National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Bladder Cancer

Asia Consensus Statements Version 1

[2016]

–Based upon NCCN Guidelines Bladder Cancer Version 2.2015–

NCCN.org

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Conflict of Interest (COI)

All panel members have disclosed COI associated with the Asia Consensus Statements of NCCN Guidelines (NCCN ACS). For more information, please contact the NCCN ACS secretariat.

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Preamble

Authorization

The National Comprehensive Cancer Network® (NCCN®) supports and authorizes selected disease-specific expert oncology groups to develop the Asia Consensus Statements (ACS) 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 ultimate goal of improving the lives of patients with cancer in Asia.

Genesis and Development Process

This collaborative project was initiated by NCCN and Reno Medical K.K. (M3 group). The formation of the disease-specific panel of Asian experts is the first step for the development of the ACS for the specific tumor type. The chair and members of the NCCN panel are then nominated to discuss, develop, and approve manuscripts. Each disease-specific consensus discussion includes assessing the pertinent sections of the latest NCCN Guidelines for potential adaptation. The agreed-upon modifications to the recommendations in the NCCN Guidelines are documented, categorized, and supported with evidence wherever possible, and are validated and approved by 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 the final consensus reached by the panel is based on the NCCN categories of evidence:

Category	Level of evidence*	Level of consensus
1	High	Uniform
2A	Lower	Uniform
2B	Lower	Non-uniform
3	Any	Major disagreement

*High-level evidence includes randomized, controlled clinical trials and meta-analyses. Typically, high-level evidence is 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 potential high-level evidence (presented at major meetings but before peer-reviewed publications).

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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Application of This Document

The statements contained herein are with reference to NCCN Guidelines: Bladder Cancer (Version 2.2015). As such, for contextual comprehension of the statements, refer to the version of NCCN Guidelines: Bladder Cancer noted above. To view the most recent and complete versions of all NCCN Guidelines, visit www.nccn.org. 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 NCCN Guidelines: Bladder Cancer (Version 2.2015). As NCCN is committed to maintaining up-to-date NCCN Guidelines, NCCN and the Asian panel members are likewise committed to the provision of comprehensive ACS which will be updated from time to time. All persons who use NCCN guidelines and the statements should note that the recommendations are applicable to 80 - 85% of patients, and if less than 5% of patients fall into a particular situation, there may not be any recommendations in the guidelines nor the statements 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 no treatment guideline will fit 100% of patients for 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 among countries. This should be discussed in the future for the ACS.

NCCN Guidelines have reached an ideal level of care, and now is on the step toward being a global standard. As described above, there is no clinical practice guideline covering whole world without any complementation or regional adaptation. We hope that the ACS works as a bridge between NCCN Guidelines and Asian clinical practice, and helps people who aspire for a treatment framework of cancer.

Bladder Cancer Overview

— The Asian Landscape and Asia Consensus Statements

An estimated 148,568 new cases of bladder cancer would be diagnosed in Asian countries (115,646 men and 32,922 women) in 2012.[1] Bladder cancer is the 14th most common cancer in Asia, while 4th in the United States and 11th in the world. During the same period, approximately 69,294 deaths (52,816 men and 16,478 women) resulted from bladder cancer in Asian countries.
An estimated age-standardized rate (ASR) of incidence of bladder cancer shows variety in Asian countries. In the GLOBOCAN data, ASRs (per 100,000) of incidence of bladder cancer were between 1.5 in the Philippines and 5.6 in Japan, while that in the United States was 11.6 in 2012.[1] There is a marked difference in the incidence rate of bladder cancer among the United States and Asian countries.

Some of the imaging modalities listed in NCCN Guidelines may be unavailable at some facilities and centers in Asian countries. Moreover, BCG is not approved for use in adjuvant intravesical treatment in some Asian countries.
It is therefore difficult to establish the unified clinical practice guidelines for bladder cancer in Asia or introduce the Western guidelines directly into Asian countries. However, a certain consensus would be derived from accumulation of data and experience for Asian region. Consequently the Asia Consensus Statements (ACS) of NCCN Guidelines for Bladder Cancer can be produced like those for kidney and prostate cancers.

The ACS of NCCN Guidelines for Bladder Cancer Ver.1 [2016] were produced under the auspices of the following academic organizations; Asia Pacific Society of Uro-oncology, Japan Society of Clinical Oncology, and the Korean Urological Oncology Society.

Reference

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Elser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 24/4/2015.

Asia Consensus Statements (ACS)

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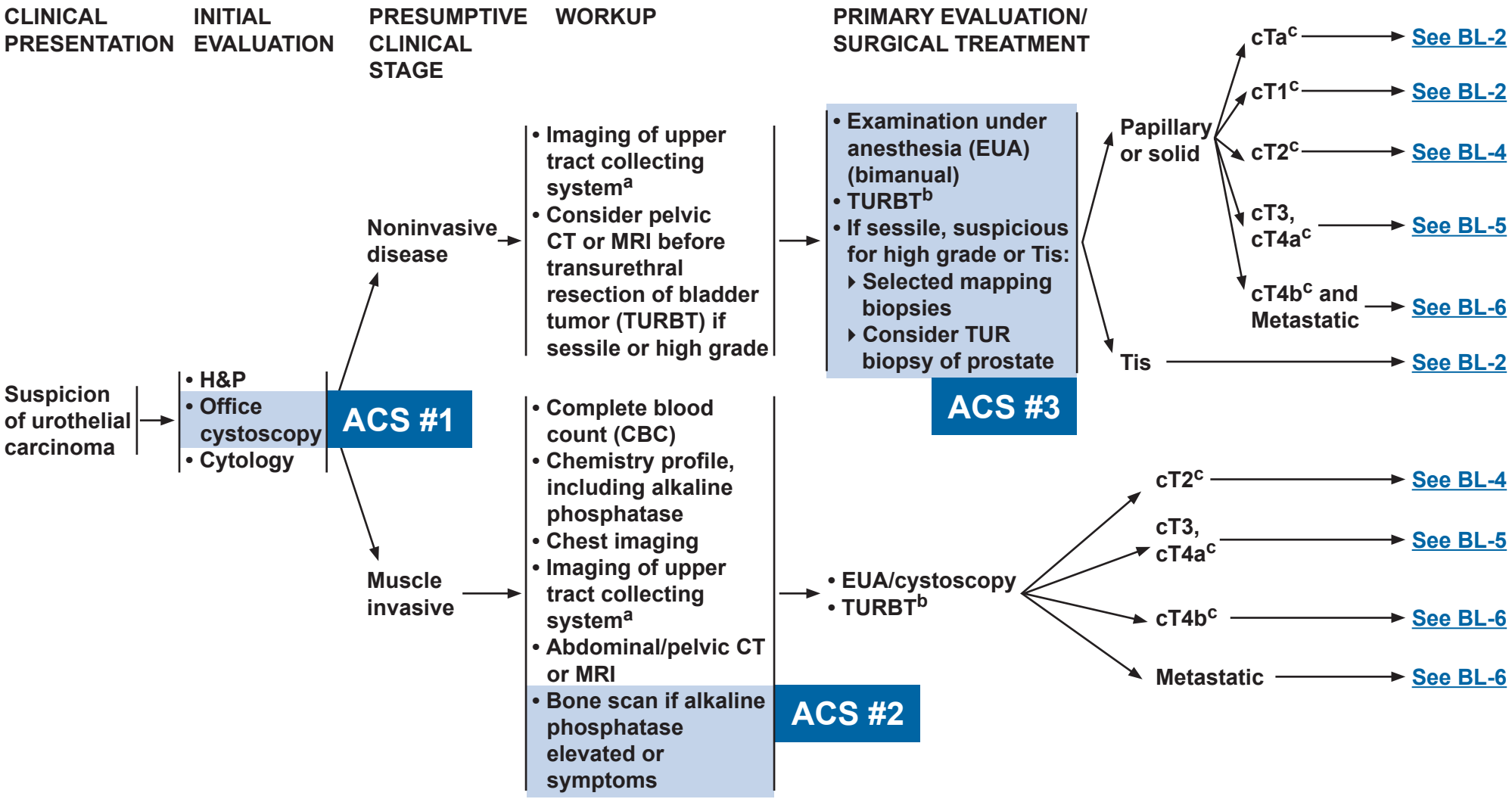

[a]Imaging may include one or more of the following: CT urography, renal ultrasound or CT without contrast with retrograde pyelogram, ureteroscopy, or MRI urogram.

ACS #4

[b]See Principles of Surgical Management (BL-A).

[c]The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection) and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.

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.

ACS #1: Cystoscopy for Initial Evaluation

The popular use of either a rigid or a flexible cystoscopy is varied among Asian countries.

[Cross ref: Guidelines page BL-1]

Discussion:

A rigid cystoscopy is usually used in China,[1,2] the Philippines and Taiwan while either a rigid or a flexible cystoscopy is used in each facility in other countries.

Reference

1. Shen YJ, Zhu YP, Ye DW, et al. Narrow-band imaging flexible cystoscopy in the detection of primary non-muscle invasive bladder cancer: a "second look" matters? Int Urol Nephrol 2012;44(2):451-457.
2. Zhu YP, Shen YJ, Ye DW, et al. Narrow-band imaging flexible cystoscopy in the detection of clinically unconfirmed positive urine cytology. Urol Int 2012;88(1):84-87.

ACS #2: Bone Scan for Muscle Invasive Bladder Cancer

The criteria for bone scan in some Asian countries are different from those in the others.

