NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Asia Consensus Statement

Prostate Cancer

Version 2.2013

NCCN.org
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Preamble

Authorization
The National Comprehensive Cancer Network (NCCN) supports and authorizes selected disease-specific expert oncology groups to develop
Asian Consensus Statements which reflect regional differences in care, based upon the recommendations of the NCCN Clinical Practice
Guidelines in Oncology® (“NCCN Guidelines”) and subject to approval by NCCN and representatives of NCCN’s panels.

Objectives
These statements are designed to provide clear documentation of modifications from the “parent” NCCN Guidelines, outlining those relating to
genetic variation in the metabolism of agents or differences in the regulatory environments in participating Asian countries. The main objective
of this initiative is the widespread provision and implementation of clinical resources that describe optimal, evidence-based treatment
recommendations with the goal of ultimately improving the lives of patients in Asia with cancer.

Genesis and Development Process
This collaborative project was initiated by the NCCN and Reno Medical K.K. (M3 Group) Formation of individual, disease-specific panels of
Asian experts is the first step towards the development of an NCCN Asia Consensus Statement for the respective tumor type. Additionally, an
NCCN panel chair or member is nominated to participate in the discussion, development, and approval of resultant manuscripts. During each
disease-specific consensus discussion, pertinent sections of the latest NCCN Guidelines are assessed for potential adaptation. The agreed-
upon modifications of the recommendations of the NCCN Guidelines are documented, categorized, and supported with evidence wherever
possible, and are validated and approved by the NCCN.

Background of Panel members
Each Panel comprises multidisciplinary specialists from different Asian countries who are involved in the patient care and management of the
specific disease.
Consensus

Categorization of final consensus reached by the panel is based on the NCCN categories of evidence:

<table>
<thead>
<tr>
<th>Category</th>
<th>Level of evidence*</th>
<th>Level of consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High</td>
<td>Uniform</td>
</tr>
<tr>
<td>2A</td>
<td>Lower</td>
<td>Uniform</td>
</tr>
<tr>
<td>2B</td>
<td>Lower</td>
<td>Non-uniform</td>
</tr>
<tr>
<td>3</td>
<td>Any</td>
<td>Major disagreement</td>
</tr>
</tbody>
</table>

* High level of evidence includes randomized, controlled clinical trials, and meta-analyses. Typically, high level evidence are published in peer-reviewed journals. Lower level evidence includes phase II studies, retrospective studies, and clinical experience of experts. Lower level evidence may also include preliminary results of potentially high level evidence (presented at major meetings but before peer-reviewed publication).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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The statements contained herein reflect the consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these recommendations is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application of the Asia Consensus Statements and disclaims any responsibility for their application or use in any way. The statements are copyrighted by National Comprehensive Cancer Network. All rights reserved. These statements and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2013.

Application of this Document

The statements contained herein are with reference to the NCCN Clinical Practice Guidelines in Oncology®: Prostate Cancer (V.4.2013). As such, for contextual comprehension of the statements, please refer to the version of the NCCN Clinical Practice Guidelines in Oncology®: Prostate Cancer (V.4.2013) noted above. To view the most recent and complete versions of all NCCN Guidelines, please refer to the NCCN Guidelines in English at www.nccn.org. The NCCN Guidelines may not be reproduced in any form without the express written permission of NCCN. All rights reserved.
Limitations

In this preliminary component of a novel, ongoing exercise, the statements have been compiled by experts upon review of the NCCN Clinical Practice Guidelines in Oncology®: Prostate Cancer (V.4.2013). As NCCN is committed to maintaining up-to-date NCCN Guidelines, the NCCN and the Asian panel members are likewise committed to the provision of comprehensive Asia Consensus Statement which will be updated from time to time. All persons who use the NCCN Guidelines and Statements should note that the recommendations are applicable to 80 – 85% of the patients, and if less than 5% of the patients fall into a particular situation, there may not be any recommendations in the Guideline nor the Statement for these patients. In this case and at all times, clinicians are advised to use their own clinical judgment to determine the best way to manage each patient.

Comments from Panel Members

It is general consideration that any treatment guideline does not fit 100% of patients owing to various reasons. For Asian patients in economically underdeveloped countries and lower-health-system established countries, they are unavailable for the majority of patients and the situation varies between countries. This should be discussed in the future for the Asia Consensus Statement (ACS).

We believe the guidelines are there to provide an ideal level of care and have gone to the next step by trying to find out what percentage of patients who are treated adhere to the recommendations of the guidelines. We argue that in the near future, there are always reasons for the figures to deviate from 100% adherence when this is presented to the international arena with different regulatory bodies, very different populations and financial structures. However, the presence of the ACS is important to provide people with a framework they can begin to aspire to and then gradually may get there.
Prostate Cancer Overview  
– The Asian Landscape and Asia Consensus Statement

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 However, The ASR (per 100,000) of prostate cancer in Singapore has risen 7-fold over the past 2 decades from 4 in 1988-1992 to 28.0 in 2007-2011².³ In recent years, there is a marked rise in incidence of prostate cancer in large urban centers in Asia, especially in Beijing (19.3/100,000), Shanghai (32.3/100,000), Delhi (11.5/100,000)⁴, Singapore (28.0/100,000), although the absolute incidence and numbers remain lower than that of western countries (see Appendix E and F). And the incidence between Asian countries varies greatly. This is another feature of prostate cancer in Asia (see Appendix A, B, E, and G).

Similarly, prostate cancer also results in less mortality in Asians compared to whites and mortality rates also fluctuate among Asian countries.¹,⁵ This holds true despite the comparatively poorer prognosis typical of Asian patients, many of whom are already in late stage disease upon diagnosis.⁶ 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.⁵ 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.⁵ These discrepancies in incidence, mortality, and predictive value of traditional prognostic factors are attributed to genetic⁶-¹² and environmental factors among populations.

In addition to these, different Asian countries have greatly different healthcare insurance systems as well as economic situations. There may be different medical services available within the same nation due to factors such as economic circumstances. This means that for the Asian region, where the countries are diverse, not only having different epidemiology but also including different ethnic groups, economies, cultures, social systems, and healthcare environments, it is difficult to establish unified therapeutic evidence and standardized clinical practice guidelines for the treatment of prostate cancer.
However, this diversity is the real world. Standing on this reality, we believe that Asia can greatly contribute to the world’s advancement in prostate cancer treatment by preparing practice guidelines that address this complexity of the world.

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.\textsuperscript{13} Other analyses have shown decreased risk of osteoporosis in Japanese men compared to Caucasian men treated with ADT.\textsuperscript{14,15} 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.

The Asia Consensus Statement (ACS): Prostate Cancer is an attempt by physicians from Asian countries to fuse the data and experience they have accumulated in Asia with the western evidence, i.e., the NCCN Guidelines. The ACS will make the NCCN Guidelines effective even in the diverse Asian healthcare environments. The ACS is not just a collection of statements for better treatment of prostate cancer limited to Asia; it is also the embodiment of Asian commitment to the improvement of prostate cancer treatment worldwide.

