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The Role of Nephrectomy for Kidney Cancer in the Era of Targeted and Immune Therapies

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OVERVIEW

Although two phase III trials support the recommendation of nephrectomy followed by interferon alpha in metastatic renal cell carcinoma (RCC), this procedure cannot be applied to every patient with this condition. Systemic therapy has changed from interferon alpha to antiangiogenic-targeted therapy, and the clinical impact of nephrectomy in the era of targeted therapy has not been proven. The SEER database shows that only 35% of patients with advanced RCC undergo nephrectomy as their initial treatment. Retrospective studies showed improved overall survival (OS) outcomes with nephrectomy and interleukin-2 (IL-2) therapy; however, the inherent selection bias of younger and healthier patients receiving IL-2 likely accounts for this finding. Neoadjuvant therapy has demonstrated only modest efficacy in unresectable disease, and if remission is obtained with systemic therapy, it is unclear whether nephrectomy has any incremental benefit. In the absence of proven benefit of nephrectomy in the setting of targeted therapy, it seems advisable for patients with RCC with severely symptomatic disease, competing comorbidities, poor performance status, or unresectable disease to avoid nephrectomy and proceed directly to systemic therapy. The clinical implications of deferred cytoreductive nephrectomy for patients with metastatic RCC are poorly understood, and patient cohorts that do not undergo this procedure are likely to be comprised of patients with unfavorable disease characteristics. Unfortunately, the completed trials of targeted therapy were 90% comprised of patients with prior nephrectomy (the majority of trials incorporate prior nephrectomy as an eligibility requirement) and hence may not reflect the outcomes of the majority of the patients with advanced RCC who have not undergone nephrectomy. Newer therapies such as nivolumab and cabozantinib have also been evaluated for a population in which 90% of the patients underwent nephrectomy. Future clinical trials and registry studies must focus on the therapeutic treatment and overall outcome of patients without nephrectomy and treated with contemporary systemic therapy.

Editor's Note:

The following article is based on the 2016 ASCO Annual Meeting Education Session “Cytoreductive Nephrectomy in Renal Cell Carcinoma: A Debate.” The author reviews the pros and cons of cytoreductive nephrectomy and whether recent advances in systemic therapy warrant physicians to proceed directly to systemic therapy as in other metastatic solid tumors, without the integral step of cytoreductive nephrectomy.

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Kidney cancer is one of the few malignancies in which surgical resection of the primary disease, or cytoreductive nephrectomy, has held tremendous importance. Historically, systemic therapy was underdeveloped and ineffective, and surgical resection was considered the only hope of remission. However, an analysis of the Surveillance, Epidemiology, and End Results Program (SEER) database revealed that only 539 of the 1,537 (35%) cases diagnosed with advanced RCC between 2000 and 2013 had nephrectomy as their initial therapy.¹

The major advances in systemic therapy of RCC in recent years beg the fundamental question whether a large enough impact has been made to consider proceeding directly to systemic therapy as in other metastatic solid tumors, without the integral step of cytoreductive nephrectomy. The pros and cons of this procedure are summarized in Table 1.

NEPHRECTOMY IN THE CONTEXT OF IMMUNE THERAPY

Renal cell carcinoma is unique in the fact that randomized trials have actually been conducted to establish the role of nephrectomy in metastatic disease.²⁻⁴ The results revealed that patients subjected to nephrectomy followed by interferon alpha in the presence of metastatic disease experienced OS benefit (Table 2). The reasons for this benefit remain unclear. It does not appear that nephrectomy boosted the response rates to interferon therapy, as the response rate remained at a dismal 3.3% and 3.6% in the cytoreductive nephrectomy and interferon-alone arms, respectively, regardless of whether the patients were randomly selected to undergo nephrectomy or not. Retrospective case series have been reported favoring cytoreductive nephrectomy prior to immune therapy, such as IL-2, because of OS benefit.⁵ However, the inherent biases of a retrospective study are prominently prevalent in the IL-2 population, as this is a stringently selected group of patients with excellent cardiopulmonary status and no brain metastases, which predicts a better OS regardless of choice or sequence of therapy. In fact, even the patients with a performance status of 1 within the IL-2-treated patient cohort had a minimal benefit in OS favoring cytoreductive nephrectomy; median OS was 6.9 months in the cytoreductive nephrectomy arm and 4.8 months in the interferon-alone arm.⁵

