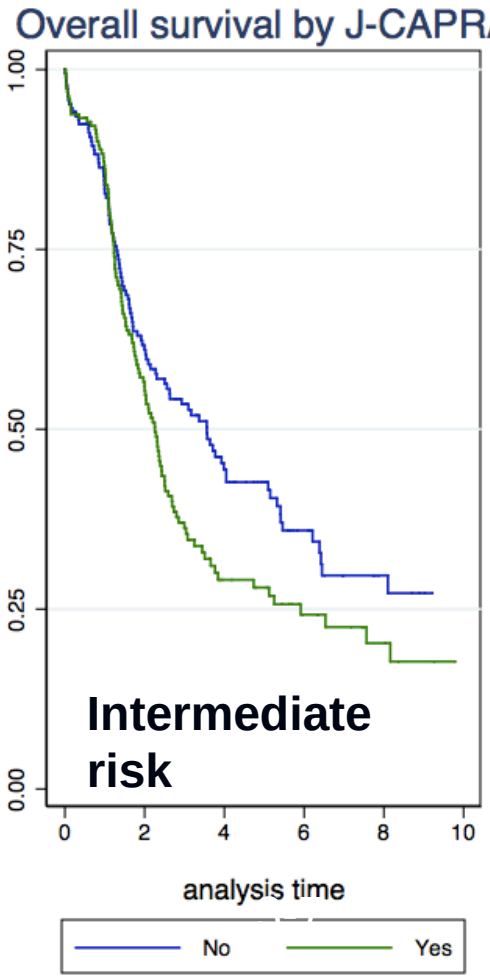
In Japan, PSA screening is done for less than 10%.

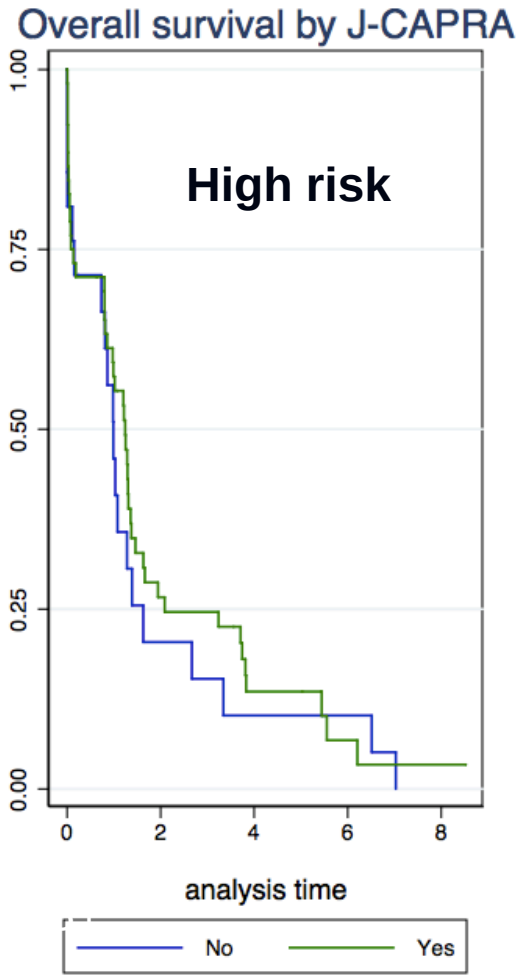
J-CAPRA: Overall Survival in CaPSURE US patients



