Guidelines

Evidence-based clinical practice guidelines for renal cell carcinoma (Summary – JUA 2007 Edition)

Tomoaki Fujioka,† Wataru Obara1 and The Committee for establishment of the clinical practice guidelines for the management of renal cell carcinoma and the Japanese Urological Association†*

†Department of Urology, Iwate Medical University School of Medicine, Morioka, Iwate; †Japanese Urological Association, Tokyo, Japan

Abstract: The text of these guidelines was published for general clinicians, general urologists, and patients, with the aim of providing a system of effective and efficient clinical practices for managing renal cell carcinoma based on evidence-based medicine–intended techniques. The guidelines contain the answers to a total of 21 clinical questions (CQ) that were formulated under the headings of ‘risk factors and prophylaxis,’ ‘diagnosis,’ ‘surgical treatment and local treatment,’ and ‘systemic treatment,’ along with the recommendation grades and systems/algorithms for clinical practice based on structured abstracts prepared through critical reviews of the relevant published reports; the literature search was conducted using the key words for each CQ. An abridged edition of these guidelines can be found on the web pages of the Japan Society of Clinical Oncology and the Medical Information Network Distribution Service.

Key words: clinical practice guidelines, renal cell carcinoma, webifying.

Introduction

In October 2005, the Japan Society of Clinical Oncology (JSCO) constituted a working team for ‘Research on application and evaluation of clinical practice guidelines for cancer’ (Team leader, Prof. Koichi Hirata; First Department of Surgery, Sapporo Medical University), as part of the 2005 to 2006 Ministry of Health, Labor and Welfare (MHLW) mission of ‘Thorough Research for the Evaluation of Medical Technologies,’ to start the process of establishing clinical practice guidelines for seven types of cancers (colorectal cancer, esophageal cancer, carcinoma of the biliary tract, pancreatic cancer, ovarian cancer, renal cell carcinoma (RCC), and skin cancer), with a view to publishing the guidelines on the internet. The Japanese Urological Association (JUA) constituted a committee, the ‘RCC Subcommittee,’ for establishing clinical practice guidelines for managing RCC, and published ‘Clinical practice guidelines for managing RCC,’ edited by the JUA in October 2007 (Table 1). Prior to the publication of these guidelines, ‘The Abridged Edition of the Clinical Practice Guidelines for Managing RCC and Clinical Practice Algorithm’ was published in the web pages of the JSCO in April 2007. In addition, preparation is ongoing for publishing the entire text of the guidelines in the web pages of the JSCO and the Medical Information Network Distribution Service (MINDS). The method of preparation and an outline of the guidelines are presented in the present paper.

Editorial Comment

Current status of use of molecular targeted drugs in Japan

On the following pages, we present the English version of guidelines published in Japan before molecular targeted drugs for renal cancer became available. This editorial briefly summarizes the current status of use of molecular targeted drugs in Japan.

In recent years, approaches have been proposed in various management guidelines in Western countries concerning indications and applications of molecular targeted drugs developed to target molecules with important roles in the onset and progression of renal cell carcinoma. In Japan, sorafenib (Nexavar) and sunitinib (Sutent) were approved for national health insurance coverage and launched in April and June 2008, respectively.

The results of a phase II clinical study on sorafenib carried out in Japan on 131 patients with renal cancer who had been treated previously with cytokines after nephrectomy, who were inoperable or who had metastatic cancer showed that the effects were equivalent to those obtained in other developed countries. In a phase II clinical study in Japan on sunitinib in 51 patients who had been untreated or treated with cytokines after nephrectomy, who were inoperable or resistant to cytokine treatment.

It is necessary to bear in mind that there are differences in incidences of adverse events between Western countries and Japan when molecular targeted drugs are used.

All patients given sorafenib and sunitinib must be registered as part of the post-marketing surveillance process. As of February 2009, more than 1300 patients have been registered for sorafenib and more than 400 for sunitinib.

With the availability of molecular targeted drugs, major changes are occurring in the treatment of progressive renal cell carcinoma in Japan.

Tomoaki Fujioka MD
Department of Urology, Iwate Medical University School of Medicine
Morioka, Japan
tomof@iwate-med.ac.jp

© 2009 The Japanese Urological Association

339
Preparation of guidelines for the management of RCC

Purpose

These evidence-based medicine (EBM)–intended guidelines, namely, guidelines based on ‘conscientious, accurate, careful utilization of optimal up-to-date information to make a medical decision for an individual patient,’ are aimed at providing guidance for a systematic approach to effective and efficient clinical practices in the management of RCC by emphasizing the evidence available for each medical practice and indicating the grade of each recommendation, taking into consideration its current status.

Method

The guidelines were prepared according to ‘A guide to preparing clinical practice guidelines for cancer, 4th edition; JSCO.’ First, utilizing the
accumulated expertise of the committee members responsible for establishing the guidelines, a total of 174 clinical questions (CQ) relevant to clinical practices were raised, assembled and arranged, to eventually select a total of 21 most relevant CQ, including six related to diagnosis and prophylaxis, eight related to surgical and local treatments, and seven related to systemic treatment. Key words were identified to conduct a search of the literature for articles relevant to each of the CQ. A search of PubMed or Japan Centra Revuo Medicina (Igakushi Chuo-Zasshi) and the Cochrane Library was conducted to retrieve relevant articles published during the 10-year period from 1996 to 2005. A total of 748 articles extracted were allotted to a total of 269 reviewers, that is, affiliates and referees of the JSCO, at 67 universities, for critical reviews of the articles, followed by compilation of primary structured abstracts from them. In addition, the members of the committee for the development of the guidelines who were involved in the preparation of the respective CQ, as well as members of a supporting committee, redrafted the primary structured abstracts for re-evaluation of their evidence levels and then selected 236 articles for compiling the secondary structured abstracts. Based on these final structured abstracts, a clinical practice algorithm and ‘recommendation grade,’ ‘rationale,’ and ‘description’ were created for each CQ.

The evidence levels and recommendation grades were rated according to ‘A guide to preparing clinical practice guidelines for cancer;’ while the answers and recommendation grades for the CQ prepared that were based on a low level of evidence were based on discussions and agreements among members of the committee for the development of the guidelines (Consensual recommendations) (Tables 2,3). Namely, recommendation grade C was subdivided into recommendation grade C1 (a treatment or practice that can be performed routinely although there is insufficient evidence) and recommendation grade C2 (a treatment or practice that should not be adopted routinely because there is insufficient evidence).

### Clinical practice guidelines for managing RCC

#### Algorithm of clinical practice for RCC (Fig. 1)

The descriptions of the disease stages of RCC are adopted from ‘General Rule for Clinical and Pathological Studies on Renal Cell Carcinoma, 3rd edition.’ In the present guidelines, nephrectomy is classified into the following three types: open or laparoscopic nephrectomy to remove the entire kidney together with the circumferential fat tissues after fixing the renal vein as a curative treatment of cancer, conventional radical nephrectomy performed together with adrenalectomy, and extirpation of the affected parts of the kidney aimed at reducing the tumor burden. Comments are provided in regard to the rationale for each procedure in the clinical practice algorithm. While the use of molecular-targeted drugs for patients with progressive diseases had not been approved in Japan at the time of publication of the present guidelines (October 2007), the guidelines refer to these drugs because of the possible significant changes in the clinical treatment of RCC with the introduction of such drugs.

#### Clinical problems/clinical questions (CQ)

All the CQ, their recommendation grades and rationales are listed below.

**CQ 1**

Is it recommended to call attention to obesity, occupations, lifestyle habits, environment, and genetic factors with respect to development of RCC?

**Recommendation Grade B:** Obesity, smoking, and workplaces where organic solvents or metals are used may increase the risk of development of RCC. Accordingly, it is recommended to call a patient’s attention to such risk factors, if any are present. Particular caution is required in patients with dominantly inherited kidney cancers, including von Hippel-lindau (VHL) disease and Birt-Hogg Dube (BHD) syndrome.

#### Rationale

According to a survey by the Japanese Society of RCC in 2002, the age-adjusted incidence rate of RCC is 8.2 and 3.7 per 100 000 population in men and women, respectively. Risk factors for RCC include obesity, hypertension and smoking. In regard to obesity, individuals with a body mass index (BMI) of >30 kg/m² are at a fourfold higher risk of developing RCC as compared to individuals with a BMI in the normal range. The risk in individuals with hypertension has been reported to be twice as high as that in normotensive individuals (evidence level 2a). Among lifestyle habits, smoking has been reported as a risk factor (2b). By contrast, ingestion of vegetables and fruits has been reported to lower the incidence of RCC by approximately half. With respect to occupations and workplaces, exposure to oil-related chemicals or metals such as cadmium was shown to be associated with an increase in the risk of development of RCC (2b).