[Cross ref: Guidelines page BL-1]

Discussion:

In the Philippines, symptomatic patients or those who present with elevated alkaline phosphatase usually get a bone scan. In Japan, however, bone scan is a common practice for patients with muscle invasive bladder cancer, regardless of their alkaline phosphatase level and symptoms. In other Asian countries, bone scan is performed if the patient has an elevated alkaline phosphatase level or is symptomatic.[1,2]

Reference

1. Brismar J, Gustafson T. Bone scintigraphy in staging of bladder carcinoma. Acta Radiol 1988;29(2):251-252.
2. Braendengen M, Winderen M, Fossa SD. Clinical significance of routine pre-cystectomy bone scans in patients with muscle-invasive bladder cancer. Br J Urol 1996;77(1):36-40.

ACS #3: Primary Evaluation/Surgical Treatment for Non-Muscle Invasive Bladder Cancer (NMIBC)

- **TURBT**
- **If sessile, suspicious for high grade or Tis:**
  - **Mapping biopsies for selected patients**
  - **Consider TUR biopsy of prostate**

[Cross ref: Guidelines page BL-1]

Discussion:

Bimanual examination is easy to do but its clinical importance and usefulness are controversial in many Asian countries. This method was deleted in the latest clinical guidelines in Japan and South Korea. However, bimanual examination during cystoscopy is mandatory in the Philippines.

In the Philippines, mapping biopsies are recommended in patients with grossly suspicious mucosa. In China and Japan, random (pre-selected) biopsies at TURBT are recommended for risk stratification when concomitant carcinoma *in situ* (CIS) is suspected. If tumors in the trigone or bladder neck, or multiple tumors are present, the biopsy of prostatic urethra is also recommended.[1-3] In South Korea, it is important to consider the damage to the urothelium and the risk of tumor implantation, so mapping biopsies are indicated for patients planned for partial cystectomy or with unidentifiable/superficial-only tumor despite positive cytology. In Singapore, mapping biopsies are to pick up CIS, and the prostate biopsy is to facilitate planning for cystectomy. In Indonesia, mapping biopsies are recommended in patients with positive

cytology without visible tumor during cystoscopy. In Thailand, mapping biopsies are performed in patients with suspicion of CIS.

Reference

1. Matzkin H, Soloway MS, Hardeman S. Transitional cell carcinoma of the prostate. J Urol 1991;146(5):1207-1212.
2. Mungan MU, Canda AE, Tuzel E, et al. Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. Eur Urol 2005;48(5):760-763.
3. Liedberg F, Anderson H, Bläckberg M, et al. Prospective study of transitional cell carcinoma in the prostatic urethra and prostate in the cystoprostatectomy specimen. Incidence, characteristics and preoperative detection. Scand J Urol Nephrol 2007;41(4):290-296.

ACS #4: Imaging of Upper Tract Collecting System

Imaging may include one or more of the following:

- **CT urography**
- **Renal ultrasound or CT without contrast with retrograde pyelogram**
- **Ureteroscopy**
- **MRI Urogram**
- **IVP or IVU**

[Cross ref: Guidelines page BL-1]

Discussion:

CT is the first choice for the workup of non-muscle invasive bladder cancer (NMIBC) in many Asian countries. In South Korea, chest CT is not routinely performed but is considered if abnormal findings are detected on plain chest x-ray. In Japan, CT and bone scintigraphy are used for N and M staging, and positron emission tomography (PET) is also an option.[1]

In Japan, MRI is mainly used for clinical T staging.[2,3] In South Korea, it is believed to be helpful in suspicious cases of >T3 or invasion to pelvic bone. In the Philippines, MRI is used only for selected cases wherein better delineation of possible extra-vesical extension is considered.

Both intravenous pyelogram (IVP) and intravenous urography (IVU) are important for the detection of cancer in the renal pelvis and ureter.[4] However, IVP and IVU are rarely used in many Asian countries except for facilities lacking other modalities such as CT and MRI. In fact, IVP and IVU could substitute for imaging during CT urography.

Reference

1. Lu YY, Chen JH, Liang JA, et al. Clinical value of FDG PET or PET/CT in urinary bladder cancer: a systemic review and meta-analysis. Eur J Radiol 2012;81(9):2411-2416.
2. Schrier BPH, Witjes JA, Narumi Y, et al. Imaging in the assessment of urinary bladder carcinoma. In: Lerner SP, Schoenberg MP, Sternberg CN, eds. Textbook of Bladder Cancer, Taylor & Francis/Abington, 2006;p191-205.
3. Green DA, Durand M, Gumpeni N, et al. Role of magnetic resonance imaging in bladder cancer: current status and emerging techniques. BJU Int 2012;110(10):1463-1470.
4. European Association of Urology. Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1 and CIS). European Association of Urology Guidelines. 2014 edition, p10-16.

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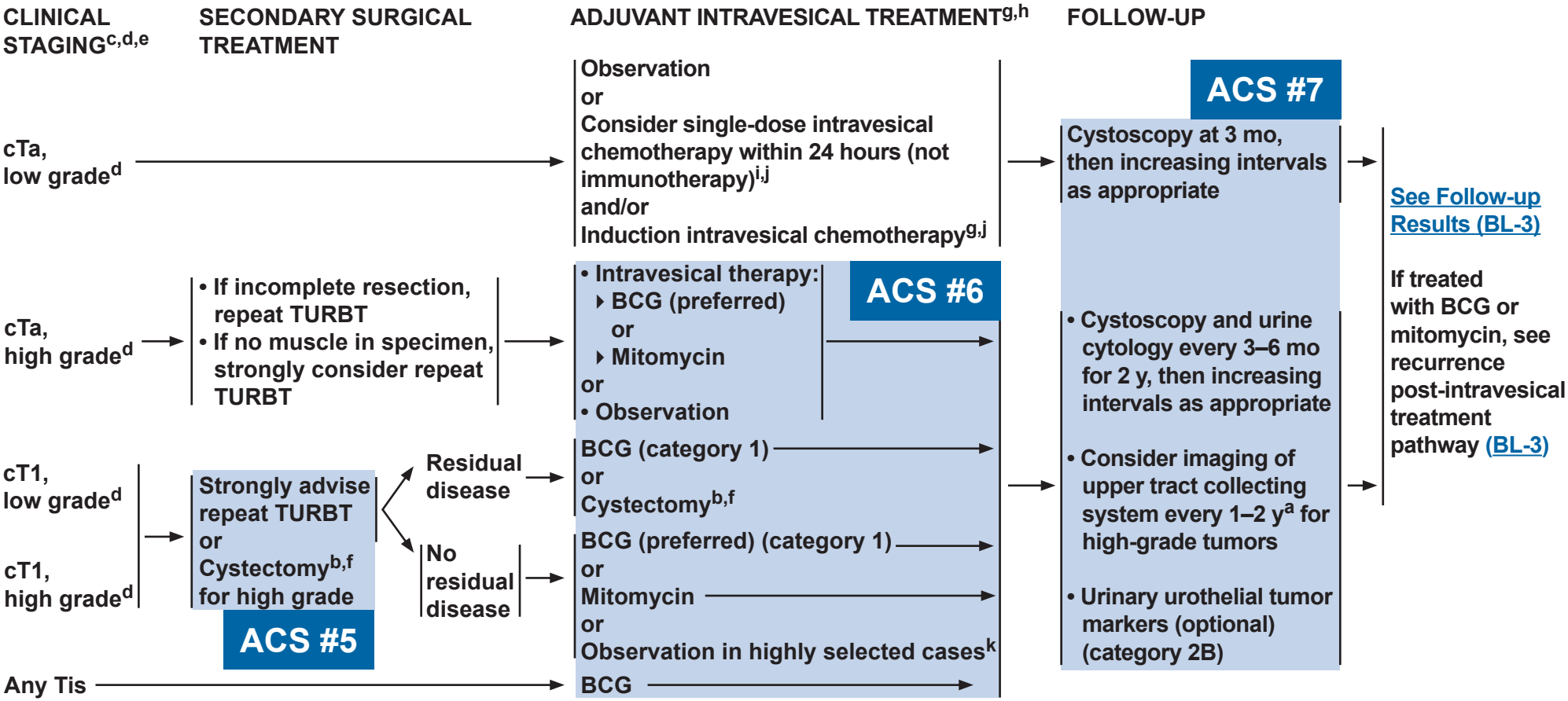


[a]Imaging may include one or more of the following: CT urography, renal ultrasound or CT without contrast with retrograde pyelogram, ureteroscopy, or MRI urogram.

[b]See Principles of Surgical Management (BL-A).

[c]The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection) and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.

[d]Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153. See Principles of Pathology Management (BL-B)

[e]See Probability of Recurrence (BL-C) and Non-Urothelial Cell Carcinoma of the Bladder (BL-D).

[f]See Follow-Up After Cystectomy and Bladder Preservation (BL-E).

[g]Indications for adjuvant therapy: Based on probability of recurrence and progression to muscle-invasive disease, such as size, number, and grade.

[h]See Principles of Intravesical Treatment (BL-F).

[i]Immediate intravesical chemotherapy, not immunotherapy, may decrease recurrence.

[j]Although there is no intravesical chemotherapy standard for cTa low grade, mitomycin is most commonly used.

[k]Highly selected cases with small-volume tumors with limited lamina propria invasion and no CIS.

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.

