



National
Comprehensive
Cancer
Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Kidney Cancer

Asia Consensus Statements Version 3

[2016]

–Based upon NCCN Guidelines Kidney Cancer Version 3.2015–

NCCN.org

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Conflict of Interest (COI)

All panel members have disclosed their 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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Table of Contents

- Preamble
- Kidney Cancer Overview – The Asian Landscape and Asia Consensus Statements
- Asia Consensus Statements (ACS)
 - ACS #1 : TNM Staging System for Kidney Cancer
 - ACS #2 : Partial Nephrectomy
 - ACS #3 : Active Surveillance
 - ACS #4 : Ablative Techniques for Non-surgical Candidates
 - ACS #5 : Cytoreductive Nephrectomy
 - ACS #6a : Availability and Affordability of Kidney Cancer Drugs in Asia
 - ACS #6b : Availability and Prevalence of Cytokines in Asia
 - ACS #7 : Systemic Therapy for Non-clear Cell Histology
 - ACS #8 : Duration of Follow-up
 - ACS #9 : Imaging Modality for Follow-up

Table of Contents

- **Appendices**

- A) Estimated Incidence and Mortality Rates of Kidney Cancer in the Panel Members' Countries; Overall
- B) Estimated Incidence and Mortality Rates of Kidney Cancer in the Panel Members' Countries; Male
- C) Estimated Incidence and Mortality Rates of Kidney Cancer in the Panel Members' Countries; Female
- D) Estimated Incidence and Mortality Rates of Kidney Cancer, Top 20 in the World; Overall
- E) Estimated Incidence and Mortality Rates of Kidney Cancer, Top 20 in the World; Male
- F) Estimated Incidence and Mortality Rates of Kidney Cancer, Top 20 in the World; Female
- G) Life Expectancy and Incidence/Mortality Rate of Patients with Kidney Cancer in the Panel Members' Countries
- H) Criteria for Nephron-sparing Surgery in the Panel Members' Countries
- I) Active Surveillance (AS) in the Panel Members' Countries
- J) Major Drugs for the Treatment of Kidney Cancer in the Panel Members' Countries
- K) Post Marketing All-case Surveillance in the Panel Members' Countries
- L) Post Marketing All-case Surveillance in South Korea
- M) Availability and Prevalence of IL-2 for the Treatment of Kidney Cancer in the Panel Members' Countries
- N) Imaging Modalities Used for Initial Workup and Follow-up in the Panel Members' Countries
- O) Health Insurance System in the Panel Members' Countries
- P) Clinical Practice Guidelines in the Panel Members' Countries
- Q) Japanese Clinical Practice Guideline for Renal Cell Carcinoma

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: Kidney Cancer (Version 3.2015). As such, for contextual comprehension of the statements, refer to the version of NCCN Guidelines: Kidney 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: Kidney Cancer (Version 3.2015). 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 guidelines 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.

Kidney Cancer Overview

— The Asian Landscape and Asia Consensus Statements

Approximately 208,500 new cases of kidney cancer are diagnosed in the world each year, accounting for just under 2% of all cancers.¹ Of the different types of kidney cancer, renal cell carcinoma (RCC) is the predominant form, accounting for about 85% of cases, while renal pelvis cancer accounts for most of the remainder.² A number of studies have also found that Asians have a significantly lower incidence rate of RCC and higher survival rate than other races/ethnicities, while Blacks have a significantly higher incidence rate and lower survival rate than all other races/ethnicities, despite having more localized cancer.^{3,4}

RCC is a male-dominant disease. In Asia, as in other parts of the world, the incidence rate of RCC is approximately twice as high in males than in females.⁵ Based on GLOBOCAN 2012, age-standardized rates (ASRs) of incidence (overall data) for kidney cancer in Asian countries varied between 8.0 (in South Korea) and 0.9 (in India). As for male, those were between 11.7 (in South Korea) and 1.3 (in India), and those for female were between 4.7 (in South Korea) and 0.6 (in India). Whereas, those in the United States were 11.7 for overall, 15.9 for male, and 8.5 for female, respectively in 2012.⁵ There is a marked difference in the incidence rate of kidney cancer between the United States and Asian countries.

Asian countries have many 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 have diverse 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 kidney cancer. This diversity reflects the real world, however, and we believe that Asia can greatly contribute to the world's advancement in kidney cancer treatment by preparing practice guidelines helpful in this part of the world.

The ACS: Kidney Cancer is an attempt by physicians from Asian countries to fuse the data and experience which have been accumulated in Asia with the western evidence, ie, the NCCN Guidelines. The ACS will make the NCCN Guidelines effective even in the diverse Asian healthcare environments. The ACS is not only a collection of statements for better treatment of kidney cancer limited to Asia; it is also the embodiment of Asian commitment to the improvement of kidney cancer treatment worldwide.

The revising of the ACS: Kidney Cancer Version 2.2011 to Version 3 [2016] is under the auspices of the following academic organizations: Asia Pacific Society of Uro-oncology (TBD), The Korean Urological Oncology Society, and Japan Society of Clinical Oncology.

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Asia Consensus Statements (ACS)

Table 1
American Joint Committee on Cancer (AJCC)
TNM Staging System for Kidney Cancer (7th ed., 2010)

Primary Tumor (T)

ACS #1

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2b	Tumor more than 10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2 T3	N1 N0 or N1	M0 M0
Stage IV	T4 Any T	Any N Any N	M0 M1

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

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.

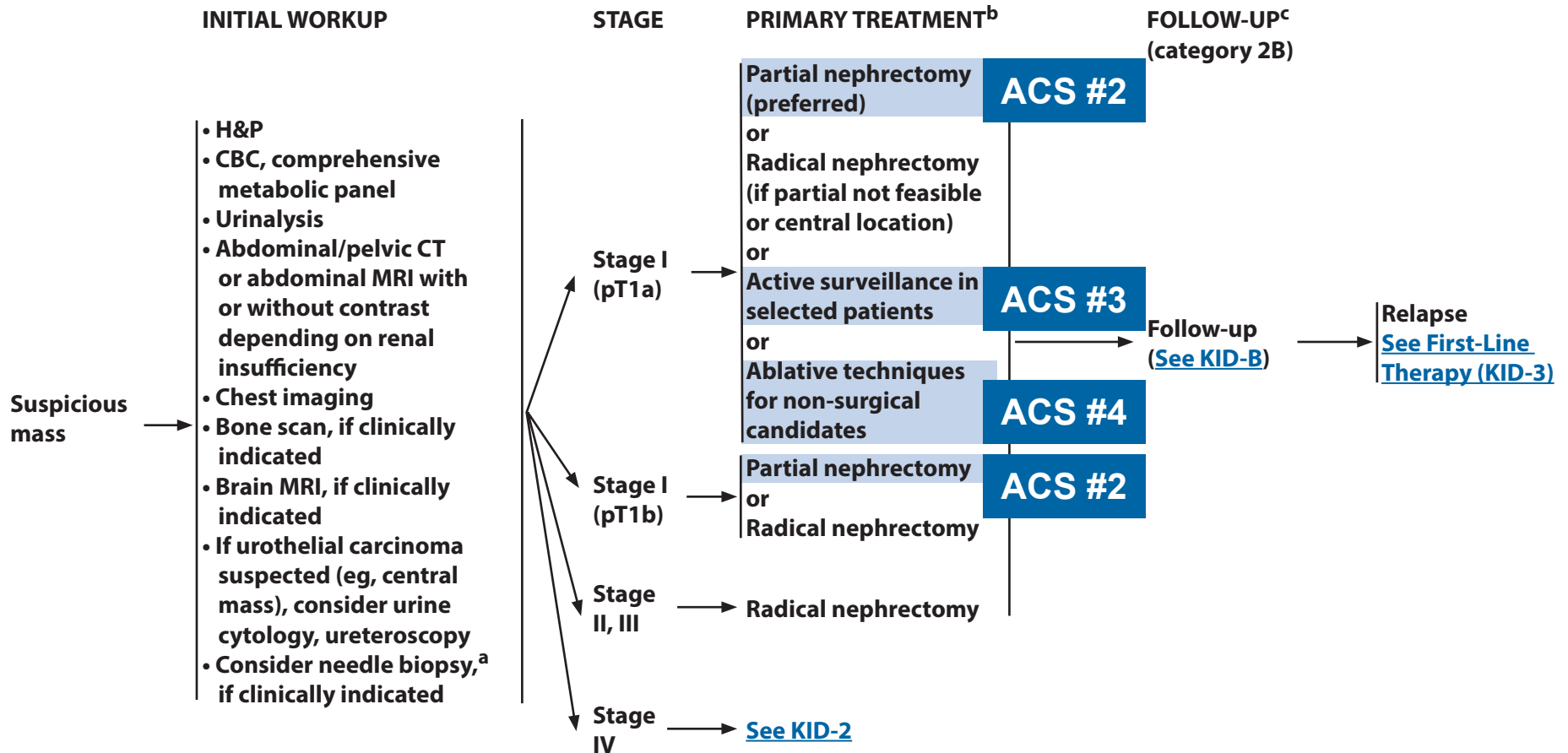
ACS #1: TNM Staging System for Kidney Cancer

TNM staging system conforms to NCCN Guidelines version 3.2015.

[Cross ref: Guidelines page ST-1]

Discussion:

The ACS #5 on NCCN Asia Consensus Statements version 2.2011 has been revised. The staging now conforms to NCCN Guidelines version 3.2015.



^aBiopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery, and radiofrequency ablation strategies.

^bSee Principles of Surgery (KID-A).

^cNo single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

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.

