



European Association of Urology

# **GUIDELINES ON RENAL CELL CANCER\***

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## Abstract

- Objectives:** On behalf of the European Association of Urology (EAU) Guidelines for Diagnosis, Therapy and Follow-up of Renal Cell Carcinoma Patients were established. Criteria for recommendations were evidence based, and included aspects of cost-effectiveness and clinical feasibility.
- Method:** A systematic literature research using Medline Services was conducted. References were weighted by a panel of experts on RCC.
- Results:** RCC is characterised by a constant rise in incidence over the last 50 years, with a predominance of men over women and an incidence peak in the 6th and 7th decade. There is no risk factor established and the current TNM system (UICC, 1997) is endorsed for staging purposes. Clinical signs and symptoms of RCC are becoming less frequent, incidental discovery constitutes already a majority of cases. Diagnosis is established by ultrasound and abdominal CT, extension assessment in routine cases is done by chest X-ray. Additional examinations may be required in select cases. Therapy of choice in organ-confined RCC is surgery. Radical tumornephrectomy is considered as a standard. Efficacy and side effects of organ-sparing surgery, lymphadenectomy and inclusion/omission of ipsilateral adrenalectomy in selected cases is the matter of ongoing clinical research. In metastatic cases, tumornephrectomy should only be considered in the context of modern systemic immunotherapy. A follow-up at regular intervals is recommended because certain cases of recurrences may be candidates for surgery and/or immunomodulating therapy.
- Conclusion:** A rise in incidence, improved diagnostic procedures, and evolving multimodality therapeutic concepts justify the need for rational guidelines on this most challenging urologic malignancy.

# 1. BACKGROUND

Renal cell carcinoma (RCC) accounts for about 2% of all cancers, with a world-wide annual increase of 1.5 – 5.9% (1, 2). The mean age at the time of diagnosis is about 70 years and there is a predominance of men over women in the range of 1.5 – 3.1. The mortality from RCC is increasing parallel to trends in incidence (2). World-wide mortality is expected to increase from 54,000 deaths in 1985 to 102,000 deaths in 2000. It may reach or even exceed that of bladder cancer in certain areas.

The increased incidence of RCC is primarily due to enhanced detection of tumours by expanded use of imaging techniques, such as ultrasound and computed tomography (CT) (2). At present, 25 – 40% of clinically diagnosed RCC are found incidentally. A total of 25 – 30% of patients with RCC have overt metastases at initial presentation and, in addition, a substantial fraction of patients have subclinical metastases at that time explaining the hitherto unsatisfactory outcome of treatment (3, 4).

A slight to moderate improvement in survival has been observed in most countries. Survival is closely related to initial stage; 5-year survival is 50 – 90% for localised disease, decreasing to 0 – 13% for metastatic disease (3).

# 2. CLASSIFICATION

RCC represents the greater part of malignant tumours of the kidney (80% - 90%). The remainder include transitional cell carcinomas, non-epithelial kidney tumours and Wilms' tumours (5,6). The TNM 97 classification is recommended and differs from TNM 92 in stage T1 (tumour size  $\leq 7$  cm) and stage T2 ( $>7$  cm). It also differs in N1 (one node) and N2 (more than one node) involvement, while the N3 subcategory has been removed.

Robson's classification (1969) is commonly used and the relationship with TNM 97 is as follows:

- Robson's Stage I = T1-2
- Robson's Stage II = T3a
- Robson's Stage IIIa = T3b-c
- Robson's Stage IVa = T4
- Robson's Stage IIIb = N1-2
- Robson's stage IVb = M1 (6-8)

Traditionally RCC have been classified according to the nuclear (7-9) or cellular morphology (10). New morphologic, cytogenetic and molecular studies make it possible to distinguish five types of carcinomas:

- Clear – cell: 60 – 85%
- Chromophilic: 7 – 14%
- Chromophobic: 4 – 10%
- Oncocytic: 2 – 5%
- Collecting duct: 1 – 2% (10).

Recent attempts have been made to generate a molecular classification (11).

There are no generally accepted risk factors for RCC. There are some epidemiologic data indicating that a smoking habit, obesity or exposure to certain heavy metals such as cadmium may favour the development of RCCs.