ACS #5: Treatment for cT1 after Primary Evaluation

- **Strongly advice repeat TURBT**
- **Cystectomy for high grade with additional conditions in some Asian countries**

[Cross ref: Guidelines page BL-2]

Discussion:

Routine repeat transurethral resection is advised to non-muscle invasive bladder cancer patients.[1,2] In Indonesia, radical cystectomy for cT1 high grade is recommended when the patient has multiple >3 cm tumors. In South Korea, radical cystectomy is deemed as a salvage treatment after the failure of bladder preservation or BCG therapy or when any unresectable tumor exists. In Japan, cystectomy is recommended in patients for whom BCG has failed, in those with micropapillary or large high grade T1 tumors, and in those with positive margins in the second TUR specimen. In Taiwan and Thailand, cystectomy is considered only for T1 high grade. Repeat TURBT is called second TURBT in Asian countries.
In the Philippines, partial cystectomy is also recommended if feasible.

Reference

1. Schwaibold HE, Sivalingam S, May F, et al. The value of a second transurethral resection for T1 bladder cancer. BJU Int 2006;97(6):1199-1201.
2. Shen YJ, Ye DW, Yao XD, et al. Repeat transurethral resection for non-muscle invasive bladder cancer. Chin J Surg 2009;47(10):725-727.

ACS #6: Adjuvant Intravesical Treatment for High-Grade NMIBC

Chemotherapy is used for adjuvant intravesical treatment after TURBT if BCG is not available.

[Cross ref: Guidelines page BL-2]

Discussion:

Tice strain of BCG is used in South Korea and Taiwan, while Tokyo 172 and Connaught strains are used in Japan.[1,2] BCG is not available in some Asian countries, such as Indonesia. In these countries, chemotherapy is used as an adjuvant intravesical treatment after TURBT. Preference for using doxorubicin or mitomycin-C varies in each country. Also, gemcitabine is used for patients who failed BCG, doxorubicin, and mitomycin-C. In Japan, South Korea, and Thailand, the recommended regimen of intravesical BCG for CIS is once weekly for 6-8 weeks as induction therapy;[2,3] and every 3 months for 1 year; and every 6 months for the next 2 years as maintenance therapy.

Reference

1. Akaza H, Hinotsu S, Aso Y, et al. Bacillus Calmette-Guérin treatment of existing papillary bladder cancer and carcinoma in situ of the bladder. Four-year results. The Bladder Cancer BCG Study Group. Cancer 1995;75(2):552-559.
2. Akaza H, Koiso K, Ozono S, et al. PMCJ-9 Study Group in Japan. A clinical study of PMCJ-9 (Bacillus Calmette-Guérin Connaught strain) treatment of superficial bladder cancer and carcinoma in situ of the bladder. Jpn J Clin Oncol 2003;33(8):382-390.
3. Hinotsu S, Akaza H, Isaka S, et al. Sustained prophylactic effect of intravesical bacille Calmette-Guérin for superficial bladder cancer: A smoothed hazard analysis in a randomized prospective study. Urology 2006;67(3):545-549.

ACS #7: Follow-up after Adjuvant Intravesical Treatment

Most Asian centers have a check using cystoscopy at 3 months after adjuvant intravesical treatment, then increasing intervals as appropriate.

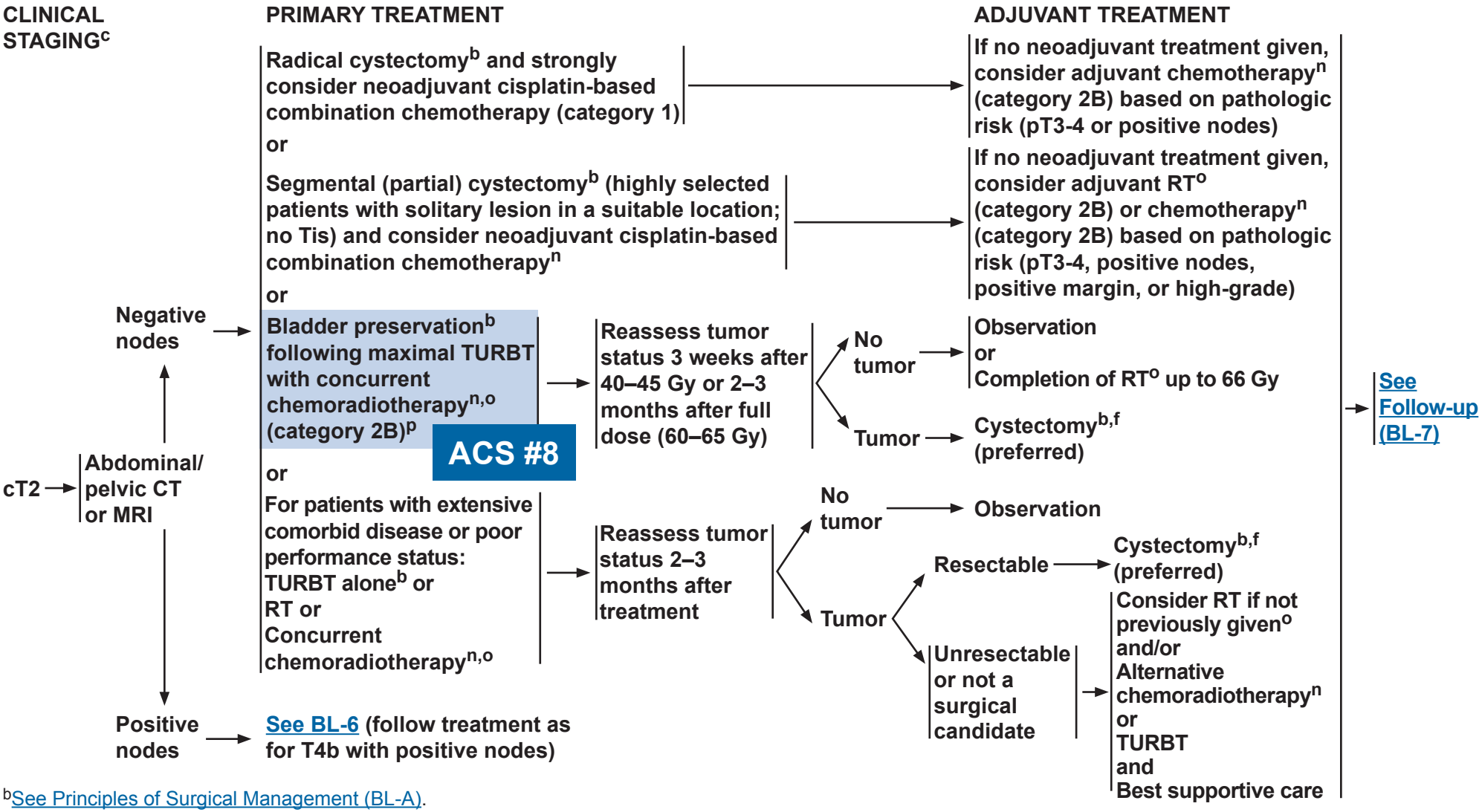
[Cross ref: Guidelines page BL-2]

Discussion:

In the Philippines, cystoscopy is performed every 3 months for at least 1 year. In Taiwan, cystoscopy is conducted every 3 months for 1 year, and then increasing intervals as appropriate. In China and Japan, cystoscopy is carried out every 3 months for 2 years, and then increasing intervals as appropriate.[1,2] Urinary urothelial markers such as nuclear matrix protein 22 (NMP22) and bladder tumor antigen (BTA) can be used in Asian countries. In Japan, NMP22 is approved as a screening test by the national health insurance system only for patients with a strong suspicion for urothelial carcinoma, while BTA is used for the detection of recurrent bladder cancer. In China and Indonesia, NMP22 is used but is not mentioned in the clinical guidelines and is uncommon, respectively. In South Korea, cytology and NMP22 are common practices and covered by the health insurance, although routine urine cytology can be cost-ineffective for the follow-up of NMIBC.[3] In the Philippines, both NMP22 and BTA are unavailable.

Reference

1. Solsona E, Iborra I, Dumont R, et al. The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. J Urol 2000;163(3 pt 1):685-689.
2. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49(3):466-477.
3. Ok BG, Ji YS, Ko YH, et al. Usefulness of urine cytology as a routine work-up in the detection of recurrence in patients with prior non-muscle-invasive bladder cancer: practicality and cost-effectiveness. Korean J Urol 2014;55(10):650-655.



[b] See Principles of Surgical Management (BL-A).
[c] The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection) and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[f] See Follow-Up After Cystectomy and Bladder Preservation (BL-E).
[n] See Principles of Chemotherapy Management (BL-G).
[o] See Principles of Radiation Management of Invasive Disease (BL-H).
[p] There are data to support equivalent survival rates, but not uniform consensus about the role of these approaches. Not all institutions have experience with these multidisciplinary treatment approaches, which require a dedicated team.

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.

ACS #8: Bladder Preservation for cT2

Perioperative treatments for bladder preservation vary considerably among Asian countries.

[Cross ref: Guidelines page BL-4]

Discussion:

In South Korea, radiation therapy for bladder preservation can be an option for patients for whom radical cystectomy is unsuitable. In the Philippines, many cT2 patients undergo radical cystectomy because of high cost for neoadjuvant chemotherapy plus radiation. In China, standard TURBT + radiation + adjuvant chemotherapy is more common for bladder preservation than neoadjuvant chemotherapy. In Japan, some novel bladder preservation therapies have been examined.[1-4] In Taiwan, maximal TURBT followed by concurrent chemoradiotherapy with or without neoadjuvant chemotherapy is an option for selected patients.[5]

In Taiwan, radiotherapy with full course of 60-65 Gy is followed by cystoscopic re-evaluation for the response 2-3 months later. If residual tumor is documented, cystectomy is recommended. The alternative practice is the interval cystoscopic re-evaluation in the middle of radiotherapy course, at 1-3 weeks after 40-45 Gy. If residual disease is documented, cystectomy is recommended. If no residual disease is identified and the cytology/biopsy are negative, completion of full-course radiotherapy up to 66 Gy is recommended.

