

## Kidney Cancer Working Group Report

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Kidney cancer accounts for approximately 2% of all cancers worldwide, with renal cell carcinoma being the most common form and this report is focused on renal cell carcinoma. Globally, the incidence and mortality rates are increasing by 2–3% per decade. Kidney cancer is less common in Asia compared with the West. Cigarette smoking, obesity, acquired cystic kidney disease and inherited susceptibility are known risk factors for kidney cancer. The National Comprehensive Cancer Network Guidelines recommend surgical excision as first line of treatment for Stage I, II or III kidney cancer patients and Stage IV patients with resectable tumours. Immunotherapy has a 20-year history in treatment of metastatic kidney cancer. High-dose interleukin-2 (IL-2) is administered in some countries, whereas low-dose IL-2 and interferon-alpha (IFN- $\alpha$ ) are popular in Japan. Molecular-targeted drugs, including sunitinib, bevacizumab and sorafenib, are being used for previously untreated and refractory patients. Asian and non-Asian populations have shown large differences in the incidences of adverse events with sorafenib and sunitinib. Consensus Statement: Kidney cancer is relatively uncommon in Asia compared with the West, but its incidence is increasing in more developed Asian nations. Guidelines from the National Comprehensive Cancer Network, etc., for treating metastatic renal cell carcinoma are based on Phase III clinical trials conducted primarily in Western patients. Targeted therapies are now becoming primary recommendations, but efficacy/toxicity data from Asian patients are lacking. Some drugs cause adverse effects in Asians because their recommended dosages are optimal for Caucasians but may be too high for Asians. Further research is necessary to develop optimal treatment strategies for Asians.

*Key words: Renal cell carcinoma – Asia – Guidelines – Racial differences*

### THE WORKING REPORT UROLOGICAL CANCER

Kidney Cancer presentation was divided into five chapters: epidemiology, risk factors, treatment of local disease, systemic therapy for metastatic disease and the Working Group's consensus statement. The consensus statement is focused on renal cell carcinoma (RCC) and was prepared on the basis of evidence from data published in peer-reviewed journals or texts, or abstracts from renowned international congresses, such as AUA, ASCO, ESMO and EAU.

### EPIDEMIOLOGY

Kidney cancer accounts for approximately 2% of all cancers worldwide. RCC is the most common form of kidney cancer (1). The rates of incidence vary more than 10-fold among regions (2). The more-developed countries show higher incidences of kidney cancer in both males and females, whereas the incidences in both sexes are lower in the less-developed countries. Higher incidences of kidney cancer are seen in Europe, North America, Argentina, Oceania and Japan. Lower incidence rates are seen in Africa and other Asian

**Table 1.** Overview of RCC epidemiology (1,2)

|   |
|---|
| Kidney cancer accounts for approximately 2% of all cancers worldwide (1)                              |
| Renal cell carcinoma (RCC) is the most common form of kidney cancer (1)                               |
| Rates of incidence vary more than 10-fold between regions, with higher rates in developed nations (2) |
| Globally the incidence and mortality rates are increasing 2–3% per decade (2)                         |

countries. Japan shows higher incidences than those seen in other Asian countries (3). Globally, the incidence and mortality rates for kidney cancer are increasing by 2–3% per decade (Table 1). The incidence of kidney cancer in each of three global regions, Asia, Europe and the USA, is increasing with time. Although the reason is unclear, the incidence is decreasing in Sweden (4).

There are racial disparities in RCC incidence and survival. Data from the California Cancer Registry show a lower incidence and higher survival among Asians and Pacific Islanders compared with whites, blacks and Hispanics. However, regardless of race, the incidence is increasing (5).

In Japan, the percentage of incidental kidney tumours has been increasing. This may be due to the increased prevalence of screening and imaging systems. However, and unfortunately, in Malaysia and other developing countries symptomatic tumours still account for 80–90% of kidney tumour cases (expert opinion).