The Asia Consensus Statement: Prostate Cancer V.1. 2011 was revised to V.2. 2013 is under the auspices of the following academic organizations: Asia Pacific Society of Uro-oncology, Asian Pacific Prostate Society, and Japan Society of Clinical Oncology.
References

Statements
NCCN Guidelines Version 4.2013
Prostate Cancer

Asia Consensus Statement (ACS) #1

INITIAL PROSTATE CANCER DIAGNOSIS

Life expectancy
≤5 y and asymptomatic

Life expectancy
>5 y or symptomatic

Bone scan if any of these:
- T1 and PSA >20
- T2 and PSA >10
- Gleason score ≥8
- T3, T4 symptomatic

Pelvic CT or MRI if any of these:
- T3, T4
- T1-T2 and nomogram indicated probability of lymph node involvement >10%

No further workup or treatment until symptomatic, except for high-risk patients

Bone scan if any of these:
- T1c
- Gleason score ≤6
- PSA <10 ng/mL
- Fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core
- PSA density <0.15 ng/mL/g

Clinically Localized:
Very low:

Low:
- T1-T2a
- Gleason score 2-6
- PSA <10 ng/mL

Intermediate:
- T2b-T2c or
- Gleason score 7 or
- PSA 10-20 ng/mL

High:
- T3a or
- Gleason score 8-10 or
- PSA >20 ng/mL

Locally Advanced:
Very high:
- T3b-T4

Metastatic:
- Any T, N1
- Any T, Any N, M1

See Initial Therapy (PROS-2)
See Initial Therapy (PROS-3)
See Initial Therapy (PROS-4)

Preferred treatment for any therapy is approved clinical trial.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

See Principles of Life Expectancy Estimation (PROS-A).

In selected patients where complications such as hydronephrosis or metastasis can be expected within 5 y, androgen deprivation therapy (ADT) or radiation therapy (RT) may be considered. High-risk factors include bulky T3-T4 disease or Gleason score 8-10.

Patients with multiple adverse factors may be shifted into the next highest risk group.
Statement 1: Initial Prostate Cancer Diagnosis, Initial Clinical Assessment, Staging Workup, and Recurrence Risk in Asia

The statement on Initial Prostate Cancer Diagnosis, Initial Clinical Assessment, Staging Workup, and Recurrence Risk in NCCN Guidelines PROS-1 is mostly applicable in Asian countries.

[Cross ref: Guidelines Page PROS-1]
NCCN Guidelines Version 4.2013
Prostate Cancer

**RECURRANCE RISK**
Clinically Localized:
Very Low:
• T1c
• Gleason score ≤ 6
• PSA <10 ng/mL
• Fewer than 3 prostate biopsy cores positive, ≤ 50% cancer in any core
• PSA density <0.15 ng/mL/g

Low:
• T1-T2a
• Gleason score ≤ 6
• PSA <10 ng/mL

**EXPECTED PATIENT SURVIVAL**

< 20 y<sup>d</sup> →

Active surveillance (category 2B)<sup>e</sup>
• PSA at least as often as every 6 mo
• DRE at least as often as every 12 mo
• Repeat prostate biopsy as often as every 12 mo

≥ 20 y → See Initial Therapy for Low recurrence risk below

≥ 10 y →

Active surveillance<sup>e</sup>
• PSA at least as often as every 6 mo
• DRE at least as often as every 12 mo
• Repeat prostate biopsy as often as every 12 mo

RT<sup>f</sup> (Daily IGRT with IMRT/3D-CRT) or brachytherapy

Radical prostatectomy (RP)<sup>g</sup>
± pelvic lymph node dissection (PLND) if predicted probability of lymph node metastasis ≥ 2%

**INITIAL THERAPY**

**ADJUVANT THERAPY**

ACS #2

ACS #3a

ACS #3b

Progressive disease<sup>h</sup>

See Initial Clinical Assessment (PROS-1)

Adverse features:<sup>i</sup>

RT<sup>f</sup> or Observation

Lymph node metastasis:
Observation
or ADT<sup>j</sup>
or ADT + RT (category 2B)<sup>l</sup>

See Monitoring (PROS-5)

See Principles of Life Expectancy Estimation (PROS-A).

The Panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. See NCCN Guidelines for Prostate Cancer Early Detection. Active surveillance is recommended for these subsets of patients.

Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses. See Principles of Active Surveillance (PROS-B).

See Principles of Radiation Therapy (PROS-C).

See Principles of Surgery (PROS-D).

Criteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.

Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.

See Principles of Androgen Deprivation Therapy (PROS-E).

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Statement 2: Initial Therapy for Very Low Risk Patients in Asia

The management of very low risk patients with life expectancy \( \geq 20 \) y should follow the algorithm for low risk patients with life expectancy \( \geq 10 \) y, the same as in the NCCN Guidelines Version 4. 2013.

- Active surveillance
- RT or brachytherapy
- RP ± PLND

Discussion:

1. Life expectancy and active surveillance
   A life expectancy of \( \geq 20 \) y corresponds to about 59 yrs in Beijing, 60 yrs in Shanghai, 57 yrs in South Korean, and 60 yrs in Japan. Active surveillance in patients at these age is unusual in these countries.
   In a country with lower average life-span, the physician should consider both the life expectancy in the country and the actual age of patient in deciding take active surveillance.

2. Brachytherapy
   Brachytherapy is not a popular option in most Asian countries except Japan.
Statement 3: Initial Therapy for Low Risk Patients in Asia

a) For low risk patients with life expectancy < 10 y
   Active surveillance is the preferred treatment option. If the patient is unable to commit, primary ADT may be a possible treatment option in selected patients.
   • Active surveillance
   • ADT

b) For low risk patients with life expectancy ≥ 10 y
   If patients are unable to commit to RP ± PLND, RT or brachytherapy or active surveillance, primary ADT may be considered as a possible treatment option.
   • RP ± PLND
   • RT or brachytherapy
   • Active surveillance
   • ADT

[Cross ref: Guidelines Page PROS-2]
Discussion:

a) For low risk patients with life expectancy < 10 y

Active surveillance: Active surveillance remains uncommon in Asia. There is no evidence showing that active surveillance is beneficial to the Asian population. We should bear in mind that active surveillance itself is meant to minimize overtreatment and risks of complications that follow.

ADT: There is no evidence showing that ADT can be a definitive treatment for patients in this category; however, it is expected to prolong the PFS and improve cancer-related symptoms. 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]). Its efficacy in Asians is demonstrated in a study by Ueno et al., where the 8-year cancer-specific survival rate was 97.6% for 135 low risk patients and 95.5% for 196 intermediate risk patients who were treated by primary ADT, with 61% of these patients in the T1c- T2 category. 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.

b) For low risk patients with life expectancy ≥ 10 y

RP ± PLND: Ji et al. reported that, in patients of D'Amico low risk, extended PLND was not superior to standard PLND in terms of biochemical progression free-survival and might be omitted to reduce operation time and complication.

Brachytherapy: Brachytherapy is not a popular option in most Asian countries except in Japan.