Reference

1. Azuma H, Inamoto T, Ibuki N, et al. Novel bladder preservation therapy for locally invasive bladder cancer: combined therapy using balloon-occluded arterial infusion of anticancer agent and hemodialysis with concurrent radiation. Int J Oncol 2010;37(4):773-785.
2. Azuma H, Inamoto T, Takahara K, et al. Effect of a novel bladder preservation therapy, BOAI-CDDP-radiation (OMC-regimen). Int J Oncol 2013;43(1):79-87.
3. Miyanaga N, Akaza H, Hinotsu S, et al. Background Variables for the Patients with Invasive Bladder Cancer Suitable for Bladder-preserving Therapy. Jpn J Clin Oncol 2007;37(11):852-857.
4. Koga F, Kihara K, Yoshida S, et al. Selective bladder-sparing protocol consisting of induction low-dose chemoradiotherapy plus partial cystectomy with pelvic lymph node dissection against muscle-invasive bladder cancer: oncological outcomes of the initial 46 patients. BJU Int 2012;109(6):860-866.
5. Lin CC, Hsu CH, Cheng JC, et al. Induction cisplatin and fluorouracil-based chemotherapy followed by concurrent chemoradiation for muscle-invasive bladder cancer. Int J Radiat Oncol Biol Phys 2009;75(2):442-448.

PRINCIPLES OF CHEMOTHERAPY MANAGEMENT

Perioperative chemotherapy (neoadjuvant or adjuvant)

- **Regimens**
  - **DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3 or 4 cycles[1,2]**
  - **Gemcitabine and cisplatin for 4 cycles[3,4]**
  - **CMV (cisplatin, methotrexate, and vinblastine) for 3 cycles[5]**

ACS #9

- **Randomized trials and meta-analyses show a survival benefit for cisplatin-based neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer.[1,6,7]**
- **Meta-analysis suggests a survival benefit to adjuvant therapy for pathologic T3, T4 or N+ disease at cystectomy.[7]**
- **Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.**
- **DDMVAC is preferred over standard MVAC based on category 1 evidence showing DDMVAC to be better tolerated and more effective than conventional MVAC in advanced disease.[2,8] Based on these data, the traditional dose and schedule for MVAC is no longer recommended.**
- **Perioperative gemcitabine and cisplatin is a reasonable alternative to DDMVAC based on category 1 evidence showing equivalence to conventional MVAC in the setting of advanced disease.[4,9]**
- **For gemcitabine/cisplatin, both 21- and 28-day regimens are acceptable. Better dose compliance may be achieved with fewer delays in dosing using the 21-day schedule.[10]**
- **Neoadjuvant chemotherapy may be considered for select patients with upper tract urothelial carcinoma, particularly for higher stage and/or grade tumors, as renal function will decline after nephroureterectomy and may preclude adjuvant therapy.**
- **Carboplatin should not be substituted for cisplatin in the perioperative setting.**
  - **For patients with borderline renal function or minimal dysfunction, a split-dose administration of cisplatin may be considered (such as 35 mg/m^2 on days 1 and 2 or days 1 and 8) (category 2B). While safer, the relative efficacy of the cisplatin-containing combination administered with such modifications remains undefined.**
  - **For patients who are not candidates for cisplatin, there are no data to support a recommendation for perioperative chemotherapy.**

Continued on BL-G 2 of 4 and BL-G 3 of 4

References on BL-G 4 of 4

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.

ACS #9: Perioperative Chemotherapy (Neoadjuvant or Adjuvant)

- **Regimens**
  - **MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) with or without growth factor support for 3 or 4 cycles**
  - **Gemcitabine and cisplatin for 4 cycles**
  - **CMV (cisplatin, methotrexate, and vinblastine) for 3 cycles**

[Cross ref: Guidelines page BL-G 1 of 4]

Discussion:

Both MVAC and GC (gemcitabine and cisplatin) are available in all Asian countries. In some Asian countries, GC is the first-line chemotherapy. Growth factor support in the treatment of MVAC depends on the patient's condition.

In China, adjuvant GC is commonly used with growth factor for 4 to 6 cycles. In Japan, MVAC is performed for 2 or 3 cycles.[1]

Some panel members mentioned that dose-dense MVAC (DDMVAC) has a high risk of side effects. Another panel member, however, suggested that DDMVAC should be considered as an option for perioperative chemotherapy.

Reference

1. Kitamura H, Tsukamoto T, Shibata T, et al. Randomised phase III study of neoadjuvant chemotherapy with methotrexate, doxorubicin, vinblastine and cisplatin followed by radical cystectomy compared with radical cystectomy alone for muscle-invasive bladder cancer: Japan Clinical Oncology Group study JCOG0209. Ann Oncol 2014;25(6):1192-1198.

PRINCIPLES OF RADIATION MANAGEMENT OF INVASIVE DISEASE

Carcinoma of the Bladder

- Precede radiation therapy alone or concurrent chemotherapy and radiation by maximal TUR of the tumor when safely possible.
- Simulate and treat patients when they have an empty bladder. **ACS #10**
- Use multiple fields from high-energy linear accelerator beams.
- For invasive tumors, consider low-dose preoperative radiation therapy prior to segmental cystectomy (category 2B).
- Concurrent chemotherapy and radiation therapy or radiation therapy alone is most successful for patients without hydronephrosis and without extensive carcinoma in situ associated with their muscle-invading tumor.
- For patients with stage Ta, T1, or Tis, external beam radiation therapy (EBRT) alone is rarely appropriate. For patients with recurrent Ta-T1 disease usually following BCG therapy but without extensive Tis who are not candidates for cystectomy, concurrent chemotherapy and radiation therapy may be considered as a potentially curative alternative to radical cystectomy, which is the standard treatment by NCCN Guidelines.
- Treat the whole bladder with or without pelvic lymph nodes with 40 to 45 Gy and then boost the bladder tumor to a total dose up to 66 Gy excluding, if possible, normal areas of the bladder from the high-dose volume.
- When irradiating the bladder only or bladder tumor boost, consider daily image guidance.
- Concurrent chemotherapy with radiation therapy is encouraged for added tumor cytotoxicity, and can be given without increased toxicity over radiation therapy alone. Concurrent 5-FU and mitomycin C can be used instead of cisplatin in patients with low or moderate renal function. Such therapy is optimally given by dedicated multidisciplinary teams.
- Concurrent chemotherapy with radiation therapy or radiation therapy alone should be considered as potentially curative therapy for medically inoperable patients or for local palliation in patients with metastatic disease.
- When giving palliative radiation for metastatic bladder cancer or for recurrent pelvic tumor, combining radiation with radiosensitizing chemotherapy should be considered. See BL-G 3 of 4 for agents. Chemotherapy should not be used concurrently with high-dose (>3 Gy per fraction) palliative radiation.

Continued on next page

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.

ACS #10: Principles of Radiation Management of Invasive Disease

The sentence "Simulate and treat patients when they have an empty bladder." is acceptable in many Asian countries.

[Cross ref: Guidelines page BL-H 1 of 2]

Discussion:

In some Asian countries, simulation and treatment are performed when patients have an empty or a full bladder, based on the simulation specifications.

Table 1 (Continued)

American Joint Committee on Cancer (AJCC)
TNM Staging System for Bladder Cancer (7th ed., 2010)

Clinical Staging
Primary tumor assessment includes bimanual examination under anesthesia before and after endoscopic surgery (biopsy or transurethral resection) and histologic verification of the presence or absence of tumor when indicated. Bimanual examination following endoscopic surgery is an indicator of clinical stage. The finding of bladder wall thickening, a mobile mass, or a fixed mass suggests the presence of T3 and/or T4 disease, respectively. Appropriate imaging techniques for extravesical extension of the primary tumor and lymph node evaluation should be incorporated into clinical staging. When indicated, evaluation for distant metastases includes imaging of the chest, biochemical studies, and isotopic studies to detect common metastatic sites.

Pathologic Staging
Microscopic examination and confirmation of extent are required. Total cystectomy and lymph node dissection generally are required for this staging; however, a pathologic staging classification should be given for partial cystectomy specimens. Laterality does not affect the N classification.

ACS #11

Histologic Grade (G)
For urothelial histologies, a low- and high-grade designation is used to match the current World Health Organization/International Society of Urological Pathology (WHO/ISUP) recommended grading system:

LG Low grade
HG High grade

If a grading system is not specified, generally the following system is used:

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Histopathologic Type
The histologic types are as follows:

Urothelial (transitional cell) carcinoma
- In situ
- Papillary
- Flat
- With squamous differentiation
- With glandular differentiation
- With squamous and glandular differentiation

Squamous cell carcinoma
Adenocarcinoma
Undifferentiated carcinoma

The predominant cancer is urothelial (transitional cell) carcinoma. Histologic variants include micropapillary and nested subtypes.

ACS #11: Pathologic Staging

TNM staging system of AJCC (7th ed., 2010) in the NCCN Guidelines is different from that of UICC (7th ed., 2009).

[Cross ref: Guidelines page ST-2]

Discussion:

In many Asian countries, there is no disagreement with the NCCN parent Guidelines that pathologic ("p") staging cannot be made without radical cystectomy.

In Japan and South Korea, however, "p" staging can be made using an endoscopically-sampled specimen (biopsy or TUR). In Taiwan, "p" staging is made in some facilities if muscle layer is included in an endoscopically-sampled specimen. In the Philippines, deep muscle biopsies are mandatory in TURBT to get an accurate pathologic staging of the primary tumor.