Data from Keio University (Tokyo, Japan) for the period from 1985 to 2003 revealed the characteristics of RCC in Japan (Table 2) (6). A total of 545 patients underwent radical or partial nephrectomy. Three-quarters of the patients were male, and the mean age at diagnosis was 58 years. The mean tumour size was 4.8 cm. Radical surgery was performed for 82% and nephron-sparing surgery was performed for 18% of the patients. Adjuvant immunotherapy, such as IFN- $\alpha$  or IL-2, was administered to 22% of the patients. Regarding the T stage, T1a accounted for 50%, T1b 20% and T2 around 13%. Thus, over 80% were T2 or less, and curative surgery is possible for those cases. N1 plus N2 accounted for about 5% of the cases and M1 accounted for 8%. These characteristics may be similar in other institutions in Japan, but it is unclear whether they are similar in other Asian countries.

**RISK FACTORS**

Cigarette smoking, obesity, acquired cystic kidney disease and inherited susceptibility, such as Von Hippel–Lindau disease, are established risk factors for kidney cancer (Table 3) (7,8). Factors that need further study or remain controversial include dietary factors, such as protein, dietary fat, a ‘Western’ diet, and inadequate intake of protective fruits and vegetables. Also in need of further study are possible roles for hypertension and/or antihypertensive

**Table 2.** Characteristics of Japanese RCC patients who underwent surgical treatment at Keio University Hospital between 1985 and 2003 (6)

|                                |      |        |
|--------------------------------|------|--------|
| No. patients                   | 545  |        |
| No. sex: (%)                   |      |        |
| M                              | 419  | (76.9) |
| F                              | 126  | (23.1) |
| Mean age at diagnosis          | 58.1 |        |
| Mean tumour size (cm)          | 4.82 |        |
| No. nephrectomy type (%)       |      |        |
| Radical                        | 447  | (82.0) |
| Nephron sparing                | 98   | (18.0) |
| No. adjuvant immunotherapy (%) | 121  | (22.2) |
| No. TNM T (%)                  |      |        |
| T1a                            | 272  | (49.9) |
| T1b                            | 109  | (20.0) |
| T2                             | 69   | (12.7) |
| T3a                            | 56   | (10.3) |
| T3b                            | 30   | (5.5)  |
| T3c                            | 2    | (0.4)  |
| T4                             | 7    | (1.3)  |
| No. TNM N (%)                  |      |        |
| N0                             | 516  | (94.5) |
| N1                             | 14   | (2.6)  |
| N2                             | 15   | (2.8)  |
| No. TNM M (%)                  |      |        |
| M0                             | 499  | (91.6) |
| M1                             | 46   | (8.4)  |

medications, use of analgesics, reproductive factors and hormones, occupational exposures and inadequate physical activity (7–9).

**TREATMENT OF LOCAL DISEASE**

Many guidelines have been established for kidney cancer by various societies around the world, including the National Comprehensive Cancer Network (NCCN), EAU and ESMO (10–12). For treatment of local disease, the NCCN Guidelines state that surgical excision is the first line of treatment for patients with Stage I, II or III kidney cancer (10). For Stage IV, nephrectomy plus surgical metastasectomy is recommended for patients with a potentially surgically resectable, solitary metastatic site. For Stage IV patients with a potentially surgically resectable primary lesion and multiple metastatic sites, the recommended treatment is cytoreductive nephrectomy in select patients prior to systemic therapy. Medical treatment is recommended for surgically unresectable Stage IV disease. Thus, surgery is the first choice of treatment for local and resectable kidney tumours.

**Table 3.** Risk factors of RCC (7–9)

| Established                             | Needing further study or controversial   |
|---|--|
| Cigarette smoking (7,8)                 | Dietary factors (7–9)<br>Protein, dietary fat, ‘Western diet’<br>Vegetables and fruit (protective)   |
| Obesity (7,8)                           | Hypertension and/or antihypertensive medications (7,9)   |
| Acquired cystic kidney disease (7)      | Analgesics (7)   |
| Inherited susceptibility (e.g. VHL) (7) | Reproductive factors and hormones (e.g. parity, oral contraceptives) (7)<br>Occupational exposures (e.g. asbestos, cadmium, hydrocarbons, gasoline, trichloroethylene) (7,8)<br>Physical activity (protective) (8) |

The Japanese Urological Association Guidelines also provide an algorithm for the management of local tumours (Table 4) (13). As in the NCCN Guidelines, it is recommended that T1a, T1b and T2 without metastasis be treated by partial or radical nephrectomy. The surgery can be open surgery or laparoscopic. In the case of N1 or T3 stage disease, nephrectomy plus lymph node dissection and/or extirpation of tumour emboli is recommended. Thus, again, surgery is the treatment of first choice for local RCC.

