The role of adjuvant therapy in non-metastatic RCC

Ivar Bleumer, MD,[1] Pieter H. M. de Mulder, MD,[2] Peter F. A. Mulders, MD[1]

[1]Department of Urology, University Medical Center Nijmegen, The Netherlands
[2]Department of Medical Oncology, University Medical Center Nijmegen, The Netherlands

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Renal cell carcinoma (RCC) presents as localized disease in 54% of the cases. For these patients, surgery is the primary curative treatment. Unfortunately, up to 65% of all patients show recurrent disease. For metastatic RCC non-specific immunotherapy is currently the treatment of choice. Nevertheless, several new modalities, e.g. WX-G250, oncophage and anti-angiogenic compounds like sunitinib and sorafenib are being explored with favorable results. Still, their place in the primary treatment of advanced RCC has yet to be determined. Because of the high percentage of recurrent disease, there is a need to identify these patients with conventional and molecular risk factors. Furthermore, adjuvant therapy to reduce risk of recurrence of RCC following nephrectomy is of clinical relevance.

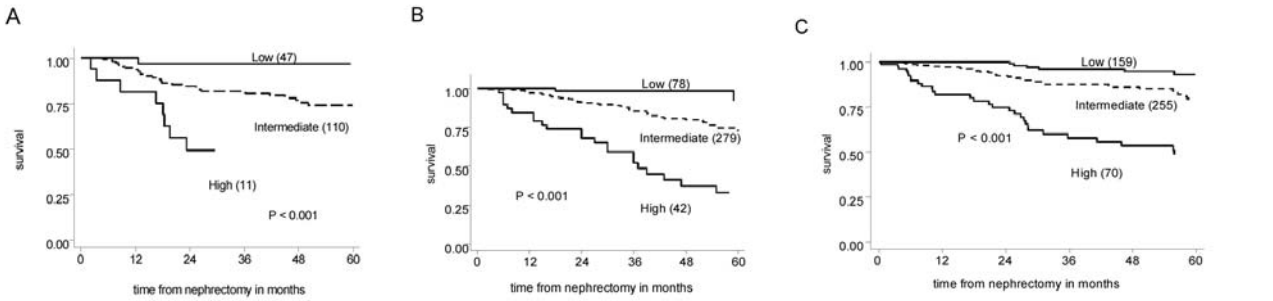
A review of recent literature was performed on the topics prognostic models, risk factors and adjuvant treatment for non-metastasized RCC.
Combining classical risk factors for progression of RCC has shown to be effective for stratifying patients into risk groups. The UCLA integrated staging system (UISS) is the currently the only validated prognostic model. Whether molecular markers are able to better identify high-risk patients is still under investigation. Adjuvant therapy has been explored in the treatment for RCC and the use of non-specific cytokine regimens has so far not shown to be effective in the adjuvant setting. More specific therapies, e.g. WX-G250, oncophage and anti-angiogenic drugs are clinically active in patients with advanced RCC. Large randomized clinical trials with these drugs are currently ongoing to evaluate their effect in patients with localized RCC.

Key Words: renal cell carcinoma, adjuvant therapy, prognostic models, risk factors

Introduction

Renal cell carcinoma is the most common renal tumor, the third malignancy within urological oncology and comprises 2%-3% of all cancers. It is also the most lethal urological malignancy, responsible for an approximate 100,000 deaths per year worldwide.[1] RCC was conventionally thought to arise primarily from the proximal convoluted tubules. Indeed, this is the case for most of the clear-cell subtype of RCC, which accounts for 70% to 80% of all RCCs. However, other histological subtypes e.g. papillary or chromophobic RCC, typically arise from more distal components of the nephron. RCC occurs almost twice as often in men compared to women and the peak incidence of RCC is seen between 50-70 years of age. Around 75% of all

Address correspondence to Dr. P. F. A. Mulders, Department of Urology, University Medical Center Nijmegen, Geert Grooteplein 10, P.O. Box 9101, 6500 HB Nijmegen The Netherlands



A, Kaplan-Meier curves for 177 patients from the University Medical Center Nijmegen with localized renal cell carcinoma. Patients are stratified into 3 distinct survival curves based on low, intermediate, and high-risk characteristics. B, Kaplan-Meier curves for 399 patients from MD Anderson with localized renal cell carcinoma. Patients are stratified into 3 distinct survival curves based on low, intermediate, and high-risk characteristics. C, Kaplan-Meier curves for 484 patients from UCLA with localized renal cell carcinoma. Patients are stratified into 3 distinct survival curves based on low, intermediate, and high-risk characteristics.