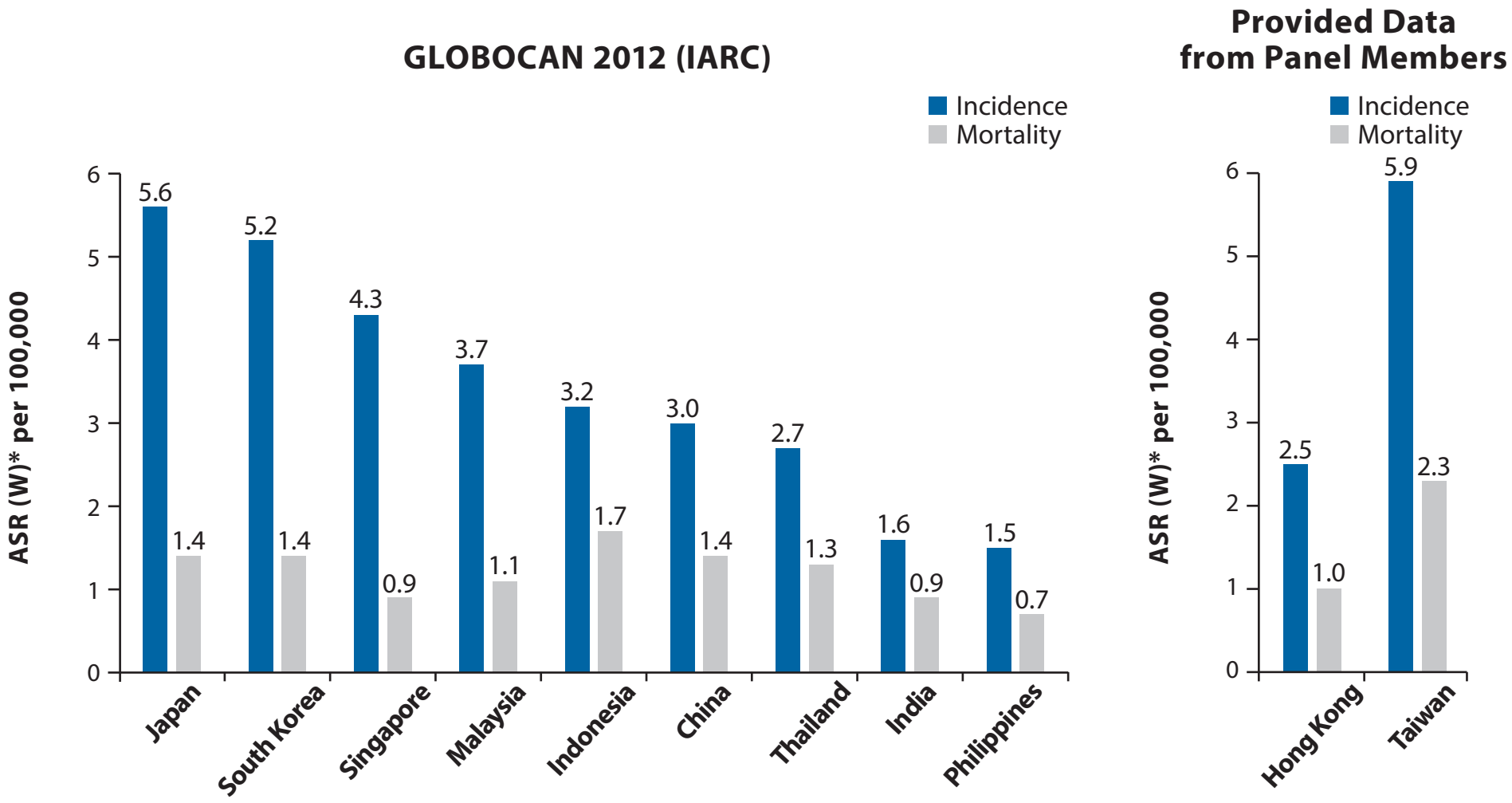
The difference of the "p" staging process among some Asian countries may result from the difference of the TNM staging system between AJCC and UICC. The general rules of the TNM system of UICC (7th ed., 2009) say that "the pathological assessment of the primary tumour (pT) entails a resection of the primary tumour or biopsy adequate to evaluate the highest pT category."[1] In that case, if a TURBT sample includes muscle layer and the tumor is not embedded in muscle layer, "p" staging can be made.

Reference

1. Sobin LH, Gospodarowicz MK, Wittekind CH, eds. TNM Classification of Malignant Tumours, Seventh Edition. International Union Against Cancer (UICC). Wiley-Blackwell;2009:p8.

Appendices

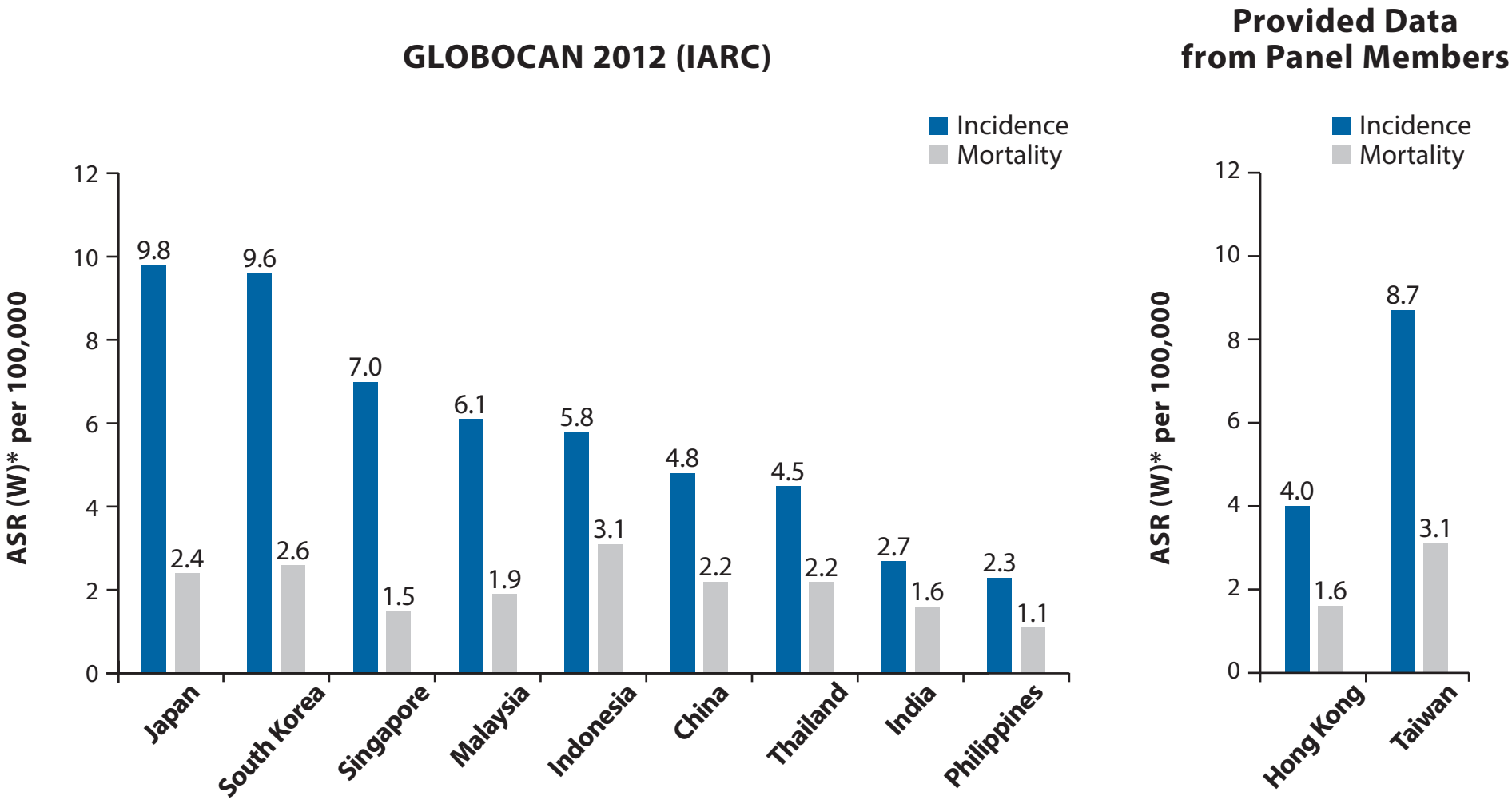
A) Estimated Incidence and Mortality Rates of Bladder Cancer, in the Panel Members' Countries; Overall



*ASR(W): Age-standardized rate with world standard population

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Elser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 17/6/2015.