ADT: ADT is indicated in patients in this category in some countries including South Korea and Japan. Extensive experience with ADT in Japan seems to suggest a mild toxicity profile for Asian that differs from the one observed in Western studies; however, ADT has been associated with some side effects, including metabolic and cardiovascular effects in the literature (see Statement 12). ADT may be considered if patients are unable to commit to other treatment options.
References


NCCN Guidelines Version 4.2013
Prostate Cancer

RECURRENT RISK
Clinically Localized:

EXPECTED PATIENT SURVIVAL\(^a\)
- Active surveillance\(^a\)
  - PSA as often as every 6 mo
  - DRE as often as every 12 mo
  - \(\leq 10\) y

Intermediate:\(^c\)
- T2b-T2c or
- Gleason score 7 or
- PSA 10-20 ng/mL

\(\geq 10\) y\(^k\)

INITIAL THERAPY
- RT\(^f\) (Daily IGRT with IMRT/3D-CRT) ± short-term neoadjuvant/ concomitant/adjuvant ADT (4-6 mo) ± brachytherapy

ADJUVANT THERAPY
- Progressive disease\(^h\)
  See Initial Clinical Assessment (PROS-1)
- Undetectable PSA
  See Monitoring (PROS-5)
- Detectable PSA
  See Post-Radiation Therapy Recurrence (PROS-7)

ACS#4a

ACS#4b

ACS#5a

ACS#5b

Adverse features:\(^i\)
- RT\(^f\) or Observation
- Lymph node metastasis: Observation or ADT\(^j\) or ADT + RT (category 2B)\(^j\)

\(^a\)See Principles of Life Expectancy Estimation (PROS-A).
\(^c\)Patients with multiple adverse factors may be shifted into the next highest risk group.
\(^e\)Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses. See Principles of Active Surveillance (PROS-B).
\(^f\)See Principles of Radiation Therapy (PROS-C).
\(^g\)See Principles of Surgery (PROS-D).
\(^h\)Criteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.
\(^i\)Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
\(^j\)See Principles of Androgen Deprivation Therapy (PROS-E).
\(^k\)Active surveillance of intermediate and high-risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Statement 4: Initial Therapy for Intermediate Risk Patients in Asia

a) For intermediate risk patients with life expectancy < 10 y
   Primary ADT may be considered as a possible treatment option.
   • RT ± short-term ADT (4-6 mo) ± brachytherapy
   • ADT
   • Active surveillance [Category 2B]

b) For intermediate patients with life expectancy ≥ 10 y
   If patients are unable to commit to RP or RT, primary ADT may be considered as a possible
treatment option.
   • RP ± PLND
   • RT ± short-term ADT (4-6 mo) ± brachytherapy
   • ADT

[Cross ref: Guidelines Page PROS-3]

Discussion:

a) For intermediate risk patients with life expectancy < 10 y
   RT ± short-term ADT (4-6 mo) ± brachytherapy: Brachytherapy is not popular in Asian countries except Japan.
ADT: In the Ueno retrospective study, the 8-year cancer-specific survival rate was found to be 95.3% for 399 patients (61% in the T1c-T2 category) who were treated with combined androgen blockade (CAB) as primary ADT. 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.

Active surveillance [Category 2B]: Although Statement 4a includes active surveillance, some panel members expressed reservations. The Japanese clinical practice guidelines do not recommend active surveillance (see Appendix O).

b) For intermediate risk patients with life expectancy ≥ 10 y

RP + PLND: Ji et al. reported that, in patients of D’Amico intermediate risk, extended PLND (ePLND) was superior to standard PLND in terms of biochemical progression free-survival. Even Ji’s study supports the use of ePLND, but studies presented in AUA meeting 2013 did not support the value of treatment of ePLND as it did not improve biological recurrence or survival. Although ePLND has the potential benefit of more extensive oncological pelvic lymph node clearance, this has to be balanced with the risks of more severe vascular complications, lymphedema and longer operating time. We should really judge patient’s life expectancy by the comorbidity, general condition, etc.

RT ± short-term ADT (4-6 mo) ± brachytherapy: Brachytherapy is not popular in Asian countries except Japan. In Japan, a phase III multicenter randomized controlled study on the efficacy and safety of short-term neoadjuvant ADT + 125I brachytherapy ± adjuvant ADT has begun.

ADT: ADT is also recommended to this subset of patients who are unable to have RT or RP. Data from Japanese patients indicate significant prolongation of PFS and OS.
References


Statement 5: Adjuvant Therapy for Intermediate Risk Patients After Radical Prostatectomy in Asia

a) For patients with adverse features†
   - RT
   - Observation
   - ADT
   †Adverse features: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA

b) For patients with lymph node metastasis
   - ADT ± RT
   - Observation

[Cross ref: Guidelines Page PROS-3]

Discussion:

a) For patients with adverse features

ADT: Although data has shown that post-prostatectomy ADT is beneficial for lymph node-positive patients, there is limited information on ADT in node-negative cases.1 ADT might be an option for certain patients who have detectable PSA and/or positive surgical margins.
b) For patients with lymph node metastasis

   ADT ± RT: A Korean retrospective analysis showed that adjuvant ADT in node-positive prostate cancer did not reduce or delay disease progression or improve survival. However, in patients with pT3b disease, adjuvant ADT and radiotherapy were reported to be helpful.²

   Observation: Observation is recommended only to those patients who have undetectable PSA after lymphadenectomy. Recent practice has become more aggressive; observation seems to be chosen less often.

References

NCCN Guidelines Version 4.2013
Prostate Cancer

RECURRENT RISK
Clinically Localized:
High:
- T3a or
- Gleason score 8-10 or
- PSA >20 ng/mL

Locally Advanced:

Very High:
T3b-T4

Metastatic:
Any T, N1
Any T, Any N, M1

INITIAL THERAPY

RT^f (Daily IGRT with IMRT/3D-CRT) + long-term neoadjuvant/concomitant/adjuvant ADT (2-3 y)^i (category 1)
or RT^f (Daily IGRT with IMRT/3D-CRT) + brachytherapy ± long-term neoadjuvant/concomitant/adjuvant ADT (2-3 y)^i or RP^g + PLND (selected patients with no fixation)

ADJUVANT THERAPY

Adverse features:^i
RT^f or Observation

Undetectable PSA

Lymph node metastasis:
ADT^j
or Observation
or ADT + pelvic RT (category 2B)^j

Detectable PSA

See Post-Radical Prostatectomy Recurrence (PROS-6)

See Monitoring (PROS-5)

See Post-Radical Prostatectomy Recurrence (PROS-6)

See Monitoring (PROS-5)

See Monitoring (PROS-5)

See Monitoring (PROS-5)

ADJUVANT THERAPY

Adverse features:^i
RT^f or Observation

Undetectable PSA

Lymph node metastasis:
ADT^j
or Observation
or ADT + pelvic RT (category 2B)^j

Detectable PSA

See Post-Radical Prostatectomy Recurrence (PROS-6)

See Monitoring (PROS-5)

See Monitoring (PROS-5)

See Monitoring (PROS-5)

See Monitoring (PROS-5)

^iAdverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
^jSee Principles of Androgen Deprivation Therapy (PROS-E).
^gSee Principles of Surgery (PROS-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Statement 6: Initial Therapy for High Risk Patients in Asia

Primary ADT may be considered for high risk patients.
- RT ± long-term ADT (2-3 y) ± brachytherapy
- RP (+ PLND)†
- ADT

†Selected patients with no fixation

Discussion:

RT ± long-term ADT (2-3 y) ± brachytherapy: Brachytherapy is not popular in Asian countries except Japan. In Japan, a phase III multicenter randomized controlled study on the efficacy and safety of RT (EBRT) + hormonal therapy (short- or long-term) + 125I brachytherapy has begun.1

RP + (PLND): Recently, there is more evidence supporting offering high risk patients RP rather than RT.2,3 Ji et al. reported that extended PLND was superior to standard PLND in terms of biochemical progression free-survival.4

