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Contemporary Management in Metastatic Renal Cell Carcinoma

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1. Introduction

In addition to advancing our understanding of RCC, improved abdominal imaging technology has caused a migration of tumor stage and alteration of surgical strategies, with tumors commonly being diagnosed at an earlier stage. Despite these advances, the prognosis for patients with metastatic RCC is poor. Of the total number of patients with renal cancer, approximately a third either presents with or later develops metastatic disease. Unfortunately, for these patients, contemporary systemic therapies are generally ineffective—median survival is less than 1 year. Despite adjuvant systemic chemotherapy, hormonal or cytokine therapies, used alone or in combination, overall response rates rarely exceed 20% and durable, complete responses are rare. Targeted therapy in the management of metastatic renal cell cancer is newly introduced to urology practise. These drugs were used in very limited number of patients and only for clear cell histology. No recommendation to use these drugs for other than clear cell histology was seen in the literature. Nevertheless, there is a encouraging responses in trials with limited number of patients in the literature. Future advances are expected.

Spontaneous remissions in 0.8–7.0% of patients are reported in surgical series of clinical trials with previous surgical intervention. The role of surgical intervention in patients with metastatic renal cancer can be twofold. First, to render a patient clinically free of all sites of metastases ('metastasectomy'). Second, to resect the primary tumor prior to initiation of systemic therapy ('cytoreductive nephrectomy').

Studies that examine combinations of surgery and systemic therapy aim to improve survival in this high-risk group. In an attempt to address this important clinical issue, two randomized, prospective clinical trials were organized in the US (Southwest Oncology Group [SWOG]) and Europe (European Organization for Research and Treatment of Cancer [EORTC]) under similar entry criteria. The trials compared treatment of metastatic renal cancer with cytoreductive nephrectomy plus IFNα-2b versus IFNα-2b alone. Median survival of patients that underwent cytoreductive nephrectomy plus IFNα-2b was significantly greater than that of those treated with IFNα-2b only.

More recent metastasectomy studies also identified favorable clinical and surgical characteristics that were associated with a positive enhancement of outcome, but metastasectomy has never been assessed in a randomized clinical trial. It is not certain that

metastasectomy can be curative, but operative intervention can provide effective palliation for symptomatic metastases in sites such as bone, the brain, and the adrenal gland. Ultimately a prospective clinical trial comparing metastasectomy to best standard systemic therapy will define the exact role of this approach.The occasionally unpredictable natural history of renal cancer and varying patient selection criteria can make the interpretation of outcomes from different centers difficult. As a conclusion although there is a tendency in favor of surgery, operative intervention for metastatic renal cancer is still controversial.

The aim of this review is more recent management modalities in the management of metastatic renal cell carcinoma. In addition, the role of surgery in metastatic RCC have been emphasised.

2. The role of nephrectomy

Although it is a part of multidisciplinary approach in the management of metastatic renal cell carcinoma (RCC), the role of Cytoreducive nephrectomy is still controversial in urologic literature. Recently according to some multicentric prospective randomized trials, because of providence little survival advantage, cytoreductive nephrectomy has gained some popularity. The objectives of nephrectomy in metastatic disease are avoidance of local symptoms and negative effects of primary tumor on immunological system (asynergy) and obtaining suitable nominee for immunotherapy, increasing patient quality of life and probably increased response to systemic therapy and finally increased overall survival. On the other hand, to prevent new metastases from primary tumor, capture of circulating immune cells, especially lymphocytes, which absorbed from primary tumor and so properties of immune pressure of primary tumor on immune system. Decreasing tumor burden may help the effectiveness of systemic therapy on tumor.