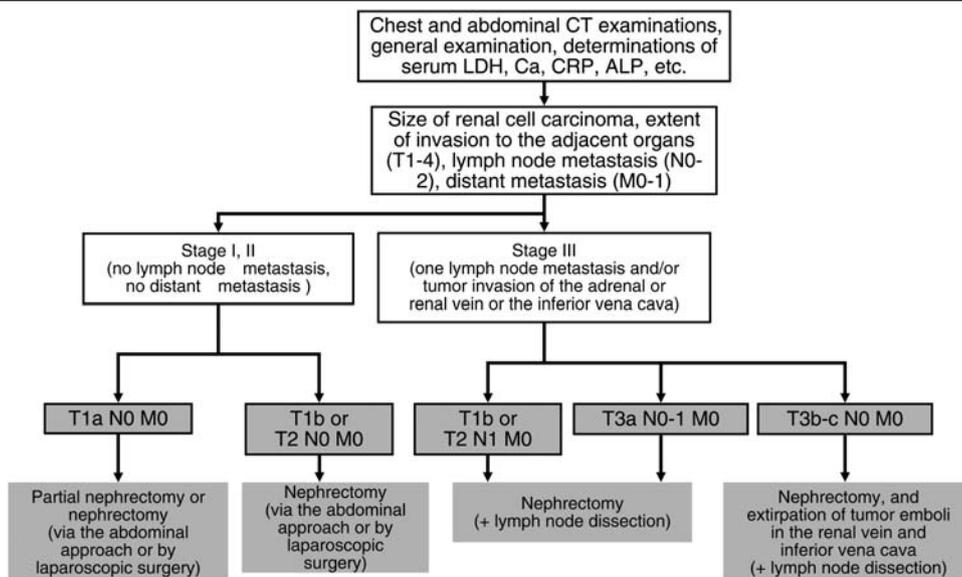
There are various advantages and limitations with each approach to the management of local tumours (Table 5) (14). In the case of radical nephrectomy, the oncological effectiveness has been established, and laparoscopic surgery is possible. However, this treatment presents an increased risk of chronic kidney disease. In the case of partial

nephrectomy, the oncological effectiveness is similar to that of radical nephrectomy, it preserves renal function, and in selected patients it can be performed laparoscopically. However, with partial nephrectomy there is a slight risk of postoperative haemorrhage or urinary leak. Recently, some institutions performed minimally invasive procedures, including radiofrequency ablation or cryoablation. However, limitations of such techniques are that their long-term oncological effectiveness has not yet been established and local recurrence rates are somewhat higher than with open or laparoscopic surgery. Active surveillance has also become a management choice, but again, the long-term oncological outcomes have not yet been established, and patient compliance with follow-up is essential.

**SYSTEMIC THERAPY FOR METASTATIC DISEASE**

Kidney cancer patients have been treated with immunotherapy using IFN-α or IL–2 for more than 20 years. High-dose IL–2 is administered in other countries, and the objective response rate (ORR) has been 21–23% (14). A distinguishing feature is that the durable complete response rate has been 5–7%. Low-dose IL–2 and IFN-α are more popular in Japan, showing an ORR of 10– 15%. However, if this combination therapy is applied to patients with only lung metastasis, ORR reaches around 40% (15). Meta-analysis has shown an improvement in the weighted median overall survival (OS) with IFN-α compared with the control (14). Distinguishing features are that there is no evidence of a dose–response relationship and no correlation between the response rate and the OS.