ADT: In most Asian countries other than Japan, combined androgen blockade (CAB) is not a standard ADT. The NCCN Guidelines Version 4. 2013 (PROS-E, Optimal ADT) says that CAB provides no proven benefit over castration alone in patients with metastatic disease, but as in the ASCO guidelines,5 primary CAB can be considered as an option for high risk patients.6,7 In the study by Akaza et al., long-term treatment with CAB with bicalutamide (80 mg daily, the dose licensed in Japan) was shown to improve overall survival compared to LHRH-agonist monotherapy (HR 0.78, p<0.0498) in patients with late stage prostate cancer.6 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).8 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. In addition, ADT alone is an option for patients, who are not candidates for radical treatments due to their comorbidities. (Please also see Statement 12)
References


POST-RADICAL PROSTATECTOMY RECURRENCE

Failure of PSA to fall to undetectable levels

Undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations

ACS#7a
Studies negative for distant metastases

RT\textsuperscript{f} ± neoadjuvant/concomitant/adjuvant ADT\textsuperscript{f} or Observation

ACS#7b
Studies positive for distant metastases

ADT\textsuperscript{f} ± RT to site of metastases, if in weight-bearing bones, or symptomatic\textsuperscript{f} or Observation

Progression

See Advanced Disease (PROS-8) and (PROS-9)

\textsuperscript{f} See Principles of Radiation Therapy (PROS-C).

\textsuperscript{f} See Principles of Androgen Deprivation Therapy (PROS-E).

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Statement 7: Treatment Options for Post-Radical Prostatectomy Recurrence in Asia

a) For patients with negative studies for distant metastasis
   • RT ± ADT
   • ADT
   • Observation

b) For patients with positive studies for distant metastasis
   • ADT ± RT (for sites of ‘oligo’ metastases)
   • Observation

Discussion:

a) For patients with negative studies for distant metastasis
   Observation: Observation is an option for patients with short life expectancy or multiple comorbidities.

b) For patients with positive studies for distant metastasis
   ADT ± RT (for sites of ‘oligo’ metastases): There is no clear evidence that supports RT for metastases in Asian patients, In patients who have ‘oligo’ metastases, however, RT may have some benefits.
   Observation: Observation is an option for patients with short life expectancy or multiple comorbidities.
**Prostate Cancer**

**POST-RADIATION THERAPY RECURRENCE**

- **Candidate for local therapy:**
  - Original clinical stage T1-T2, NX or N0
  - Life expectancy >10 y
  - PSA now <10 ng/mL

- **Prostate biopsy positive, studies negative for distant metastases**
  - Observation
  - RPg
  - Cryosurgery
  - Brachytherapy

- **Prostate biopsy negative, studies negative for distant metastases**
  - Observation
  - ADT
  - Clinical trial
  - More aggressive workup for local recurrence (eg, repeat biopsy, MR spectroscopy, endorectal MRI)

- **Studies positive for distant metastases**
  - ADT
  - Observation

- **Not a candidate for local therapy**

- **Post-RT rising PSA or Positive DRE**

---

*See Principles of Radiation Therapy (PROS-C).*

*See Principles of Surgery (PROS-D).*

*See Principles of Androgen Deprivation Therapy (PROS-E).*

*RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus - 1) PSA rise by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; and 2) the date of failure is determined "at call" (not backdated). They recommended that investigators be allowed to use the ASTRO Consensus Definition after EBRT alone (with no hormonal therapy) with strict adherence to guidelines as to "adequate follow-up" to avoid the artifacts resulting from short follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature.*

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Statement 8: Treatment Options for Post-Radiation Therapy Recurrence in Asia

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

- ADT
- Observation
- RP (Salvage RP)

Cryosurgery and brachytherapy are not widely used in Asia.

Discussion:

ADT: Currently, information is lacking that compares ADT salvage therapy with other treatment modalities after primary treatment failure. No prospective studies offer 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, had an improved OS compared to those given late ADT.1,2 A retrospective study by Moul et al. also revealed that early ADT following RP delayed metastases in patients despite not having a significant impact on OS.3 Although there is no evidence that supports ADT in Asian patients with post RT recurrence, ADT is widely used in Asian countries.

Observation: Observation is an option for patients with short life expectancy or multiple comorbidities.
References


ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER

- Abiraterone acetate\(^1\) or enzalutamide (category 1, post-docetaxel therapy)
- Cabazitaxel (category 1, post-docetaxel)\(^q\)
- Radium-223 for symptomatic bone metastases (category 1, post-docetaxel)\(^s\)
- Salvage chemotherapy
- Docetaxel rechallenge\(^q\)
- Mitoxantrone\(^q\)
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole
  - Steroids
  - DES or other estrogen
- Sipuleucel-T\(^t\)
- Clinical trial

- Docetaxel\(^q\) (category 1)
- Radium-223 for symptomatic bone metastases (category 1)\(^s\)
- Mitoxantrone\(^q,u\)
- Abiraterone acetate\(^j,u\)
- Enzalutamide\(^j,u\)
- Palliative RT or radionuclide for symptomatic bone metastases
- Clinical trial

- Sipuleucel-T (category 1)\(^t\)
- Secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Abiraterone acetate\(^j\) (category 1)
  - Enzalutamide\(^j\)
  - Ketoconazole
  - Steroids
  - DES or other estrogen
- Docetaxel\(^v\)
- Clinical trial

Yes →

No →

Studies positive for metastases

- Maintain castrate serum levels of testosterone and
- Denosumab (category 1) or zoledronic acid (category 1) if bone metastases

Symptomatic

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

\(^1\)See Principles of Androgen Deprivation Therapy (PROS-E).
\(^q\)See Principles of Chemotherapy/Immunotherapy (PROS-F).
\(^s\)Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-C, page 2/2).
\(^t\)Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. Sipuleucel-T is not indicated in patients with hepatic metastases or life expectancy <6 months.
\(^u\)For patients who are not candidates for docetaxel-based regimens.
\(^v\)Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or hepatic metastases despite lack of symptoms.
Statement 9: Treatment Options for Bone Metastases of Castration-Recurrent Prostate Cancer in Asia

Drugs, such as denosumab, which are potentially effective in treating bone metastases of prostate cancer, including castration-recurrent prostate cancer are not widely available in all parts of Asia. Denosumab is available in Hong Kong, Japan, Malaysia, Philippines, Singapore, Taiwan and selected centers. Zoledronic acid is available in most Asian countries (appendix Q).

[Cross ref: Guidelines Page PROS-10]

Discussion:
In Asian countries, the PSA screening test is uncommon and patients often have metastases at the time of diagnosis. ADT (medical or surgical castration) is usually indicated in such patients. If the cancer recurs after ADT, only a limited number of drugs are available for use. We have few medicines potentially effective in treating bone metastases, in particular.
Statement 10: Life Expectancy and Early Detection 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 steps toward prostate cancer diagnosis are warranted.

2) There are few countries in Asia that have a government-led PSA early detection program. In some nations, however, the cost for PSA testing is covered by insurance and some institutions have their own early detection programs, and these have been successful in detecting patients with prostate cancer in their early stages.