PRINCIPLES OF SURGERY

- Nephron-sparing surgery (partial nephrectomy) is appropriate in selected patients, for example:
 - ▶ Small unilateral tumors (Patients with T1a and selected T1b and T2a tumors)
 - ▶ Uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer

ACS #2

- Open, laparoscopic, or robotic surgical techniques may be used to perform radical and partial nephrectomies.
- Regional lymph node dissection is optional but is recommended for patients with adenopathy on preoperative imaging or palpable/visible adenopathy at time of surgery.
- If adrenal gland is uninvolved, resection may be omitted.
- Special teams may be required for extensive inferior vena cava involvement.
- Observation or ablative techniques (eg, cryosurgery, radiofrequency ablation):
 - ▶ Can be considered for patients with clinical stage T1 renal lesions who are not surgical candidates.
 - ▶ Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery, and radiofrequency ablation strategies.
 - ▶ Randomized phase III comparison with surgical resection (ie, radical or partial nephrectomy by open or laparoscopic techniques) has not been done.
 - ▶ Ablative techniques are associated with a higher local recurrence rate than conventional surgery.^{a,b}
- Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have:
 - ▶ Excellent performance status (ECOG PS <2)
 - ▶ No brain metastasis

^a Campbell SC, Novick AC, Beldegrun A, et al. Practice Guidelines Committee of the American Urological Association. Guideline for management of the clinical T1 renal mass. J Urol 2009;182:1271-1279.

^b Kunkle DA, Uzzo RG. Cryoablation or radiofrequency ablation of the small renal mass: A meta-analysis. Cancer 2008;113:2671-2680.

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 #2: Partial Nephrectomy

Partial nephrectomy is recommended for technically feasible Stage I tumors.

[Cross ref: Guidelines page KID-1 and KID-A]

Discussion:

Partial nephrectomy is recommended for both T1a and T1b in China, India, Japan, and Taiwan.¹ The criteria for nephron-sparing surgery in Asian countries are summarized (see appendix H).

Taiwan: Sixty percent of cases of partial nephrectomy are through robotic surgery.

Thailand: Only T1a tumors (a tumor size of less than 4 cm) is eligible for partial nephrectomy. Partial nephrectomy can be an option in selected cases of T1b (4-7 cm).

References

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ACS #3: Active Surveillance

Active surveillance can be an option in Asia. Only a limited number of patients receive active surveillance.

[Cross ref: Guidelines page KID-1]

Discussion:

Active surveillance can be an option for selected cases (eg, elderly patients or patients with comorbidities). In elderly patients, biopsy preceding active surveillance can be omitted for tumors with typical findings for RCC, and it can be performed for atypical tumors or tumors whose diagnosis is difficult with imaging. Further evidence will be needed to define tumor parameters, characteristics, and the follow-up schedule for active surveillance in Asia. The status of active surveillance and biopsy preceding active surveillance are summarized (see appendix I).

South Korea: The survival outcome and pathologic characteristics of RCC in Korean men are similar to those in men in the US SEER database. Active surveillance can therefore be an advisable option for Korean patients (Source: Clinical guidelines on Renal Cell Carcinoma 2012, Korean Urological Oncology Society).

ACS #4: Ablative Techniques for Non-surgical Candidates

Cryotherapy can be an option. Further clinical evidence on cryotherapy is required in Asian countries.

[Cross ref: Guidelines page KID-1]

Discussion:

Although the low invasiveness of cryotherapy as compared with nephrectomy can make it common in the future, the currently available national data from Asian countries is insufficient. More data on the clinical outcome of cryotherapy in Asia is needed.

China: Several centers have used cryotherapy to treat small renal tumors with good results.

Japan: Patients are now reimbursed by health insurance for cryotherapy for small renal tumors. In some institutes, the rate of cryotherapy is clearly increasing.

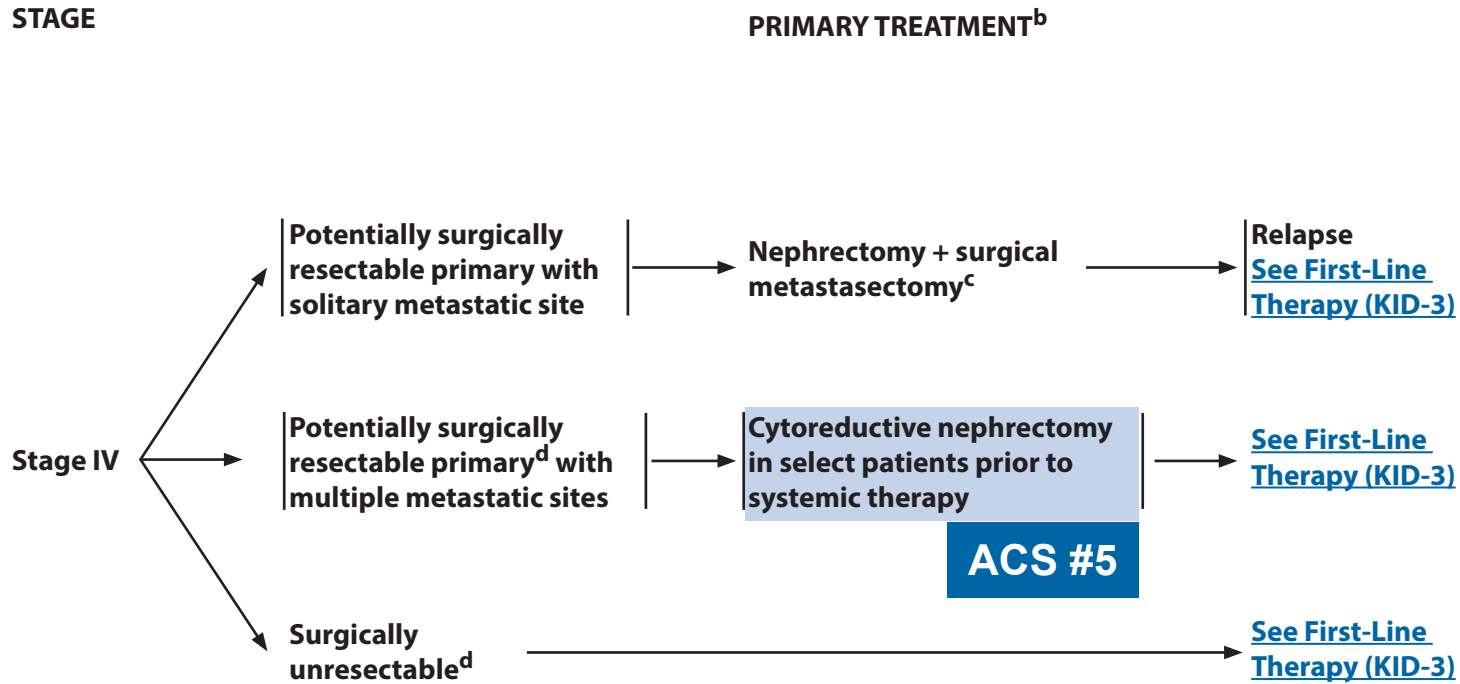
South Korea: There is not enough national data regarding cryotherapy.

Philippines: Cryotherapy is available only at one center, and RFA is about to be introduced (patients generally receive partial nephrectomy).

Singapore: Cryotherapy is offered at two institutions for small renal masses, and RFA at four.

Taiwan: There is not enough national data regarding cryotherapy.

Thailand: Cryotherapy is available only at one center.



^b [See Principles of Surgery \(KID-A\).](#)

^c No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient requirements.

^d Individualize treatment based on symptoms and extent of metastatic disease.

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: Cytoreductive Nephrectomy

Cytoreductive nephrectomy preceding systemic therapy is recommended in selected patients with good performance status and resectable tumor.

[Cross ref: Guidelines page KID-2]

Discussion:

According to the NCCN Guidelines (Version 3.2015; MS-9), lung-only metastasis, good prognostic features, and good performance status are factors for patient selection for cytoreductive nephrectomy.¹ In Asia, defining strict criteria for patient selection remains controversial, however, good performance status and resectability of tumor could be positive parameters for the selection. Although percentage of resectable volume of tumor is a likely parameter, further evidence is required for it.

