

## The Management of Renal Cell Carcinoma

### 1. Introduction

#### Renal cell carcinoma in Singapore

From 1990 to 1998, there are about 600 cases of renal cell carcinoma registered with the Singapore Cancer Registry . Unlike other urological malignancies that have seen many major breakthroughs, advanced renal cancer continues to have dismal prognosis where effective treatment is lacking. However, a widely noted trend of increased early detection of renal cell carcinoma through the liberal use of imaging modalities this may be translated into better survival prognosis. (1)

#### 1.2 Guideline development and target group

This present guideline is an outcome of comprehensive literature review of major reports and extensive discussion amongst the renal cancer workgroup. The recommendations were presented in the First Uro-oncology Consensus Meeting held in March 1999 at National Cancer Centre, Singapore. This guideline was derived from the consensus drawn from the above named meeting.

The guideline will serve as an updated reference of the practical management of patients suffering from renal cell carcinoma for family physicians, as well as specialists interested in the practice of uro-oncology.

\* Trends in cancer incidence in Singapore 1968-1992, Singapore Cancer registry

### 2 Levels of evidence and grades of recommendation

#### Levels of evidence

| Level      | Type of Evidence  |
|------------|---|
| <b>Ia</b>  | Evidence obtained from meta-analysis of randomised controlled trials.   |
| <b>Ib</b>  | Evidence obtained from at least one randomised controlled trial.  |
| <b>IIa</b> | Evidence obtained from at least one well-designed controlled study without randomisation  |
| <b>IIb</b> | Evidence obtained from at least one other type of well-designed quasi-experimental study.   |
| <b>III</b> | Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies. |
| <b>IV</b>  | Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.                             |

#### Grades of recommendation

| Grade                                       | Recommendation  |
|---|---|
| <b>A</b><br>(evidence levels Ia, Ib)        | Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.                                   |
| <b>B</b><br>(evidence levels IIa, IIb, III) | Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.  |
| <b>C</b><br>(evidence level IV)             | Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality. |
| <b>GPP</b><br>(good practice points)        | Recommended best practice based on the clinical experience of the guideline development group.  |

### 3 Executive summary of recommendations

Wide availability of imaging modalities has led to early detection of renal lesions. It is advisable that the nature of these lesions be delineated by appropriate definitive imaging **(B/III)**

1. While the Robson's staging system is widely accepted, The TNM stage classification system should be adopted to allow accurate documentation of pathological data, which carries important prognostic information. **(B/III)**
2. Localised renal cell carcinoma should be treated by surgery where radical nephrectomy remains the standard therapy. **(B/III)**  
Nephron-sparing surgery can be considered for incidental small lesions or patients with underlying impaired renal function. **(B/III)**
3. Role of surgery is limited in advanced renal cell carcinoma or recurrent disease. **(B/III)**
4. Outside the context of clinical trials, immunotherapy may be considered as an off-protocol treatment option for recurrent a metastasis disease. **(GPP)**

### 4 Diagnosis & staging of renal cell carcinoma

Renal cell carcinoma is a relatively rare tumour, accounting for about 3% of all adult malignancies. The male to female ratio is about 2:1. Macroscopic haematuria, loin pain and loin mass are cardinal symptoms of renal cell carcinoma, but presence of all these symptoms are infrequent. Unfortunately, significant number of patients has metastatic or in-operable disease on first presentation. [\(2\)](#)

The delineation of renal lesion and definitive diagnosis of renal cell carcinoma almost relies solely on radiological imaging.

#### 4.1 Evaluation of renal lesions

Renal lesions other than simple renal cysts detected on ultrasonography or other imaging modalities should be further evaluated by Computed Tomography (CT) abdomen. **(B/III)** [\(3\)](#)

##### 4.1.1 Indeterminate renal lesion

Despite the use of CT, magnetic resonance imaging (MRI) as well as other imaging modalities, a small proportion of renal lesions may not have their exact nature defined – these are generally assigned indeterminate lesions. Biopsy of these indeterminate renal masses is reserved for patients with suspected inflammatory lesions, abscesses, metastases and those with suspected RCC where a definitive preoperative diagnosis is preferable due to high surgical risks. The relatively low diagnostic yield and accuracy of preoperative biopsy of small solid renal masses may not justify the potential morbidity and risk of needle tract seeding. **(III/B Not recommended)** [\(3, 4\)](#)

#### 4.2 Staging of RCC

##### 4.2.1 Computed Tomography (CT)

In the staging of renal tumour, CT is currently accepted as the most reliable and accurate. **(B/III)** [\(5 - 8\)](#)

However, there are limitations in using CT in the evaluation of perinephric fat involvement, lymphatic infiltration, vascular extension and extension to adjacent organ.