# 3. DIAGNOSIS

Clinical symptoms of RCC, such as haematuria, palpable tumour and flank pain, are becoming less frequent. Asymptomatic tumours are more commonly diagnosed (12). Clinical examination has a limited role in diagnosing RCC, but it may be valuable in assessing co-morbidity (12). In case of haematuria, additional tumours of the genitourinary tract should be excluded (13). The most commonly assessed laboratory parameters are:

- Haemoglobin and erythrocyte sedimentation rate: prognosis
- Creatinine: overall kidney function
- Alkaline phosphatase: liver metastasis, bone metastasis.

Serum calcium is frequently included in the preoperative assessment because of its association with paraneoplastic manifestation, which may have clinical implications (14).

The majority of tumours are diagnosed by abdominal ultrasound performed for various reasons. Standard radiological procedure is an abdominal CT-scan with and without contrast medium. It serves to document the diagnosis of RCC and provides information on the function and morphology of the contralateral kidney (15).

Additional diagnostic procedures, such as magnetic resonance imaging, angiography or fine needle biopsy, have a very limited role, but may be considered in selected cases (16).

### **Extension assessment**

Abdominal CT scan assesses primary tumour extension and provides information on venous involvement and on metastatic spread to loco-regional lymph nodes, adrenals, contralateral kidney, liver etc (15). Chest X-ray is performed to assess pulmonary spread. If indicated by signs and symptoms, other diagnostic procedures may be applied, such as bone scan, brain CT, chest CT (12).

## **4. TREATMENT**

Only radical surgery offers a reasonable chance of curing the disease (17). The chances of cure by surgery most strongly depend on stage (primarily) and grade (secondarily) of the disease (e.g. following TNM classification) (18). Standard operative procedure is a radical nephrectomy including Gerota's fascia (19). There is no evidence to favour a specific surgical approach. In selected cases of small (< 4 cm) peripheral lesions, an organ sparing approach may be considered. Final evaluation of oncologic efficacy is pending (20, 21).

Adrenalectomy is generally recommended. The sparing of the ipsilateral adrenal gland in the case of a smaller tumour of the lower half of the kidney is currently being evaluated in ongoing clinical research (22). A formal lymph node dissection is a valuable diagnostic tool (staging); however, therapeutic efficacy is unproven (23).

If surgery cannot eradicate all tumour deposits, tumour nephrectomy remains palliative therapy and should be considered in the context of multimodality treatment (e.g. in conjunction with immunotherapy or experimental therapies) (24, 25).

Certain cases, such as bilateral tumours, a solitary tumour-bearing kidney, multifocal lesions, renal insufficiency, or an occasional palliative situation, will require individual decisions not amenable to general guidelines.

## **5. FOLLOW-UP**

### **Rational for follow up**

Follow up of patients with RCC after surgical treatment is recommended to detect local recurrence and distant metastases as early as possible to permit additional treatment when indicated and if possible. Such therapy may include resection of pulmonary metastasis or local recurrences; certain cases may also be candidates for immunomodulating therapy. With this background in mind, a regular postoperative follow up of patients with RCC is proposed (26,27,28)

### **Principles**

Prognostic factors and the type of surgical intervention (radical vs partial or nephron sparing surgery) are relevant in determining the most efficient follow up regimen. The only established prognostic factor is tumour stage according to the TNM system (28). After nephron sparing tumour resection (elective or mandatory indication), the local recurrence rate may vary between 0 and 10% (20,27). In a small proportion of patients with a genetic predisposition, a different follow-up procedure may be required (29,30).

### **Follow-up procedures**

The first assessment is at 4-6 weeks and includes:

- Physical examination to exclude surgical complications
- Serum creatinine to assess the remaining kidney function
- Haemoglobin to assess recovery of perioperative blood loss.

If these values are normal, repeat investigation is usually unnecessary. Urine analysis is not needed for routine follow up.