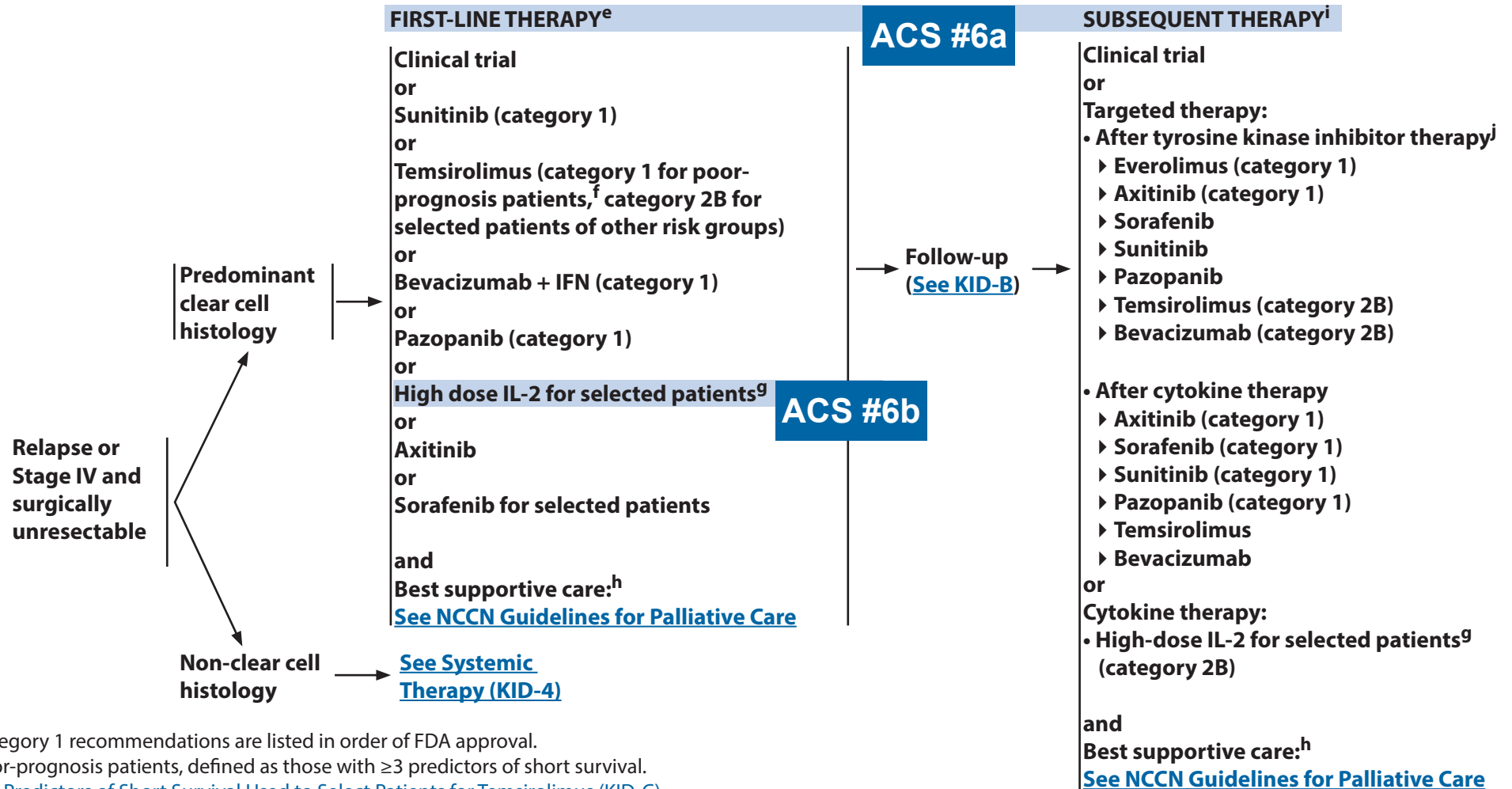
Philippines: Cytoreductive nephrectomy is common despite limited survival.

Taiwan: Patients with good performance status receive cytoreductive nephrectomy.

Thailand: Nephrectomy usually precedes systemic therapy, and neoadjuvant targeted therapy is occasionally performed in unresectable cases.

References

1. Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? *Cancer* 2010;116(14):3378-3388.



^e Category 1 recommendations are listed in order of FDA approval.

^f Poor-prognosis patients, defined as those with ≥ 3 predictors of short survival.
[See Predictors of Short Survival Used to Select Patients for Temsirolimus \(KID-C\).](#)

^g Patients with excellent performance status and normal organ function.

^h Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.

ⁱ Chemotherapy (category 3) in clear cell and non-clear cell RCC with predominant sarcomatoid features has shown modest response to gemcitabine + doxorubicin or gemcitabine + capecitabine.

^j Currently available tyrosine kinase inhibitors include: axitinib, pazopanib, sorafenib, or sunitinib.

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 #6a: Availability and Affordability of Kidney Cancer Drugs in Asia

The availability and affordability of kidney cancer drugs are different among Asian countries.

[Cross ref: Guidelines page KID-3]

Discussion:

The availability of kidney cancer drugs in Asian countries is summarized (see appendix J). In some countries, post-marketing surveillance of kidney cancer drugs has been performed, and the results of surveillance have started to be published (see appendix K and L).^{1,2,3,4,5,6}

China: Sorafenib, sunitinib and everolimus has been approved.^{7,8}

Japan: Temezirolimus has been approved as first-line and everolimus as second-line, but it is common to use everolimus or temezirolimus as second-line for relapses after TKI treatment. Comparison of second-line temezirolimus and sorafenib after the failure of sunitinib has demonstrated that sorafenib is better than temezirolimus in terms of survival.

S-1 has been widely available in Asian countries as a stomach cancer drug. Result of phase II trial of S-1 in Japanese patients with cytokine-refractory mRCC has shown that S-1 is active against mRCC, and thus S-1 is one of candidate drugs for further phase III trial in RCC patients.^{9,10}

Singapore: Patients treated with sunitinib had fair amount of side effects at the recommended dose of 50 mg,¹¹ and thus attenuated dose of 37.5 mg is preferred.

South Korea: Bevacizumab + IFN- α can be used for advanced/metastatic mRCC, although patients are not reimbursed for it. The NHI reimbursement policy allows patients with clear cell pathology to be reimbursed for second-line systemic therapy with everolimus after failed first-line VEGFr-TKI (Health Insurance Review & Assessment Service Recommendation on Chemotherapy, 2015).

Taiwan: The governmental insurance covers all kidney cancer drugs available in the country. The drug use is as per the NCCN Guidelines. Continuance of the drug is decided after evaluating the patient's response at 3 months. Good response or stable disease: the drug will be continued; poor response: progressive disease, shift to second-line. For poor risk patients, temsirolimus is the first priority.

Thailand: Sorafenib, sunitinib and everolimus have been approved.

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ACS #6b: Availability and Prevalence of Cytokines in Asia

The prevalence of cytokine use varies among Asian countries.

[Cross ref: Guidelines page KID-3]

Discussion:

The treatment with interleukin (IL)-2 in Asia is at low doses in comparison to that in Europe and the United States. In general, urologists use low-dose IL-2, whereas clinical oncologists use high-dose IL-2. As for interferon (IFN)- α use, IFN- α monotherapy is one of treatment options in some Asian countries (see appendix M).

China: IL-2 is occasionally used in combination with IFN- α , and the CUA RCC Guidelines suggest the use of these drugs for relapses of Stage IV, surgically unresectable RCC.

Indonesia: Only IL-2 is available, however, it is uncommon.

Japan: Treatment with IFN- α and/or IL-2 has been performed with favorable results,^{1,2} especially in patients with lung metastases,³ and IL-2 is recommended for use as monotherapy or in combination with IFN- α for advanced RCC.^{4,5} However, the use of cytokine therapy is now decreasing after the introduction of molecular targeted therapy.

Philippines: In the Philippines, IFN- α is widely available and is preferred over IL-2 as cytokine treatment. However, more and more clinicians are turning to targeted agents as first-line therapy.

South Korea: IL-2 can be used in first-line therapy for stage IV RCC, optionally in combination with IFN- α or IFN- α + fluorouracil, and patients are reimbursed by the NIH for it. After the advent of TKIs, however, the use of IL-2 is uncommon (Health Insurance Review & Assessment Service Recommendation on Chemotherapy, 2015).

Taiwan: IFN- α is commonly used and IL-2 is seldom used for the treatment of RCC.

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SYSTEMIC THERAPY^{i,k}

**Relapse or
Stage IV and
surgically
unresectable**

→ **Non-clear cell
histology** →

Clinical trial (preferred)
or
**Temsirolimus (category 1 for poor-prognosis patients;^f
category 2A for other risk groups)**
or
Sorafenib
or
Sunitinib
or
Pazopanib
or
Axitinib
or
Everolimus
or
Bevacizumab
or
Erlotinib

and
Best supportive care:^h
[See NCCN Guidelines for Palliative Care](#)

ACS #7

→ **Follow-up**
(See KID-B)

^f Poor-prognosis patients, defined as those with ≥3 predictors of short survival. [See Predictors of Short Survival Used to Select Patients for Temsirolimus \(KID-C\).](#)

^h Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.

ⁱ Chemotherapy (category 3) in clear cell and non-clear cell RCC with predominant sarcomatoid features has shown modest response to gemcitabine + doxorubicin or gemcitabine + capecitabine.

^k Partial responses have been observed to cytotoxic chemotherapy (carboplatin + gemcitabine or carboplatin + paclitaxel) with collecting duct or medullary subtypes.

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 #7: Systemic Therapy for Non-clear Cell Histology

Chemotherapy should be considered as a treatment option of systemic therapy for non-clear cell RCC.

[Cross ref: Guidelines page KID-4, MS-19, and MS-20]

Discussion:

In the NCCN Guidelines (Version 3.2015; MS-19), chemotherapy is stated as potential option in patients with limited subtypes of non-clear cell RCC such as collecting duct or medullary carcinoma. Affordability of each drug is different among Asian countries as stated in ACS statement 6a. Considering these facts and economic status of each Asian country, chemotherapy should be included as a treatment option for other types of non-clear cell RCC.

China: Particularly GC protocol for non-clear cell RCC is mentioned in CUA Guidelines.

Korea: Only temsirolimus can be used for non-clear cell RCC under the national insurance system.

Taiwan: Chemotherapy is a treatment option in addition to targeted therapy for non-clear cell RCC.