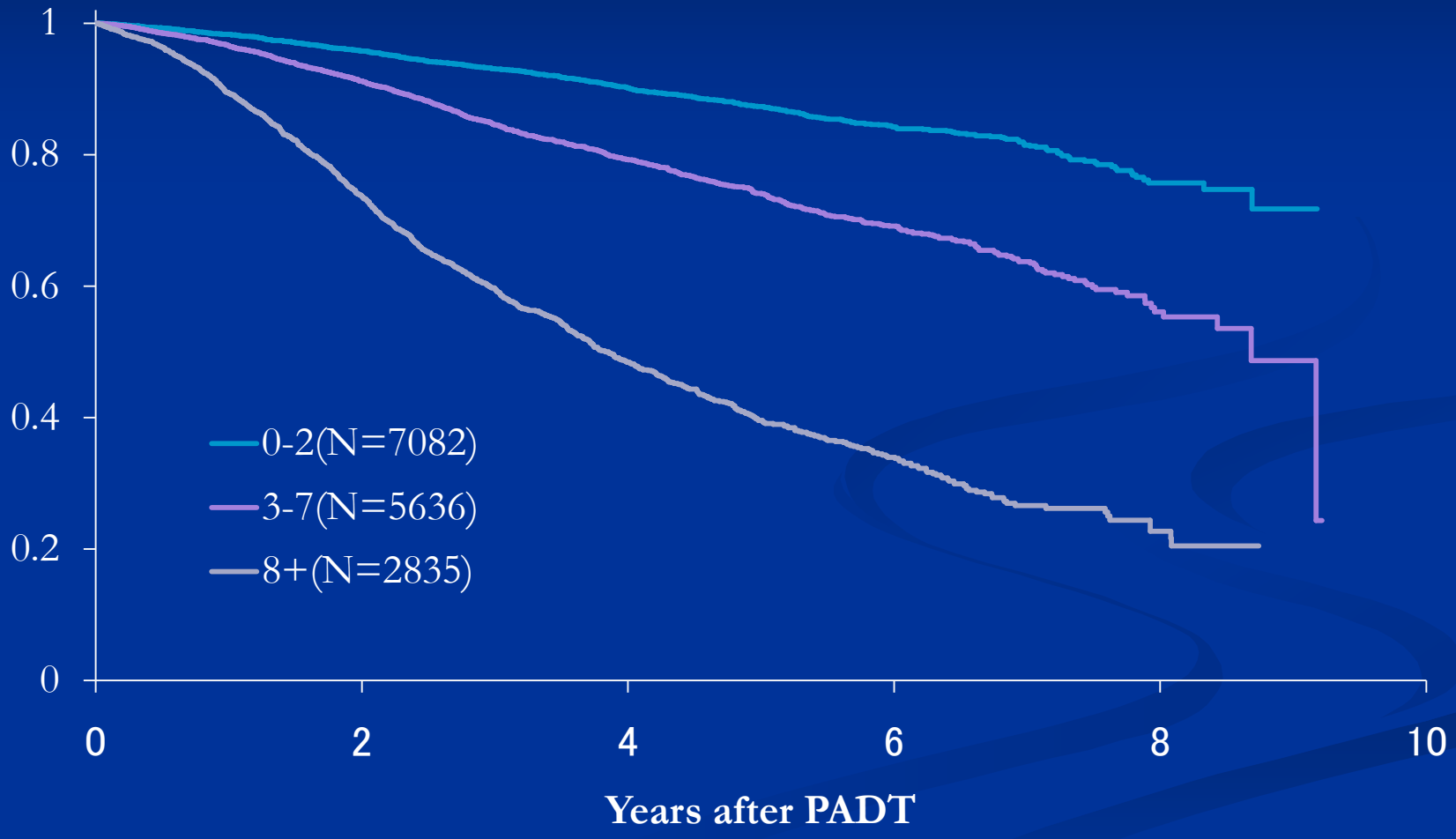
J-CAPRA: PADT outcomes by CAB
US patients