Discussion:

a) Life expectancy in Asian countries

Life expectancy and average age vary significantly among countries in the Asia Pacific region. Studies also have found significant discrepancies in age-specific PSA values among patients of different ethnicities. Several Asian countries, including China, Taiwan, Japan, and Korea, have investigated the normal range of PSA levels for their population. Therefore, the Asia Panel recommends that physicians in those countries that have local data on age-specific PSA levels follow the local guidelines to determine PSA cutoff values for prostate biopsy or further testing.
**b) Early detection in Asia**

PSA screening is not as common in Asian as in US and European countries. In the Philippines, regular screening annual (DRE and PSA) is conducted on Father’s Day (June), “Pa DRE”. PSA screening also is conducted as part of annual executive examinations at private hospitals. In Taiwan and Japan, screening programs are common but vary among urologists. In South Korea, recently, the proportion of low-risk and clinically localized prostate cancer patients have increased. A possible reason for this increase is that in South Korea, for patients aged >40 yrs with LUTS who desire PSA measurement, the national healthcare insurance supports PSA testing. In India, and other Asian countries, only opportunistic screening is performed.

Also in the clinical presentation of prostate cancer differs in Asia compared to the West. Unlike the US and Europe, patients are often diagnosed with late stage disease in Asia. Asian patients with prostate cancer also have a lower survival: 5-year survival rate is 33% in China vs 90% in the US. Most of the difference is attributed to the lack of routine PSA or other means of prostate cancer screening in many Asian countries.

**Comments from panel members:**

- China: Even we do not have the data representing the current status of prostate cancer in China, but the stage migration is happening in big cities like Shanghai, Beijing. We are seeing more early stage prostate cancer patients than we used to.
- India: Incidence of prostate cancer is increasing in India every year. The Cancer Registry of India shows that prostate cancer has become 2nd most common cancer in males in Delhi. However, in other towns, prostate cancer mortality remains between 4th -8th. We are seeing more early stage prostate cancer patients than we used to due to availability of PSA and increasing awareness in the public.

Note: The NCCN Prostate Cancer Early Detection Guidelines have not been discussed by the Asia Panel.
References

Statement 11: Active Surveillance in Asia

While still uncommon in the Asian region, an increasing number of countries and institutions are starting to adopt active surveillance strategies in selected cases.

[Cross ref: Guidelines Page PROS-B]

Discussion:

The NCCN recommends active surveillance for low and intermediate risk patients to prevent overtreatment of prostate cancer and treatment-related morbidity observed in the US. However, patients in Asia may not be able to participate in such a program due to economic or geographic circumstances. Patients at risk also are less likely to be assessed for prostate cancer due to less regular physical examinations and less use of screening programs, which leads to higher frequency of late-stage presentation in Asian countries (see Statement 10). Furthermore, response to ADT may be different in the Asian population; a better safety profile has been observed with ADT in Japanese men (see Statement 12). Given these conditions, many oncologists in Asia opt for some kind of treatment in lieu of active surveillance even in low and intermediate risk patients, despite the lack of supportive data. More studies on the Asian population are needed to shed light on the appropriateness of these practices. All treatment options have advantages and disadvantages; the physician and the patient should thoroughly discuss all of these factors and available alternatives selecting therapy. Active surveillance protocols for Asia can be based on the NCCN Prostate Guidelines and use the PRIAS study protocol results for additional guidance.

The situation around active surveillance in panel member countries as of December 2013:

• Hong Kong: If patients with hypertension or diabetes mellitus who regularly visit the panel member’s institutions are found to have higher PSA levels than normal, they will be referred to the urologists. Those patients with very low risk or low risk prostate cancer are recommended active surveillance.

• Japan: According to the data in 2010, only 6% of newly diagnosed patients undergo active surveillance.
• Philippines: Few are adopting active surveillance as a treatment strategy. Even when chosen, the protocol for active surveillance (i.e. frequency of PSA, DRE and repeat biopsies) is not standardized.
• Singapore: About 30% of patients in the panel member’s institutions are on active surveillance.
• South Korea: Some studies have been initiated to investigate the benefit of active surveillance.3

References
Statement 12: Androgen Deprivation Therapy in Asia

ADT has been accepted as a major treatment in Asia, but its efficacy and safety profile in the Asian population seem different than in the Western population. In particular, primary ADT can be more effective than in the West. Nevertheless, care must be taken to avoid adverse effects when ADT is used, especially in patients with significant comorbidities.

1) The extensive ADT experience in Japan suggests that the effect of ADT on bone mineral density in Asians seems different from the effects reported in Caucasian patients.
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. Although it could not be necessarily extrapolated to the whole of Asia, extensive experience with ADT in Japan seems to suggest a mild toxicity profile in Asians that differs from that reported in Western studies.\(^4\) Given the physiologic, genetic, and lifestyle differences between Asians and Caucasians, race-specific data are needed to evaluate ADT side effects 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. Asian data has been limited, with research findings primarily reported 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 of the J-CaP database conducted in Japan 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) revealed that 51% of Japanese patients with prostate cancer received primary ADT between 2004 and 2006, compared with 20% in the US database.\(^10\)

A direct comparison study between the J-CaP database and the CaPSURE database found that patients treated with primary ADT in Japan, compared to those in the US, had more than 3-fold higher cause-specific survival adjusted for multiple factors, which included disease risk group and type of ADT. Furthermore, combined androgen blockade (CAB) improved outcomes compared to ADT in J-CaP but not in CaPSURE.\(^11\)
**ADT and bone**

Loss of bone mineral density (BMD) has been cited as a major risk from ADT, since ADT may lead to osteoporosis and fractures. However, a study by Wang et al. has shown that the situation may be different for Japanese men. Comparing the effects of ADT on BMD and osteoporosis in 80 men with prostate cancer, the researchers found a mild but insignificant increase in osteoporosis between ADT-treated and ADT-naïve patients (10.8%, 4 of 37) for ADT-treated vs. 2.3%, (1 of 43) for ADT-naïve group); patients treated with ADT had an average of 23.5 months of therapy. A follow-up study with more patients (n=158) showed a mild increase in the prevalence of osteoporosis between ADT-naïve patients, those treated for less than two years, and those treated for more than two years (4.5%, 12.1%, 10.8%, respectively). Noting the small numbers compared with the figures reported by studies on Caucasian or black populations, the researchers concluded that the relationship between ADT and bone is different in East Asians and suggested that genetic or environmental influences may be involved.

The NCCN Guidelines recommend a DEXA scan before the start of ADT and a follow-up DEXA scan. In the Asian region, however, DEXA scans can be performed in routine practice only in some countries. Furthermore, Asia has no consensus or guidelines on measurement of serum levels of 25-hydroxy vitamin D or intake of vitamin D (drug products or supplements) for the prevention of fractures in patients on ADT due to a reduced BMD or osteoporosis.

**ADT and cardiovascular risk**

ADT has been linked to increased cardiovascular morbidity and mortality in recent studies, although most were unable to substantiate an elevated risk of cardiovascular mortality. The relationship is even more unclear in the Asian population, since there are no large studies exploring a possible effect. Speaking from clinical experience, however, the Asia Panel notes that combined ADT with anti-androgen has a different safety profile in Asia from that reputed in the US. According to the Asia Panel, in India, 50 mg of bicalutamide has been used with no increase in risk of cardiovascular events; in Japan, 80 mg is often prescribed and has been well-tolerated, with low risk of cardiovascular events.