FOLLOW-UP^{a,b} (category 2B)

Stage I (pT1a)

Follow-up During Active Surveillance

ACS #8

- H & P every 6 mo for 2 y, then annually up to 5 y after diagnosis
- Comprehensive metabolic panel and other tests as indicated every 6 mo for first 2 y, then annually up to 5 y after diagnosis
- Abdominal imaging:
 - ▶ Abdominal CT or MRI within 6 mo of surveillance initiation, then CT, MRI or US at least annually
- Chest imaging:
 - ▶ Chest x-ray or CT annually to assess for pulmonary metastases, if biopsy positive for RCC
- Pelvic imaging, as clinically indicated
- CT or MRI of head or MRI of spine, as clinically indicated
- Bone scan, as clinically indicated

ACS #9

Follow-up After Ablative Techniques

ACS #8

- H & P every 6 mo for 2 y, then annually up to 5 y after diagnosis
- Comprehensive metabolic panel and other tests as indicated every 6 mo for first 2 y, then annually up to 5 y after diagnosis
- Abdominal imaging:
 - ▶ Abdominal CT or MRI with and without contrast at 3-6 mo following ablative therapy unless otherwise contraindicated then CT, MRI or US, annually for 5 y
- Chest imaging:
 - ▶ Chest x-ray or CT annually for 5 y for patients who have biopsy proven low risk RCC, nondiagnostic biopsies or no prior biopsy
- Repeat biopsy:
 - ▶ New enhancement, a progressive increase in size of an ablated neoplasm with or without contrast enhancement, new nodularity in or around the treated zone, failure of the treated lesion to regress over time, satellite or port site lesions
- Pelvic imaging, as clinically indicated
- CT or MRI of head or MRI of spine, as clinically indicated
- Bone scan, as clinically indicated

ACS #9

[Continued on next page](#)

^a Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.

^b No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years at the discretion of the physician. Further study is required to define optimal follow up duration.

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.

FOLLOW-UP^{a,b}
(category 2B)

Stage I (pT1a) and (pT1b)

Follow-up After a Partial or Radical Nephrectomy

ACS #8

- H & P every 6 mo for 2 y, then annually up to 5 y after nephrectomy
- Comprehensive metabolic panel and other tests as indicated every 6 mo for 2 y, then annually up to 5 y after nephrectomy

• Abdominal imaging:

▶ After Partial Nephrectomy:

- ◊ Baseline abdominal CT, MRI, or US within 3-12 mo of surgery
- ◊ If the initial postoperative scan is negative, abdominal CT, MRI, or US may be considered annually for 3 y based on individual risk factors

▶ After Radical Nephrectomy:

- ◊ Patients should undergo abdominal CT, MRI or US within 3-12 mo of surgery
- ◊ If the initial postoperative imaging is negative, abdominal imaging beyond 12 mo may be performed at the discretion of the physician

ACS #9

- Chest imaging: Chest x-ray or CT annually for 3 y, then as clinically indicated
- Pelvic imaging, as clinically indicated
- CT or MRI of head or MRI of spine, as clinically indicated
- Bone scan, as clinically indicated

[Continued on next page](#)

^a Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.

^b No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years at the discretion of the physician. Further study is required to define optimal follow up duration.

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.

FOLLOW-UP^{a,b} (category 2B)

Stage II or III

Follow-up After a Radical Nephrectomy

ACS #8

- H & P every 3-6 mo for 3 y, then annually up to 5 y after radical nephrectomy and then as clinically indicated thereafter
- Comprehensive metabolic panel and other tests as indicated every 6 mo for 2 y, then annually up to 5 y, after radical nephrectomy, then as clinically indicated thereafter

Abdominal imaging:

ACS #9

- ▶ Baseline abdominal CT or MRI within 3-6 mo, then CT, MRI or US (US is category 2B for Stage III), every 3-6 mo for at least 3 y and then annually up to 5 y
 - ▶ Imaging beyond 5 y: as clinically indicated
 - ▶ Site specific imaging: as symptoms warrant
- Chest imaging:
 - ▶ Baseline chest CT within 3-6 mo after radical nephrectomy with continued imaging (CT or chest x-ray) every 3-6 mo for at least 3 y and then annually up to 5 y
 - ▶ Imaging beyond 5 y: as clinically indicated based on individual patient characteristics and tumor risk factors
 - Pelvic imaging, as clinically indicated
 - CT or MRI of head or MRI of spine, as clinically indicated
 - Bone scan, as clinically indicated

[Continued on next page](#)

^a Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.

^b No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years at the discretion of the physician. Further study is required to define optimal follow up duration.

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.

FOLLOW-UP^c (category 2B)

Follow-up for Relapsed or Stage IV and Surgically Unresectable Disease

ACS #8

- H & P every 6-16 weeks for patients receiving systemic therapy, or more frequently as clinically indicated and adjusted for type of systemic therapy patient is receiving

- Laboratory evaluation as per requirements for therapeutic agent being used

- Chest, abdominal and pelvic imaging:

ACS #9

- ▶ CT or MRI imaging to assess baseline pretreatment or prior to observation

- ▶ Follow up imaging every 6-16 weeks as per physician discretion and per patient clinical status. Imaging interval to be adjusted upward and downward according to rate of disease change and sites of active disease.

- Consider CT or MRI of head at baseline and as clinically indicated. Annual surveillance scans at physician discretion.

- MRI of spine as clinically indicated.

- Bone scan as clinically indicated.

^c No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.

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: Duration of Follow-up

The duration of follow-up in NCCN Guidelines (Version 3.2015) is generally acceptable, although long-term follow-up should also be considered.

[Cross ref: Guidelines page KID-B]

Discussion:

Monitoring the growth of the tumor is required for 5 years after diagnosis or surgery. Depending on the growth of tumor during 5 years of monitoring, further annual follow-up can be considered. Five years would be minimum duration for the follow-up of patients who receive active surveillance. Additionally, some recurrent or metastatic cases have been reported 10 or 15 years after surgery. Therefore long term follow-up is recommended.

ACS #9: Imaging Modality for Follow-up

In Asia, CT is mainly performed for staging and follow-up, and MRI can be an option.

[Cross ref: Guidelines page KID-B]

Discussion:

CT is mainly performed for follow-up purposes in most Asian countries because of clinical or economic reasons. Although MRI is not frequently used for follow-up in Asia, it is used in some countries because of their cost-effectiveness or for patients with renal impairment. Depending on the country, ultrasound (US) is preferred because it is cost-effective. Imaging modalities common in the initial workup and follow-up in Asian countries are summarized (see appendix N).

China: MRI has been increasingly common as it is not very costly and is superior to CT.

India: MRI after partial or radical nephrectomy is uncommon; patients with any doubt or positive finding undergo CT.

Japan: MRI for follow-up purpose is very uncommon, because CT is superior to MRI in resolution.

South Korea: MRI for follow-up purpose is uncommon; however, after the CT or MRI, or clinical trials, there is methodology. In relapsed or stage IV and surgically unresectable cases, PET-CT is performed if there is something suspicious.

Singapore: Patients with renal impairment/CKD receive MRI.

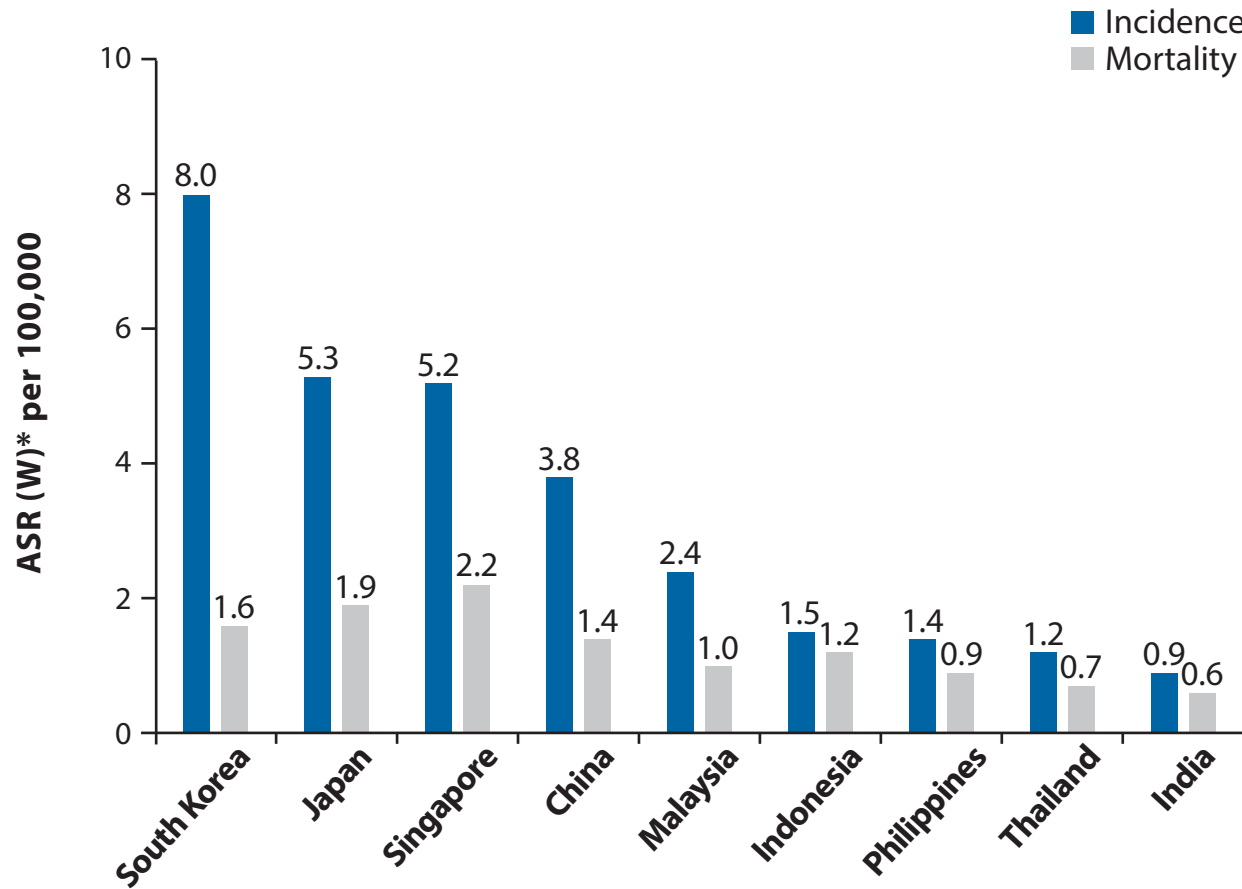
Taiwan: MRI in the follow-up schedule is uncommon because of long waiting time (about 1 or 2 months). CT (and possibly US) is useful.