Concerning genetic factors, a marked increase in the risk is noted in individuals with dominantly inherited kidney cancer syndromes, including VHL disease which is associated with central nervous system hemangioblastoma, or BHD syndrome which is associated with small tumors on the facial skin. Approximately 40% of relatives of patients with VHL disease develop RCC (1a), (1b). Organic solvents and some species of
CQ 2

What are the types of examinations that are useful for early detection of RCC?

Recommendation Grade B: Abdominal ultrasonography (US) is useful for early detection of RCC, while a computed tomography (CT) scan would yield a definitive diagnosis.

Recommendation Grade C2: Neither examination of the urine for microscopic hematuria nor intravenous pyelography is useful.

Rationale

Among 219,640 individuals who underwent abdominal US during routine health examination, 192 cases (0.09%) were found to have RCC, (2b). A similar detection rate around 0.1% was reported by several studies, which is higher than that of other malignancies. The proportion of stage I + II RCC was 74.6% among those found to have RCC incidentally during routine examination. This proportion of stage I + II RCC was significantly higher as compared with the proportion (35.8%) of patients with symptoms (4). On the other hand, abdominal CT is considered to be useful for making a definitive diagnosis of RCC. The procedure is superior to abdominal US, particularly for demonstrating small RCC such as in cases of VHL disease (3b). From the standpoint of the detection rate and the cost-effectiveness, it would be better to perform abdominal US first as a screening test and then employ CT for a definitive diagnosis.

It has been reported that urinalysis is not helpful for the detection of RCC. Emamian et al. performed abdominal US in 686 individuals who underwent mass screening with urinary occult-blood test strips. While 30 cases (5%) showed a positive urinary occult-blood test, the incidence rate of morphological abnormalities of the kidney in positive and negative urinary occult-blood tests was 10% and 8.4%, respectively, which was not a statistically significant difference (2b).
Onset, risk factors, screening

Chest and abdominal CT examinations, general examination, determinations of serum LDH, Ca, CRP, ALP, etc.

Size of renal cell carcinoma, extent of invasion to the adjacent organs (T1-4), lymph node metastasis (N0-2), distant metastasis (M0-1)

Follow up

Stage I, II (no lymph node metastasis, no distant metastasis)

Stage III (one lymph node metastasis and/or tumor invasion of the adrenal or renal vein or the inferior vena cava)

Stage IV (regional spread beyond the fascia of Gerota and/or 2 or more lymph node metastases and/or distant metastases)

T1a N0 M0

Partial nephrectomy or nephrectomy*1 (via the abdominal approach or by laparoscopic surgery)

T1b or T2 N0 M0

Nephrectomy*1 (via the abdominal approach or by laparoscopic surgery)

T1b or T2 N1 M0

Nephrectomy*2 (+ lymph node dissection)

T3a N0-1 M0

Nephrectomy*2, and extirpation of tumor emboli in the renal vein and inferior vena cava (+ lymph node dissection)

T3b-c N0 M0

No remote metastasis (M0)

Remote metastasis (M1)

T1-3 N2 M0

Nephrectomy*2 (+ lymph node dissection)

T4 N0-2 M0

Nephrectomy*2 Combined resection of adjacent organs showing tumor infiltration (+ lymph node dissection)

Nephrectomy*3 (+ lymph node dissection)

Nonresectable kidney

Surgery (resection of metastatic foci) [CQ 13]
Drug therapy [CQ 16, 17, 19, 20]
Radiation therapy (local treatment) [CQ 15]

Fig. 1 Algorithm of clinical practice for renal cell carcinoma. LDH, lactate dehydrogenase; Ca, calcium; CRP, C-reactive protein; CT, computed tomography; ALP, alkaline phosphatase.
Nor is intravenous pyelography useful for the detection of RCC. Dikranian et al. analyzed 247 asymptomatic patients with microscopic hematuria who underwent both intravenous pyelography and US. Three and five patients were found to have tumor lesions in the kidney by intravenous pyelography and US, respectively. However, two patients who were finally diagnosed with RCC had been found to have an abnormality by US (3b).10

CQ 3

Are screening tests for RCC recommended in dialysis patients?
Recommendation Grade B: Screening tests would be recommended in dialysis patients, taking into consideration the increased incidence of RCC in these patients, as improved prognosis can be expected with early detection and early treatment. Regular medical examinations by abdominal US and CT would be beneficial for young patients and those on long-term maintenance dialysis, in particular.

Rationale

The incidence rate of RCC has been reported to be higher in dialysis patients than in healthy individuals, but in-depth data on the incidence are limited. Data on the prognosis in these patients are even more limited. Among 260 renal transplant recipients who underwent native nephrectomy, 11 (4.2%) had RCC (3b).11 RCC was found in eight (3.8%) of 206 renal transplant candidates (12b).12 In Japan, Satoh et al.13 reported 38 patients with RCC and 16 patients with urothelial carcinoma among 6201 chronic maintenance dialysis patients participating in a prognostic survey (3b). Ishikawa et al.14,15 performed a prospective follow-up study of 96 patients undergoing chronic dialysis and reported a high incidence rate of RCC (1/245 patient-years) in the 38 patients who were followed up for 15 years and a higher incidence of RCC associated with acquired cystic disease of the kidney (ACDK) in men than in women (3b). Based on a questionnaire survey of 489 patients in dialysis centers in Japan, an annual incidence rate of RCC of 82 per 100 000 was reported in patients who had undergone dialysis for 5 years or less and 625 per 100 000 in patients who had undergone dialysis for 25 years or longer.

As described above, there is no question as to the importance of regular screening tests for patients on long-term maintenance dialysis, although unfortunately, no evidence is available at present on the most appropriate screening methods and test intervals.

CQ 4

What should the next examination be when any renal tumor is detected during a routine medical examination or complete medical check?
Recommendation Grade B: Abdominal contrast-enhanced CT would be recommended, as it is the imaging modality with the highest resolution for renal tumors.

Rationale

While various diagnostic imaging modalities, including CT and magnetic resonance imaging (MRI), have been used for the detection of these lesions, a contrast-enhanced CT is widely recognized as the most indispensable diagnostic modality for renal tumors. Hilton et al. emphasized in their review on diagnostic imaging16 that no further examination is required when a contrast-enhanced CT is performed for the diagnosis of RCC. However, they recommend MRI as the most desirable diagnostic technique in patients who cannot be given intravenous injection of any contrast medium because of hypersensitivity to such agents or renal dysfunction (3a). As the importance of a contrast-enhanced CT examination for close examination of renal tumors has been established beyond doubt, as described above, there have been no reports of randomized controlled trials comparing the diagnostic precision of contrast-enhanced CT with that of other techniques.

Nonetheless, differential diagnosis of small renal tumors is often difficult. Such tumors are typified by renal angiomyolipoma, oncocytoma, and complex renal cysts. Garant et al. examined the parenchymal phase of imaging in which maximally dense staining of the tumor could be observed in 33 patients (37 lesions) undergoing contrast-enhanced CT, and reported that the parenchymal renal cortex phase showed the highest sensitivity and specificity for dense tumor staining and that scanning in the parenchymal renal cortex phase must be ensured during examination by helical CT (2b).17 Outwater et al. measured the signals of water and lipids in the area of interest by gradient-echo MRI and determined the signal intensity ratio (OIR) to evaluate whether or not the precision of diagnosis of RCC can be improved by this technique. They reported finding a significant decrease of the OIR in typical clear cell carcinoma as compared with that in other tumors, as the tumor tissue in clear cell carcinoma contains lipids (4).18 Li et al. compared the results of preoperative diagnostic imaging by CT with those of pathological diagnosis to study the precision of diagnosis. They found that RCC accounted for 95% or more of the renal tumors measuring 4 cm or larger in size, but 80% of the lesions measuring smaller than 4 cm in size, indicating the difficulty in the differential diagnosis of small renal tumors (4).19

CQ 5

Are chest CT, bone scintigraphy, and positron emission tomography (PET) recommended for the staging of RCC?
Recommendation Grade A: Chest CT is necessary in the staging of RCC.

Recommendation Grade C1: Bone scintigraphy is not as useful as a diagnostic technique for the staging of RCC because of its low specificity, whereas it is considered to be useful in patients who are suspected of having bone metastasis based on an elevated serum alkaline phosphatase level or the presence of bone pain.

Recommendation Grade B: Benefits of fluorodeoxyglucose (FDG)–PET test are expected for detecting distant metastases and for the diagnosis of recurrent tumors during follow-up.