If alkaline phosphatase is abnormal preoperatively, repeat measurement is recommended because

recurrent or persistent alkaline phosphatase elevation after surgery suggests distant metastasis, or residual tumour (31,32). Alkaline phosphatase elevation together with bone pain is suspicious for bone metastasis. Elevation may also occur in case of liver metastasis or paraneoplastic manifestations.

A chest X-ray is recommended to detect pulmonary metastases, which occur most commonly within 3 years after surgery. Imaging of the contralateral kidney is advocated in case of enhanced risk of developing metachronous occurrence (as in familial papillary RCC or VHL (von Hippel-Lindau disease)). Imaging of the retroperitoneum by abdominal CT or ultrasound is recommended only after nephron sparing surgery or after radical surgery in locally advanced disease, e.g. T3, T4.

A recommended follow-up scheme is shown in Table 1.

**TABLE 1: Recommended follow-up scheme for renal cell carcinoma**

Stage	Visit	Examination	Optional	Purpose
All T	4-6 weeks after surgery	Physical ex. Creatinine Hb	AP <sup>1</sup>	Exclude complications of surgery Establish remaining kidney function <sup>2</sup> To check recovery of perioperative blood loss
T1, T2	Every 6 months for 3 years Every year from 3-5 years <sup>3</sup>	Physical exam Chest X-ray	AP <sup>2</sup> Kidney imaging	Exclude complications of surgery and LR and LN metastases Exclude pulmonary metastases and LR after partial nephrectomy
T3, T4	Every 6 months for 3 years Every year from 3-10 years	Physical exam Chest X-ray Retroperitoneal imaging		Exclude complications of surgery and LR and LN metastases Exclude pulmonary metastases and LR after partial nephrectomy To detect LR, contralateral metastases or neo-occurrence

AP = alkaline phosphatase; LR = local recurrence; LN = lymph node

<sup>1</sup> If elevated preoperatively (recurrent or persisting elevation suggests distant metastases or residual tumour) when bone pain is present, suspicion of bone or liver metastasis.

<sup>2</sup> If the postoperative level is abnormal, it should be repeated at the regular visits.

<sup>3</sup> There is a small, but continuous, risk of recurrence or metastasis from 5 - 15 yrs.

## 6. References

### 1. Parkin DM, Pisani P, Ferlay J.

Estimates of the world-wide incidence of eighteen major cancers in 1985. *Int J Cancer* 1993; 54: 594-606.

### 2. McCredie M.

Bladder and kidney cancers. *Cancer Surv* 1994; 19: 343-368.

### 3. Motzer RJ, Matzumdar M, Bacik J, Russo P, Berg WJ, Metz EM.

Effect of cytokine therapy on survival for patients with advanced Renal Cell Carcinoma. *J. Clin. Oncol.* 2000; 18: 1928-1935.

### 4. Johnsen JA, Hellsten S.

Lymphatogenous spread of renal cell carcinoma: an autopsy study. *J Urol* 1997; 157: 450-453.

### 5. Gelb AB.

Renal cell carcinoma. Current prognosis factors. *Cancer* 1997; 80: 981 - 986.

### 6. Motzer RJ, Bancer NH, Nanus DM.

Renal cell carcinoma. *N Engl J Med* 1996; 355: 865-875.

### 7. Dobin LH, Wittekind CH.

TNM Classification of Malignant Tumour, 5e ed. Wiley: New York, 1997, pp. 296-302.