##### 4.2.2 Magnetic Resonance Imaging (MRI)

MRI is performed for patients with contrast allergy, renal impairment, and equivocal findings on CT abdomen (with respect to the nature of the lesion as well as the organ of origin). **(III/B)** [\(9\)](#)

MRI is more accurate than CT for Stage IIIa and IV tumors and is useful for evaluating adjacent organ invasion, and extent of inferior vena caval (IVC) tumor thrombus. Assessment for the extent of tumour thrombus can be further complemented by the use of Doppler ultrasound as well as inferior venography, which is more invasive. [\(10\)](#) **(III/B)**

#### 4.2.3 Angiography

Currently, angiography has no role in diagnosis as it is invasive and the findings are often non-specific. This should be restricted to indications such as preoperative vascular mapping in preparation for nephron sparing surgery, or in angio-infarction of large tumors. **(GPP)**

#### 4.2.4 Chest x-ray (CXR) & Computer Tomography of Thorax

In the routine pre-operative staging for clinically localized renal tumour, a plain CXR suffices and CT thorax is generally not required. **(III/B)** [\(11\)](#)

However, CT has a much higher sensitivity in the detection of pulmonary metastasis as compared to CXR. The indications for CT thorax will include the following **(GPP)**:

- Patient with chest symptoms.
- As part of a protocol for experimental immune/chemotherapy.
- Single pulmonary nodule seen on CXR especially if resection is being considered.

CT thorax is unnecessary when multiple pulmonary nodules are seen on CXR.

#### 4.2.5 Bone Scan

Bone scan has no routine role in the metastatic work-up of RCC and should be omitted. [\(12\)](#)

The 1997 Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) TNM staging classification [\(13\)](#) is preferred to the Robson's stage classification. [\(14\)](#) This latest version of the TNM system has been shown to provide useful prognostic information and allow for easier stage for stage comparison of survival results from different series. [\(15\)](#) **(B/III)** (Please refer to Annex 1)

## 5 Treatment of renal cell carcinoma

### 5.1 Incidental Renal Tumours

With the advent and increased use of ultra-sound and CT scans for the assessment of abdominal complaints, there is an increasing number of renal masses detected incidentally. Renal tumours thus detected tend to be small and are often of lower grade and stage carrying better prognosis [\(16, 17\)](#).

#### 5.1.1 Management of incidental complex cysts / renal masses

Open surgical exploration with frozen section and intent of nephrectomy (total/partial) is the treatment of choice for true indeterminate masses with a possibility of malignancy in good surgical risk patients. [\(3\)](#) **(III/B)**

Occasionally, interval imaging may provide the clue to the nature of the indeterminate lesion and may be preferable in some patients. Surveillance by regular imaging follow-up may also be considered for patients with poor surgical risks. [\(18, 19\)](#) **(GPP)**

### 5.2 Radical Nephrectomy

The accepted standard treatment for non-metastatic renal cell carcinoma is radical nephrectomy. This entails the early ligation of renal artery, followed by the renal vein and then en bloc removal of the kidney, perirenal fat within and including the Gerota fascia as well as the upper ureter. **(III/A)** [\(14, 20\)](#).

- Adrenalectomy

Adrenalectomy has been part of radical nephrectomy in Robson's series. Recent evidences suggest that it need not routinely be part of radical nephrectomy, since adrenalectomy does not improve survival. [\(21, 22\)](#).