Rationale

The most common site of distant metastasis is the lung, therefore the usefulness of chest CT in the staging of RCC has been established beyond doubt. On the other hand, routine use of bone scintigraphy is not recommended because of the relatively low frequency of bone metastases in patients with RCC (Guidelines for diagnostic imaging – 2003: edited by the Japanese College of Radiology and the Japan Radiological Society). Furthermore, the guidelines of the US NCCN do not recommend the routine use of bone scintigraphy in patients without elevation of the serum alkaline phosphatase level or bone pain. Staedenherz et al.20 studied the diagnostic precision of bone scintigraphy in 36 patients with RCC suspected of having bone metastasis, based on the results of CT, MRI, and clinical symptoms. They reported large variations in the sensitivity of bone scintigraphy and found no typical pattern in this test. Accordingly, they do not recommend the use of this technique routinely except for selected patients based on their
past medical histories and physical findings (3b). Koga et al.\textsuperscript{21} also studied the benefits of bone scintigraphy in 205 patients with RCC and reported that the sensitivity and specificity of bone scintigraphy were 94\% and 86\%, respectively. They concluded that this test can be omitted in patients with no bone-related symptoms and that it is not recommended for use in the staging of RCC in the absence of specific clinical pointers (3b).

In their review, Levine\textsuperscript{22} suggested that chest CT should also be obtained at the time of abdominal CT, and that bone scintigraphy should be performed in patients with bone pain (3a).

FDG-PET has been widely used in recent years, and numerous reports have described the benefits of use of this technique in cancer patients. Safaei et al.\textsuperscript{23} tried to use PET postoperatively for re-staging lesions that had definitively been diagnosed as RCC by examination of surgically resected specimens in 36 cases, to evaluate the usefulness of PET. According to the results of the study, the accuracy of re-staging by PET was 89\%. They reported confirming the high accuracy of PET, which could, therefore, be very useful for the staging of RCC when used in combination with other relevant examination techniques (4).

Aide et al.\textsuperscript{24} conducted a comparison of 35 RCC patients who underwent PET preoperatively and 18 RCC patients who underwent PET postoperatively, and reported a high sensitivity (97\%) but poor specificity (47\%) of PET for the diagnosis of the primary tumors; on the other hand, PET exhibited comparable sensitivity and specificity to CT for the evaluation of distant metastasis in patients with RCC (4). Kang et al.\textsuperscript{25} compared the sensitivity and specificity of PET and CT for the diagnosis of the primary and metastatic foci in 66 patients with RCC. They reported a lower sensitivity of PET than that of CT for the diagnosis of either the primary or the metastatic foci, although the technique was found to exhibit very high specificity, suggesting its potential clinical usefulness (2b).

**CQ 6**

Are measurements of the erythrocyte sedimentation rate and C-reactive protein (CRP) as prognostic factors recommended in cases of RCC?

**Recommendation Grade B**

Erythrocyte sedimentation rate (ESR) and CRP are important prognostic factors in case of RCC and are recommended as pretreatment examinations.

Rationale

Markers of inflammation are relatively well recognized in Japan as prognostic factors. While few prospective studies or homogeneous randomized controlled trial (RCT) relating to these prognostic factors have been conducted, results of large-scale retrospective studies were reported recently in Europe and the USA.

Sengupta et al. conducted a retrospective study of the cause-specific survival (CSS) rate in 1075 patients with RCC who were treated at the Mayo Clinic. When elevated ESR was defined as \( \geq 22 \) mm/h in male patients and \( \geq 27 \) mm/h in female patients, elevated ESR was observed in 46.6\% of the eligible cases. The results of both univariate and multivariate analyses of the clinical and pathological factors, including ESR, in patients with RCC have revealed that elevated ESR is a significant prognostic factor in patients treated by nephrectomy (2b). Ljungberg et al. analyzed the effects of six markers of inflammation on the prognosis in 170 patients with RCC who underwent surgical treatments. All of the six markers were found to have an influence on the prognosis and the results of multivariate analysis revealed the ESR to be a significant prognostic factor in relation to the grade of atypia and the stage of the carcinoma (2b).\textsuperscript{27}

Numerous studies have been performed on CRP. Lamp et al. evaluated the CSS rate in 100 patients with clear cell carcinoma who underwent radical surgery and reported significantly lower survival rates in the patients with high serum CRP values (\( \geq 10 \) mg/L). The results were also confirmed by multivariate analysis (2b). Matsuda et al. pointed out the importance of preoperative high serum CRP values as a prognostic factor from the viewpoint of postoperative prognosis (4). Fujikawa et al. examined the influence of CRP on the prognosis in patients with metastatic RCC and the potential usefulness of CRP measurement in determining the indications for nephrectomy in this subset of patients. They reported from the results that nephrectomy should be performed in patients with high serum CRP levels if their performance status (PS) was satisfactory (4). In addition, high serum CRP levels were also shown to be associated with the survival rates of RCC patients treated with interferon (IFN)-\( \alpha \) or interleukin (IL)-2, besides those of the patients undergoing surgery.

**CQ 7**

Is laparoscopic nephrectomy recommended for stage I or II RCC?

**Recommendation Grade B**

Laparoscopic surgery is recommended in cases of stage I or II RCC as one of the standard operative procedures, as the safety, survival rate and non-recurrence rate associated with this procedure are not significantly different from those associated with open nephrectomy.

Rationale

While some reports have indicated that the time required for laparoscopic nephrectomy is comparable to that required for open nephrectomy (3b),\textsuperscript{31,32} others have suggested that the former procedure often takes a significantly longer time (3b).\textsuperscript{31} However, most reports describe that the blood loss during laparoscopic nephrectomy is significantly lesser than that during open nephrectomy (3b).\textsuperscript{31,32} While it is difficult to evaluate the incidence of complications, reportedly, the incidence of complications associated with laparoscopic nephrectomy ranges from approximately 10\% to 20\% and is generally comparable to that associated with open nephrectomy (3b).\textsuperscript{31,32}

Concerning the postoperative course, it has been reported that the total dose of antianalgesic agents required is significantly lower (3b),\textsuperscript{31,32} that the postoperative interval until a patient is fit for oral intake/ambulation is significantly shorter (3b),\textsuperscript{31} and that the duration of hospital stay is significantly shorter (3b)\textsuperscript{31,32} in patients undergoing laparoscopic surgery; thus, laparoscopic surgery is considered to be significantly less invasive than open surgery.

While most studies on survival and non-recurrence rates have been retrospective, both medium- and long-term postoperative observations of patients undergoing nephrectomy have indicated the absence of any significant differences in these measures between the two procedures for nephrectomy (2b).\textsuperscript{34}

While laparoscopic partial nephrectomy may be indicated in patients with renal tumors measuring up to 4 cm in size, no fixed operative procedure has been established yet for these cases (level 2b).\textsuperscript{35}

**CQ 8**

Is partial nephrectomy recommended in patients with RCC measuring up to 4 cm in diameter (T1a)?

**Recommendation Grade B**

Partial nephrectomy is recommended, as its cancer control is comparable to that of radical nephrectomy and it is especially beneficial from the aspect of maintenance of the renal functions.
Rationale

Partial Nephrectomy (PN) is an absolute indication for solitary kidney, renal insufficiency, and bilateral RCC, while it is one of the surgical treatment options for contralateral RCC, especially those measuring up to 4 cm in size. In addition, PN has an operation outcome almost similar to radical nephrectomy (RN), as the 5-year CSS rate and recurrence rate with the tumors measuring up to 4 cm undergoing PN ranged from 97.8% to 100% and 0.8% to 1.6%, respectively (2a).36

The following complications associated with PN are reported: urorhea (7.4%), acute kidney tubular necrosis/impairment of renal function (6.3%), dialysis (4.9%), infections/abscess (3.2%), hemorrhage (2.8%), periprocedural treatment-related death (1.6%), reoperative surgery (1.9%), and traumatic injury of the spleen (0.6%) (3a).17 Most complications associated with PN occurred in the early postoperative stage (occurring within 30 days of surgery), while there are few reports on the late complications.

Mckieran et al. conducted a 10-year prospective study to compare 173 patients who underwent RN with those of 117 patients who underwent PN. Preoperative risk factors for impairment of renal functions had been comparable between the two groups of patients. They reported that the risk of development of renal insufficiency (creatinine ≥ 2.0 mg/dL) was significantly higher in the patients who underwent RN (P = 0.008) as compared with that in those who underwent PN, and that PN was beneficial for maintenance of adequate renal function for a long period of time (2C).38

Girbert et al. also commented that there is no rationale for considering a surgical margin of 1 cm, even though it seems to have been recommended up until now, and that a good prognosis can be expected if the surgical margin is free from tumor (level 2a).39 In regard to the relevance of the tumor site, it has been recognized that exophytic tumors and tumors not showing spread to the renal sinus can be removed more easily by laparoscopic PN, with a lower incidence of complications. However, the long-term oncological outcomes in patients undergoing laparoscopic PN have not been clearly elucidated at present (3a).40

CQ 9

Is nephrectomy recommended in patients with metastatic RCC?