There are numerous reports indicating that cytoreductive nephrectomy improves host immune reaction to the metastases and is likely to decrease the levels of immunosuppressive factors. It also normalized the nuclear factor-kappa B and various other immune defects.^{6,7} Clinically spontaneous regressions have been observed. A perioperative (neoadjuvant) checkpoint inhibitor trial has been proposed based on the finding that peripheral blood PD-1 expression is reduced significantly after cytoreductive nephrectomy.⁸ Expression of PD-1 in tumor-infiltrating lymphocytes was associated with a more aggressive phenotype of RCC (larger tumors, higher nuclear grade, and sarcomatoid differentiation) and increased risk of cancer-specific death, as reported in a study led by the Mayo Clinic (risk ratio of 2.24; $p = .004$).⁹ However, a recent report evaluating tumor PD-L1 expression in 417 cases of clear cell RCC from The Cancer Genome Atlas database reported a lack of association between PD-L1 expression and unfavorable tumor characteristics and an improved OS outcome (hazard ratio [HR] 0.59; $p = .006$).¹⁰

Unfortunately, modern immunotherapy trials cannot inform the benefits of treatment for patients who have not undergone nephrectomy. For immune checkpoint inhibitors, the recently reported randomized trial of nivolumab versus everolimus mainly included patients who had undergone nephrectomy.¹¹ Similarly for patients on antiangiogenic or mTOR inhibitor therapies, approximately 90% of the patients included had nephrectomy prior to study enrollment.^{12–16} Studies are ongoing to evaluate the impact of PD-1 inhibition on biomarkers of immune response pre- and post-nephrectomy. Phase II trials such as ADAPTeR () are assessing the response and changes in immune-related markers after the neoadjuvant administration of nivolumab for 8 weeks followed by nephrectomy.

NEPHRECTOMY IN THE CONTEXT OF VEGF INHIBITOR THERAPY

The clinical implications of deferred nephrectomy for patients with metastatic renal cancer are not well understood. As in the case of immunotherapy trials, the percentage of patients who had undergone nephrectomy in a majority of clinical trials evaluating VEGF inhibitors is greater than 90%. The report by Choueiri et al,¹⁷ which suggested that patients treated with targeted therapy had a Karnofsky performance status less than 80% or poor-risk disease as gauged by the Memorial Sloan Kettering Cancer Center criteria, experienced no benefit from cytoreductive nephrectomy ($p = .08$ and $.06$, respectively; Table 2). A separate report used data from the International Metastatic Renal Cell Carcinoma Database Consortium database, which included 982 patients treated with nephrectomy and targeted therapy and 676 patients treated with targeted therapy alone.¹⁸ Although patients treated with cytoreductive nephrectomy had significantly better OS compared with those treated with targeted agents (median OS, 20.6 vs. 9.5 months, respectively; HR 0.60; 95% CI, 0.52–0.69), it is important to recognize that selection bias is at play; patients with poor-risk disease comprised only 28% of those treated with cytoreductive nephrectomy versus 54% of the group who did not undergo the procedure. In addition, only 1% of patients who did not undergo cytoreductive nephrectomy had favorable risk characteristics.