8. **Guinan PD, Vogelang NJ, Fremgen AM, et al.**  
Renal cell carcinoma: tumour size, stage and survival. *J Urol* 1995; 159: 901-903.
9. **Fuhrman SA, Lasky LC, Limas C.**  
Prognostic significance of morphologic parameters in renal cell carcinoma. *Am J Surg Pathol* 1982; 6: 655-663.
10. **Störkel S, Enle E, Adlanka K, Amin M, Bostowick D, et al.**  
Classification of renal carcinoma. *Cancer* 1997; 80: 987-989.
11. **Zambrano NR, Lubensky IA, Merino MJ, Linehan WM, Walther MC.**  
Histopathology and molecular genetics of Renal tumours: Toward unification of a classification system. *J Urol* 1999; 162: 1246-1258.
12. **Belldegrun A, de Kernion JB.**  
Renal tumours; in: *Campbell's Urology*, Ed. Walsh, P.C., Retik, A.B., Vaughan, E.D., Wein, A.J. W.B. Saunders, Philadelphia 1998: 2283-2326.
13. **Messing EM, Young TB, Hunt VB, Emoto SE and Wehbie JM.**  
The significance of asymptomatic microhematuria in men 50 or more years old: Findings of a home screening study using urinary dipsticks. *J Urol* 1987; 137: 919-922.
14. **Sufrin G, Chasan S, Golio A, Murphy GP.**  
Paraneoplastic and serologic syndromes of renal adenocarcinoma. *Semin Urol* 1989; 7: 158-171.
15. **Bechtold RE, Zagoria RJ.**  
Imaging approach to staging of renal cell carcinoma. *Urol Clin N Am* 1997; 24: 507.
16. **Newhouse JH.**  
The radiologic evaluation of the patient with renal cancer. *Urol Clin N Am* 1993; 20: 231-246.
17. **Godley PA, Stinchcombe TE.**  
Renal Cell Carcinoma. *Curr Opin Oncol* 1999; 11: 213-217.
18. **Giberti C, Oneto F, Martorana G, Rovida S, Carmignani G.**  
Radical Nephrectomy for Renal Cell Carcinoma: Long-term results and Prognostic Factors on a Series of 328 Cases. *Eur Urol* 1997; 31: 40-48.
19. **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: 159-162.
20. **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: 674-678.
21. **Novick AC.**  
Nephron-sparing Surgery for Renal Cell Carcinoma. *Br J Urol* 1998; 82: 321-324.
22. **Wunderlich H, Schlichter A, Reichelt O et al.**  
Real Indications for Adrenalectomy in Renal Cell Carcinoma Carcinoma. *Eur Urol* 1999; 35: 272-276.
23. **Schafhauser W, Ebert A, Brod J, Petsch S, Schrott KM.**  
Lymph node Involvement in Renal cell Carcinoma and Survival Chance by Systematic Lymphadenectomy. *Anticancer Res* 1999; 19: 1573-1578.
24. **Figlin RA.**  
Renal Cell Carcinoma: Management of Advanced Disease. *J Urol* 1999 Feb; 161 (2): 381-386; discussion 386-387.
25. **Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R.**  
Radical nephrectomy plus interferon-alpha based immunotherapy compared with interferon-alpha alone in metastatic renal cell carcinoma: a randomized trial. *Lancet* 2001; 358: 966-970.
26. **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: 28-31.
27. **Hafez KS, Novick AC, Campbell SC.**  
Patterns of tumour recurrence and guidelines for follow up after nephron sparing surgery for sporadic renal cell carcinoma. *J Urol* 1997; 157: 2067-2070.
28. **Levy DA, Slaton JW, Swanson DA, Dinney CP.**  
Stage specific guidelines for surveillance after radical nephrectomy for local renal carcinoma. *J Urol* 1998; 159: 1163-1167.
29. **Störkel S, van den Berg E.**  
Morphological classification of renal cancer. *World J Urol* 1995; 13: 153:158.
30. **Kovacs G.**  
The value of molecular genetic analysis in the diagnosis. *World J Urol* 1994; 12: 64-68.
31. **Bos SD et al.**  
Routine bone scan and serum alkaline phosphatase for staging in patients with RCC is not cost-

effective. Eur J Cancer 1995; 31A: 2422.

**32. Atlas I, Kwam D, Stone N.**

Value of serum alkaline phosphatase and radionuclide bone scans in patients with renal cell carcinoma. Urology 1991; 38: 220-222.

\* These EAU Guidelines on Renal Cell Cancer are endorsed by all members of the EAU Oncological Urology Group (Chairman: C. Abbou). Members of the Oncological Urology Group are the EAU Working parties on: Bladder Cancer, Testis Cancer, Penile Cancer, Prostate Cancer & Renal Cell Cancer.

**ABBREVIATIONS USED IN THE TEXT**

RCC: renal cell carcinoma  
CT: computed tomography  
TNM: tumour node metastasis  
VHL: van Hippel Lindau