Recommendation Grade A: Nephrectomy would still be recommended in patients with metastatic RCC (mRCC), if the patient has a good PS and can receive postoperative immunotherapy with IFN.

Rationale

The European Organization for Research and Treatment of Cancer (EORTC) and the Southwest Oncology Group (SWOG) reported large-scale RCT conducted to evaluate the benefits of nephrectomy in patients with mRCC (1b).41,42 In both studies, comparisons were made between two groups, a group of patients who underwent nephrectomy followed by IFN-α, and a group of patients who received monotherapy with IFN-α without surgery. Mckisch et al. (EORTC 30947) compared the prognoses between 42 patients undergoing nephrectomy + IFN-α 2b treatment and 42 patients receiving IFN-α 2b monotherapy, and reported finding no difference in the early response of IFN-α therapy to metastatic foci. On the other hand, they reported an average median survival to be 17 months in the combined group of nephrectomy and IFN-α and 7 months in the IFN-α group, and also both progression-free survival (PFS) and overall survival (OS) to be significantly longer in the former group than in the latter group (1b).41 Flanigan et al. (SWOG 8949) also compared the prognoses between 120 patients treated with nephrectomy + IFN-α 2b and 121 patients treated with IFN-α 2b monotherapy and reported finding no difference in the early response of IFN-α to metastatic foci. They also reported an average median survival to be 11.1 months in the group of nephrectomy + IFN-α 2b and 8.1 months in the group of IFN-α 2b, with respective one-year survival rates of 49.7% and 36.8%. Thus, the prognosis in the former group was significantly better than that in the latter group in this comparison (1b).32 Furthermore, Flanigan et al. conducted a meta-analysis of the integrated results of these two studies and reported that combined treatment with nephrectomy + IFN improved the survival of the patients, irrespective of the PS, site of metastases, and presence or absence of measurable lesions, with a difference in the survival between the two groups of 5.8 months (1a).43

CQ 10

Is lymph node dissection recommended during radical nephrectomy?

Recommendation Grade C2: When neither distant metastases nor enlarged lymph nodes are found, there is very little likelihood of lymph node metastasis and of lymph node dissection contributing in any significant measure to improvement of the survival rates. Consequently, lymph node dissection is not recommended in such cases.

Recommendation Grade C1: When lymph node metastases are suspected, on the other hand, prolongation of the survival rate may be expected with lymph node dissection along with radical nephrectomy, followed by postoperative adjuvant therapy. Therefore, lymph node dissection is recommended in such cases.

Rationale

Only one prospective RCT has been conducted until now (Blom et al.), in which the benefits of lymph node dissection were evaluated in RCC patients with no tumor metastasis (cT1-3N0M0). Among 336 patients who underwent lymph node dissection along with radical nephrectomy, lymph node metastasis was found in seven (16%) of 43 patients who had palpable lymph nodes during operation and 4 (1%) of 229 patients who had no palpable lymph nodes (P < 0.001). On the other hand, among 346 patients who did not undergo lymph node dissection, 29 had palpable lymph nodes; six (20.7%) of these patients with palpable lymph nodes had lymph node metastases and the 5-year survival rate of these patients was 82%. In cases where adequate preoperative diagnostic work-up is performed properly, the incidence of lymph node metastasis is very low (3.3%) and there was no difference in the incidence of complications between patients in whom lymph node dissection was undertaken and those in whom it was not. The clinical benefit of lymph node dissection during radical nephrectomy has, however, not been demonstrated (2b).44 Pantuck et al. reported an incidence rate of lymph node metastasis of less than 0.5% in 900 patients who underwent nephrectomy, in whom the primary carcinoma was limited to the kidney, the tumor size was smaller than 7 cm, and lymph node metastasis was not suspected during preoperative workup (4).45 Minervini et al. reported the absence of any difference in the 5-year survival rates between 108 patients who underwent radical nephrectomy, with no lymph node metastasis being suspected, and 49 patients who underwent both radical nephrectomy and lymph node dissection. The 5-year survival rates in the former group and the latter group were 79% and 78%, respectively (3b).46

On the other hand, long-term survivors after undergoing lymph node dissection and postoperative adjuvant therapy have been reported among those with no distant metastasis but suspected lymph node
metastasis, suggesting that improved prognosis may be expected with lymph node dissection (3b). In a study by Canfield et al., the mean survival in 40 patients with no distant metastasis but lymph node metastasis in whom lymph node dissection was undertaken was 20.3 months, while 30% of these patients did not develop recurrence and the pN1 patients had a better prognosis as compared to the pN2 patients. They recommended lymph node dissection followed by postoperative adjuvant therapy in patients with lymph node metastasis. However, Lam et al. claim that lymph node dissection should not yet be recommended strongly, because no results of RCT are available at present (3a).

CQ 11
Is preservation of the adrenal on the affected side recommended during nephrectomy in RCC patients?
Recommendation Grade C1: Considering the recent trends in nephrectomy for RCC, the adrenal gland of the affected side may be preserved if preoperative diagnostic imaging does not provide any evidence of spread or metastasis to the gland, while even in such cases, caution should be exercised in considering preservation of the adrenal gland in patients with a large size of the primary tumor.

Rationale
Lam et al. reviewed the following several reports (2a). Paul et al. conducted nephrectomy and adrenalectomy on the affected side in 866 patients with RCC and found metastasis to the adrenals in 27 (3.1%) of the patients; six of them had a solitary metastasis in the adrenal glands (2c). Results of multivariate analyses have revealed that the independent prognostic factors for adrenal metastasis of RCC included tumor size (tumors measuring 8 cm or larger in diameter were associated with an increased incidence of metastasis) and the presence or absence of metastasis to organs, including the adrenal glands, as detected by diagnostic imaging (4). Tsui et al. reported that the proportion of adrenal metastasis was low in their series of 511 patients undergoing nephrectomy. They indicated that remarkable improvements in the diagnostic imaging techniques in recent years enabled them to detect adrenal metastasis preoperatively (4). Based on the results mentioned above, Lam et al. eventually concluded that preservation of the adrenal gland of the affected side should be attempted as far as possible, especially in cases of negative results of preoperative CT, in the light of avoidance of potential adrenal insufficiency that may be introduced because of potential metastasis to the contralateral adrenal gland in the future (3a).

However, Siemer et al. reported that adrenalectomy on the affected side may be recommended in patients with tumors measuring 4 cm or larger or those with carcinomas that are not localized to specific organs and classified as stage pT3 or higher (2c). Furthermore, it has been reported that the long-term prognosis in patients with isolated adrenal metastasis from primary RCC undergoing adrenalectomy together with nephrectomy was comparable to that of patients undergoing the same procedure in the absence of metastasis to the adrenal glands (2c), supporting the benefit of adrenalectomy.

CQ 12
Is tumor thrombectomy recommended in RCC patients with an inferior vena cava thrombus?
Recommendation Grade B: Among RCC patients with a tumor thrombus in the inferior vena cava (IVC), tumor thrombectomy is recommended, but only in patients with a localized RCC without either regional lymph node metastasis or distal metastasis.

Rationale
Blute et al. conducted a retrospective review of the outcomes of surgery in 503 patients with vena cava tumor thrombus and found a significant difference in the cancer-specific 5-year survival rate between a group of 332 patients without either regional lymph node metastasis or distal metastasis (59.1%) and a group of 171 patients with metastasis (5.8–17.2%) (3a). Similarly, Kuczky et al. pointed to lymph node metastasis (5-year survival rate, 7.8%) and distal metastasis (5-year survival rate, 7.4%) as poor prognostic factors (2a).

In the aforementioned study by Blute et al., a significant difference in the survival rate between cases of a tumor thrombus in the renal vein and those of the thrombus in the IVC was observed, whereas no significant difference was found between cases of a tumor thrombus in the inferior vena cava and those of the thrombus in the right atrium. Kim et al. also reported a significant difference in the survival rate between cases of a tumor thrombus in the renal vein (5-year survival rate, 81.3%) and those of the thrombus in the IVC (5-year survival rate, 52.7%) (4). Nonetheless, tumor thrombectomy is also associated with a certain risk of perioperative death (approximately 2%) (4). Accordingly, caution should be exercised in selecting candidates for such treatment procedures.