Thailand: MRI is performed for patients with renal impairment/CKD.

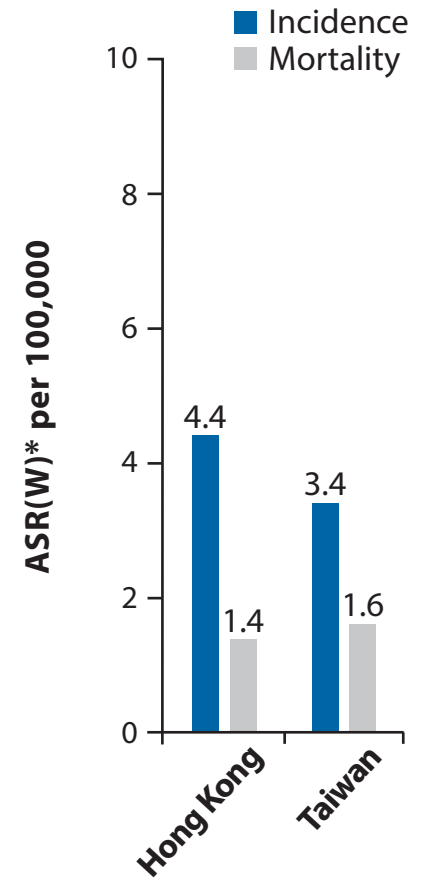
Appendices

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

GLOBOCAN 2012 (IARC)



Provided Data from Panel Members

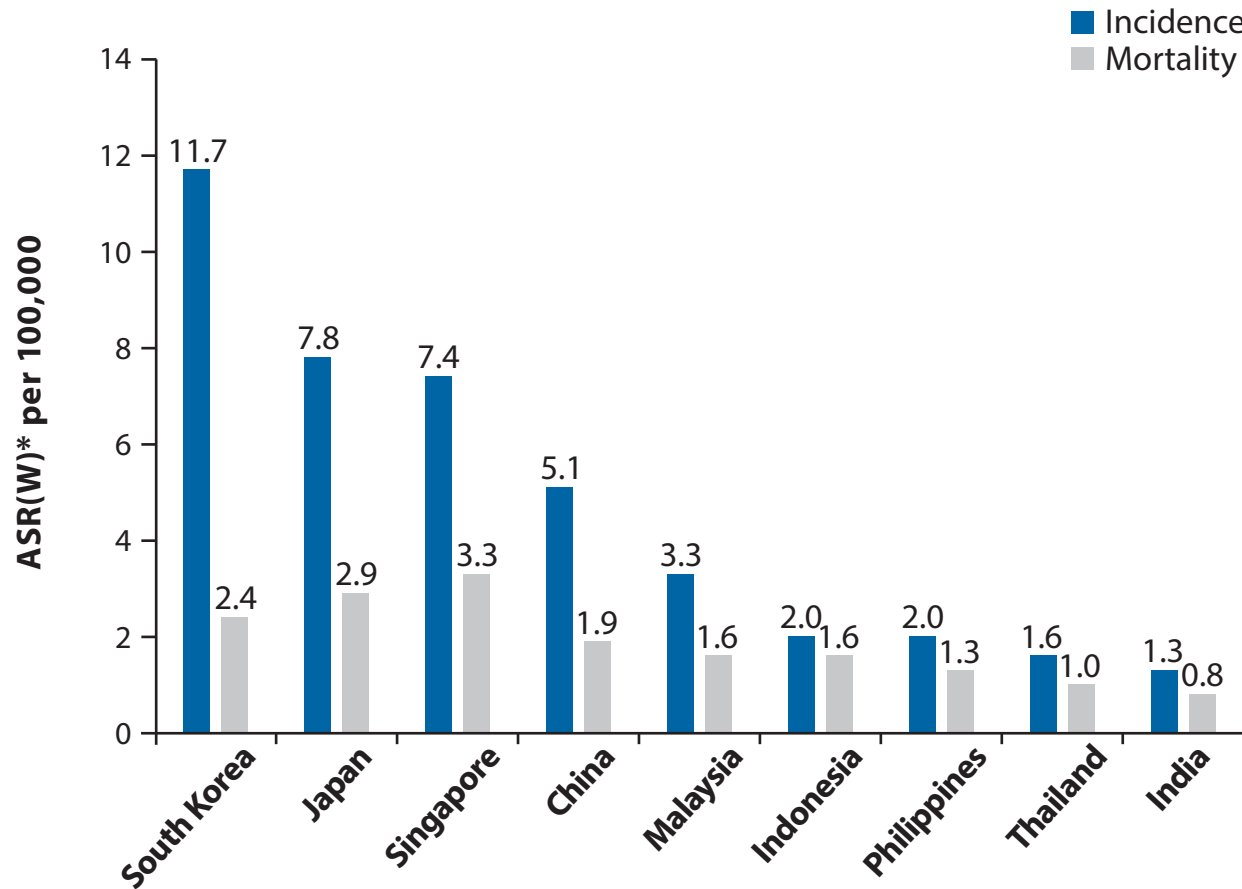


*ASR(W): Age-standardized rate with world standard population

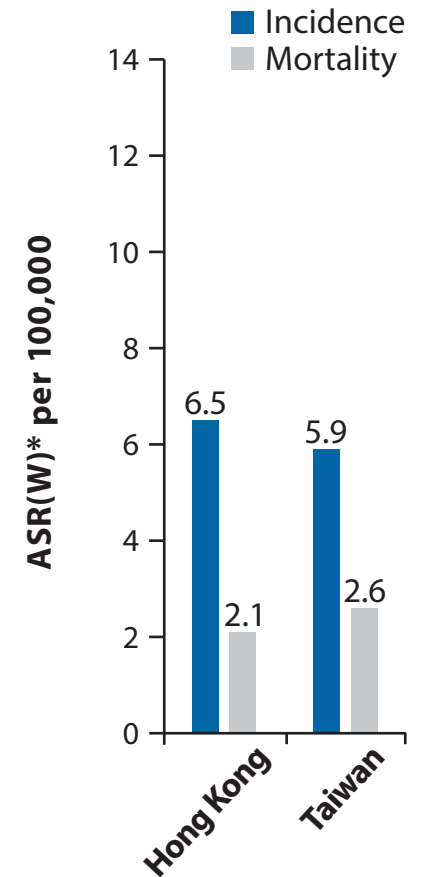
Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Elser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on 1/7/2015.

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

GLOBOCAN 2012 (IARC)