Figure 1. Kaplan-Meier curves for patients from three different institutions to validate the UISS.

patients present with localized or locally advanced RCC. For these patients surgery is the primary curative treatment. Unfortunately, 35%-65% of all patients show recurrent disease.[2] Once metastasized, prognosis is poor. Standard treatment for metastatic RCC (mRCC) is non-specific immunotherapy. These regimens have shown to induce long-term clinical responses, but only in a small subset of patients and with considerable toxicity.[3] New treatment modalities like monoclonal antibody WX-G250 and a variety of anti-angiogenic agents show favorable results as second-line post cytokine treatment, but their place in the primary treatment of mRCC has yet to be established.[4-6]

It is of importance to identify risk factors for patients with localized disease as to the development of a recurrence. Furthermore, once the patients who most likely develop mRCC are identified, adequate adjuvant treatment is needed to prevent or delay recurrent disease and improve survival.

Conventional risk factors and prognostic models

At the moment, the TNM classification is used to predict the development of metastatic disease for patients with localized disease following nephrectomy. However, a great variety of other conventional risk factors are discussed in literature able to predict recurrent disease post-operatively. The most important clinical- and pathological variables are the ECOG performance status, Fuhrman pathological grade, tumor necrosis, and microvascular invasion. In the past years several prognostic models have been proposed that combine the TNM classification with the abovementioned risk factors, the most important being the Kattan-nomogram and the UICC staging system.[7,8] Both models are able to identify high-risk patients that might benefit from extra screening and adjuvant therapy. The UISS has been validated by external databases,[8] Figure 1 and 2.

T Stage	1				2	3				4
Fuhrman Grade	1-2		3-4			1		>1		⇩
ECOG PS	0	≥1	0	≥1		0	≥1	0	≥1	
Risk Group	Low	Intermediate							High	

Figure 2 Decision box to determine the appropriate risk category of patients with localized RCC.

Molecular markers

As discussed, the mentioned prognostic models are able to identify patients at risk to develop mRCC. Still, the natural history of RCC is unpredictable and therefore we need molecular markers to evaluate the biological behavior of RCC in the individual patient. A great variety of molecular biomarkers are discussed in literature describing the potential use of in the diagnosis and prognosis of RCC. Furthermore, RCC specific biomarkers can be used as targets in the development of new therapy strategies.

Cytogenics, proliferation and anti-apoptotic markers

Genetic alterations, loss of heterozygosity (LOH) and changes from the regular diploid pattern are well known to play a significant part in the development of cancer. Consequently, these cytogenetic changes are also thought to be at least partly responsible for recurrent disease. Many studies describe the association of aneuploidy and LOH on several chromosomes to be prognostic factors. However, these are mainly univariate analyses. Even more so, studies contradicting these results make that for the time being cytogenetic abnormalities cannot be integrated in prognostic models. Nevertheless, gene expression profiling will provide a vast amount of information undoubtedly leading to better understanding in the biology of RCC.[9,10]

Proliferation and apoptosis are terms that are unmistaken related to oncology. P53 is probably the most commonly mutated gene in human cancers involved in cell death. However, despite their favorable results in univariate analysis, p53, and other well studied biological markers involved in apoptosis and proliferation (bcl-2, Bax, AgNOR, PCNA, Ki-67) have so far not proven to be independent markers for RCC.[11-17]

Hypoxia inducible pathway

The Von-Hippel-Lindau (VHL) gene is important in cellular oxygen homeostasis. In the normal physiological situation, the VHL protein (pVHL) binds and deactivates the hypoxia-inducible factor-1a (HIF-1a). However, under hypoxic circumstances pVHL does not bind to HIF-1a leading to an increased transcription of a variety of HIF regulated genes such as VEGF, platelet-derived growth factor, erythropoietin, carbonic anhydrase IX (CA-IX) and tumor growth factor alpha. In up to 70% of RCC VHL is inactivated thus mimicking the hypoxic situation and leading to overproduction of the abovementioned genes.[18,19] Especially low expression of CA-IX is suggested to predict poor survival in mRCC.[20] For non-metastatic RCC CA-IX has not yet shown to be an independent prognostic factor.