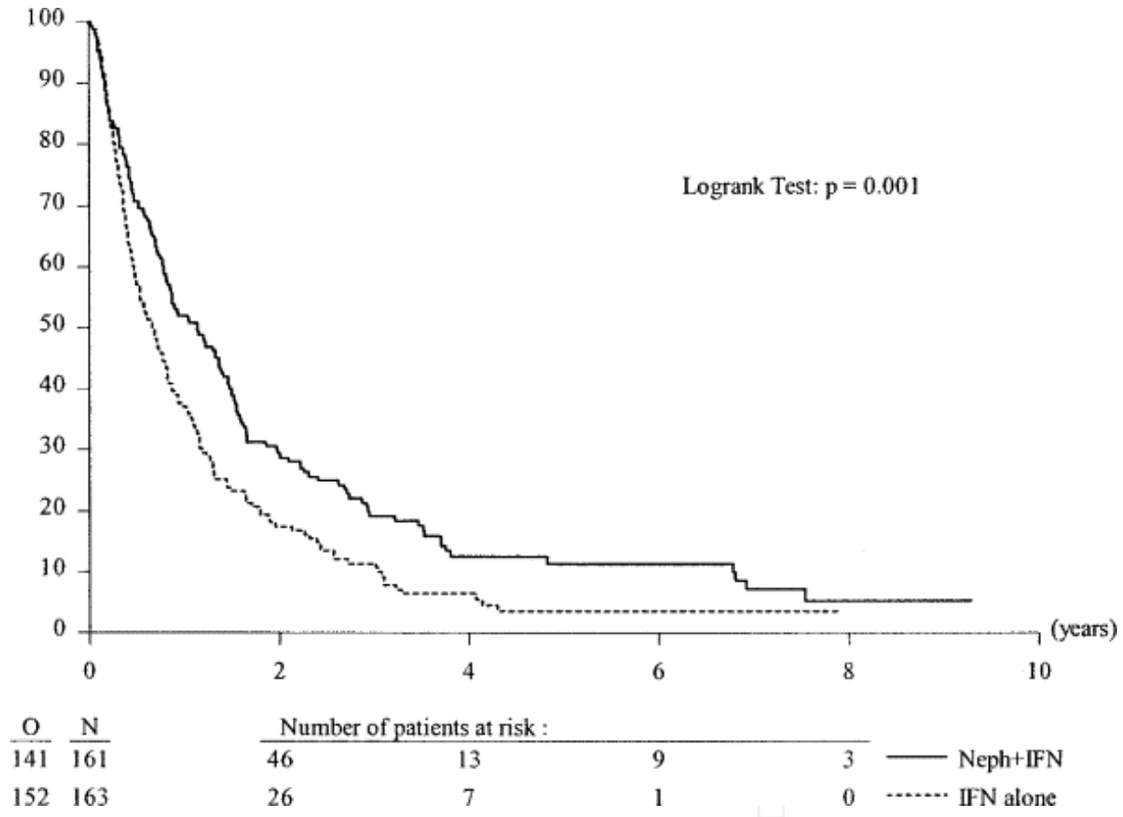
Surgical mortality rates are reported as 2-11%. In NCI trial, 62% patients can take immunotherapy and response rate is 18% in 195 patients. In this trial 38% patients cannot take immunotherapy because of complications of nephrectomy or rapid deterioration in general performance after progression of the disease (6). Some oncological centers recommend primary immunotherapy in order to avoid surgical morbidity especially in patients with clinical regression in metastatic sites (7,8).

Actually, two points provide that nephrectomy is a safe procedure; one is observation of spontaneous regression phenomena in metastatic sites after nephrectomy which is very rare. Freed has reported that 51 patients presented spontaneous regression after nephrectomy in literature (9). Similarly, NCI reported 4 patients (4.4%) have demonstrated spontaneous regression in 99 patients (10). In these 4 patients have only lung metastases and they were in remission for mean 24.3 months. Although spontaneous remission rates are very low, it is still very objective data in favor of nephrectomy. The other point for nephrectomy is unresponsiveness of primary tumor to systemic therapy. Radical nephrectomy may help to increase objective responses to systemic therapy. It has been obtained 32% objective response with immunotherapy after nephrectomy in 55 patients, but 4.7% response rate has been observed with same immunotherapeutic regimen in insitu tumor (11). Recently, surgical technique for cytoreductive nephrectomy is getting importance. Minimal invasive techniques gain popularity. While laparoscopic experience increased, laparoscopic radical nephrectomy performance is increasing in