Provided Data from Panel Members

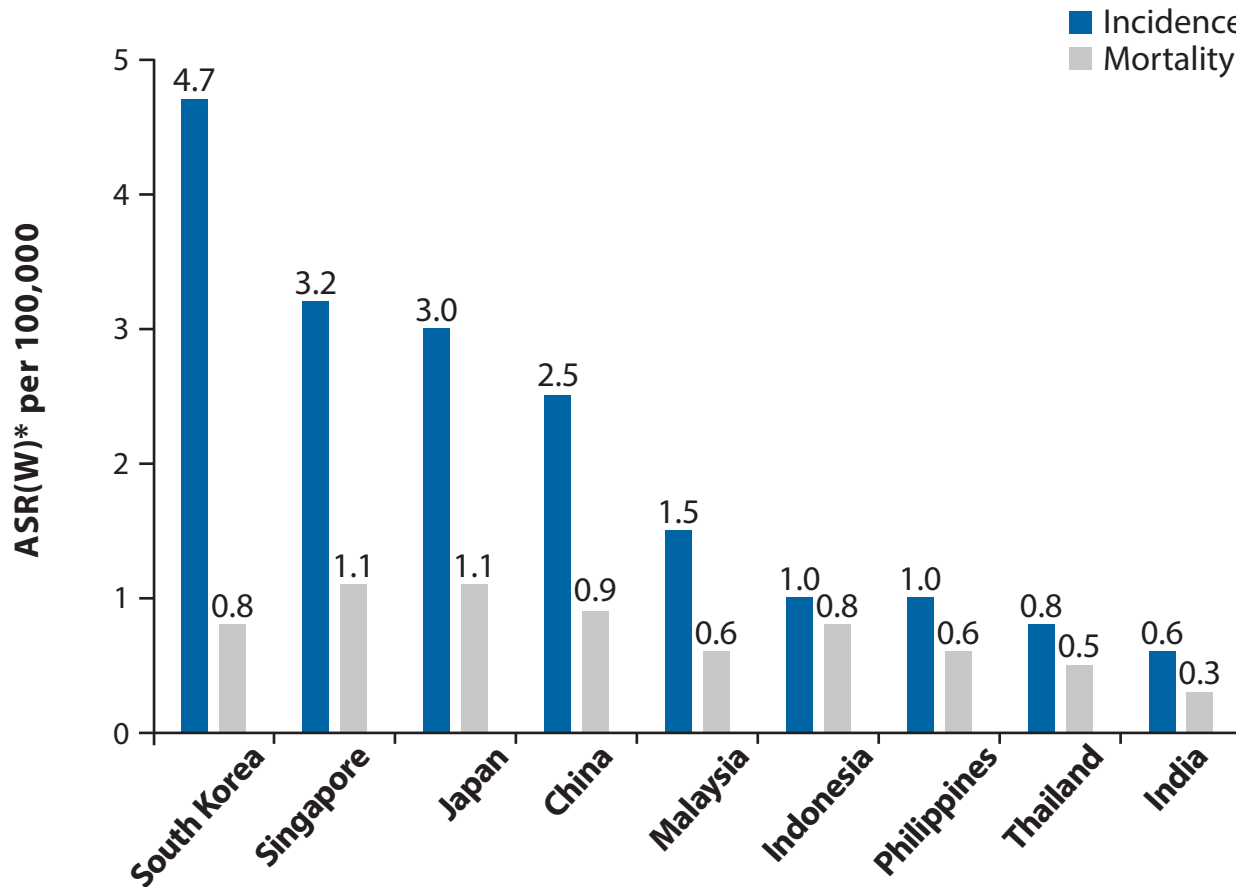


*ASR(W): Age-standardized rate with world standard population

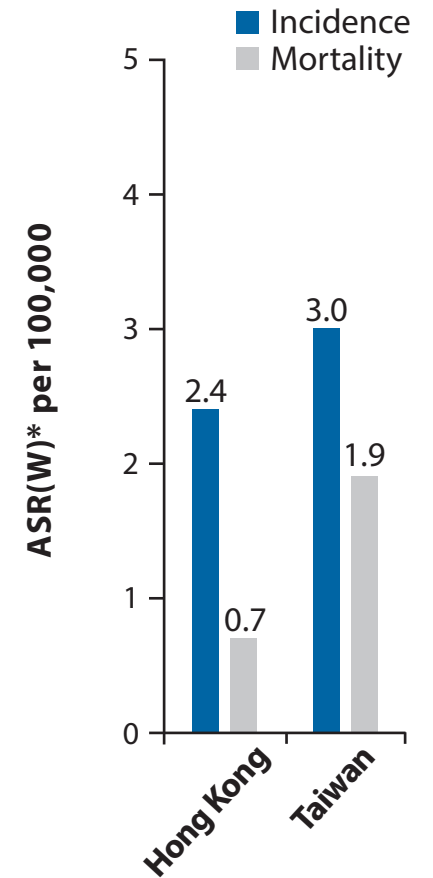
Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Elser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on 1/7/2015.

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

GLOBOCAN 2012 (IARC)



Provided Data from Panel Members

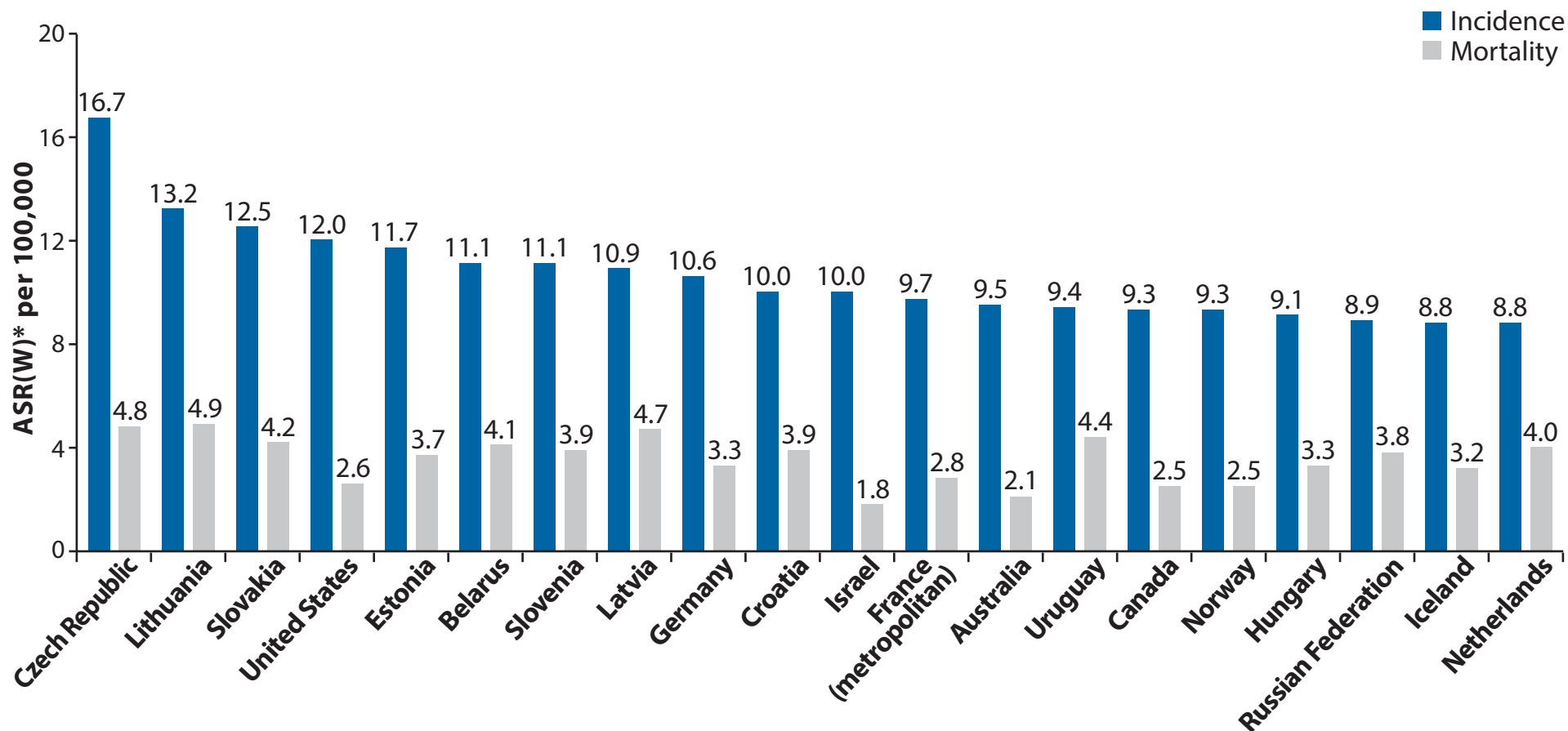


*ASR(W): Age-standardized rate with world standard population

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 1/7/2015.

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

GLOBOCAN 2012 (IARC)

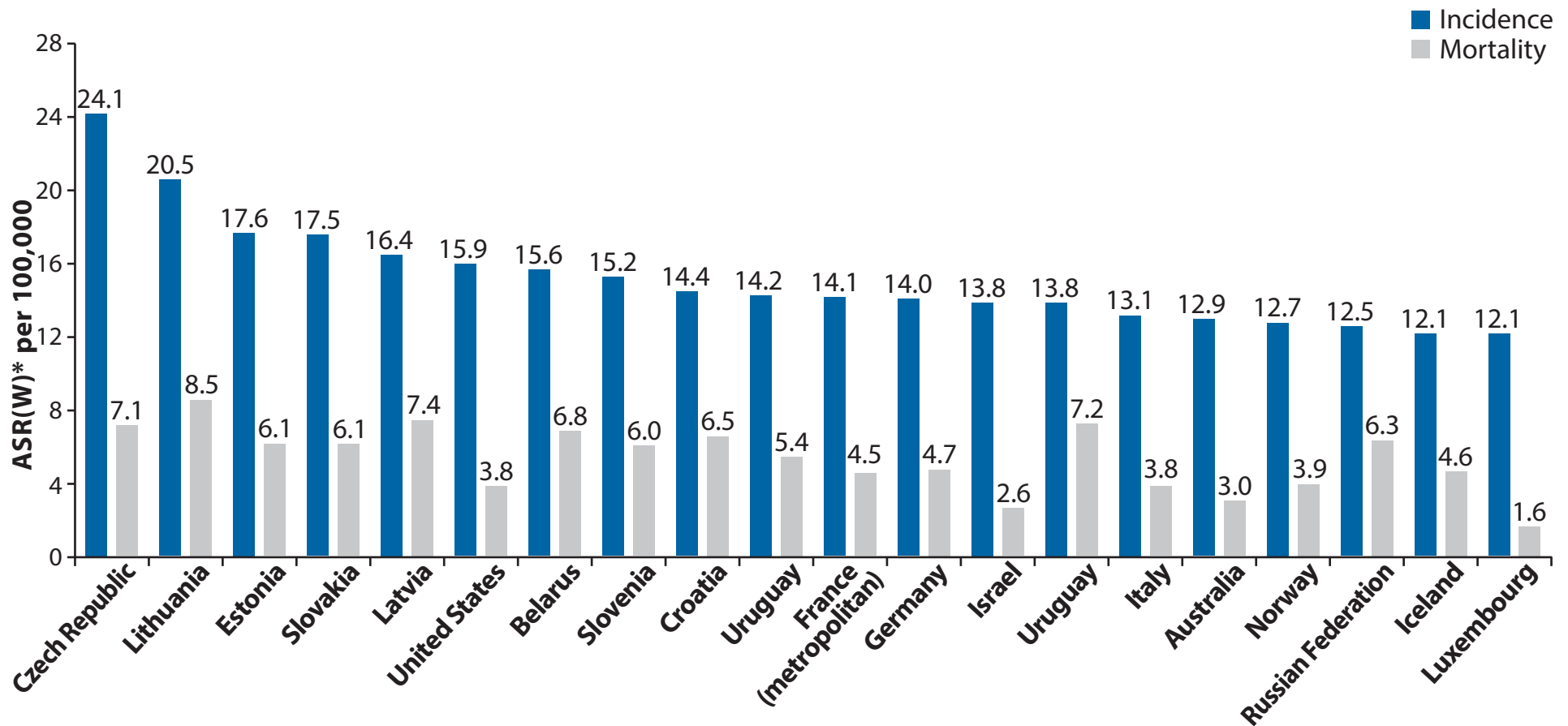


*ASR(W): Age-standardized rate with world standard population

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 1/7/2015.