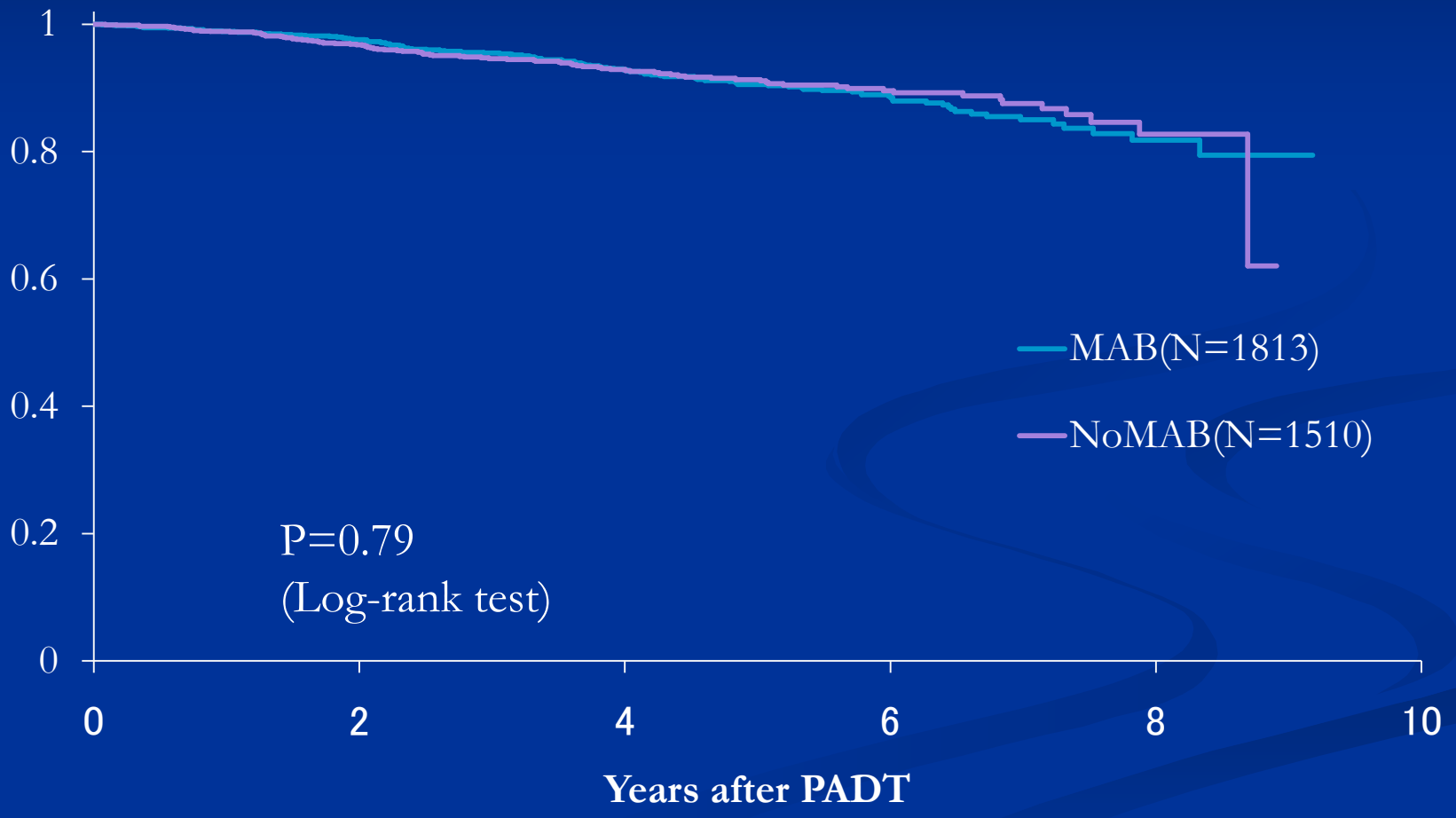




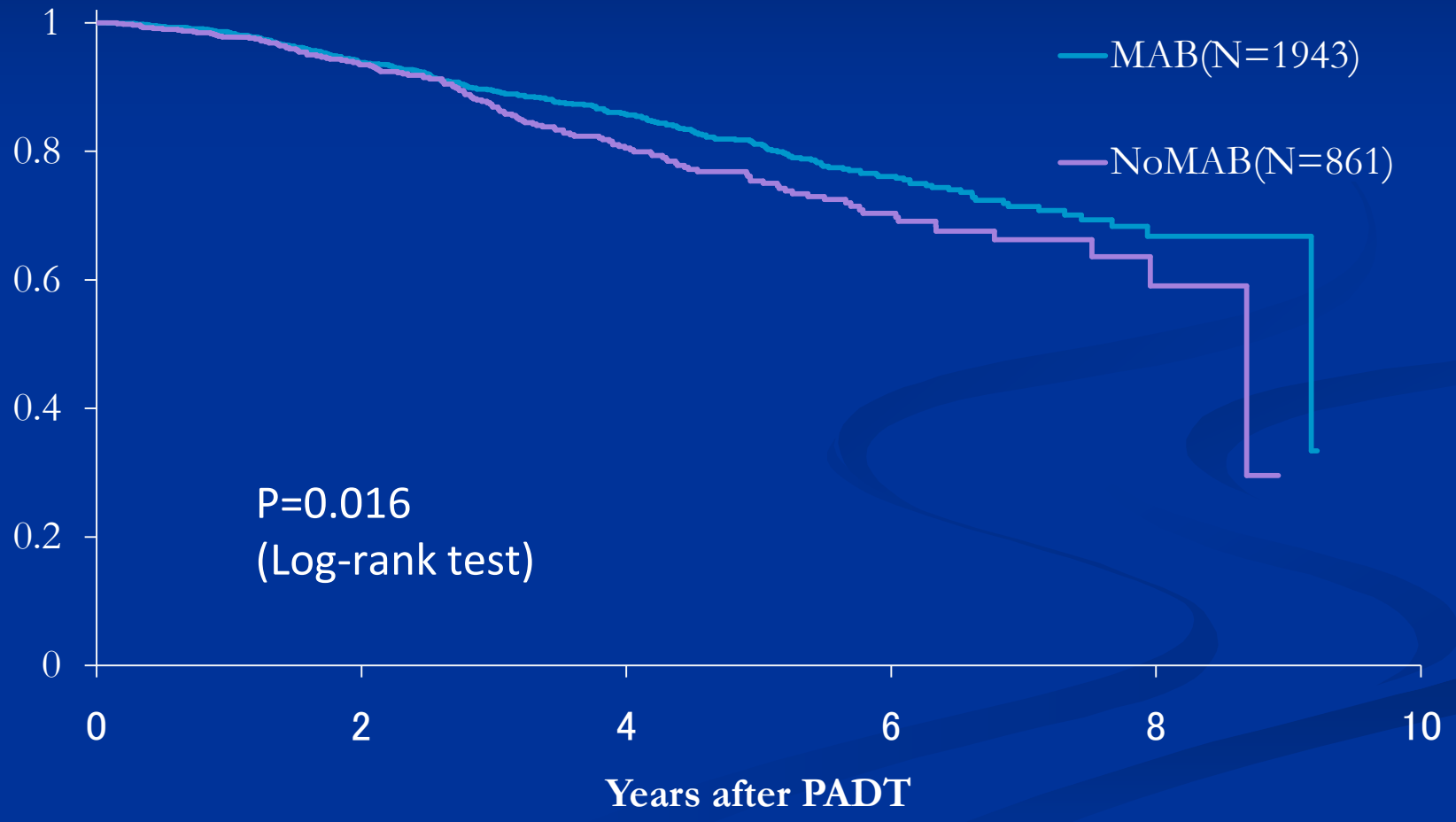
Overall survival by J-CAPRA score Japanese patients