**Table 4.** Algorithm for the management of local tumour (JUA Guidelines) (13)



**Table 5.** Advantages and limitations of various approaches for the management of local tumour (14)

|                     | Advantages   | Limitations  |
|---------------------|--|--|
| Radical nephrectomy | Established oncological effectiveness; can be done laparoscopically  | Increased risk of chronic kidney disease; might predispose to morbid cardiac events and increased mortality rates  |
| Partial nephrectomy | Oncological effectiveness similar to radical nephrectomy; preserves renal function; selective cases can be done laparoscopically | Small risk of postoperative haemorrhage or urinary leak; complex cases typically require conventional open surgery   |
| Thermal ablation    | Minimally invasive; repeat ablation possible   | Long-term oncological effectiveness not established; local recurrence rates higher than with surgical excision; conventional surgical salvage occasionally required and can be complicated by fibrotic reaction; radiographic parameters for success not well established; difficult to adequately treat tumours >3.5 cm in diameter |
| Active surveillance | Morbidity of intervention avoided in most patients, deferred in others; average growth rates and risk of metastasis seem low     | Long-term oncological outcomes not established; most series have substantial selection bias and limited follow-up; compliance with follow-up required  |

Regarding the prognosis of metastatic RCC patients in the cytokine era, Naito et al. reported in 2009 that 82% of 1324 metastatic RCC patients underwent cytokine therapy and showed a median survival of 21 months and a one-year survival rate of 64% (16). These data are considerably better than the data that have been reported in Western countries. Moreover, it is noteworthy that 28% of the patients underwent metastasectomy, so perhaps metastasectomy played an important role in generating these good results of longer survival and progression-free survival (PFS).

With regard to systemic therapy for metastatic disease using molecular-targeted drugs, a treatment algorithm was reported for RCC in the ASCO meeting (Table 6) (17). For previously untreated patients with good or intermediate risk, sunitinib or bevacizumab plus IFN- $\alpha$  was recommended as the first-line therapy, while other options consist of high-dose IL-2 or sorafenib. For untreated, poor-risk patients, temsirolimus was recommended as the first-line therapy, while sunitinib was an option. In the case of cytokine-refractory RCC patients, sorafenib was recommended as the first-line therapy, and sunitinib, bevacizumab plus IFN- $\alpha$  and temsirolimus were presented as options. For vascular endothelial growth factor (VEGF)-inhibitor-refractory RCC patients, the first-choice in second line therapy was everolimus. Asian guidelines are now being updated to include the latest data.

There are now five molecular-targeted therapies available in the world. All five are available in the USA, Korea, Malaysia and the Philippines, but only sorafenib and sunitinib were available in Japan as of late 2009. Temsirolimus or everolimus may be approved in 2010. Clinical data are available for sorafenib and sunitinib in terms of the median PFS data from Asian and Western studies of metastatic RCC. When sunitinib was used as the first-line therapy, the results were almost the same in Western and Japanese studies, at around 11 months for the PFS (18,19). As second-line therapies, sorafenib showed somewhat better median PFS results in Japan compared with the Western data (20,21), but sunitinib again showed no large difference (19,22). Thus, overall, there is no large difference in the PFS between Asian and Western data.

**Table 6.** Algorithm for the treatment of metastatic RCC in ASCO (17)

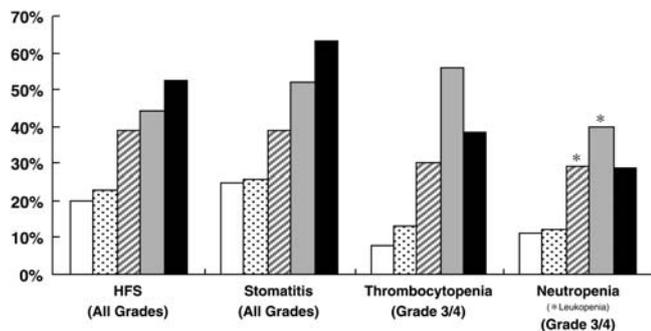
| Treatment status          | Treatment options              |  |
|---------------------------|--------------------------------|--|
|                           | Level I                        | ≥ level II                                     |
| Untreated                 |                                |  |
| Good or intermediate risk | Sunitinib<br>Bevacizumab + IFN | High-dose IL-2<br>Sorafenib                    |
| Poor risk                 | Temsirolimus                   | Sunitinib                                      |
| Previously treated        |                                |  |
| Cytokine                  | Sorafenib                      | Sunitinib<br>Bevacizumab + IFN<br>Temsirolimus |
| VEGFR inhibitor           | Everolimus                     | Data lacking                                   |
| mTOR inhibitor            | Data lacking                   | Data lacking                                   |

In terms of the ORR, Chinese and Japanese studies of sorafenib showed better rates than seen in a Western Phase III trial (20,21,23). For sunitinib, there were no differences between the Western and Japanese ORR data (18,19). However, the Korean rate was quite low, although that study is still ongoing and may show improvement later (24).