Pre-operative CT abdomen is highly sensitive and specific in diagnosing adrenal involvement. (23, 24) There is no need to perform ipsilateral adrenalectomy if the CT films show normal adrenal glands. However, adrenalectomy is necessary if there are adrenal abnormalities on pre-operative CT films or gross extension of the renal tumour into adrenal gland seen intra-operatively. (25) Adrenalectomy is also indicated if the renal tumour is large ( $\geq 5\text{cm}$ ) or if it is located in the upper pole of the kidney. (III/C) (23, 24).

It may be noted that adrenalectomy does not usually form part of partial and laparoscopic nephrectomy.

- Lymphadenectomy

The controversy regarding the need for lymphadenectomy as an integral component of radical nephrectomy has largely been settled. To date, there has been limited evidence to support extensive lymphadenectomy, 5-year survival improved by about 10% only. (26)

As RCC metastasise via both lymphatic and haematologic routes and the lymphatic drainage of kidney is variable (27), the workgroup is of the opinion that extensive lymph node dissection is not recommended. (III/B).

- Venous tumour thrombus extension

Radical nephrectomy can be carried out despite the presence of inferior vena caval (IVC) thrombus. (III/B) (28 - 32)

It is reported that RCC with venous tumour thrombus extension, even into the vena cava, do not necessarily carry an ominous prognosis if they are completely excised and are not associated with perinephric fat, contiguous visceral invasion or regional nodal or distant metastases. (33)

However, tumour infiltration into endothelial wall of IVC is an adverse prognostic factor. (28)

### 5.3 Nephron Sparing Surgery (Partial Nephrectomy)

Radical nephrectomy has been the standard therapy for localised RCC in patients with a normal contralateral kidney (14, 20). However, in patients with a solitary functioning kidney or bilateral tumour, renal sparing surgery (partial nephrectomy) is often the preferred option. (III/B) (34). This procedure can also be considered in patients with associated diseases like hypertension or diabetes mellitus which may cause chronic renal impairment. (III/B) (35)

Special consideration needs to be made regarding offering elective nephron-sparing surgery to patients with normal contralateral kidneys. There are numerous recent reports of excellent 5 year cancer-specific survival results of approximately 90% (36 - 38) which is comparable to contemporary radical nephrectomy series. (III/B) Elective nephron sparing surgery should be limited to small RCC of  $< 4\text{cm}$ . (III/B) (39, 40)

However, several factors continue to be in favour of radical nephrectomy. These include the low risk of contralateral kidney renal dysfunction as defined in long-term follow-up studies of living-related donor nephrectomy patients, and the low-risk (1-2%) of development of metachronous renal tumour in the normal contralateral kidney. On the other hand, there remains a risk of local tumour recurrence after nephron-sparing surgery (overall 2% reported in the literature). In addition, there are occasional cases of unsuspected multifocal tumours that would not be removed by partial excision. (41)

It is also important to note that nephron-sparing surgery is technically more demanding and carries a higher morbidity. Local experience of 18 partial nephrectomies for renal cell carcinoma has shown that it is feasible in small renal cancer, and can be offered in selected patients. (III/B) (43)

### 5.4 Laparoscopic Radical Nephrectomy

Laparoscopic radical nephrectomy for renal tumours requires less post-operative analgesia than open surgery, with faster recovery and shorter hospitalisation period. (43) It is a feasible operation, with reproducible operative results (44, 45), but the experience has been limited to very few centres. Even amongst centres with major laparoscopic nephrectomy experiences, many are not extending their indications to malignant diseases routinely. (46)

It must be noted that complications are presently higher than open surgery. While local or port recurrence appears rare, comparative survival outcome studies are lacking. (44, 45). It is recommended that such

surgical approach be limited to clinical research settings. **(GPP)**

### 5.5 Follow-up Protocols for Renal Cell Carcinoma

The follow up protocol of patients with renal cell carcinoma after treatment may be guided by the pathological stage. [\(47, 48\)](#) **(III/B)**

Regular history, physical examination, serum liver function tests and CXR are indicated. Bone and brain scans are considered only when history is suggestive of metastasis. Routine CT scan of abdomen is controversial. [\(47, 48\)](#).