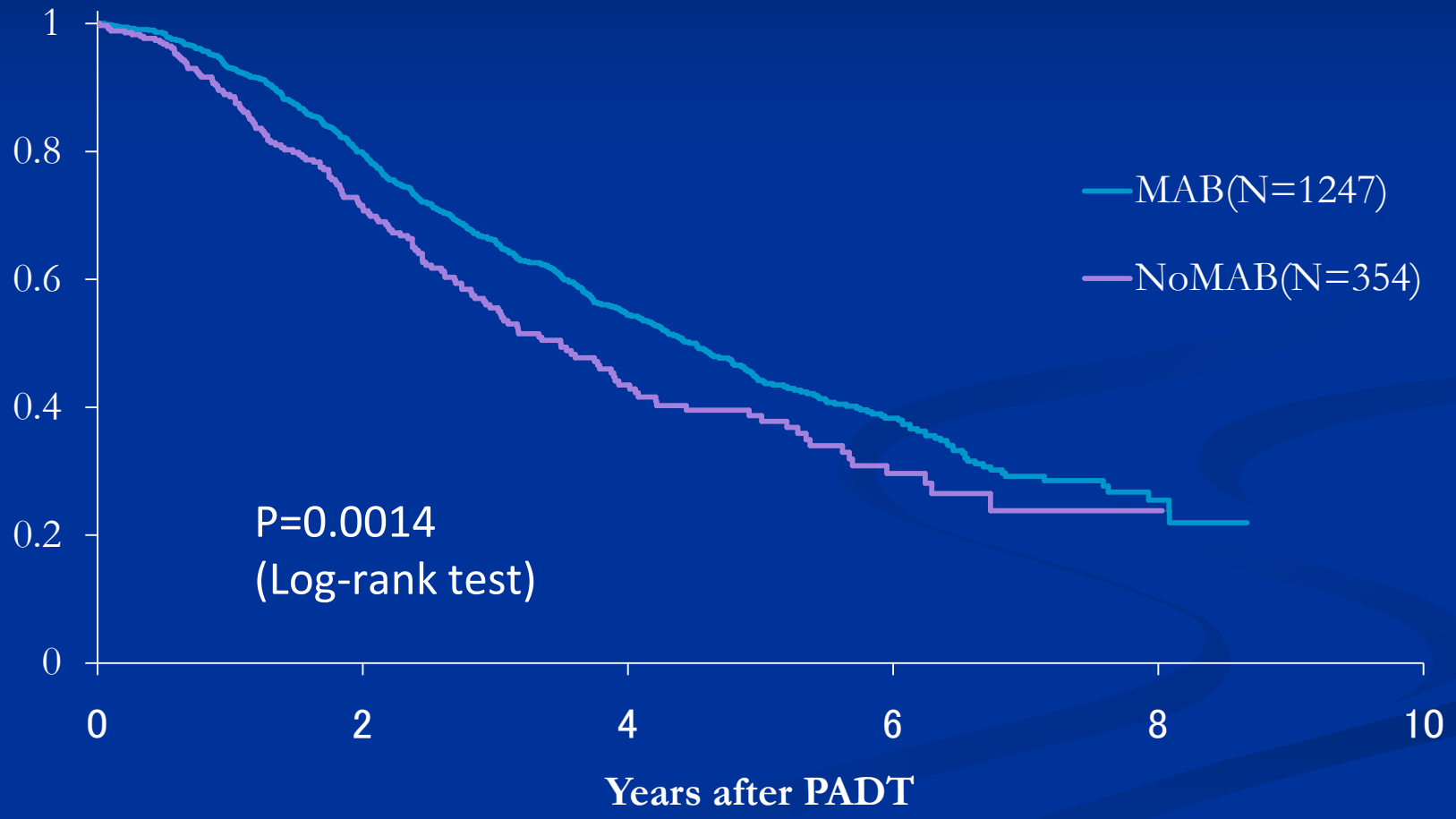
Overall survival by Hormone therapy in J-CAPRA score 0 to 2 and Age <=75 Japanese patients