In data from the sunitinib expanded access Programme, the efficacy of sunitinib was similar in Asian and non-Asian populations in terms of both the PFS and the OS (Table 7) (25). However, large differences have been found in the incidences of adverse events with sorafenib and sunitinib in those populations. For example, the incidence of hand-foot syndrome with sorafenib was very high in Japanese patients and even higher in Chinese patients, compared with Western patients (20,21,23). Hypertension was also much higher in incidence as an adverse event of sorafenib in Asian patients compared with Western patients. With sunitinib, treatment-related hematological adverse events, including thrombocytopenia and neutropenia, were much more

**Table 7.** Sunitinib expanded access Programme: Asian subpopulation analysis (25)

|              | Asian<br>(n = 325) | Non-Asian<br>(n = 4,024) | Total<br>(n = 4,349) |
|--------------|--------------------|--------------------------|----------------------|
| Median PFS   | 8.7 m              | 10.9 m                   | 10.9 m               |
| 95% CI       | 8.1–11.1           | 10.5–11.3                | 10.3–11.2            |
| Alive, n (%) | 202 (62%)          | 2,250 (56%)              | 2,452 (56%)          |
| Median OS    | 18.9 m             | 18.4 m                   | 18.4 m               |
| 95% CI       | 15.5–23.5          | 17.4–19.2                | 17.4–19.2            |

**Figure 1.** Sunitinib treatment-related adverse events and severe haematologic adverse events (18,19,24,25).

common in Japanese patients (Fig. 1) (18,19). Those events were also elevated in incidence in Korean patients, and in Asian patients in the expanded access Programme (24,25). Sunitinib also showed higher incidences of hand–foot syndrome and stomatitis in Asian patients compared with Western patients (25).

Determination of the blood concentration of sunitinib in Western and Asian populations revealed that the concentration of this tends to be higher in Asians, in females and exaggerated in Asian females (26).

Bevacizumab is an antibody directed at VEGF protein, and combination of bevacizumab plus IFN- $\alpha$  shows a better ORR and OS compared with IFN- $\alpha$  (27,28). Temsirolimus shows significantly better PFS and OS than those with IFN- $\alpha$  in the poor-risk patients (29). Everolimus targeted RCC patients refractory to sorafenib, sunitinib or both (30). Therefore, ORR was quite low and PFS period was also short. Nevertheless, the results were still significantly better than those with the placebo. It is on the basis of such results that these three molecular-targeted agents are available in the world.

## CONSENSUS STATEMENT

In terms of epidemiology, kidney cancer is relatively uncommon in Asia compared with the West. However, the incidence is increasing in more developed Asian nations. As

more Asian nations develop economically and become more Westernized, along with the higher rates of smoking and the growing problem of obesity in Asia, it can be foreseen that the incidence of kidney cancer will continue to approach that in the West. Increased use of imaging techniques has contributed to an increase in incidental kidney cancer and early discovery of kidney cancer. For treatment of kidney cancer, guidelines from the NCCN, EAU, ESMO and other organizations have been developed based on Phase III clinical trials that were conducted primarily in Western patients. Targeted therapies are now the primary recommended treatments of choice for metastatic RCC. However, cytokines are still more widely used in some Asian countries and have been proved to be effective in selected patient populations, such as those with only lung metastasis. There is a need for more Asian clinical data. Because the pivotal trials demonstrating the benefit of targeted therapies were conducted primarily in the Western world, there is a lack of efficacy and/or toxicity data for most of those therapies in Asian patients. Some drugs are known for their adverse effects resulting from recommended dosages that are optimal for Caucasian patients but may be too high for Asian patients, possibly due to lower body surface area, or genetic and pharmacological differences. It is recommended that targeted drugs be investigated further in Asian populations to develop an optimal treatment strategy for kidney cancer in Asians in accordance with pharmacogenetic information, efficacy and tolerability.

## Conflict of interest statement

None declared.

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