literature. The surgery time is longer, but postoperative analgesic requirements and hospital stay are decreasing. Therefore patients can take systemic therapy earlier than open surgery (Mean 35 vs 67 day). Patients without immunotherapy in case of disease progression are 13-77 % in literature (16). The shared conclusion of all the reports in literature is that the patients for cytoreductive nephrectomy have to be selected and they have to be in good ECOG performance status.

The last clues for nephrectomy are quality of life. Hematuri, pain and paraneoplastic syndromes including anemia, anorexia, hypertension, hypocalcaemia etc. can be controlled with nephrectomy.

In conclusion, multidisciplinary approach including surgery stands in the forefront. But some questions are on the agenda. Timing and coordination. Which one should be the first, nephrectomy or systemic therapy?



O: Observation
N: Nephrectomy
Fig. 1. SWOG and EORTC trials

3. Metastasectomy

For a long time, if possible excision of metastases is recommended. Complete metastasectomy was performed in Kierney" report. 59% and 31% 3 and 5 years survival was obtained in 77 patients with metastatic RCC. These survivals were significantly different from patients within conservative follow (20,21). In another retrospective study with 278

patients, complete and incomplete metastasis resection can provide 44% vs 14% 5-years survival advantage (22).

In conclusion, the presence of solitary metastases and localization are important factors for clinical improvement. Resection of solitary metastases is recommended for survival and also quality of life.

4. Systemic treatments

4.1 Cytotoxic drugs

Standard cytotoxic drugs are generally ineffective. Response rates were reported below 10%. Response rate was reported 17% with Gemcitabine and 5-Florourasil combination in phase II study. Gemcitabine and capecitabine combination is effective as 20%. But grade 3-4 toxicity was reported. Same regimen reported by CALGB, Survival was 12% and stable disease rate was 59% in this study. Nevertheless toxicity was always a problem. 36% of patients could not continue the treatment protocol. The main problem is neutropenie and hand-food syndrome. Therefore, phase III studies can not be conducted.

4.2 Immunotherapy

Standard theurepathic regimen is still lack in the management of metastatic RCC. But interferon and interleukin therapy is in management list in many centers. Histological type is the most important factor for the response. The only histological type which is sensitive to immunotherapy is clear cell RCC. Granular, papillary or sarcomatoid type variants are resistant to immunotherapy. The main mechanism of cytokines is still contraversial. Cytokines are binding to specific receptors on tumor cells and initiate intracellular and intercellular signal mechanism. IL-2 is a potent stimulator of T cell proliferation. Anti-tumor T cells rapidly begin to proliferation, then tumor-specific cytotoxic T lymphocytes=CTL, natural killer lymphocytes=NK and probably intratumoral lymphocytes=TIL become active and try to kill tumor cell. However, interferons have some antiangiogenetic effects. Absence of anemia and hypocalcaemia, normal lactic dehydrogenase, prior nephrectomy and good performance status increase possibility of positive response.

The main expectations for immunotherapy in metastatic RCC

- Overhelming of T-lymphocite dysfunction, dendrtic cell dysfunction, soluble inhibitory factors secreted from tumor cells (IL-10),
- The changes of T-lymphocite antigen receptors and transmission of signals (TCRdelta, decreasing p56 levels, NFkappaB compliment changes)
- Identification of unique tumor surface antigens
- Vaccination manuplations for immun tolerence

Current immunotheraupeutic cytokines are;

- Interferons
- İnterleukins
- Colony-stimulating factors (CSF)
- Tumor necrosis factor (TNF)

4.3 Interferon

IFN-alpha is approved for the management of metastatic RCC in Europe and it is used routinely in Urological practise. Response rates are 10-25%. Recently, with recombinant forms response rates are increased to 29%. Survival advantage is 3-5 months. Toxicities are flu-like syndromes, dryness in skin and mucosal membranes, mental changes and depression. Combination with IL-2 is frequently applied in many centers. Dosage scheme is controversial.