Overall survival by Hormone therapy in J-CAPRA score 3 to 7 and Age <=75 Japanese patients



Overall survival by Hormone therapy in J-CAPRA score 8+ and Age <=75 Japanese patients



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Prostate Cancer

Version 1.2011

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Ovarian Cancer

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- Borderline Epithelial Ovarian Cancer (Low Malignant Potential)
- Less Common Ovarian Histologies

Pancreatic Adenocarcinoma

Primary Peritoneal Cancer (See Ovarian Cancer)

Prostate Cancer

Small Cell Lung Cancer

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Asia Consensus Statement

Prostate Cancer

V.1.2011

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NCCN acknowledges and appreciates the contribution by our Asian Panels:
http://www.nccn.org/international/asia.asp.

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NCCN Asian Consensus Statement
Prostate Cancer Panel

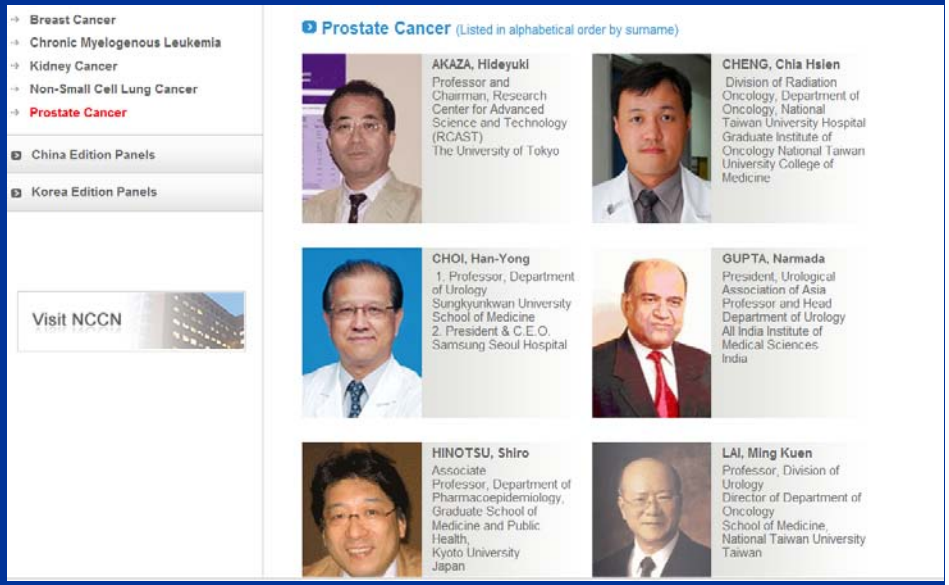


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Table of Contents

Prostate Cancer Overview – The Asian Landscape

Although prostate cancer is the number one cancer diagnosed in men in the western world, its incidence in Asia is much lower — rates in Asian countries are up to 60 times less than those reported by the US.[1] A study of 1988–1992 data on prostate cancer in 15 countries worldwide found the highest risk in the US population, with blacks leading with an age-adjusted incidence of 79.9, followed by whites with a rate of 47.9 (per 100,000 person-years); in contrast, all five Asian countries in the study (Singapore, Japan, Hong Kong, India, and China) had incidence levels lower than 10.[1] Incidence between Asian countries also varies significantly, with rates in the Philippines many times higher in comparison to rates in China.[4]

Similarly, prostate cancer also results in less mortality in Asians compared to whites and mortality rates also fluctuate among Asian countries.[1,2,3] This holds true despite the comparatively poorer prognosis typical of Asian patients, many of whom are already in late stage disease upon diagnosis.[1,4] In one study comparing prognostic factors and survival in six Asian-American subgroups (Chinese, Filipino, Japanese, Korean, South Asian, and Vietnamese), all Asian subgroups had prognostic factors that predict for poorer survival than whites, which included more advanced disease and higher grade tumors.[4] Nevertheless, it was found that every subgroup except for South Asian and Vietnamese had significantly better survival than whites: South Asian and Vietnamese subgroups had statistically equal rates compared with whites.[4] These discrepancies in incidence, mortality, and predictive value of traditional prognostic factors are attributed to genetic and environmental factors among populations.