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

GLOBOCAN 2012 (IARC)

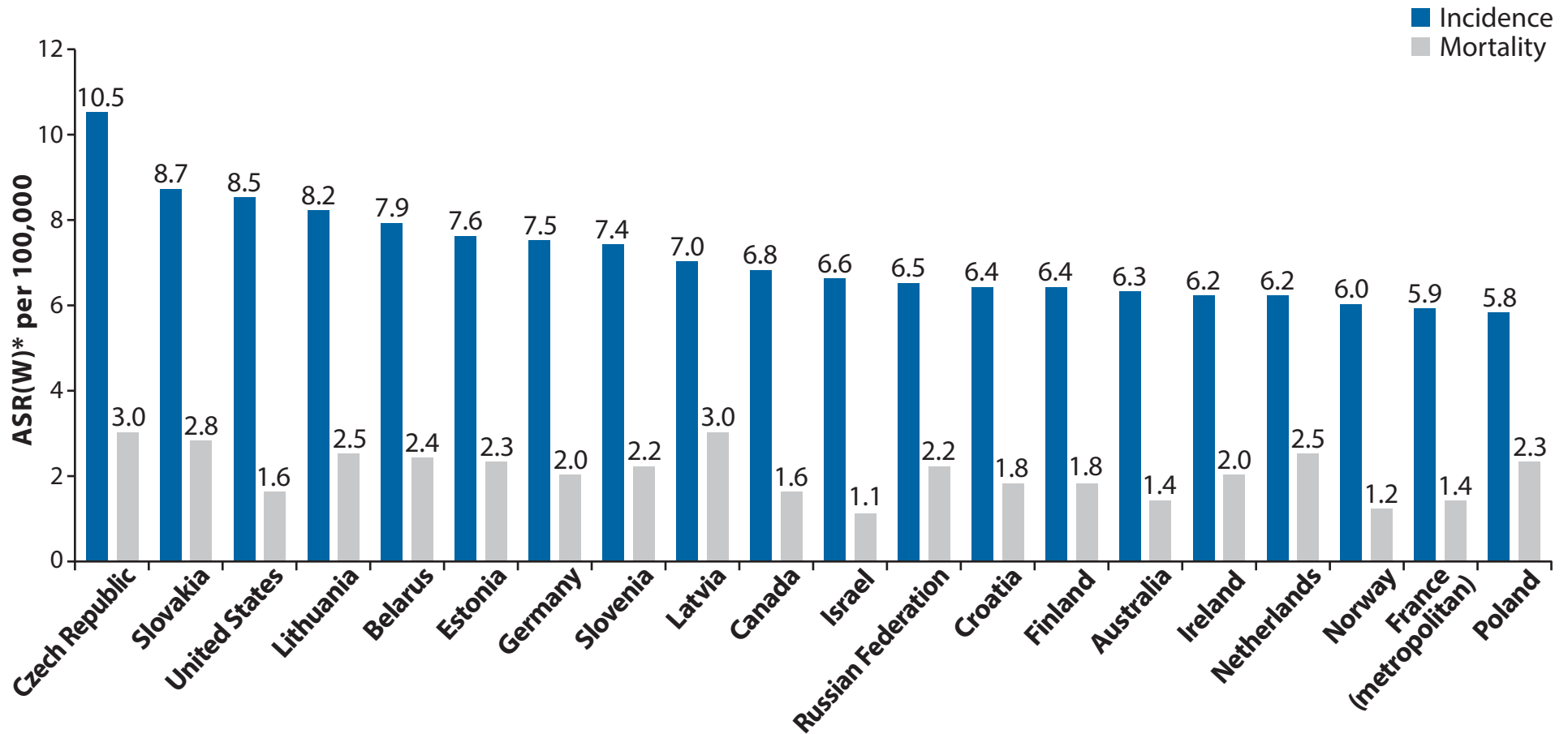


*ASR(W): Age-standardized rate with world standard population

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 1/7/2015.

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

GLOBOCAN 2012 (IARC)



*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 1/7/2015.

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

	Life Expectancy	Incidence / Mortality Rate*
China	72.38 (male) & 77.37 (female) [2010, National Bureau of Statistics]	5.75 / 1.89 [2012, Chinese Cancer Registry Annual Report] [4.5/1.45 in 2009]
Hong Kong	81.1 (male) & 86.7 (female) [2013]	4.4 (male 6.5 , female 2.4) / 1.6 (male 2.1 , female 0.7) [2012]
India	67 (male) & 69 (female) [2011, Ministry of Health and Family Welfare]	0.9 / 0.6 [GLOBOCAN 2012]
Indonesia	69.59 (male) & 74.88 (female) [2014]	1.5 / 1.2 [GLOBOCAN 2012]
Japan	80 (male) & 86 (female) [2010, Ministry of Health, Labour and Welfare]	7.3 / 1.9 [2011 / 2012] (C64-C66, C68: ICD-10)
Malaysia	–	–
Philippines	68.55 [2012, WHO]	Limited data from registries of urologic training institutions
Singapore	80.2 (male) & 84.6 (female) [Ministry of Health 2008-2013]	8.1 / 2.9 [National Disease Registry Office 2009-2013]
South Korea	78.51 (male) & 85.06 (female) [2013]	5.9 (male 8.7 , female 3.4) / 1.9 [2012 / 2013] [Ministry of Health & Welfare, Cancer Statistics 2012]
Taiwan	76.7 (male) & 83.3 (female) [2012]	3.4 (male 5.9 , female 3.0) / 1.6 (male 2.6 , female 1.9) [2011]
Thailand	70.7 (male) & 77.4 (female) [2014]	1.2 / 0.7 [2012]

* 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) Criteria for Nephron-sparing Surgery in the Panel Members' Countries

	Criteria
China	T1 and T2 depending on technical feasibility, size of tumor, and location.
Hong Kong	T1 and T2 depending on size of tumor and location.
India	T1 and T2 depending on size of tumor and location.
Indonesia	T1a (≤ 4 cm), and selected cases of T1b (4-7 cm).
Japan	Partial nephrectomy is recommended for T1a and T1b tumors, and can be optional for T2 tumors. Indication of partial nephrectomy relies on both tumor size and tumor location.
Malaysia	–
Philippines	Tumor size < 4 cm, sometimes greater (T1a and T1b) where technically feasible; the use of renal anatomic classification systems (RENAL or PADUA scoring) to prognosticate difficulty of surgery is also employed.
Singapore	Tumor size < 4 cm, technically feasible, anatomical or functional solitary kidneys, presence of CKD, tumor size < 7 cm in selected exophytic lesions in high volume centers.
South Korea	There is no specific definition of a cut-off size, and nephron-sparing surgery may be performed whenever technically feasible. However, we take caution for pT3a > 4 cm, as it may have aggressive features.
Taiwan	Tumor size (< 7 cm), T1a (majority), T1b (selected cases); > 7 cm (in angiomyolipoma case and highly selected RCC, ex. Single kidney)
Thailand	T1a (≤ 4 cm), T1b (4-7 cm; selected cases).

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

I) Active Surveillance (AS) in the Panel Members' Countries

	Status of AS	Biopsy Preceding AS
China	Only indicated in short life expectancy, with serious comorbidities and small RCC patients.	Not stringently required.
Hong Kong	Uncommon. RFA is considered in special cases.	Preferable to have biopsy before AS.
India	Uncommon. RFA is considered in special cases.	Uncommon.
Indonesia	AS is uncommon.	No biopsy in case of AS.
Japan	AS is not so common. It would be recommended for small renal mass (SRM) in elderly patients, or patients with comorbidity.	Renal mass biopsy preceding AS is uncommon. However, it is increasing slightly especially in patients with SRM whose diagnosis is difficult with imaging.
Malaysia	–	–
Philippines	Not a common option; employed only in patients with poor surgical risk factors and patients of very advanced age with small renal masses or solitary kidneys.	Low rate of needle biopsies preceding active surveillance.
Singapore	Option in patients with small renal masses <4 cm and significant comorbidities / poor surgical candidate.	Advised for biopsy preceding AS.
South Korea	No definite guidelines for AS for RCC. AS is seldom performed, and depends on physician's discretion.	If AS has been decided on, biopsy may be omitted for definite tumors. Biopsy may be performed for indefinite tumors. However, it depends on physician's preference.
Taiwan	In selected cases: small tumor, elderly patient, patient can not tolerate surgery because of major comorbidity.	Percutaneous biopsy is suggested in all cases.
Thailand	AS is uncommon, and it depends on physician's decision.	No biopsy in AS.

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

J) Major Drugs for the Treatment of Kidney Cancer in the Panel Members' Countries

	Approved	Application Filed
China	IFN-α, IL-2, sorafenib, sunitinib, everolimus. ^{6,7}	Temsirolimus, axitinib.
Hong Kong	Sunitinib, pazopanib, bevacizumab + IFN, temsirolimus, everolimus, axitinib, sorafenib.	–
India	IFN-α, IL-2, sorafenib, sunitinib, temsirolimus, pazopanib, everolimus, axitinib, bevacizumab.	–
Indonesia	Sorafenib, sunitinib, pazopanib, temsirolimus.	–
Japan	IFN-α, IL-2, sorafenib, sunitinib, temsirolimus, pazopanib, everolimus, axitinib.	–
Malaysia	–	–
Philippines	IFN-α, sorafenib, sunitinib, temsirolimus, pazopanib, everolimus.	–
Singapore	Sunitinib, pazopanib, bevacizumab + IFN, temsirolimus, everolimus, axitinib, sorafenib, IL-2.	–
South Korea	IFN-α, IL-2, sorafenib, sunitinib, temsirolimus, pazopanib, everolimus, bevacizumab.	–
Taiwan	IFN-α, IL-2, sorafenib, sunitinib, temsirolimus, pazopanib, everolimus, axitinib.	–
Thailand	IFN-α, IL-2, sorafenib, sunitinib, temsirolimus, pazopanib, everolimus, axitinib.	–

Note: References are listed on ACS #6a. Data has been collected from the panel members as of July 2015.