IFN-beta and gamma are ineffective.

4.4 Interleukin-2 (IL-2)

A group of cytocine which are activated and regulated lymphocite growing and/ or differantiation

First described one is IL-2.

It is produced by activated CD4+ lymphocites.Cytotoxic T cells are stimulated by IL-2. CD8+ T cells, monocytes, lymphocyte activated killer lymphocytes (LAK) are activated and tumor necrosis factor is secreted. It is reported that IL-2 is as effective as 15% in many series. Rekombinant IL-2 (rIL-2)

- Bolus high-dose *i.v.* infusion= highly toxic
- İnhalation
- Response rate 7-27%
- Only clear cell type is respondable

Recently, there are more than 10 interleukin described other than IL-2 (IL-4; IL-7; IL-12 have been still investigating)

4.5 Cytokine combination therapy

Class I MHC Ag expression + T-lymphocite activation

- Synergy
- Mean 22% response
- Similar response rate as seen in high-dose IL-2

Phase 1 and 2 studies showed that response rates were 6-30%. Retrospective series showed that 15% and 20% response rates, but these results are not statistically significant. Nevertheless, mean survival is a little bit meaningful (9.1 vs 13 mos).

4.6 Targeted therapies

Since more new agents have been produced and limited number of prospective, randomized, placebo-controlled studies have been reported, Therefore, we have evaluated only;

1. Sorafenib (Nexavar®)
2. Sunitinib (Sutent®)
3. Bevasizumab (Avastin®) + IFN-alfa

4. Temsirolimus (Torisel®) in this review

Sorafenib and/or sunitinib, a multikinase inhibitor of tumor-cell prolferation and angiogenesis, have been shown some activity, in two double blind, placebo-controlled trial in patients with metastatic renal cell ca. All the patients' histology were clear cell ca (24,25). Renal cell carcinoma is most aggressive and mortal genitourinary cancer with more than 40% of patients dying of cancer (26). Unfortunately, no reliable treatment alternative has been still conducted for especially metastatic RCC. Recently, investigations in targeted therapy including multikinase inhibition and antiangioenesis encouraged the clinicans that they have some activity in the management of metastatic RCC. Survival benefit with the targeted therapy was demonstrated in two double blind, placebo-controlled study in the treatment of metastatic disease (24,25). Nevertheless, there are still many unresponded questions. Response rate in different histological type is not clear. We have administered sorafenib in a patient with metastatic RCC with sarcomatoid differentiation and obtained excellent result.

This case report might be an evidence that antiangiogenic agents can be used in any histologic type of renal cell carcinoma.

Additional data on the durability of the response may further clarify the complete response and survival benefit