**ADT and diabetes**

ADT is causally linked to decreased sensitivity to insulin in studies based on the Western population. Studies are needed to evaluate whether a similar connection exists between ADT and diabetes in Asian patients.
References


Appendices
### A) Life Expectancy and Incidence of Prostate Cancer

(Information provided by the panelists)

<table>
<thead>
<tr>
<th>Country</th>
<th>Life expectancy at Birth</th>
<th>Incidence (/100,000 ASR*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>71 (National average)</td>
<td>9.92 (National average),</td>
</tr>
<tr>
<td></td>
<td>79 (Beijing), 80 (Shanghai) [2011, male]</td>
<td>13.13 (in cities), 3 (in rural area)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19.3 (Beijing), 32.3 (Shanghai) [2009]</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>81 [2010, male]</td>
<td>28.1, 45.3** [2010]</td>
</tr>
<tr>
<td>India</td>
<td>67 [2012, male]</td>
<td>6.5 -7.5 [2002]</td>
</tr>
<tr>
<td>Indonesia</td>
<td>69 [2012]</td>
<td>11 [2008]</td>
</tr>
<tr>
<td>Japan</td>
<td>80 [2012, male]</td>
<td>31.2 [2008]</td>
</tr>
<tr>
<td>Korea</td>
<td>77 [male]</td>
<td>25.3 [2010]</td>
</tr>
<tr>
<td>Malaysia</td>
<td>72 [male]</td>
<td>12 [2010]</td>
</tr>
<tr>
<td>Taiwan</td>
<td>76 [2012, male]</td>
<td>28.8, 37.8** [2010]</td>
</tr>
<tr>
<td>Thailand</td>
<td>71 [2012, male]</td>
<td>6.4 [2006]</td>
</tr>
</tbody>
</table>

*Age-standardized rates. **Crude incidence rate

Note: Data based on information as of December 2013 collected from the panelists.
## B) Incidence and Mortality of Prostate Cancer

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence Cumulative risk* [%]</th>
<th>ASR** (world)</th>
<th>Mortality Cumulative risk* [%]</th>
<th>ASR** (world)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>0.5</td>
<td>4.3</td>
<td>0.2</td>
<td>1.8</td>
</tr>
<tr>
<td>India</td>
<td>0.4</td>
<td>3.7</td>
<td>0.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Indonesia</td>
<td>1.2</td>
<td>10.6</td>
<td>0.8</td>
<td>8.0</td>
</tr>
<tr>
<td>Japan</td>
<td>2.7</td>
<td>22.7</td>
<td>0.4</td>
<td>5.0</td>
</tr>
<tr>
<td>Korea</td>
<td>2.9</td>
<td>22.4</td>
<td>0.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Malaysia</td>
<td>1.1</td>
<td>9.2</td>
<td>0.6</td>
<td>5.8</td>
</tr>
<tr>
<td>Philippines</td>
<td>1.1</td>
<td>10.1</td>
<td>0.5</td>
<td>5.3</td>
</tr>
<tr>
<td>Singapore</td>
<td>2.2</td>
<td>20.0</td>
<td>0.3</td>
<td>3.9</td>
</tr>
<tr>
<td>Taiwan</td>
<td>2.5</td>
<td>20.8</td>
<td>0.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Thailand</td>
<td>0.6</td>
<td>6.5</td>
<td>0.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Cumulative risk [0-74], **ASR (age-standardized rates) per 100,000

### C) Prostate Cancer Incidence by Age

<table>
<thead>
<tr>
<th></th>
<th>Total cases</th>
<th>0-14</th>
<th>15-39</th>
<th>40-44</th>
<th>45-49</th>
<th>50-54</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-74</th>
<th>75+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>China</strong></td>
<td>33,802</td>
<td>0.0</td>
<td>0.1</td>
<td>0.4</td>
<td>1.0</td>
<td>2.7</td>
<td>3.7</td>
<td>7.2</td>
<td>24.3</td>
<td>55.9</td>
<td>89.6</td>
</tr>
<tr>
<td><strong>India</strong></td>
<td>14,630</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td>0.3</td>
<td>2.3</td>
<td>6.4</td>
<td>13.3</td>
<td>24.0</td>
<td>39.5</td>
<td>61.1</td>
</tr>
<tr>
<td><strong>Indonesia</strong></td>
<td>9,033</td>
<td>-</td>
<td>0.0</td>
<td>-</td>
<td>0.8</td>
<td>5.5</td>
<td>23.4</td>
<td>41.6</td>
<td>61.1</td>
<td>118.0</td>
<td>172.8</td>
</tr>
<tr>
<td><strong>Japan</strong></td>
<td>38,619</td>
<td>0.1</td>
<td>0.1</td>
<td>0.5</td>
<td>1.4</td>
<td>5.8</td>
<td>28.7</td>
<td>64.4</td>
<td>162.9</td>
<td>276.3</td>
<td>403.8</td>
</tr>
<tr>
<td><strong>Korea</strong></td>
<td>6,382</td>
<td>-</td>
<td>0.1</td>
<td>0.9</td>
<td>2.6</td>
<td>11.7</td>
<td>36.8</td>
<td>98.0</td>
<td>183.3</td>
<td>245.6</td>
<td>288.7</td>
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<tr>
<td><strong>Malaysia</strong></td>
<td>821</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>1.2</td>
<td>4.6</td>
<td>14.8</td>
<td>29.5</td>
<td>65.8</td>
<td>95.0</td>
<td>157.4</td>
</tr>
<tr>
<td><strong>Philippines</strong></td>
<td>2,491</td>
<td>-</td>
<td>0.1</td>
<td>0.6</td>
<td>2.5</td>
<td>3.2</td>
<td>9.8</td>
<td>29.5</td>
<td>69.9</td>
<td>111.9</td>
<td>190.7</td>
</tr>
<tr>
<td><strong>Singapore</strong></td>
<td>616</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
<td>-</td>
<td>6.4</td>
<td>25.0</td>
<td>68.6</td>
<td>131.7</td>
<td>219.2</td>
<td>378.9</td>
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<tr>
<td><strong>Taiwan</strong></td>
<td>3,635</td>
<td>-</td>
<td>0.0</td>
<td>0.3</td>
<td>2.4</td>
<td>10.1</td>
<td>23.8</td>
<td>81.0</td>
<td>132.6</td>
<td>258.4</td>
<td>338.5</td>
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<tr>
<td><strong>Thailand</strong></td>
<td>2,134</td>
<td>-</td>
<td>0.1</td>
<td>0.2</td>
<td>0.4</td>
<td>1.5</td>
<td>4.0</td>
<td>13.2</td>
<td>43.0</td>
<td>59.5</td>
<td>157.4</td>
</tr>
</tbody>
</table>

