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Guidelines on Renal Cell Cancer

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Key Words

Guidelines · Renal cell cancer · Diagnosis · Therapy · Follow-up

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 renal cell carcinoma (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. The therapy of choice in organ-confined RCC is surgery. Radical tumour nephrectomy is considered as a standard. Efficacy and side-effects of organ-sparing surgery, lymphadenectomy and inclusion/omission of ipsilateral adrenalectomy in selected cases is a matter of ongoing clinical research. In metastatic cases, tumour nephrectomy 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.

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Background

Renal cell carcinoma (RCC) accounts for about 2% of all cancers, with a worldwide 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 in parallel to trends in incidence [2].

Worldwide 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 the initial stage; 5-year survival is 50–90% for localised disease, decreasing to 0–13% for metastatic disease [3].

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 ≤ 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–T2; Robson's stage II = T3a; Robson's stage IIIa = T3b–T3c; Robson's stage IVa = T4; Robson's stage IIIb = N1–N2, and Robson's stage IVb = M1 [6–8].

Traditionally RCCs 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%, and collecting duct carcinomas: 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.

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), and alkaline phosphatase (liver and bone metastases).

Serum calcium is frequently included in the preoperative assessment because of its association with paraneoplastic manifestations, which may have clinical implications [14].

The majority of tumours are diagnosed by abdominal ultrasound performed for various reasons. A 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

An abdominal CT scan demonstrates primary tumour extension and provides information on venous involvement and metastatic spread to locoregional lymph nodes, adrenals, the controlateral kidney or to the liver, for example [15]. A 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 or chest CT [12].

Treatment

Only radical surgery offers a reasonable chance of curing the disease [17]. The chances of cure by surgery most strongly depend on the stage (primarily) and grade (secondarily) of the disease (e.g. following TNM classification) [18]. A standard operative procedure is a radical nephrectomy including Gerota's fascia [19]. There is no evidence to

Table 1. Recommended follow-up scheme for RCC

Stage	Visit	Examination	Optional	Purpose
All T	4–6 weeks after surgery	physical exam creatinine Hb	AP[a]	exclude complications of surgery establish remaining kidney function[b] to check recovery of perioperative blood loss
T1, T2	every 6 months for 3 years	physical exam	AP[b] kidney imaging	exclude complications of surgery and LR and LN metastases
	every year from 3 to 5 years	chest X-ray		exclude pulmonary metastases and LR after partial nephrectomy
T3, T4	every 6 months for 3 years	physical exam		exclude complications of surgery and LR and LN metastases
	every year from 3 to 10 years[c]	chest X-ray		exclude pulmonary metastases and LR after partial nephrectomy
		retroperitoneal imaging		to detect LR, contralateral metastases or neo-occurrence

AP = Alkaline phosphatase; LR = local recurrence; LN = lymph node.

[a] If elevated preoperatively (recurrent or persisting elevation suggests distant metastases or residual tumour), when bone pain is present or bone or liver metastases are suspected.

[b] If the postoperative level is abnormal, it should be repeated at regular visits.

[c] There is a small, but continuous, risk of recurrence or metastasis from 5 to 15 years.

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].

In certain patients, e.g. in patients with bilateral tumours, a solitary tumour-bearing kidney, multifocal lesions, renal insufficiency, or in an occasional palliative situation, individual decisions not amenable to general guidelines, will be required.

Follow-Up

Rationale for Follow-Up

The follow-up of patients with RCC after surgical treatment is recommended to detect local recurrence and distant metastases as early as possible to enable additional treatment when indicated and if possible. Such therapy may include resection of a 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 suggested [26–28].

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 (either elective or mandatory), 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, and 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]. In patients with elevated alkaline phosphatase levels combined with bone pain a bone metastasis may be suspected. Elevated levels may also be found in patients with liver metastases 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 disease (as in familial papillary RCC or 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.

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