Several trials are seeking to prospectively evaluate the role of cytoreductive nephrectomy for patients being treated with targeted therapy. The CARMENA trial studying nephrectomy followed by sunitinib versus sunitinib alone will likely shed light on the question of whether cytoreductive nephrectomy remains relevant in the context of anti-VEGF therapy for metastatic renal cancer. The primary endpoint is OS, and secondary endpoints are progression-free survival and operative complication rates. The study has completed accrual, and results are awaited. The SURTIME study is randomly selecting patients with metastatic RCC to receive sunitinib followed by nephrectomy versus sunitinib alone. The study will address whether patients with adequate response to systemic therapy should receive surgical consolidation with nephrectomy.

SYNERGY BETWEEN NEPHRECTOMY AND SYSTEMIC THERAPY: REALITY OR PERCEPTION?

Despite a hypothesized synergy between systemic therapy and nephrectomy, it has not been borne out in clinical practice. For example, the randomized trials of nephrectomy and interferon versus interferon alone reported identical response rates of approximately 3% in

both arms. An adjuvant trial of sunitinib versus sorafenib versus placebo (ASSURE/ECOG 2805) reported lack of benefit for either of the agents postnephrectomy.¹⁸ The only data that suggest potential synergy come from retrospective trials of patients treated with IL-2 showing an improved outcome achieved for patients who underwent nephrectomy as compared with those without nephrectomy.⁵ Neoadjuvant therapy has also shown only modest benefit in advanced RCC.¹⁹ In summary, until the results of randomized trials are available, no synergy has been proven to date between targeted antiangiogenic therapy and cytoreductive nephrectomy in RCC.

THE IMPORTANCE OF MULTIDISCIPLINARY TEAM INPUT: COLLECTIVE WISDOM AND THE FUTURE OF PATIENT-CENTERED CARE AND RESEARCH

Typically, patients who are not offered cytoreductive nephrectomy have poor performance status, major comorbidities, and limited access to care. Racial disparity in rates of nephrectomy has also been shown to have an impact on patient outcomes. In a SEER database analysis of advanced RCC, patients of African-American origin were noted to have a worse OS outcome as compared with white patients with metastatic RCC, and an interaction effect was noted with the disparity in rates of nephrectomy.²⁰ However, whether this finding reflects other inherent biases noted above is unknown. This observation highlights the need for data collection regarding the factors commonly considered toward the decision-making process of nephrectomy.

In addition, cytoreductive nephrectomy carries a certain risk that has to be factored into the decision. The major complication rates of cytoreductive nephrectomy have been reported to be about 5%, and 11% of the patients did not start systemic therapy within 60 days after nephrectomy because of surgical complications. Overall, 61% of patients did not start systemic therapy in a timely fashion. The presence of liver metastases, intraoperative transfusion, and pathologic nodal involvement were noted to be predictors of delay of systemic therapy more than 60 days after cytoreductive nephrectomy.²¹

It is not advisable to reflexively send the patient for nephrectomy upon diagnosis of advanced kidney cancer. Multidisciplinary evaluation to carefully weigh the risk and benefit ratio factoring in whether the bulk of the patient's symptoms are related to the cancer or to other comorbidities would be important. Renal cancer is a heterogeneous disease,²² and to date, the resection of resistant clones is still considered an ideal way to manage the problem. Stage IV disease within RCC spans a wide spectrum of outcomes, and risk prognostication is critically important before nephrectomy is considered.

The reported efficacy of targeted therapy for patients with metastatic renal cancer is mainly known only in the setting of cytoreductive nephrectomy. This means that current clinical trial-based data regarding efficacy of systemic therapy in RCC do not apply to a large magnitude of the patient population treated. As systemic therapy options and efficacies evolve, the role of nephrectomy requires re-evaluation. It does not seem appropriate to subject every patient with metastatic renal cancer to the morbidity, adverse events, cost, and

potential delay of systemic therapy that result from the nephrectomy procedure. In addition, special efforts must be made to collect information regarding the efficacy of specific systemic therapies for the patients who are not candidates for nephrectomy. It is likely that the presence of nephrectomy is an objective measure that reflects a subgroup within RCC that has a distinctly favorable outcome.