Rates per 100,000. Rates based on less than 10 cases are *italicized.*

---

### D) Prostate Cancer Mortality by Age

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Cases</th>
<th>0-14</th>
<th>15-39</th>
<th>40-44</th>
<th>45-49</th>
<th>50-54</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-74</th>
<th>75+</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>14,297</td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
<td>0.3</td>
<td>0.8</td>
<td>1.2</td>
<td>2.4</td>
<td>7.9</td>
<td>19.3</td>
<td>47.5</td>
</tr>
<tr>
<td>India</td>
<td>10,422</td>
<td>0.0</td>
<td>0.7</td>
<td>0.4</td>
<td>-</td>
<td>-</td>
<td>0.7</td>
<td>4.9</td>
<td>13.3</td>
<td>27.7</td>
<td>50.0</td>
</tr>
<tr>
<td>Indonesia</td>
<td>6,841</td>
<td>-</td>
<td>0.0</td>
<td>-</td>
<td>0.5</td>
<td>3.3</td>
<td>12.2</td>
<td>25.2</td>
<td>39.4</td>
<td>86.4</td>
<td>170.5</td>
</tr>
<tr>
<td>Japan</td>
<td>9,989</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.0</td>
<td>0.2</td>
<td>0.7</td>
<td>3.0</td>
<td>6.8</td>
<td>19.6</td>
<td>42.8</td>
</tr>
<tr>
<td>Korea</td>
<td>1,204</td>
<td>-</td>
<td>-</td>
<td>0.0</td>
<td>0.0</td>
<td>0.2</td>
<td>0.7</td>
<td>2.3</td>
<td>6.7</td>
<td>16.2</td>
<td>35.9</td>
</tr>
<tr>
<td>Malaysia</td>
<td>508</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.6</td>
<td>2.2</td>
<td>6.3</td>
<td>14.7</td>
<td>34.7</td>
<td>57.0</td>
<td>127.3</td>
</tr>
<tr>
<td>Philippines</td>
<td>1,290</td>
<td>-</td>
<td>-</td>
<td>0.0</td>
<td>0.5</td>
<td>0.7</td>
<td>1.3</td>
<td>5.4</td>
<td>13.9</td>
<td>26.8</td>
<td>52.2</td>
</tr>
<tr>
<td>Singapore</td>
<td>125</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.2</td>
<td>5.3</td>
<td>13.9</td>
<td>37.4</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1,116</td>
<td>-</td>
<td>-</td>
<td>0.1</td>
<td>0.2</td>
<td>0.8</td>
<td>3.1</td>
<td>9.5</td>
<td>21.0</td>
<td>49.2</td>
<td>151.6</td>
</tr>
<tr>
<td>Thailand</td>
<td>683</td>
<td>-</td>
<td>0.0</td>
<td>0.1</td>
<td>-</td>
<td>0.5</td>
<td>0.8</td>
<td>3.4</td>
<td>9.3</td>
<td>19.3</td>
<td>58.1</td>
</tr>
</tbody>
</table>

Rates per 100,000. Rates based on less than 10 cases are *italicized*.

---

E) Prostate Cancer Incidence Top 20 in Asia [ASR]

GLOBOCAN 2008 (IARC)

F) Prostate Cancer Incidence Top 20 in The World [ASR]

GLOBOCAN 2008 (IARC)

G) Prostate Cancer Incidence Top 20 in Asia [cumulative risk, Age: 0-70]

H) Prostate Cancer in Hong Kong [2010]

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases registered</td>
<td>1,492</td>
<td>319</td>
</tr>
<tr>
<td>Rank</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Proportion of all cancers</td>
<td>10.7%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>72</td>
<td>79</td>
</tr>
<tr>
<td>Crude rate*</td>
<td>45.3</td>
<td>9.7</td>
</tr>
<tr>
<td>Age-standardized rate (world)**</td>
<td>28.1</td>
<td>5.5</td>
</tr>
<tr>
<td>Lifetime risk before age 75</td>
<td>1 in 31</td>
<td>1 in 290</td>
</tr>
<tr>
<td>Mortality: Incidence ratio</td>
<td></td>
<td>0.21</td>
</tr>
</tbody>
</table>

*All rates are expressed per 100,000  **Rates are standardized to the age distribution of the WHO 2000 World Standard Population. 
Source: Hong Kong Cancer Registry, Hospital Authority (Department of Health)
I) Prostate Cancer in Indonesia [stage distribution and Age distribution]
J) Prostate Cancer in Japan [J-CaP2010]

a) Distribution of Main Treatment

- Prostatectomy: 32%
- Radiation: 21%
- Primary Androgen Deprivation Therapy: 40%
- Others: 6%

b) Distribution of Main Treatment by Age & T Category

*The width of each age group and each T category represents percentage of patients.
K) Prostate Cancer in Taiwan [stage distribution in 2009 and 2010]

2009

- Stage I: 0.5%
- Stage II: 47.9%
- Stage III: 9.9%
- Stage IV: 27.0%
- Unknown: 14.7%

2010

- Stage I: 10.6%
- Stage II: 38.2%
- Stage III: 12.9%
- Stage IV: 33.2%
- Unknown: 5.1%

[Bureau of Health Promotion, Ministry of Health and Welfare]
L) Prostate Cancer in Thailand [stage distribution and mortality by age]

![Stage distribution](image)

![Mortality by age](image)

(information provided by the panelists)
<table>
<thead>
<tr>
<th>Country</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>There is national insurance and small portion of the population have private insurance.</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>No insurance scheme, subsidized healthcare provided by government. Many new drugs have to be self-financed by patients, with funding for poor income group for some drugs.</td>
</tr>
<tr>
<td>India</td>
<td>Private healthcare care insurance system covers about 10% population. Government and semi government establishment employees are covered free healthcare. We have government hospitals, where Govt subsidise the treatment and mostly free, whereas as new corporate hospitals are coming up in large number, treating insurance covered population or having employer-funded schemes.</td>
</tr>
<tr>
<td>Indonesia</td>
<td>An estimated 40% of Indonesian have some form of health insurance provided by the National Health Insurance scheme which covers the Government employees and low-income earners. Private insurance coverage is about 3% of the population.</td>
</tr>
<tr>
<td>Japan</td>
<td>There is a health-insurance system that covers all citizens. Private insurance is also widespread.</td>
</tr>
<tr>
<td>Korea</td>
<td>National health insurance covers all the treatment related with prostate cancer. (But it does not cover robotic surgery. Only private insurances support this treatment.)</td>
</tr>
<tr>
<td>Malaysia</td>
<td>There is no national insurance. Small portion of the population have private insurance. Treatments for government servants, retirees, and senior citizens (60 and above) are free in government hospital.</td>
</tr>
<tr>
<td>Philippines</td>
<td>For the gainfully employed population (50%), there is a national healthcare insurance called PhilHealth but this covers only about 30% of the cost of care for radical prostatectomy or radiation treatment; there is minimal coverage for androgen deprivation. Majority of patients pay out of pocket for their healthcare.</td>
</tr>
<tr>
<td>Singapore</td>
<td>Government mandated national insurance (Medisave, Medishield, Medifund) for different levels of coverage of basic hospitalization and medical care draw funds from worker’s monthly salary. The scheme requires patients to pay a deductible component upfront before insurance coverage kicks in. Additional coverage requires private insurance that is becoming more prevalent.</td>
</tr>
<tr>
<td>Taiwan</td>
<td>We have National Health Insurance for every citizen, with a salary-based monthly premium to the government.</td>
</tr>
<tr>
<td>Thailand</td>
<td>Universal Coverage Scheme (UCS): 74.6%, Civil Servant Medical Benefit Scheme (CSMBS): 8.01%, Compulsory Social Security Scheme (SSS): 12.9%, Private health insurance: 2.16%</td>
</tr>
</tbody>
</table>
## N) Clinical Guidelines in Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>Domestic clinical guidelines</th>
<th>Publication/Revision</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>Yes, By Chinese Urological Association</td>
<td>Published in 2007, Revised every two years; The 2013 ed. will come out soon.</td>
<td>No</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>No, No central guideline; There are guidelines and protocols for individual institute.</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>India</td>
<td>No</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Yes, By the Indonesian Urological Association</td>
<td>Published in 2012</td>
<td>No</td>
</tr>
<tr>
<td>Japan</td>
<td>Yes, By the Japanese Urological Association</td>
<td>Published in 2006, Revised in 2012</td>
<td>No</td>
</tr>
<tr>
<td>Korea</td>
<td>Yes, A translation form of NCCN guideline ver. 2007</td>
<td>Revised in 2013</td>
<td>NCCN GL</td>
</tr>
<tr>
<td>Malaysia</td>
<td>No</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>Philippines</td>
<td>Yes, AUA guidelines in 2005 were adopted with minor revisions regarding PSA screening and biopsy threshold.</td>
<td>Published in 2005, Revised in 2013</td>
<td>Yes</td>
</tr>
<tr>
<td>Singapore</td>
<td>Yes</td>
<td>Published in 2013 (The latest version 2012)</td>
<td>Yes</td>
</tr>
<tr>
<td>Taiwan</td>
<td>Yes Guidelines by: 1. National Health Research Institute 2. Individual medical centers (e.g. National Taiwan University Hospital)</td>
<td>1. Published in 1999, Revised in 2003 and 2010, 2. Published in 2000, Revised every year The 5th ed. (June 2013)</td>
<td>1. No 2. Yes</td>
</tr>
<tr>
<td>Thailand</td>
<td>Yes, By Thai Urological Association</td>
<td>Published in January 2013</td>
<td>No</td>
</tr>
</tbody>
</table>
O) Japanese Guidelines on the Treatment of Prostate Cancer