CQ 13
Are surgical treatments recommended for metastatic foci?
Recommendation Grade B: Surgical treatments for metastatic foci are recommended in patients with mRCC, when they have good PS and the metastatic foci are resectable.

Rationale
Results of nonrandomized studies suggest that extension of survival by surgical treatments can be expected in patients with mRCC when they have a good PS and the metastatic foci are limited to the lungs or adrenal glands (3b). In addition, improvement in the survival rates was reported after resection of metastatic foci in cases where the interval from nephrectomy to the occurrence of metastasis was 2 years or longer (3b).

For evaluating the benefits of surgical treatments by organ class, Pfannschmidt et al. conducted pulmonary resection in 191 patients and reported the 5-year survival rates in the curative resection (n = 149) and non-curative resection among these patients of 41.5% and 22.1%, respectively; they also reported significantly longer survival in patients with less than seven metastatic foci (4). Althausen et al. conducted a retrospective review of the treatment results of bone resection in 38 patients with bone metastasis from RCC and reported 5-year and 10-year survival rates of 55% and 39%, respectively. In addition, it was reported that the prognostic factors included the time of appearance of the metastasis after the nephrectomy and the sites and number of metastatic foci (4). Leibovich et al. reported that the prognostic factors in patients undergoing surgical treatments include the presence or absence of symptoms, the time of appearance of the metastasis after the nephrectomy, sites and number of metastatic foci, stage of the tumor thrombi, presence or absence of tumor necrosis, and completeness of resection of the metastatic foci. They also reported that a scoring algorithm of the prognostic factors may be a possible stratification tool to predict sur-
vival for patients with mRCC (4). According to their report, complete resection of a solitary metastatic focus is a good prognostic factor, whereas liver metastasis and metastasis appearing within 2 years of nephrectomy for the primary cancer are poor prognostic factors (62).

CQ 14
Are percutaneous local treatments recommended for patients with small-sized RCC?
Recommendation Grade C1: Percutaneous local treatments are recommended for patients with small-sized RCC who are not considered to be suitable candidates for radical treatment because of a poor performance status or complications, or when the patients refuse surgery. The efficacy of radiofrequency ablation (RFA) or cryoablation as percutaneous local treatments for small-sized RCC has not been compared with that of partial nephrectomy.

Rationale
RFA is conducted under echo-, CT-, or MRI-guidance, while the treatment outcomes are evaluated by contrast-enhanced CT or MRI. Gervais et al. treated 100 tumors in 85 patients by percutaneous RFA. While these patients underwent 114 and 12 sessions of percutaneous RFA under CT- and echo-guidance, respectively, complete necrosis of the tumor was found in 77 of 85 patients (91%) and 90 of 100 tumors (90%). It occurred within 6 months of treatment in all 77 patients except for one. Complete necrosis was found in 52 tumors measuring smaller than 3 cm in size and 68 exophytic-type tumors, but in none of the tumors measuring 5.5 cm or larger in size; new tumors and distant metastases were found in three patients each. Thus, it was reported that small-sized tumors (smaller than 3 cm in size) and exophytic-type tumors were predictive factors for necrosis (4). McDougal et al. evaluated 20 tumors in 16 patients who had undergone RFA four or more years previously; at that time, the patients had complications or had refused to undergo surgery. According to these authors, at the evaluation conducted four or more years after the treatment, percutaneous RFA performed for the treatment of exophytic-type tumors measuring less than 5 cm in diameter appeared to have served as a more effective radical treatment method as compared with surgical resection, and there were no complications associated with the treatment procedure (4).

Cryoablation can also be performed under CT- or MRI-guidance. Gupta et al. treated 20 patients by CT-guided cryoablation and reported the disappearance on CT images of 15 out of 16 tumors that could be followed up for at least one month, and that patients with central-type tumors measuring 5 cm in size presented with perinephric hemorrhage and were hospitalized for receiving blood transfusion (4). Shingleton et al. treated 22 tumors in 20 patients by this treatment procedure under MRI-guidance and found postoperative abscess of the wound area in one patient, reporting that no recurrence or progression occurred during an average observation time of 9.1 months (4).

However, these treatment procedures should be considered only in those patients who are not suitable for more radical treatments because of their poor performance status or the presence of complications, as no comparative evaluation of the outcomes has been performed between these procedures and radical nephrectomy or partial nephrectomy, and also the long-term outcomes after these treatments have not been assessed adequately.

CQ 15
Is radiation therapy recommended for the treatment of metastatic RCC?

Recommendation Grade B: Gamma knife or stereotactic radiotherapy may be effective for brain metastasis from RCC.
Recommendation Grade B: Pain relief and improved quality of life (QOL) can be obtained with external beam radiation therapy for bone metastasis from RCC.

Rationale
Wowra et al. and Sheehan et al. reported the benefits of gamma knife radiotherapy for brain metastasis in RCC patients (3b). They treated 350 lesions in 160 RCC patients with brain metastasis by gamma knife radiotherapy. These patients could receive the treatment repeatedly as outpatients, and 72% showed improvement of neurological symptoms, with a good local control rate (95%). In addition, Sheehan et al. treated 140 lesions in 69 RCC patients with brain metastasis by gamma knife radiotherapy, and also reported a good local control rate (96%). Based on these results, gamma knife radiotherapy is considered to be one of the effective treatment strategies to control brain metastasis in patients with RCC. However, the improvement of survival by this treatment modality has not yet been elucidated.

Benefits of stereotactic radiation therapy for brain metastasis in RCC patients have been reported as well. Mori et al. and Goyal et al. who performed stereotactic radiation therapy in 35 and 29 RCC patients with brain metastasis, respectively, reported good local control rates and few complications (3b). Ikushima et al. performed stereotactic radiation therapy in 29 RCC patients with brain metastasis and reported better local control rates accomplished by this treatment procedure than by conventional radiation therapy (2b).

Lee et al. reported the benefits of (external beam) radiation therapy for symptomatic relief in RCC patients with bone metastasis (3b). Twenty-four patients were treated with external beam radiation at 30 Gy/10 fr and 83% of the patients obtained relief of site-specific pain, while 33% showed improvement of QOL.

CQ 16
Is monotherapy with cytokines, including IFN-α or IL-2, recommended for treatment of patients with advanced RCC?
Recommendation Grade A: Monotherapy with IFN-α is recommended for treatment of patients with advanced RCC.
Recommendation Grade B: Monotherapy with IL-2 is recommended for treatment of patients with advanced RCC.

Rationale
Two reliable RCT conducted to evaluate the benefits of monotherapy with IFN-α have been reported. In the first, conducted by Medical Research Council Renal Cancer Collaborators, 350 patients were assigned to either treatment with IFN-α or with medroxyprogesterone. Superior results were demonstrated in the IFN-α treatment group in response rate, PFS, and OS (1a). In the second RCT, performed by Pyrhonen et al., 160 patients were assigned to either treatment with IFN-α + vinblastine or to vinblastine monotherapy. Superior efficacy was demonstrated in the IFN-α + vinblastine arm in response rate, PFS, and OS (1b). Based on the above results, it was concluded that monotherapy with IFN-α may be recommended for patients with advanced RCC.

No reliable RCT conducted to evaluate efficacy of IL-2 have been reported, although a phase II study reported a 14% response rate (3b). Based on these data, FDA approved the use of IL-2 for the treatment of advanced RCC. Furthermore, reliable RCT conducted using different
dosage levels of IL-2 revealed that the response rate of IL-2 at higher dose levels was superior to that at lower dose levels, although the PFS and OS were comparable irrespective of the dose levels (1b).77,78 While the lower dose levels were comparable to the price-listed doses in Japan, the higher dose levels were approximately 10 times higher than those used in Japan.

CQ 17

Is combined therapy with IFN-α + IL-2 or with IFN-α + any chemotherapy recommended for patients with advanced RCC?

Recommendation Grade C1: Combined therapy with IFN-α + IL-2 is recommended for patients with advanced RCC, as an increased response rate can be expected.

Recommendation Grade C2: Combined therapy with IFN-α + 5-FU may be effective.

Recommendation Grade C2: Combined therapy with IFN-α + vinblastine is not recommended, as no significant benefit has been shown with this combined therapy.