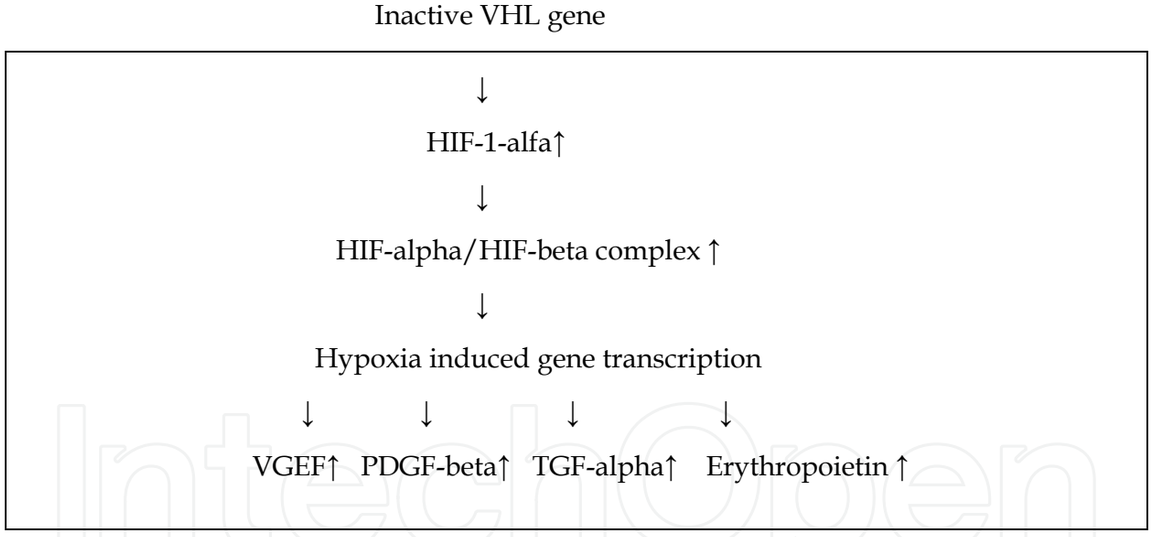


Fig. 2. Loss of VHL gene and pathways

Small molecule inhibitors have mainly targeted growth factor signals, cell cycle regulatory factors and angiogenesis. Growth factors like VGEF and PDGF have been effective by transmembrane tyrzin kinase receptors which expressed in endothelial cells. They have triggered autophosphorilazition of intracellular tyrozin kinase receptors and protein activation link with the attachment of extracellular parts of receptors. Recently many small molecule inhibitors have been discovered (27,28,29). Raf kinase inhibitors like sorafenib and sunitinib, multiple kinase like VEGFR-2, VEGFR-3 and PDGFR inhibitors or mTOR inhibitors like temsirolimus, everolimus and epidermal growth factor receptor tyrosine kinase inhibitors like erlotinib and lapatinib are the most popular molecules nowadays

(30,31). Nevertheless, still prospective, placebo-controlled studies are significantly lacking in describing the most effective treatment modality in the management of metastatic RCC (32).

5. Conclusion

Cytotoxic chemotherapy and immunotherapy are less effective treatment modalities in the management of metastatic RCC. However, better understanding of promotion of RCC caused newly produced many targeted therapies. Now, it is early to say that newly introduced drugs can solve the problem, but they are encouraging. .Due to SWOG and EORTC studies which are the most reliable studies in the literature, still primary nephrectomy and combination immunotherapy modalities are the only acceptable choice in patients with good performance status for the treatment of metastatic RCC.

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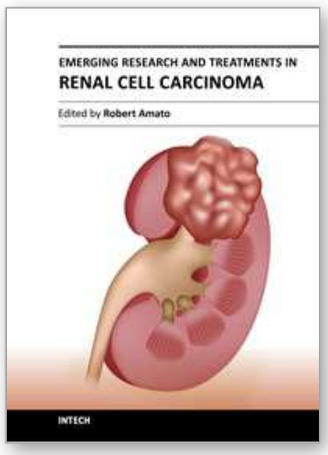

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The field of renal cell cancer has undergone a significant resurgence. This book summarizes up-to-date research and innovative ideas for the future in this rapidly changing field, which encompasses medicine, surgery, radiation oncology, basic science, pathology, radiology, and supportive care. This book is aimed at the clinician or scientist who has an interest in renal cell cancer, whether they are academic or nonacademic. The book covers tumor biology, molecular biology, surgery techniques, radiation therapy, personal testimonies, and present and future treatments of the disease that are on the horizon. The goal was to produce a textbook that would act as an authoritative source for scientists and clinicians and interpret the field for trainees in surgery, medicine, radiation oncology, and pathology.

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