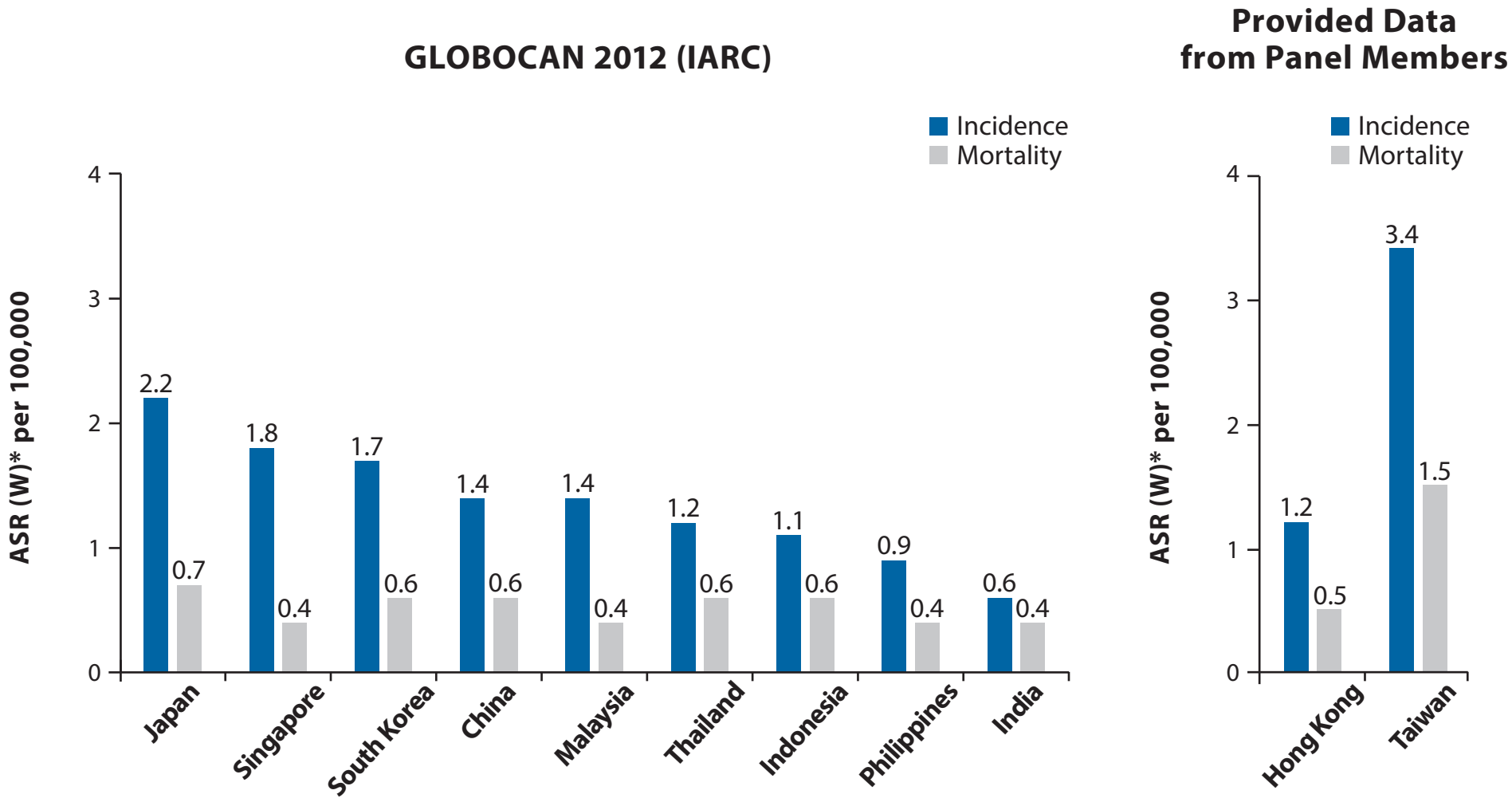
B) Estimated Incidence and Mortality Rates of Bladder Cancer, in the Panel Members' Countries; Male



*ASR(W): Age-standardized rate with world standard population

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Elser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 17/6/2015.

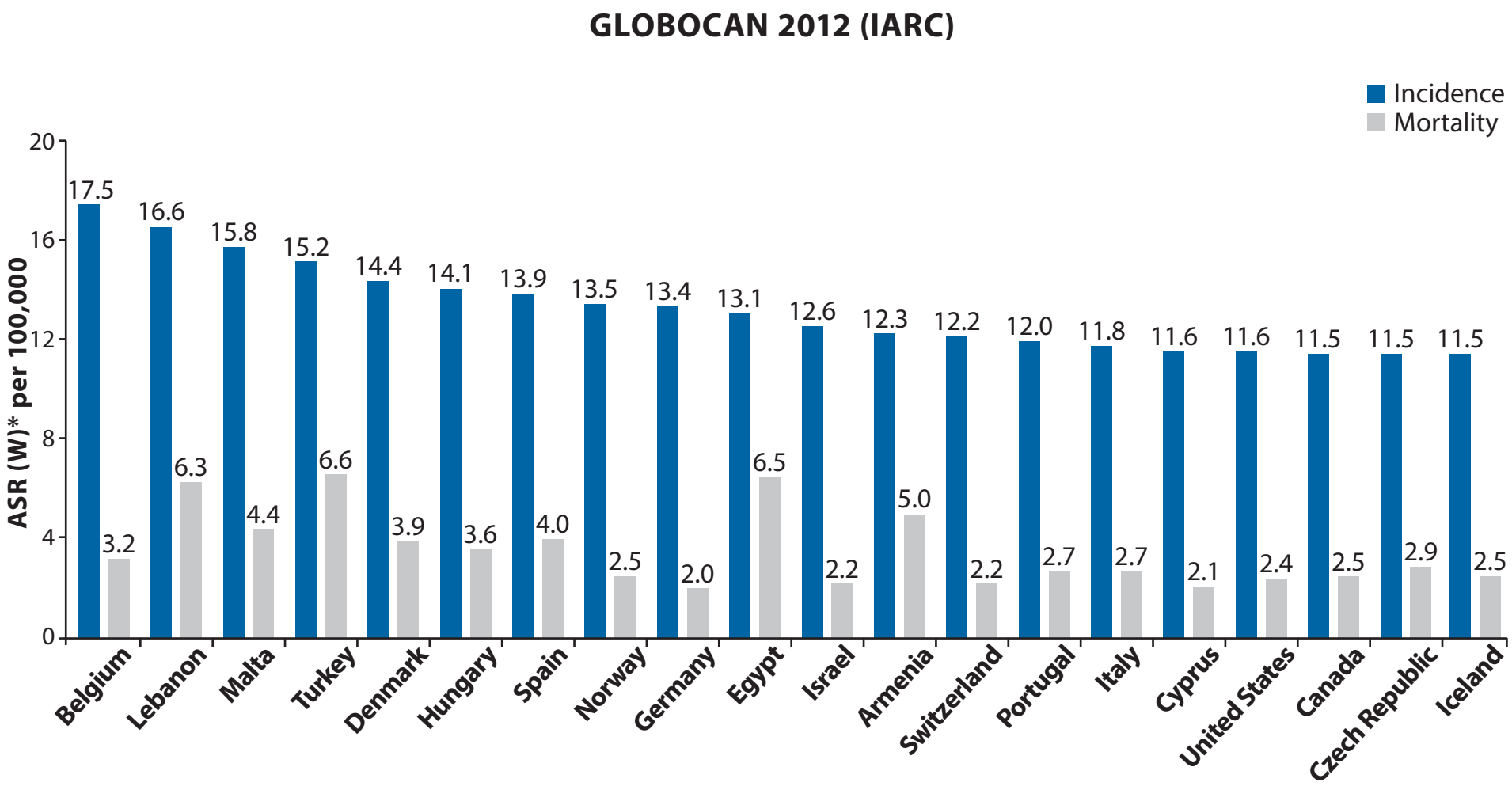
C) Estimated Incidence and Mortality Rates of Bladder Cancer, in the Panel Members' Countries; Female



*ASR(W): Age-standardized rate with world standard population

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Elser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 17/6/2015.

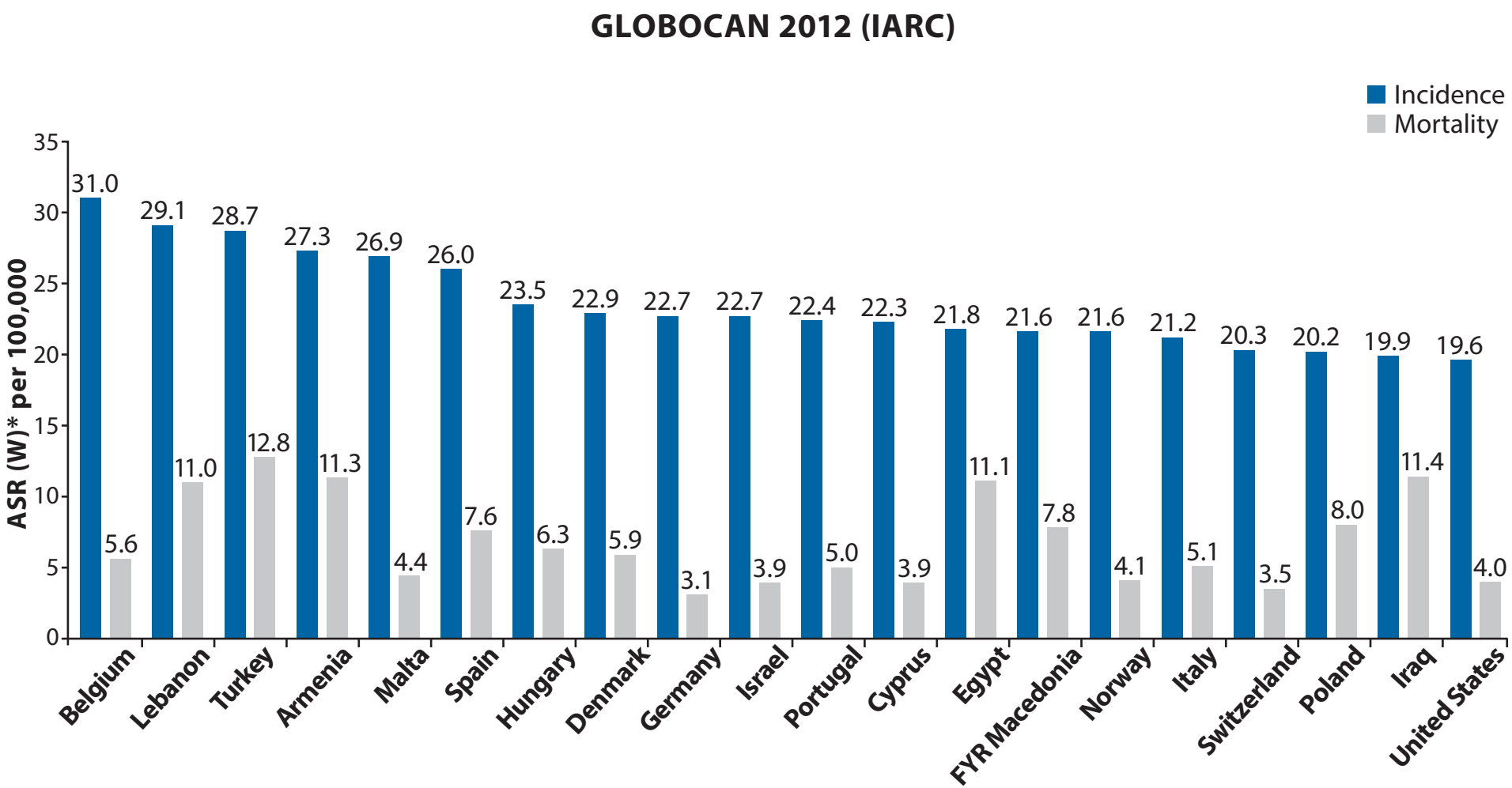
D) Estimated Incidence and Mortality Rates of Bladder Cancer, Top 20 in the World; Overall