Few studies have been done to examine differences between Asian and Western patients. One researcher observed that second- or third-generation Japanese-American men would have a higher risk of prostate cancer compared to Japanese men in Japan, which suggests that environmental or dietary factors may be at play.[4] Other analyses have shown decreased risk of osteoporosis in Japanese men compared to Caucasian men treated with ADT.[5,6] Currently, most of the standard treatments in Asia are based on findings from Caucasian-based studies. There is a large unmet need for clinical trials in the Asian population to confirm their applicability in Asia.

Finally, availability of treatments, diagnostic equipment, and access to laboratory facilities also are issues of concern in Asia, particularly in developing countries.

This guideline will begin to address some of these aforementioned areas in order to help the local oncology community optimize clinical management for their patients. It will also highlight areas where further research should be conducted to clarify existing practices.

References

1. Hsing AW, Tsao, L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. *Int J Cancer (Pred Oncol)*. 2000;85:60-67
2. Dubey D. The routine use of prostate-specific antigen for early detection of cancer prostate in India: Is it justified? *Indian Journal of Urology*. 2009;25(2):177-184. Review
3. Robbins AS, Koppie TM, Gomez SL, et al. Differences in prognostic factors and survival among white and Asian men with prostate cancer, California, 1995-2004. *Cancer*. 2007;110:1255–1263
4. Liu ZY, Sun YH, Xu CL, et al. Age-specific PSA reference ranges in Chinese men without prostate cancer. *Asian Journal of Andrology*. 2009;11:100–103
5. Wang W, Yuasa T, Tsuchiya N, et al. Bone mineral density in Japanese prostate cancer patients under androgen-deprivation therapy. *Endocrine-Related Cancer*. 2008;15:943–952
6. Yuasa T, Maita S, Tsuchiya N, et al. Relationship between bone mineral density and androgen-deprivation therapy in Japanese prostate cancer patients. *Urology*. 2010 May;75(5):1131–1137

Statement 4: Initial Therapy for Low Risk Patients in Asia

For low risk patients with life expectancy < 10 y, if patients are unable to commit to an active surveillance program, RT or primary ADT may be considered as possible treatment options.

[Cross ref: Guidelines Page PROS-2]

Discussion:

Please refer to *Statement 15* for a discussion on active surveillance in Asia and *Statement 16* for a discussion on ADT for Asian patients.

Kupelian et al. reported similar efficacy for RT and radical prostatectomy in patients with T1-T2 prostate cancer (note that radical prostatectomy is not recommended for patients with life expectancy < 10 y — see *NCCN Guidelines MS-7*).[1] Primary ADT has been used in Japan for over 80% of low risk patients (PSA of 10 µg/L or less and Gleason score of 6 or less and 1992 tumor category T1c or T2a [D'Amico classification]).[2] Its safety in Asians is demonstrated in a study by Ueno et al., where the 8-year survival rate was 95.3% for 399 patients who were treated by combined androgen blockade as primary ADT, with 61% of these patients in the T1c-T2 category.[3] Nevertheless, risks associated with ADT, impact of ADT on quality of life, and alternatives to ADT should be discussed thoroughly with the patient prior to initiating ADT.

References

1. Kupelian PA, Potters L, Khuntia D, et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy ≥ 72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int. J. Radiation Oncology Biol. Phys.* 2004;58(1):25–33
2. Hinotsu S, Akaza H, Usami M, et al. Current status of endocrine therapy for prostate cancer in Japan – Analysis of primary androgen deprivation therapy on the basis of data collected by J-CaP. *Jpn J Clin Oncol.* 2007:37(10):775–781
3. Ueno S, Namiki M, Fukagai T, et al. Efficacy of primary hormonal therapy for patients with localized and locally advanced prostate cancer: A retrospective multicenter study. *Int J Urol.* 2006;13:1494–1500

Statement 5: Initial Therapy for Intermediate Risk Patients in Asia

For intermediate risk patients with life expectancy < 10 y, ADT may be considered in addition to active surveillance.

[Cross ref: Guidelines Page PROS-3]

Discussion:

Please refer to *Statement 15* for a discussion on active surveillance in Asia and *Statement 16* for a discussion on ADT for Asian patients.