Rationale

Several reports (1b),79 (2b),80 have suggested that improved response rates may be expected following combined therapy with IFN-α + IL-2 as compared to monotherapy with either of the cytokines. In contrast, other reports (2a),81 suggest that combined therapy with IFN-α + IL-2 does not contribute to improvement of the response rate or prolongation of the survival time. Nevertheless, it should be noted that the dose levels of IL-2 used in these studies were not the low dose levels that have been used in Japan. In a clinical study performed in Japan (4),82 efficacy of combined therapy with IFN-α and low doses of IL-2 was reported in RCC patients with lung metastasis. The predictive factors for efficacy of cytokine therapy include a good PS, post-nephrectomy, longer metastasis-free survival time, fewer metastatic foci, and lung metastasis (4),82 while the constitutions of the patients should be taken into account in each study and RCT would be required to draw definitive conclusions.

Other drugs used for combined therapy with the cytokines include Futraful (5FU), vinblastine (VBL), and 13-cis retinoic acid (CRA). While numerous reports have indicated a weak significance of combined therapy with cytokines + 5FU, the only large-scale clinical trial performed by Negrier et al. (2b).83 No evidence has been obtained on the significance of combined cytokine + CRA therapies or VBL with cytokines.

CQ 18

Are adjuvant cytokine therapies recommended for preventing tumor recurrence in patients who have undergone radical nephrectomy for the treatment of stage I or II RCC?

Recommendation Grade C2: Adjuvant therapies with cytokines are not recommended to prevent recurrence after radical nephrectomy in patients with stage I or II RCC because no RCT have demonstrated the preventive effects of IFN-α, IL-2 or both with or without 5FU against tumor recurrence in patients with stage I or II RCC after nephrectomy.

Rationale

Messing et al. conducted an RCT to evaluate the efficacy of IFN-α therapy in preventing recurrence in 283 patients with RCC assigned to either nephrectomy followed by IFN-α injections as adjuvant therapy or nephrectomy alone; they found no significant difference in the relapse-free time or survival time between the two groups (1b).84 Pizzocaro et al. conducted an RCT to compare the prognosis in 247 patients with stage II or III RCC assigned to receiving either IFN-α for 6 months or no treatment. There were no significant differences in 5-year overall and relapse-free survival rates between the two groups. In this RCT, no benefit of IFN-α was shown for patients at any pT stage. However, patients staged as pN2-pN3 in the IFN-α group showed a better prognosis than those in the untreated group when stratified by pN category (1b).85 Accordingly, treatment with IFN-α is not recommended as adjuvant therapy for preventing recurrence after radical nephrectomy in patients with stage I or II RCC.

Clark et al. compared the 5-year survival and relapse-free rates in 69 patients with high-risk renal tumor assigned to either IL-2 treatment or no treatment, and reported no differences between the two groups (2b).86 Atzpodien et al. conducted an RCT in 203 patients with high-risk RCC to evaluate the efficacy of treatment with the combination of IFN-α, IL-2, and 5FU as adjuvant therapy after nephrectomy, and reported no benefits of such therapy in overall or recurrence-free survival rates (1b).87

CQ 19

Are molecular-targeted therapies recommended for patients with advanced RCC?

Recommendation Grade B: Molecular-targeted therapies (with sorafenib, sunitinib, temsirolimus, and bevacizumab) are recommended for patients with advanced RCC, as they have been shown to be effective for reducing the tumor size and prolongation of the survival time.

Rationale

Molecular-targeted therapies are now being developed and clinically applied with the recent advances in the elucidation of the mechanisms of carcinogenesis in RCC.

A prospective, randomized, three-treatment arm comparative clinical trial of bevacizumab was conducted in RCC patients with progressive disease (PD) after treatment with IL-2. The disease progression-free rates observed 4 months after the start of treatment in the high-dose group, low-dose group, and placebo group were 64%, 39%, and 20%, respectively, with a significant difference observed between the high-dose group and placebo group (1b).88 Patients showing PD after cytokine therapy were treated with sunitinib. Partial response (PR) was achieved in 25 out of 63 patients and the average PFS was 8.7 months (4).89 In a prospective randomized study conducted to compare sunitinib with IFN-α in untreated patients with advanced RCC, the total number of patients in whom complete response (CR) or PR was observed was significantly greater in the sunitinib group (31%) than in the IFN-α group (6%). In addition, the PFS observed in the sunitinib group (11 months) was significantly longer than that observed in the IFN-α group (5 months) (1b).90 In a phase II, placebo-controlled, randomized, discontinuation trial of sorafenib as second line systemic therapy in groups of patients with intermediate-grade RCC and a good prognosis, a significantly longer PFS was observed in the sorafenib group (24 weeks) as compared with that in the placebo group (6 weeks). Thus, inhibition of disease progression by sorafenib was demonstrated (1b).91 In a prospective RCT of temsirolimus in so-called poor prognosis patients with three or more Motzer’s risk factors, the efficacy of monotherapy with temsirolimus was compared with that of monotherapy with IFN-α or combined
therapy with IFN-α + temsirolimus. The mean OS time observed in the temsirolimus monotherapy group (10.9 months) was significantly longer than that in either the INF-α monotherapy group (7.3 months) or that in the INF-α + temsirolimus group (8.4 months) (1b).92

CQ 20

Are there any promising treatments for advanced RCC patients who do not respond to cytokine therapies?

Recommendation Grade B: Molecular-targeted therapies could be effective in advanced RCC patients who do not respond to cytokine therapies.

Recommendation Grade C1: Reduced-intensity stem cell transplantation or certain fluorinated pyrimidines could also be effective in such patients.

Rationale

Treatment with molecular-targeted therapies, as described in CQ 19 above, could be effective in cases that do not show satisfactory response to cytokine therapies. Other possibly effective therapies include reduced-intensity stem cell transplantation (RIST). In a study in which RIST was performed in 19 patients who did not show satisfactory response to cytokine therapies, CR and PR were achieved in three and seven patients, respectively, with an overall response rate of 53%, and the durations of the response in the three CR patients were 27, 25, and 16 months (4).93 Similar results with RIST were reported in a subsequent study published from another institution (PR in four out of 12 patients [4]).94 Nevertheless, the incidence of treatment-related death appeared to be rather high; death occurred in two out of the 19 patients,93 and four out of the 12 patients94 in the studies reported above.

In another study, an anticancer agent capecitabine was administered to 25 patients who did not show satisfactory response to cytokine therapy, and PR, minor response, stable disease, and PD were observed in two, five, 13, and three patients, respectively. Of the 23 patients eligible for analysis, and grade 3, 4, or 5 adverse events were recorded in only three patients during a median observation period of 13 months (4).95 In one study of combined therapy with 13-cis retinoic acid + IFN-α, PR was achieved in two of 11 patients, however, the details of this study were not clear (4).96 When efficacy of WX-250, an antibody targeted against carbonic anhydrase IX (G250/MN), was evaluated in 27 patients who did not show satisfactory response to cytokine therapies, SD was observed after 17 weeks’ treatment in 10 patients; treatment was continued further in these patients, with CR obtained in one patient after 38 weeks (4).97

CQ 21

What is the appropriate protocol for follow up after radical nephrectomy?

Recommendation Grade C1: According to the risk of recurrence and metastasis after radical nephrectomy, relevant follow-up protocol should be established.

Rationale

The primary objective of follow up after radical nephrectomy is early detection of recurrence or metastasis (3a).1 The representatives of postoperative follow-up protocols are described below.

According to the guidelines of the EAU, patients at low risk of recurrence and metastasis are followed up after radical nephrectomy by chest radiograph and US, but not CT (3a).98 However, patients who have symptoms derived from recurrence or metastasis should be examined by CT. In patients at intermediate or high risk of recurrence or metastasis, the evaluations by chest radiograph and abdominal CT are required. According to the guidelines of the NCCN, chest radiograph and abdominal CT should be conducted at 4 to 6 months after radical nephrectomy and as needed thereafter. Clinical examinations and blood biochemical tests should be conducted every 6 months for the first 2 years after radical nephrectomy and once every year until 5 years after the surgery. According to the recent review published in the USA, many reports recommend blood tests and chest radiograph every 6 to 12 months after radical nephrectomy for patients with stage pT1 or pT2 RCC, and blood tests and chest/abdominal CT every 6 months for patients with stage pT3 or pT4 RCC (3a).99 In addition, follow up by chest/abdominal CT should be performed more than 5 years after radical nephrectomy, because of late recurrence.

As described above, different protocols are recommended by different investigators as regards appropriate follow-up evaluations after radical nephrectomy (3a).99,100 For follow up after radical nephrectomy, the relevant follow-up examinations should be established according to the risk of recurrence and metastasis, including the stage and grade of RCC (3a).98

Abbreviations

ACDK, acquired cystic disease of the kidney; BMI, body mass index; EAU, European Association of Urology; ESR, erythrocyte sedimentation rate; JSCO, Japan Society of Clinical Oncology; NCCN, National Cancer Comprehensive Network; OS, overall survival; PFS, progression-free survival; PS, Performance status; RCC, renal cell carcinoma; RCT, randomized controlled trial.

