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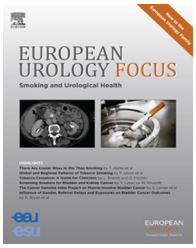

Platinum Priority – Review – Kidney Cancer

Follow-up After Treatment for Renal Cell Carcinoma: The Evidence Beyond the Guidelines

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Abstract

Context: Postoperative follow-up is considered the standard of care for nonmetastatic renal cell carcinoma (RCC). However, level 1 evidence regarding a proper follow-up protocol for RCC is still lacking, making clinical practice extremely heterogeneous.
Objective: To evaluate systematically and summarise the evidence supporting the current clinical guidelines on follow-up after RCC treatment.
Evidence acquisition: A search of Medline, PubMed and Scopus was performed to identify articles published in the last 5 yr addressing the role of follow-up in the RCC setting. Relevant studies were then screened, and the data were extracted, analysed, and summarised. The Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria were applied.
Evidence synthesis: Although several series regarding oncologic outcomes and protocols of surveillance after nephrectomy for localised RCC have been published in the literature, the individual preferences of the treating urologist make the daily clinical scenario extremely heterogeneous regarding follow-up indications and modality. Clinical guidelines support a stage-specific stratification of patient prognosis based on pathologic staging or prognostic models. In the context of a prospectively durable follow-up protocol exposing patients to several imaging tests, concerns about radiation exposure must be taken into account. A better understanding of tumour biology, which would lead to a correct individualisation of patient prognosis through the use of validated prognostic tools, would allow for a more tailored follow-up treatment.
Conclusions: A consensus regarding the pattern and modalities of surveillance after treatment for RCC is still lacking. A standardised evidence-based surveillance protocol that would allow for the early detection of recurrences and limit unnecessary radiation exposure and unwarranted costs is mandatory.
Patient summary: A surveillance protocol after treatment for a renal tumour is essential for the early detection and treatment of eventual metastases. A general consensus regarding timing and modalities for follow-up protocol still does not exist, but published evidence commonly sustains some general principles.

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1. Introduction

Follow-up for adult cancer survivors has traditionally focussed on the early detection of cancer recurrence to allow for more efficacious treatment in terms of clinical progression and, ideally, cancer control [1]. Despite the increasing relevance of adjuvant systemic treatments, postoperative follow-up remains the standard of care after treatment for nonmetastatic kidney cancer [2–4].

Isolated local recurrence of renal cell carcinoma (RCC) occurs in only 1–2% of patients following surgery with curative intent [5]. Surgical resection has been advocated as an effective strategy in this subset of patients, leading to survival rates between 30% and 75% [5,6]. Similarly, lymph node progression during follow-up was reported in about 4% of cases [7]. In this context, the largest reported series of surgically treated patients with nodal recurrence after radical nephrectomy (RN) showed durable postoperative progression-free survival (median: 12.7 mo) and a low rate of cancer-related mortality (9%) [8]. Regarding metastatic progression after treatment, the overall incidence is between 10% and 15% [9]. Published data in the cytokine treatment era, regarding survival outcomes of patients with metastases after surgery for RCC, show that early treatment improves the 5-yr survival rate by 5–20% [10]. Patients with untreated RCC metastases showed a 5-yr survival rate of 2.7–9% [11]. Indeed, the advent of tyrosine kinase inhibitors antiangiogenic agents (sunitinib, sorafenib, pazopanib), monoclonal antibodies (bevacizumab), and mammalian target of rapamycin inhibitors (temsirolimus) has led to improved overall survival (OS) rates in patients with metastatic disease [12,13]. Moreover, several studies support the potential curative benefit of surgical metastases resection in selected patients with oligometastatic disease [14]. For instance, improved survival outcomes have been reported for patients undergoing resection of solitary lung metastasis, with a 5-yr survival rate of 40% [14], although poorer prognoses have been associated with the surgical resection of liver and bone lesions and for patients with multiple metastatic sites [14,15].

In this context, international urologic guidelines have provided different surveillance protocols for patients treated for RCC. This review summarises the available evidence supporting the current guidelines and highlights the current needs relative to improving patient care following primary treatment.

2. Evidence acquisition

An initial search was carried out using the Medline, PubMed, and Scopus databases. We largely selected publications from the past 5 yr (2010–2014) but did not exclude commonly referenced and highly regarded older publications. The search terms used were (renal cancer OR renal carcinoma OR kidney cancer) AND (follow-up OR recurrence OR progression) [Title/Abstract]. Abstracts were reviewed by the panel for relevance to the defined review question. If it was not clear from the abstract whether the paper might contain relevant data, the full paper was assessed. The references cited in all full-text articles were also assessed for additional relevant articles. Non-English articles were excluded from the analysis. With the consensus of the authors, the relevant studies were then selected and screened, and the data were extracted, analysed, and summarised after an interactive peer review process of the panel. The Preferred Reporting Items for Systematic Reviews and Meta-analysis flowchart was used to report the numbers of papers identified and included or excluded at each stage (Fig. 1).

3. Evidence synthesis

3.1. *Imaging modalities*

Radiologic imaging modalities currently applied for surveillance after primary treatment of RCC include chest x-ray, computed tomography (CT), magnetic resonance imaging (MRI), diagnostic ultrasound, and bone scan. Chest x-ray was the modality used historically to detect pulmonary metastases; however, the use of chest CT is currently increasing [2–4] due to its superior sensitivity and specificity in detecting lung lesions. In a retrospective analysis of patients treated surgically for RCC, almost half of the patients who developed pulmonary metastases during follow-up were not detected with chest x-ray and were diagnosed symptomatically outside follow-up [16]. However, it remains disputable if chest x-ray is appropriate in patients with a low likelihood of recurrence. Currently all clinical guidelines support the use of either abdomen CT or MRI for the detection and characterisation of suspected RCC recurrence [2–4]. The role of fluorodeoxyglucose positron emission tomography (FDG-PET) for the follow-up of RCC has been suggested [17]. Published data regarding the role of FDG-PET in the restaging of RCC show overall sensitivity and specificity rates of 64–87% and 75–100%, respectively [17]. These data underscore the more valuable role of FDG-PET in detecting recurrent disease, compared with its accuracy in detecting primary RCC. Recurrent metastatic foci seem to be more FDG avid, resulting in a higher sensitivity for FDG-PET. In a survey of 23 patients undergoing FDG-PET in a follow-up setting for RCC, PET correctly detected recurrence in all cases in the peritoneum, bone, muscle, and adrenal gland, whereas accuracy for detecting lesions in the brain, thyroid, liver, or contralateral kidney was low [18]. In 21% of cases, FDG-PET provided additional information with respect to the CT [18].

Despite the small number of patients included, the data just described look promising and warrant future investigation regarding the accuracy of PET imaging in detecting RCC recurrence. In this context, the novel PET radiotracer iodine 124-cG250, a monoclonal antibody targeting the carbonic anhydrase IX protein on the cell membrane of RCC, has shown promising data regarding its ability to distinguish clear cell RCC from other benign and malignant renal masses, thus motivating research in the field of molecular imaging [19]. Currently, routine application of a PET scan in a follow-up protocol for RCC may not be recommended but may play a complementary role to CT or MRI imaging in