Adjuvant therapy

As mentioned, a significant percentage of patients treated with curative intent will develop metastatic disease. Using prognostic models, patients can be identified with low- or high-risk respectively for recurrent disease. For the low-risk patients watchful waiting seems adequate treatment. However, for the high-risk patients adjuvant treatment might decrease the chance to develop advanced disease.

Non-specific immunotherapy

Since non-specific immunotherapy has shown to induce clinical responses in patients with progressive mRCC, clinical trials have been performed evaluating the effect of non-specific immunotherapy on the recurrence rate of RCC. Pizzocaro et al reported a multicentric randomized controlled trial that compared adjuvant recombinant interferon alfa-2b with observation after radical nephrectomy in patients with non-metastatic RCC.[21] The 5-year overall and event-free survival probabilities were 0.665 and 0.671, respectively, for controls and 0.660 and 0.567, respectively, for the treated group; the differences were not statistically significant. Only within the pN+ subgroup a protective effect was observed.

Clark et al performed a prospective, randomized, controlled phase III trial that assessed one course of high-dose bolus interleukin-2 (IL-2) or observation after nephrectomy in patients macroscopically free of disease.[22] No clinical meaningful benefit was observed. The triple combination of subcutaneous interleukin-2 (sc-rIL-2), subcutaneous interferon-alpha2a (sc-rIFN-alpha2a), and intravenous 5-fluorouracil (iv-5-FU) according to the standard Atzpodien regimen also failed to show clinical benefit in high-risk patients.[23] Although the difference in the cytokine regimens used makes it difficult to compare these trials, their common conclusion is that no benefit in recurrence-free survival or disease-specific survival was observed. The large phase III randomized MRC/EORTC 30955 trial investigates the effect of interleukin-2; interferon-alpha and 5-fluorouracil versus observation only in non-metastatic RCC. Study results are expected shortly and will hopefully give a more definitive answer as to the role of combination cytokines for patients with a high-risk to develop recurrent disease.

Specific immunotherapy

The past decade optimalization of specific immunotherapy has been largely evaluated for advanced RCC.[3] By inducing immune responses directed specifically against micrometastasis patients that are macroscopically free of disease may be prevented from recurrent disease. Furthermore, these specific immunotherapy approaches lack the considerable side effects observed with high-dose cytokine regimens.

In the development of specific immunotherapy the identification of RCC associated antigens is crucial. However, despite compelling evidence that RCC is an immunogenic tumor, until recently only a few specific tumor antigens, such as RAGE, are known. RAGE, initially defined through CTL technology, is expressed in a minor percentage of RCC, and therefore a sub optimal target.[24-28] In this aspect the identification of the RCC-associated antigen CA-IX is of interest. CA-IX is expressed in >95% of all clear cell RCC tumors, Figure 3. Moreover, no expression can be detected in normal kidney tissue, including foetal kidney, and in other normal tissues the expression is highly restricted and limited to large bile ducts and gastric epithelium.[29] WX-G250 (Rencarex®) is a chimeric monoclonal antibody that recognizes the CA-IX antigen and is identified and developed for diagnostic and therapeutic purposes. Recently, two clinical trials have evaluated the effect of WX-G250 in advanced RCC showing clinical benefit without the toxicity observed with the non-specific cytokine regimens.[4,30] This has led to the initiation of the ARISER trial in which patients with non-metastatic RCC are randomized between treatment with WX-G250 or a placebo. The trial is currently ongoing.