FACTORS TO BE CONSIDERED PRIOR TO CYTOREDUCTIVE NEPHRECTOMY

Histology (Clear Cell or Non-clear Cell)

Non-clear cell histology has suboptimal systemic therapy options, and hence cytoreductive nephrectomy maybe a more important component of the management. However, poor prognostic characteristics such as liver metastases, impaired performance status, and the unresectable nature of the disease should be considered as relative contraindications to cytoreductive nephrectomy.

Patient Performance Status

Retrospective studies show that patients with impaired performance status failed to benefit from cytoreductive nephrectomy.

Current/Impending Symptoms From Disease

Delay in systemic therapy because of cytoreductive nephrectomy is a concern for symptomatic patients with RCC.

Burden of Metastatic Disease

Patients with liver metastases or nodal involvement were likely to have a higher complication rate with cytoreductive nephrectomy that resulted in more than a 60-day delay in systemic therapy.

Memorial Sloan Kettering Cancer Center Risk Criteria

Multivariate analysis revealed no benefit from cytoreductive nephrectomy for patients with poor risk characteristics per the Memorial Sloan Kettering Cancer Center's risk classification.

Risk of Surgical Complications

Patients with impaired performance status and comorbidities are likely to have a higher complication rate from cytoreductive nephrectomy.

CASE ILLUSTRATIONS

Deferral of Nephrectomy as a Result of Disease Symptoms and Burden

Case 1.—A 68-year-old man presented with malena, anemia (hemoglobin of 4.0 g/dL), and hip pain. Imaging revealed a large renal mass, hip metastases, and lung metastases. Colonoscopy showed large mucosal lesions, the biopsy of which revealed clear cell RCC.

This patient, given the life-threatening nature of his metastatic disease, would not be a candidate for nephrectomy. The patient was started on an oral anti-VEGF tyrosine kinase inhibitor. His hemoglobin improved within 2 weeks of starting therapy, and his lesions were clinically responding. Clearly, this case needed to proceed to systemic therapy rapidly, and attempting cytoreductive nephrectomy for this patient was likely to have a deleterious effect. This case also raises the dilemma of whether to consider a nephrectomy at a later date after initial response to targeted therapy. There is no evidence to support that cytoreductive nephrectomy would be beneficial at this time in this case. The concerns comprise discontinuing VEGF inhibitor therapy, the regrowth potential of his disease, and patient safety during surgery. In a clinical trial of preoperative sunitinib followed by cytoreductive nephrectomy, about 36% (17 of 47) of patients had disease progression during the break from systemic therapy, confirming the concerns regarding this approach.¹⁹ The patient continues to be treated without nephrectomy and with systemic therapy alone.

Case 2.—A 58-year-old man presented with severe dyspnea, noted to be related to pleural effusion. A 6-cm left-sided renal mass was noted. Thoracentesis was performed, and lung and pleural metastases were noted. Cytology revealed malignant cells, and biopsy of kidney revealed clear cell cancer. The patient was treated with targeted therapy and demonstrated a response with complete resolution of the pleural effusion and stable renal mass. In this case, nephrectomy was considered advisable to render the patient in clinical complete remission. However, there were valid concerns of holding systemic therapy and risking progression of disease during cytoreductive nephrectomy and the healing period after the procedure.

Case 3.—A 52-year-old man was hospitalized with hypercalcemia; his corrected calcium was 15 mg/dL, and workup revealed a renal mass and bilateral lung and bone lesions, including one in the sacrum. Biopsy of bone showed clear cell cancer consistent with renal primary. This patient needs to proceed directly to systemic therapy, as attempting a nephrectomy in the presence of uncontrolled metastatic disease would result in worsening patient condition and compromise survival outcome.

Deferral of Nephrectomy as a Result of Comorbid Conditions

Case.—An 85-year-old woman with coronary artery disease and angioplasty with stent placement 4 months ago presented with microscopic hematuria. Workup revealed a 7-cm right renal mass and bilateral lung masses. Biopsy of the lung lesion demonstrated clear cell carcinoma consistent with renal primary. Cytoreductive nephrectomy was considered risky because of the patient's cardiac condition, and, hence, systemic therapy was started with clinical response. Currently, the patient remains free of progression for the last 10 months.