*ASR(W): Age-standardized rate with world standard population

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Elser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 17/6/2015.

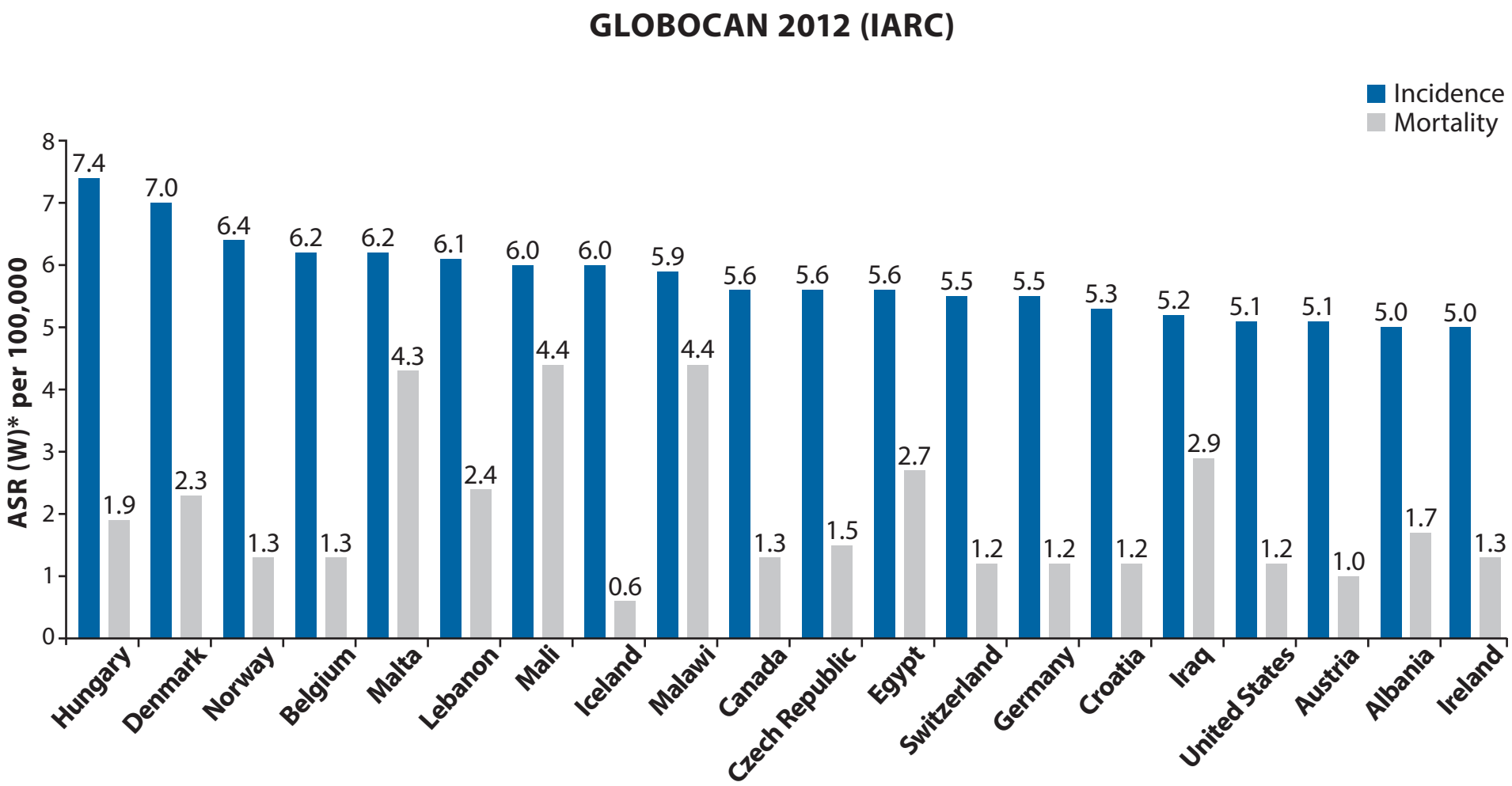
E) Estimated Incidence and Mortality Rates of Bladder Cancer, Top 20 in the World; Male



*ASR(W): Age-standardized rate with world standard population

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Elser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 17/6/2015.

F) Estimated Incidence and Mortality Rates of Bladder Cancer, Top 20 in the World; Female



*ASR(W): Age-standardized rate with world standard population

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Elser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 17/6/2015.

G) Life Expectancy and Incidence/Mortality Rate of Patients with Bladder Cancer in the Panel Members' Countries

	Life Expectancy	Incidence/Mortality Rate*
China	**72.38** (male) & **77.37** (female) [2010, National Bureau of Statistics]	**6.61** / **2.60** [2012, Chinese Cancer Registry Annual Report]
Hong Kong	**81.1** (male) & **86.7** (female) [2013]	**2.5** / **1.0** [2012]
India	**67** (male) & **69** (female) [2011, Ministry of Health and Family Welfare]	**1.6** / **0.9** [2012, GLOBOCAN]
Indonesia	**69.59** (male) & **74.88** (female) [2014]	**3.2** / **1.7** [2012, GLOBOCAN]
Japan	**80** (male) & **86** (female) [2010, Ministry of Health, Labour and Welfare]	**5.0** / **1.4** [2011 for incidence / 2013 for mortality]
Malaysia	–	–
Philippines	**68.55** [2012, WHO]	**1.5** / **0.7** [2012, GLOBOCAN]
Singapore	**80.2** (male) & **84.6** (female) [Ministry of Health 2008-2013]	**7.1** / **1.7** (male) & **1.9** / **0.5** (female) [National Registry Disease Office 2003-2007]
South Korea	**78.51** (male) & **85.06** (female) [2013]	**4.4** (male **8.3**, female **1.5**) / **2.5** [2012 for incidence / 2013 for mortality]
Taiwan	**76.7** (male) & **83.3** (female) [2012]	**8.7** / **3.12** (male) & **3.36** / **1.5** (female) [2011]
Thailand	**70.7** (male) & **77.4** (female) [2014]	**6.1** / **3.4** (male) & **2.2** / **1.0** (female) [2008]

* Incidence/Mortality rate is age-standardized rate (ASR) per 100,000.
Note: Data has been collected from the panel members as of July 2015.

H) Clinical Guidelines for Bladder Cancer in the Panel Members' Countries

	Domestic Clinical Guidelines	Year of Publication/Revision	English Version
China	**Yes.** By Chinese Urological Association.	Published in **2007.** Revised in **2014.**	**No**
Hong Kong	**No**	–	–
India	**No**	–	–
Indonesia	**Yes.** By Indonesian Urological Association.	Published in **2014.**	**No**
Japan	**Yes.** By the Japanese Urological Association.	Published in **2009.** Revised in **2015.**	**Yes**
Malaysia	–	–	–
Philippines	**No.** But following NCCN and AUA recommendations.	–	–
Singapore	**Yes**	Published in **2001.**	–
South Korea	**Yes.** By the Korean Urological Oncology Society.	Published in **2005.** Will be revised in **2015.**	**No**
Taiwan	**Yes.** By the Taiwan Urological Association.	Published in **2011.** Revised in **2014.** Revising every year.	**Yes**
Thailand	**No.** But consensus was reached in 2013.	–	–

Note: Data has been collected from the panel members as of July 2015.