In patients who develop solitary lung metastasis but have long disease free interval and good performance status, resection of the metastatic lesion may be considered. [\(49\)](#) **(III/B)**

### 5.6 Metastatic Renal Cell Carcinoma

Patients with a single resectable metastatic site should be considered for surgical resection. [\(49\)](#) This is especially so if the patient is asymptomatic, has good performance status, and a long disease-free interval between the initial nephrectomy and subsequent development of the metastatic disease. **(III/B)**

Patients with unresectable / multiple metastatic disease may consider participation in innovative clinical trials of immunotherapy, where clear study parameters and end-point are spelt out, and the response is monitored by dedicated research clinician and supported by other personnel as well as facilities. Such patients can be treated with immunotherapy first, and considered for surgical resection if disease is responding. **(GPP)** If clinical trial is not an option, selected patients may still be offered immunotherapy. Alpha interferon (a -IFN) may be considered as first line treatment since it has the best data so far. However, the response rate and absolute benefit from a -IFN is modest at best [\(50, 51\)](#), and durable response is seen only in a minority of patients.

Patient selection for immunotherapy is important. The favourable factors for response include good performance status, prior nephrectomy with long disease-free interval, non-bulky pulmonary and/or soft tissue metastasis, and lack of tumour-related symptoms. **(GPP)**

There are some suggestion that combination therapy including use of Interleukin-2 may improve the response rate, and also the survival. [\(52\)](#) This can be considered for patients with good performance status and good organ-system function. [\(53, 54\)](#) **(GPP)**

Palliative care is a valid option in selected groups of patients, including elderly patients and patients with unfavourable prognostic factors for response. These include bulky visceral or bony metastasis, short disease-free interval after initial nephrectomy, extensive prior treatment and unresected tumours. **(GPP)** [\(54\)](#)

### 5.7 Role of Surgery in Advanced RCC

There is little indication for surgical resection of local cancer if there is clinically obvious extensive nodal disease (N2), or frank metastatic disease. [\(53\)](#)

Palliative nephrectomy may be performed if the patient has significant uncontrolled symptoms such as pain or transfusion-resistant haematuria. Under such conditions, transarterial angioinfarction may also be used. However, there is no survival benefits with palliative nephrectomy as the sole treatment. **(III/B)** [\(55\)](#)

Delayed adjunctive nephrectomy may be considered upon demonstration of partial or complete response to immunotherapy, especially if objective response is evident within 1 month of commencement of therapy. **(GPP)** [\(56\)](#)

Cytoreductive surgery (resection of the primary tumour prior to immunotherapy) may be considered if the patient is to receive subsequent immunotherapy for the metastatic disease, because a large tumour volume load may inhibit the immune response. However, this observation has not been confirmed in randomised studies. Only a few series documented the survival data. [\(56, 57\)](#) Median survival of 12-21 months had been reported. **(GPP)**

Selected patients with recurrent RCC should be considered for resection with a curative intent. They have a good opportunity for long-term survival, particularly those with a solitary recurrence and/or long-term disease-free interval. **(III/B)** [\(49\)](#)

## 6 Clinical Audit

### 1. *Pre-operative diagnosis*

Pre-operative diagnosis of renal cancer utilising available imaging modalities should be established in majority of patients.

### 2. *Choice of surgery*

Radical nephrectomy should be regarded as the standard therapy for localised cancer. The option of nephron sparing surgery in selected groups may be discussed regarding its advantages and disadvantages. Number of radical and partial nephrectomy in each centre should be documented accordingly

### 3. *Operative mortality and morbidity*

Standard radical nephrectomy should be associated with a low incidence of mortality and major morbidity. A slightly higher morbidity in association with nephron sparing surgery may be expected. The surgical outcome in each case should be documented.

### 4. *Survival data*

Post-operative patients should be followed up and recurrence or metastasis should be documented. Crude survival as well as cancer specific survival should be compiled.