References

1 Chow WH, Gridley G, Fraumeni JF Jr, Järvholm B. Obesity, hypertension, and the risk of kidney cancer in men. N. Engl. J. Med. 2000; 343: 1305–11.
2 Coughlin SS, Neaton JD Randall B, Sengupta A. Predictors of mortality from kidney cancer in 332 547 men screened for the Multiple Risk Factor Intervention Trial. Cancer 1997; 79: 2171–7.
3 Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlagel B, Schill W. Occupational risk factors for renal cell carcinoma: Agent-specific results from a case–control study in Germany. MURC Study Group. Multicenter urothelial and renal cancer study. Int. J. Epidemiol. 2000; 29: 1014–24.
4 Kaelin WG Jr. The von Hippel-Lindau tumor suppressor gene and kidney cancer. Clin. Cancer Res. 2004; 10: 6290s–5.
5 Schmidt LS, Nickerson ML, Warren MB et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dube syndrome. Am. J. Hum. Genet. 2005; 76: 1023–33.
6 Mihara S, Kuroda K, Yoshioka R, Koyama W. Early detection of renal cell carcinoma by ultrasonographic screening, based on the results of 13 years’ screening in Japan. Ultrasound Med. Biol. 1999; 25: 1033–9.
7 Lightfoot N, Conlon M, Kreiger N et al. Impact of noninvasive imaging on increased incidental detection of renal cell carcinoma. Eur. Urol. 2000; 37: 521–7.
8 Jamis-Dow CA, Choyke PL, Jennings SB, Linehan WM, Thakore KN, Walther MM. Small (< or =3-cm) renal masses: Detection with CT versus US and pathologic correlation. Radiology 1996; 198: 785–8.
9 Emamian SA, Nielsen MB, Pederson JF. Can dipstick screening for hematuria identify individuals with structural renal abnormalities? A sonographic evaluation. Scand. J. Urol. Nephrol. 1996; 30: 25–7.
10 Dikranian AH, Petitti DB, Shapiro CE, Kosco AF. Intravenous urography in evaluation of asymptomatic microscopic hematuria. J. Endourol. 2005; 19: 595–7.
11 Denton MD, Magee CC, Ovswoorie C et al. Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: A pathologic analysis. Kidney Int. 2002; 61: 2201–9.
12 Gulanikar AC, Daily PP, Kilambi NK, Hamrick-Turner JE, Butkus DE. Prospective pretransplant ultrasound screening in 206 patients for acquired renal cysts and renal cell carcinoma. Transplantation 1998; 66: 1669–72.
13 Satoh S, Tsujiya N, Habauchi T, Ishiyama T, Seimo K, Kato T. Renal cell and transitional cell carcinoma in a Japanese population: underlying maintenance dialysis. J. Urol. 2005; 174: 1749–53.
14 Ishikawa I, Satoo Y, Nakamura M et al. Fifteen-year follow-up of acquired renal cystic disease: A gender difference. Nephron 1997; 75: 315–20.
15 Ishikawa I. Present status of renal cell carcinoma in dialysis patients in Japan: Questionnaire study in 2002. Nephron Clin. Pract. 2004; 97: c11–16.
16 Hilton S. Imaging of renal cell carcinoma. Semin. Oncol. 2000; 27: 150–9.
17 Garant M, Bonaldi VM, Taourel P, Pinsky MF, Bret PM. Enhancement deoxyglucose whole-body positron emission tomography (PET) for characterising renal cancer and detecting distant metastases: A comparison with CT. [J. Urol. 2001; 165: 1356–9.
18 Li G, Cuilleron M, Gentil-Perret A, Tostain J. Characteristics of metastatic renal cell carcinoma in patients with ESRD pre-transplantation. Cancer 2001; 94: 1703–11.
19 Jonass S, Vander Eeckt K, van Poppel H. The indications for partial nephrectomy in the treatment of renal cell carcinoma. Nat. Clin. Pract. Urol. 2006; 3: 198–205.
20 Uzzo RG, Novick AC. Nephron-sparing surgery for renal tumors: Indications, techniques and outcomes. J. Urol. 2001; 166: 6–18.
21 McKiernan J, Simmons R, Katz J, Russo P. Natural history of chronic renal insufficiency after partial and radical nephrectomy. Urology 2002; 59: 816–20.
22 Gilbert SM, Russo P, Benson MC, Olsson CA, McKiernan JM. The evolving role of partial nephrectomy in the management of renal cell carcinoma. Curr. Oncol. Rep. 2003; 5: 239–44.
23 Weise ES, Winfield HN. Laparoscopic partial nephrectomy. J. Endourol. 2005; 19: 634–42.
24 Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alpha-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: A randomized trial. Lancet 2001; 358: 966–70.
25 Flanigan RC, Salmon SE, Blumenstein BA et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N. Engl. J. Med. 2001; 345: 1655–9.
26 Pantuck AJ, Zisman A, Dorey F et al. Regional lymph node dissection in patients with metastatic renal cell cancer. A combined analysis. J. Urol. 2004; 171: 1071–6.
27 Blom JH, van Poppel H, Marechal JM et al. Radical nephrectomy with and without lymph node dissection: Preliminary results of the EORTC randomized phase III protocol 30881. EORTC Genitourinary Group. Eur. Urol. 1999; 36: 570–5.
28 Pantuck AJ, Zisman A, Dorey F et al. Nephrectomy in the treatment of renal cell carcinoma: Is it useful in patients with no suspected adrenopathy before or during surgery? BJU Int. 2001; 88: 169–72.
29 Canfield SE, Kamat AM, Sanchez-Ortiz RF, Detry M, Swanson DA, Wood CG. Renal cell carcinoma with nodal metastases in the absence of distant metastatic disease (clinical stage T3aN1-2M0): The impact of aggressive surgical resection on patient outcome. J. Urol. 2006; 175: 864–9.
30 Lam JS, Shvarts O, Pantuck AJ. Changing concepts in the surgical management of renal cell carcinoma. Eur. Urol. 2004; 45: 692–705.
31 Paul R, Mordhorst J, Lehy H, Hartung R. Incidence and outcome of patients with adrenal metastases of renal cell cancer. Urology 2001; 57: 878–82.
32 Paul R, Mordhorst J, Busch R, Lehy H, Hartung R. Adrenal sparing surgery during radical nephrectomy in patients with renal cell cancer: A new algorithm. J. Urol. 2001; 166: 59–62.
33 Tsu KH, Shvarts O, Barbaric Z, Figlin R, de Kernion JB, Beldegrun A. Is adrenalectomy a necessary component of radical nephrectomy? UCLA experience with 511 radical nephrectomies. J. Urol. 2000; 163: 437.
34 Siemer S, Lehmann J, Kamradt J et al. Adrenal metasteses in 1635 patients with renal cell carcinoma: Outcome and indication for adrenalectomy. J. Urol. 2004; 171: 2155–9. Discussion 2159.
35 Kuczyk M, Wegener G, Jonas U. The therapeutic value of adrenalectomy in case of solitary metastatic spread originating from...
primary renal cell cancer. Eur Urol. 2005; 48: 252–7. Epub 2005 Apr 21.

54 Blute ML, Leibovich BC, Lohse CM, Cheville JC, Zincke H. The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. BJU Int. 2004; 94: 33–41.

55 Kuczyk MA, Munch T, Machtens S, Grunewald V, Jonas U. The impact of extracorporal circulation on therapy-related mortality and long-term survival of patients with renal cell cancer and intracaval neoplastic extension. World J. Urol. 2002; 20: 227–31. Epub 2002 Aug 7.

56 Kim HL, Zisman HL, Han KR, Figlin H, Belldegrun AS. Prognostic significance of venous thrombus in renal cell carcinoma. Are renal vein and inferior vena cava involvement different? J. Urol. 2004; 171: 588–91.

57 Staepler G, Brkovic D. The role of radical surgery for renal cell carcinoma with extension into the vena cava. J. Urol. 2000; 163: 1671–5.

58 Antonelli A, Zani D, Cuzzoli A, Cunico SC. Surgical treatment of metastases from renal cell carcinoma. Arch. Ital. Urol. Androl. 2005; 77: 125–8.

59 van der Poel HG, Roukema JA, Horenblas S, van Geel AN, Debruyne FM. Metastasectomy in renal cell carcinoma: A multicenter retrospective analysis. Eur Urol. 1999; 35: 197–203.

60 Pfannschmidt J, Hoffmann H, Muley T, Krysa S, Trainer C, Althausen P, Althausen A, Jennings LC, Mankin HJ. Prognostic factors for survival after pulmonary resection of metastatic renal cell carcinoma. Ann. Thorac. Surg. 2002; 74: 1653–7.