In the Ueno retrospective study, the 8-year survival rate was found to be 95.3% for 399 patients (61% in the T1c-T2 category) who were treated by combined androgen blockade (CAB) as primary ADT (see *Statement 4*). Noting decreased toxicity with ADT for Asians, the benefits may outweigh the risks for this patient population in Asia. Nevertheless, risks associated with ADT, impact of ADT on quality of life, and alternatives to ADT should be discussed thoroughly with the patient prior to initiating ADT.

Statement 6: Initial Treatment for Intermediate Risk Patients After Radical Prostatectomy in Asia

After radical prostatectomy, if either adverse pathological features or lymph node metastasis is observed and it is unlikely patients can be observed regularly, RT and ADT may be considered for adjuvant therapy.

[Cross ref: Guidelines Page PROS-3]

Discussion:

Findings regarding adjuvant therapy following radical prostatectomy are highly controversial. Although data has shown benefit for using ADT post-prostatectomy in lymph node-positive patients, there is limited information on ADT in node-negative cases.[1] Similarly, RT has been shown to improve overall survival in patients with a high risk of recurrence after radical prostatectomy, but data is pending as to its use in lymph-positive patients. Nevertheless, the lack of regular screening and challenges with active surveillance prompt oncologists in Asia to opt for treatment even in intermediate-risk patients or patients with low life expectancy (see *Statement 14* and *Statement 15*). Risks, benefits, and treatment alternatives should be thoroughly discussed with the patient regardless of therapy selected.

References

1. Verhagen PC, Schröder FH, Collette L, et al. Does Local Treatment of the Prostate in Advanced and/or Lymph Node Metastatic Disease Improve Efficacy of Androgen-Deprivation Therapy? A Systematic Review. *European Urology*. 2010;58(2):261–269. Review
2. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol*. 2009;181:956–962

Statement 7: Initial Therapy for High Risk Patients in Asia

Primary ADT is an additional option for high risk patients in Asia with life expectancy < 10 y.

[Cross ref: Guidelines Page PROS-4]

Discussion:

Primary ADT, particularly combined or total androgen blockade (CAB), has been a standard treatment for high risk patients.[1,2,3] In the study by Akaza et al., long-term treatment with CAB with bicalutamide (80 mg daily) was shown to improve overall survival compared to LHRH-agonist monotherapy (HR 0.78, p<0.0498) in patients with late stage prostate cancer.[1] It is noted that in the Widmark study of locally advanced cancer patients in Europe, RT combined with ADT was shown to result in superior 10-year survival compared to the ADT-only group (3 months of CAB followed by continuous flutamide treatment).[4] However, the efficacy of long-term CAB has not been compared to combination therapy with RT and ADT. Therefore, CAB remains an option for high risk patients with low life expectancy in Asia.

Note: ADT also appears to have a different toxicity profile in Asians. Please also see Statement 16 for a discussion on ADT in Asia.

References

1. Akaza H, Hinotsu S, Usami M, et al. Combined androgen blockade with bicalutamide for advanced prostate cancer. *Cancer*. 2009 Aug;115(15):3437–3445
2. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol*. 2007 Apr 20;25(12):1596–605
3. Hinotsu S, Akaza H, Usami M, et al. Current status of endocrine therapy for prostate cancer in Japan analysis of primary androgen deprivation therapy on the basis of data collected by J-CaP. *Jpn J Clin Oncol*. 2007 Oct;37(10):775–781
4. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet*. 2009 Jan 24;373(9660):301–308

Statement 9: Clarification on Diagnostics

The Asia Panel noted that ProstaScint is not available in Asia.*

[Cross ref: Guidelines Page PROS-6]

* **Editor's note: Please note that ProstaScint has been removed as an option in the latest 2011 NCCN Guidelines on prostate cancer.**

(Version V.1.2011 of the NCCN Guidelines on prostate cancer has not been reviewed by the Asia Panel in this document.)

Statement 12: Primary Salvage Therapy Following Radiotherapy in Asia

The Asia Panel noted that cryosurgery and brachytherapy are not popular in Asian countries.

[Cross ref: Guidelines Page PROS-7]

Discussion:

The Asia Panel noted that the facilities and expertise for cryosurgery and brachytherapy are not available in many parts of Asia.

Statement 13: Options for Salvage Therapy in Asia

ADT may be an additional treatment option for patients with positive biopsy and negative studies for metastases after primary treatment with RT.