Tumor cells express a variety of tumor-associated antigens, most likely also RCC-specific antigens that so far have not yet been identified. Consequently, vaccinating patients with autologous tumor cells has the theoretical advantage that the complete antigen repertoire specific of an individual patient is presented to the immune system leading to more powerful and specific responses. Jocham et al presented a phase III trial randomized controlled trial in the Lancet describing the effect of an autologous tumor cell vaccine in patients with stage pT2-3b pN0-3 M0 RCC.[31] A total of 379 patients were evaluated according the intention-to-treat analysis. At 5-year and 70-month follow-up, the hazard ratios for tumor progression were 1.58 (95% CI 1.05-2.37) and 1.59 (1.07-2.36), respectively, in favor of the vaccine group (p=0.0204, log-rank test). Five-year and 70-month progression-free survival rates were 77.4% and 72%, respectively, in the vaccine group and 67.8% and 59.3%, respectively, in the control group. These data indicate that tumor vaccines may be advantageous as adjuvant treatment, although, no survival benefit has been reported.

An alternative method of individualized cancer vaccines is the use of heat shock proteins (hsp), a group of glycoproteins that are the most common and abundant proteins in all forms of life. They are thought to play a role in presenting antigens to the cell surface to facilitate the immune system in recognizing dysfunctional cells. The combination of these hsp's bound to RCC-specific antigens is highly immunogenic. One of the hsp's is HSP-96 and has been investigated as oncophage® (vitespen). Clinical trials in advanced RCC, melanoma and colon cancer are promising.[32-34] A large phase III trial has been performed evaluating the effect of this approach for non-metastatic RCC of which the results are expected in the second half of 2006.

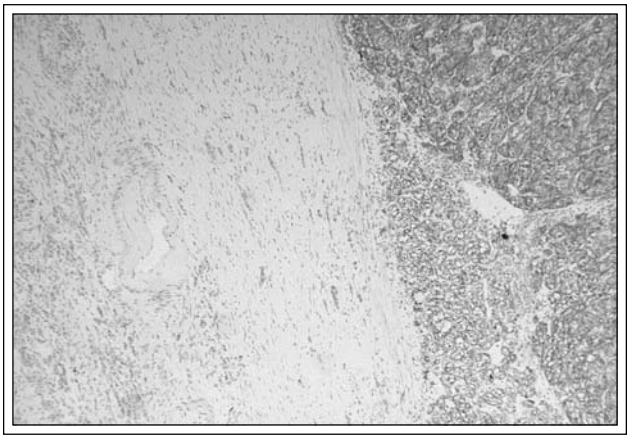


Figure 3. CA-IX expression of RCC.

Anti-angiogenic drugs

As mentioned, mutations in the VHL gene are found in most clear cell RCC and many of the gene products that are upregulated as a consequence of these mutations are involved in angiogenesis and proliferation. Subsequently, new therapies are being explored to block these growth factors. These new treatment modalities include VEGF neutralizing antibodies (bevacizumab),[5] tyrosine kinase inhibitors (sunitinib)[35] and targeting of the Raf kinase pathway (sorafenib).[36] Based on the promising results, sorafenib is the first drug in a decade to be approved by the FDA for the use in patients with advanced RCC. More recently also sunitinib has been approved for the treatment of RCC.

Both sorafenib and sunitinib will be tested alone versus placebo in a large, three-arm, randomized trial of adjuvant therapy conducted by international cooperative groups.

Conclusions

A significant percentage of patients develop metastatic RCC despite a nephrectomy with curative intent. Prognostic models are proposed to stratify patients into low/intermediate/high risk groups. Current models use traditional risk factors like TNM, histological findings and the performance status of the patients. Additional markers are needed to further enhance the ability to identify high-risk patient. CA-IX seems to fulfill the characteristics of such a marker. Especially gene profiling is expected to give is more insight in the biological activity of an individual tumor.

The past few years several trials have been performed evaluating non-specific cytokine regimens as adjuvant treatment for patients with non-metastatic RCC. Unfortunately, no clinical benefit was observed. Also a vaccine of autologous tumor cells did not show an improved survival. Further research is ongoing. Other approaches (e.g. WX-G250, oncophage, sorafenib, sunitinib) have proven to be effective in advanced RCC and are, subsequently also explored for their effectiveness in an adjuvant setting. Randomized clinical trials are currently ongoing. □

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