### 5. *Response to immunotherapy*

Patients with recurrent or metastatic disease who opt for immunotherapy should have their response monitored

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## 8 References

1. Chow WH, Devesa SS, Warren JL, Franmeni JF Jr, Rising incidence of renal cell cancer in the United States JAMA 1999; 281:1628-31
2. Beldegrun A, deKernion JB. Renal tumours in Walsh PC, Retik AB, Darracott Vaughan E Jr, Wein AJ (Eds) Campbell's Urology, WB Saunders, 1998:2292-3
3. Wolf JS Jr Evaluation and management of solid and cystic renal masses. J.Urol. 1998; 159(4): 1120-33.
4. Campbell SC, Novick AC, Herts B, et al. Prospective evaluation of fine needle aspiration of small, solid renal masses: accuracy and morbidity. Urology. 1997;50(1):25-9.
5. Dinney CP, Awad SA, Gajewski JB, et al. Analysis of imaging modalities, staging systems, and prognostic indicators for renal cell carcinoma. Urology. 1992;39(2):122-9.
6. Kopka L, Fischer U, Zoeller G, Schmidt C, Ringect RH, Grabbe E. Dual-phase helical CT of the kidney:

value of the corticomedullary and nephrographic phase for evaluation of renal lesions and preoperative staging of renal cell carcinoma. *AJR Am J Roentgenol* 1997;169:6,1573-8

7. Bechtold RE, Zagoria RJ. Imaging approach to staging of renal cell carcinoma. *Urol. Clin. North Am.* 1997;24(3):507-22

8. Miller K. Renal cell carcinoma. Guidelines for diagnosis and treatment *Urol Int.* 1999; 63:6-9

9. Oto A, Herts BR, Remer EM, Novick AC. Inferior vena cava tumor thrombus in renal cell carcinoma: staging by MR imaging and impact on surgical treatment. *AJR. AM.J.Roentgenol.* 1998:171(6):1619-24

10. Bos SD, Mensink HJ. Can duplex Doppler ultrasound replace computerized tomography in staging patients with renal cell carcinoma? *Scand. J. Urol. Nephrol.* 1998;32(2):87-91.

11. Lim DJ, Carter MF. Computerized tomography in the preoperative staging for pulmonary metastases in patients with renal cell carcinoma. *J.Urol.* 1993;150(4):1112-4.

12. Staudenherz A, Steiner B, Puig S, Kainberger F, Leitha T. Is there a diagnostic role for bone scanning of patients with a high pretest probability for metastatic renal cell carcinoma? *Cancer* 1999;85(1):153-5.

13. Guinan P, Sobin LH, Algaba F, et al. TNM staging of renal cell carcinoma: Workgroup No. 3. Union International Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). *Cancer* 1997;80(5):992-3.

14. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. *J.Urol.* 1969;101(3):297-301.

15. Javidan J, Stricker HJ, Tamboli P et al. Diagnostic significance of the 1997 TNM classification of renal cell carcinoma *J Urol* 1999; 162:1277-81

16. Gudbjartsson T, Einarsson GV, Magnússon J. A population-based analysis of survival and incidental diagnosing of renal cell carcinoma patients in Iceland, 1971-1990. *Scand.J.Urol.Nephrol.* 1996;30(6):451-5.

17. Sweeney JP, Thornhill JA, Graiger R, McDermott TE, Butler MR. Incidentally detected renal cell carcinoma: pathological features, survival trends and implications for treatment. *Br.J.Urol.* 1996;78(3):351-3.

18. Bosniak MA. The current radiological approach to renal cysts. *Radiology* 1986;158(1):1-10.

19. Bosniak MA, Birnbaum BA, Krinsky GA, Waisman J. Small renal parenchymal neoplasms: further observations on growth. *Radiology* 1995;197(3):589-97.

20. Guinan PD, Vogelzang NJ, Fremgen AM, et al. Renal cell carcinoma: tumor size, stage and survival. Members of the Cancer Incidence and End Results Committee. *J.Urol.* 1995;153(3 Pt 2):901-3.

21. Kozak W, Höltl W, Pummer K, Maier U, Jeschke K, Bucher A. Adrenalectomy --still a must in radical renal surgery? *Br.J.Urol.* 1996;77(1):27-31.