[Cross ref: Guidelines Page PROS-7]

Discussion:

Patients with localized or locally advanced prostate cancer who failed or progressed after primary therapy (RT or radical prostatectomy) may be given salvage ADT. Currently, there is no information comparing ADT salvage therapy with other treatment modalities after primary treatment failure. There are also no prospective studies offering evidence for improved survival with salvage ADT. However, two retrospective analyses on post-RT salvage ADT have shown that patients who were given early ADT, particularly before metastases, have an improved OS compared to those who were given late ADT.[1,2] A retrospective study by Moul et al. also found that early ADT following radical prostatectomy delayed metastases for patients despite not having a significant impact on OS.[3] Further studies are needed to evaluate ADT against localized treatment such as RT/radical prostatectomy, brachytherapy, and cryosurgery.

References

1. Shipley WU, DeSilvio, M, Pilepich MV, et al. Early initiation of salvage hormone therapy influences survival in patients who failed initial radiation for locally advanced prostate cancer: A secondary analysis of RTOG protocol 86-10. *Int J Radiat Oncol Biol Phys*. 2006;64(4):1162–1167
2. Souhami L, Bae K, Pilepich M, et al. Timing of salvage hormonal therapy in prostate cancer patients with unfavorable prognosis treated with radiotherapy: A secondary analysis of Radiation Therapy Oncology Group 85-31. *Int J Radiat Oncol Biol Phys*. 2010 Mar 29. [Epub ahead of print]
3. Moul JW, Wu H, Sun L, et al. Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. *J Urol*. 2008 May;179(5 Suppl):S53–59

Statement 14: Life Expectancy and Screening in Asia

(1) Life expectancy varies among Asian countries. Doctors are advised to use local guidelines on age-related PSA cut-off values wherever possible to determine whether further diagnosis is necessary.

(2) Screening practices are not routine for many Asian countries. Contrary to the US and Europe, most cases of prostate cancer in Asian countries are diagnosed at advanced stages of disease.

[Cross ref: Guidelines Page PROS-A]

Discussion:

Life expectancy in Asian countries

Life expectancy and average age vary significantly among countries in the Asia Pacific region.[1] Studies also have found significant discrepancies in age-specific PSA values among patients of different ethnicities.[2,3,4] Several Asian countries, including China, Taiwan, Japan, and Korea, have investigated the normal levels for their local population; therefore, the Asia Panel recommends that countries with local data on age-specific PSA levels to follow local guidelines to determine PSA cutoff values for biopsy or further testing.[5,6,7]

Screening and detection in Asia

PSA screening is not as common in Asian as US and European countries. In the Philippines, there is a regular screening in the form of an annual DRE and PSA examination conducted on Father's Day (June), "Pa DRE"; screening also is conducted as part of annual executive examinations at private hospitals.[8] In Taiwan and Japan, screening programs are common but vary among urologists.[9,10] In India, China, and other Asian countries, only opportunistic screening is performed.[11]

Also of note is the difference in the clinical presentation of prostate cancer in Asia compared to the West. Unlike the US and Europe,

Statement 16: Androgen Deprivation Therapy in Asia

(1) The effect of ADT on bone mineral density in Asians is different from the effects seen in studies of Caucasian subjects.

(2) There is a lack of data regarding the cardiovascular impact of ADT in the Asian population; current data on the relationship between ADT and cardiovascular risks are controversial.

(3) There is a lack of data on the relationship between ADT and diabetes in the Asian population.

[Cross ref: Guidelines Page PROS-E]

Discussion:

ADT has been associated with decreased bone mineral density, decreased insulin sensitivity, and increased cardiovascular risk in the literature.[1,2] However, most of these studies pertain to a Caucasian-based patient population. Furthermore, extensive experience with ADT in Japan seems to suggest a mild toxicity profile for Asians that differs from the one observed in Western studies.[4] Given the physiologic, genetic, and lifestyle differences between Asians and Caucasians, race-specific data are needed to evaluate these claims in the Asian population.[3,4]

Prescribing trends

ADT is indicated for metastatic prostate cancer and ADT in combination with radiotherapy is standard treatment for high-risk and locally advanced prostate cancer; its value in low risk patients or patients with localized disease remains unclear. Moreover, Asian data has been limited, with research findings primarily coming from studies on the Japanese population.

In Japan, primary ADT has been used widely in the treatment of prostate cancer for many years.[4,5] A study in Japan of the J-CaP database found that 45.9% of patients with T1c-T3N0M0 prostate cancer had primary ADT, a number much higher than corresponding data from US and Europe;[5] a recent study comparing data from the Nara Uro-Oncological Research Group (NUORG) and the American Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) found 51% of Japanese prostate cancer patients received primary ADT between 2004 and 2006, compared with 20% in the US database.[10]

Thank you for your attention