Clinical practice algorithm for prostate cancer 2012*
(The Japanese Urological Association)

Male, ≥50 years

Risk-benefit discussion and agreement about PSA test

PSA test

Normal PSA value

Abnormally high PSA value

Whole-body assessment
PSA re-evaluation
Digital rectal examination
Imaging

Diagnosis

PSA re-evaluation

Assessment by urologist

Other prostate diseases suspected

Prostate cancer suspected

TRUS-guided biopsy

Biopsy negative

Biopsy positive

Observation and/or adequate treatments

Staging

Clinically localized

Locally advanced

Metastatic

Low risk (D’Amico)

Intermediate risk (D’Amico)

High risk (D’Amico)

Initial therapy

Active Surveillance

Surgery

Radiation therapy

Hormone therapy

Discussion and agreement about the initial therapy

Translated into English from Japanese Clinical Guideline by a ACS member.
P) Philippine Urological Association Clinical Practice Guidelines for the Management of Prostate Cancer

Q) Major Drugs for the Treatment of Prostate Cancer and Drugs Under Study

<table>
<thead>
<tr>
<th>Country</th>
<th>Approved</th>
<th>Application filed</th>
<th>Under study</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>Bicalutamide, Dexamethasone, Docetaxel, Estramustine phosphate, Flutamide, Goserelin acetate</td>
<td>Leuprolrel acetate, Prednisolone, Strontium (89Sr) chloride, Triptorelin pamoate, Zoledronic acid</td>
<td>Abiraterone acetate, Degarelix acetate, Radium-223 dichloride, Enzalutamide</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>Abiraterone acetate, Bicalutamide, Cabazitaxel, Degarelix acetate, Denosumab, Docetaxel</td>
<td>Flutamide, Goserelin acetate, Leuprolrel acetate, Triptorelin pamoate, Zoledronic acid</td>
<td>Enzalutamide*, Radium-223 dichloride* *Pending registration</td>
</tr>
<tr>
<td>India</td>
<td>Bicalutamide, Dexamethasone, Docetaxel, Estramustine phosphate, Flutamide, Goserelin acetate</td>
<td>Leuprolrel acetate, Prednisolone, Strontium (89Sr) chloride, Triptorelin pamoate, Zoledronic acid</td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td>Bicalutamide, Cabazitaxel, Cyproterone acetate, Docetaxel</td>
<td>Flutamide, Goserelene acetate, Leuprolrel acetate, Zoledronic acid</td>
<td>Abiraterone acetate</td>
</tr>
</tbody>
</table>

Note: Data based on information as of December 2013 collected from the panelists.
Q) Major Drugs for the Treatment of Prostate Cancer and Drugs Under Study

<table>
<thead>
<tr>
<th>Country</th>
<th>Approved</th>
<th>Application filed</th>
<th>Under study</th>
</tr>
</thead>
</table>
| **Japan** | • Betamethasone  
• Bicalutamide  
• Chlormadinone acetate  
• Degarelix acetate  
• Denosumab  
• Dexamethasone  
• Docetaxel  
• Estramustine phosphate | • Ethinylestradiol  
• Flutamide  
• Goserelin acetate  
• Leuprorelin acetate  
• Prednisolone  
• Strontium (89Sr) chloride  
• Zoledronic acid | • Abiraterone acetate  
• Cabazitaxel  
• Enzalutamide | • Enzalutamide  
• ITK-1 [personalized peptide vaccine]  
• Orteronel [androgen synthesis inhibitor]  
• Radium-223 dichloride |
| **Korea** | • Abiraterone acetate  
• Bicalutamide  
• Cyproterone acetate  
• Docetaxel  
• Estramustine phosphate  
• Flutamide | • Goserelin acetate  
• Leuprolide acetate  
• Mitoxantrone  
• Strontium (89Sr) chloride  
• Triptorelin pamoate  
• Zoledronic acid | • Degarelix  
• Enzalutamide  
• Radium-223 dichloride | • Enzalutamide  
• Orteronel [androgen synthesis inhibitor]  
• Radium-223 dichloride |
| **Malaysia** | • Abiraterone acetate  
• Bicalutamide  
• Cabazitaxel  
• Cyproterone acetate  
• Degarelix acetate  
• Denosumab | • Diptherelin  
• Docetaxel  
• Flutamide  
• Goserelin acetate  
• Leuprolide acetate  
• Zoledronic acid | • Enzalutamide | |

Note: Data based on information as of December 2013 collected from the panelists.
### Q) Major Drugs for the Treatment of Prostate Cancer and Drugs Under Study

<table>
<thead>
<tr>
<th>Country</th>
<th>Approved</th>
<th>Application filed</th>
<th>Under study</th>
</tr>
</thead>
</table>
| Philippines | • Abiraterone acetate  
• Bicalutamide  
• Cyproterone acetate  
• Denosumab  
• Docetaxel | • Flutamide  
• Goserelin acetate  
• Leuprorelin acetate  
• Triptorelin pamoate  
• Zoledronic acid | • Cabazitaxel  
• Degarelix acetate |
| Singapore | • Abiraterone acetate  
• Bicalutamide  
• Cabazitaxel  
• Denosumab | • Docetaxel  
• Gosereline acetate  
• Leuprorelin acetate  
• Zoledronic acid | • Enzalutamide  
• Degarelix acetate  
• Radium-223 dichloride  
• Orteronel  
[androgen synthesis inhibitor] |
| Taiwan | • Bicalutamide  
• Cabazitaxel  
• Cyproterone acetate  
• Degarelix acetate  
• Denosumab  
• Docetaxel | • Flutamide  
• Goserelin acetate  
• Leuprorelin acetate  
• Triptorelin pamoate  
• Zoledronic acid | • Abiraterone acetate  
• Enzalutamide  
• Radium-223 dichloride  
• ARN-509  
[antiandrogen]  
• Orteronel  
[androgen synthesis inhibitor] |
| Thailand | • Abiraterone acetate  
• Bicalutamide  
• Cabazitaxel  
• Ciproterone acetate  
• Docetaxel | • Flutamide  
• Gosereline acetate  
• Leuprorelin acetate  
• Zoledronic acid | • Radium-223 dichloride |

Note: Data based on information as of December 2013 collected from the panelists.