22. Leibovitch I, Raviv G, Mor Y, Nativ O, Goldwasser B. Reconsidering the necessity of ipsilateral adrenalectomy during radical nephrectomy for renal cell carcinoma. *Urology.* 1995;46(3):316-20.

23. Kardar AH, Arafa M, Al Suhaibani H, et al. Feasibility of adrenalectomy with radical nephrectomy. *Urology.* 1998;52(1):35-7.

24. Gill IS, McClennan BL, Kerbl K, Carbone JM, Wick M, Clayman RV. Adrenal involvement from renal cell carcinoma: predictive value of computerized tomography. *J.Urol.* 1994;152(4):1082-5.

25. Sandock DS, Seftel AD, Resnick MI. Adrenal metastases from renal cell carcinoma: role of ipsilateral adrenalectomy and definition of stage. *Urology.* 1997;49(1):28-31.

26. Herrlinger A, Schrott KM, Schott G, Sigel A. What are the benefits of extended dissection of the regional renal lymph nodes in the therapy of renal cell carcinoma. *J.Urol.* 1991;146(5):1224-7.

27. Johnsen JA, Hellsten S. Lymphatogenous spread of renal cell carcinoma: an autopsy study. *J.Urol.* 1997;157(2):450-3.

28. Hatcher PA, Anderson EE, Paulson DF, Carson CC, Robertson JE. Surgical management and prognosis of renal cell carcinoma invading the vena cava. *J.Urol.* 1991;145(1):20-3.

29. Marshall FF, Steinberg GD, Pound CR, Partin AW. Radical surgery for renal-cell carcinoma: caval

- neoplastic excision, adrenalectomy, lymphadenectomy, adjacent organ resection. *World J.Urol.* 1995;13(3):159-62.
30. Skinner DG, Pritchett TR, Lieskovsky G, Boyd SD, Stiles QR. Vena caval involvement by renal cell carcinoma. Surgical resection provides meaningful long-term survival. *Ann.Surg.* 1989;210(3):387-92.
31. Stief CG, Schafers HJ, Kuczyk M, et al. Renal-cell carcinoma with intracaval neoplastic extension: stratification and surgical technique. *World J.Urol.* 1995;13(3):166-70.
32. Li MK, Yip, SKH, Cheng WS. Inferior Vena cava thrombectomy for renal cell carcinoma with thrombus. *Ann Acad Med Singapore* 1999;28:508-11
33. Kuczyk MA, Bokemeyer C, Köhn G, et al. Prognostic relevance of intracaval neoplastic extension for patients with renal cell cancer. *Br.J.Urol.* 1997;80(1):18-24.
34. Marberger M, Pugh RC, Auvert J, et al. Conservation surgery of renal carcinoma: the EIRSS experience. *Br.J.Urol.* 1981;53(6):528-32.
35. Steinbach F, Stockle M, Muller SC, et al. Conservative surgery of renal cell tumors in 140 patients: 21 years of experience. *J.Urol.* 1992;148(1):24-9.
36. D'Armiento M, Damiano R, Feleppa B, Perdona S, Oriani G, De Sio M. Elective conservative surgery for renal carcinoma versus radical nephrectomy: a prospective study. *Br.J.Urol.* 1997;79(1):15-9.
37. Van Poppel H, Bamelis B, Oyen R, Baert L. Partial nephrectomy for renal cell carcinoma can achieve long term tumor control. *J Urol* 1998; 160:674-8
38. Herr HW. Partial nephrectomy for unilateral renal carcinoma and a normal contralateral kidney: 10-year follow-up. *J.Urol.* 1999;161(1):33-4.
39. Licht MR, Novick AC, Goormastic M. Nephron sparing surgery in incidental versus suspected renal cell carcinoma. *J.Urol.* 1994;152(1):39-42.
40. Miller J, Fischer C, Freese R, Altmannsbeiger M, Weidner W. Nephron sparing surgery for renal cell carcinoma – is tumour size a suitable parameter for indication. *Urology* 1999;54:988-93
41. Cheng WS, Farrow GM, Zincke H. The incidence of multicentricity in renal cell carcinoma. *J.Urol.* 1991;146(5):1221-3.
42. Yip SK, Cheng WS, Tan BS, Li MK, Foo KT. Partial nephrectomy for renal tumours: the Singapore General Hospital experience. *J R Coll Surg Edinb* 1999 44:156-60
- 43 McDougall E, Clayman RV, Elashry OM. Laparoscopic radical nephrectomy for renal tumor: the Washington University experience. *J. Urol.* 1996;155(4):1180-5.
44. Barrett PH, Fentie DD, Taranger LA. Laparoscopic radical nephrectomy with morcellation for renal cell carcinoma: the Saskatoon experience. *Urology.* 1998;52(1):23-8.
45. Ono Y, Kato N, Kinukawa T, Matsuura O, Ohshima S. Laparoscopic radical nephrectomy: the Nagoya experience. *J.Urol.* 1997;158(3 Pt 1):719-23.
46. Rassweiler J, Fornara P, Weber M, et al. Laparoscopic nephrectomy: the experience of the laparoscopy working group of the German Urologic Association. *J.Urol.* 1998;160(1):18-21.
47. Sandock DS, Seftel AD, Resnick MI. A new protocol for the follow-up of renal cell carcinoma based on pathological stage. *J.Urol.* 1995;154(1):28-31.
48. Hafez KS, Novick AC, Campbell SC. Patterns of tumor recurrence and guidelines for follow up after nephron sparing surgery for sporadic renal cell carcinoma. *J.Urol.* 1997;157(6):2067-70.
49. Kavolius JP, Mastorakos DP, Pavlovich C, Russo P, Burt ME, Brady MS. Resection of metastatic renal cell carcinoma. *J.Clin.Oncol.* 1998;16(6):2261-6.
50. Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Medical Research Council Renal Cancer Collaborators. *Lancet* 1999;353(9146):14-7.
51. Henriksson R, Nilsson S, Colleen S, et al. Survival in renal cell carcinoma-a randomized evaluation of tamoxifen vs interleukin 2, alpha-interferon (leucocyte) and tamoxifen. *Br.J.Cancer* 1998;77(8):1311-7.
52. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon

alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Français d'Immunothérapie. N.Engl.J.Med. 1998;338(18):1272-8.

53. Motzer RJ, Bander NH, Nanus DM. Renal cell carcinoma. N.Engl.J.Med. 1996;335(12):865-75.

54. Vogelzang NJ, Stadler WM. Kidney cancer. Lancet 1998;352(9141):1691-6.

55. Dekernion JB, Ramming KP, Smith RB. The natural history of metastatic renal cell carcinoma: a computer analysis. J.Urol. 1978;120(2):148-52.

56. Rackley R, Novick A, Klein E, Bukowski R, McLain D, Goldfarb D. The impact of adjuvant nephrectomy on multimodality treatment of metastatic renal cell carcinoma. J.Urol. 1994;152(5 Pt 1):1399-403.

57. Fallick ML, McDermott DF, LaRock D, Long JP, Atkins MB. Nephrectomy before interleukin-2 therapy for patients with metastatic renal cell carcinoma. J.Urol. 1997;158(5):1691-5.

## Annex 1

### The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification

#### TNM definitions

##### Primary tumor (T)

**TX:** Primary tumor cannot be assessed

**T0:** No evidence of primary tumor

**T1:** Tumor 7 cm or less in greatest dimension limited to the kidney

**T2:** Tumor more than 7 cm in greatest dimension limited to the kidney

**T3:** Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia

**T3a:** Tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia

**T3b:** Tumor grossly extends into the renal vein(s) or vena cava below the diaphragm

**T3c:** Tumor grossly extends into the renal vein(s) or vena cava above the diaphragm

**T4:** Tumor invades beyond Gerota's fascia

##### Regional lymph nodes (N)

**NX:** Regional lymph nodes cannot be assessed

**N0:** No regional lymph node metastasis

**N1:** Metastasis in a single regional lymph node

**N2:** Metastasis in more than 1 regional lymph node

Note: Laterality does not affect the N classification.

##### Distant metastasis (M)

**MX:** Distant metastasis cannot be assessed

**M0:** No distant metastasis

**M1:** Distant metastasis