I) Cystoscopy and Imaging Modalities in the Panel Members' Countries

	Cystoscopy	Imaging Modalities
China	Rigid cystoscopy is more popular than flexible cystoscopy.	CT and MRI.
Hong Kong	Flexible cystoscopy.	CT and PET.
India	Rigid cystoscopy is more popular than flexible cystoscopy.	USG, CT, PET.
Indonesia	Mostly using rigid cystoscopy.	CT Urography with contrast (more common), or IVU. MRI is less common.
Japan	Flexible cystoscopy is more popular than rigid cystoscopy.	MRI is mainly used for the clinical T staging. CT and bone scintigraphy are used for N/M staging. PET is an option.
Malaysia	–	–
Philippines	Both flexible and rigid cystoscopies are available and used.	CT, MRI and PET where necessary.
Singapore	Flexible cystoscopy.	CT urogram.
South Korea	Flexible cystoscopy is used in institutions that are equipped. If not equipped, rigid type is used.	CT is the first-choice for staging workup; reimbursed by Korean National Health Insurance (NHI). MRI can be helpful in suspicious cases of >T3 or invasion to pelvic bone. Chest CT is not routinely performed, but is considered if abnormal findings are detected on plain chest x-ray.
Taiwan	Rigid cystoscopy is more popular than flexible cystoscopy.	CT or MRI. CT is more common. Bone scintigraphy is routine for >T2 before radical cystectomy.
Thailand	Rigid cystoscopy is more popular than flexible cystoscopy.	CT scan and bone scan.

Note: Data has been collected from the panel members as of July 2015.

J) Risk Stratification of NMIBC in the Panel Members' Countries

	cTa, low grade	cTa, high grade	cT1, low grade	cT1, high grade	cTis
China	Low risk (if multiple, recurrent, and greater than 3 cm: high risk)	High risk	High risk	High risk	High risk
Hong Kong	Low risk	–	Intermediate risk	High risk	High risk
India	Low risk	Intermediate risk	Intermediate risk	High risk	High risk
Indonesia	Low risk	Intermediate risk	High risk	High risk	High risk
Japan	Low risk	Intermediate risk (if multiple or recurrent: high risk)	Intermediate risk	High risk	High risk
Malaysia	–	–	–	–	–
Philippines	Low risk	Intermediate risk	Intermediate risk	High risk	High risk
Singapore	Low risk	High risk	Intermediate risk	High risk	High risk
South Korea	Low risk	High risk	High risk	High risk	High risk
Taiwan	Low risk	Intermediate risk (need discussion)	Intermediate risk	High risk	High risk
Thailand	Low risk	Intermediate risk	Intermediate risk	High risk	High risk

Note: Data has been collected from the panel members as of July 2015.

K) Health Insurance System in the Panel Members' Countries

	Health Insurance System
China	There is one health insurance system that covers citizens in the city and another health insurance system that covers citizens in the countryside. Private insurance is also widespread, especially in the urban area.
Hong Kong	Only non-mandatory private insurance.
India	Government and private insurance covering approximately 20% of the population.
Indonesia	Government health insurance covering 50% of the population (as of January 2015), and approximately 5% private insurance.
Japan	There is the health insurance system that covers all citizens. Private insurance is also widespread.
Malaysia	–
Philippines	Government health insurance covering less than 50% of the population, and coverage is limited. Many still pay out of pocket.
Singapore	Standard coverage by government mandated 3-tier health coverage with patient co-payment; Medisave, Medishield, Medifund. Additional private insurance is optional but increasingly widespread.
South Korea	South Korea has a National Health Insurance (NHI) system, which is compulsory and required by law. Every resident in the country is eligible regardless of nationality or profession. The National Health Insurance Corporation (NHIC) is the only public insurance institution operated by the Ministry of Health and Welfare in South Korea. Additional private insurance is also widespread.
Taiwan	There is the government insurance system that covers all citizens. Private insurance is not very common and only in some citizens.
Thailand	1. Civil Servants' Medical Benefit Scheme (CSMBS) for government officers and their families (8.01%). 2. Social Security System (SSS) for other workers in private sector and some of government officers (12.9%). 3. Universal Coverage (UC) for the rest of the population (74.6%).

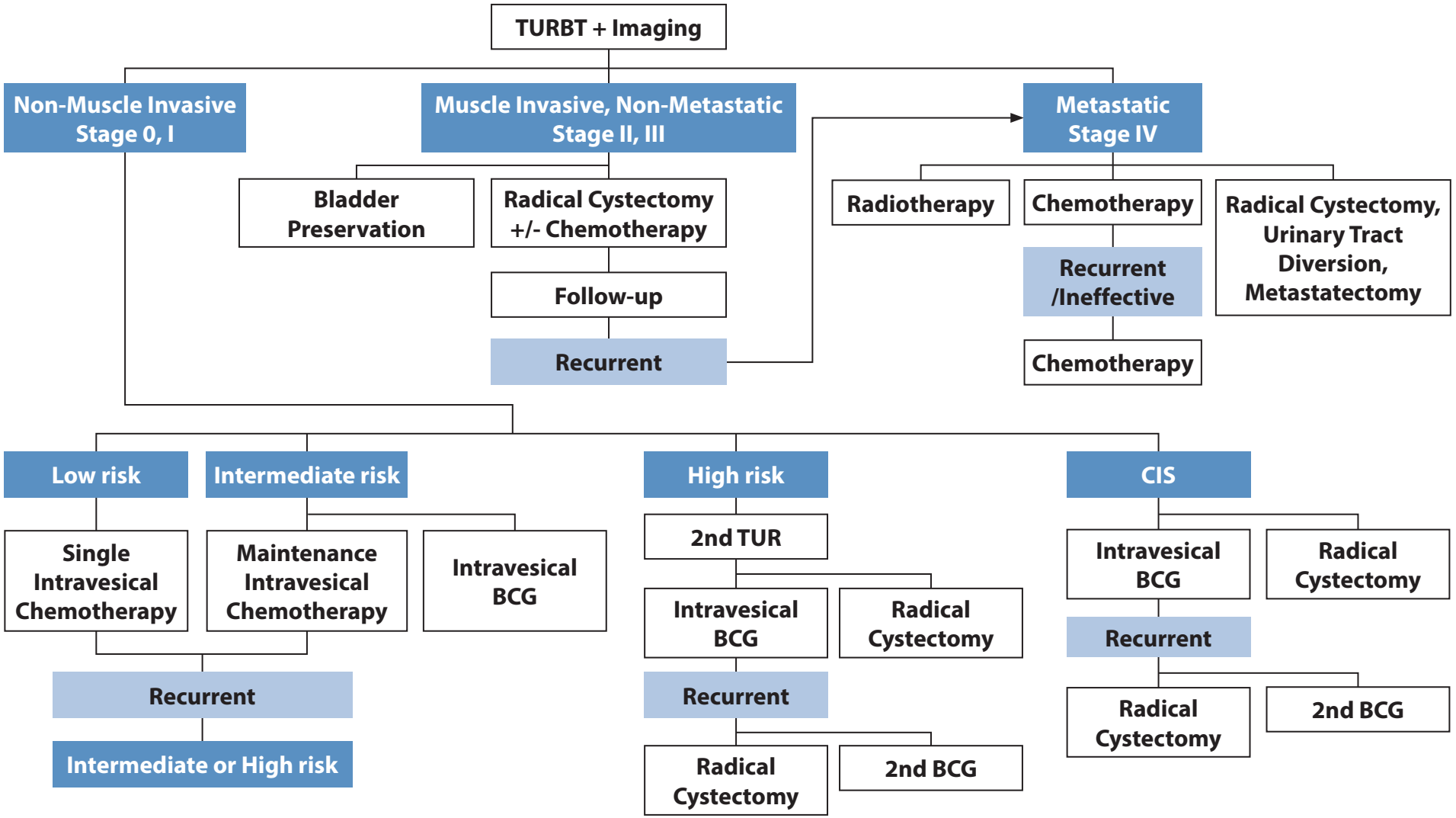
Note: Data has been collected from the panel members as of July 2015.

L) Major Drugs for the Treatment of Bladder Cancer in the Panel Members' Countries

	Approved	Under Study
China	Pirarubicin, epirubicin, doxorubicin, mitomycin-C, methotrexate, vinblastine, cisplatin, gemcitabine, APL-1202 (oral nitroxoline derivative).	–
Hong Kong	Cisplatin, doxorubicin, methotrexate, vinblastine, carboplatin, gemcitabine.	Anti-PD-L1.
India	Cisplatin, doxorubicin, methotrexate, vinblastine, carboplatin, gemcitabine.	–
Indonesia	Intravesical: mitomycin-C. Chemotherapy: cisplatin, vinblastine, doxorubicin, methotrexate, gemcitabine, carboplatin.	–
Japan	BCG, methotrexate, vinblastine, doxorubicin, cisplatin, gemcitabine.	Anti-PD-1, anti-PD-L1, S-588410.
Malaysia	–	–
Philippines	Mitomycin-C, BCG, methotrexate, vinblastine, doxorubicin, cisplatin, gemcitabine.	–
Singapore	Mitomycin-C, BCG, methotrexate, vinblastine, doxorubicin, cisplatin, gemcitabine.	–
South Korea	Intravesical: BCG, mitomycin-C, doxorubicin, epirubicin. Chemotherapy: gemcitabine, cisplatin, carboplatin, methotrexate, vinblastine, doxorubicin.	–
Taiwan	Cisplatin, 5-fluorouracil, leucovorin, gemcitabine, paclitaxel, doxorubicin, methotrexate, vinblastine, carboplatin, mitomycin-C, BCG, epirubicin.	Anti-PD-1, anti-PD-L1.
Thailand	Mitomycin-C, BCG, methotrexate, vinblastine, cisplatin, gemcitabine.	Oral BGJ398 (Pan FGF-R kinase inhibitor).

Note: Data has been collected from the panel members as of July 2015.

M) Treatment Algorithm of Bladder Cancer in Japanese Clinical Practice Guidelines



Advanced and translated from Japanese into English by Japanese ACS members.
Source: Japanese Urological Association eds. Clinical Practice Guidelines for Bladder Cancer 2015. Igaku Tosho Shuppan;2015:p2.