61 Althausen P, Althausen A, Jennings LC, Mankin HJ. Prognostic factors and surgical treatment of osseous metastases secondary to renal cell carcinoma. Cancer 1997; 80: 1103–9.

62 Leibovich BC, Cheville JC, Lohse CM et al. A scoring algorithm to predict survival for patients with metastatic clear cell renal cell carcinoma: A stratification tool for prospective clinical trials. J. Urol. 2005; 174: 1759–63. Discussion 63.

63 Gervais DA, Arelanno RS, McGovern FJ, McDougal WS, Mueller PR. Radiofrequency ablation of renal cell carcinoma: Part 1, Indications, results, and role in patient management over a 6-year period and ablation of 100 tumors. AJR Am. J. Roentgenol. 2005; 185: 64–71.

64 McDougal WS, Gervais DA, McGovern FJ, Mueller PR. Long-term followup of patients with renal cell carcinoma treated with radio frequency ablation with curative intent. J. Urol. 2005; 174: 61–3.

65 Varkarakis IM, Allaf ME, Inagaki T et al. Percutaneous radio frequency ablation of renal masses: Results at a 2-year mean followup. J. Urol. 2005; 174: 456–60.

66 Gupta A, Allaf ME, Kavoussi LR et al. Computerized tomography guided percutaneous renal cryoaiblation with the patient under conscious sedation: Initial clinical experience. J. Urol. 2006; 175: 547–52.

67 Shingleton WB, Sewell PE Jr. Percutaneous renal tumor cryoaiblation with magnetic resonance imaging guidance. J. Urol. 2001; 165: 773–6.

68 Wowra B, Siebels M, Muacevic A, Kreth FW, Mack A, Hofstetter A. Repeated gamma knife surgery for multiple brain metastases from renal cell carcinoma. J. Neurosurg. 2002; 97: 785–93.

69 Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lundsford LD. Radiosurgery in patients with renal cell carcinoma metastasis to the brain: Long term outcomes and prognostic factors influencing survival and local tumor control. J. Neurosurg. 2003; 98: 342–9.

70 Mori Y, Kondziolka D, Flickinger JC, Logan T, Lunsford LD. Stereotactic radiosurgery for brain metastasis from renal cell carcinoma. Cancer 1998; 83: 344–53.

71 Goyal LK, Suh JH, Reddy CA, Barnett GH. The role of whole brain radiotherapy and stereotactic radiosurgery on brain metastases from renal cell carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 2000; 47: 1067–12.

72 Ikushima H, Tokuyue K, Suni M et al. Fractionated stereotactic radiotherapy of brain metastasis from renal cell carcinoma. Int. J. Radiat. Oncol. Biol. Phys. 2000; 48: 1389–93.

73 Lee J, Hodgson D, Chow E et al. A phase II trial of palliative radiotherapy for metastatic renal cell carcinoma. Cancer 2005; 104: 1894–900.

74 Medical Research Council Renal Cancer Collaborators. Interferon-alpha and survival in metastatic renal carcinoma: Early results of a randomized controlled trial. Lancet 1999; 353: 14–17.

75 Pyrhornen S, Salminen E, Ruutu M et al. Prospective randomized trial of interferon alpha-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. J. Clin. Oncol. 1999; 17: 2859–67.

76 Frye G, Fisher RI, Rosenberg SA, Sznl M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J. Clin. Oncol. 1995; 13: 688–96.

77 Yang JC, Sherry RM, Steinberg SM et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J. Clin. Oncol. 2003; 21: 3127–32.

78 McDermott DF, Regan MM, Clark JI et al. Randomized phase III trial of high-dose interferon-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. J. Clin. Oncol. 2005; 23: 133–41.

79 Negrier S, Escudier B, Lasset C et al. Recombinant human interleukin-2, recombinant human interferon alpha-2a, or both in metastatic renal-cell carcinoma. Groupe Francais d’Immunothérapie. N. Engl. J. Med. 1998; 338: 1272–8.

80 Atzpodien J, Hoffmann R, Franzke M, Stief C, Wandert T, Reitz M. Thirteen-year, long-term efficacy of interferon 2alpha and interleukin 2-based home therapy in patients with advanced renal cell carcinoma. Cancer 2002; 95: 1045–50.

81 Bukowski RM. Natural history and therapy of metastatic renal cell carcinoma: The role of interleukin-2. Cancer 1997; 80: 1198–220.

82 Akaza H, Tsukamoto T, Ohnishi T, Miki T, Kinouchi T, Naito S. A low-dose combination therapy of interleukin-2 and interferon-alpha is effective to lung metastases of renal cell carcinoma: A multicenter open study. Int. J. Clin. Oncol. 2006; 11: 434–40.

83 Negrier S, Caty A, Lesimple T et al. Treatment of patients with metastatic renal carcinoma with a combination of subcutaneous interleukin-2 and interferon alfa with or without fluorouracil. Groupe Francais d’Immunotherapie, Federation Nationale des Centres de Lutte Contre le Cancer. J. Clin. Oncol. 2000; 18: 4009–15.

84 Messing EM, Manola J, Wilding G et al. Phase III study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma: An Eastern Cooperative Oncology Group/Intergroup Trial. J. Clin. Oncol. 2003; 21: 1214–22.

85 Pizzocaro G, Piva L, Colavita M et al. Interferon adjuvant to radical nephrectomy in Robson stage T1 and T2 renal cell carcinoma: A multienricentric randomized study. J. Clin. Oncol. 2001; 19: 425–31.

86 Clark JI, Atkins MB, Urba WJ et al. Interferon high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: A cytokine working group randomized trial. J. Clin. Oncol. 2003; 21: 3313–40.

87 Atzpodien J, Schmitt N, Gertenbach U et al. Prospective randomized trial of interferon-alfa and interferon-alpha2a-based chemoimmunotherapy in renal cell carcinoma post tumour nephrectomy: Results of a prospectively randomized trial of the German Cooperative Renal Carcinoma Chemoimmunotherapy Group (DGCCIN). Br. J. Cancer 2005; 92: 843–6.

88 Yang JC, Haworth L, Sherry RM. A randomized trial of bevacinumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N. Engl. J. Med. 2003; 349: 427–34.

89 Motzer RJ, Michaelson MD, Redman BG et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J. Clin. Oncol. 2006; 24: 16–24.
90 Reddy K. Phase III study of sunitinib malate (SU11248) versus interferon-alpha as first line treatment in patients with metastatic renal cell carcinoma. *Clin. Genitourin. Cancer* 2006; 5: 23–5.

91 Ratain MJ, Eisen T, Stadler WM et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 2006; 24: 2505–12.

92 Hudes G. A phase III randomised 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor risk patients with advanced renal cell carcinoma (adv RCC). *J. Clin. Oncol.* 2006; 24: 930s.

93 Childs R, Chernoff A, Contentin N et al. Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation. *N. Engl. J. Med.* 2000; 343: 750–8.

94 Rini BI, Zimmerman T, Stadler WM, Gajewski TF, Vogelzang NJ. Allogeneic stem-cell transplantation of renal cell cancer after nonmyeloablative chemotherapy: Feasibility, engraftment, and clinical results. *J. Clin. Oncol.* 2002; 20: 2017–24.

95 Wenzel C, Locker GJ, Schmidinger M et al. Capecitabine in the treatment of metastatic renal cell carcinoma failing immunotherapy. *Am. J. Kidney Dis.* 2002; 39: 48–54.

96 Casali A, Sega FM, Casali M, Serrone L, Terzoli E. 13-cis retinoic acid and interferon alfa-2a in the treatment of metastatic renal cell carcinoma. *J. Exp. Clin. Cancer Res.* 1998; 17: 227–9.

97 Bleumer I, Knuth A, Oosterwijk E et al. A phase II trial of chimeric monoclonal antibody G250 for advanced renal cell carcinoma patients. *Br. J. Cancer* 2004; 90: 985–90.

98 Mickisch G, Carballido J, Hellsten S et al. Guidelines on renal cell carcinoma. *Eur. Urol.* 2001; 40: 252–5.

99 Rouviere O, Bouvier R, Négrier S, Badet L, Lyonnet D. Nonmetastatic renal-cell carcinoma: Is it really possible to define rational guidelines for post-treatment follow-up? *Nat. Clin. Pract. Oncol.* 2006; 3: 200–13.

100 Russo P. Renal cell carcinoma. In: Johnson FE, Virgo KS (eds). *Cancer Treatment Follow-up.* Mosby, St Louis, 1997; 444–61.