K) Post Marketing All-case Surveillance in the Panel Members' Countries

	Post Marketing All-case Surveillance
China	Post marketing data of sorafenib, sunitinib and everolimus are consistent with the published.
Hong Kong	No all-case surveillance, but retrospective analysis of patients in post-targeted therapy era is ongoing.
India	Data not available.
Indonesia	Data not available.
Japan	Post marketing all-case surveillances on sorafenib, sunitinib and everolimus are to be published. ^{1,2}
Malaysia	–
Philippines	No published post-marketing surveillance data yet. Studies may be under way.
Singapore	Asian patients noted to have lower adverse effects with dose reduction of sunitinib.
South Korea	The consensus is that the clinical benefits of sunitinib, sorafenib, and everolimus outweigh safety issues. The toxicity profile of these drugs in Korean men is presented in appendix L. ^{3,4}
Taiwan	Incidence for hand-foot syndrome of sunitinib are higher than in western countries. ^{5,6}
Thailand	Data not available.

Note: References are listed on ACS #6a. Data has been collected from the panel members as of July 2015.

L) Post Marketing All-case Surveillance in South Korea

	Sunitinib ³ (n=74)	Everolimus ⁴ (n=100)	Sorafenib
Hematologic (%)			Data not yet available.
Anemia	85	80	
Leukopenia	55	–	
Neutropenia	60	16	
Thrombocytopenia	70	35	
Lymphocytopenia	–	28	
Non-hematologic (%)			
Hand-foot syndrome	47	–	
Hypertension	31	–	
Diarrhea	16	12	
Asthenia	57	47	
Nausea	44	24	
Vomiting	–	6	
Stomatitis	50	44	
Rash	19	32	
Edema	–	7	
Abdominal pain	26	24	
Hemorrhage	26	14	
Pneumonitis	–	27	
Pneumonia	–	7	

Note: References are listed on ACS #6a. Data has been collected from the panel members as of July 2015.

M) Availability and Prevalence of IL-2 for the Treatment of Kidney Cancer in the Panel Members' Countries

	Availability and Prevalence
China	IL-2 is available. 18 MIU / d, IH, 5 d / W 1 week, 9 MIU q12 hr, d1-2, 9 MIU QD, d 3-5 3 weeks.
Hong Kong	Available but not used.
India	Available but not used.
Indonesia	IL-2 is not commonly used.
Japan	Favorable results were obtained by treatment with IFN- α or low dose IL-2, or their combination, especially for patients with lung metastases. High dose IL-2 is not available in Japan.
Malaysia	–
Philippines	IL-2 is available, but not commonly used.
Singapore	IL-2 available. 600,000 IU over 15 min q8 hr up to 14 doses.
South Korea	Cytokine therapy (IL-2 or IL-2 + IFN- α or IL-2 + IFN- α + fluorouracil) is available and is reimbursed by the NHI. However, it is seldom used after the advent of TKIs.
Taiwan	Use IL-2 is uncommon, treatment is by medical oncologist only.
Thailand	IL-2 is not commonly used.

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

N) Imaging Modalities Used for Initial Workup and Follow-up in the Panel Members' Countries

	Initial Workup	Follow-up
China	CR or MRI is used. Bone scintigraphy is only indicated with bone syndrome, elevated alkaline phosphatase (ALP) level, T3 and higher stage or N1 patients.	Chest x-ray, abdominal US, and CT
Hong Kong	CT, MRI, PET	CT
India	US and CT	US and CT
Indonesia	CT with contrast (most common) or MRI. Bone scintigraphy as indicated by symptoms or elevated ALP level. Chest CT if suspicious lesions present in chest x-ray.	CT or MRI
Japan	US is used for screening, but not for staging.	CT scan is common. Interval of CT scan depends on the pathologic stage. Bone scintigraphy is not routinely done, but used only for patients with symptoms.
Malaysia	–	–
Philippines	CT, MRI, PET	CT
Singapore	CT thorax and abdomen	CT thorax and abdomen
South Korea	Abdominal-pelvic CT, chest imaging, and bone scan if clinically indicated. US or MRI may be considered if indefinite findings on CT.	Abdominal-pelvic CT, chest imaging, and bone scan if clinically indicated.
Taiwan	CT, bone scintigraphy, MRI for IVC thrombus	CT and sonography
Thailand	CT and MRI for whole abdomen	Abdominal US, CT, and chest x-ray

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

O) 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 used by some citizens.
Thailand	<ol style="list-style-type: none"> 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%).

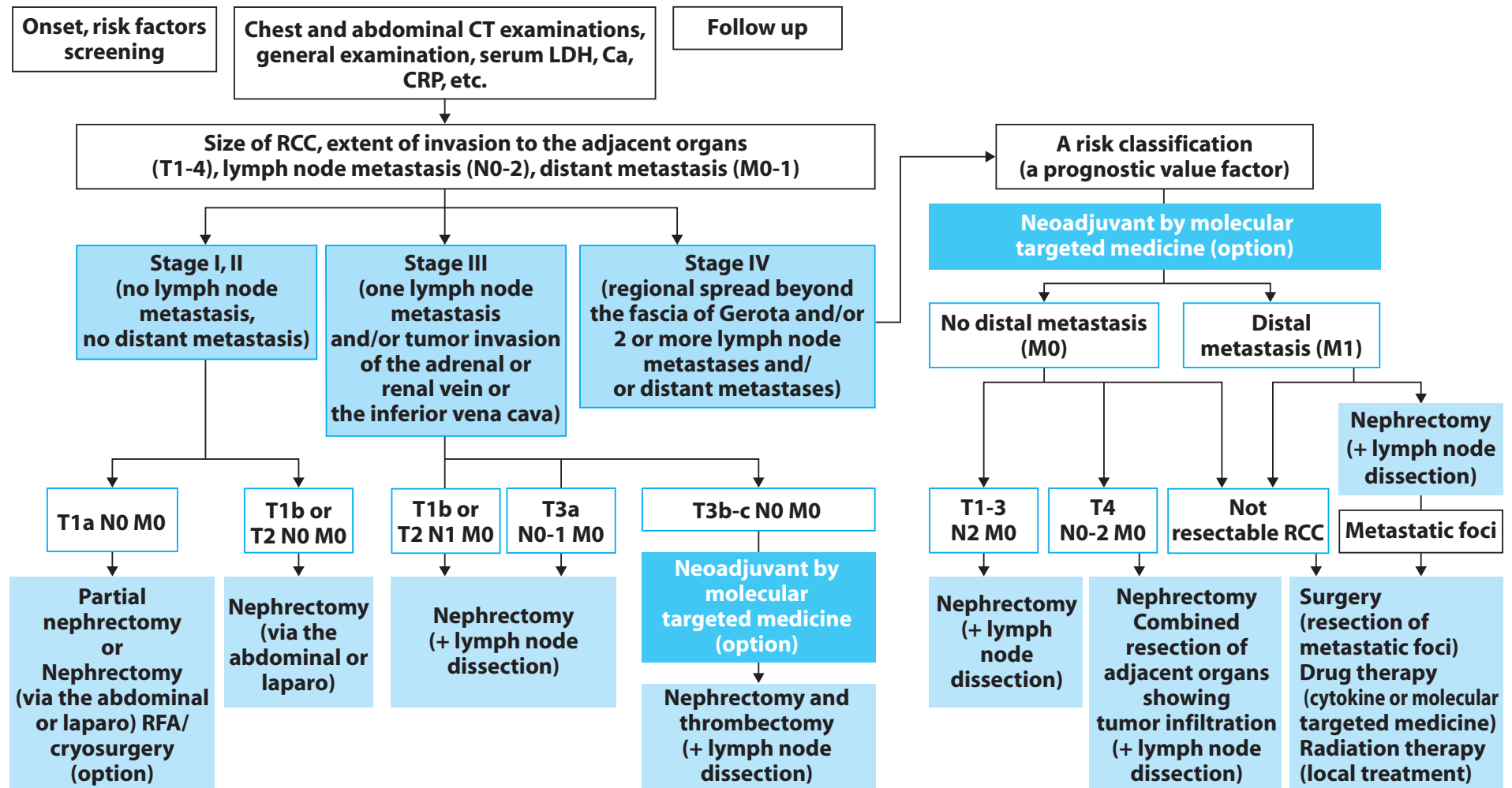
Note: Data has been collected from the panel members as of July 2015.

P) Clinical Practice Guidelines in the Panel Members' Countries

	Domestic Clinical Guidelines	Year of Publication / Revision	English Version
China	By the Chinese Urological Association and Chinese Society of Clinical Oncology.	Published in 2006 . Revised in 2014 .	–
Hong Kong	Guidelines in individual institutes.	–	–
India	No guidelines available.	–	–
Indonesia	By Indonesian Urological Association.	1st edition in 2012 .	–
Japan	By the Japanese Urological Association.	Published in 2009 . Revised in 2011 .	Yes
Malaysia	–	–	–
Philippines	Following NCCN and AUA recommendations.	–	–
Singapore	Yes	2012	Yes
South Korea	By the Korean Urological Oncology Society.	Published in 2003 . Revised in 2012 .	–
Taiwan	By Taiwan Urological Association. Available from each medical center.	Published in 2011 . Revised in 2014 . Will be revised every year.	Yes
Thailand	–	–	–

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

Q) Japanese Clinical Practice Guideline for Renal Cell Carcinoma



Translated from Japanese into English by Japanese ACS members.

Source: Japanese Urological Association eds. Clinical Practice Guidelines for Kidney Cancer 2011. Kanehara & Co.;2011;p 6.