CONCLUSION

Absence of cytoreductive nephrectomy is a very common occurrence in advanced RCC (65% of cases) and warrants further clinical and research investigation. The efficacy and toxicity reports from clinical trials of targeted and immune therapy predominantly represent the patient population that has had cytoreductive nephrectomy and need to be interpreted and applied in the appropriate context. The complication rates of nephrectomy range from 7% to

21%¹⁹ and may have implications in the delay of or inability to administer systemic therapy. Outcome-based research and interventional trials focusing on the clinical treatment of patients with metastatic RCC not undergoing nephrectomy represent a critical unmet need.

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KEY POINTS

- Two phase III trials support the recommendation of nephrectomy in metastatic renal cancer when compared with interferon therapy alone; however, the clinical applicability of this finding is not clear in the era of targeted therapy.
- A delay in systemic therapy (because of nephrectomy) can have deleterious effects on the survival of patients with metastatic renal cancer.
- Patients with poor-risk disease or predicted survival less than 12 months are unlikely to benefit from nephrectomy. The clinical implications of deferred nephrectomy for patients with metastatic renal cancer are not well understood.
- Surveillance, Epidemiology, and End Results Program database analysis revealed that 65% of patients with advanced renal cancer do not undergo nephrectomy as their initial treatment. This patient population warrants further study, especially as it is not included in current clinical trials.

TABLE 1.

Pros and Cons of Nephrectomy in Metastatic Renal Cell Carcinoma

Pros of Nephrectomy in Metastatic RCC	Cons of Nephrectomy in Metastatic RCC
Control of symptoms from primary tumor	Complications of surgery
Phase III trials showing OS benefit	No benefit proven with targeted therapy No change in response to systemic therapy
Resection of resistant clones	Delay of systemic therapy
Long-term remissions noted with surgical resection of metastatic RCC	Impaired creatinine clearance, increased risk of hypertension
Nephrectomy patients comprise 90% of clinical trial patient population	Unlikely to benefit patients with comorbidities and impaired performance status

Abbreviations: RCC, renal cell carcinoma; OS, overall survival

Summary of Study Data on Nephrectomy and Systemic Therapy

TABLE 2.

First Author, Reference	Type of Study	No. of Patients	Results
Flanigan and Yonover²	Phase III	241	Median OS: CN + IFN: 11.1 months; IFN: 8.1 months; PFS 0; p = .05; Median OS: CN + IFN: 17.4 months; IFN: 11.7 months; PFS 1; p = .08; Median OS: CN + IFN: 6.9 months; IFN: 4.8 months
Mickisch et al³	Phase III	84	Median OS: CN + IFN: 17 months; IFN: 7 months (HR 0.54; 95% CI, 0.31–0.94)
Flanigan et al⁴	Meta-analysis	331	Median OS: CN + IFN: 13.6 months; IFN: 7.8 months (HR 0.69; p = .002)
Pantuck et al⁵	Retrospective	89	CN + IL-2: median OS, 16.7 months; 5-year OS, 19.6%
Choueiri et al¹⁷	Retrospective targeted-therapy era	314 (CN: 201; no CN: 113)	Median OS: 19.8 months (CN) vs. 9.4 months (no CN); HR 0.44; p < .01; multivariate analysis: no benefit; p = .08; poor risk: no benefit; p = .06
Heng et al¹⁸	Retrospective targeted-therapy era	1,658 (CN: 982; no CN: 676)	Median OS: 20.6 months (CN) vs. 9.5 months (no CN); p < .0001

Abbreviation: CN, cytoreductive nephrectomy; OS, overall survival; IFN, interferon; PFS, progression-free survival; N/A, not applicable.